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MINOR XANTHONES FROM THE BARK OF *CRATOXYLUM COCHINCHINENSE*

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Key Word Index—*Cratoxylum cochinchinense*; Hypericoideae; Guttiferae; xanthone; 11-hydroxy-1-isomangostin; 1,3,5,6-tetrahydroxyxanthone; xanthonolignoid; 5′-demethoxycadensin G; bisxanthone; cratoxyxanthone.

Abstract—Three new xanthone derivatives, 11-hydroxy-1-isomangostin, a xanthonolignoid (5′-demethoxycadensin G) and a bisxanthone, as well as the known compound 1,3,5,6-tetrahydroxyxanthone, were isolated from the bark of *Cratoxylum cochinchinense*. Their structures were elucidated mainly by a combination of high-field NMR spectroscopic techniques.

INTRODUCTION

We have previously reported [1] the isolation of the major constituents (xanthones, triterpenoids and tocopherols) of the bark of *Cratoxylum cochinchinense* (Lour.) Bl. A further examination of some complex minor fractions has led to the isolation, following extensive HPLC purification, of one known and three new xanthone derivatives.

RESULTS

The UV spectrum of the first compound, 11-hydroxy-1-isomangostin (**1**), was consistent with a xanthone nucleus. The compound was obviously phenolic since it gave a positive ferric chloride test and contained appropriate bands in its IR spectrum. Its mass spectrum showed a molecular ion (*m/z* 426.1676) which corresponded to the formula $C_{24}H_{26}O_7$, revealing the presence of two units of unsaturation more than required by the basic xanthone structure. Two of the oxygen atoms were present as phenolic hydroxyl groups since the compound formed a dimethyl ether derivative upon treatment with methyl iodide. Neither hydroxyl was present in the *peri* position since the ^{1}H NMR spectrum (Table 1) lacked resonances for a chelated hydroxyl. The ^{1}H NMR spectrum contained signals for two aromatic protons [δ_H 6.72 (1H, *s*, H-5) and 6.40 (1H, *s*, H-4)]. The chemical shifts revealed that these also were not in the *peri* position while the absence of coupling between these protons indicated that they were on different rings. There were also resonances for a trisubstituted double bond [δ_H 5.31 (1H, *br t*, J = 6.8 Hz, H-16)], an oxygenated methine [δ_H 3.82 (1H, *dd*, J = 5.7 and 7.8 Hz, H-11)], a methoxyl group [δ_H 3.77 (3H, *s*, OMe)], two vinyl methyl groups [δ_H 1.81 (3H, *br s*, H_3-18) and 1.64 (3H, *br s*, H_3-19)] and two tertiary methyl groups [δ_H 1.43 and 1.30 (each 3H, *s*, H_3-13 and H_3-14)]. The COSY spectrum showed that the olefinic proton was coupled to both vinyl methyl groups as well as to a strongly deshielded methylene group [δ_H 4.09 (2H, *d*, J = 6.8 Hz, H_2-15)] indicating the presence of a 3-methylbut-2-enyl substituent. The chemical shift of the methylene protons revealed that this substituent must be attached to the xanthone nucleus *peri* to the carbonyl group [2]. In the heteronuclear multiple bond correlation (HMBC) spectrum [3] (Table 2), the olefinic proton showed five correlations, four due to ^2J and ^3J couplings within the 3-methylbut-2-enyl substituent with the fifth being a ^3J coupling to an aromatic carbon (C-8). The protons of the methylene group also showed correlations with carbons of the 3-methylbut-2-enyl group as well as a ^2J correlation to C-8. Two additional ^3J correlations allowed the identification of C-7 and C-8a with the former carbon being distinguished by a ^3J correlation to protons of its methoxyl substituent. The more deshielded aromatic proton showed four correlations with aromatic carbons, two of which were C-7 and C-8a. It followed that this proton must be attached to C-5 since no correlation with C-8 was observed. The other two carbons could then be assigned as C-4b and C-6, although no differentiation could be made between them. Both positions carried an oxygen substituent, a hydroxyl at C-6 and the xanthone ether linkage at C-4b. The nature of the C-6 substituent was unequivocally established by difference NOE studies upon the dimethyl ether derivative (**2**). Irradiation of the most deshielded methoxyl group [δ_H 3.93 (6-OMe)] enhanced the signal due to H-5, showing that the parent compound **1** had a free hydroxyl group attached to C-6.

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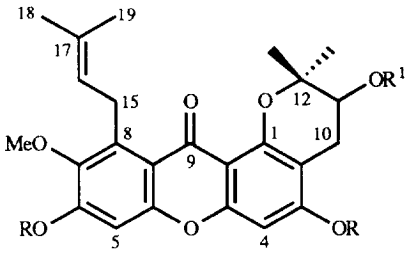
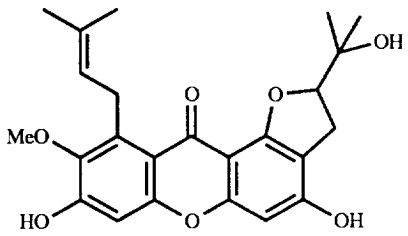


1 R = R^1 = H
2 R = Me; R^1 = H
4 R = Me; R^1 = Ac



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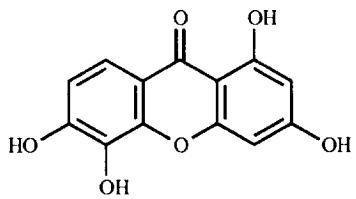

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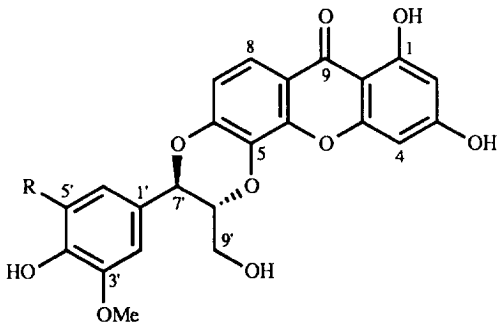


	R
6	H
7	OMe

After establishing the nature of one ring, it followed that the other ring carried the second phenolic hydroxyl group and the more shielded aromatic proton as well as two other substituents. Each set of tertiary methyl protons showed a ^2J correlation to an oxygenated singlet carbon as well as a ^3J correlation to the oxygenated methine carbon. The oxygenated methine proton in turn showed correlations to the tertiary methyl carbons (^3J), the oxygenated singlet carbon (^2J), the vicinal methylene carbon (^2J) and an aromatic carbon (^3J). These observations, as well as the remaining unassigned unit of unsaturation, could be accommodated in a 2,2-dimethylchroman-3-ol moiety. The dihydropyran ring must be positioned at C-1 and C-2 of the xanthone nucleus since, as previously mentioned, the compound lacked *peri* hydrogens and hydroxyls. The observation of ^3J correlations between the dihydropyran methylene protons and two oxygenated aromatic carbons established that C-1 carried the ether oxygen and that C-3 was hydroxylated. Thus, the remaining unsubstituted aromatic carbon could be assigned as C-4. Compound **1** is therefore 11-hydroxy-1-isomangostin. Irradiation of the C-3 methoxyl protons of the dimethyl ether derivative (**2**) caused enhancements of the resonances due to H-4 and H_2-10. An isomeric structure (**3**) could be discounted as **2** readily formed a monoacetate (**4**) which showed the expected deshielding of H-11 ($\Delta\delta_H$ = 1.23). The ^{1}H and ^{13}C NMR chemical shifts for **1**, **2** and **4** are given in Table 1. Compound **1** is the 11-hydroxylated analogue of 1-isomangostin, a metabolite of *Garcinia mangostana* [4]. Their ^{1}H NMR shifts were in good agreement.

The second compound (**5**) was also a xanthone. Its ^{1}H NMR spectrum (see Experimental) contained signals for a chelated phenolic hydroxyl group, and two pairs of aromatic protons, one *meta*-coupled and the other *ortho*-coupled. The mass spectrum showed the molecular ion at *m/z* 260, consistent with the molecular formula $C_{13}H_8O_6$ and with the presence of four hydroxyl groups. Comparison of the physical data with literature values established the identity of **5** as 1,3,5,6-tetrahydroxyxanthone [5].

The third compound, 5′-demethoxycadensin G (**6**), $C_{23}H_{18}O_9$ (*m/z* 438.0946) possessed a ^{1}H NMR spectrum (Table 3) that included resonances which were almost identical to those of 1,3,5,6-tetrahydroxyxanthone [δ_H 13.07 (1H, *s*, 1-OH), 7.70 (1H, *d*, *J* = 8.9 Hz, H-8), 7.01 (1H, *d*, *J* = 8.9 Hz, H-7), 6.47 (1H, *d*, *J* = 2.1 Hz, H-4) and 6.26 (1H, *d*, *J* = 2.1 Hz, H-2)]. A combination of HMQC and HMBC spectroscopy (Table 4) helped to identify all of the carbon atoms of this subunit. In addition, there were signals in the ^{1}H NMR spectrum characteristic of three aromatic protons [δ_H 7.18 (1H, *d*, *J* = 1.9 Hz, H-2′), 7.03 (1H, *dd*, *J* = 1.9 Hz, J_{AB} = 8.0 Hz, H-6′), 6.92 (1H, *d*, J_{AB} = 8.0 Hz, H-5′)], two oxygenated methines [δ_H 5.21 (1H, *d*, *J* = 7.9 Hz, H-7) and 4.32 (1H, *ddd*, *J* = 2.5, 3.7, and 7.9 Hz, H-8)], a hydroxymethyl [δ_H 3.94 (1H, *dd*, *J* = 3.7 Hz, J_{AB} = 12.6 Hz, H-9′) and 3.63 (1H, *dd*, *J* = 2.5 Hz, J_{AB} = 12.6 Hz, H-9′)] and a methoxyl group [δ_H 3.89 (3H, *s*, OMe)]. The COSY spectrum showed that the oxygenated methines and hydroxymethyl form a linear system whilst the further deshielding of the end methine indicated its attachment to the trisubstituted

Table 1. ^1H (500 MHz) and ^{13}C (125 MHz) NMR shifts for compounds **1**, **2** and **4**

H	1*	2†	4†	C	1*	2†	4†
4	6.40 *s*	6.35 *s*	6.36 *s*	1	155.9[a]	154.2[a]	154.2[a]
5	6.72 *s*	6.68 *s*	6.68 *s*	2	105.0	103.9	103.3
10	2.56 *dd* (7.8, 16.8)	2.68 *dd* (5.3, 17.3)	2.66 *dd* (5.5, 17.5)	3	161.0	161.6	161.2
	2.94 *dd* (5.7, 16.8)	2.87 *dd* (5.3, 17.3)	2.98 *dd* (5.5, 17.5)	4	94.2	90.3	90.2
11	3.82 *dd* (5.7, 7.8)	3.80 *br t* (5.3)	5.05 *t* (5.5)	4a	157.6	157.2[b]	157.2[b]
13	1.30[a] *s*	1.40[a] *s*	1.42[a] *s*	4b	154.9[a]	154.1[a]	154.1[a]
14	1.43[a] *s*	1.47[a] *s*	1.43[a] *s*	5	102.1	97.8	97.8
15	4.09 *d* (6.8)	4.10 *m*	4.12 *m*	6	155.8[a]	156.7[b]	156.7[b]
16	5.31 *br t* (6.8)	5.33 *m*	5.21 *br t* (6.7)	7	144.3	144.0	144.0
18	1.81 *br s*	1.83 *br s*	1.84 *br s*	8	137.6	137.4	137.4
19	1.64 *br s*	1.66 *br s*	1.67 *br s*	8a	115.1	115.2	115.2
3-OMe		3.88 *s*	3.88[b] *s*	9	176.3	176.3	176.2
6-OMe		3.93 *s*	3.93[b] *s*	9a	107.7	108.2	108.2
7-OMe	3.77 *s*	3.78 *s*	3.78 *s*	10	27.1	26.4	23.6
11-OAc			2.07 *s*	11	69.0	68.7	70.2
				12	78.5	77.9	77.3
				13	20.6[b]	22.0[c]	21.1[b]
				14	26.0[b]	25.9[c]	25.9[b]
				15	26.6	26.0	26.0
				16	125.8	124.1	124.1
				17	130.5	131.0	130.9
				18	26.1	24.6	24.8
				19	18.3	18.2	18.2
				3-OMe		55.7[d]	55.7[d]
				6-OMe		55.9[d]	55.8[d]
				7-OMe	61.0	60.8	60.8
				11-OAc			22.4
							170.6

*In acetone-d_6.
†In $CDCl_3$.
[a–d]Signals within a column may by interchanged.
Assignments for **1** are based on COSY, HMQC and HMBC experiments.

Table 2. HMBC correlations observed for compound **1** (^1H: 500 MHz, acetone-d_6)

H	Correlations to
4	^2J: C-3, C-4a
	^3J: C-2, C-9a
5	^2J: C-4b, C-6
	^3J: C-7, C-8a
10	^2J: C-2, C-11
	^3J: C-1, C-3, C-12
11	^2J: C-12
	^3J: C-2, C-13, C-14
13, 14	^2J: C-12
	^3J: C-11
15	^2J: C-8, C-16
	^3J: C-7, C-8a, C-17
16	^3J: C-8, C-18
18	^2J: C-17
	^3J: C-16, C-19
19	^2J: C-17
	^3J: C-16, C-18
7-OMe	^3J: C-7

benzene ring, The HMBC spectrum (Table 4) showed a ^3J correlation between the more shielded methine proton and one of the aromatic carbons (C-1′), thus identifying the site of attachment of the three carbon chain to the benzene ring. Similarly, ^3J correlations of the benzylic methine proton served to identify C-2′ and C-6′. The multiplicity of H-6′ revealed that C-5′ was also unsubstituted and therefore that C-3′ and C-4′ were both substituted. The methoxyl protons correlated with one of the oxygenated benzene carbons and this must be C-3′ as both H-2′ and H-6′ showed a ^3J correlation to a second oxygenated aromatic carbon (C-4′). This phenylpropanoid moiety and the tetrahydroxyxanthone were combined to give a xanthonolignoid structure (**6**) where H-7′ and H-8′ are *trans* orientated. This structure was supported by the presence of mass spectral peaks at *m/z* 180 (coniferyl alcohol) and *m/z* 260 (tetrahydroxyxanthone).

Efforts to determine unambiguously the orientation of the xanthone–phenylpropanoid ether linkages by both HMBC and SINEPT [6] experiments were unsuccessful since no correlations between the two subunits were observed. Presumably this is because the H–C–C–C

Table 3. ^{1}H and ^{13}C NMR shifts for compounds **6** and **7**

H	6*	6†	7†‡	C	6*	C	6*
1-OH	13.07 *s*	12.97 *s*	12.97 *s*	1	164.8	1′	128.4
2	6.26 *d* (2.1)	6.35 *br s*	6.38 *d* (1.1)	2	99.2	2′	112.2
4	6.47 *d* (2.1)	6.16 *br s*	6.19 *d* (1.1)	3	166.3	3′	148.7
7	7.01 *d* (8.9)	7.05 *d* (8.8)	7.05 *d* (8.8)	4	94.9	4′	148.4
8	7.70 *d* (8.9)	7.62 *d* (8.8)	7.61 *d* (8.8)	4a	158.8	5′	115.9
2′	7.18 *d* (1.9)	7.05 *d* (1.8)	6.77 *s*	4b	147.2	6′	121.8
5′	6.92 *d* (8.0)	6.82 *d* (8.1)	—	5	115.7	7′	77.9
6′	7.03 *dd* (1.9, 8.0)	6.90 *dd* (1.8, 8.1)	6.77 *s*	6	150.3	8′	79.7
7′	5.21 *d* (7.9)	5.12 *d* (7.8)	5.10 *d* (7.8)	7	114.5	9′	61.6
8′	4.32 *ddd* (2.5, 3.7, 7.9)	4.35 *m*	4.35 *m*	8	117.8	3′-OMe	56.5
9′	3.63 *dd* (2.5, 12.6)	3.42 *m*	3.42 *dd* (4.3, 12.2)	8a	132.9		
	3.94 *dd* (3.7, 12.6)	3.71 *m*	3.67 *m*				
3′-OMe	3.89 *s*	3.79 *s*	3.74 *s*	9	180.8		
5′-OMe			3.74 *s*	9a	103.3		

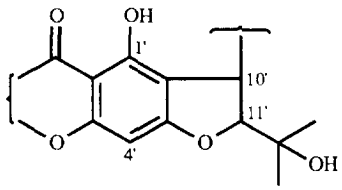
*In acetone-d_6.
†In DMSO-d_6.
‡Taken from ref. [7].

Table 4. HMBC correlations observed for compound **6** (^{1}H: 500 MHz, acetone-d_6)

H	Correlations to
1-OH	^2J: C-1,
	^3J: C-2, C-9a
2	^2J: C-1, C-3
	^3J: C-4, C-9a
4	^2J: C-3, C-4a
	^3J: C-2, C-9a
7	^2J: C-6
	^3J: C-5, C-8a
8	^2J: C-8a
	^3J: C-4b, C-6, C-9
2′	^2J: C-1′
	^3J: C-4′, C-6′, C-7′
5′	^2J: C-6′
	^3J: C-1′, C-3′
6′	^3J: C-4′, C-7′
7′	^2J: C-1′, C-8′
	^3J: C-2′, C-6′, C-9′
8′	^2J: C-7′
9′	^2J: C-8′
	^3J: C-7′
3′-OMe	^3J: C-3′

dihedral angle is close to 90° and the corresponding ^3J value is close to zero. The orientation is assumed to be the same as that established for the other cadensins because of the close similarity between the ^{1}H NMR spectrum of **6** and that of its methoxylated analogue cadensin G (**7**) from *Psorospermum febrifugum* [7] (Table 3). The assignment of the ^{13}C NMR spectrum (Table 3) is based upon HMQC and HMBC experiments (Table 4).

The final compound, which ^{1}H and ^{13}C NMR revealed to be a dimethyl ether, could not be obtained sufficiently pure for spectroscopic analysis even after HPLC on C_{18} cyano and diol packings. It was therefore converted to the corresponding pentamethyl ether (**10**) which could be obtained in a purer state. The UV spectrum of **10** suggested a xanthone structure, whilst the complexity of the ^{1}H and ^{13}C NMR spectra suggested a bisxanthone structure. This was supported by the CI-mass spectrum which contained peaks at *m/z* 877 ($[M+H]^+$) and 878 ($[M+2H]^+$). The ^{1}H NMR spectrum (Table 5) of the pentamethyl ether showed two very deshielded singlets indicating the presence of two chelated hydroxyl groups. In addition, the resonances for three aromatic protons and three 3-methylbut-2-enyl substituents could be discerned. This left three nuclear substituents as well as one unit of unsaturation unaccounted for. In addition to the above groups, there were signals due to two vicinal deshielded methines, one without an oxygen substituent [δ_H 5.18 (1H, *d*, $J=6.0$ Hz); δ_C 36.7 (*d*)] and one bearing an oxygen [δ_H 4.71 (1H, *d*, $J=6.0$ Hz); δ_C 98.2 (*d*)], a tetrasubstituted oxygenated carbon [δ_C 92.8 (*s*)] and two tertiary methyls [δ_H 1.32 and 1.29 (each 3H, *s*); δ_C 18.2 and 25.8 (each *q*)]. HMBC spectroscopy (Table 6) was extremely useful in elucidating the structure of this compound. The correlations of the more deshielded chelated hydroxyl proton [OH-1′] and of the aromatic proton at δ_H 6.45 [H-4′] established the resonances due to one aromatic ring, thus showing its 1,3-dioxygenated nature. The deshielded methine proton at δ_H 5.18 [H-10′] showed correlations with C-1′, C-2′ and C-3′ of this aromatic ring, clearly establishing that the methine carbon is attached to C-2′ and distinguishing between C-2′ and C-9a′ and between C-3′ and C-4a′. The oxygenated methine proton also showed a correlation to C-3′ which could only be explained if the methine and the aromatic carbon were connected by an ether oxygen. Correlations between the two methine protons and the oxygenated singlet carbon and the two tertiary methyl carbons established the presence of part structure **8**. H-10′ showed additional correlations to three other aromatic carbons (C-3, C-4



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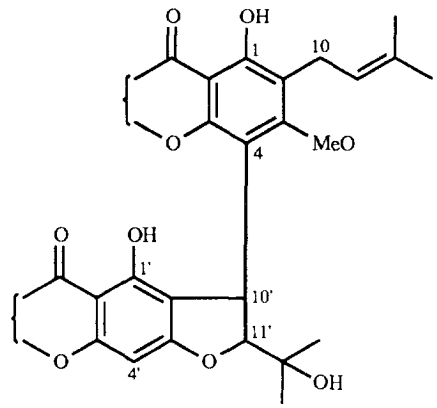

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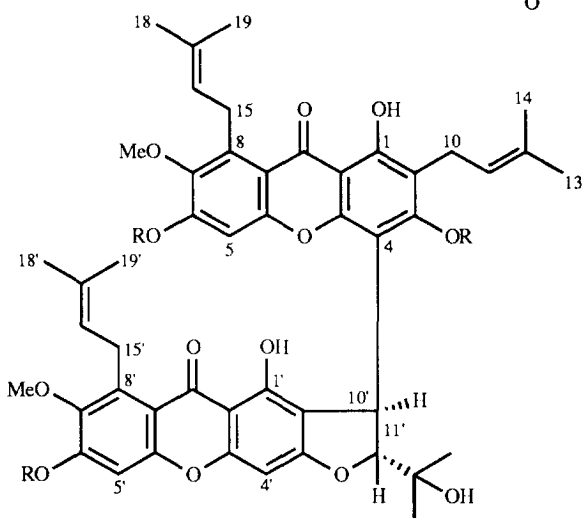


	R
10	Me
11	H

and C-4a), one of which (C-4) also correlated with H-11′. A methoxyl group was placed at C-3 because of its correlation with the most deshielded methoxyl protons. Further correlations between the protons of a 3-methylbut-2-enyl methylene group [H_2-10] and C-1, C-2 and C-3, and between the other chelated hydroxyl proton [1-OH] and C-1, C-2 and C-9a extended part structure **8** to give **9**. NOE difference spectroscopy revealed the *trans* nature of H-10′ and H-11′; saturation of either proton enhanced the resonance due to the other proton.

The two remaining rings between them bear four methoxyl groups, two 3-methylbut-2-enyl groups and two aromatic protons. The ^2J and ^3J correlations observed between the 3-methylbut-2-enyl group protons and the aromatic carbons and between the aromatic protons and the aromatic carbons indicated that each ring carried the same substituents and that the 3-methylbut-2-enyl group was *para* to an aromatic proton. The aromatic protons must therefore be attached to C-5 and C-5′ since they were not sufficiently deshielded to be in *peri* positions and also because no correlations were observed between the aromatic hydrogens and the carbonyl groups. The chemical shifts of the 3-methylbut-2-enyl methylene groups were in agreement with their being attached to C-8 and C-8′. C-6, C-6′, C-7 and C-7′ must therefore carry methoxyl groups and this was borne out by the observed HMBC correlations. Although it was not possible to observe correlations across the central ring of each xanthone nucleus, it was nevertheless possible to assign the signals to the B and B′ rings on the basis of the chemical shifts of H-5 and H-5′. The chemical shift observed for H-5 of a xanthone with the same B-ring substitution pattern is *ca* 6.8 ppm. One of the protons was thus significantly deshielded. This could be assigned as H-5 of cratoxyxanthone since this proton would be expected to lie in the shielding zone of the second xanthone nucleus.

The original compound differed from **10** only in that it possessed two methoxyl groups rather than five. Their ^{13}C NMR shifts [δ_C 61.8 (*q*) and 61.9 (*q*)] indicated that they were *ortho*-disubstituted limiting them to positions C-3, C-7 and C-7′. The C-3 methoxyl of **11** was significantly more deshielded than the other methoxyl groups, presumably due to its proximity to the ring current of the other xanthone nucleus. The ^{1}H and ^{13}C NMR spectra of the original compound did not contain any resonances characteristic of this C-3 methoxyl. The original natural product, cratoxyxanthone, must therefore be **11**.

Table 5. ^1H (500 MHz) and ^{13}C NMR (125 MHz) chemical shifts for **10** in $CDCl_3$

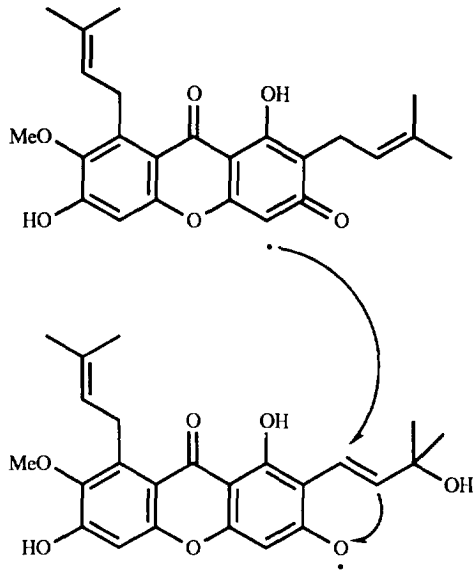
Pos.	δ_H	δ_C	Pos.	δ_H	δ_C
1	13.47 *s* (OH)	160.3	1′	13.50 *s* (OH)	158.4
2		116.9	2′		110.6
3		161.9	3′		167.4
4		112.0	4′	6.45 *s*	86.8
4a		152.4	4a′		157.5
4b		155.1	4b′		155.4
5		97.9	5′		98.2
6	6.34 *s*	158.3	6′	6.75 *s*	158.1
7		144.1	7′		144.3
8		137.4	8′		137.4
8a		111.8	8a′		112.0
9		182.6[a]	9′		182.1[a]
9a		106.8	9a′		104.3
10	3.28 *dd* (5.8, 14.6) 3.46 *dd* (7.6, 14.6)	22.8	10′	5.18 *d* (6.0)	36.7
11	5.31 *br t* (6.2)	122.7	11′	4.71 *d* (6.0)	98.2
12		131.7	12′		92.8
13	1.72 *br s*	25.8	13′	1.29 *s*	23.8[b]
14	1.82 *br s*	18.0	14′	1.32 *s*	25.6[b]
15	4.04 *m*	22.1[c]	15′	4.04 *m*	26.2[c]
16	5.13 *br t* (6.0)	123.1	16′	5.13 *br t* (6.0)	123.1
17		131.7	17′		131.7
18	1.61	25.8	18′	1.62	25.8
19	1.79	18.2	19′	1.79	18.2
3-OMe	4.11 *s*	62.3			
6-OMe	3.87 *s*	55.8	6′-OMe	3.96 *s*	56.0
7-OMe	3.71 *s*	60.9	7′-OMe	3.76 *s*	60.9

[a–c]Interchangeable assignments.

Table 6. HMBC correlations observed for compound **10** (^1H: 500 MHz, $CDCl_3$)

H	Correlations to	H	Correlations to
1-OH	^2J: C-1	1′-OH	^2J: C-1′
	^3J: C-2, C-9a		^3J: C-2′, C-9a′
		4′	^2J: C-3′, C-4a′
			^3J: C-2′, C-9a′
5	^2J: C-4b, C-6	5′	^2J: C-4b′, C-6′
	^3J: C-7		^3J: C-7′
10	^2J: C-2, C-11	10′	^2J: C-4, C-2′, C-11′
	^3J: C-1, C-3, C-12		^3J: C-3, C-4a, C-1′, C-3′, C-12′
11	^3J: C-13, C-14	11′	^2J: C-10′
			^3J: C-4, C-3′, C-13′, C-14′
13, 14	^2J: C-12	13′, 14′	^2J: C-12′
	^3J: C-11		^3J: C-11′
15	^2J: C-8, C-16	15′	^2J: C-8′, C-16′
	^3J: C-7, C-8a, C-17		^3J: C-7′, C-8a′, C-17′
16	^3J: C-8, C-18, C-19	16′	^3J: C-8′, C-18′, C-19′
18, 19	^2J: C-17	18′, 19′	^2J: C-17′
	^3J: C-16		^3J: C-16′
3-OMe	^3J: C-3		
6-OMe	^3J: C-6	6′-OMe	^3J: C-6′
7-OMe	^3J: C-7	7′-OMe	^3J: C-7′

Naturally occurring bisxanthones which have previously been reported include ether-linked C-glucosides from *Swertia punicea* [8], chiratanin, an Ar-O-Ar′ ether-linked bisxanthone from *Swertia chirata* [9], bis-tetrahydroxyxanthones from fungi and lichens [10, 11], Ar-Ar′-linked compounds from *Ploiarium alternifolium* [12] and *Swertia macrosperma* [13], the garcilivins from *Garcinia livingstonei* which are linked through 3-methyl-2-butenyl side chains [14] and the mesuabixanthones from *Mesua ferrea* [15]. Cratoxyxanthone is the first example of a



Scheme 1.

bisxanthone with the xanthone–xanthone linkage between an aromatic carbon and a C_5 side chain. It can be envisaged as arising from the coupling of two mangostin-derived radicals as depicted in Scheme 1.

EXPERIMENTAL

UV: MeOH. IR: KBr. $[\alpha]_D$: $CHCl_3$. ^1H NMR: 500 MHz and ^{13}C NMR: 125 MHz, in $CDCl_3$ (unless otherwise specified) relative to TMS at δ0.00. ^{13}C NMR multiplicities were determined using the DEPT pulse sequence. 2D and difference NOE experiments were carried out using standard Bruker micropragrammes. Difference NOE spectra were recorded using a relaxation delay of 2.5 s and a total irradiation time of 2 s.

DQF Phase-sensitive COSY experiments were run using 90 degree pulses and a relaxation delay of 2 s. In t_1, 512 increments were used with zero-filling to 1 K before 2D Fourier transformation. In t_2, 2 K points were used with no zero-filling. Gaussian multiplication was used in both dimensions to emphasize cross-peaks.

Proton-detected HMQC experiments were optimized for $^1J_{CH}$ = 140 Hz. The relaxation delay was 2.5 s. In t_1, 512 increments were used with zero-filling to 1 K before 2D Fourier transformation. In t_2, 2 K points were used with no zero-filling. Gaussian multiplication was used in both dimensions to improve the signal to noise ratio and to suppress truncation errors. Proton-detected HMBC experiments were performed under the same conditions with the addition of modulation tuning which was optimized for $^nJ_{CH}$ = 10 Hz.

Minor polar frs were available from an earlier study of the extract [1]. Repeated HPLC purification gave 11-hydroxy-1-isomangostin (**1**, 5 mg, silica gel, 4.6 × 250 mm, 45% EtOAc–hexane), 1,3,5,6-tetrahydroxyxanthone (**5**, 2 mg, C_{18} 5 μm, 4.6 × 250 mm, 80% Me_2CO–H_2O), 5′-demethoxycadensin G (**6**, 9 mg, silica gel, 4.6 × 250 mm, 45% EtOAc–hexane) and an impure bisxanthone, cratoxyxanthone (**10**, 49 mg, C_{18} 5 μm, 4.6 × 250 mm, 80% Me_2CO–H_2O).

11-Hydroxy-1-isomangostin (**1**). Yellow gum, $[\alpha]_D$ 0.0 (*c* 0.9), *m/z* 426.1676 ($C_{24}H_{26}O_7$ requires *m/z* 426.1679). UV λ_{max} nm (log ε): 244 (4.35), 306 (4.10), 336 (3.87). IR ν_{max} (KBr) cm^{-1}: 3450 (br, OH), 1623 (chelated C=O), 1612 (aromatic ring). EIMS 70 eV *m/z* (rel. int.): 426 ($[M]^+$, 71), 411 (26), 393 (16), 383 (31), 355 (62), 339 (100), 323 (18), 311 (16), 299 (13), 285 (22), 71 (17), 69 (15), 57 (22). ^1H and ^{13}C NMR: see Tables 1 and 2.

11-Hydroxy-3,6-di-O-methyl-1-isomangostin (**2**). 11-Hydroxy-1-isomangostin (4 mg) was methylated using MeI–K_2CO_3 in Me_2CO to afford, after flash chromatography (silica gel, EtOAc–hexane) and HPLC (silica, 5 μ, 40% EtOAc–hexane), the dimethyl ether derivative (3 mg), as a gum, *m/z* 454.1981 ($C_{26}H_{30}O_7$ requires *m/z* 454.1992). UV λ_{max} nm (log ε): 254 (4.34), 286 (4.01), 298 (4.12), 334 (4.12). IR ν_{max} ($CHCl_3$) cm^{-1}: 3390 (br, OH), 1635 (C=O), 1593 (aromatic ring). EIMS 70 eV *m/z* (rel. int.): 454 ($[M]^+$, 53), 440 (14), 412 (25), 411 (15), 386 (10), 383 (100), 382 (41), 368 (49), 367 (39), 352 (25), 339 (11), 328 (10), 314 (19). ^1H and ^{13}C NMR: see Table 1.

11-Acetoxy-3,6-di-O-methyl-1-isomangostin (**4**). The 3,6-dimethyl ether (3 mg) was acetylated with acetic anhydride–pyridine in the usual manner to yield, after HPLC (silica, 5 μ, 40% EtOAc–hexane), the monoacetate (3 mg), as a gum, *m/z* 496.2098 ($C_{28}H_{32}O_8$ requires *m/z* 496.2097). UV λ_{max} nm (log ε): 244 (4.2), 254 (4.2), 302 (3.9), 336 (3.6). IR ν_{max} ($CHCl_3$) cm^{-1}: 1723 (MeCO), 1636 (C=O), 1592 (aromatic ring). EIMS 70 eV *m/z* (rel. int.): 496 ($[M]^+$, 63), 454 (27), 453 (16), 437 (10), 422 (22), 421 (17), 394 (11), 393 (11), 384 (29), 383 (44), 382 (34), 369 (13), 368 (57), 367 (28), 353 (14), 352 (18), 351 (15), 350 (15), 339 (10), 316 (18), 314 (25), 313 (13), 191 (10), 187 (10), 149 (20), 121 (13), 111 (20). ^1H and ^{13}C NMR: see Table 1.

1,3,5,6-Tetrahydroxyxanthone (**5**). UV λ_{max} nm (log ε: 246 (3.9), 282 (3.5), 328 (3.6). IR ν_{max} (KBr) cm^{-1}: 3440 (br, OH), 1641 (C=O), 1599. EIMS 70 eV *m/z* (rel. int.): 260 ($[M]^+$, 100), 116 (9), 84 (17), 57 (12). ^1H NMR (Me_2CO-d_6): 13.19 (1H, *s*, OH), 7.61 (1H, *d*, *J* = 8.7 Hz, H-8), 6.96 (1H, *d*, *J* = 8.7 Hz, H-7), 6.42 (1H, *d*, *J* = 2.0 Hz, H-4), and 6.22 (1H, *d*, *J* = 2.0 Hz, H-2). ^{13}C NMR (Me_2CO-d_6): 181.1, 165.9, 164.8, 158.8, 152.4, 145.9, 133.4, 117.3, 114.7, 113.7, 103.0, 98.8, 94.7.

5′-Demethoxycadensin G (**6**). Gum, *m/z* 438.0946 ($C_{23}H_{18}O_9$ requires *m/z* 438.0951). UV λ_{max} nm (log ε): 250 (4.8), 282 (4.2), 320 (4.4). IR ν_{max} cm^{-1} (KBr): 3400 (br, OH), 1640 (C=O), 1604, 1567, 1504, 1440, 1271, 1101. EIMS 70 eV *m/z* (rel. int.): 438 ($[M]^+$, 16), 301 (25), 261 (16), 260 (100), 180 (28), 137 (38), 124 (15), 119 (10). ^1H and ^{13}C NMR: see Table 3.

Cratoxyxanthone (**10**). ^1H NMR: 13.65 (1H, *s*, OH), 13.50 (1H, *s*, OH), 6.47 (1H, *s*), 6.38 (1H, *s*), 6.18 (1H, *br s*), 5.45 (1H, *d*, *J* = 5.0 Hz), 5.35 (1H, *br t*, *J* = 7.2 Hz), 5.29 (1H, *m*), 5.10 (1H, *m*), 4.71 (1H, *d*, *J* = 5.1 Hz), 4.01 (4H, *m*), 3.80 (3H, *s*, OMe), 3.66 (3H, *s*. OMe), 3.50 (1H, *d J* = 6.9 Hz), 1.87, 1.83, 1.75, 1.75, 1.73, 1.59 (each 3H, *br s*, vinyl methyl), 1.51 and 1.42 (each 3H, *s*, Me). ^{13}C NMR: 180.2 (*s*, C=O), 181.6 (*s*, C=O), 167.2 *s*), 159.3 (*s*), 159.0

(*s*), 156.7 (*s*), 155.1 (*s*), 154.9 (*s*), 154.5 (*s*), 154.3 (*s*), 153.0 (*s*), 142.6 (*s*), 142.5 (*s*), 136.9 (*s*), 136.7 (*s*), 133.4 (*s*), 132.0 (*s*), 132.0 (*s*), 123.3 (*d*), 123.1 (*d*), 122.1 (*d*), 111.9 (*s*), 111.5 (*s*), 111.1 (*s*), 110.6 (*s*), 105.9 (*s*), 104.2 (*s*), 103.6 (*s*), 101.3 (*d*), 101.2 (*d*), 97.7 (*d*), 87.9 (*d*), 73.8 (*s*), 61.9 (*q*), 61.8 (*q*), 35.9 (*d*), 26.4 (*t*), 26.4 (*t*), 26.2 (*q*), 25.9 (*q*), 25.9 (*q*), 25.7 (*q*), 23.6 (*q*), 22.1 (*t*), 18.2 (*q*), 18.2 (*q*), 18.0 (*q*).

Cratoxyxanthone trimethyl ether: Crude cratoxyxanthone (25 mg) was methylated in the usual manner and purified by flash chromatography (silica, EtOAc–hexane gradient) and HPLC to give a gum (20 mg). UV λ_{max} nm (log ε): 246 (4.53), 262 (4.58), 3.10 (4.40), 350 (3.90). IR ν_{max} cm^{-1} (KBr): 1631 (C=O), 1600, 1594 (aromatic ring). EIMS 70 eV *m/z* (rel. int.): 438 (32), 420 (7), 395 (50), 380 (68), 367 (32), 337 (100), 323 (13), 293 (7), 176 (12). CIMS (reagent gas CH_4) *m/z* (rel. int.): 878 ($[M+2]^+$, 2), 877 ($[M+1]^+$, 2), 876 ($[M]^+$, 1), 480 (4), 468 (5), 467 (18), 439 (100), 437 (23), 421 (26), 383 (15), 381 (23). ^1H and ^{13}C NMR: see Table 5.

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