Synthesis of Condensed Tannins. Part 10.† 'Dioxane-linked' Profisetinidins

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Isolation of a natural 2,3-*trans*-3,4-*trans*:2',3'-*trans*-3',4'-*cis*-diastereoisomer of the hitherto unique [3,4':3',4]-*O*,*O*-linked bis-(2,3-*trans*-3,4-*cis*-3',4',7-trihydroxyflavan) from a common source, the heartwood of *Acacia mearnsii*, has prompted synthesis of their hexamethyl ethers by self-condensation of (+)-3',4',7-trimethoxy-2,3-*trans*-flavan-3,4-*trans*-diol with BF_3–diethyl ether in dioxane. The major 3,4-*cis*:3',4'-*cis* isomeric product of synthesis is subject to further condensation, and to inversion at a single C-2 chiral centre.

Simple and complex dibenzo-α-pyrones accompany the profisetinidins in a chromogenic fraction of the heartwood extract.

Apart from the so-called A-group of biflavanoid procyanidins possessing an ether link between C-2 and C-7 of different units in addition to a C-4 to C-8' carbon–carbon link,[1-3] the natural ether-linked condensed tannins are atypical, the latter type of C–C bonding predominating almost to exclusion amongst flavanoid oligomers. A single exception hitherto was the doubly ether-linked 'dioxane-type' biflavanoid isolated by Drewes and Ilsley [4] from the heartwood of the black wattle (*Acacia mearnsii*). This structurally symmetrical profisetinidin (3) was shown to possess the 2,3-*trans*-3,4-*cis*:2',3'-*trans*-3',4'-*cis* relative stereochemistry. A stereochemically asymmetrical 2,3-*trans*-3,4-*trans*:2',3'-*trans*-3',4'-*cis* diastereoisomer (5) has now been isolated from a pink-coloured fraction derived from the same source, and characterized as its hexamethyl ether (6). Synthesis of the hexamethyl ether derivatives of both isomers and hence definition of their absolute configurations was effected by self-condensation of the trimethyl ether of (+)-mollisacacidin (2) [(+)-3',4',7-tri-*O*-methyl-leucofisetinidin].

Whereas the ^{1}H n.m.r. spectrum of the previously known [4] all-2,3-*trans*-3,4-*cis*-profisetinidin hexamethyl ether (4) exhibits a single heterocyclic AMX spin system, $J_{2,3}$ 10.0, $J_{3,4}$ 4.6 Hz, closely resembling that of the 'monomeric' 3',4',7-trimethoxy-2,3-*trans*-flavan-3,4-*cis*-diol in both chemical shifts and coupling constants, the heterocyclic region of the corresponding derivative (6) of the newly isolated profisetinidin is relatively complex and comprised two such spin systems. Their coupling constants, $J_{2,3}$ 10.0, $J_{3,4}$ 9.0 Hz and $J_{2,3}$ 10.7, $J_{3,4}$ 3.5 Hz, are indicative of 2,3-*trans*-3,4-*trans* and 2,3-*trans*-3,4-*cis* configurations of the constituent units, respectively. Molecular asymmetry of the hexamethyl ether (6) is also reflected in six individual methoxy-proton resonances compared with three paired (equivalent) resonances of the corresponding symmetrical isomer (4). The c.d. spectra of these compounds (Figure 1) are in line with the anticipated [5] synchronous positive Cotton effect at low wavelength (230 nm) resulting from the 4*S*,4'*S* configuration of the symmetrical ether (4), compared with the weaker negative effect at similar wavelength as a product of the counteracting effects of the 4*R*,4'*S* configuration of the asymmetrical ether (6).

Synthesis of the natural doubly ether-linked profisetinidins (3) and (5) poses a problem in that acid-induced self-condensation of the free-phenolic form of (+)-mollisacacidin (1) in protic media induces C–C bonding, leading to low yields of [4,6]-linked biflavanoids and a triflavanoid, while the reaction gives an abundance of high condensates.[6] Repeated application of acid-induced (HOAc) ethanolic conditions by Clark-Lewis [7] to 4',7,8-trimethoxy-2,3-*trans*-flavan-3,4-*trans*-diol, aimed at promoting solvolysis at C-4, produced (*ca.* 10% yield) the bis-(4',7,8-trimethoxy) analogue of compound (4) as the sole product. These limitations were partly overcome by using boron trifluoride–diethyl ether as catalyst, known for promoting the formation of ether- rather than C–C-links,[8] for effecting the desired self-condensation of (+)-mollisacacidin trimethyl ether (2) at ambient temperature. The resulting condensation in dioxane solution [*cf.* Scheme: (2) + (2) ⟶ (4), (6), (7) ⟶ (8), (10)] gives a 15.3% yield of the methyl ethers of the known 3,4-*cis*:3',4'-*cis*-isomer (4), 0.5% of the new 3,4-*trans*:3',4'-*cis*-isomer (6), and 0.13% of a novel 2,3-*cis*-3,4-*cis*:2',3'-*trans*-3',4'-*cis*-isomer (7) the last mentioned obviously resulting from inversion at C-2 of the main product of condensation, product (4).

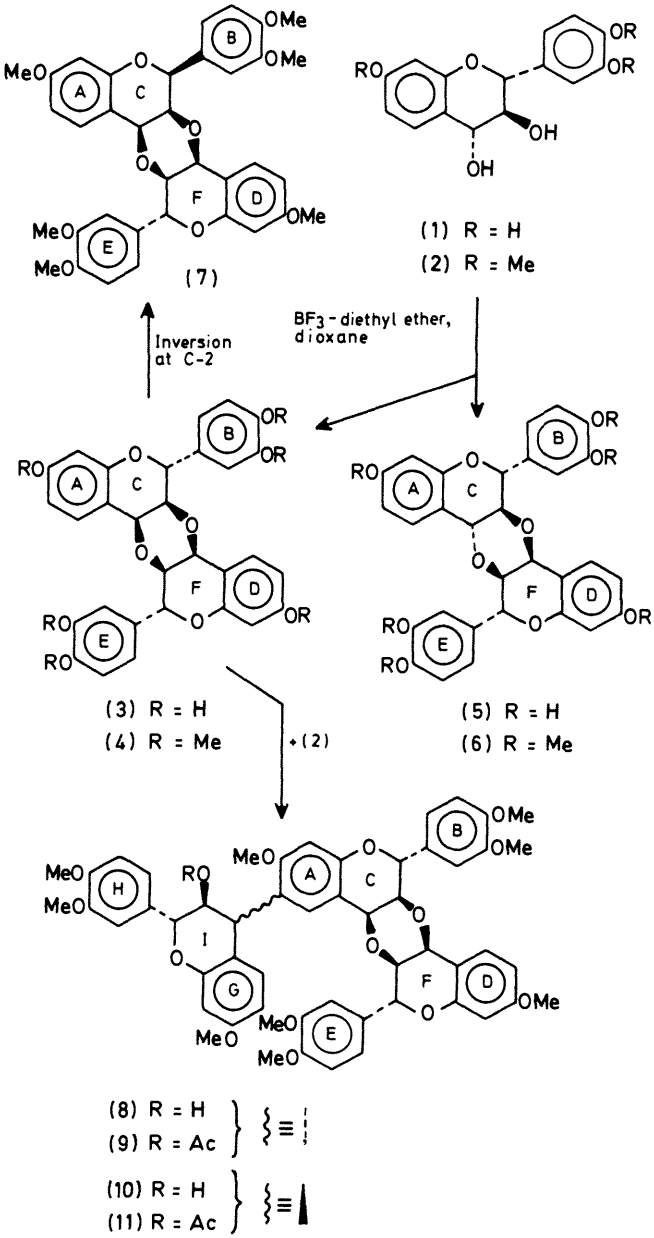
The identity of the new synthetic analogue (7) formed in very low yield could not be established by ^{1}H n.m.r. spectroscopy at 80 MHz due to overlap of heterocyclic resonances, but at 500 MHz two AMX systems could readily be distinguished ($J_{2,3} < 0.5$, $J_{3,4}$ 3.0; $J_{2',3'}$ 10.5, $J_{3',4'}$ 2.5 Hz) and hence the relative stereochemistry assigned; the coupling constants correlating with a 2,3-*cis*-3,4-*cis*:2',3'-*trans*-3',4'-*cis* relative configuration on the assumption of 5-point coplanar (sofa) and twisted boat conformations for the C- and F-ring, respectively. The c.d. spectrum affirms a 4*S*,4'*S* configuration through evidence of a strong positive Cotton effect in the low-wavelength region (Figure 1).

The yields in which the three ether-linked derivatives (4), (6), and (7) are formed are apparently inversely proportional to the degree of combined steric strain in their heterocyclic (C and F) and bridging 'dioxane' rings (*cf.* Table and reference 9). Presumed formation of the 2,3-*cis*-isomer (7) from the predominant product of the condensation [3,4-*cis*:3',4'-*cis*-isomer (4)] by inversion at C-2 also implies conformational inversion of the C-ring, with the 2-phenyl group assuming an *equatorial* position as in almost all 2,3-*cis*-flavanoids.

From their synthesis *via* the self-condensation of (2*R*,3*S*,-4*R*)-3',4',7-trimethoxyflavan-3,4-diol (2) the absolute configurations of the doubly ether-linked profisetinidin derivatives (4), (6), and 7) may be assigned as (2*R*,3*S*,4*S*:2'*R*,-3'*S*,4'*S*), (2*R*,3*S*,4*R*:2'*R*,3'*S*,4'*S*), and (2*S*,3*S*,4*S*:2'*R*,3'*S*,4'*S*), respectively.

Significant by-products of the condensation are two triflavanoid profisetinidin derivatives (8) and (10) (0.8 and 2.0%

† Part 9 is J. A. Delcour, D. Ferreira, D. G. Roux, *J. Chem. Soc., Perkin. Trans. 1*, 1983, 1711.



Scheme.

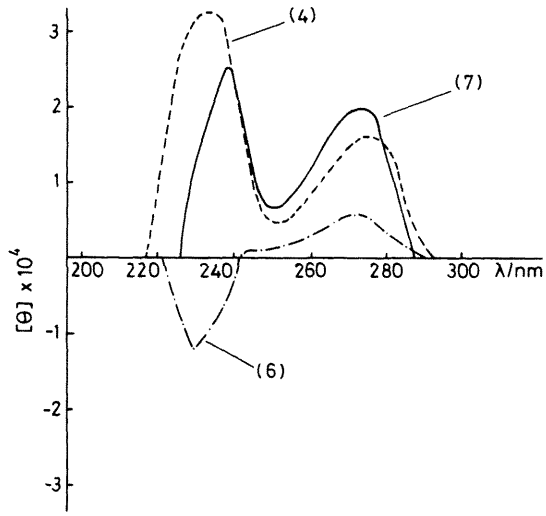


Figure 1. C.d. spectra of the hexamethyl ether derivatives (4), (6), and (7) of the ether-linked profisetinidins in acetonitrile

Table. Ring conformations of the hexamethyl ethers of ether-linked profisetinidins [a]

Relative stereochemistry of hexamethyl ether	Conformation of ring systems		
	C	F	' Dioxane '
(4) 2,3-*trans*-3,4-*cis* : 2',3'-*trans*-3',4'-*cis*	sofa	sofa	twisted boat
(6) 2,3-*trans*-3,4-*trans* : 2',3'-*trans*-3',4'-*cis*	half chair–sofa [b]	half chair–sofa [b]	twisted chair
(7) 2,3-*cis*-3,4-*cis* : 2',3'-*trans*-3',4'-*cis*	sofa	twisted boat	twisted boat

[a] As judged from Dreiding models. [b] Intermediate ring conformations.

yield) formed from C–C condensation of the parent compound (2) as the electrophile with the main product of condensation, the 3,4-*cis*:3',4'-*cis*-isomer (4). ^{1}H N.m.r. analysis of their complex heterocyclic resonances * is accomplished after conversion into the monoacetates (9) and (11), thus simplifying the spectra by deshielding those 3-H(I) resonances which are useful for defining the stereochemistry of the attached GHI-units. Both the relative chemical shifts and coupling constants (δ 6.09; $J_{2,3}$ 9.0, $J_{3,4}$ 9.0 Hz and δ 5.81; $J_{2,3}$ 6.0, $J_{3,4}$ 5.0 Hz) confirm (*cf.* reference 10) their 2,3-*trans*-3,4-*trans* and 2,3-*trans*-3,4-*cis* stereochemistry, respectively, while coupling constants of ' dioxane '-bridged biflavanoid moieties of both compounds are in agreement with those of the symmetrical isomer (4). The point of bonding in the A-ring (at C-6) is evident from high-field aromatic singlets. The mass fragmentations (M^+ 984) and c.d. spectra (Figure 2) correlate with the proposed structures (9) and (11), the effects of chirality at C-4 of the introduced unit obviously dominating the amplitude of the Cotton effects at 220—240 nm relative to the more modest contributions by the bis-(3,4-*cis*:3',4'-*cis*) ' dioxane '-linked moiety (*cf.* Figure 1).

The only notable side-reactions to the above are the formation of 1,3-dioxolane-type condensates [(12), (13), and (14)] of the 3,4-*cis*-diol function of the 4-epimer of the parent compound (2) with acetaldehyde, propionaldehyde, and acetone; presumably all are products of BF_3-induced rearrangement and degradation of dioxane.

The pale pink colour of the heartwood of the black wattle was previously attributed to the presence of (+)-mollisacacidin, bi- and tri-flavanoids with a terminal 3,4-diol function,[6] and higher oligomers, all of which possess potential chromogenic properties. Chromatographic separation on cellulose has, however, led not only to the isolation of the new profisetinidin (5) from a pink fraction of extract obtained from freshly cut wood, but also to evidence of fisetin (3',4',7-trihydroxyflavonol), 3,8,9-trihydroxy- and 3,9,10-trihydroxy-6*H*-dibenzo[*b*,*d*]pyran-6-ones (15) and (17), and also a complex dibenzo-α-pyrone, (2'*S*,3'*R*)-9-(5',6'-dihydroxy-2'-hydroxymethyl-2',3'-dihydrobenzo[*b*]furan-3-yloxy)-6H-dibenzo-[*b*,*d*]pyran-6-one (19), a group of compounds which are similarly associated in the heartwood of *Umtiza listerana*.[11] The compounds were identified as their methyl ethers (16)

* ^{1}H N.m.r. spectra of the monoacetates were recorded at 100 °C (in $CDCl_3$) in order to surmount the effects of rotational isomerism.

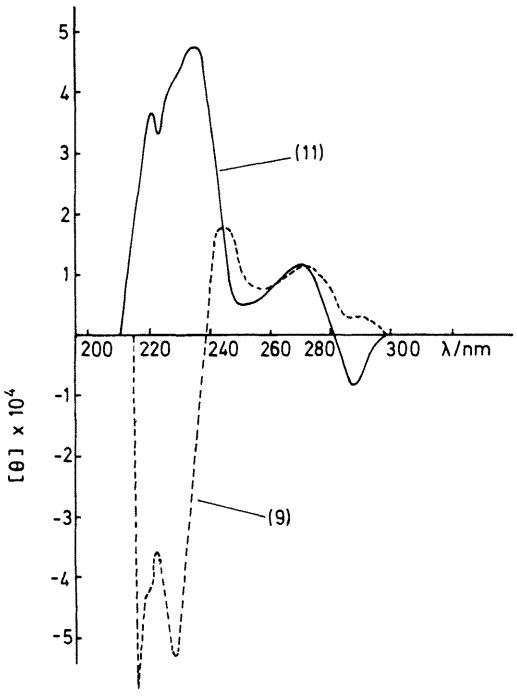
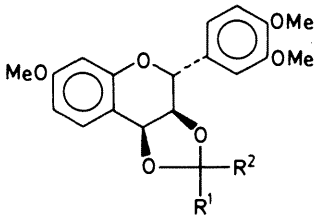


Figure 2. C.d. spectra of the nonamethyl ether acetate derivatives (9, 11) of ether-linked profisetinidin ' trimers ' in methanol

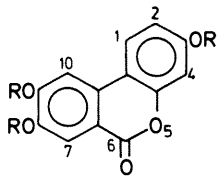


(12) R^1 = H, R^2 = Me
(13) R^1 = H, R^2 = Et
(14) R^1 = R^2 = Me

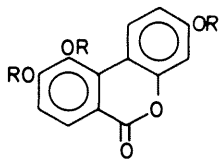
and (18) or methyl ether acetate (20). The dibenzo-α-pyrones (15) and (17) belong to a class of metabolites known for their cytotoxicity, while their more complex counterpart (19) possesses chromogenic capability based on the 9-(dihydrobenzofuran-3-yloxy) moiety.[11]

Experimental

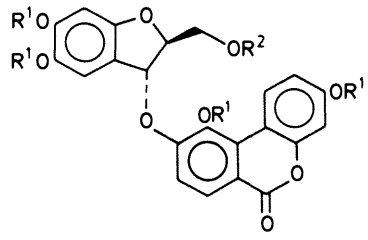
^{1}H N.m.r. spectra were recorded on Bruker WP-80 and WM-500 FT spectrometers in $CDCl_3$ or C_6D_6 with Me_4Si as internal standard. Determination of coupling constants required suitable (× 5) scale expansion. Mass spectra were obtained with a Varian CH-5 instrument, and c.d. data in acetonitrile or methanol on a Jasco J-20 spectropolarimeter. Analyses (C and H) were by the Analytische Laboratorien, Postfach 1249, D-5250 Engelskirchen, West Germany. T.l.c. was done on DC-Plastikfolin, Kieselgel 60 PF_{254} (0.2 mm) and the plates were sprayed with H_2SO_4–HCHO (40 : 1) after development. Preparative plates (p.l.c.) [20 × 20 cm; Kieselgel PF_{254} (1.0 mm)] were air-dried and used without prior activation. Methylations were performed with an excess of diazomethane in methanol–diethyl ether during 48 h, while acetylations were in acetic anhydride–pyridine. Evaporations were done under reduced pressure at 50 °C in a rotary evaporator.



(15) R = H
(16) R = Me



(17) R = H
(18) R = Me



(19) R^1 = R^2 = H
(20) R^1 = Me, R^2 = Ac

Isolation of Metabolites from the Heartwood of Acacia mearnsii

The wax-free methanol soluble extract (2.14 kg) of the heartwood of the black wattle was subjected to chromatography on cellulose columns (5 × 125 cm) in batches (20 g per column) with water (4 l per column) as eluant. After development the cellulose was extruded, and a pink band located 25—40 cm from the upper end was extracted with acetone. After evaporation of the solvent a pink solid (12.7 g) was obtained. The solid was separated by p.l.c. (220 plates) by development (× 2) in benzene–acetone–methanol (70 : 25 : 5, v/v/v) to give four fractions at R_F 0.69 (179 mg), 0.53 (224 mg), 0.46 (292 mg), and 0.38 (215 mg). The various components were identified by ^{1}H n.m.r. spectroscopy, m.s., and c.d. (where applicable).

3,8,9-*Trimethoxy*-6H-*dibenzo*[b,d]*pyran*-6-*one* (16).—Methylation of the R_F 0.69 fraction followed by p.l.c. on 10 plates in benzene–acetone (9 : 1, v/v) gave the *trimethyl ether* (R_F 0.55) as a white solid (17.1 mg) which was crystallized from ethanol–$CHCl_3$, m.p. 178 °C (Found: C, 67.0; H, 5.0. $C_{16}H_{14}O_5$ requires C, 67.1; H, 4.9%); δ (80 MHz; $CDCl_3$) 7.84 (d, $J_{1,2}$ 7.5 Hz, 1-H), 7.31 (s, 7-H), 7.28 (s, 10-H), 6.90 (dd, J 7.5 and 2.5 Hz, 2-H), 6.81 (d, J 2.5 Hz, 4-H), and 4.80, 3.99, and 3.87 (each s, OMe); *m/z* 286 (M^+, 100%), 271 (M − 15, 23), and 243 (M − 15 − 28, 10.3); $\lambda_{max.}$ $CHCl_3$ 252.5, 259, 312, and 337.5 nm (log ε 4.25, 4.31, 3.93, and 3.70, respectively); $\nu_{max.}$ $CHCl_3$ 1 722 cm^{-1} (lactone C=O).

(2'S,3'R)-9-(2'-*Acetoxymethyl*-5',6'-*dimethoxy*-2',3'-*dihydrobenzo*[b]*furan*-3-*yloxy*)-3,10-*dimethoxy*-6H-*dibenzo*-[b,d]*pyran*-6-*one* (20).—Methylation of the R_F 0.53 fraction and p.l.c. separation (× 2) in 1,2-dichloroethane–acetone (95 : 5, v/v) on 14 plates gave the tetramethyl ether at R_F 0.54. Subsequent acetylation gave the 9-(dihydrobenzofuran-3-yloxy)dibenzo-α-pyrone derivative as a white solid (15 mg). The ^{1}H n.m.r. spectrum (80 MHz; $CDCl_3$) proved identical to that of the same derivative of a metabolite isolated from *Umtiza listerana*; [11] *m/z* 552 (M^+, 72%).

The R_F 0.46 fraction, after methylation and p.l.c. separation (× 2) in 1,2-dichloroethane–acetone (95 : 5, v/v), gave two products at R_F 0.84 (37 mg) and 0.63 (93 mg).

3,9,10-*Trimethoxy*-6H-*dibenzo*[b,d]*pyran*-6-*one* (3,9,10-*Tri*-O-*methylfasciculiferol* [12]) (18).—The tri-*O*-methyl derivative (R_F 0.84, 37 mg) was isolated as yellow needles from methanol, m.p. 195 °C (lit.,[12] 196 °C). The ^{1}H n.m.r. spectrum (80 MHz; $CDCl_3$) proved identical with that previously recorded for the same derivative from *Acacia fasciculifera* [12] and *Umtiza listerana*,[11] and also to its synthetic counterpart; [11] *m/z* 286 (M^+, 100%), 271 (76), 256 (7.8), 228 (23), 200 (6.3), and 185 (14.8).

3,3′,4′,7-*Tetra*-O-*methylfisetin*.—The tetra-*O*-methyl derivative (R_F 0.63, 93 mg) was obtained as yellow needles from acetone, m.p. 151 °C (lit.,[13] 152 °C). The ^{1}H n.m.r. spectrum (80 MHz; $CDCl_3$) proved identical with that of an authentic sample; *m/z* 342 (M^+, 8.8%), 150 (16.1), and 149 (100).

[3,4′:3′,4]-O,O-*Linked* 2,3-trans-3,4-trans:2′,3′-trans-3′,4′-cis-*Profisetinidin Hexamethyl Ether* (6).—Methylation of the R_F 0.38 fraction followed by p.l.c. separation (× 2) in 1,2-dichloroethane–acetone (95 : 5, v/v) gave the *hexamethyl ether* (R_F 0.84, 13 mg) from ethanol–$CHCl_3$ as fine, white needles, m.p. 264 °C (Found: C, 68.7; H, 5.8. $C_{36}H_{36}O_{10}$ requires C, 68.8; H, 5.8%); δ (80 MHz; C_6D_6) 7.12—6.33 (m, 12 × ArH), 5.64 [d, *J* 10.7 Hz, 2-H(F)], 5.08 [d, *J* 10.0 Hz, 2-H(C)], 5.02 [d, *J* 9.0 Hz, 4-H(C)], 4.56 [d, *J* 3.5 Hz, 4-H(F)], 4.22 [dd, *J* 10.7 and 3.5 Hz, 3-H(F)], 3.96 [dd, *J* 10.0 and 9.0 Hz, 3-H(C)], and 3.65, 3.63, 3.60, 3.58, 3.39, and 3.38 (each s, OMe); c.d. (Figure 1).

Synthesis of Hexamethyl Ethers of [3,4′:3′,4]-O,O-*Linked Profisetinidins*

A solution of (+)-mollisacacidin trimethyl ether [(+)-3′,4′,7-trimethoxyflavan-3,4-diol] (2) of known [14] (2*R*,3*S*,4*R*) absolute configuration (8 × 200 mg portions) in dioxane (20 ml) was treated with the BF_3–diethyl ether complex (Merck) (1 ml) for 4.5 h at ambient temperature. The combined solutions were successively diluted with water (100 ml) and 0.1M HCl (100 ml) and then extracted with EtOAc (4 × 150 ml). The combined extracts were washed with water (5 × 200 ml) and the solvent was evaporated off. Separation of the product by p.l.c. [20 plates; benzene–acetone (95 : 5 v/v), × 2) gave five fractions at R_F 0.57 (35 mg), 0.52 (35 mg), 0.48 (7.6 mg), 0.41 (320 mg), and 0.06 (99 mg).

1,3-*Dioxolane-type Condensates of* (+)-3′,4′,7-*Trimethoxy*-2,3-trans-*flavan*-3,4-cis-*diol*

Further separation of the R_F 0.57 fraction from the primary fractionation by p.l.c. (× 3) in hexane–ethyl acetate (8 : 2, v/v) gave two compounds at R_F 0.39 (3 mg) and 0.33 (5 mg).

Isopropylidene Derivative (14).—This compound, R_F 0.39, was isolated as a solid,[15] δ (80 MHz; $CDCl_3$) 5.08 [d, *J* 5.1 Hz, 4-H(C)], 4.55 [d, *J* 9.8 Hz, 2-H(C)], 4.30 [dd, Σ*J* 14.9 Hz, 3-H(C)], and 1.56 and 1.48 (each s, CH_3); *m/z* 372 (M^+, 13.8%) and 179 (100).

Ethylidene Derivative (12).—This compound, R_F 0.33, was isolated as a *solid* (Found: C, 66.9; H, 6.1. $C_{20}H_{22}O_6$ requires C, 67.0; H, 6.2%); δ (80 MHz; $CDCl_3$) 5.25 (q, *J* 7.0 Hz, CH), 4.92 [d, *J* 5.5 Hz, 4-H(C)], 4.43 [d, *J* 9.5 Hz, 2-H(C)], 4.22 [dd, Σ*J* 15.0 Hz, 3-H(C)], and 1.47 (d, *J* 7.0 Hz, CH_3); *m/z* 358 (M^+, 13.8%), 221 (13.0), 207 (14.3), 179 (100), 151 (32), 137 (2.3), and 135 (9.5).

Propylidene Derivative (13).—This compound, R_F 0.52, from the primary fractionation was isolated as a *solid* (Found: C, 67.0; H, 6.6. $C_{21}H_{24}O_6$ requires C, 67.1; H, 6.5%); δ (80 MHz; $CDCl_3$) 5.09 (t, *J* 4.4 Hz, CH), 4.91 [d, *J* 5.25 Hz, 4-H(C)], 4.44 [d, *J* 9.5 Hz, 2-H(C)], 4.23 [dd, Σ*J* 14.75 Hz, 3-H(C)], 1.95—1.62 (m, CH_2), and 1.00 (t, *J* 7.0 Hz, CH_3); *m/z* 372 (M^+, 17.5%), 192, (100), 179 (4.0), and 151 (32).

[3,4′:3′,4]-O,O-*Linked* ' *Dimeric* ' *Profisetinidins*

The 2,3-trans-3,4-trans:2′,3′-trans-3′,4′-cis-*Isomer* (6).—The synthetic hexamethyl ether, R_F 0.48, was isolated as a solid (7.6 mg), with ^{1}H n.m.r., m.s., and c.d. data identical with those of the corresponding derivative of the natural product isolated from *A. mearnsii* (see above); c.d. (Figure 1).

Further separation (× 2) of the R_F 0.41 fraction (320 mg) by p.l.c. in 1,2-dichloroethane–acetone (98 : 2, v/v) gave two products, R_F 0.40 (233 mg) and 0.33 (2 mg).

The 2,3-trans-3,4-cis:2′,3′-trans-3′,4′-cis-*Isomer* (4).—The symmetrical synthetic hexamethyl ether, R_F 0.40, was isolated as needles, m.p. 179 °C (lit.,[4] 175 °C) from ethanol–water. The ^{1}H n.m.r. spectrum (80 MHz; $CDCl_3$) was identical with that of the corresponding derivative of the natural product isolated from *A. mearnsii*; [4] c.d. (Figure 1).

The 2,3-cis-3,4-cis:2′,3′-trans-3′,4′-cis-*Isomer* (7).—The *hexamethyl ether*, R_F 0.33, was isolated as a solid, δ (500 MHz; $CDCl_3$) 7.305 (d, *J* 1.5 Hz, 2′-H), 7.071 (d, *J* 8.8 Hz, 5-H), 6.965 (dd, *J* 8.5 and 1.5 Hz, 6′-H), 6.910 (d, *J* 8.5 Hz, 5′-H), 6.868 (dd, *J* 8.5 and 1.5 Hz, 6′-H), 6.866 (d, *J* 8.5 Hz, 5′-H), 6.612 (d, *J* 1.5 Hz, 2′-H), 6.492 (d, *J* 8.5 Hz, 5-H), 6.478 (dd, *J* 8.5 and 2.5 Hz, 6-H), 6.400 (d, *J* 2.3 Hz, 8-H), 6.285 (d, *J* 2.4 Hz, 8-H), 6.147 (dd, *J* 8.5 and 2.1 Hz, 6-H), 4.909 [d, *J* 3.0 Hz, 4-H(C)], 4.871 [s, $J < 0.5$ Hz, 2-H(C)], 4.712 [d, *J* 2.5 Hz, 4-H(F)], 4.700 [d, *J* 10.5 Hz, 2-H(F)], 4.538 [dd, Σ*J* 13.0 Hz, 3-H(F)], 4.243 [d, *J* 3.0 Hz, 3-H(C)], and 3.928, 3.914, 3.841, 3.822, 3.714, and 3.673 (each s, OMe); c.d. (Figure 1).

The mass fragmentation spectra of the hexamethyl ethers (4), (6), and (7) are respectively as follows: *m/z* 628 (M^+; 9.2, 5.5, 12.0%), 449 (3.8, 12.1, 3.6), 298 (100, 100, 100), 297 (43, 50, 43), 283 (9.8, 17.3, 10.4), 267 (9.4, 9.1, 9.7), and 151 (36, 38, 35).

6-*Flavan*-4-*yl Derivatives of* [3,4′:3′,4]-O,O-*Linked* 2,3-trans-3,4-cis:2′,3′-trans-3′,4′-cis-*Profisetinidin*

Acetylation and p.l.c. separation (× 4) in benzene–acetone (95 : 5, v/v) of the R_F 0.06 (99 mg) fraction consisting of a mixture of the methyl ethers (8) and (10) gave two products at R_F 0.34 (11.9 mg) and 0.29 (30.8 mg).

The 6-(2,3-trans-3,4-trans-3-*Acetoxy*-3′,4′,7-*trimethoxyflavan*-4-*yl*) *Derivative* (9).—The *monoacetate*, R_F 0.34 (11.9 mg), was obtained as a solid (Found: C, 68.1; H, 5.8. $C_{56}H_{56}O_{16}$ requires C, 68.3; H, 5.7%); δ (80 MHz; C_6D_6; 100 °C) 7.21—6.53 (m, 15 × ArH), 6.68 [s, 8-H(A)], 6.44 [s, 5-H(A)], 6.09 [t, Σ*J* 18.0 Hz, 3-H(I)], 5.19 [d, *J* 8.75 Hz, 2-H(C)], 5.13 [d, *J* 10.0 Hz, 2-H(F)], 5.08 [d, *J* 9.0 Hz, 2-H(I)], 4.78 [d, *J* 4.5 Hz, 4-H(C)], 4.73 [d, *J* 4.4 Hz, 4-H(F)], 4.66 [d, *J* 9.0 Hz, 4-H(I)], 4.35 [dd, *J* 10.0 and 4.4 Hz, 3-H(F)], 4.30 [dd, *J* 8.75 and 4.5 Hz, 3-H(C)], 3.31—3.56 (s, 9 × OMe), and 1.44 [s, 3-OAc(I)]; c.d. (Figure 2).

The 6-(2,3-trans-3,4-cis-3-*Acetoxy*-3′,4′,7-*trimethoxyflavan*-4-*yl*) *Derivative* (11).—The *monoacetate*, R_F 0.29 (30.8 mg), was obtained as a solid (Found: C, 68.2; H, 5.7. $C_{56}H_{56}O_{16}$

requires C, 68.3; H, 5.7%); δ (80 MHz; C_6D_6; 100 °C) 7.22—6.28 (m, 15 × ArH), 6.77 [s, 8-H(A)], 6.41 [s, 5-H(A)], 5.81 [dd, *J* 6.0 and 5.0 Hz, 3-H(I)], 5.42 [d, *J* 6.0 Hz, 2-H(I)], 5.16 [d, *J* 9.0 Hz, 2-H(F)], 5.09 [d, *J* 10.0 Hz, 2-H(C)], 5.06 [d, *J* 5.0 Hz, 4-H(I)], 4.65 [d, *J* 4.5 Hz, 4-H(C)], 4.61 [d, *J* 4.75 Hz, 4-H(F)], 4.31 [dd, *J* 10.0 and 4.5 Hz, 3-H(C)], 4.31 [dd, *J* 9.0 and 4.75 Hz, 3-H(F)], 3.56—3.28 [s, 9 × OMe], and 1.49 [s, 3-OAc(I)]; c.d. (Figure 2).

The mass fragmentation spectra (appearance potential at 280 and 330 °C, respectively) of the monoacetates (9) and (11) are, respectively, *m/z* 984 (M^+, —, 23%), 924 [(M − 60); 100, 30), 610 (40, 17.6), 448 (11.3, 11.0), 357 (2.1, 3.1), 315 (6.7, 7.5), 314 (22, 28), 313 (6.0, 4.7), 298 (58, 100), 297 (30, 33), 222 (12.8, 13.1), 180 (42, 22), and 151 (62, 45).

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