



The novel flavan-3-ol, (2*R*,3*S*)-guibourtinidol and its diastereomers[☆]

Reinier J.J. Nel^a, Makhosazana Mthembu^a, Johan Coetzee^a, Hendrik van Rensburg^a,
Elfranco Malan^{a,*}, Daneel Ferreira^{b,*}

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

^bNational Center for the Development of Natural Products, Research Institute of Pharmaceutical Sciences, School of Pharmacy, The University of Mississippi, Mississippi, MS 38677, USA

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Abstract

The novel (2*R*,3*S*)-guibourtinidol, representing the first flavan-3-ol with 4',7-dihydroxy phenolic substitution pattern, was identified in the heartwood of *Cassia abbreviata*. Asymmetric dihydroxylation of (*E*)-1-(4'-*O*-methoxymethylphenyl)-3-(2'',4''-di-*O*-methoxymethylphenyl)-propene with AD-mix- α or AD-mix- β and subsequent acid-catalyzed cyclization afforded the four free phenolic guibourtinidol diastereomers, essentially enantiopure and in good yield. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: *Cassia abbreviata*; Flavanoids; Phenolics; Asymmetric dihydroxylation

1. Introduction

Pro- and leucoguibourtinidins with their 4',7-dihydroxy phenolic functionality represent a relatively rare group of proanthocyanidins which, while occurring as minor components in Australian *Acacia* species (Tindale & Roux, 1974), predominate in the Southern African species, *Guibourtia coleosperma* (Roux & De Bruyn, 1963; Saayman & Roux, 1965; Steynberg, Ferreira & Roux, 1983, 1987), *Julbernardia globiflora* (Pelter, Amenechi, Warren & Harper, 1969), *Acacia luederitzii* (Du Preez, Rowan & Roux, 1970; Ferreira, Du Preez, Wijnmaalen & Roux, 1985) and *Cassia abbreviata* (Malan, Swinny, Ferreira & Steynberg, 1996). A limited number of guibourtinidol derivatives were also found in *Cassia fistula* (Patil & Deshpande,

1982) and *Colophospermum mopane* (Malan et al., 1990).

Continuation of the work on *Cassia abbreviata* (Malan et al., 1996) revealed the presence of the novel (2*R*,3*S*)-4',7-dihydroxyflavan-3-ol, guibourtinidol **1**, representing the first entry into the guibourtinidol series of diastereomeric flavan-3-ols. The structure of compound **1** and stereoselective synthesis of the free phenolic diastereomers **1** and **4–6** are described here.

2. Results and discussion

Guibourtinidol **1** was initially purified and identified as the 4',7-di-*O*-methyl-3-*O*-acetyl derivative **2**. The ¹H NMR spectrum (Table 1) showed an ABMX spin system in the heterocyclic region and ABX and AA'BB' spin patterns for two aromatic rings. When taken in conjunction with the presence of an *O*-acetyl (δ 1.98) and two *O*-methyl (δ 3.82, 3.80) resonances, these features were reminiscent of the protons of 4',7-di-*O*-methyl-3-*O*-acetylflavan-3-ol (Van Rensburg, Van Heerden & Ferreira, 1997b). The aromatic spin sys-

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* Corresponding authors. Tel.: +1-91-601-232-1572; fax: +1-91-601-232-7062.

E-mail address: dferreir@olemiss.edu (D. Ferreira).

Table 1

^1H (300 MHz) and ^{13}C (75.46 MHz) NMR data for guibourtinidols **1**, **4–6** and derivative **2** at 296 K. Splitting patterns and J -values (Hz) are given in parentheses

Position	2 $^1\text{H}(\text{CDCl}_3)$	1/6 $^1\text{H}[(\text{CD}_3)_2\text{CO}]$	4/5 $^1\text{H}[(\text{CD}_3)_2\text{CO}]$	2 $^{13}\text{C}(\text{CDCl}_3)$	1/6 $^{13}\text{C}[(\text{CD}_3)_2\text{CO}]$	4/5 $^{13}\text{C}[(\text{CD}_3)_2\text{CO}]$
2	5.12 (d, 6.5)	4.66 (d, 8.0)	4.98 (d, 1.5)	78.6	82.4	79.1
3	5.30 (m)	4.02 (m)	4.20 (m)	69.8	67.7	66.4
4 _{eq}	2.99 (dd, 5.0, 16.0)	2.93 (dd, 5.0, 16.0)	3.09 (dd, 4.0, 16.0)	28.7	33.3	33.2
4 _{ax}	2.82 (dd, 7.0, 16.0)	2.74 (dd, 9.0, 16.0)	2.73 (dd, 3.5, 16.0)	28.7	33.3	
5	6.95 (d, 9.0)	6.88 (d, 9.0)	6.87 (d, 8.0)	130.5	130.5	130.9
6	6.53 (dd, 2.5, 9.0)	6.39 (dd, 2.5, 9.0)	6.37 (dd, 2.5, 8.0)	108.4	108.6	108.6
7				159.9	157.2	157.0
8	6.54 (d, 2.5)	6.30 (d, 2.5)	6.33 (d, 2.5)	101.6	102.8	103.0
9				154.8	155.6	155.8
10				111.4	111.9	111.0
1'				130.5	130.7	130.6
2'/6'	7.30 (d, 9.0)	7.24 (d, 9.0)	7.33 (d, 9.0)	128.0	129.0	128.6
3'/5'	6.90 (d, 9.0)	6.83 (d, 9.0)	6.82 (d, 9.0)	114.3	115.2	114.9
4'				159.9	157.6	157.2
OMe	3.82, 3.80 (each s)			55.7, 55.6		
OMe	1.98 (s)			21.4, 170.6		

tems were differentiated via the appropriate correlation experiments using the H-2(C) and H-4_{eq}(C) resonances as reference signals. The 2,3-*trans* relative configuration was evident from the $^3J_{2,3}$ -value of 6.5 Hz, such a small coupling constant presumably reflecting significant contributions of A-conformers to the ensemble of conformers related to the C-ring (Tobiason & Hemingway, 1994). A high amplitude negative Cotton effect (−3864) at 283.9 nm in the CD spectrum of derivative **2** was in accordance with chiroptical data of flavan-3-ol derivatives with (2*R*,3*S*) absolute configuration (Korver & Wilkins, 1971; Van Rensburg et al., 1997b). The FAB mass spectrum showed a molecular ion at m/z 327 $[\text{M}-\text{H}]^+$, thus confirming the $\text{C}_{19}\text{H}_{20}\text{O}_5$ molecular formula for compound **2**.

Guibourtinidol **1** was also purified as the peracetate **3** which afforded the free phenolic form via alkaline hydrolysis under an N_2 atmosphere, i.e. conditions which do not effect epimerization at C-2 of the thermodynamically more stable 2,3-*trans*-flavan-3-ol **1** (Kennedy, Munro, Powell, Porter & Foo, 1984). Assignment of the ^{13}C NMR spectra (Table 1) of derivative **2** and of the free phenols, (2*R*,3*S*)-guibourtinidol **1**, (2*S*,3*R*)-guibourtinidol **6** (*ent*-guibourtinidol), (2*R*,3*R*)-guibourtinidol **4** (epiguibourtinidol) and (2*S*,3*S*)-guibourtinidol **5** (*ent*-epiguibourtinidol) were based on HMBC and HMQC experiments.

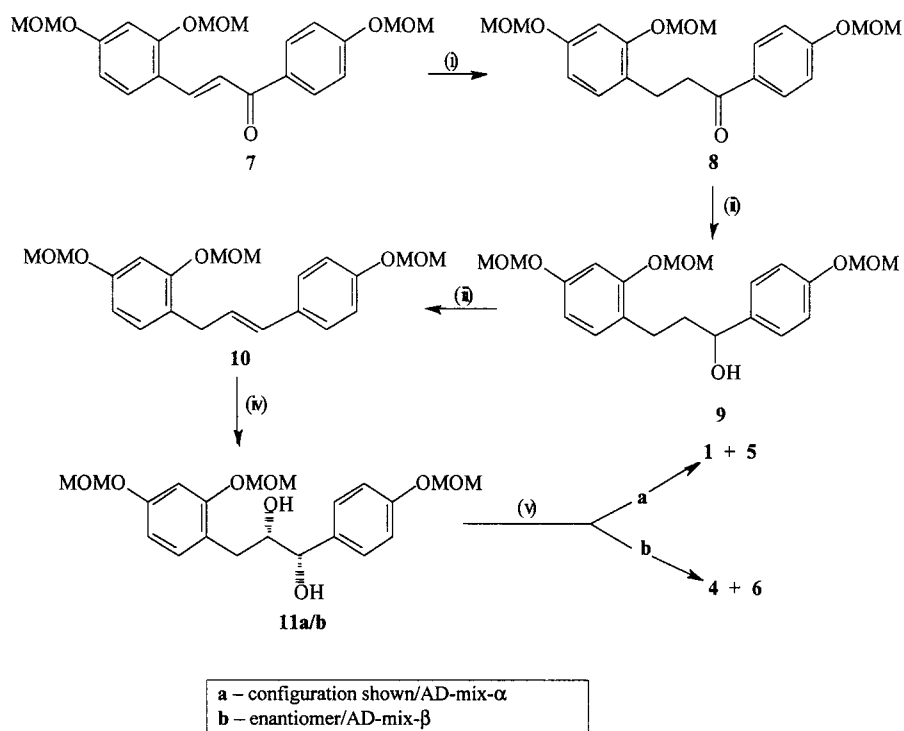
The identification of guibourtinidol **1** as the first naturally occurring flavan-3-ol with 4',7-dihydroxy phenolic substitution presented the opportunity to synthesize the four diastereomers **1** and **4–6** by adapting our recently developed protocol towards flavan-3-ol derivatives via asymmetric dihydroxylation of 1,3-diarylpropenes and subsequent acid-catalyzed cyclization (Van Rensburg, Van Heerden, Bezuidenhout &

Ferreira, 1997a; Van Rensburg et al., 1997b) to the first synthesis of free phenolic flavan-3-ols. Owing to the acid lability of methoxymethyl derivative, the MOM functionality was used as a protecting group.

The (*E*)-*retro*-2,4,4'-tri-*O*-methoxymethylchalcone **7** (Scheme 1) was prepared in 72% yield by base-catalyzed condensation of 2,4-di-*O*-methoxymethylbenzaldehyde and 4-*O*-methoxymethylacetophenone. Hydrogenation of chalcone **7** in the presence of 5% Pd/C afforded the *retro*-dihydrochalcone **8** in quantitative yield. Subsequent reduction with NaBH_4 gave the 1,3-diarylpropan-1-ol **9** (99%) which was converted into the (*E*)-1,3-diarylpropene **10** (69%) using SOCl_2 and 1,8-diazabicyclo[5.4.0]undec-7-ene (1,8-DBU).

Treatment of the (*E*)-1,3-diarylpropene **10** with AD-mix- α in the two-phase system $t\text{BuOH}:\text{H}_2\text{O}$ (1:1) (Jeong, Sjö & Sharpless, 1992; Kolb, Van Nieuwenhze & Sharpless, 1994; Sharpless et al., 1992; Wang, Zhang & Sharpless, 1993) afforded the (1*S*,2*S*)-*syn*-diol **11a** ($^3J_{1,2}=6.3$ Hz) in high yield (79%) and optical purity (99% ee). The (1*R*,2*R*)-*syn*-diol **11b** (78% yield, 99% ee) was similarly obtained by using AD-mix- β in the same two-phase system. The enantiomeric purity of the diols was determined by ^1H NMR using $\text{Eu}(\text{tfc})_3$ as a chiral shift reagent while the absolute configuration was assigned according to the Sharpless model (Jeong et al., 1992; Sharpless et al., 1992; Van Rensburg et al., 1997b).

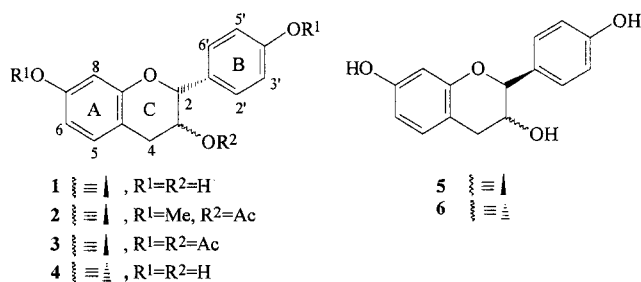
Simultaneous deprotection and cyclization of the (1*S*,2*S*)-*syn*-diol **11a** with 3M HCl in methanol at 60°C gave (2*R*,3*S*)-2,3-*trans*-4',7-dihydroxyflavan-3-ol **1** (guibourtinidol, 60% yield, 99% ee) and the (2*S*,3*S*)-2,3-*cis*-4',7-dihydroxyflavan-3-ol **5** (*ent*-epiguibourtinidol, 18% yield, 99% ee). The (1*R*,2*R*)-*syn*-diol **11b** similarly afforded the (2*S*,3*R*)- and (2*R*,3*R*)-4',7-



Scheme 1. Reagents and conditions: (i) $\text{H}_2/5\%$ Pd-C; (ii) NaBH_4 in EtOH; (iii) SOCl_2 in CH_2Cl_2 , then DBU; (iv) AD-mix- α or AD-mix- β , t -BuOH:H $_2\text{O}$ (1:1), MeSO_2NH_2 , 0°C ; (v) 3M HCl, MeOH-H $_2\text{O}$ (3:1), reflux.

dihydroxyflavan-3-ols **6** (*ent*-guibourtinidol, 61%, 99% ee) and **4** (epiguibourtinidol, 20%, 99% ee), respectively. The optical purity of the flavan-3-ols was assessed by ^1H NMR using $\text{Eu}(\text{tfc})_3$ as a chiral shift reagent for the per-*O*-acetates, which consistently indicated the presence of a single enantiomer. Comparison of the CD data (see Experimental) of the synthetic 2,3-*trans*-(**1/6**; $^3J_{2,3} = 8.0$ Hz) and 2,3-*cis*-(**4/5**; $^3J_{2,3} = 1.5$ Hz) with published data (Korver et al., 1971; Van Rensburg et al., 1997b), confirmed the absolute stereochemistry of the flavan-3-ols and also the configuration at C-2 of the *syn*-diols **11a/b** as was derived from the Sharpless model (Jeong et al., 1992; Sharpless et al., 1992; Van Rensburg et al., 1997a, 1997b). ^1H and ^{13}C NMR data of the flavan-3-ols **1** and **4–6** are collated in Table 1.

We have thus demonstrated that the synthetic protocol to flavan-3-ol derivatives (Van Rensburg et al., 1997a, 1997b), i.e. asymmetric dihydroxylation of 1,3-diarylpromers and subsequent acid-catalyzed cyclization of intermediate *syn*-diols, may be efficiently adapted to access for the first time free phenolic analogues of both 2,3-*trans*- and 2,3-*cis*-configuration in acceptable yields and in a highly stereoselective fashion. This method is currently being applied to include the full range of naturally occurring flavan-3-ols and of radio labelled analogues for much needed biosynthetic studies.



3. Experimental

^1H NMR spectra were recorded on a Bruker AM-300 spectrometer for solutions as indicated, with TMS as internal standard. FAB mass spectra were recorded on a VG 70-70E instrument with a VG 11-250J data system and an iontech saddlefield FAB gun. TLC was performed on precoated Merck plastic sheets (silica gel PF $_{254}$, 0.25 mm) and the plates were sprayed with H_2SO_4 -HCHO (40:1, v/v) after development. Preparative plates (PLC) [20 $\times$ 20 cm, Kieselgel PF $_{254}$ (1.0 mm)] were air dried and used without prior activation. Column chromatography was performed on Sephadex LH-20 in various columns, solvent systems and flow rates (to be specified in each instance). Flash column chromatography (FLC) was on Merck Kieselgel 60 (230–400 mesh) under a positive pressure

by means of compressed N₂. Methylations were performed with an excess of diazomethane in MeOH-Et₂O over a period of 48 h at –15°C, while acetylations were conducted in Ac₂O-pyridine at ambient temperature. Evaporations were done under reduced pressure at ambient temperature in a rotary evaporator, and freeze-drying of aqueous solutions on a Virtis 12 SL freezemobile.

3.1. Isolation of phenolic compounds.

Heartwood drillings (2.7 kg) were repeatedly extracted with Me₂CO (3 × 2.5 L) for 24 h periods at room temperature (25°C). The extract was concentrated by evaporation under vacuum at 35°C. The concentrate was dissolved in H₂O and then freeze-dried to give a pale-brown powder (340.0 g). Two portions (25 g) of the Me₂CO extract were separated on Sephadex LH-20/EtOH columns (5 × 160 cm) with flow rate of 1 ml/min, 32 min fractions. The fractions from columns A and B were combined as follows: C₁ (tubes 17–28, 594.9 mg), C₂ (29–40, 126 mg), C₃ (48–57, 232 mg), C₄ (69–77, 144 mg), C₅ (78–86, 132 mg), C₆ (91–103, 400 mg), C₇ (109–133, 2.72 g), C₈ (134–144, 1.34 g), C₉ (145–154, 3.67 g), C₁₀ (155–189, 7.34 g), C₁₁ (190–207, 1.69 g), C₁₂ (208–237, 3.34 g), C₁₃ (238–288, 2.33 g), C₁₄ (289–341, 2.75 g), C₁₅ (342–376, 508 mg), C₁₆ (377–404, 432 mg), C₁₇ (405–442, 615 mg), C₁₈ (443–471, 235 mg), C₁₉ (472–940, 614 mg) and C₂₀ (942–1500, 802 mg). Only fraction C₆ will be dealt with here.

Methylation of a PLC purified portion (200 mg) [*R*_f 0.64, benzene-Me₂CO-MeOH (6:3:1)] of fraction C₆ followed by PLC separation in benzene-Me₂CO (9:1, ×1) afforded four bands [*R*_f 0.91 (4.7 mg), 0.71 (7 mg), 0.54 (10.4 mg), 0.42 (13 mg)] of which only the latter band was acetylated. Purification by PLC in benzene yielded the permethylaryl ether acetate **2**, *R*_f 0.22 (12.3 mg). The remaining bands still comprised mixtures and were not further investigated.

The remaining portion of fraction C₆ (200 mg) was acetylated and purified by PLC in benzene-Me₂CO (96:4, ×2) to afford a main band at *R*_f 0.54 (5.8 mg) which gave the full acetate **3** of guibourtinidol **1**. The acetylated compound was hydrolyzed in 1% KOH and MeOH for 5 min under N₂ at reflux temp. to give the free phenolic compound **1**, *R*_f 0.46 (5.7 mg).

The low yields of the permethylaryl ether acetate **2** and the full acetate **3** may be ascribed to the extremely complex phenolic mixture which permits the isolation of only those compounds which are visible as discrete bands on PLC.

3.1.1. 4',7-Di-*O*-methyl-3-*O*-acetyl guibourtinidol **2**

Yellowish brown amorphous solid, δ_{H} and δ_{C} NMR (Table 1); CD: $\Delta \epsilon_{\text{max}}$ [λ (nm)] –3864 (284), +5481

(239), –551 (230), +21.7 (227), +503 (217) (found: M^+ , 328.1279. C₁₉H₂₀O₅ requires M^+ , 328.1273).

3.1.2. Guibourtinidol **1**

Tan amorphous solid, ¹H and ¹³C NMR spectral data (Table 1), CD — see below (Found: M^+ , 258.0881. C₁₅H₁₄O₄ requires M^+ , 258.0893).

3.2. Stereoselective Synthesis of Guibourtinidols **1** and **4–6**

3.2.1. 4,4'-Tri-*O*-methoxymethyl-retro-chalcone **7**

To a solution of 4-*O*-methoxymethylacetophenone (3 mmol) was added 50% *aq.* KOH (0.4 ml/mmol acetophenone) and the mixture was stirred at rt for 30 min. 2,4-Di-*O*-methoxymethylbenzaldehyde (3.6 mmol) was added and the mixture was stirred at rt until disappearance of the acetophenone. Water (50 ml) was added and the mixture was extracted with Et₂O (4 × 20 ml). Drying of the extracts with Na₂SO₄ followed by evaporation and FLC in hexane-benzene-Me₂CO (5:4:1) afforded the title compound **7** (*R*_f 0.34 in hexane-benzene-Me₂CO, 5:4:1) as light-yellow needles from EtOH (72% yield), m.p. 46–47°C; δ_{H} (CDCl₃) 8.13 (d, *J* 15.8, H- β), 8.04 (d, *J* 9.1, H-2',6'), 7.62 (d, *J* 9.0, H-6), 7.55 (d, *J* 15.8, H- α), 7.13 (d, *J* 9.1, H-3',5'), 6.87 (d, *J* 2.4, H-3), 6.76 (dd, *J* 9.0 and 2.4, H-5), 5.29, 5.27, 5.22 (3 × s, OCH₂OCH₃), 3.53, 3.52, 3.51 (3 × s, OCH₂OCH₃) (Found: M^+ , 388.1517. C₂₁H₂₄O₇ requires M^+ , 388.1522).

3.2.2. 2,4,4'-Tri-*O*-methoxymethyl-retro-dihydrochalcone **8**

A solution of the retro-chalcone **7** (16 mmol) in EtOH (200 ml) was hydrogenated over 5% Pd–C (1 mg/10 mg chalcone) until all the chalcone was consumed (TLC). The catalyst was filtered off and the EtOH evaporated to afford the title compound **8** (*R*_f 0.47 in hexane-benzene-Me₂CO, 5:4:1) as a colourless oil in quantitative yield: δ_{H} 7.97 (d, *J* 9.1, H-2',6'), 7.12 (d, *J* 8.3, H-6), 7.08 (d, *J* 9.1, H-3',5'), 6.81 (d, *J* 2.4, H-3), 6.66 (dd, *J* 8.3 and 2.4, H-5), 5.25, 5.21, 5.16 (3 × s, OCH₂OCH₃), 3.50, 3.49 (×2) (2 × s, OCH₂OCH₃), 3.22 (m, β -CH₂), 3.01 (m, α -CH₂) (Found: M^+ , 390.1671. C₂₁H₂₆O₇ requires M^+ , 390.1679).

3.2.3. 1-(4'-*O*-Methoxymethylphenyl)-3-(2'',4''-di-*O*-methoxymethylphenyl)-1-propanol **9**

To a solution of the retro-dihydrochalcone **8** (15 mmol) in EtOH (200 ml) was added NaBH₄ (60 mmol, 4 equiv.) and the mixture was stirred at rt for 12 h. It was diluted with H₂O (100 ml), extracted with Et₂O (3 × 100 ml), the combined extracts dried (Na₂SO₄) and the solvent evaporated to give the title alcohol **9** as a colourless oil in quantitative yield (*R*_f 0.21 in hex-

ane-benzene-Me₂CO, 5:4:1); δ_{H} 7.30 (d, *J* 8.8, H-2',6'), 7.06 (d, *J* 8.2, H-6''), 7.03 (d, *J* 8.8, H-3',5'), 6.80 (d, *J* 2.3, H-3''), 6.66 (dd, *J* 8.2 and 2.3, H-5''), 5.19 ($\times 2$), 5.16 (3 $\times$ s, OCH₂OCH₃), 4.63 (m, H-1), 3.50 ($\times 2$), 3.48 (3 $\times$ s, OCH₂OCH₃), 2.69 (m, 3-CH₂), 2.03 (m, 2-CH₂) (Found: M^+ , 392.1841. C₂₁H₂₈O₇ requires M^+ , 392.1836).

3.2.4. (*E*)-1-(4'-*O*-Methoxymethylphenyl)—3-(2'',4''-di-*O*-methoxymethylphenyl)-propene **10**

Freshly distilled SOCl₂ (24 mmol, 2 equiv.) was added dropwise to a solution of the alcohol **9** (12 mmol) in dry CH₂Cl₂ (15 ml), the mixture was stirred at rt for 5 min, dry benzene (20 ml) was added and the mixture evaporated to dryness at 50°C. The resulting chloropropane was dissolved in dry benzene (15 ml), 1,8-DBU (24 mmol, 2 equiv.) was added and the solution was refluxed for 12 h. Satd. *aq.* NH₄Cl was added and the mixture was extracted with Et₂O (3 $\times$ 50 ml), the combined extract washed with water (50 ml), dried (Na₂SO₄) and evaporated to dryness. The mixture was purified by PLC in hexane-benzene-Me₂CO (5:4:1) to give propene **10** as a clear oil (*R*_f 0.62, 69%); δ_{H} 7.28 (d, *J* 8.9, H-2',6'), 7.10 (d, *J* 8.3, H-6''), 6.97 (d, *J* 8.9, H-3',5'), 6.82 (d, *J* 2.4, H-3''), 6.68 (dd, *J* 8.3 and 2.4, H-5''), 6.37 (d, *J* 15.7, H-1), 6.23 (dt, *J* 15.7 and 6.6, H-2), 5.21, 5.18, 5.17 (3 $\times$ s, OCH₂OCH₃), 3.50, 3.49 ($\times 2$), (3 $\times$ s, OCH₃OCH₃), 3.48 (d, *J* 6.6, 3-CH₂) (Found: M^+ , 374.1722. C₂₁H₂₆O₆ requires M^+ , 374.1730).

3.2.5. (1*S*,2*S*)-*syn*-1-(4'-*O*-Methoxymethylphenyl)-3-(2'',4''-di-*O*-methoxymethyl-phenyl)-propane-1,2-diol **11a**

A 10 ml round-bottomed flask, equipped with a magnetic stirrer was charged with *t*BuOH (2.5 ml), water (2.5 ml) and AD-mix- α or - β (700 mg). Stirring of the mixture at rt produced two clear phases; the lower *aq.* phase appearing bright yellow. MeSO₂NH₂ (47.6 mg, 0.5 mmol, 1 equiv.) was added, the mixture was cooled to 0°C and treated with propene **10** (0.5 mmol) in Me₂CO (0.5 ml) in one batch. The resulting heterogeneous slurry was stirred vigorously at 0°C for 24 h, Na₂SO₃ (750 mg) was added and the mixture was allowed to warm to rt and stirred for 30 min. EtOAc (30 ml) was added and the organic layer was separated; the *aq.* phase was further extracted with EtOAc (3 $\times$ 15 ml), the combined extracts were dried (Na₂SO₄), evaporated to dryness and the mixture separated by PLC in benzene-Me₂CO (9:1) to give the *syn*-diol **11a** as a colourless oil (*R*_f 0.12, 79%); δ_{H} 7.33 (d, *J* 8.9, H-2',6'), 7.05 (d, *J* 8.9, H-3',5'), 7.04 (d, *J* 8.4, H-6''), 6.79 (d, *J* 2.3, H-3''), 6.67 (dd, *J* 8.4 and 2.3, H-5''), 5.19, 5.15, 5.13 (3 $\times$ s, OCH₂OCH₃), 4.49 (dd, *J* 4.4 and 3.0, H-1), 3.93 (m, H-2), 3.49, 3.48, 3.43 (3 $\times$ s, OCH₂OCH₃), 3.03 (d, *J* 4.4, 1-OH), 2.76 (dd, *J*

13.8 and 4.2) and 2.64 (dd, *J* 13.8 and 8.9) (3-CH₂), 2.57 (d, *J* 4.3, 2-OH); CD: $\Delta \epsilon_{\text{max}}$ [λ (nm)] -230 (271), +4200 (232) (Found: M^+ , 408.1791. C₂₁H₂₈O₈ requires M^+ , 408.1784).

3.2.6. (1*R*,2*R*)-*syn*-1-(4'-*O*-Methoxymethylphenyl)-3-(2'',4''-di-*O*-methoxymethyl-phenyl)-propane-1,2-diol **11b**

CD: $\Delta \epsilon_{\text{max}}$ [λ (nm)] +210 (272), -4300 (233); The ¹H NMR spectral data corresponded to those indicated for **11a** (Found: M^+ , 408.1789. C₂₁H₂₈O₈ requires M^+ , 408.1784).

3.3. General procedure for preparation of the flavan-3-ols

A solution of the diol **11a/11b** (100 mg, 0.25 mmol) and 3 M HCl (0.4 ml) in H₂O:MeOH [1:3 (0.6 ml)] was stirred at 60°C for 5 h and then diluted with ice water (10 ml). The *aq.* solution was extracted with Et₂O (4 $\times$ 20 ml), dried (Na₂SO₄) and the solvent evaporated. Purification by PLC in CHCl₃-MeOH (9:1) afforded the 2,3-*trans*-flavan-3-ols **1** (*R*_f 0.38, 60%) and **6** (61%) as well as the 2,3-*cis*-analogues **4** (*R*_f 0.33, 20%) and **5** (18%).

3.3.1. (2*R*,3*S*)-4',7-Dihydroxyflavan-3-ol **1**

δ_{H} and δ_{C} (Table 1); CD: $\Delta \epsilon_{\text{max}}$ [λ (nm)] = -1800 (275), +3000 (239) (Found: M^+ , 258.0889. C₁₅H₁₄O₄ requires M^+ , 258.0893).

3.3.2. (2*S*,3*R*)-4',7-Dihydroxyflavan-3-ol **6**

CD: $\Delta \epsilon_{\text{max}}$ [λ (nm)] +1700 (274), -3000 (239). The ¹H and ¹³C NMR spectral data corresponded to those indicated for **1** (Found: M^+ , 258.0883. C₁₅H₁₄O₄ requires M^+ , 258.0893).

3.3.3. (2*S*,3*S*)-4',7-Dihydroxyflavan-3-ol **5**

δ_{H} and δ_{C} (Table 1); CD: $\Delta \epsilon_{\text{max}}$ [λ (nm)] +2500 (274), -1200 (238) (found: M^+ , 258.0897. C₁₅H₁₄O₄ requires M^+ , 258.0893).

3.3.4. (2*R*,3*R*)-4',7-Dihydroxyflavan-3-ol **4**

CD: $\Delta \epsilon_{\text{max}}$ [λ (nm)] = -2500 (272), +1000 (238). The ¹H and ¹³C NMR spectral data corresponded to those indicated for **5** (Found: M^+ , 258.0884. C₁₅H₁₄O₄ requires M^+ , 258.0893).

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References

- Du Preez, I. C., Rowan, A. C., Roux, D. G. (1970). Biflavanoid proanthocyanidin carboxylic acids and related biflavanoids from *Acacia luederitzii* var. *retinens*. *J. Chem. Soc., Chem. Commun.*, 492–493.
- Ferreira, D., Du Preez, I. C., Wijnmaalen, J. C., & Roux, D. G. (1985). Biflavanoid guibourtinidin carboxylic acids and their biflavanoid homologs from *Acacia luederitzii*. *Phytochemistry*, 24(10), 2415–2422.
- Jeong, K., Sjö, P., & Sharpless, K. B. (1992). Asymmetric dihydroxylation of enynes. *Tetrahedron Lett.*, 33(27), 3833–3836.
- Kennedy, J. A., Munro, M. G. H., Powell, H. K. J., Porter, L. J., & Foo, L. Y. (1984). The protonation reactions of catechin, epicatechin and related compounds. *Aust. J. Chem.*, 37(4), 885–892.
- Kolb, H. C., Van Nieuwenhze, M. S., & Sharpless, K. B. (1994). Catalytic asymmetric dihydroxylation. *Chem. Rev.*, 94(8), 2483–2547.
- Korver, O., & Wilkins, C. K. (1971). Circular dichroism of flavanols. *Tetrahedron*, 27(22), 5459–5465.
- Malan, J. C. S., Steynberg, P. J., Steynberg, J. P., Young, D. A., Bezuidenhout, B. C. B., & Ferreira, D. (1990). Oligomeric flavanoids. Part 14: proguibourtinidins based on (–)-fisetinidol and (+)-epifisetinidol units. *Tetrahedron*, 46(8), 2883–2890.
- Malan, E., Swinny, E., Ferreira, D., & Steynberg, P. J. (1996). The structure and synthesis of proguibourtinidins from *Cassia abbreviata*. *Phytochemistry*, 41(4), 1209–1213.
- Nel, R. J. J., Van Heerden, P. S., Van Rensburg, H., & Ferreira, D. (1998). Enantioselective synthesis of flavonoids. Part 5. Poly-oxygenated β -hydroxydihydrochalcones. *Tetrahedron Lett.*, 39(31), 5623–5626.
- Patil, A. D., & Deshpande, V. H. (1982). A new dimeric proanthocyanidin from *Cassia fistula* sapwood. *Indian J. Chem. B*, 21(7), 626–628.
- Pelter, A., Amenechi, P. I., Warren, R., Harper, S. H. (1969). Structures of two proanthocyanidins from *Julbernadia globiflora*. *J. Chem. Soc. (C)*, 2572–2579.
- Roux, D. G., & De Bruyn, G. C. (1963). Condensed Tannins 17: isolation of 4',7-dihydroxyflavan-3,4-diol from *Guibourtia coleosperma*. *Biochem. J.*, 87, 439–444.
- Saayman, H. M., & Roux, D. G. (1965). Configuration of guibourtacacidin and synthesis of isomeric racemates. *Biochem. J.*, 96, 36–42.
- 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. (1992). The osmium-catalyzed asymmetric dihydroxylation: a new ligand class and a process improvement. *J. Org. Chem.*, 57(10), 2768–2771.
- Steynberg, J. P., Ferreira, D., & Roux, D. G. (1983). The first condensed tannins based on a stilbene. *Tetrahedron Lett.*, 24(38), 4147–4150.
- Steynberg, J. P., Ferreira, D., & Roux, D. G. (1987). Synthesis of condensed tannins. Part 18. Stilbenes as potent nucleophiles in regio- and stereospecific condensation. Novel guibourtinidol-stilbenes from *Guibourtia coleosperma*. *J. Chem. Soc. Perkin Trans., I*, 1705–1712.
- Tindale, M. D., & Roux, D. G. (1974). Extended phytochemical survey of Australian species of *Acacia*: chemotaxonomical and phylogenetic aspects. *Phytochemistry*, 13(5), 829–839.
- Tobiason, F. L., & Hemingway, R. W. (1994). Predicting heterocyclic ring coupling constants through a conformational search of tetra-*O*-methyl-(+)-catechin. *Tetrahedron Lett.*, 35(14), 2137–2140.
- Van Rensburg, H., Van Heerden, P. S., Bezuidenhout, B. C. B., & Ferreira, D. (1997a). Enantioselective synthesis of the four catechin diastereomer derivatives. *Tetrahedron Lett.*, 38(17), 3089–3092.
- Van Rensburg, H., Van Heerden, P. S., & Ferreira, D. (1997b). Enantioselective synthesis of flavonoids. Part 3. *Trans*- and *cis*-flavan-3-ol methyl ether acetates. *J. Chem. Soc., Perkin Trans., I*, 3415–3421.
- Wang, Z., Zhang, X., & Sharpless, K. B. (1993). Asymmetric dihydroxylation of aryl allyl ethers. *Tetrahedron Lett.*, 34(14), 2267–2270.