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Gnetulin, a Dimer of 3′,4,5′-Trihydroxy-3-methoxystilbene from *Gnetum ula*

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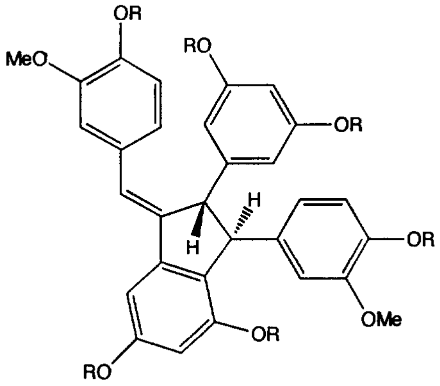
Abstract: Gnetulin, a dimer of 3′,4,5′-trihydroxy-3-methoxystilbene, isolated from *Gnetum ula*, has been assigned structure and relative configuration (1) on the basis of long range COSY and NOE difference experiments on the peracetate (2).

Oligomers of resveratrol, 3,4′,5-trihydroxystilbene, are well documented[1]. The presence of stilbenes in the wood of *Gnetum ula* is well known[2], in particular 3,4,5′-trihydroxy-3′-methoxystilbene. We now report the isolation and structural elucidation of a new dimer, gnetulin (1), formally derived from 3′,4,5′-trihydroxy-3-methoxystilbene, from the same source.

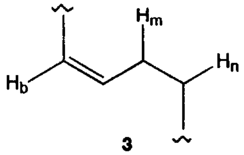
Gnetulin was isolated from the wood of *G. ula* and purified as the acetate (2), $C_{42}H_{38}O_{14}$, mp 182 °C. Its ^1H and ^{13}C NMR properties [Tables 1 and 2] revealed the presence of six acetates, two methoxyl groups, eleven aromatic protons and a three spin system involving a trisubstituted double bond proton H_b [δ_H 7.18 (d, J 1.9 Hz)] and two methines H_m [δ_H 4.40 (t, J 2.3 Hz)] and H_n [δ_H 4.33 (d, J 2.8 Hz)]. The magnitude of the coupling between H_b and H_m suggests an allylic relationship as in (3). The twenty-four double bond equivalents are accommodated by the six acetates, four benzene rings, the double bond and one further ring. The spin systems associated with the aromatic rings, apart from ring B, were established as in (4)-(7) by decoupling experiments and confirmed by a COSY spectrum. The evidence necessary for determining the relationship of H_b, H_m, H_n and the aromatic rings and for siting the methoxyl groups was obtained from long range COSY and NOE difference experiments as follows.

In ring A the methoxyl group protons (δ_H 3.70) correlate only with H_l and hence the methoxyl group is *ortho* to H_l. The methine H_n correlates with both H_k and H_l and its position between them is confirmed by NOE experiments (*vide infra*). The remaining position must bear an acetate as in (4). Confirmation of part-structure (4) was obtained from NOE difference experiments. Irradiation of the methoxyl protons afforded a large NOE at H_l while irradiation of H_n gave substantial NOEs at H_k and H_l.



1 R = H

2 R = Ac



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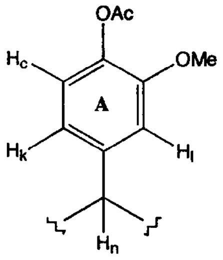

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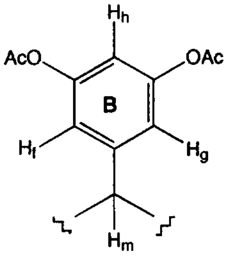

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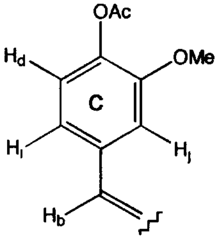

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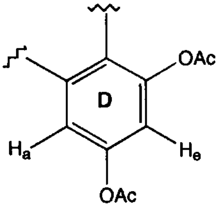

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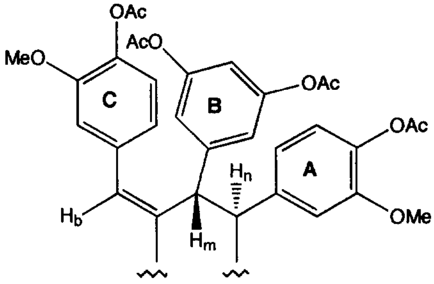

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The accidental equivalence of H_f, H_g and H_h in ring B caused an initial problem which was readily resolved, as in (**5**), by the fact that H_m both correlates with and has a large NOE to the resonance of these equivalent protons. The observations of pairs of equivalent carbons at δ_C 151.4 and 117.3 supports the presence of part-structure (**5**).

The olefinic proton H_b correlates with all the protons, H_d, H_i and H_j, of ring C but NOEs from H_b to H_i and H_j place the double bond as in (**6**). A large NOE from the shielded methoxyl group (δ_H 3.49) to H_j indicates that this methoxyl group is *ortho* to H_j. The other position *ortho* to the methoxyl group must be occupied by an acetate. Assembly of the above units leads to the part structure (**8**).

Ring D has two *meta*-coupled protons H_a and H_e, two acetates and two carbon substituents. The arrangement as in (**7**) is based on the following evidence. Since only ring D remains to be attached it is clear that the non-aromatic ring must be five-membered. The observation of a large NOE between H_b and H_a reveals the orientation of ring D and simultaneously the E configuration of the double bond and leads to structure (**1**) for the dimer. The *trans* relative stereochemistry of H_m and H_n follows from NOE difference results. In addition to the NOEs described above irradiation of H_n afforded a substantial NOE at the H_f, H_g, H_h ensemble while irradiation of H_m yielded NOEs at H_j and H_l.

Gnetulin (**1**) is clearly derived from 3′,4,5′-trihydroxy-3-methoxystilbene as in (**9**). The resveratrol dimer pallidol (**10**), from *Cissus pallida,* has a similar type of structure though further cyclisation has occurred[3]. Pallidol is racemic but, unfortunately, loss of the gnetulin sample precluded measurement of its optical rotation.

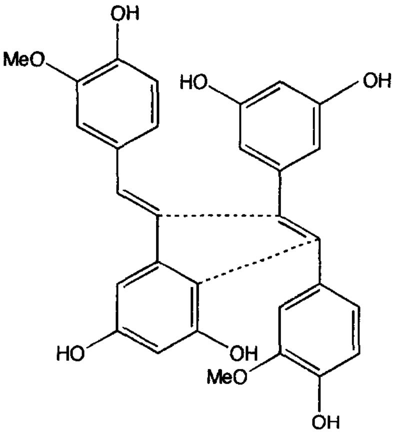
Table 1. ^{1}H NMR Chemical Shifts of Gnetulin (**1**)

	δ_H	J Hz		δ_H	J Hz
H_a	7.40	(d, 1.9)	H_i	6.79	(dd, 8.1, 1.9)
H_b	7.18	(d, 1.9)	H_j	6.67	(d, 1.8)
H_c	6.92	(d, 8.1)	H_k	6.64	(dd, 8.1, 1.9)
H_d	6.87	(d, 8.0)	H_l	6.60	(d, 1.9)
H_e	6.86	(d, 2.4)	H_m	4.40	(t, 2.3)
H_f H_g H_h	6.79	(s)	H_n	4.33	(d, 2.8)
OMe	3.70, 3.49		OAc	2.33, 2.27, 2.23, 2.22(2), 1.81	

Table 2. ^{13}C NMR Chemical Shifts of Gnetulin (**1**)

(s)	(s)	(d)	(d)	(q)
151.4(2)	141.8	124.6	113.8	55.8
151.3	141.6	122.9	112.3	55.6
151.2	139.0	122.5	111.3	21.0
150.8	138.7	121.9	110.5	20.9(2)
147.9	134.5	119.3		20.5(2)
146.1	133.8	117.3(2)	58.2	20.1
145.1		116.5	58.0	

(CO) 168.9, 168.8, 168.7, 168.4(2), 167.6



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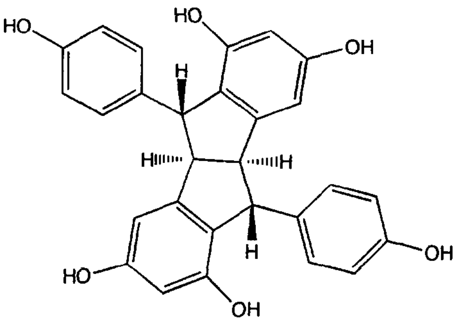

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EXPERIMENTAL

Isolation

The wood of *G. ula* was cut into small pieces, defatted with light petroleum and extracted with Me_2CO in a soxhlet. Removal of the solvent gave a residue which was dissolved in H_2O and exhaustively extracted into EtOAc in a liquid-liquid extractor. The EtOAc soluble material (25 g) was chromatographed over silica gel to give the products reported earlier[2]. Elution with EtOAc afforded a brown gum which was acetylated in Ac_2O/pyridine and purified by chromatography [$CHCl_3$:MeOH - 99:1] to give gnetulin acetate (**2**) (150 mg), mp 182° (needles ex MeOH). [UV (MeOH) λ_{max} 205, 280, 325, 340 nm. IR (KBr) ν_{max} 1760, 1685, 1510, 1365, 1200, 1120, 1025, 900 cm^{-1}. MS *m/z* 764 (M^+, 10), 722 (90), 68 (96), 638 (70), 595 (35), 554 (20), 512 (15), 545 (29), 432 (20), 390 (30), 368 (35), 328 (10), 312 (8), 225 (25), 58 (28).

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