Stereoselective Synthesis of Flavonoids. Part 8.† Free Phenolic Flavan-3-ol Diastereoisomers

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Asymmetric dihydroxylation of a series of poly-*O*-methoxymethyl-1,3-diarylpropenes with AD-mix-α or AD-mix-β and subsequent acid-catalyzed cyclization of the intermediate *syn*-diols permits the first synthetic access to all four diastereoisomers of free phenolic flavan-3-ols in high enantiomeric excess and yield.

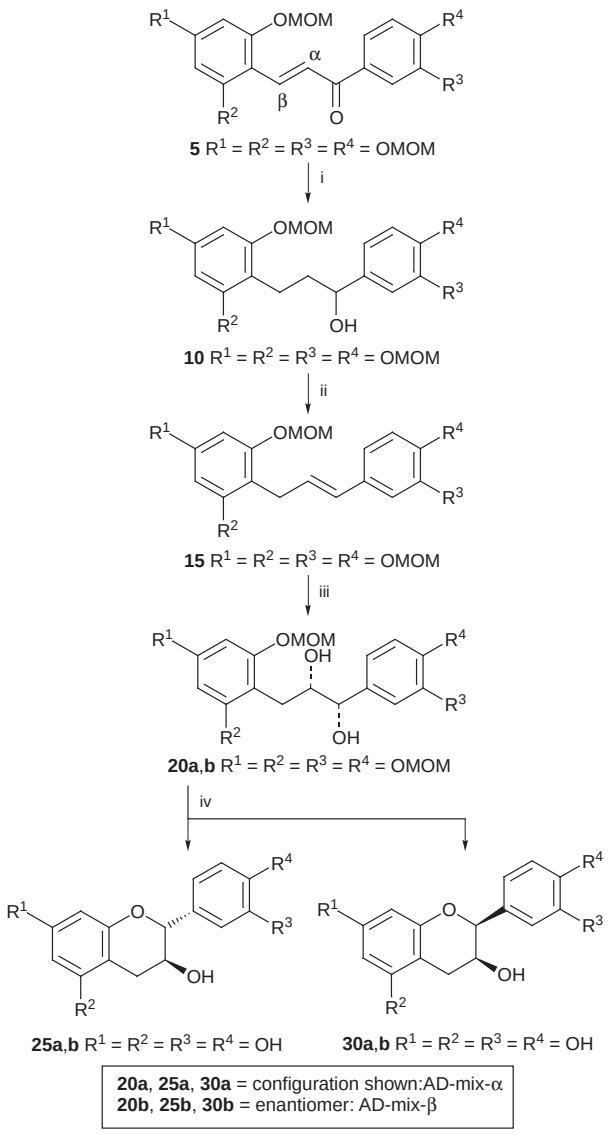
Flavan-3-ols play a key role in the chemistry of the condensed tannins.[1,2] From a synthetic perspective their limited availability in natural sources recently prompted exploration of methods aimed at generation of all four diastereoisomeric permethylaryl ether derivatives of a selection of analogues exhibiting the phenolic oxygenation patterns of the naturally occurring compounds.[3,4] This method of asymmetric dihydroxylation of 1,3-diarylpropenes and subsequent cyclization of intermediate *syn*-diols is herein adjusted to target the four diastereoisomers of free phenolic flavan-3-ols for the first time.

Consecutive reduction of the *O*-methoxymethylated (*E*)-*retro*-chalcones, *e.g.* **5** ($J_{\alpha,\beta}$ 15.9–16.0 Hz) using 5% Pd/C and $NaBH_4$ afforded the corresponding propanols, *e.g.* **10**, in almost quantitative yields (Scheme 1). Treatment of the propanols with thionyl chloride and 1,8-diazabicyclo[5.4.0]undec-7-ene (1,8-DBU) afforded exclusively the (*E*)-1,3-diarylpropenes, *e.g.* **15** ($J_{1,2}$ 15.7–16.0 Hz) in yields of 60–69%.

Treatment of the *E*-propenes at 0 °C with AD-mix-α in the two-phase system Bu^tOH:H_2O (1:1)[5] gave the (1*S*,2*S*)-*syn* diols, *e.g.* **20a** ($J_{1,2}$ 5.6–6.3 Hz) in good yields (75–79%) and essentially enantiopure (99% ee). Dihydroxylation using AD-mix-β similarly afforded the (1*R*,2R)-*syn* diols, *e.g.* **20b**. These conversions proceeded slowly over periods of 24–48 hours. The enantiomeric purity of the diols was established by ^1H NMR using $Eu(tfc)_3$ as chiral shift reagent, and absolute configurations according to the Sharpless model.[5]

Simultaneous deprotection and cyclization of the (1*S*,2*S*)-*syn* diols, *e.g.* **20a**, with 3 M HCl in *aqueous* methanol gave the free phenolic (2*R*, 3S)-2,3-*trans*-flavan-3-ols, *e.g.* catechin **25a** ($J_{2,3}$ 7.5–8.0 Hz; 50–65% yields) and the (2*S*,3*S*)-2,3-*cis* analogues, *e.g.* *ent*-epicatechin **30a** ($J_{2,3}$ *ca.* 1.5 Hz; 14–21% yields) in excellent enantiomeric excesses. The (1*R*,2*R*)-*syn* diols, *e.g.* **20b**, similarly afforded the (2*S*,3*R*)-2,3-*trans*-, *e.g.* *ent*-catechin **30b** (49–64% yields) and the (2*R*,3*R*)-2,3-*cis*-flavan-3-ols, *e.g.* epicatechin **30b** (12–20% yields). NMR measurements of the flavan-3-ol per-*O*-acetates in the presence of $Eu(tfc)_3$ as chiral shift reagent consistently indicated the presence of a single enantiomer.

The dihydroxylation/cyclization sequence is also effective for 4-*O*-benzyl-2′-*O*-methoxymethyl-*retro*-chalcone providing that acetone is used as co-solvent in the oxidation step. Since the amount of acetone could only be raised to 20% relative to the amount of Bu^tOH while still maintaining the requisite two-phase solvent system, the limited solubility of *O*-benzyl ethers thwarted their use as protecting protocol.



Scheme 1 *Reagents and conditions*: i, Pd/H_2, EtOH then $NaBH_4$, EtOH; ii, $SOCl_2$, CH_2Cl_2, then 1,8-DBU, benzene, reflux; iii, AD-mix-α or AD-mix-β, Bu^tOH:H_2O 1:1 (v/v), $CH_3SO_2NH_2$, 0 °C; iv, 3 M HCl, MeOH:H_2O 3:1 (v/v)

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The CD data of the extensive series of free phenolic flavan-3-ols indicated that analogues with 2*R* and 2*S* absolute configurations gave negative and positive Cotton effects, respectively, in the *ca*. 280 nm region (^1L_b transition).[8]

The sign of the Cotton effect of the ^1L_a transition at *ca*. 240 nm is consistently opposite to that at long wavelength. The combined use of ^{1}H NMR coupling constants and these CD data thus permits unequivocal assessment of the absolute configuration of free phenolic flavan-3-ols.

We have thus developed the first synthetic protocol to access for the first time all four diastereoisomers of free phenolic flavan-3-ols, *e.g*. the quibourtinidols, fisetinidols, afzelechins and catechins in essentially enantiopure form. The method is currently extended to target radio labelled compounds required for key biosynthetic studies in the flavonoid field.

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Techniques used: ^{1}H NMR, CD

References: 17

Table 1: Intermediate products in the conversion of chalcones **1**–**5** into flavan-3-ols **21a/b**–**30a/b**

Table 2: CD data of 2,3-*trans*- and 2,3-*cis*-flavan-3-ols **21a/b**–**30a/b**

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