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On the structures of plukenetiones B, D, and E and their relationships to other polycyclic polyprenylated acylphloroglucinols

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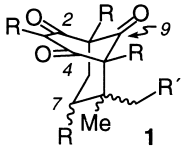
Abstract

Three polycyclic polyprenylated benzoylphloroglucinol natural products, plukenetiones B, D, and E, are shown to be diastereomeric to the related compounds, nemorosone II and sampsonione G.

A large number of polycyclic polyprenylated acylphloroglucinol (PPAP) derivatives have been isolated from plants of the family Guttiferae of diverse geographical origin recently,[1–18] and some of these compounds have been shown to have moderate to high levels of biological activity.[7,15–19] The PPAPs feature a bicyclo[3.3.1]nonane-2,4,9-trione skeleton decorated with prenyl or geranyl groups and an acyl group at C(1), C(3), or C(5) (**1**). Many PPAPs have also undergone secondary cyclizations involving the β-diketone and pendant olefinic groups to afford adamantanes, homoadamantanes, dihydrofuro-fused structures, and the like. A literature search reveals a high degree of homology between many of the PPAPs reported from diverse species. This communication clarifies the structures of several members of one class of PPAPs, the plukenetiones,[3,4] and elucidates their relationships to the nemorosones[1,2] and the sampsoniones.[5–7]



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one R = acyl;
other R = prenyl , geranyl, or rearranged geranyl;
R´ = H or prenyl

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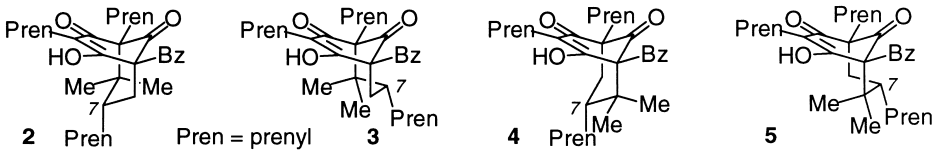
In 1996, a Brazilian team reported the isolation of a new PPAP, nemorosone, from the floral resin of a *Clusia* species.[1] *O*-Methylation of the highly tautomerizable monosubstituted β-diketone of nemorosone produced the corresponding β-methoxyenone as a single isomer, and extensive NMR studies of this derivative, including NOE studies to clarify the stereochemistry, established the structure of nemorosone to be **2**. The same team reported the isolation of the related compounds, 7-*epi*-nemorosone and nemorosone II, from floral resins of similar species in 1999,[2] and their structures were determined to be **3** and **4**, respectively, again by characterization of the corresponding β-methoxyenones. Nemorosone II differed from nemorosone by the location of the methyl groups with respect to the benzoyl group, whereas nemorosone and 7-*epi*-nemorosone differed in the orientation of the C(7) prenyl group (*exo* and *endo*, respectively).



Nearly simultaneously with the second report, a joint West Indian–Canadian team reported the isolation of another set of PPAPs, plukenetiones B–G, from the fruit of a *Clusia* species.[4] Plukenetiones D and E, a rapidly interconverting pair of tautomeric β-diketones, were converted to a pair of isomeric β-acetoxyenones, and extensive NMR studies of these derivatives established the structure of plukenetione D/E to be 'closely related to nemorosone, differing only in the position of the *gem*-dimethyl group on the bicyclononane'.[4] However, the stereochemistry at C(7) in plukenetione D/E was not investigated, and therefore it was possible that plukenetione D/E had either the structure **4**, now known to belong to nemorosone II,[2] or the structure **5**, that of 7-*epi*-nemorosone II, the one member of the nemorosone series not yet reported by the Brazilian team.

Now that a compound with structure **4**, viz. nemorosone II, has been unambiguously identified,[2] it is possible to clarify the question of the structure of plukenetione D/E. The task is not as straightforward as comparing the reported spectra, however, because nemorosone II has been characterized as its *O*-methyl enol ether,[2] whereas plukenetione D/E has been characterized as its enol acetates.[4] Nevertheless, careful comparison of the NMR spectra of the compounds in question (Table 1) reveals several features that suggest that plukenetione D/E has the structure **5**.

- The diastereotopic H atoms of the ring CH_2 groups of *O*-methylnemorosone and *O*-methylnemorosone II (which have chair conformations in the more saturated ring) resonate 0.52 and 0.53 ppm apart.[1,2] By contrast, the diastereotopic H atoms of the ring CH_2

Table 1
^{1}H and ^{13}C NMR chemical shifts of the *O*-methylnemorosones and *O*-acetylplukenetiones D and E

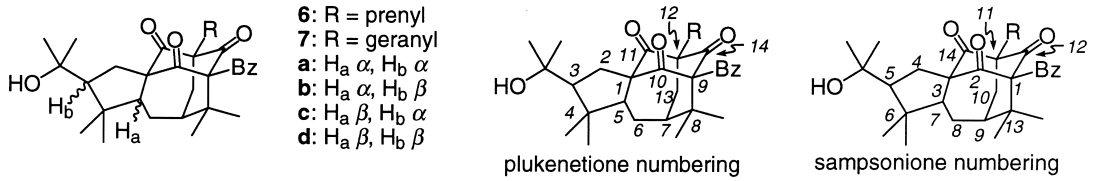
Compound (ring conformation)	ring CH_2 (^{1}H)	geminal Me's (^{13}C)	C(7) (^{13}C)
O-methylnemorosone (chair)[1]	1.94, 1.42 ($\Delta\delta$ 0.52)	25.6, 17.9 ($\Delta\delta$ 7.7)	42.5
O-methylnemorosone II (chair)[2]	2.03, 1.50 ($\Delta\delta$ 0.53)	23.4, 15.7 ($\Delta\delta$ 7.7)	43.7
O-methyl-7-*epi*-nemorosone (boat)[2]	2.12, 1.90 ($\Delta\delta$ 0.22)	27.2, 23.9 ($\Delta\delta$ 4.3)	48.6
O-acetylplukenetione D (unknown)[4]	2.22, 2.11 ($\Delta\delta$ 0.11)	27.1, 23.3 ($\Delta\delta$ 3.8)	48.3
O-acetylplukenetione E (unknown)[4]	2.40, 2.16 ($\Delta\delta$ 0.24)	26.6, 22.0 ($\Delta\delta$ 4.6)	48.0

groups of *O*-methyl-7-*epi*-nemorosone (which has a boat conformation in the more saturated ring) and *O*-acetylplukenetiones D and E resonate only 0.11–0.24 ppm apart.[2,4]

- The diastereotopic Me groups of *O*-methylnemorosone and *O*-methylnemorosone II (chairs) resonate 7.7 ppm apart in the ^{13}C NMR spectrum.[1,2] By contrast, the diastereotopic Me groups of *O*-methyl-7-*epi*-nemorosone (boat) and *O*-acetylplukenetiones D and E resonate only 3.8–4.6 ppm apart.[2,4]
- The C(7)'s of *O*-methylnemorosone and *O*-methylnemorosone II (chairs) resonate at δ 42.5 and 43.7.[1,2] By contrast, the C(7)'s of *O*-methyl-7-*epi*-nemorosone (boat) and *O*-acetylplukenetiones D and E resonate at δ 48.0–48.6.[2,4]

These data suggest that plukenetione D/E has a boat conformation in the more saturated ring, similar to 7-*epi*-nemorosone. Therefore, plukenetione D/E must have the structure **5** and can also be named as 7-*epi*-nemorosone II.

The Commonwealth team that discovered plukenetione D/E also isolated plukenetione B at the same time.[4] The structure of plukenetione B was shown to be **6** by extensive NMR studies. A NOESY spectrum was acquired, but it was inconclusive, and therefore the stereochemistry of plukenetione B was left indeterminate in the publication describing this compound.[4] Meanwhile, in three papers appearing in 1998, 1999 and 2000, a Singaporean team reported the isolation of a new series of PPAPs, sampsoniones A–M, from several *Hypericum* species.[5–7] The structures and stereochemistries of the sampsoniones were established by extensive NMR studies, including NOE experiments. Sampsonione G in particular was shown to have structure **6b**, and the closely related sampsonione C was shown to have structure **7c**.[6]



With the structure of sampsonione G unambiguously established to be **6b**,[6] the stereochemistry of plukenetione B can now be assigned. The following lines of evidence suggest that the structure of plukenetione B is **6c**.

- The chemical shifts of the ring carbons of plukenetione B are within 0.3 ppm of those of sampsonione C (**7c**), whereas the chemical shifts of the ring carbons of plukenetione B differ from those of sampsonione G (**6b**) by up to 7.3 ppm (Table 2).[4,6]
- The Singaporean team has isolated several other sampsoniones with homoadamantane structures similar to **6** and **7**, all of which have either α,β or β,α configurations at H_a and H_b (as in **6b** and **6c**),[7] and none of which have the α,α or β,β configurations (as in **6a** and **6d**). Furthermore, molecular models reveal that structures **6a** and **6d** suffer from steric crowding of the isopropanol group on the concave face of the five-membered ring.
- A model of **6c** shows no uncoupled H's which are close in space, perhaps explaining the inconclusive NOESY experiment carried out on plukenetione B.

Therefore, plukenetione B probably has the structure **6c**, differing from sampsonione G in the configurations at two of its six stereocenters.

Table 2
^{13}C NMR chemical shifts of the cage carbons of plukenetione B and sampsoniones C and G

Plukenetione B[4]		Sampsonione C[6]			Sampsonione G[6]		
Carbon	δ	Carbon	δ	Δδ	Carbon	δ	Δδ
1	73.2	3	73.1	–0.1	3	73.2	0.0
2	33.2	4	33.1	–0.1	4	31.0	–2.2
3	57.6	5	57.5	–0.1	5	58.9	1.3
4	44.9	6	44.8	–0.1	6	46.7	1.8
5	57.6	7	57.5	–0.1	7	54.6	–3.0
6	28.6	8	28.6	0.0	8	24.7	–3.9
7	43.8	9	43.8	0.0	9	42.2	–1.6
8	50.9	13	50.7	–0.2	13	47.7	–3.2
9	80.8	1	80.9	0.1	1	81.5	0.7
10	204.1	2	203.9	–0.2	2	204.1	0.0
11	206.5	14	206.3	–0.2	14	205.5	–1.0
12	68.9	11	68.9	0.0	11	67.6	–1.3
13	42.6	10	42.3	–0.3	10	35.3	–7.3
14	204.8	12	204.7	–0.1	12	204.3	–0.5

With the assignment of structure **5** to plukenetione D/E and **6c** to plukenetione B, the biogenetic relationship among the three PPAP families of the nemorosones, plukenetiones, and sampsoniones is clarified. The adamantane and homoadamantane structures of plukenetiones A and B and several of the sampsoniones are derived from plukenetione D/E or more highly prenylated analogs by oxidative cyclization of the *β*-diketone upon the *endo* C(7) prenyl group. Such a pathway is not available for the C(7) *exo*-isomers, nemorosone and nemorosone II, but it is available for 7-*epi*-nemorosone II (plukenetione D/E). Future studies of the Guttiferae may eventuate in the isolation of natural products derived from cyclization of 7-*epi*-nemorosone itself.

Acknowledgements

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