Oligomeric flavanoids. Part 19.† Reductive cleavage of the interflavanyl bond in proanthocyanidins

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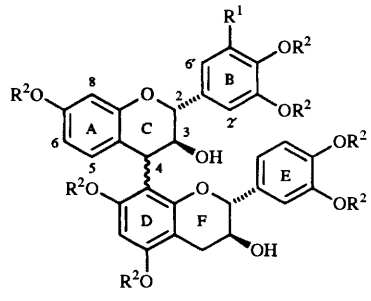
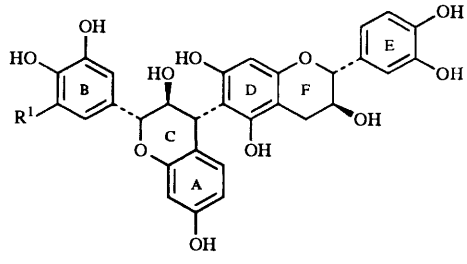
The interflavanyl bond in profisetinidins **1**, **4** and **6**, and methyl ethers **3**, **5**, **28** and **29** and procyanidins **24** and **26**, and their methyl ethers **25** and **27** is readily subject to cleavage with sodium cyanoboranuide in trifluoroacetic acid at 0 °C. This method will contribute significantly to the structure elucidation of the 5-deoxy (A-ring) proanthocyanidins from important commercial sources. Boltzmann-averaged heterocyclic ring coupling constants as determined by a conformational global search routine (GMMX) and NOE difference spectroscopy were used to assign unequivocally the diastereotopic methylene protons in the ^{1}H NMR spectra of flavan-3-ols, a prerequisite for corroboration of the cleavage mechanism.

Introduction

The readily occurring cleavage of the interflavanyl bond in proanthocyanidins exhibiting C-5 oxygenation of the A-ring of their chain-extender units with sulfur nucleophiles under acid catalysis has played a key role in the structure elucidation of this complex group of natural products.[2,3] In the 5-deoxy series of compounds, *e.g.* the fisetinidol-(4,8)- and -(4,6)-catechin profisetinidins **1**. **4** and **6**, and the analogous prorobinetinidins **2** and **7** from the commercially important bark of *Acacia mearnsii* (black wattle),[4] this C(sp^3)–C(sp^2) bond is remarkably stable under a variety of conditions[5,6] and has hitherto resisted all efforts at cleavage in a controllable manner. Such a stable interflavanyl bond has adversely affected both the structure investigation of the polyflavanoid tannins in black wattle bark and of those from other commercial sources, *e.g. Schinopsis spp.* (quebracho) as well as the establishment of the absolute configuration of the chain-terminating flavan-3-ol moiety in the 5-deoxyoligoflavanoids. We have therefore embarked on the development of a method to cleave the interflavanyl bond in profisetinidins efficiently under conditions sufficiently mild to allow the isolation and identification of the constituent flavanyl units. Detailed results relevant to the utilization of sodium cyanoboranuide in trifluoroacetic acid (TFA)[7] are discussed here.



1 ≡ , $R^1 = R^2 = H$
2 ≡ , $R^1 = OH$, $R^2 = H$
3 ≡ , $R^1 = H$, $R^2 = Me$
4 ≡ , $R^1 = R^2 = H$
5 ≡ , $R^1 = H$, $R^2 = Me$



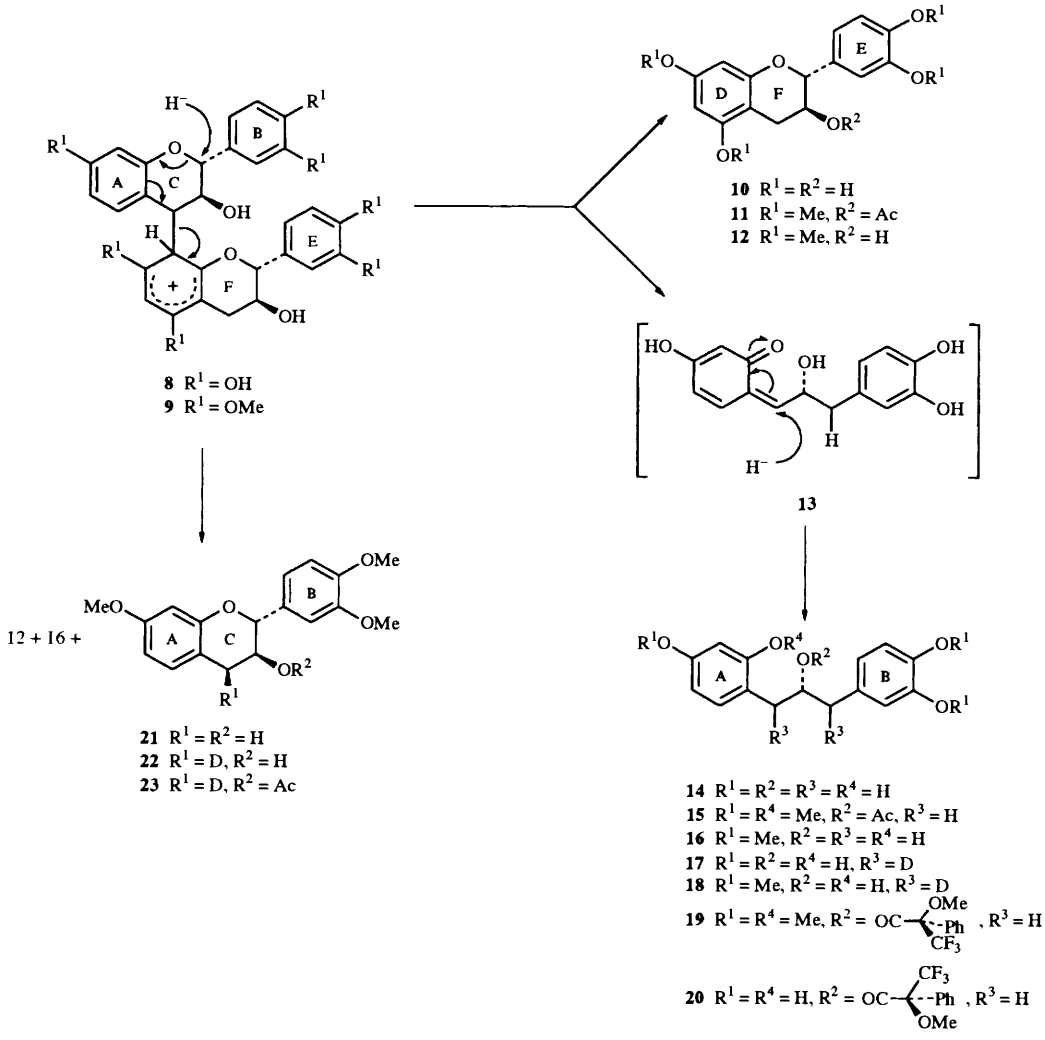
6 $R^1 = H$
7 $R^1 = OH$

Results and discussion

Treatment of the fisetinidol-(4α,8)-catechin **1**,[6] representing a typical tannin unit of commercial wattle extract, with sodium cyanoboranuide[8] (24 molar excess) in TFA for 6 h at 0 °C under nitrogen gave conversion into a mixture comprising the starting material **1** (24% recovery), catechin **10** (15%) and the (2*R*)-1-(2,4-dihydroxyphenyl)-3-(3,4-dihydroxyphenyl)propan-2-ol **14** (16%) (54% recovery of material) (Scheme 1). The structures of compounds **10** and **14** were elucidated by comparison of the physical data [^{1}H NMR and CD (circular dichroism)] of their methyl ether acetates **11** and **15**[9] with those of authentic samples. Similar treatment of the fisetinidol-(4β,8)- and -(4α,6)-catechin profisetinidins[6] **4** and **6** with their respective more and less labile interflavanyl bonds compared with the C(4)–C(8) bond in compound **1** under acidic conditions[10] also afforded a mixture consisting of starting material (**4**, **6**; 16, 12% recovery, respectively), catechin (**10**; 17, 4% respectively), and the (2*R*)-1,3-diarylpropan-2-ol (**14**; 18, 4% respectively) (50 and 20% recovery of material). Although the yields of catechin **10** and the 1,3-diarylpropan-2-ol **14** could be increased to 24 and 25%, respectively, and the recovery of starting material **1** decreased to 11% by employing more mild conditions [9 molar excess of $Na(CN)BH_3$; 3 h], the recovery of material could not be improved beyond ~ 50%.

Similar conditions also effected cleavage of the interflavanyl bond in the fisetinidol-(4α,8)-catechin hepta-*O*-methyl ether **3** to afford tetra-*O*-methylcatechin (**12**, 21%), the 1,3-diarylpropan-2-ol (**16**, 12%), and tri-*O*-methylfisetinidol (**21**, 12%). Such a cleavage of the interflavanyl bond in the permethylaryl ether **3** introduces an important dimension to these results in relation to the chemistry of the 5-deoxyoligoflavanoids where the additional chromatographic steps involved with derivatization are often prerequisites for sample purity. The 'liberation' of the chain-terminating flavan-3-ol unit **10** irrespective of whether the phenol **1** or methyl ether **3** is

† Part 18, ref. 1.



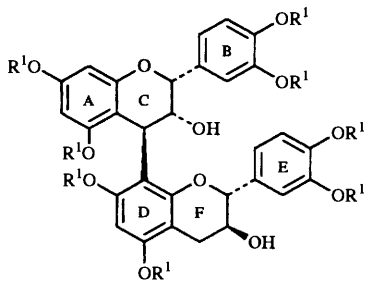
Scheme 1 Proposed route to the cleavage of the interflavanyl bond and of the C-ring in profisetinidin **1**

employed, provides a powerful probe towards addressing the hitherto unsolved problem of defining the absolute configuration at the stereocentres of this moiety in naturally occurring proanthocyanidins that are often synthetically inaccessible due to the unavailability of the flavan-3,4-diol and/or flavan-3-ol precursors.

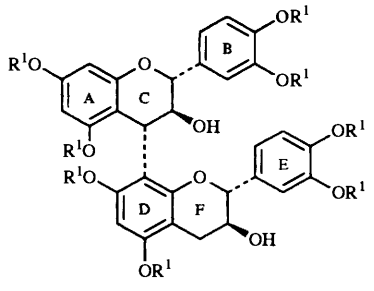
The mild conditions effecting simple cleavage of the strong interflavanyl bond in the profisetinidins **1**, **4** and **6** prompted application of the same protocol to the procyanidins B-1 **24** and B-3 **26**, and their respective methyl ethers **25** and **27** with less rigid C(4)–C(8) linkages compared with those in the profisetinidins **1** and **4**. Thus, treatment of procyanidin B-1 **24** with $Na(CN)BH_3$ (8 molar excess) in TFA for 1 h at 0 °C under nitrogen gave a mixture comprising the starting material **24** (14% recovery), catechin **10** (20%) and epicatechin (21%, the C-3 epimer of compound **10**). Under identical conditions procyanidin B-3 **26** afforded catechin **10** (35%) and a residue of 15% starting material. With a 12 molar excess of reducing agent the permethylaryl ethers **25** and **27** gave, within 30 min, respectively tetra-*O*-methylcatechin **12** (31%), tetra-*O*-methylepicatechin (33%) and starting material **25** (10% recovery), and tetra-*O*-methylcatechin **12** (56%) and starting material **27** (12% recovery).

Whereas the heterocyclic ring of the catechin DEF moiety invariably remains intact during the reductive process, cleavage of both the (4,6)- and (4,8)-interflavanyl bonds in the free phenolic profisetinidins **1**, **4** and **6** is apparently associated with the simultaneous opening of the C-ring of the chain-extender unit. Protonation of the electron-rich phloroglucinol D-ring[11,12] in profisetinidin **1** (Scheme 1), and concomitant delivery of the equivalent of a hydride ion at C-2 of the C-ring (see also below) of intermediate **8** effects the concurrent rupture of the pyran C-ring and of the C(4)–C(8) bond to give catechin **10** and the *o*-quinone methide intermediate **13**, which is subsequently reduced to the 1,3-diarylpropan-2-ol **14**. Such an interdependence of the cleavage of the O–C(2) and C(4)–C(8) bonds was demonstrated by the inability of the reagent to effect rupture of the heterocycle of catechin **10**. The resistance to reductive cleavage of the benzyl ether functionality of catechin **10** contrasts with the formation of flavans or 1,3-diarylpropanes when flavanones were treated with $Na(CN)BH_3$ in TFA.[13] The selective cleavage of the interflavanyl bond in procyanidins B-1 **24** and B-3 **26**, and their permethylarylethers **25** and **27** presumably results from the relative lability of this bond imposing a high degree of S_N1 character to the processes of protonation and delivery of hydride ion.

In order to corroborate the mechanism for cleavage of the interflavanyl bond in the profisetinidin biflavanoids (Scheme 1), sodium cyanotrideuterioboranuide in TFA was utilized. Under these conditions the fisetinidol-(4α,8)-catechin **1** [9 moles of $Na(CN)BD_3$; 2 h] was converted into catechin **10** (26%) and the (2*R*)-dideuterio-1,3-diarylpropan-2-ol **17** (25%).



24 R^1 = H
25 R^1 = Me



26 R^1 = H
27 R^1 = Me

while the permethylaryl ether **3** and the fisetinidol-(4β,8)-catechin hepta-*O*-methylether **5** [both 12 moles of Na(CN)BD_3 and 0.5 h] both gave tetra-*O*-methylcatechin **12** (12, 32% resp.). the dideuterio-1,3-diarylpropan-2-ol tri-*O*-methyl ether **18** (14, 16% resp.) and the 4β-deuteriofisetinidol derivative **22** (12, 14% resp.). Formation of the deuteriated 1,3-diarylpropan-2-ols **17** and **18** (mixtures of diastereoisomers) with retention of the absolute configuration‡ at C(2) thus confirms our conjecture regarding the genesis of the propan-2-ols *via* reduction of the *o*-quinone methide **13**. Retention of the absolute configuration at C-2 in the 1,3-diarylpropan-2-ols **14** and **16** was confirmed by using the α-methoxy-α-(trifluoromethyl)phenylacetic acid [(*R*)-(+)- and (*S*)-(−)-MTPA] esters **19** and **20**.[14,15] The ^{1}H NMR data of these compounds indicated significant shielding of the B-ring protons [$\Delta\delta$ −0.06, 2-H(B); −0.09, 5-H(B); −0.01, 6-H(B)] in the (*R*)-(+)-MTPA ester **19** and shielding of the A-ring protons [$\Delta\delta$ −0.04, 3-H(A); −0.08, 5-H(A); −0.10, 6-H(A)] in the (*S*)-(−)-MTPA ester **20** when compared with the chemical shifts of the same protons in the (*S*)-(−)- and (*R*)-(+)-MTPA esters respectively, a phenomenon which is in accord with the appropriate configuration correlation model of Dale and Mosher.[14]

The protonated species **8** presumably also serves as precursor to the 4β-deuteriotri-*O*-methylfisetinidol **22** *via* delivery of hydride ion from the β-face in a predominant S_N2 mode. Owing to the slow decomposition of Na(CN)BD_3 in acidic medium, the deuteriated fisetinidol derivative **22** was contaminated with a small quantity of tri-*O*-methylfisetinidol **21**. This admixture nevertheless strongly indicated the position of the deuterium label as being 4β since the chemical shift of the 4α-H(C) doublet δ 2.94. $^3J_{3,4\alpha}$ 5.0 Hz) in the ^{1}H NMR spectrum of the methyl ether acetate **23** coincides with the two lines at δ 2.94 of the 4α-H(C) double doublet (δ 2.97, $^3J_{3,4\alpha}$ 5.0, $^3J_{4\alpha,4\beta}$ 16.5 Hz) in the spectrum of the 3-*O*-acetyl derivative of compound **21** hence leaving the double doublet at δ 2.79 ($^3J_{3,4\beta}$ 7.0. $^3J_{4\alpha,4\beta}$ 16.5 Hz), 'characteristic' of the 4β-H(C) resonance in this derivative, intact.

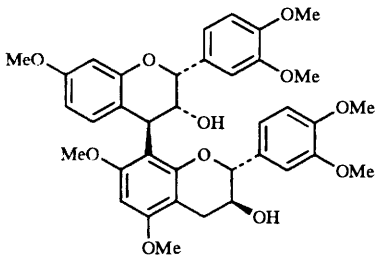
A notable feature of the reductions employing Na(CN)BD_3 and the fisetinidol-(4α,8)- and (4β,8)-catechin hepta-*O*-methyl ethers **3** and **5** is the persistent formation of the 4β-deuteriotri-*O*-methylfisetinidol **22** regardless of the C-4(C) configuration of the starting material. This observation prompted an investigation of the structural features of the substrates that direct the stereochemistry of the delivery of hydride ion at C-4 in intermediates of type **9**. Whereas treatment of the *ent*-epifisetinidol-(4β,8)-catechin hepta-*O*-methyl ether **28** with Na(CN)BD_3 (12 mol. equiv; 0.5 h; 0 °C) afforded the 4β-deuteriotri-*O*-methyl-*ent*-epifisetinidol **31** (18.5%), tetra-*O*-methylcatechin **12** (32%) and the (2*S*)-1,3-diarylpropan-2-ol **33** (6%, see Experimental section for CD evidence of the enantiomeric relationship of derivative **34** with the same derivative of compound **18**). the *ent*-fisetinidol-(4β,8)-catechin hepta-*O*-methyl ether **29** gave 4α-deuteriotri-*O*-methyl-*ent*-fisetinidol (13%, the enantiomer of compound **22**), tetra-*O*-methylcatechin **12** (24%) and a (2*S*)-1,3-diarylpropan-2-ol (12%) with ^{1}H NMR and CD spectra of its acetyl derivative virtually identical with those of compound **34**.

Similar to the observation of the deuteriofisetinidol derivative **22** being slightly contaminated with the 4-H analogue **21** the ^{1}H NMR spectrum of the 4β-deuterio-*ent*-epifisetinidol derivative **32** also shows the presence of the 4-H compound (*O*-acetate of **30**) in very low quantity. This shows that the chemical shift of the 4-H doublet (δ 2.88. $^3J_{3,4\alpha}$ 2.5 Hz) in compound **32** coincides with the two lines at δ 2.8 of the double doublet (δ 2.91, $^3J_{3,4}$ 2.5, $^3J_{4\alpha,4\beta}$ 17.5 Hz) of that 4-H in the acetate of compound **30** which is usually associated with the 4β hydrogen, hence apparently indicating a 4α deuterium label.

Since the unambiguous assignment of the orientation of the deuterium atom is a prerequisite for a mechanistic conclusion, the validity of the chemical shifts of the diastereotopic methylene protons in the flavan-3-ols with both 2,3-*trans* and 2,3-*cis* configuration had to be ascertained. The relationship between coupling constants ($^3J_{HH}$) and torsional angles as depicted by the Karplus equation has undoubtedly evolved into the most powerful method for the elucidation of heterocyclic ring stereochemistry in flavonoids. It has, however, been shown[16] that such a simple approach is often hampered by the fact that the observed $^3J_{HH}$ couplings are averaged values on the NMR timescale. Similar to cyclohexene, the flavonoid heterocycle exhibits a low inversion barrier between the two half-chair local minima (*E*- and *A*-conformers respectively). Fast conformational exchange on the NMR timescale then results in the observed vicinal coupling constants reflecting the Boltzmann-average rather than a single heterocyclic ring conformation. Although the methylene protons of, especially, fisetinidol display a significant difference in the magnitude of the $^3J_{HH}$ coupling with 3-H(C) (see Table 3, later), sound stereochemical conclusions would thus only become possible once the ensemble of conformers significantly populated at ambient temperature can be determined with reasonable accuracy.

In an effort to predict the heterocyclic ring coupling constants of tetra-*O*-methylcatechin, Tobiason and Hemingway[17] employed a global search routine (GMMX) to determine the family of conformers which contributes to the observed $^3J_{HH}$ couplings. Boltzmann-averaging of the vicinal coupling constants over all the conformers in the final ensemble then resulted in a striking reproduction of the experimental values ($J_{2,3}$ 8.15, $J_{3,4eq}$ 5.25, $J_{3,4ax}$ 9.84 Hz *versus* observed values of 8.1, 5.5 and 9.0 Hz, respectively). The success of this method, as well as an awareness of the importance of being able to describe

‡ Designation of the absolute configuration changes from 3*S* (C-ring) in the biflavanoids, *e.g.* **1**, to 2*R* in the propan-2-ols, *e.g.* **16** due to changes in the priorities of ligands attached to the stereocentres.



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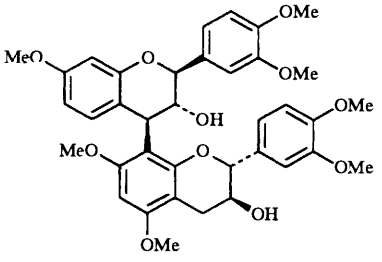

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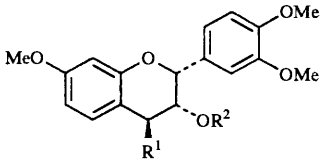
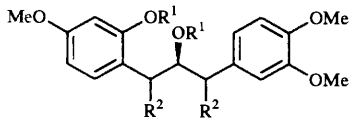
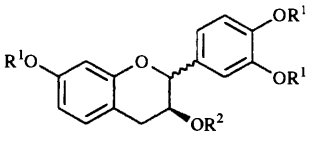


30 $R^1 = R^2 = H$
31 $R^1 = D, R^2 = H$
32 $R^1 = D, R^2 = Ac$



33 $R^1 = H, R^2 = D$
34 $R^1 = Ac, R^2 = D$



35 ≡ , $R^1 = R^2 = H$
36 ≡ , $R^1 = Me, R^2 = Ac$
37 ▲ , $R^1 = R^2 = H$
38 ▲ , $R^1 = Me, R^2 = H$
39 ▲ , $R^1 = Me, R^2 = Ac$

accurately the total ensemble of conformers significantly populated at ambient temperature rather than assuming an equilibrium between preferred *E*- and *A*-conformers. prompted us to utilize a similar approach in exploring the potential-energy surface (PES) of fisetinidol and epifisetinidol. Such an approach will also permit unambiguous differentiation of the diastereotopic methylene protons.

The GMMX 1.0 program[18] was used to search the conformational space of the 2,3-*trans* and 2.3-*cis* flavan-3-ols **21** and **38** (calculation details are summarized in the Experimental section). In order to assess the capability of the GMMX algorithm to predict heterocyclic ring coupling constants of 5-deoxyflavan-3-ols, searches were also conducted on the free phenols **35** and **37** as well as the methyl ether acetate derivatives **36** and **39** of fisetinidol and epifisetinidol. Two calculations starting from totally different points on the PES (*E*- and *A*-conformers respectively) were performed for every molecule to confirm that the conformational space was comprehensively searched (see Tables 3–6).

The data in Table 3 indicate that the heterocyclic ring coupling constants were predicted with an acceptable degree of accuracy for fisetinidol **35** and its methyl ether **21**. thus facilitating explicit assignment of the methylene protons on the basis of the magnitude of the vicinal couplings. Coupling constants calculated for the most stable *E*- and *A*-conformers identified during the search (Table 4) furthermore indicate that failure of the GMMX algorithm to predict $^3J_{HH}$ values correctly for the methyl ether acetate derivative **36** stems from an underestimation of the contribution of *A*-conformers to the final ensemble. Although this may suggest a collapse in the ability of the forcefield to predict the conformational behaviour of acetylated flavans accurately. it should be pointed out that the conformational searching was done in the gas phase. Any effect that solvents may have on the C-ring conformations are therefore not taken into account. Since it has been established that solvents do influence the magnitude of $^3J_{HH}$-values[19] and thus the heterocyclic ring conformation of flavans, this phenomenon may also be related to a solvent–solute interaction.

In contrast to fisetinidol. no conclusive assignments based on the magnitude of predicted $^3J_{HH}$ values (Table 5) could be made for epifisetinidol. If the margin of error in the predicted values was taken into account the difference between the $J_{3,4\alpha}$ and $J_{3,4\beta}$ values observed for epifisetinidol (~ 1.0–2.0 Hz) was too small to permit conclusion. Judging from the data in Tables 5 and 6 the MMX forcefield is furthermore less efficient in predicting the heterocyclic coupling constants of epifisetinidol and its derivatives.

Nuclear Overhauser enhancement (NOE) difference spectroscopy where inter-nuclear double resonance (INDOR) effects were avoided *via* multiple irradiation points for each on-resonance site.[20] however, facilitated unambiguous differentiation of the diastereotopic methylene protons of both fisetinidol and epifisetinidol. A strong NOE effect between 2- and 4-Hα (C-ring) as well as a three-spin relayed NOE (negative enhancement)[21] between 2- and 4-Hβ(C) in the methyl ether derivative **38** permitted unequivocal assignment of the diastereotopic protons at C-4 of epifisetinidol. The observed NOE between 2- and 4-Hβ(C) as well as a negative relayed NOE between 2- and 4-Hα(C) in methyl ether derivative **21** similarly confirmed the assignments made for the C-4 protons of fisetinidol in Table 3.

The formation of the 4β-deuterio-fisetinidol- and -*ent*-epifisetinidol derivatives **22** and **31** from the reduction of the profisetinidin *O*-methyl ethers **3, 5** and **28** with $Na(CN)BD_3$, and of the enantiomer of compound **22** during reduction of the *ent*-fisetinidol-(4β.8)-catechin derivative **29**, indicates that the deuterium ion is consistently delivered at C-4 from the side opposite to the 2-aryl group of the C-ring. This presumably indicates that delivery of the hydride ion occurs from a complex between the reducing agent and the C-ring heterocyclic oxygen lone pair *trans* to the 2-aryl group. such transfer being most readily facilitated in an *A*-conformer[16] **40**.

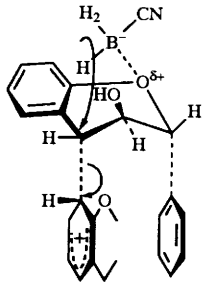
The potential of this development towards the structural elucidation of the proanthocyanidin condensed tannins. especially the 5-deoxy analogues. from important commercial sources is clear. In addition the method should facilitate the ready definition of the absolute configuration of the chain-terminating flavan-3-ol moiety in 5-deoxyoligoflavanoids, especially in view of the demonstration that these units may also be comprised of *ent*-catechin and *ent*-epicatechin.[22,23]

Table 1 ^{1}H NMR peaks (δ_H) of the 1,3-diarylpropan-2-ol derivatives **15**, **16**-$(OAc)_2$, **18**-$(OAc)_2$, **19**, **20** and **34** at 300 MHz (23 °C) in $CDCl_3$. Splitting patterns and J values (Hz) are given in parentheses

Proton	**15**	**16**-$(OAc)_2$	**18**-$(OAc)_2$	**19**	**20**	**34**
3-H(A)	6.40 (d, 2.0)	6.55 (d, 2.5)	6.56 (d, 2.5)	6.42 (d, 2.5)	6.38 (d, 2.5)	6.56 (d, 2.0)
5-H(A)	6.38 (dd, 2.0, 9.5)	6.70 (dd, 2.5, 8.5)	6.71 (dd, 2.5, 8.5)	6.38 (dd, 2.5, 8.0)	6.30 (dd, 2.5, 8.5)	6.71 (dd, 2.5, 8.5)
6-H(A)	6.99 (d, 9.5)	7.11 (d, 8.5)	7.11 (d, 8.5)	7.00 (d, 8.0)	6.90 (d, 8.5)	7.11 (d, 8.5)
2-H(B)	6.69 (d, 2.0)	6.68 (d, 2.0)	6.69 (d, 2.5)	6.66 (d, 2.0)	6.72 (d, 2.0)	6.69 (d, 2.5)
5-H(B)	6.76 (d, 8.0)	6.76 (d, 8.5)	6.70 (d, 8.5)	6.67 (d, 8.5)	6.73 (d, 8.5)	6.76 (d, 8.5)
6-H(B)	6.71 (dd, 2.0, 8.0)	6.69 (dd, 2.0, 8.5)	6.76 (dd, 2.5, 8.5)	6.73 (dd, 2.0, 8.5)	6.78 (dd, 2.0, 8.5)	6.70 (dd, 2.5, 8.5)
1-H	2.90 (dd, 5.0, 14.0) 2.68 (dd, 7.5, 14.0)	2.73 (dd, 7.5, 14.0) 2.64 (dd, 6.0, 14.0)	2.67 (d, 5.5)	2.76–3.20 (m)	2.80–2.97 (m)	2.67 (d, 5.5)
2-H	5.29 (m)	5.12 (m)	5.10 (dd, 5.5, 7.5)	5.60–5.70 (m)	5.63–5.74 (m)	5.10 (dd, 5.5, 7.5)
3-H	2.78 (d, 6.5)	2.68 (dd, 6.0, 14.0) 2.79 (dd, 7.5, 14.0)	2.71 (d, 7.5)	2.76–3.20 (m)	2.80–2.97 (m)	2.71 (d, 7.5)
OMe	3.75 (2-A), 3.77 (4-A), 3.84 (3-B), 3.83 (4-B), each s	3.75 (4-A), 3.84 (3-B), 3.83 (4-B), each s	3.75 (4-A), 3.84 (3-B), 3.83 (4-B), each s	3.70 (2-A), 3.74 (4-A), 3.73 (3-B), 3.80 (4-B), each s; 3.23 (MTPA, m)	3.75 (2-A), 3.76 (4-A), 3.77 (3-B), 3.85 (4-B), each s; 3.21 (MTPA, m)	3.75 (4-A), 3.84 (3-B), 3.83 (4-B), each s
OAc	1.87 (s)	2.15 (2-A), 1.92, each s	2.15 (2-A), 1.93, each s			2.15 (2-A), 1.93, each s
MTPA-phenyl				7.05–7.39	7.03–7.32	

Table 2 ^{1}H NMR peaks (δ_H) of the 4-deuteriofisetinidol derivatives **23** and **32** at 300 MHz (23 °C) in $CDCl_3$. Splitting patterns and J values (Hz) are given in parentheses

Ring	Proton	*23*	*32*
A	5	6.93 (d, 8.5)	6.97 (d, 9.0)
	6	6.49 (dd, 2.0, 8.5)	6.53 (dd, 2.0, 9.0)
	8	6.51 (d, 2.0)	6.54 (d, 2.0)
B	2	6.86 (d, 2.0)	7.02 (d, 2.0)
	5	6.81 (dd, 2.0, 8.0)	6.85 (dd, 2.0, 8.5)
	6	6.89 (d, 8.0)	6.95 (d, 8.5)
C	2	5.06 (d, 6.5)	5.05 (br s, ~1.0)
	3	5.33 (dd, 6.5, 5.0)	5.37 (dd, 1.0, 2.5)
	4α	2.94 (d, 5.0)	2.89 (d, 2.5)
	OMe	3.75 (7-A), 3.83 (3-B), 3.85 (4-B), each s	3.76 (7-A), 3.89 (3-B), 3.87 (4-B), each s
	OAc	1.94, s	1.90, s



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Experimental

^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer for solutions in $CDCl_3$ with Me_4Si as internal standard. J Values are given in Hz. Mass spectra were obtained with a Kratos MS-80 instrument and CD data in MeOH on a JASCO J-710 spectropolarimeter. TLC was performed on pre-coated Merck plastic sheets (silica gel 60 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 × 20 cm, Kieselgel PF_{254} (1.0 mm) were air-dried and used without prior activation. Separations on Sephadex LH-20 were on a column (100 × 3 cm) in EtOH at a flow rate of ~0.8 cm^3 min^{-1} (16 min fractions). Methylations were performed with an excess of diazomethane in MeOH–diethyl ether over a period of 48 h at −15 °C, while acetylations were in acetic anhydride–pyridine at ambient temperature. Evaporations were done under reduced pressure at ~50 °C on a rotary evaporator. Authenticated samples of the biflavanoids were available from our collection of reference compounds.

General reduction and work-up procedure

The biflavanoid was dissolved in TFA (100 mg in 1 cm^3) at 0 °C under nitrogen. $Na(CN)BH_3$ or $Na(CN)BD_3$ was added in portions over a period of 30 min at this temperature. The reaction was quenched by the careful addition of water and the pH of the mixture was adjusted to ~6.9 (Merck special indicator, pH 4.0–7.0) with 2% aq. $NaHCO_3$. The mixture was extracted with ethyl acetate (3 × 50 cm^3) and the combined extracts were stirred for 15 min with 2–3 drops of tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF). Drying over Na_2SO_4 followed by evaporation off of the solvent and separation on Sephadex LH-20 gave the monomeric compounds, which were then further derivatized, separated and identified.

Calculations

Calculations were done on a SUN SPARCstation 10 running SunOS Release 4.1.3. GMMX 1.0,[18] a global search routine based on the MMX forcefield of PC-Model[24] was used to explore conformational space. Input for the default statistical search method [alternation between internal (bonds) and external (cartesian) coordinates] was prepared with PC-Model's graphical users interface treating aromatic carbons as type-40 atoms. The hydrogen-bond function was activated and default dielectric constants (ε = 1.5) were used. Searches were allowed to run until default cut-off criteria were reached. Search bond variables were set up as follows: C^9–O^1, O^1–C^2 and C^2–C^3 each with 12 degrees of freedom; C^2–C^1, C^3–O, C^7–O, $C^{3'}$–O and $C^{4'}$–O each with 3 degrees of freedom. Two degrees of freedom were allowed for the ester bond in the methyl ether acetate derivatives. Pyran ring closure angles were left at default values. Boltzmann populations were determined for the final ensemble of conformers covering an energy span of 3.0 kcal mol^{-1},§ the probability P_i of a conformer existing

§ 1 cal = 4.184 J.

Table 3 GMMX search results and observed heterocyclic ring coupling constants for fisetinidols

Compound	Starting point[a]	Total number of conformers[b]	Unique conformers[c]	Final ensemble[d]	$J_{2,3}$ (Hz)	$J_{3,4\alpha}$ (Hz)	$J_{3,4\beta}$ (Hz)
	Observed coupling constants ([$^2H_6$]acetone)				7.5	5.0	8.5
35	*E*	2613	330	226	8.06	5.21	9.77
	A	2777	313	210	8.23	5.28	9.97
	Observed coupling constants ($CDCl_3$)				8.25	5.5	9.5
21	*E*	7127	1174	638	8.04	5.22	9.74
	A	5032	1000	589	8.08	5.24	9.79
	Observed coupling constants ($CDCl_3$)				6.5	5.0	6.5
36	*E*	9110	1183	400	8.69	5.34	10.50
	A	3841	695	342	8.41	5.25	10.19

[a] Point (*E*- or *A*-conformer respectively) on the potential-energy surface (PES) where the search was initiated. [b] Total number of conformers considered during the search. [c] Number of unique conformers (carbon backbone only) kept within a 3.5 kcal mol^{-1} window. [d] Final ensemble of conformers (hydrogens attached) kept within a 3.0 kcal mol^{-1} window.

Table 4 Most stable *E*- and *A*-conformers in the final ensemble for fisetinidols[a]

		E_{min} (kcal mol^{-1})	$J_{2,3}$ (Hz)	$J_{3,4\alpha}$ (Hz)	$J_{3,4\beta}$ (Hz)
35	*E*-conformer	14.66	9.01	5.62	10.80
	A-conformer	15.98	1.97	2.77	3.11
21	*E*-conformer	29.25	9.00	5.62	10.80
	A-conformer	30.48	1.71	2.88	3.03
36	*E*-conformer	27.16	9.07	5.39	10.94
	A-conformer	28.80	1.72	2.81	3.09

[a] Since different starting points on the PES gave similar results, only ensembles originating from searches started at the respective *E*-conformers are shown.

being evaluated from eqn. (1) where exp $(-E_i/RT)$ is the Boltzmann factor with the sum evaluated at 300 K.[17]

$$P_i = \frac{\exp(-E_i/RT)}{\sum_{i=1} \exp(-E_i/RT)} \quad (1)$$

The vicinal proton coupling constants (J_i) calculated by a modified Karplus equation were Boltzmann-averaged over all the conformers in the ensemble according to eqn. (2).[17]

$$\langle J \rangle = \sum_{i=1} P_i J_i \quad (2)$$

Fisetinidol-(4α,8)-catechin 1

The title compound **1** (100 mg) was reduced with $Na(CN)BH_3$ (100 mg) for 3 h at 0 °C. Work-up and separation afforded three fractions (first 300 cm^3 of eluent discarded). 1 (tubes 28–42). 26 mg; 2 (66–86), 30 mg and 3 (87–114). 15 mg. Methylation of fraction 1 followed by PLC in benzene–acetone (7:3 v/v) afforded a band at R_f 0.61 (34 mg), which was acetylated, and purified by PLC in benzene–acetone (9:1 v/v) to give (2*R*)-acetoxy-1-(2,4-dimethoxyphenyl)-3-(3,4-dimethoxyphenyl)-propane **15** as an amorphous solid (R_f 0.50; 31 mg) (Found: M$^+$, 374.1727. $C_{21}H_{26}O_6$ requires M, 374.1729); δ_H (Table 1); CD $[\theta]_{291.6}$ 0.1 × 10^1, $[\theta]_{280.2}$ −5.7 × 10^2, $[\theta]_{254}$ − 1.8 × 10^2, $[\theta]_{238.2}$ − 7.1 × 10^2, $[\theta]_{233}$ − 4.7 × 10^2, $[\theta]_{221.7}$ − 1.7 × 10^3 and $[\theta]_{215.3}$ 1.2 × 10^1.

Fraction 2 (30 mg) was methylated and the mixture was resolved by PLC in benzene–acetone (7:3, v/v) to give a band at R_f 0.61 (35 mg). Acetylation followed by PLC in benzene–acetone (9:1 v/v) gave the tetramethyl ether acetate **11** of catechin (R_f 0.55; 33 mg) with ^{1}H NMR and CD spectra identical with those of an authentic sample.

Methylation of fraction 3 (15 mg) and subsequent PLC in benzene–acetone (7:3 v/v) afforded a band at R_f 0.38 (16 mg), which was acetylated, and purified by PLC in benzene–acetone (9:1 v/v) to give the hepta-*O*-methyl ether diacetate of profisetinidin **1** (R_f 0.30; 15 mg) with ^{1}H NMR and CD data identical with those of an authentic specimen.

Fisetinidol-(4β,8)-catechin 4

The profisetinidin **4** (300 mg) was reduced with $Na(CN)BH_3$ (804 mg) for 6 h at 0 °C. Work-up and separation gave three fractions (first 200 cm^3 of eluent discarded). 1 (tubes 48–58). 54 mg; 2 (60–70). 51 mg and 3 (80–92). 48 mg. Successive methylation/separation and acetylation/purification according to the procedures in the preceding paragraph of fraction 1 afforded the propan-2-ol derivative **15** (69 mg), of fraction 2 the catechin derivative **11** (68 mg), and of fraction 3 the hepta-O-methyl ether diacetate of profisetinidin **4** (64 mg).

Fisetinidol-(4α,6)-catechin 6

The title compound **6** (200 mg) was reduced with $Na(CN)BH_3$ (536 mg) for 8 h at 0 °C. Work-up and separation afforded three fractions (first 200 cm^3 of eluent discarded). 1 (tubes 38–53). 12 mg; 2 (60–72). 10 mg and 3 (80–95). 36 mg. Successive derivatization and purification as above of fraction 1 gave the propan-2-ol derivative **15** (16 mg), of fraction 2 the catechin derivative **11** (13.5 mg), and of fraction 3 the methyl ether acetate of profisetinidin **6** (47 mg).

Fisetinidol-(4α,8)-catechin hepta-*O*-methyl ether 3

The profisetinidin derivative **3** (50 mg) was reduced with $Na(CN)BH_3$ (100 mg) for 1 h at 0 °C. Work-up afforded a mixture (150 mg), which was resolved by PLC in benzene–acetone (8:2 v/v) into two bands at R_f 0.56 (24.1 mg) and 0.33 (8.3 mg). The former band was acetylated and the resulting mixture was separated by PLC in hexane–ethyl acetate–acetone (80:17:3 v/v, × 3) to give catechin tetramethyl ether acetate **11** (R_f 0.43; 11 mg) and the trimethyl ether acetate of fisetinidol **21** (R_f 0.46; 6.3 mg). Acetylation of the R_f 0.33 band (8.3 mg) followed by PLC in benzene–acetone (9:1 v/v) afforded the *methyl ether diacetate* of the (2*R*)-propan-2-ol **16** (R_f 0.28; 6.5 mg) as an amorphous solid (Found: M$^+$, 402.1676. $C_{22}H_{26}O_7$ requires M, 402.1679); δ_H(Table 1); CD $[\theta]_{350}$ −8.7 × 10^1, $[\theta]_{297.1}$ −2.5 × 10^2, $[\theta]_{280.1}$ −3.5 × 10^3, $[\theta]_{252}$ 0.2 × 10^1, $[\theta]_{243.1}$ 2.3 × 10^3, $[\theta]_{238.6}$ 3.3 × 10^1, $[\theta]_{234.7}$ −1.6 × 10^3, $[\theta]_{228.7}$ −0.4 × 10^1, $[\theta]_{218.2}$ 1.8 × 10^3, $[\theta]_{212.7}$ 3.9 × 10^2, $[\theta]_{207.4}$ 2.2 × 10^3 and $[\theta]_{203.1}$ 8.3 × 10^2.

Epicatechin-(4β,8)-catechin (procyanidin B-1) 24

The title compound **24** (50 mg) was reduced with $Na(CN)BH_3$ (43 mg) for 1 h at 0 °C. Work-up and methylation afforded a

Table 5 GMMX search results and observed heterocyclic ring coupling constants for epifisetinidols

Compound	Starting point[a]	Total number of conformers[b]	Unique conformers[c]	Final ensemble[d]	$J_{2,3}$ (Hz)	$J_{3,4\alpha}$ (Hz)	$J_{3,4\beta}$ (Hz)
	Observed coupling constants ([$^2H_6$]acetone)				br s	4.5	3.5
37	*E*	2111	244	155	0.61	3.04	3.18
	A	2482	281	166	0.59	3.05	3.15
	Observed coupling constants ($CDCl_3$)				br s	4.5	2.5
38	*E*	6342	850	385	0.64	3.07	3.24
	A	7399	1022	494	0.62	3.08	3.19
	Observed coupling constants ($CDCl_3$)				br s	4.5	2.5
39	*E*	6969	780	305	0.67	3.02	2.91
	A	9960	849	299	0.68	3.02	2.93

[a] Point (*E*- or *A*-conformer respectively) on the potential-energy surface (PES) where the search was initiated. [b] Total number of conformers considered during the search. [c] Number of unique conformers (carbon backbone only) kept within a 3.5 kcal mol^{-1} window. [d] Final ensemble of conformers (hydrogens attached) kept within a 3.0 kcal mol^{-1} window.

Table 6 Most stable *E*- and *A*-conformers in the final ensemble for epifisetinidols[a]

		E_{min} (kcal mol^{-1})	$J_{2,3}$ (Hz)	$J_{3,4\alpha}$ (Hz)	$J_{3,4\beta}$ (Hz)
37	*E*-conformer	14.51	0.53	2.89	3.00
	A-conformer	16.2	4.62	5.21	11.05
38	*E*-conformer	29.27	0.47	2.96	2.93
	A-conformer	30.77	5.01	5.36	10.95
39	*E*-conformer	26.81	0.64	2.83	3.04
	A-conformer	29.23	5.39	5.32	10.97

[a] Since different starting points on the PES gave similar results, only ensembles originating from searches started at the respective *E*-conformers are shown.

mixture (70 mg), which was resolved by PLC in benzene–acetone (7:3 v/v) to give three bands at R_f 0.73 (14 mg), 0.60 (13.5 mg) and 0.43 (10 mg). Acetylation of the R_f 0.73 band followed by PLC in benzene–acetone (9:1 v/v) afforded 3-*O*-acetyl-3′,4′,5,7-tetra-*O*-methylepicatechin (R_f 0.58; 14 mg), while similar treatment of the R_f 0.60 band gave catechin tetramethyl ether acetate **11** (R_f 0.60; 13.5 mg). The R_f 0.43 band consisted of procyanidin B-1 octa-*O*-methyl ether **25**.

Procyanidin B-1 octa-*O*-methyl ether 25

Reduction of compound **25** (70 mg) with $Na(CN)BH_3$ (76 mg) for 30 min at 0 °C followed by work-up afforded a mixture (68 mg), which was resolved by PLC in benzene–acetone (7:3 v/v) into three bands at R_f 0.74 (23 mg), 0.66 (22 mg) and 0.44 (7 mg). Acetylation, and purification by PLC in benzene–acetone (9:1 v/v) of the R_f 0.74 and 0.66 bands, gave, respectively, 3-*O*-acetyltetra-*O*-methylepicatechin (R_f 0.58; 23 mg) and the catechin derivative **11** (R_f 0.60; 21.8 mg). The R_f 0.44 band comprised starting material **25**.

Catechin-(4α,8)-catechin (procyanidin B-3) 26

Procyanidin B-3 **26** (50 mg) was reduced with $Na(CN)BH_3$ (43 mg) for 1 h at 0 °C, and the mixture was worked-up and methylated to give a residue (60 mg), which was separated by PLC in benzene–acetone (7:3 v/v) to give two bands at R_f 0.57 (25 mg) and 0.32 (11 mg). Acetylation of the former band followed by PLC in benzene–acetone (85:15 v/v) afforded the catechin derivative **11** (R_f 0.61; 25 mg). The same treatment of the R_f 0.32 band gave the octa-*O*-methyl ether diacetate of procyanidin B-3 (R_f 0.4; 10.2 mg).

Procyanidin B-3 octa-*O*-methyl ether 27

The title compound **27** (90 mg) was reduced with $Na(CN)BH_3$ (98 mg) for 30 min at 0 °C. Work-up afforded a mixture (72 mg), which was acetylated, and subsequently separated by PLC in benzene–acetone (85:15 v/v) to give 3-*O*-acetyltetra-*O*-methylcatechin **11** (R_f 0.61; 51 mg) and the octa-*O*-methyl ether diacetate of procyanidin B-3 (R_f 0.40, 12 mg).

Reductions with sodium cyanotrideuterioboranuide

Fisetinidol-(4α,8)-catechin hepta-*O*-methyl ether 3. Reduction of the title compound **3** (100 mg) with $Na(CN)BD_3$ (120 mg) for 30 min at 0 °C and work-up gave a mixture (98 mg), which was subjected to PLC in benzene–acetone (8:2 v/v) to give two bands at R_f 0.47 (50 mg) and 0.25 (44 mg). The latter band comprised starting material **3**. Acetylation of the R_f 0.47 band followed by PLC in benzene–acetone (9:1 v/v) gave two fractions at R_f 0.46 (35 mg) and 0.35 (14 mg). The R_f 0.35 band gave the *diacetate* of the (2*R*)-1,3-dideuterio-1,3-diarylpropan-2-ol **18** as an amorphous solid (Found: M^+, 404.1790. $C_{22}H_{24}D_2O_7$ requires M, 404.1803); δ_H(Table 1): CD $[\theta]_{271.2}$ -3.4×10^2, $[\theta]_{255.9}$ 3.5×10^1, $[\theta]_{247.2}$ 7.7×10^1, $[\theta]_{235}$ 3.6×10^3, $[\theta]_{225.30}$ -4.3×10^2, $[\theta]_{219.7}$ 2.6×10^3, $[\theta]_{216.7}$ 2.2×10^1, $[\theta]_{213.7}$ -3.0×10^3 and $[\theta]_{211.1}$ 5.2×10^1. The R_f 0.46 band was further resolved by PLC in hexane–ethyl acetate–acetone (80:17:3 v/v) to give the catechin derivative **11** (R_f 0.31; 32 mg) and the 4β-deuteriofisetinidol derivative **23** as an amorphous solid (R_f 0.35; 14 mg) (Found: M^+, 359.1482. $C_{20}H_{21}DO_6$ requires M, 359.1478); δ_H(Table 2); CD $[\theta]_{299.7}$ 0, $[\theta]_{286.4}$ -1.1×10^4; $[\theta]_{266.6}$ -2.6×10^1, $[\theta]_{239.8}$ 5.3×10^3, $[\theta]_{232.8}$ 2.4×10^1, $[\theta]_{220.2}$ -2.8×10^3, $[\theta]_{215.5}$ 6.4×10^1, $[\theta]_{209.9}$ 2.1×10^3 and $[\theta]_{203}$ 1.4×10^3.

***ent*-Epifisetinidol-(4β,8)-catechin hepta-*O*-methyl ether 28.** The profisetinidin derivative **28** (70 mg) was reduced with $Na(CN)BD_3$ (84 mg) for 30 min at 0 °C. Work-up gave a mixture (68 mg), which was resolved by PLC in benzene–acetone (8:2 v/v) into two bands at R_f 0.27 (16 mg) and 0.48 (58 mg). Acetylation of the former band followed by PLC in benzene–acetone (9:1 v/v) gave the di-*O*-acetyl derivative of the starting material (R_f 0.41; 15 mg). The R_f 0.48 band was similarly acetylated, and resolved by PLC in benzene–acetone (9:1 v/v) to give 3-*O*-acetyltetra-*O*-methylcatechin **11** (R_f 0.65; 32 mg) and two additional bands at R_f 0.56 (18 mg) and 0.46 (6 mg). The R_f 0.56 band gave 3-O-*acetyl*-4β-*deuterio*-3′,4′,7-*tri*-O-*methyl*-ent-*epifisetinidol* **32** as an amorphous solid (Found: M^+, 359.1474. $C_{20}H_{21}DO_6$ requires M, 359.1478); δ_H(Table 2); CD $[\theta]_{289.7}$ 1.9×10^2, $[\theta]_{271.2}$ -3.4×10^2, $[\theta]_{255.9}$ 3.5×10^1, $[\theta]_{247.2}$ 7.7×10^1, $[\theta]_{235}$ 3.6×10^3, $[\theta]_{225.3}$ -4.3×10^2, $[\theta]_{219.7}$ 2.6×10^3, $[\theta]_{216.7}$ 2.2×10^1, $[\theta]_{213.7}$ -3.0×10^3 and $[\theta]_{211.2}$ 5.2×10^1. The R_f 0.46 band afforded the (2S)-1,3-*dideuterio*-1,3-*diarylpropan*-2-*ol* **34** as an amorphous solid (Found: M^+, 404.1795. $C_{22}H_{24}D_2O_7$ requires M, 404.1803); δ_H(Table 1); CD $[\theta]_{289.7}$ 1.0×10^2, $[\theta]_{271.2}$

4.0×10^2, $[\theta]_{255.9}$ 2.5×10^2, $[\theta]_{247.2}$ 3.9×10^2, $[\theta]_{242.9}$ -0.9×10^1, $[\theta]_{234.4}$ -2.6×10^3, $[\theta]_{228.4}$ -1.6×10^1, $[\theta]_{222.8}$ 3.2×10^3 and $[\theta]_{210}$ 2.3×10^2.

***ent*-Fisetinidol-(4β,8)-catechin hepta-*O*-methyl ether 29.** Reduction of the title compound (90 mg) with $Na(CN)BD_3$ (107 mg) for 30 min at 0 °C and work-up afforded a mixture (89 mg), which was separated by PLC in benzene–acetone (8:2 v/v) to give two bands at R_f 0.47 (46 mg) and 0.25 (30 mg). The latter band gave starting material **29**. Acetylation of the R_f 0.47 band followed by PLC in benzene–acetone (9:1 v/v) afforded two fractions at R_f 0.46 (34 mg) and 0.35 (12 mg). The latter band comprised the (2*S*)-1,3-dideuterio-1,3-diarylpropan-2-ol **34** with ^1H NMR and CD data identical with those described above. The R_f 0.46 band was further resolved by PLC in hexane–ethyl acetate–acetone (80:17:3 v/v) to give the catechin derivative **11** (R_f 0.31: 22 mg) and 3-O-*acetyl*-4α-*deuterio*-3′,4′,7-*tri*-O-*methyl*-ent-*fisetinidol*, the enantiomer of compound **23** as an amorphous solid (R_f 0.35: 11.5 mg) (Found: M^+, 359.1476. $C_{20}H_{21}DO_6$ requires M, 359.1478); δ_H(see compound **23** Table 2); CD $[\theta]_{296.4}$ -0.4×10^1, $[\theta]_{286.6}$ 9.5×10^3, $[\theta]_{272.5}$ -0.3×10^1, $[\theta]_{262.9}$ -5.5×10^2, $[\theta]_{238.9}$ -5.8×10^3, $[\theta]_{230.4}$ -0.9×10^1, $[\theta]_{224.4}$ 2.0×10^3, $[\theta]_{213.6}$ 2.0×10^1 and $[\theta]_{209.6}$ -2.0×10^3.

(*R*)-(+)- and (*S*)-(−)-MTPA esters of (2*R*)-1-(2,4-dimethoxyphenyl)-3-(3,4-dimethoxyphenyl)propan-2-ol

The Mosher acid chlorides were prepared from the corresponding α-methoxy-α-(trifluoromethyl)phenyl acetic acids (MTPA) and oxalyl dichloride according to the standard literature procedure.[15] The title 1,3-diarylpropan-2-ol (20 mg), triethylamine (48 mm^3) and a catalytic amount of 4-(dimethylamino)pyridine were dissolved in dry dichloromethane (5 cm^3). A solution of (*S*)-(+)-MTPA chloride (1.1 mol equiv.) in dry dichloromethane (3 cm^3) was added and the mixture was stirred for 2 h at room temperature. Water (5 cm^3) was added and the mixture was extracted with ethyl acetate (3 × 20 cm^3). The combined organic phase was dried (Na_2SO_4), the solvent was evaporated off and the residue (31 mg) was separated by PLC in benzene–acetone (9:1 v/v) to afford the (*S*)-(−)-MTPA ester **20** (R_f 0.61: 29 mg) as an amorphous solid, δ_H (Table 1). Repetition of the procedure but with the (*R*)-(−)-MTPA chloride gave the (*R*)-(+)-MTPA ester **19** as an amorphous solid, δ_H (Table 1).

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