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SEVEN XANTHONOLIGNOIDS FROM *PSOROSPERMUM FEBRIFUGUM*

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Key Word Index—*Psorospermum febrifugum*; Guttiferae; Vismieae; xanthonolignoids; cadensin G.

Abstract—Chemical investigation of ethanolic extract of *Psorospermum febrifugum* has led to the isolation of seven xanthonolignoids. This paper represents the first report on the presence of xanthonolignoids in the genus *Psorospermum*. Five of these compounds are new natural products. Only marginal cytotoxic activity has been found to be associated with members of this group of xanthones.

INTRODUCTION

The significant antitumour and cytotoxic activities associated with the ethanolic extract of *Psorospermum febrifugum* have promoted a detailed chemical investigation of the plant extract. Prior studies in our laboratory have established the absolute stereochemistry and routes to the synthesis of the parent antileukemic furanoxanthone, psorospermin [1]. In a continuing search for antitumour agents, recent investigations have revealed a series of new biologically active furanoxanthones [2] and vismiones. In this investigation, we now wish to report the isolation and biological evaluation of the first reported xanthonolignoids from the genus *Psorospermum*.

Xanthonolignoids represent a rare class of natural products having only five compounds previously reported [3]. A procedure has been established to determine the regiochemistry of the site of ring fusion.

RESULTS AND DISCUSSION

The fractionation of the ethanolic extract of *P. febrifugum* has been described in a previous report [2]. In addition to the furanoxanthones and vismiones, bioactivity directed isolation has led to the isolation of a series of new compounds belonging to the xanthonolignoid group. The structures of these compounds were established based upon data from UV, IR, MS, ^{1}H and ^{13}C NMR analysis. A polyoxygenated xanthone nucleus was suggested for all of the compounds based on IR and UV spectra. Mass spectral analysis was of particular significance in elucidating their structures based on the major ion fragments which were produced through cleavage of the dioxane ring. The *m/z* values observed for F_1 and F_2 or F_3 indicate the number of hydroxyl or methoxyl groups attached to either the xanthone framework or the cinnamoyl alcohol component of the molecule (Table 1).

The substitution pattern around the aromatic systems was further analysed by ^{1}H NMR. A four-spin system consisting of a doublet at *ca* 5 ppm coupled to a double doublet of doublets at *ca* 4.4 ppm and two double doublets at *ca* 3.7 and 3.4 ppm is reminiscent of the cinnamoyl-1,4-dioxane ring (Table 2).

A molecular formula of $C_{24}H_{20}O_8$ and $C_{25}H_{22}O_9$ were established for compounds **1** and **2**, respectively, by high resolution mass measurements. All spectral data indicated that compound **1** was a dimethoxylated xanthonolignoid, kielcorin [3], while compound **2** was a trimethoxylated homologue, cadensin D [4–6]. Accurate mass measurement indicated that compound **3** has the same molecular formula ($C_{25}H_{22}O_9$) as compound **2**. The difference in the *m/z* values observed for F_1, F_2, and F_3 in the mass spectrum of **3**, when compared to that of **2**, suggested that compound **3** is also a trimethoxylated xanthonolignoid with two methoxyl groups attached to the xanthone nucleus and only one to the phenyl group (Table 1). The ^{1}H NMR of **3** showed signals for seven aromatic protons in the downfield portion of the spectrum. A contiguous three-spin system consisting of a pair of doublets and a triplet accounts for three adjacent spins of ring A protons and a singlet at δ7.1 for the C-1 proton was observed. The absence of a downfield signal at *ca* δ8.3 suggested the methoxyl substitution at the C-8 position. The multiplicity of the remaining three aromatic protons indicated a 1,3,4-substitution pattern on the cinnamoyl portion as the C-6 proton appears as a double doublet with *J* values corresponding to *ortho* and *meta* coupling with the 5′ and 2′ protons respectively. The presence of a phenolic OH group at the 4′ position and the regiochemistry of the C_3 unit relative to the phenyl group were confirmed by base catalysed ring opening of the dioxane ring. The structure of isocadensin D (**3**) was further confirmed by ^{13}C NMR as the carbon chemical shift values obtained for **3** were found to be comparable to those reported for kielcorin. The presence of a significant $[M-60]^+$ ion fragment, and an absorption band at 1730 cm^{-1} in the IR spectrum of **4** and the presence of a singlet at δ2.00 integrating for three protons suggested the presence of an acetate group in the structure of **4**. The

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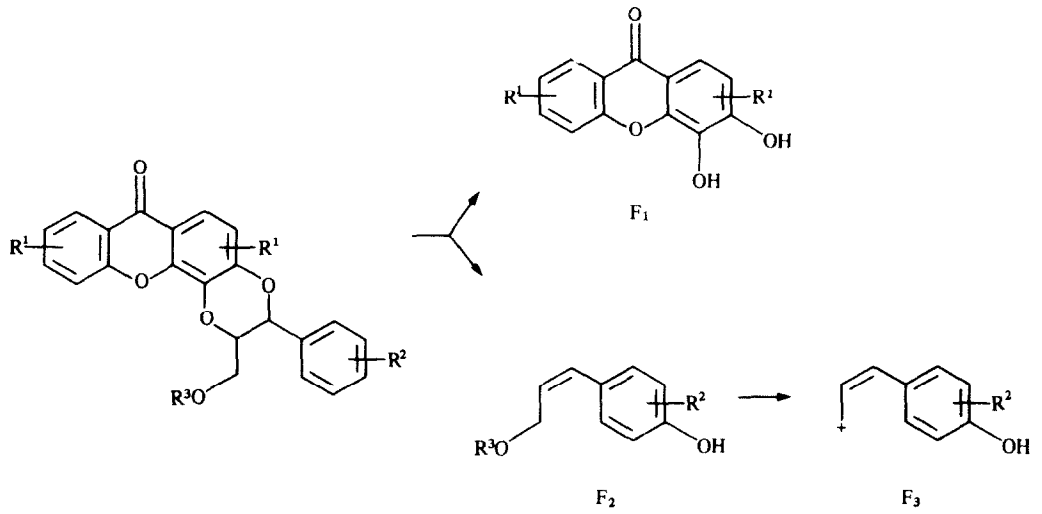
Table 1.



Compound	M + H+	F1 + H+	F2 + H+	F3	Others
1	437(13)	259(62)	181(72)	163(100)	275(31)
2	467(100)	259(63)	211(55)	193(72)	287(15)
3	467(32)	289(82)	181(72)	163(100)	303(5)
4	509(6)	289(53)	181(38)	163(88)	449(86)
					303(20)
5	497(11)	289(100)	211(39)	193(84)	163(27)
					467(3)
6	513(0,5)	305(26)	211(100)	193(68)	163(39)
7	469(32)	261(100)	211(67)	193(74)	

*MS data were obtained in CI mode with CH_4 as reagent gas.

†Most of the structural formulae were confirmed by accurate mass measurements in EI mode.

mass fragmentation pattern of compound **4** was found to have the same 2,8,3′-trimethoxylated xanthonolignoid skeleton as that of compound **3**. The resonance of the C-9′ protons at a relatively downfield position at δ3.97 and 4.33, (Table 2) indicates that the acetoxy function is attached to the C-9′ position. Compound **4** was thus identified to be isocadensin D monoacetate.

High resolution mass analysis indicated a molecular formula of $C_{26}H_{24}O_{10}$ for compound **5**. Other spectral data indicated a tetramethoxylated xanthonolignoid framework. With the ion fragment F_1 and F_2 having been observed at *m/z* 211 and 289 respectively, suggesting that two methoxyl groups are attached to the xanthone skeleton while the other two reside on the phenyl group. ^{1}H NMR analysis indicated that compound **5** has two methoxyl groups located at the C-2 and C-8 positions. A 1,3,4,5-substitution pattern is suggested around the phenyl group for compound **5**. The appearance of the C-2′ and C-6′ protons as a singlet at δ6.73 integrating for two protons is rationalized by the symmetry of the syringenin moiety. Compound **5** was named cadensin F.

The CI mass fragmentation pattern of compound **6** suggested a syringenic lignan moiety (*m/z* 211 for F_2) and a xanthone moiety (*m/z* 306 for F_1) carrying two methoxyl and one hydroxyl group. The presence of a hydroxyl group on the xanthone nucleus was revealed by the formation of a triacetate and a UV bathochromic shift (34 nm) on addition of sodium acetate. The ^{1}H NMR spectrum of **6** was typical of cadensin F, (Table 2). The only difference was the presence of two protons at 6.41 and 6.31 ppm with *meta* coupling (1.8 Hz) instead of three contiguous protons from δ7.62 to 6.84, indicating that compound **6** was 6-hydroxycadensin F. The molecular formula of $C_{24}H_{20}O_{10}$ was established for compound **7** by HRMS, and CI ion mass fragments observed at *m/z* 261 and 211 in the mass spectrum of **7** suggested the presence of two hydroxyl groups on the xanthone nucleus and two methoxyl groups on the cinnamoyl fragment. The presence of two *ortho* coupled spins at δ7.61 and 7.05 (J = 8.8 Hz) indicated the absence of any substituents on ring C of the xanthone framework. The presence of a D_2O exchangeable signal at δ12.97 and a 67 nm $AlCl_3$/HCl induced bathochromic shift in the UV spectrum of **7**, indicated the presence of an OH group *peri* to the xanthone carbonyl. The presence of two *meta*-coupled spins at δ6.38 and 6.19 (J = 1.1 Hz) suggested the presence of the second hydroxyl group at position 6 which is confirmed by a 25 nm sodium acetate induced bathochromic shift in the UV spectrum. Compound **7**, named cadensin G, is the first xanthonolignoid reported with no substituent at position C-2.

Cytotoxic activity data obtained for this class of xanthones indicated a borderline activity against P-388 cells in culture. As reported above, the ED_{50} results obtained by

Table 2. ^{1}H NMR data of compounds 1–7

H	1*	2*	3*	4†	5†	6*	7*
1	7.21 *s*	7.21 *s*	7.10 *s*	7.25 *s*	7.34 *s*	7.07 *s*	7.61 *d* (8.8)
2	—	—	—	—	—	—	7.05 *d* (8.8)
5	7.69 *d* (8.2)	7.69 *dd* (7, 0.6)	7.14 *d* (8.4)	7.04 *d* (8.4)	7.13 *d* (8.4)	6.41 *d* (1.8)	6.19 *d* (1.1)
6	7.85 *ddd* (8.2, 8, 1.6)	7.84 *ddd* (8, 7, 1.6)	7.70 *t* (8.4)	7.47 *t* (8.4)	7.62 *t* (8.4)	—	—
7		7.48 *dt* (7, 0.6)	6.97 *d* (8.4)	6.68 *d* (8.4)	6.84 *d* (8.4)	6.36 *d* (1.8)	6.38 *d* (1.1)
8	8.21 *dd* (8, 1.6)	8.21 *dd* (8, 1.6)					
2′	7.07 *d* (1, 2)	6.77 *s*	7.05 *d* (1.8)	6.77 *d* (1.6)	6.73 *s*	6.75 *s*	6.77 *s*
5′	6.83 *d* (8.0)		6.82 *d* (8.1)	6.84 *d* (8.1)	—	—	—
6′	6.91 *dd* (8, 1.2)	6.77 *s*	6.89 *dd* (8.1, 1.8)	6.80 *dd* (8.1, 1.6)	6.73 *s*	6.75 *s*	6.77 *s*
7′	5.07 *d* (7.8)	5.06 *d* (7.8)	5.04 *d* (7.8)	4.92 *d* (8)	5.11 *d* (8.1)	4.99 *d* (7.9)	5.10 *d* (7.8)
8′	4.40 *ddd* (7.8, 4.2, 1.5)	4.45 *ddd* (7.8, 4.4, 2.1)	4.37 *ddd* (7.8, 5, 2)	4.27 *ddd* (8, 4.5, 2.9)	4.12 *ddd* (8.1, 3.5, 2.5)	4.38 *m*	4.35 *m*
9′a	3.44 *dd* (12.5, 4.2)	3.45 *dd* (12.5, 4.4)	3.42 *dd* (12.5, 5)	3.97 *dd* (12.3, 4.5)	3.61 *dd* (13, 3.5)	3.41 *m*	3.42 *dd* (12.4, 4.3)
9′b	3.70 *dd* (12.5, 1.5)	3.72 *dd* (12.5, 2.1)	3.70 *dd* (12.5, 2)	4.33 *dd* (12.3, 2.9)	3.99 *dd* (13, 2.5)	3.70 *m*	3.67 *m*
OMe	3.78, 3.85	3.99, 3.82 3.80	3.89, 3.85 3.82	3.99, 3.82 3.80	4.02, 3.96 3.91 (6H)	3.82, 3.80 3.76 (6H)	3.74 (6H)

*Chemical shifts are from spectra run in DMSO-d_6.
†Chemical shifts are from spectra run in $CDCl_3$.

screening these compounds against human tumour cell lines, A549 (human lung carcinoma), MCF-7 (breast carcinoma) and HT-29 (human colon adenocarcinoma), indicated that these compounds have only marginal cytotoxic activities.

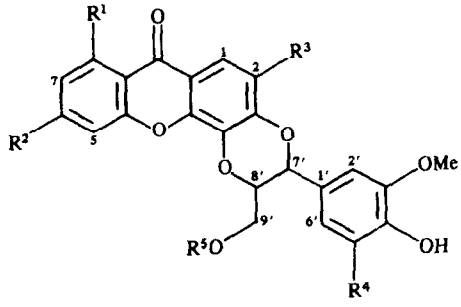
EXPERIMENTAL

Plant material. Psorospermum febrifugum Spach. (Guttiferae) roots were collected in Tanzania by Mr Leonard Mwasumbi of the University of Dar-es-Salaam. Specimens were authenticated at the Economic Botany Laboratory, Beltsville Agricultural Research Center, Beltsville, Maryland, where a voucher specimen is on deposit.

Extraction and isolation. The extraction and fractionation procedures carried out on the roots of *P. febrifugum* were reported in detail in a previous paper [2]. 19 major fractions (F1–F19) were obtained by silica gel chromatography of the active $CHCl_3$ extract II. Mp: uncorr. ^{1}H NMR spectra were obtained in the solvent indicated at 470 MHz at the Purdue University Biological Magnetic Resonance Laboratory whereas the ^{13}C NMR spectra were recorded at 50.16 MHz in DMSO-d_6. Chemical shifts are given in δ (ppm) and spectra were referenced to the solvent peak.

4 g of F9 were extracted with MeOH, the MeOH soluble portion (3.7 g) was partitioned between 5% aq. Na_2CO_3, 100 ml, and EtOAc, 3 × 100 ml. The combined organic extract was washed with water, dried and evapd *in vacuo* to yield 1.8 g of the neutral fraction A_1. This residue was chromatographed on low pressure silica gel column (2.5 × 100 cm, 80 g). Elution was initiated with $CHCl_3$ and the polarity was increased gradually by increasing amounts of MeOH. Fractions of 20 ml volume were collected, analysed by TLC and pooled into 7 major fractions A_3–A_9. Fraction A_3 was triturated with MeOH to yield compound **4** (35 mg) while fraction A_6 yielded compound **2** (14 mg). F11 (2 g) was triturated with MeOH and the MeOH-insoluble material was filtered to yield a white powder (70 mg). This solid was further resolved by prep. TLC using CH_2Cl_2–Me_2CO (4:1) as developing solvent, to yield the major component, compound **5**. The aq. Na_2CO_3 solution was neutralized by dil. HCl and extracted with EtOAc. The organic layer was then washed, dried and solvent removed *in vacuo* to yield 1.9 g of the acidic fraction B. Residue B was fractionated over silica gel (80 g) column using $CHCl_3$ with increasing polarity by gradual additional amounts of MeOH. 12 fractions, B1-B12, were obtained, fraction B9 yielded compound **7** (67 mg).

Fraction F10 was triturated with MeOH to yield compound **3** as a MeOH-insoluble residue, 250 mg. Fraction F13 (4.9 g) was partitioned between 60% aq. MeOH (100 ml) and hexane (100 ml × 3). The aq. layer was then extracted with $CHCl_3$ (100 ml × 3), and the $CHCl_3$ residue M_1 (1 g) was separated by a chromatotron using a 4 mm thick silica gel plate and 5% MeOH in $CHCl_3$ for elution. The collected fractions were pooled into 8 major fractions M_1–M_8. Compound **1**, 15 mg, crystallized from a methanolic solution of M_3, and compound **6** (8 mg) was isolated from M_5 as a white powder.



	R¹	R²	R³	R⁴	R⁵
1	H	H	OMe	H	H
2	H	H	OMe	OMe	H
3	OMe	H	OMe	H	H
4	OMe	H	OMe	H	Ac
5	OMe	H	OMe	OMe	H
6	OMe	OH	OMe	OMe	H
7	OH	OH	H	OMe	H

ED_{50} (μg/ml)

	A_{549}	MCF-7	HT-29
1	3	>10	3
2	>10	>10	>10
3	>10	>10	>10
4	4	>10	4
5	>10	>10	>10
6		N.T.*	
7	3	>10	4×10^{-1}

* Not tested

Kielcorin (**1**). Purified as a white powder, mp 245–246° (MeOH) (lit, mp 250–251° [3]); UV λ_{max}^{MeOH} (log ε) 317 (3.97), 277 (3.81), 255 (4.35), 238 (4.38), 204 (4.52); CIMS (CH_4), *m/z* 437 $[M+H]^+$, ^{1}H NMR (470 MHz, DMSO-d_6) see Table 2.

Cadensin D **2**. This compound was isolated as a white powder, mp 239–240° (lit. 243–245°, MeOH [4]), UV λ_{max}^{MeOH} (log ε) 247 (4.67), 316 (4.23), 360 (3.84) nm; IR ν_{max}^{KBr} 3400, 1630, 1600, 1580, 1450, 1120 cm^{-1}; EIMS *m/z* 466 (M^+) obsd 466.126; obsd 258.053 (F_1), calcd for $C_{14}H_{10}O_5$, 258.053; obsd 210.089 (F_2), calcd for $C_{25}H_{22}O_9$, 466.126; ^{1}H NMR (470 MHz, DMSO-d_6) see Table 2.

Isocadensin D (**3**). Isolated as a white powder, mp 278–279° (MeOH); UV λ_{max}^{MeOH} (log ε) nm: 240 (4.39), 242 (4.39), 247 (4.38), 310 (3.97) and 355 (3.83); IR (KBr) ν_{max}^{KBr} 3430, 1650, 1600, 1570, 1120, 1260 and 1120 cm^{-1}; CIMS (CH_4), *m/z* (relative intensity), 467 ($[M+H]^+$, 31), 289 (82), 181 (73) and 163 (100); EIMS, obsd 466.127 (M^+) calcd for $C_{25}H_{22}O_9$, 466.126; obsd 288.063 (F_1) calcd for $C_{15}H_{12}O_6$, 288.063; obsd 180.078 (F_2) calcd for $C_{10}H_{12}O_3$, 180.079; ^{1}H NMR, Table 2; ^{13}C NMR (50 MHz, DMSO-d_6) δ 55.5 (OMe), 55.6 (OMe), 56.1 (OMe), 59.8 (C-9'), 76.2 (C-7'), 77.8 (C-8), 96.6 (C-1), 106.1 (C-7), 109.5 (C-5), 111.3 (C-8a), 111.9 (C-2'), 115.1 (C-9a), 115.3 (C-5'), 120.6 (C-6'), 126.6 (C-1'), 131.9 (C-4), 134.5 (C-6), 138.7 (C-3), 139.8 (C-4a), 145.5 (C-3'), 147.2 (C-2), 147.5 (C-4'), 157.1 (C-10a), 160.0 (C-8), 173.6 (C-9). Compound **3** was found to be inactive in P-388 *in vivo* when tested at doses of 90, 45, 22.5, and 11.75 mg/kg.

Ethanolysis of compound **3**. Isocadensin D (3 mg) in NaOEt–EtOH (1.2 M, 1 ml) was heated at reflux for 0.5 hr then acidified with dilute HCl, extracted with $CHCl_3$ and then purified by prep. TLC on a 20 × 20 cm, 0.25 mm silica gel plate. UV λ_{max}^{MeOH} 234, 240 (sh), 286 and 362; $\lambda_{max}^{MeOH+NaOAc}$ nm: 238, 235 (sh), 286 and 372 nm.

Isocadensin D monoacetate (**4**). Compound **4** was isolated as white crystals, mp 240–241°, UV λ_{max}^{MeOH} (log ε) 242 (4.65), 250 (4.64), 305 (4.18), 358 (4.06); IR ν_{max}^{KBr} cm^{-1}: 3200, 1730, 1660, 1620, 1600, 1480, 1130; CIMS (CH_4), *m/z* (relative intensity) 509 ($[M+H]^+$, 7), 477 ($[M+H-MeOH]^+$, 10), 449 ($[M+H-AcOH]^+$, 86), 289 (53), 273 (48), 163 (100); EIMS, obsd 508.138 (M^+) calcd for $C_{27}H_{24}O_{10}$, 508.137; obsd 288.063 (F_1), calcd for $C_{15}H_{12}O_6$ 288.063; obsd 163.075 (F_2-AcOH), calcd for $C_{10}H_{11}O_2$, 163.076; ^{1}H NMR (470 MHz, $CDCl_3$), Table 2.

Cadensin F (**5**). Isolated as a white powder, mp 237–239° (MeOH); UV λ_{max}^{MeOH} (log ε) 244 (4.88), 249 (4.88), 310 (4.40) and 353 (4.25) nm: IR ν_{max}^{KBr} 3520, 3300, 1620, 1600, 1480, 1460, 1130 and 1100 cm^{-1}; CIMS (CH_4), *m/z* (relative intensity), 497 ($[M+H]^+$, 11), 467 ($[M+H-OMe]^+$, 4); obsd 289.071 (F_1, 100), calcd $C_{15}H_{12}O_6+H^+$, 289.071; obsd 211.097 (F_2, 39), calcd $C_{11}H_{14}O_4+H^+$, 211.097, 163 (28); EIMS obsd 496.137 (M^+) calcd $C_{26}H_{24}O_{10}$, 496.137; ^{1}H NMR (470 MHz, DMSO-d_6). 8-Methoxycadensin D is inactive in P-388 *in vivo* when tested at doses 20, 10, 5 and 2.5 mg/kg.

Cadensin F diacetate. A solution of 8-methoxycadensin D (2 mg) in dry pyridine (0.5 ml) and Ac_2O (0.5 ml) was stirred overnight at room temp. The solution was evapd *in vacuo* and the residue crystallized from MeOH. ^{1}H NMR (470 MHz), $CDCl_3$, δ 2.08 (*s*, 3H, Ac-9'), 2.32 (2, 3H, Ac-4'), 3.82 (*s*, 6H, OMe-3' and OMe-5'), 3.94 (*s*, 3H, OMe-8), 4.00 (*s*, 3H, OMe-2), 4.16 (*dd*, 1H, *J* = 12.3, 4.4 Hz, H-9'a), 4.39 (*ddd*, 1H, *J* = 7.5, 3.5, 4.4 Hz, H-8'), 4.48 (*dd*, 1H, *J* = 12.3, 3.5 Hz, H-9'b), 5.03 (*d*, 1H, *J* = 7.5, H-7'), 6.74 (*s*, 2H, H-2' and H-6'), 6.79 (*d*, 1H, *J* = 8.2 Hz, H-7), 7.15 (*d*, 1H, *J* = 8.2 Hz, H-5), 7.36 (*s*, 1H, H-1), 7.57 (*t*, 1H, *J* = 8.2 Hz, H-6).

6-Hydroxyisocadensin F (**6**). White powder, mp 256–257° (MeOH), UV λ_{max}^{MeOH} (log ε) nm: 250 (4.38), 284 (3.82), 310 (3.94) and 347 (3.71); UV $\lambda_{max}^{MeOH+NaOAc}$ 216, 250, 284, 332, 360 nm; IR ν_{max}^{KBr} cm^{-1}: 3400, 1650, 1660, 1580 and 1120; CIMS (CH_4), *m/z* (relative intensity) obsd 513.133 ($M+H^+$, 0.5) calcd for $C_{26}H_{24}O_{11}$, 513.132; obsd 305.068 (F_1+H^+, 26) calcd for $C_{15}H_{13}O_7$, 305.066, obsd 211.097 (F_2+H^+, 100) calcd for $C_{11}H_{15}O_4$, 211.097; ^{1}H NMR (470, DMSO-d_6), Table 1.

Acetylation of compound (**6**). A solution of 6-hydroxy-8-methoxycadensin D (2 mg) in dry pyridine (0.5 ml) and Ac_2O (0.5 ml) was stirred overnight. The solution was evapd to dryness *in vacuo*, and the residue crystallized from MeOH. ^{1}H NMR (470 MHz, $CDCl_3$) δ 2.08 (*s*, 3H, OAc-9'), 2.32 (*s*, 3H, OAc-4'), 2.33 (*s*, 3H, OAc-6), 3.81 (*s*, 6H, OMe-3' and 4').

Cadensin G (**7**). White powder, mp 265–266° (MeOH); UV λ_{max}^{MeOH} (log ε) nm: 218 (4.50), 243 (4.56), 281 (3.95), 320 (4.22); UV $\lambda_{max}^{MeOH+NaOAc}$ nm: 237, 265, 345; UV (MeOH + $AlCl_3$ + HCl) 215; 234, 254, 341, 387 nm: IR ν_{max}^{KBr} cm^{-1}: 3420, 1640, 1605, 1570, 1190; CIMS (CH_4) obsd 469.109 ($M+H^+$, 32) calcd for $C_{24}H_{20}O_{10}+H^+$, 469.114; obsd 211.093 (F_2+H^+, 67) calcd for $C_{11}H_{15}O_4$, 211.097; ^{1}H NMR (470, DMSO-d_6), Table 1.

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