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THE FIRST NATURAL CONDENSED TANNINS WITH (-)-CATECHIN 'TERMINAL' UNITS

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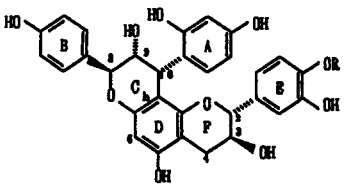
Abstract —— The functionalized 2,3-*trans*-8,9-*trans*-9,10-*cis*-3,4,9,10-tetrahydro-2*H*,8*H*-pyrano[2,3-*b*]chromenes **4** and **6** represent the first naturally occurring condensed tannins with (2*S*,3*R*)-2,3-*trans*-(-)-catechin 'terminal' moieties; the structure of **4** is unequivocally confirmed by synthesis.

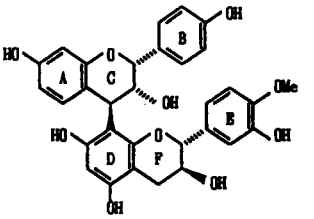
The different classes of naturally occurring condensed tannins are predominated by analogues with a (+)-catechin or (-)-epicatechin[(2*R*,3*S*)-2,3-*trans*- and (2*R*,3*R*)-2,3-*cis*-flavan-3,3′,4′,5,7-pentaol respectively] 'lower' flavan-3-ol unit[1-5]. Prototypes based on (+)-epicatechin[(2*S*,3*S*)-2,3-*cis*] are hitherto restricted to a (4*α*,8)-bis-(+)-epicatechin[6] and a profisetinidin related 2,3-*cis*-8,9-*trans*-9,10-*cis*-3,4,9,10-tetrahydro-2*H*,8*H*-pyrano-[2,3-*b*]chromene[7]. Although a large number of structures were confirmed by synthesis, many proposals regarding the absolute configuration of 'terminal' units are based on ^{1}H NMR and other data incapable of differentiating enantiomeric forms. Coupling constants of the heterocyclic protons of these moieties, *i.e.* $J_{2,3}$ *ca* 7.0 and *ca* 1.0 Hz, are generally accepted as being indicative of (+)-catechin and (-)-epicatechin units respectively. We now report on the natural occurrence of the first oligoflavanoids with (2*S*,3*R*)-2,3-*trans*-(-)-catechin 'terminal' units hence emphasizing the pitfalls encountered in defining the absolute configuration of these moieties.

In the methanol extract of the heartwood of *Julbernardia globiflora*, a member of the Caesalpinioideae, the (+)-guibourtinidol[a]-(4*α*,6)-(+)-catechin- and (-)-epicatechins[8] are accompanied by a series of C-ring isomerized metabolites, termed phlobatannins[9], apparently related to the proguibourtinidin biflavanoids. The hexamethyl ether diacetate of one of the 3,4,9,10-tetrahydro-2*H*,8*H*-pyrano[2,3-*b*]chromenes exhibits coupling constants ($J_{2,3}$ 7.3; $J_{8,9}$ 10.5; $J_{9,10}$ 6.0 Hz) reminiscent of 2,3-*trans*-8,9-*trans*-9,10-*cis* relative configuration[7,9,10] hence leading to tentative assignment of structure **1** with a (+)-catechin DEF moiety.

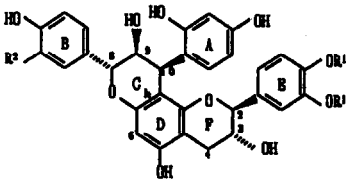
[a]3,4′,7-Trihydroxy functionality



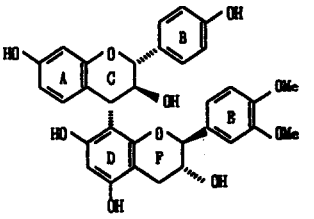
(1) R = H
(2) R = Me



(3)

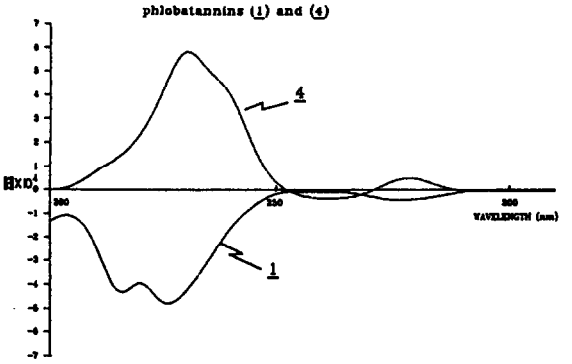


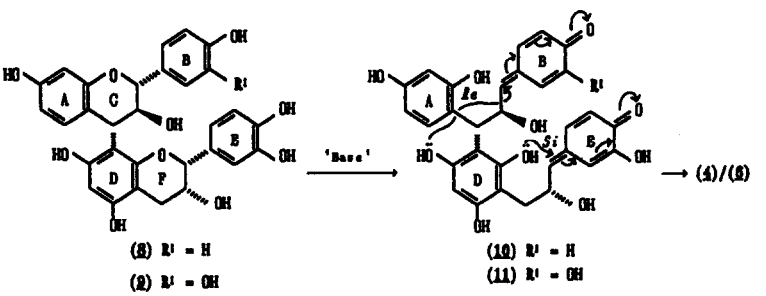
(4) $R^1 = R^2 = H$
(5) R^1 = Me, R^2 = H
(6) R^1 = H, R^2 = OH



(7)

FIGURE: C.D. curves of the hexamethyl ether diacetates of phlobatannins (1) and (4)





(8) R^1 = H
(9) R^1 = OH

(10) R^1 = H
(11) R^1 = OH

Scheme: Proposed route to the *in vivo* formation of phlobatannins (4) and (6)

Treatment of the presumed precursor selectively protected[7] at 4-OH(E), epiguibourtinidol-(4β,8)-(+)-catechin *O*-methyl ether 3, with 0.025M $NaHCO_3$-0.025M Na_2CO_3 buffer (pH 10) for 22h at 50°C under nitrogen, gave complete conversion to the 2,3-*trans*-8,9-*trans*-9,10-*cis*-3,4,9,10-tetrahydro-2*H*,8*H*-pyrano[2,3-*h*]chromene 2. It's hexamethyl ether diacetate exhibits ^{1}H NMR spectral properties identical to those of the corresponding derivative of the natural product. Comparison of CD data, however, indicates an enantiomeric relationship (Figure) for the natural and synthetic products 4 and 2. Since the proguibourtinidin 3 is incapable of epimerization at C-2(F) under basic conditions[11], the mirror-image type CD spectra of the derivatives of 1 and 4 strongly indicates a (2*S*,3*R*)-2,3-*trans*-(-)-catechin DEF moiety for the natural product 4.

Undefined contributions of the chiral centres at 2-, 3-, 8-, and 9-C to the Cotton effects at 260-290 nm in the CD spectra of the derivatives of 1 and 4 necessitates concise synthesis of the enantiomer of 1. Base-catalyzed pyran rearrangement of the (+)-guibourtinidol-(4α,8)-(-)-catechin di-*O*-methyl ether 7, available *via* standard procedures[3,7,12], affords the 2,3-*trans*-8,9-*trans*-9,10-*cis*-tetrahydro-2*H*,8*H*-pyrano[2,3-*h*]chromene 5. Its methyl ether diacetate exhibits ^{1}H NMR and CD properties identical to those of the corresponding derivative of the natural product thereby unambiguously confirming the (-)-catechin DEF moiety of the latter.

The structure of the 3-OH(B) analogue 6 from the heartwood of *Baikiaea plurijuga* (*cf* ref. 7) was similarly confirmed by base-catalyzed pyran rearrangement of (-)-fisetinidol-(4α,8)-(-)-catechin. The CD curve of the heptamethyl ether diacetate of 6 is virtually superimposable to that of the derivative of 4 hence establishing their identical absolute configurations.

The (+)-guibourtinidol- and (-)-fisetinidol-(4α,8)-(-)-epicatechins 8 and 9 may feasibly serve as biosynthetic precursors to tetrahydropyrano[2,3-*h*]chromenes 4 and 6 *via* the pyran recyclizations indicated (Scheme) for intermediate quinone-methides 10 and 11 involving both the B- and E-rings[7]. Although phlobatannins 4 and 6 may thus be considered as 'biosynthetic artefacts', demonstration of the presence of the (-)-catechin DEF unit emphasizes the extreme care to be exercised in allocating the absolute configuration of 'terminal' 2,3-*trans*-flavan-3-ol moieties in the various classes of naturally occurring condensed tannins.

Acknowledgements

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REFERENCES

1. Weinges, K.; Kaltenhauser, W.; Marx, H-D.; Nader, E.; Nader, F.; Perner, J.; Seiler, D. *Justus Liebig's Ann. Chem.*, 1968, 177, 184.
2. Haslam, E. *Phytochemistry*, 1977, 16, 1625.
3. Botha, J.J.; Ferreira, D.; Roux, D.G. *J. Chem. Soc., Perkin Trans. 1*, 1981, 1235.
4. Hemingway, R.W.; Foo, L.Y.; Porter, L.J. *J. Chem. Soc., Perkin Trans. 1*, 1982, 1209.
5. Nonaka, G.; Morimoto, S.; Kinjo, J.; Nohara, T.; Nishioka, I. *Chem. Pharm. Bull.*, 1987, 35, 149.
6. Delle Monache, F.; Ferrari, F.; Marini-Bettollo, G.B. *Gazz. Chim. Ital.*, 1971 101, 387.
7. Steynberg, J.P.; Burger, J.F.W.; Young, D.A.; Brandt, E.V.; Steenkamp, J.A.; Ferreira, D. *J. Chem. Soc., Perkin Trans. 1*, 1988, 3323.
8. Pelter, A.; Amenechi, P.I.; Warren, R.; Harper, S.H. *J. Chem. Soc. (C)*, 1969, 2572.
9. Steenkamp, J.A.; Steynberg, J.P.; Brandt, E.V.; Ferreira, D.; Roux, D.G. *J. Chem. Soc., Chem. Commun.*, 1985, 1678.
10. Burger, J.F.W.; Steynberg, J.P.; Young, D.A.; Brandt, E.V.; Ferreira, D. *J. Chem. Soc., Perkin Trans. 1*, 1989, 671.
11. Whalley, W.B. in 'The Chemistry of Flavonoid Compounds', *ed.* T.A. Geissman, *Pergamon*, 1962, p.441.
12. Foo, L.Y.; Porter, L.J. *J. Chem. Soc., Perkin Trans. 1*, 1983, 1535.

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