Tetrahedron Vol. 45, No. 24, pp. 7859 to 7868, 1989
Printed in Great Britain.

0040-4020/89 $3.00+.00

OLIGOMERIC FLAVANOIDS. PART 13[a]. SYNTHESIS OF PROFISETINIDINS BASED ON (-)-ROBINETINIDOL AND (+)-EPIFISETINIDOL

JOHANNES C.S. MALAN, JACOBUS A. STEENKAMP,
DESMOND A. YOUNG AND DANEEL FERREIRA*

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

(*Received in UK* 14 *August* 1989)

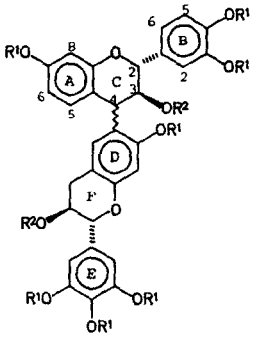
Abstract — Acid-catalyzed condensation of (+)-mollisacacidin-[(2*R*,3*S*,4*R*)-2,3-*trans*-3,4-*trans*-flavan-3,3′,4,4′,7-pentaol] with an excess of (-)-robinetinidol[(2*R*,3*S*)-2,3-*trans*-flavan-3,3′,4′,5′,7-pentaol] afforded a novel series of bi-, tri-, and tetraflavanoid profisetinidins. They are accompanied by (-)-fisetinidol-(4α,2′)-(-)-robinetinidol which results from the pyrogallol B-ring of (-)-robinetinidol serving as nucleophile competing with its resorcinol A-ring in coupling with a C-4 carbocationic intermediate. Similar condensation with (+)-epifisetinidol[(2*S*,3*S*)-2,3-*cis*-flavan-3,3′,4′,7-tetraol] led to the exclusive formation of [4,6]-interflavanyl bonds, these units being 'linearly' arranged in the tetraflavanoid analogue in contrast to the 'branched' nature of the (-)-robinetinidol homologue.

The natural occurrence of (-)-fisetinidol-(4β,6)-(-)-robinetinidol **1**, representative of the first profisetinidin in which (-)-robinetinidol serves as nucleophilic flavan-3-ol moiety in the biosynthetic pathway leading to this class of natural products, has recently been demonstrated[1]. Acid-catalyzed condensation[2,3] of (-)-robinetinidol and (+)-mollisacacidin would thus not only provide structural confirmation of the natural product but would also offer the first opportunity of establishing the course of coupling with a flavan-3-ol in which the nucleophilicity of the pyrogallol B-ring is comparable to that of the resorcinol A-ring.

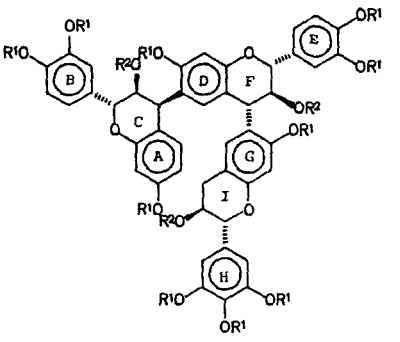
Condensation of (-)-robinetinidol and (+)-mollisacacidin under those relatively mild acidic conditions (0.1M HCl, 45°C, 24h) which provide adequate yields while ensuring selectivity[2,3], affords a mixture comprising five oligomeric profisetinidins. These include the anticipated (-)-fisetinidol-(4β,6) and (4α,6)-(-)-robinetinidols **1** and **3**, the 'linear' (-)-fisetinidol-(4β,6)-(-)-fisetinidol-(4α,6)-(-)-robinetinidol triflavanoid **5**, the 'branched' bis-(-)-fisetinidol-(4β,6;4α,8)-(-)-fisetinidol-(4α,6)-(-)-robinetinidol tetraflavanoid **7**

---

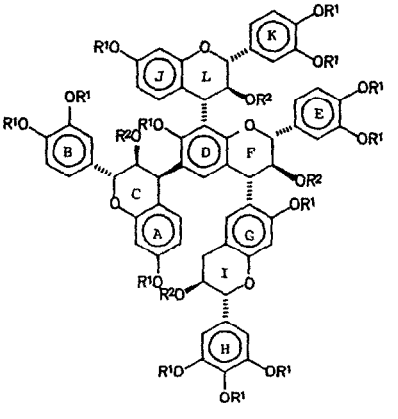
[a]Part 12. J.P. Steynberg, J.F.W. Burger, A. Cronjé, S.L. Bonnet, J.C.S. Malan, D.A. Young, and D. Ferreira, *J. Chem. Soc., Perkin Trans. 1*, 1989, paper 9/02767J/P1P



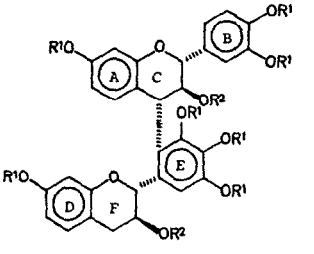
(1) ~~=— $R^1 = R^2 = H$
(2) ~~=— R^1 = Me, R^2 = Ac
(3) ~~= ····· $R^1 = R^2 = H$
(4) ~~= ····· R^1 = Me, R^2 = Ac



(5) $R^1 = R^2 = H$
(6) R^1 = Me, R^2 = Ac



(7) $R^1 = R^2 = H$
(8) R^1 = Me, R^2 = Ac



(9) $R^1 = R^2 = H$
(10) R^1 = Me, R^2 = Ac

and the (-)-fisetinidol-(4α,2′)-(-)-robinetinidol 9. The structures were derived from the physical data of the phenolic methyl ether acetates.

Comparison of ^{1}H NMR and CD data of the heptamethyl ether diacetate 2 of the (-)-fisetinidol-(4β,6)-(-)-robinetinidol 1 with those of the corresponding derivative of the natural product[1] from *Burkea africana* Hook confirmed their identity. The ^{1}H NMR spectrum of the methyl ether acetate 4 of the novel (-)-fisetinidol-(4α,6)-(-)-robinetinidol 3 exhibits a heterocyclic AMX system characteristic of the protons of a 2,3-*trans*-3,4-*trans* C-ring ($J_{2,3} = J_{3,4} = 9.0$ Hz) with the two one-proton singlets [δ6.67, H-5(D); δ6.47, H-8(D)] reminiscent of a C-6 substituted resorcinol-type D-ring[3]. A two-proton aromatic singlet (δ6.61) exhibiting benzylic coupling with H-2(F), the A-portion of a heterocyclic 2,3-*trans* (J=7.2 Hz) AMXY system, similarly indicates an 'intact' pyrogallol-type F-ring[4] thus confirming the (4,6) coupling mode. A high-amplitude negative Cotton effect (CE) at 231 nm in the CD spectrum of 4 indicates a 4α-flavanyl substituent[5,6] and hence a 4*R* absolute configuration[b].

The structure of the (-)-fisetinidol-(4β,6)-(-)-fisetinidol-(4α,6)-(-)-robinetinidol 5 is derived by comparison of the ^{1}H NMR data of its decamethyl ether triacetate 6 with those of the closely related trifisetinidol, *i.e.* the 5-deoxy (H-ring) analogue described earlier[7]. Besides replacement of the aromatic ABX system of the pyrocatechol H-ring by a two-proton singlet (δ6.66) of the pyrogallol moiety and an additional methoxy signal in the (-)-robinetinidol derivative 6, the remaining parts of the spectra are virtually superimposable. The sequence of units, *i.e.* 2,3-*trans*-3,4-*cis*(C):2,3-*trans*-3,4-*trans*(F):2,3-*trans*(I) and assignment of the full complement of resonances were hence established by the same protocol described in ref. 7. The 'trimeric' profisetinidin 5 accordingly represents both a structural and stereochemical analogue of the trifisetinidol[7] and of the unique natural triflavanoid with a terminal diol function[8], and thus the similar 2*R*,3*S*,4*S*(C):2*R*,3*S*,4*R*(F):2*R*,3*S*(I) absolute configuration. These allocations are confirmed by the striking resemblance of the CD data of 6 to those of the trifisetinidol[7].

The oligomeric tetraflavanoid analogue 7 is structurally related to triflavanoid 5 as is evident from comparison of the 300 MHz ^{1}H NMR spectral data of its tridecamethyl ether tetra-acetate 8 with that of 6. Coupling constants for the additional heterocyclic AMX system ($J_{2,3}$ 10.0, $J_{3,4}$ 9.5 Hz) indicate a 2,3-*trans*-3,4-*trans* (-)-fisetinidol moiety. The low-field position of the H-3(L) triplet (δ6.12) is characteristic of 3-axial protons geminal to an acetoxy function where this arrangement is present in 4-linked flavanyl units which are flanked at the point of their attachment to aryl rings by *ortho* oxygen substituents[7]. Such deshielding of H-3(L) in conjunction with the high-field position of

---

[b]The (4β,6)-isomer 1 (compound 4 in ref. 1) showing a negative CE at 234 nm has wrongly been assigned a 4*R* configuration. This should be changed to 4*S*.

H-4(L) (δ4.70) implies a (4,8)-linkage of the introduced (-)-fisetinidol moiety to a resorcinol-type flavanoid unit. Application of a protocol similar to that described in ref. 7 not only establishes its location at C-8(D) but also facilitates complete assignment of all aromatic proton resonances. A presedent for the (4α,8)-bis-(-)-fisetinidol JKL-DEF arrangement in 7 has recently[9] been demonstrated by identi-fication of the first natural profisetinidins and proguibourtinidins which are based on 8-C substituted (-)-fisetinidol units. Owing to the limited applicability of CD to the assignment of absolute configuration at C-4 in higher oligomers, the 2*R*,3*S*,4*S*(C):2*R*,3*S*,4*R*(F + L):2*R*,3*S*(I) absolute configuration of 7 is based on the known configuration of precursors, and from a knowledge of 3,4-*cis*- and *trans*-stereochemistry as defined by proton coupling constants.

The aforementioned products 1, 3, 5, and 7 are accompanied by the novel (-)-fisetinidol-(4α,2′)-(-)-robinetinidol 9, representing the first *in vitro*[c] example where the B-ring of the flavan-3-ol moiety serves as nucleophile competing with the resorcinol A-ring in coupling with the flavan-3,4-diol derived C-4 carbocationic intermediate[2,3]. Analysis of the ^{1}H NMR spectrum (Figure) of the heptamethyl ether diacetate 10 indicates three aromatic ABX-systems, two of which the chemical shifts are in line with 'intact' resorcinol-type rings (A and D), as well as replacement of the two-proton singlet of the pyrogallol E-ring in the conventional (4,6)-linked analogues 2 and 4 by a high-field one-proton singlet (δ6.58). The pronounced benzylic coupling of this proton with H-2(F) (δ5.51) confirms bonding of the (-)-fisetinidol unit to C-2(B) of the (-)-robinetinidol moiety. The all-*trans* configuration of heterocycle C is evident from the magnitude of the coupling constants ($J_{2,3} = J_{3,4} = 9.5$ Hz) of its H-2, -3, and -4 resonances. Definition of the different aromatic spin systems is effected by decoupling experiments using the H-2 and -4 resonances as reference signals. A high-amplitude negative CE at 233 nm in the CD spectrum of 10 is indicative of a 4α-flavanyl substituent hence confirming the 4*S* absolute configuration. The mass fragmentation spectrum of 10, exhibits, in contrast to those of 2 and 4, a prominent ion at m/z 547 (64%) following loss of acetic acid from the C ring and RDA fragmentation with hydrogen transfer of the heterocycle of the 'lower' flavan unit (*cf.* ref. 10).

Apart from the formation of the (4α,2′)-biflavanoid 9 the course of condensation of (-)-robinetinidol with (+)-mollisacacidin thus closely resembles that established for coupling of the latter with (-)-fisetinidol[7]. The (-)-fisetinidol-(4α,6)-(-)-robinetinidol 3 accordingly serves as 'activated' nucleophile in genesis of the triflavanoid 5 and the latter subsequently for the 'branched' tetraflavanoid 7. These phenomena were convincingly explained[7] by invoking both steric and conformationally dependent hyperconjugative effects which preferentially operate in the (4α,6)-isomer 3. The same effects would presumably

---

[c]The natural occurrence of C⟶E-ring linked analogues was recently demonstrated[9,10].

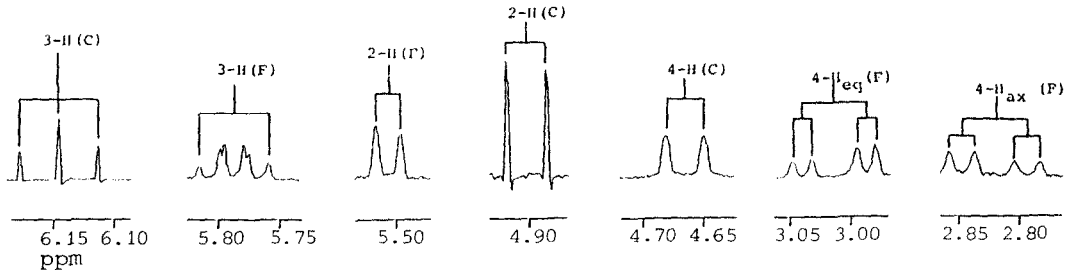
also govern the *in vivo* processes leading to the tri- and tetra-flavanoids 5 and 7. Such speculation should become evident once the natural occurrence of profisetinidins of types 5 and 7 is demonstrated. The available evidence does not permit conclusions whether compounds 1, 3, 5, 7, and 9 are kinetic or thermodynamically controlled products of reaction.

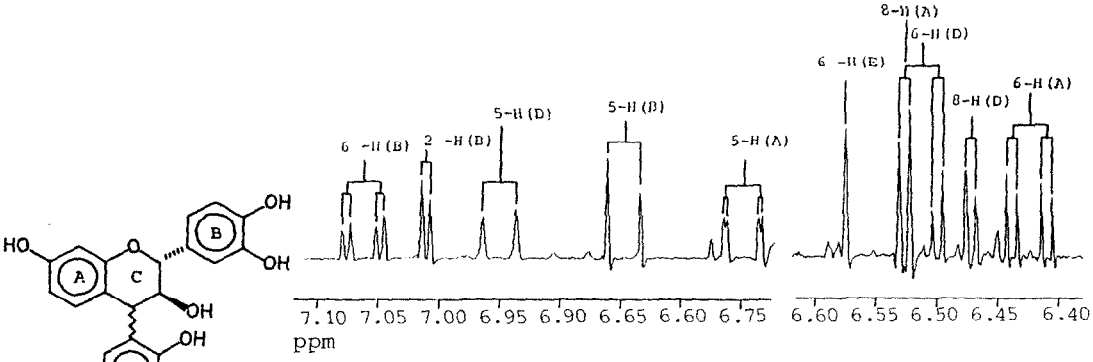
In order to broaden the range of profisetinidins based entirely on units possessive of resorcinol-type A-rings, the above methodology was extended to coupling of the readily available (+)-epifisetinidol and (+)-mollisacacidin (0.1M HCl, 40°C, 27h). The resultant mixture comprised of the known[3,10] (-)-fisetinidol-(4α,6) and (4β,6)-(+)-epifisetinidols 11, and 12, the trimeric (-)-fisetinidol-(4β,6)-(-)-fisetinidol-(4β,6)-(+)-epifisetinidol 13, and a tetraflavanoid to which a (-)-fisetinidol-(4β,6)-(-)-fisetinidol-(4α,6)-(-)-fisetinidol-(4α,6)-(+)-epifisetinidol structure 15 is tentatively assigned. Owing to the complexity of the phenolic mixture, these analogues were again characterized as their phenolic methyl ether acetates, *eg.* 14. Comparison of the ^{1}H NMR and CD data of the hexamethyl ether diacetates of the (-)-fisetinidol-(4α,6) and (4β,6)-(+)-epifisetinidols 11 and 12 with those of their natural[10] and synthetic[3] counterparts confirmed their identity.

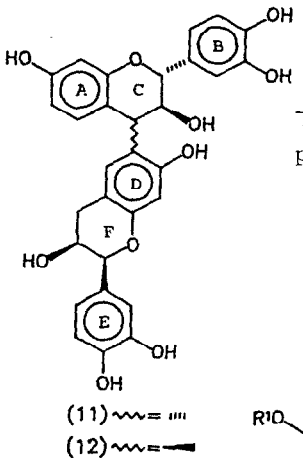
The ^{1}H NMR spectrum of the nonamethyl ether triacetate 14 of triflavanoid 13 exhibits three sharply defined acetoxy- and nine methoxy-proton resonances. The high-field aromatic region displays four aromatic singlets (δ6.64, 6.61, 6.49, 6.47) and a single ABX system hence correlating with [4,6:4,6] bonding between resorcinol-type flavanoid units. Extensive spin decoupling experiments facilitate identification of two heterocyclic AMX systems, the coupling constants ($J_{2,3}$ = 7.0, $J_{3,4}$ 5.0 Hz; $J_{2,3}$ = 6.0, $J_{3,4}$ 5.0 Hz) being compatible with a 2,3-*trans*-3,4-*cis* relative configuration. The ABMX system of the (+)-epifisetinidol moiety is assigned by the small coupling constant ($J_{2,3}$ = *ca* 1.5 Hz) of 2-H(I) (δ5.08). Owing to the narrow region (δ7.02 - 6.77) in which the protons of rings B, E, and H resonate, full assignment of the spin systems of the constituent flavanyl units was not possible. The above detail is, however, sufficient to define the bonding positions, stereochemistry at these points, and sequence of units unequivocally. A high-amplitude positive CE at 233 nm in the CD spectrum of 14 confirms the 4*S* absolute configuration at both points of interflavanyl linkage as is inferred from proton coupling constants and known absolute configuration of (+)-mollisacacidin.

The 'tetrameric' nature of the dodecamethyl ether tetra-acetate 16 is evident from four acetoxy- and twelve methoxy-proton resonances in its ^{1}H NMR spectrum. In contrast to the three high-field aromatic singlets and the BX-portions of two resorcinol-type ABX systems in the spectrum of the 'branched' tetraflavanoid derivative 8, the spectrum of 16 displays six singlets (δ6.25, 6.41, 6.43, 6.44, 6.46, 6,52) and BX-portion [δ6.51, dd, $J_{5,6}$ = 8.5 Hz, 6-H(A); δ6.53, d, $J_{6,8}$ = 2.5 Hz, 8-H(A)] of a single resorcinol-type ABX system in the same region. These features strongly indicate a [4,6:4,6:4,6] bonding sequence between the

Figure: ^{1}H NMR signals (300 MHz) of the heterocyclic- and aromatic protons of 10.

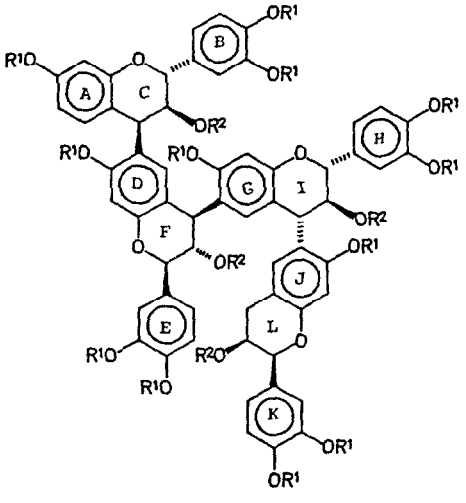






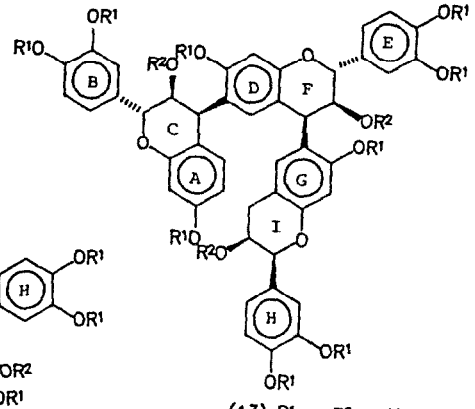
(11) ~~= ||||

(12) ~~= ▬



(15) $R^1 = R^2 = H$

(16) R^1 = Me, R^2 = Ac



(13) $R^1 = R^2 = H$

(14) R^1 = Me, R^2 = Ac

resorcinol-type (-)-fisetinidol and (+)-epifisetinidol units and thus a 'linear' arrangement for 16. Such a conjecture is supported by the chemical shifts of the respective H-3 heterocyclic resonances (δ5.52; t, $J_{2,3} = J_{3,4} = 8.5$ Hz; 5.46, dd, $J_{2,3} = 5.0$, $J_{3,4} = 4.5$ Hz; 5.44, t, $J_{2,3} = J_{3,4} = 9.0$ Hz) which indicate flanking of these protons by a single aromatic oxygen function at the point of interflavanyl linkage[7]. The coupling constants of these protons, correlated with their respective H-2 and -4 resonances *via* decoupling experiments, are compatible with a 2,3-*trans*-3,4-*cis*- and two 2,3-*trans*-3,4-*trans*-(-)-fisetinidol units. Observation of pronounced benzylic coupling of H-4 of the 2,3-*trans*-3,4-*cis*-(-)-fisetinidol moiety and H-5 (δ6.94, d, J=8.5 Hz) of the resorcinol-type ABX system facilitates its positioning as the 'terminal' ABC-moiety. Such termination of the step-wise condensation by a 2,3-*trans*-3,4-*cis*-(-)-fisetinidol unit is supported by observations that these units are less susceptible to electrophilic substitution at C-6 than their 2,3-*trans*-3,4-*trans* analogues[8]. Although the heterocyclic H-4 and aromatic H-5 resonances could be correlated by spin-decoupling experiments, severe signal overlap in the low-field aromatic region precluded similar correlations of the heterocyclic H-2 and aromatic H-2′ and -6′ signals. The above detail nevertheless strongly indicates a 'linear' arrangement of flavanyl units in the novel tetraflavanoid 15. The 4*S*(C) and 4*R*(F+I) absolute configurations indicated in this formulation are based on the known configuration of (+)-mollisacacidin and the relative stereochemistry as defined by proton coupling constants. At present we cannot satisfactorily explain the processes dictating the linear sequencing of (-)-fisetinidol units in formation of tetraflavanoid 15 as opposed to the 'branching' at the terminal unit with (-)-fisetinidol[7] and (-)-robinetinidol as nucleophiles. Factors more complex than the usually invoked steric constraints[7] obviously regulate the position of interflavanyl bonding at this level.

EXPERIMENTAL

^{1}H NMR spectra were recorded in $CDCl_3$ or $(CD_3)_2SO$ at 300 MHz with TMS as reference. CD spectra were determined in MeOH on a Jasco J-20 spectropolarimeter. Media used for the separation of components were: DC-Plastikfolin Kieselgel 60 F_{254} 0.25 mm for TLC and Kieselgel PF_{254} (1 mm, 20x20 cm) for prep. TLC, Sephadex LH-20/ethanol for CC. TLC bands were located under UV and/or with H_2SO_4-HCHO (40:1) spray reagent and compounds removed from the adsorbent by Me_2CO. Methylations were performed with excess of CH_2N_2 over 48 h at -15^0 and acetylations in Ac_2O-pyridine.

Condensation of (+)-mollisacacidin and (-)-robinetinidol

(-)-Robinetinidol (400 mg) and (+)-mollisacacidin (400 mg) were dissolved in 0.1M HCl (60 ml) and the solution heated at 45^{0}C for 24 hr. The mixture was neutralized with satd $NaHCO_3$ solution, extracted with EtOAc (3x100 ml), the extract dried (Na_2SO_4) and the solvent removed under reduced pressure at 60^{0}C. The residue (732 mg) was subjected to column chromatography on Sephadex LH-20 (2 ml/min, EtOH) to afford six fractions, 1 [RRt 0-16 hr (135 mg)], 2 [49-57 hr (55 mg)], 3 [70-80 hr (37 mg)], 4 [96-120 hr (67 mg)], 5 [148-184 hr (95 mg)], and 6 [235-281 hr (67 mg)]. Fraction 1 comprised of a mixture of the flavan-3,4-diol and flavan-3-ol precursors.

Methylation of fraction 2 and subsequent prep. TLC in C_6H_6-Me_2CO (85:15, x2) gave a band at Rf 0.33 which was acetylated to afford tri-*O*-methyl-3-*O*-acetyl-(-)-fisetinidol-(4β,6)-tri-*O*-methyl-3-*O*-acetyl-(-)-robinetinidol **2**[1] as a white amorphous solid (21 mg).

Methylation of fraction 3 and subsequent prep. TLC in C_6H_6-Me_2CO (85:15, x2) gave a band at Rf 0.28 which was acetylated to afford tri-*O*-methyl-3-*O*-acetyl-(-)-fisetinidol-(4α,6)-tri-*O*-methyl-3-*O*-acetyl-(-)-robinetinidol **4** as a *white amorphous solid* (9 mg) (Found: M^+ -60, 684.2579. $C_{41}H_{44}O_{13}$-HOAc requires M^+, 684.2571) ^{1}H NMR [$CDCl_3$, 296K]; δ7.00-6.97 [m, H-2,6(B)], 6.83 [d, J9.0 Hz, H-5(B)], 6.67 [br. s, H-5(D)], 6.6 [dd, J8.5 and 1.0 Hz, H-5(A)], 6.61 [s, H-2,6(E)], 6.52 [d, J2.5 Hz, H-8(A)], 6.47 [s, H-8(D)], 6.43 [dd, J8.5 and 2.5 Hz, H-6(A)], 5.67 [t, $J_{2,3}$ = $J_{3,4}$ = 9.0 Hz, H-3(C)], 5.26-5.33 [m, H-3(F)], 4.98 [d, $J_{2,3}$ 9.0 Hz, H-2(C)], 4.96 [d, $J_{2,3}$ 7.2 Hz, H-2(F)], 4.59 [d, $J_{3,4}$ 9.0 Hz, H-4(C)], 3.86-3.74 [7xs, 7xOMe], 2.95 [dd, J22.0 and 5.0 Hz, H-4*eq*(F)], 2.70 [dd, J22.0 and 7.0 Hz, H-4*ax*(F)], 1.91 and 1.66 [2xs, 2x3-OAc]; CD $[\Theta]_{300}$ 0, $[\Theta]_{290}$ 0.05x10^4, $[\Theta]_{284}$ 0, $[\Theta]_{275}$ -0.06x10^4, $[\Theta]_{264}$ 0, $[\Theta]_{243}$ 0.3x10^4, $[\Theta]_{231}$ -0.7x10^4, $[\Theta]_{224}$ -1.0x10^4, and $[\Theta]_{217}$ 0.

Methylation of fraction 4 and subsequent prep. TLC in C_6H_6-Me_2CO (85:15, x2) gave a band at Rf 0.47 which was acetylated to afford tri-*O*-methyl-3-*O*-acetyl-(-)-fisetinidol-(4α,2')-tri-*O*-methyl-3-*O*-acetyl-(-)-robinetinidol **10** as a *white amorphous solid* (35 mg) (Found: M^+, 744.2775. $C_{41}H_{44}O_{13}$ requires M^+, 744.2782); ^{1}H NMR [$CDCl_3$, 296K] δ7.06 [dd, J8.5 and 2.0 Hz, H-6(B)], 7.01 [d, J2.0 Hz, H-2(B)], 6.85 [d, J8.5 Hz, H-5(B)], 6.58 [s, H-6(E)], 6.75 [dd, J8.5 and 1.0 Hz, H-5(A)], 6.43 [dd, J8.5 and 2.5 Hz, H-6(A)], 6.53 [d, J2.5 Hz, H-8(A)], 6.95 [d, J8.5 Hz, H-5(D)], 6.51 [dd, J8.5 and 2.5 Hz, H-6(D)], 6.47 [d, J2.5 Hz, H-8(D)], 6.15 [t, $J_{2,3}$ = $J_{3,4}$ = 9.5 Hz, H-3(C)], 5.82 - 5.76 [m, H-3(F)], 4.90 [d, $J_{2,3}$ 9.5 Hz, H-2(C)], 5.51 [d, J6.0 Hz, H-2(F)], 4.67 [d, $J_{3,4}$ 9.5 Hz, H-4(C)], 3.91 - 3.23 [7xs, 7xOMe], 3.02 [dd, J16.0 and 4.5 Hz, H-4*eq*(F)], 2.82 [dd, J16.0 and 6.0 Hz, H-4*ax*(F)], 1.92 and 1.78 [2xs, 2x3-OAc]. CD $[\Theta]_{285}$ 0, $[\Theta]_{268}$ -4.1x10^4, $[\Theta]_{250}$ -1.5x10^4, $[\Theta]_{233}$ -28.3x10^4, and $[\Theta]_{218}$ 0.

Methylation of fraction 5 and subsequent prep. TLC in C_6H_6-Me_2CO (85:15, x2) gave a prominent band at Rf 0.28. Acetylation and prep. TLC in hexane-EtOAc-Me_2CO (6:3:1, x4) afforded tri-*O*-methyl-3-*O*-acetyl-(-)-fisetinidol-(4β,6)-tri-*O*-methyl-3-*O*-acetyl-(-)-fisetinidol-(4α,6)-tri-*O*-methyl-3-*O*-acetyl-(-)-robinetinidol **6** as a *white amorphous solid* (14 mg) (Found: M^+, 1100.4053. $C_{61}H_{64}O_{19}$ requires M^+, 1100.4042); ^{1}H NMR [$CDCl_3$, 297K] δ6.91 [d, J2.0 Hz, H-2(B)], 6.90 [dd, J9.0 and 2.0 Hz, H-6(B)], 6.97 [m, H-6(E)], 6.97 [m, H-2(E)], 6.66 [s, H-2,6(H)], 6.82 [d, J9.0 Hz, H-5(B)], 6.84 [d, J8.5 Hz, H-5(E)], 6.48 [s, H-5(D)], 6.30 [s, H-5(G)], 6.51 [dd, J8.5 and 1.0 Hz, H-5(A)], 6.32 [dd, J8.5 and 2.5 Hz, H-6(A)], 6.45 [d, J2.5 Hz, H-8(A)], 6.34 [s, H-8(D)], 6.58 [s, H-8(G)], 5.48 [dd, $J_{2,3}$ 7.0 and $J_{3,4}$ 5.0 Hz, H-3(C)], 5.64 [t, $J_{2,3}$ = $J_{3,4}$ = 9.5 Hz], 5.28 - 5.23 [m, H-3(I)], 5.13 [d, J7.0 Hz, H-2(C)], 5.03 [d, J9.5 Hz, H-2(F)], 4.84 [d, J8.0 Hz, H-2(I)], 4.68 [d, J5.0 Hz, H-4(C)], 4.61 [br. d, J9.5 Hz, H-4(F)], 2.96 [dd, J16.0 and 5.5 Hz, H-4*eq*(I)], 2.67 [dd, J16.0 and 8.0, H-4*ax*(I)], 3.87 - 3.68 [10xs, 10xOMe], 1.93, 1.81 and 1.67 [3xs, 3x3-OAc]; CD $[\Theta]_{300}$ 0, $[\Theta]_{290}$ 4.1x10^4, $[\Theta]_{250}$ 0, $[\Theta]_{235}$ 17.5x10^4, $[\Theta]_{225}$ 36.6x10^4, and $[\Theta]_{217}$ 0.

Fraction 6 was methylated and the mixture resolved by prep. TLC in C_6H_6-Me_2CO (8:2, x2) to give a main band at Rf 0.50 (2.6 mg). Acetylation afforded the tetraflavanoid derivative **8** as a *white amorphous solid* (2.8 mg); ^{1}H NMR [$CDCl_3$, 297K] δ7.06 [dd, J8.5 and 2.5 Hz, H-6(K)], 7.02 [d, J2.0 Hz, H-2(K)], 6.91 [br. dd, J8.5 and 2.0 Hz, H-6(B)], 6.89 [d, J2.0 Hz, H-2(B)], 6.85 [d, J8.5 Hz, H-5(E) and H-5(K) or H-5(B)], 6.81 [d, J8.5 Hz, H-5(B) or H-5(K)], 6.79 (br. dd, J8.5 and 1.0 Hz, H-5(J)], 6.74 [dd, J8.5 and 1.0 Hz, H-5(A)], 6.67 [br. s, H-5(D)], 6.57 [d, J2.5 Hz, H-2(E)], 6.56 [br. s, H-2,6(H)], 6.52 [d, J2.5 Hz, H-8(A) and H-8(J)], 6.52 [s, H-5(G)], 6.51 [dd, J8.5 and 2.5 Hz, H-6(E)], 6.46 [dd, J8.5 and 2.5 Hz, H-6(A) or H-6(J)], 6.43 [dd, J8.5 and 2.5 Hz, H-6(A) or H-6(J)], 6.41 [s, H-8(G)], 6.12 [t, ΣJ19.5 Hz, H-3(L)], 5.76 [m, H-3(F)], 5.56 [dd, J8.0 and 5.5 Hz, H-3(C)], 5.49 [d, J7.5 Hz, H-2(F)], 5.33 [m, H-3(I)], 5.13 [d, J8.0 Hz, 2-H(C)], 5.06 [d, J6.2 Hz, H-2(I)], 5.04 [br. d, J8.0 Hz, 4-H(F)], 4.93 [d, J10.0 Hz, 2-H(L)], 4.81 [br. d, J5.5 Hz, H-4(C)], 4.70 [br. d, J9.5 Hz, H-4(L)], 3.90 - 3.23 (12xs, 12xOMe), 2.96 and 2.79 [m, H-4*ax*(I) and H-4*eq*(I)], 1.97, 1.96, 1.77, 1.65 (each s, 4xOAc); CD $[\Theta]_{310}$ 0,

$[\Theta]_{290}$ -4.4×10^4, $[\Theta]_{275}$ 0, $[\Theta]_{268}$ 5.0×10^4, $[\Theta]_{260}$ 4.5×10^4, $[\Theta]_{246}$ 21.1×10^4, $[\Theta]_{242}$ 4.4×10^4, $[\Theta]_{234}$ 17.5×10^4, $[\Theta]_{232}$ 16.3×10^4, $[\Theta]_{230}$ 21.1×10^4, $[\Theta]_{226}$ 4.0×10^4, $[\Theta]_{222}$ 4.4×10^4, $[\Theta]_{216}$ 16.8×10^4, and $[\Theta]_{208}$ 0.

Condensation of (+)-mollisacacidin and (+)-epifisetinidol.

(+)-Epifisetinidol (3g) was dissolved in 0.1M HCl (300 ml) containing EtOH (10 ml). The solution was heated to 40°C, (+)-mollisacacidin (2.5 g) was added in portions over 3 hr and stirring continued at this temp. for 27 hr. The mixture was neutralized with satd $NaHCO_3$ solution, extracted with EtOAc (3x200 ml), the extract dried (Na_2SO_4) and the solvent removed under reduced pressure at 60°. Prep. TLC in C_6H_6-Me_2CO-MeOH (7:2:1, x2) afforded three fractions at Rf 0.42 (980 mg), 0.29 (320 mg), and 0.14 (280 mg). The excess of (+)-epifisetinidol migrated with the solvent front and was not recovered.

Methylation of the Rf 0.42 fraction and subsequent prep. TLC in $(CH_2Cl)_2$-Me_2CO (9:1, x2) gave two bands at Rf 0.34 (68 mg) and 0.30 (154 mg). Acetylation of the former band gave the hexamethyl ether diacetate (70 mg) of the (-)-fisetinidol-(4*α*,6)-(+)-epifisetinidol **11**[3], while acetylation of the Rf 0.30 band afforded the hexamethyl ether diacetate of the (-)-fisetinidol-(4*β*,6)-(+)-epifisetinidol **12**[3].

Methylation of the Rf 0.29 fraction followed by prep. TLC in $(CH_2Cl)_2$-Me_2CO (8:2, x2) gave a main band at Rf 0.54 (221 mg). Acetylation and prep. TLC in hexane-EtOAc-Me_2CO (55:30:15, x6) afforded tri-*O*-methyl-3-*O*-acetyl-(-)-fisetinidol-(4*β*,6)-tri-*O*-methyl-3-*O*-acetyl-(-)-fisetinidol-(4*β*,6)-tri-*O*-methyl-3-*O*-acetyl-(+)-epifisetinidol **14** as a *light brown amorphous solid* (17.4 mg) (Found: C, 67.2; H, 5.9. $C_{60}H_{62}O_{18}$ requires C, 67.3; H, 5.8%) ^{1}H NMR [$(CD_3)_2SO$, 453K] *δ*7.02 - 6.77 [m, 9xArom. protons, rings B,E and H], 6.65 [br. d, H-5(A)], 6.64 [br. s, H-5(D or G)], 6.61 [s, H-8(D or G)], 6.49 [s, H-8(D or G)], 6.47 [br. s, H-5(D or G)], 6.43 [d, H-8(A)], 6.42 [dd, H-6(A)], 5.41 [dd, $J_{2,3}$ 7.0, $J_{3,4}$ 5.0 Hz,H-3(C or F)], 5,34 [m, H-3(I)], 5.32 [dd, $J_{2,3}$ 6.0, $J_{3,4}$ 5.0 Hz, H-3(C or F)], 5.18 [d, $J_{2,3}$ 7.0 Hz, H-2(C or F)], 5.08 [br. d, $J_{2,3}$ 1.5 Hz, H-2(I)], 5.01 [d, $J_{2,3}$ 6.0 Hz, H-2(C or F)], 4.66 [d, $J_{3,4}$ 5.0 Hz, H-4(C or F)], 4.58 [d, $J_{3,4}$ 5.0 Hz, H-4(C or F)], 3.80 - 3.60 [9xs, 9xOMe], 2.72 [dd, H-4*ax*(F)], 3.06 [dd, H-4*eq*(F)], 1.80 - 1.50 [3xs, 3x3-OAc]; CD $[\Theta]_{300}$ 0, $[\Theta]_{290}$ -1.7×10^4, $[\Theta]_{280}$ 0, $[\Theta]_{271}$ 1.5×10^4, $[\Theta]_{248}$ 0.5×10^4, $[\Theta]_{233}$ 10.8×10^4, and $[\Theta]_{215}$ 0.

Methylation of the Rf 0.14 fraction (280 mg) and subsequent prep. TLC in $(CH_2Cl)_2$-Me_2CO (8:2, x2) gave a main band at Rf 0.38 (34 mg). Acetylation followed by prep. TLC in hexane-EtOAc-Me_2CO (55:25:20, x8) gave four bands at Rf 0.56 (3 mg), 0.52 (2 mg), 0.46 (7 mg), and 0.41 (13 mg). The first three bands still comprised of mixtures and were thus not further investigated. The Rf 0.41 band afforded the tetraflavanoid **16** as a *light brown amorphous solid* (Found: C, 67.1; H, 5.8. $C_{80}H_{82}O_{24}$ requires C, 67.3; H, 5.8%). ^{1}H NMR [$(CD_3)_2SO$, 453K] *δ*7.02 [m, 12xArom. protons (B, E, H and K rings)], 6.94 [d, J8.5 Hz, H-5(A)], 6.52, 6.46, 6.44, 6.43, 6.41 and 6.25 [6xs, H-5(D,G,J), H-8(D,G,J,)], 6.53 [d, J2.5 Hz, H-8(A)], 6.51 [dd, J8.5 and 2.5 Hz, H-6(A)], 5.52 [t, $J_{2,3}$ = $J_{3,4}$ = 8.5 Hz, H-3(I)], 5.46 [dd, $J_{2,3}$ 5.0, $J_{3,4}$ 4.5 Hz, H-3(C)], 5.44 [br. t, $J_{2,3}$ = $J_{3,4}$ = 9.0 Hz, H-3(F)], 5.35 [m, H-3(L)], 5.14 [d, $J_{2,3}$ 5.0 Hz, H-2(C)], 5.00 [d, $J_{2,3}$ 9.0 Hz, H-2(F)], 4.97 [br. d, $J_{2,3}$ *ca* 1.5 Hz,H-2(L)], 4.92 [d, $J_{2,3}$ 8.5 Hz, H-2(I)], 4.64 [d, $J_{3,4}$ 4.5 Hz, H-4(C)], 4.60 [br. t, $J_{3,4}$ 9.0 Hz, H-4(F)], 4.47 [br. d, $J_{3,4}$ 8.5 Hz, H-4(I)], 3.87 - 3.68 [8xs, 12xOMe], 1.73, 1.69, 1.67, 1.57 [4xs, 4x3-OAc]; CD $[\Theta]_{305}$ 0, $[\Theta]_{292}$ 3.9×10^4, $[\Theta]_{280}$ 0, $[\Theta]_{271}$ -0.7×10^4, $[\Theta]_{264}$ 0, $[\Theta]_{250}$ 1.4×10^4, $[\Theta]_{240}$ 0, $[\Theta]_{235}$ -1.0×10^4, and $[\Theta]_{229}$ 0.

Acknowledgements

Support by the Sentrale Navorsingsfonds of this University, the Foundation for Research Development, C.S.I.R., Pretoria, and the Marketing Committee, Wattle Bark Industry of South Africa, Pietermaritzburg, is acknowledged.

REFERENCES

1. Malan, J.C.S.; Young, D.A.; Steenkamp, J.A.; Ferreira, D. *J. Chem. Soc., Perkin Trans. 1*, 1988, 2567-2572.

2. Botha, J.J.; Ferreira, D.; Roux, D.G. *J. Chem. Soc., Chem. Commun.*, 1978, 700-702.

3. Botha, J.J.; Ferreira, D.; Roux, D.G. *J. Chem. Soc., Perkin Trans. 1*, 1981, 1235-1245.

4. Viviers, P.M.; Botha, J.J.; Ferreira, D.; Roux, D.G.; Saayman, H.M. *J. Chem. Soc., Perkin Trans. 1*, 1983, 17-22.

5. Barrett, M.W.; Klyne, W.; Scopes, P.M.; Fletcher, A.C.; Porter, L.J.; Haslam, E. *J. Chem. Soc., Perkin Trans. 1*, 1979, 2375-2377.

6. Van der Westhuizen, J.H.; Ferreira, D.; Roux, D.G. *J. Chem. Soc., Perkin Trans. 1*, 1981, 1220-1226.

7. Steenkamp, J.A.; Ferreira, D.; Roux, D.G.; Hull, W.E. *J. Chem. Soc., Perkin Trans. 1*, 1983, 23-28.

8. Viviers, P.M.; Young, D.A.; Botha, J.J.; Ferreira, D.; Roux, D.G.; Hull, W.E. *J. Chem. Soc., Perkin Trans. 1*, 1982, 535-540.

9. Malan, J.C.S.; Steenkamp, J.A.; Steynberg, J.P.; Young, D.A.; Ferreira, D. *J. Chem. Soc., Perkin Trans. 1*, 1989, in the press, paper 9/01194C/P1P.

10. Steenkamp, J.A.; Malan, J.C.S.; Roux, D.G.; Ferreira, D. *J. Chem. Soc., Perkin Trans. 1*, 1988, 1325-1330.