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A novel neolignan, mansoxetane, and two new sesquiterpenes, mansonones R and S, from *Mansonia gagei*

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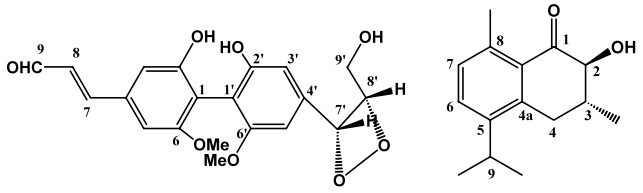
Abstract—Three new compounds, mansoxetane; 4′-(3-hydroxy-1,2-oxetanyl)-2′,2-dihydroxy-4-(2-formyl-1-ethyl)-6′,6-dimethoxy biphenyl, and mansonones R and S, together with two previously reported coumarins, mansorins A and C, and four known mansonones, mansonones C, E, G and H, were obtained from the methanolic extract of the heartwood from *Mansonia gagei* Drumm. Their structures were established by spectroscopic methods.

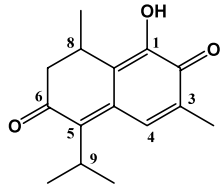
Mansonia gagei Drumm., a traditional medicinal plant of the Sterculiaceae family has been used as a cardiac stimulant, a vertigo, an antiemetic, an antidepressant and a refreshment agent.[1] Literature surveys on the chemical constituents of the *Mansonia* genus revealed that the constituents of the heartwoods and seeds of *Mansonia altissima* composed of several 1,2-naphthoquinones in mansonone type (mansonones A–H,[2,3] I[4] and L[5]) and cardiac glycosides[6](stophanthidin-2,3-di-*O*-methyl-6-deoxy-β-D-glucopyranoside and stophanthidin-3-*O*-methyl-6-deoxy-β-D-gluco-pyranoside). Since 1997, we have explored the constituents of *M. gagei* and disclosed that several new coumarins and mansonones were isolated from the dichloromethane extract of the heartwoods.[7,8] We report herein the further investigation of constituents of the methanolic extract from the heartwoods of this plant.

The methanolic extract (20 g) was fractionated using silica gel column chromatography eluting by gradient with chloroform and methanol. Final purification was achieved by MPLC on silica gel to afford three new compounds, **1** (728 mg), **2** (2.7 mg) and **3** (27.4 mg), together with two previously reported coumarins,[7] mansorins A and C, and four known mansonones,[2,3] mansonones C, E, G and H.



1

2



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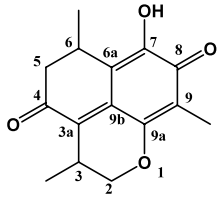

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Compound **1**, named mansoxetane, was obtained as a pale brown solid; $[\alpha]_D^{15}$ −12.8 (*c* 0.27, $CHCl_3$). High-resolution FABMS analysis gave *m*/*z* 389.1199 $(M+H)^+$ and established the molecular formula as $C_{20}H_{20}O_8$, which indicated **1** to have an unsaturation number of 11.

The presence of a *trans*-cinnamaldehyde residue in the molecule was suggested by the observation of characteristic signals at δ_H 9.66 and δ_C 193.5 ascribable to an aldehyde moiety and at δ_H 7.35 (d, $J=15.9$ Hz) and δ_H 6.60 (dd, $J=15.9$ and 7.6 Hz) arising from a *trans*-olefin, as well as on HMBC correlations between these olefinic protons and the aromatic carbons on the benz-

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ene ring (see Fig. 1). A set of *meta*-coupled protons was observed at δ 6.90 and δ 6.76 in the ^{1}H NMR spectrum, indicating that this benzene ring had four substituents, two of which were methoxy (δ_H 3.92 and δ_C 149.2) and hydroxy (δ_C 144.6). From both of the aromatic protons just mentioned above, HMBC correlations with the β-carbon (δ_C 152.8) of the acrylaldehyde function were observed, revealing that this part was located *ortho* to both of two *meta*-coupled protons. Further, HMBC correlations between both of these aromatic protons and the sp^2 quaternary carbon (δ_C 135.9) on the benzene ring were observed, indicating that the benzene ring was linked to another unit, *para* to the acrylaldehyde group.

From the ^{1}H and ^{13}C NMR spectral data (Table 1), the presence of one more C_6–C_3 unit in **1** was suggested. In analogy with the phenylpropanoid unit described above, the benzene ring in this residue had four substituents, two of which were methoxy (δ_H 3.90 and δ_C 147.2) and hydroxy (δ_C 144.2). From both of two *meta*-coupled aromatic protons (δ 6.70 and δ 6.57) on this benzene ring, HMBC correlations between the sp^3 carbon (δ_C 76.3) in one of the C_3 units were observed, indicating that the propane unit was present *ortho* to both of two *meta*-coupled protons. The chemical shifts of the three carbons in the propane unit were observed at δ_C 76.3, 78.8 and 61.3, revealing that they were aliphatic carbons bearing oxygen functions. Based on the result of acetylation of **1**, the terminal carbon of the propane unit was proved to be a primary alcohol.[9] Considering the molecular formula, the remaining two carbons must constitute an oxetane ring. A clear NOE observation between two protons (δ 4.90 and δ 4.05) on the oxetane ring revealed the stereochemical relationship of the primary alcohol and the benzene ring to be *cis*. Furthermore, HMBC correlations between both of the aromatic protons and the sp^2 quaternary carbon (δ_C 133.2) on the benzene ring were observed, indicating that this benzene ring was linked to another residue *para* to the functionalized propane group.

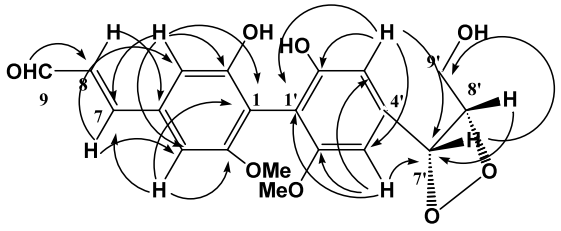

Figure 1. ^{1}H, ^{13}C long range correlations in the HMBC spectrum of **1**.

Table 1. NMR spectral data of **1**

Position	δ_C	δ_H (J in Hz)
1	135.9	–
2	144.6	–
3	111.3	6.90 (d, 1H, 1.8)
4	126.7	–
5	104.0	6.76 (d, 1H, 1.8)
6	149.2	–
7	152.8	7.35 (d, 1H, 15.6)
8	127.3	6.60 (dd, 1H, 7.9, 15.6)
9	193.5	9.66 (d, 1H, 7.6)
1′	133.2	–
2′	144.2	–
3′	108.2	6.70 (d, 1H, 1.8)
4′	127.4	–
5′	102.3	6.57 (d, 1H, 1.8)
6′	147.2	–
7′	76.3	4.90 (d, 1H, 8.2)
8′	78.8	4.05 (ddd, 1H, 3.3, 3.3, 8.2)
9′	61.3	3.60 (m, 1H), 3.90 (overlapped, 1H)
2- and 2′-OH	–	5.56 (br-s, 2H)
6-OMe	56.3	3.92 (s, 3H)
6′-OMe	56.2	3.90 (s, 3H)
9′-OH	–	2.30 (s, 1H)

All the above spectroscopic analyses enabled us to construct the structure **1** with a link between the *para* positions of each phenylpropanoid unit. To the best of our knowledge, this is the first example of a biphenylneolignan[10,11] possessing an oxetane ring.

The molecular formula of compound **2**, obtained as a pale yellow powder, was established as $C_{15}H_{20}O_2$ based on EIMS and NMR data. The ^{1}H NMR spectrum of **2** (Table 2) disclosed the presence of a set of *ortho*-coupled protons, an isopropyl group, two methyl groups and two methylene protons. The ^{13}C NMR spectrum of **2** (Table 2) also confirmed the presence of these groups and an α-hydroxy ketone moiety. The HMBC spectrum of **2** (Fig. 2) showed correlations between the *ortho*-coupled proton of the aromatic ring at δ_H 7.14 and 7.38 and the methyl carbon at δ_C 22.6 (8-CH_3) and the methine carbon of the isopropyl group at δ_C 28.3, respectively. In addition, this methyl group (8-CH_3) was correlated to an aromatic carbon at δ_C 130.5. Furthermore, one of two methylene protons (δ_H 3.21) showed correlation with two aromatic carbons at δ_C 140.6 and 130.5, and the other (δ_H 2.63) was coupled with a methine carbon at δ_C 37.4 as well as another methyl group at δ_C 19.0 (3-CH_3). HMBC correlations were also observed between the methyl group (3-CH_3) and a hydroxy carbon (δ_H 78.5). The relative stereochemistry of **2** was determined primarily on the basis of J values obtained from the ^{1}H NMR spectrum. The large coupling constant observed between H-2 and H-3 (J=12.8 Hz) implied a *trans*-diaxial orientation for this proton pair. Compound **2** was thus identified as a new natural product and named mansonone R.

Compound **3** was obtained as an orange amorphous material, and the molecular formula was determined to be $C_{15}H_{18}O_3$ from the molecular ion at m/z 247.1316 $[M+1]^+$ in the high-resolution FAB$^+$-mass spectrum. The ^{13}C NMR spectral data (Table 2) showed 14 carbon signals and the signals at δ_C 180.8 (C-2) and 200.0 (C-6) were clearly ascribable to two carbonyl carbons. Comparison of the ^{1}H and ^{13}C NMR spectral data of **3** (Table 2) with those of mansonones in the literature showed that the data of **3** were very similar to those of 7-hydroxy-2,3,5,6-tetrahydro-3,6,9-trimethylnaphtho[1,8-*b*,*c*]-pyran-4,8-dione,[12] compound **4**, (Table 2), except for the absence of the naphtho[1,8-*b*,*c*]pyran signals, and the presence of the additional isopropyl group signals at δ_H 1.28 (3H, d, J=7.0 Hz), 1.38 (3H, d, J=7.0 Hz) and 3.45 (1H, m)

Table 2. NMR spectral data of **2**, **3** and **4** [11]

Position	δ_H (J in Hz)		δ_C		Position	**4**	
	2	**3**	**2**	**3**		δ_H (J in Hz)	δ_C
1	–		201.4	144.6	7	–	143.6
2	3.95 (dd, 1H, 2.7, 12.8)		78.5	180.8	8	–	181.3
3	2.10 (m, 1H)		37.4	136.1	9	–	115.0
4	2.63 (dd, 1H, 11.9, 17.1) 3.21(overlapped, 1H)	7.55 (s, 1H)	33.7	132.4	9a	–	157.3
4a	–		140.6	135.3	9b	–	131.0
5	–		144.4	150.2	3a	–	139.4
6	7.38 (d, 1H, 7.9)		128.8	200.0	4	–	197.1
7	7.14 (d, 1H, 7.9)	2.50 (d, 1H, 15.0) 2.80 (dd, 1H, 6.4, 14.7)	130.0	46.0	5	2.60 (dd, 1H, 1.5, 16.3) 2.78 (dd, 1H, 6.6, 16.3)	44.5
8	–	3.55 (m, 1H)	139.0	28.0	6	3.55 (m, 1H)	27.5
8a	–		130.5	123.0	6a	–	115.1
9	3.19 (m, 1H)	3.45 (m, 1H)	28.3	28.5	3	3.12 (dq, 1H, 3.5, 7.1)	26.4
1-OH	–	6.86 (s, 1H)			2	4.15 (dd, 1H, 10.5, 3.5) 4.28 (dd, 1H, 10.5, 1.0)	71.9
2-OH	4.15 (d, 1H, 2.7)		–	–			
3-CH_3	1.34 (d, 3H, 6.4)	2.13 (s, 3H)	19.0	16.2	9-CH_3	1.94 (s, 3H)	8.0
8-CH_3	2.62 (s, 3H)	1.20 (d, 3H, 7.3)	22.6	20.5	6-CH_3	1.19 (d, 3H, 7.1)	20.6
9-$(CH_3)_2$	1.24 (d, 3H, 6.4)	1.38 (d, 3H, 7.0)	22.9	21.0	3-CH_3	1.16 (d, 3H, 7.1)	16.2
	1.25 (d, 3H, 6.4)	1.28 (d, 3H, 7.0)	23.5	22.7			

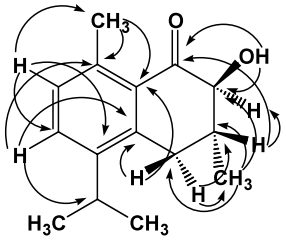

Figure 2. ^1H, ^{13}C long range correlations in the HMBC spectrum of **2**.

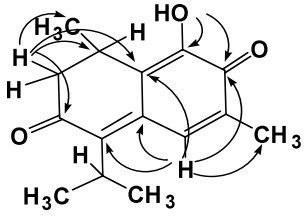

Figure 3. ^1H, ^{13}C long range correlations in the HMBC spectrum of **3**.

in **3**. The complete structure of **3**, a new natural product named mansonone S, was fully-confirmed by COSY, HMQC and HMBC experiments (Fig. 3).

Acknowledgements

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9. The general procedure for acetylation of compound **1** was carried out as follows: Compound **1** was treated with acetic anhydride in the presence of pyridine under reflux overnight to give the triacetyl derivative after workup. The molecular ion peak at m/z 514 in the mass spectrum, three singlet signals of the acetyl groups at δ_H 2.05, 2.29 and 2.31 (3H each) in ^1H NMR spectrum and three carbonyl signals at δ_C 167.5, 167.9 and 170.3 as well as three methyl carbon signals at δ_C 20.3, 20.6 and 20.7 in the ^{13}C NMR spectrum confirmed the structure of **1**.
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