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SESQUITERPENE LACTONES FROM *CARPHOCHAETE BIGELOVII*

BARBARA MEURER*, FRED C. SEAMAN and TOM J. MABRY

The Department of Botany, The University of Texas at Austin, Austin, TX 78712-7640, U.S.A.

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Key Word Index—*Carphochaete bigelovii*; Asteraceae; Eupatorieae; sesquiterpene lactones; germacrolide; guaianolide; C_{10}-diester side-chain.

Abstract—Five sesquiterpene lactones with C_{10}-diester side-chains have been identified as major constituents of a leaf surface extract of *Carphochaete bigelovii*. The structures were elucidated by spectroscopic methods and are reported for the first time. Chemosystematic implications are discussed briefly.

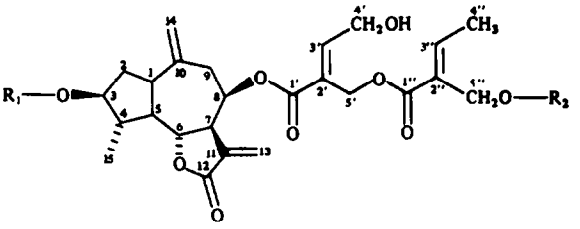
INTRODUCTION

In continuation of our studies on the Asteraceae we have investigated *Carphochaete bigelovii* A. Gray (Eupatorieae). The phytochemistry of *Carphochaete* (five species restricted to the southwest U.S.A. and Mexico) has not yet been studied. We report here the isolation and structural elucidation of five new sesquiterpene lactones (**1a–1c**, **2**, **3**) from leaf material of *C. bigelovii*. The new structures, related to provincialin [1], are four guaianolides and one germacrolide all with C_{10}-diester side-chains attached at C-8.

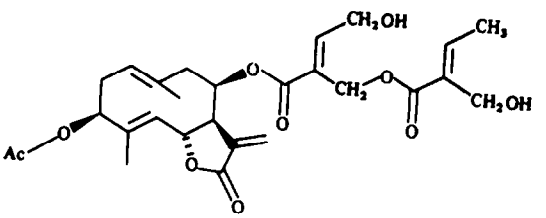
RESULTS AND DISCUSSION

The five sesquiterpene lactones were purified from a leaf surface extract by the chromatographic methods described below. The structures were derived from analysis of their ^{1}H NMR and ^{13}C NMR spectra (see Tables 1 and 2) and their mass spectral fragmentation patterns. HPLC analysis of the crude syrup indicated that compound **1a** was the major constituent of the extract (37%), while compounds **1b**, **1c**, **2** and **3** occurred in smaller amounts (9.4, 4.0, 7.9 and 5.3%, respectively). There were considerable amounts of flavonoids present, but only traces of other UV-absorbing compounds.

The spectral data of compounds **1a–1c** suggested that their structures were closely related and differed only in the number and position of their acetate moieties. The appearance of ^{1}H NMR doublets at δ6.1 (H-13a) and 5.5 (H-13b), $J_{7,13a} = 3.47$ and $J_{7,13b} = 3.07$, and the coupling patterns of the proton signals for H-1 to H-9a,b supported a guaianolide skeleton. Position C-3 must be either hydroxylated (**1b**) or acetylated (**1a**, **1c**), which was confirmed by the ^{1}H-signals for H-3 at δ3.75 for **1b**, and δ4.65 and 4.7 for **1a** and **1c**, respectively. The characteristic downfield shift of the H-8 signals indicated that the C_{10}-diester side-chains were attached at C-8 in the β-position. The relatively small $J_{7,8}$ values for compounds **1a–1c** indicated that H-8 was at the α-position [see refs. [2] and [3] for a comparison]. The proposed structure also followed from the absence of signals for H-10 and the presence of two H-14 signals at δ5.1 (*br s*) and 4.85 (*br s*). The structures of the C_{10}-diester side-chains of compounds **1a–1c** were elucidated by a 2D-COSY experiment and comparison with data reported in the literature. The side-chain of compound **1a** was described first by Herz and Wahlberg [1] for provincialin and the side-chains of compounds **1b** and **1c** were suggested to be their C-5″-



1a R_1 = Ac, R_2 = H
1b R_1 = H, R_2 = Ac
1c R_1 = R_2 = Ac



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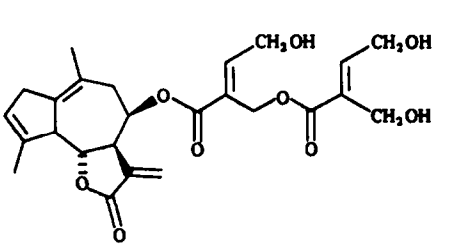

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*Permanent address: Botanisches Institut der Universität zu Köln, Gyrhofstr. 15, D-5000 Köln 41, F.R.G.

Table 1. ^{1}H NMR spectral data for sesquiterpene lactones from *Carphochaete bigelovii*

	1a	1b	1c	2	3
H-1	2.85 *ddd* $J_{1,2a} = 10.7$ $J_{1,2b} = 8.7$ $J_{1,5} = 9.8$	2.82 *m*	2.85 *m* $J_{1,2b} = 8.7$	4.9*	2.53*
H-2a	2.33 *m*	2.2 *m*	2.38 *m*	2.35 *m*	3.0 *dd*†
H-2b	1.7 *m*	1.77 *m*	1.73 *m*	2.55*	
	$J_{2a,2b} = 21$	$J_{2ab,3} = 8.7$	$J_{2a,2b} = 21$		$J_{2ab,3} = \leqslant 2$
H-3	4.65 *q*	3.75 *ddd*	4.7 *q*	5.2 *m*	5.53 *s*
H-4	2.1 *m*	2.1 *m*	2.17 *m*	—	
	$J_{4,15} = 6.6$	$J_{4,15} = 5.8$	$J_{4,15} = 6.6$		
H-5	1.9*	1.9*	1.9*	4.9*	3.36 *br d*
	$J_{5,6} = 10$			$J_{5,6} = 9$	$J_{5,6} = 10.2$
H-6	4.35 *dd*	4.4 *dd*	4.4 *dd*	5.13 *dd*	4.19 *br t*
	$J_{6,7} = 9$		$J_{8,7} = 9.3$		$J_{6,7} = 10$
H-7	3.0 *dddd*	3.0 *dddd*	3.03 *dddd*	2.94 *m*	3.02 m
	$J_{7,13a} = 3.07$	$J_{7,13a} = 2.8$	$J_{7,13a} = 3.02$	$J_{7,13a} = 3.38$	$J_{7,13a} = 3.29$
	$J_{7,13b} = 3.47$	$J_{7,13b} = 3.43$	$J_{7,13b} = 3.46$	$J_{7,13b} = 3.06$	$J_{7,13b} = 3.03$
	$J_{7,8} = 2.7$	$J_{7,8} = 3.3$	$J_{7,8} = 2.8$		$J_{7,8} = \leqslant 2$
H-8	5.59 *dd*	5.61 *dd*	5.62 *dd*	5.84 *dd*	5.64 *dd*
	$J_{8,9ab} = 4.4$	$J_{8,9a} = 4.7$ $J_{8,9b} = 3.5$	$J_{8,9ab} = 4.4$	$J_{8,9ab} = 5.4$	
H-9a	2.7 *dd*	2.75 *dd*	2.75 *dd*	2.85 *dd*	2.53 *m*
H-9b	2.32 *dd*	2.35 *dd*	2.35 *dd*	2.37*	
	$J_{9a,b} = 14$	$J_{9a,b} = 14$	$J_{9a,b} = 14.1$	$J_{9a,b} = 18$	
H-13a	5.49 *d*	5.5 *d*	5.5 *d*	5.61 *d*	5.44 *d*
H-13b	6.14 *d*	6.19 *d*	6.19 *d*	6.27 *d*	6.10 *d*
H-14	a 5.01 *br s*	5.1 *br s*	5.03 *br s*	1.59 *s*‡	1.6 *br s*‡
	b 4.85 *br s*	4.85 *br s*	4.87 *br s*		
H-15	1.1 *d*‡	1.2 *d*‡	1.15 *d*‡	1.78 *s*‡	1.88 *br s*‡
H-3′	6.97 *t*	7.04 *t*	7.04 *t*	7.1 *t*	7.0 *t*
	$J_{3',4'} = 6$	$J_{3',4'} = 5.9$	$J_{3',4'} = 6.2$	$J_{3',4'} = 5.85$	$J_{3',4'} = 5.9$
H-4′	4.4 *m*§	4.48 *m*§ $J_{4'a,b} = 6.35$	4.45 *m*§	4.52 *m*§	4.31 *d*§
H-5′	4.83 *s*§	4.92 *br s*§	4.91 *br s*§	4.3 *br s*§	4.82 *dd*§
H-3″	6.83 *q*	7.03 *q*	7.03 *q*	6.9 *q*	6.73 *t*
	$J_{3'',4''} = 7.2$	$J_{3'',4''} = 7.2$	$J_{3'',4''} = 7.2$	$J_{3'',4''} = 7.2$	$J_{3'',4''} = 4.9$
H-4″	1.85 *d*‡	1.92 *d*‡	1.9 *d*‡	1.91 *d*°	4.35 *dddd*†§
H-5″	4.21 *br s*§	4.8 *br s*§	4.79 *br s*§	4.95 *dd*†	4.19 *dd*†
Acetate	2.02 *s*‡	2.01 *s*‡	2.01 *s*‡ 2.00 *s*‡	2.12 *s*‡	

Run in $CDCl_3$ at 360 MHz; frequencies in ppm downfield from TMS.
*Obscured signal.
†centre of AB system.
‡Intensity of three protons.
§Intensity of two protons.

acetoxy derivatives. The chemical ionization (CI) mass spectra of compounds **1b** and **1c** showed peaks at *m/z* 141 and 159 due to an acetoxytiglic acid fragment. Irradiation of the H-15 methyl signal showed NOE effects on the H-3, H-4 and H-5 signals. The signal for H-6 was not enhanced. Thus the C-15 methyl group must be α-orientated, as well as H-3 and H-5. Consequently the C-5 ring system of the guaianolide skeleton must be *cis*-fused, which was confirmed by the $J_{1,5}$ value of 9.8 Hz and a comparable value recently reported for a related structure [4]. The acetate group of compounds **1a** and **1c** and the hydroxyl group of compound **1b** are attached at the C-3β position. Closely related structures like hymenopappolide have been described previously [2], but this is the first report of the provincialin side-chain and its C-5″-acetoxy derivatives on this type of guaianolide skeleton.

The ^{1}H NMR shifts and coupling patterns of the skeletal protons in compound 3 indicated that it has the same sesquiterpene skeleton as the guaianolide zuurbergenin [5] and differs only in its C-8 ester side-chain. Two 4,5-dihydroxytigliate units are joined at the C-5′ position. The triplets at δ6.73 and 7.00 (H-3′ and H-3″) indicated hydroxyl groups at the C-4′ and C-4″ positions. C-5″ was also hydroxylated, as the ^{1}H NMR spectrum showed a *br s*

Table 2. ^{13}C NMR spectral data of compounds 1a and 3

	1a	3
C-1	51.1	137.2*
C-2	35.6	37.8
C-3	79.8	126.7
C-4	43.5	135.4*
C-5	43.0	56.6
C-6	80.6	80.1
C-7	50.4	55.4
C-8	67.2	66.8
C-9	41.6	36.0
C-10	142.1	131.5*
C-11	134.8	137.2*
C-12	169.3	169.7
C-13	122.0	120.2
C-14	117.1	24.1
C-15	17.5	17.5
C-1′	165.2	165.3
C-2′	126.8	125.2
C-3′	147.9	147.9
C-4′	59.2	58.9
C-5′	56.4	58.4
C-1″	167.0	166.6
C-2″	131.6	126.0
C-3″	142.1	144.6
C-4″	14.3	59.1
C-5″	58.1	58.8
Acetate	21.2	
	171.2	

Run on a GN-500 instrument in $CDCl_3$ with TMS as internal standard; frequencies in ppm downfield from TMS. Assignments were made by a ^1H–^{13}C-correlated spectrum and comparison with data from known compounds.

*Interchangeable assignments.

at δ4.19 for the two H-5″ protons and only two methyl signals (H-14 and H-15). The CI mass spectrum generated peaks at *m/z* 133 and 343, indicating the loss of a dihydroxytiglic acid from the molecular ion. The structure of the compound was confirmed by a 2D-COSY experiment and the assignment of the side-chain carbons was established by a ^1H-^{13}C-correlated spectrum. The 4′-methylated variation of this compound has been isolated recently from *Ageratina tristis* [3].

The ^1H NMR spectrum of compound 2 indicated a germacrolide-type skeleton (a group of signals from δ4.85 to 5.3 for H-5, H-1, H-6 and H-3, and no signals corresponding to H-4 or H-10) substituted with a C_{10}-diester side-chain at the C-8 position and an acetate at the C-3 position. The *trans*-orientation of the lactone ring was also supported by the couplings $J_{7,13a} = 3.38$ and $J_{7,13b} = 3.06$. Comparison with known structures isolated from *Piptothrix areolare* (DC.) King and H. Robins. and *Isocarpha oppositifolia* (M. Miski and D. A. Gage, unpublished results; [6]) strongly supported the germacolide configuration of this skeleton. The structure of the C_{10}-diester side-chain was also 5′-[5″-hydroxytigloyl]-4′-hydroxytiglic acid. This was supported by a strong coupling between the H-3″ quartet at δ6.9 and the methyl signal at 1.9 (H-4″) in the 2D-COSY spectrum. The position of the acetate at C-3 of the skeleton was deduced from the chemical shift of the H-3 signal in the ^1H NMR spectrum. The CI mass spectral data of this compound excluded the attachment of the acetate to the side-chain; an ion at *m/z* 307 indicated the loss of $C_{10}H_{13}O_5$ from the molecular ion and an ion at *m/z* 247 resulted from the loss of an acetate from the remaining fragment.

Sesquiterpene lactones with C_{10}-diester side-chains have been isolated from different subtribes of the Eupatorieae sensu K. & R. [7] including Ageratiinae [3, 8, 9]. Liatriinae [1, 4, 10] and Critoniinae [11, 12]. This is the first report of these compounds in the subtribe Piqueriinae sensu K. & R. The terpenoid chemistries of some members of the *Piquera* group such as *Ageratum* and *Stevia* have been studied intensively [13], while many other genera have not yet been investigated. The presence of C_{10}-diester-side-chain sesquiterpene lactones may perhaps indicate a closer relationship of the genus *Carphochaete* to members of other subtribes in the Eupatorieae such as the Liatriinae or Ageratiinae. On the other hand, the distribution of provincialin-related terpenoids seems to be widespread, which reduces the chemotaxonomic value of this character, especially in terms of separating subtribes within the Eupatorieae. However, it might be a significant character at the generic level (*Liatris* [1, 4], *Piptothrix* [9]).

EXPERIMENTAL

Plant material of *Carphochaete bigelovii* was collected by A. D. Zimmermann on 8 December 1985 in Jeff Davis County (TX, U.S.A.) 5 miles SE of Ft. Davis, at the SW end of Arkansas Mesa at the CDRI Visitors' Center. (Voucher ADZ 2368 is deposited in the Plant Resources Center of the University of Texas at Austin, U.S.A.; TEX). Air-dried leaves (260 g) were washed without grinding with CH_2Cl_2 (2 × 2 l., 30 min). The crude extract was evaporated to dryness, diluted in 200 ml MeOH and filtered. After adding H_2O until an 80% aq. soln was obtained, the extract was partitioned 4 × against hexane in order to remove long-chain hydrocarbons and chlorophyll. Subsequently, the MeOH was evaporated at room temp. and the remaining aq. soln was partitioned twice against CH_2Cl_2. Any remaining H_2O was removed from the combined CH_2Cl_2 phases by stirring with $(Mg)_2SO_4$. After filtration the extract was reduced to dryness (yield: 13.5 g). The crude syrup was first chromatographed on a Sephadex-LH 20 column using CH_2Cl_2–MeOH (1:3) as an eluant; 30 fractions each of 50 ml were collected and monitored by TLC [silica gel containing a 254 nm fluorescence indicator, hexane–EtOAc (1:3), CH_2Cl_2–Me_2CO (9:1); $CHCl_3$–MeOH (9:1)]. Spots were detected under UV 254 and 365 nm (only flavonoids) and visualized by spraying with acidified vanillin. Fractions 9 + 10 and 11 + 12 were combined and chromatographed separately on a Sephadex LH 20 column using cyclohexane–CH_2Cl_2–MeOH (7:4:1) as an eluant. Eluant polarity was increased during chromatography (7:4:3). Fractions were collected and monitored by TLC (see above). Selected fractions were examined by HPLC using a Beckman binary gradient system (pumps: model 110B, controller: model 421, organizer including injector: model 340 with a 20 µl loop, detector: model 160) and an Ultrasphere ODS column (5 µm, i.d. 4.6 mm, 25 cm). Samples were separated in a stepwise gradient from 10% solvent B in solvent A to 100% solvent B (0 min: 10% B in A, 1 min: 10% to 30% B in A in 20 min, 21 min: 30% to 80%

B in A in 10 min, 31 min: 80% to 100% B in A in 10 min, 48 min: end) using 0.1% H_3PO_4 in 20% aq. MeCN as solvent A and 0.1% H_3PO_4 in MeCN as solvent B at a flow rate of 1 ml/min; compounds were detected at 214 nm and 0.5 a.u. (method modified after ref. [14]).

Purification of single compounds. Compound **1c** was isolated from fraction 6 of the second CC using the combined fractions 9 and 10 as initial material. The fraction was purified by preparative TLC on silica gel ($CHCl_3$–MeOH, 9:1). Compounds **1a**, **1b** and **2** were purified from combined fractions 97–114 of the second CC using fractions 11 + 12 as initial material. Repeated preparative TLC on silica gel ($CHCl_3$–MeOH, 9:1) gave three bands: the upper band corresponded to compound **1a**, the middle band to compound **2** and the lower band to compound **1b**. HPLC analysis indicated that compounds **1a** and **1b** were pure. Compound **2** required further purification by preparative HPLC using an isocratic system containing a Beckman Model 110A pump, a Rheodyne injection port with 500 μl loop, an Altex Ultrasphere ODS column (5 μm, i.d. 10 mm, 250 mm) and an Altex 156 Refractive Index Detector. Chromatography was performed at a flow rate of 3 ml/min using 35% aq. MeCN as an eluant and a RI detection sensitivity of 64. Peaks with R_t 20 min were collected from several injections.

Compound **3** was purified from combined fractions 124 and 125, again using fractions 11 + 12 as initial material. The pure compound was obtained from preparative TLC (silica gel, $CHCl_3$–MeOH, 9:1) giving a single band. The purity of all compounds was confirmed by HPLC.

NMR analysis was carried out on a GN-500 MHz, an NT-360 MHz or an NT-200 MHz instrument. EIMS were performed on a Dupont-Instrument Model 21-490, CI mass spectra on a Finnigan/MAT 4000 instrument and IR spectra on a Perkin–Elmer Model 1430 instrument.

4β,15-Dihydro-3β-acetoxy-8β-5'[5''-hydroxytigloyl]-4'-hydroxytigloyloxyzaluzanin C (**1a**). Pale yellow oil, HPLC, R_t 19 min (37%), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3480 (OH), 1730 (lactone), 1630, 1650, 1240. Molecular formula: $C_{27}H_{34}O_{10}$. EIMS *m/z* (rel. int.): 519 $[M+1]^+$ ($\leqslant$1), 403 $[M-C_5H_8O_3+1]^+$ ($\leqslant$1), 343 [403 − HOAc]$^+$ (2), 246 $[M-C_{10}H_{13}O_5-HOAc]^+$ (15), 228 [246 − H_2O]$^+$ (36), 213 $[C_{10}H_{13}O_5]^+$ (11), 173 [228 − 55]$^+$ (58), 115 $[C_5H_7O_3]^+$ (20), 97 [115 − H_2O]$^+$ (73), 69 [97 − C≡O$^+$]$^+$ (100), 43 [ketene]$^+$ (98). The molecular ion and major fragments were confirmed by the CIMS. CIMS *m/z* (rel. int.): 519 $[M+1]^+$ (48), 459 $[M-HOAc+1]^+$ (26), 247 $[M-C_{10}H_{13}O_5-HOAc+1]^+$ (41), 229 [247 − H_2O]$^+$ (100).

4β,15-Dihydro-8β-5'[5''-acetoxytigloyl]-4'-hydroxytigloyloxyzaluzanin C (**1b**). Pale yellow oil, HPLC R_t 17 min (9.4%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3480 (OH), 1730 (lactone), 1650, 1240. Molecular formula: $C_{27}H_{34}O_{10}$. EIMS *m/z* (rel. int.): no molecular ion was observed, 402 $[M-C_7H_{10}O_4]^+$ ($\leqslant$1), 342 [403 − HOAc]$^+$ ($\leqslant$1), 246 $[M-C_{12}H_{16}O_7]^+$ (25), 229 [246 − H_2O + 1]$^+$ (25), 173 [228 − 55]$^+$ (35), 141 $[C_7H_9O_3]^+$ (25), 115 $[C_5H_7O_3]^+$ (78), 97 [115 − H_2O]$^+$ (100), 69 [97 − C≡O$^+$]$^+$ (75), 43 [ketene]$^+$ (78). CIMS *m/z* (rel. int.): 519 $[M+1]^+$ (38.1), 459 $[M-HOAc]^+$ (30). Major fragments of the EIMS were confirmed.

4β,15-Dihydro-3β-acetoxy-8β-5'[5''-acetoxytigloyl]-4'-hydroxytigloyloxyzaluzanin C (**1c**). Pale yellow oil, HPLC R_t 27 min (4.0%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3510 (OH), 1735 (lactone), 1680, 1650, 1610, 1240–1340. Molecular formula: $C_{29}H_{36}O_{11}$. EIMS *m/z* (rel. int.): 560 $[M]^+$ (1.36), 517 $[M-ketene]^+$ (1.1), 500 $[M-HOAc]^+$ (1.5), 403 $[M-C_{12}H_8O_3+1]^+$ (1.2), 343 [403 − HOAc]$^+$ (3.3), 246 $[M-C_{12}H_{16}O_7-ketene]^+$ (11), 229 [246 − H_2O + 1]$^+$ (36), 173 [228 − 55]$^+$ (35), 141 $[C_7H_9O_3]^+$ (36), 115 $[C_5H_7O_3]^+$ (38), 97 [115 − H_2O]$^+$ (57), 69 [97 − C≡O]$^+$ (43), 43 [ketene]$^+$ (100). CIMS *m/z* (rel. int.): 561 $[M+1]^+$ (60), 501 $[M-HOAc+1]^+$ (29), 441 $[M-2HOAc+1]^+$ (32), 159 $[OH-C_7H_9O_3+1]^+$ (32), 141 $[C_7H_9O_3]^+$ (64).

3β-Acetoxy-8β-5'[5''-hydroxytigloyl]-4''-hydroxytigloyloxycostunolide (**2**). Pale yellow oil, HPLC R_t 19.5 min (7.9%). Molecular formula: $C_{27}H_{34}O_{10}$. EIMS *m/z* (rel. int.): 518 $[M]^+$ ($\leqslant$1), 402 $[M-C_5H_8O_3]^+$ ($\leqslant$1), 360 [402 − ketene]$^+$ (1.5), 246 $[M-C_{10}H_{13}O_5-HOAc+1]^+$ (3.8), 228 [246 − H_2O] (4.1). Better resolution of the smaller fragments was given by the CIMS. CIMS *m/z* (rel. int.): 519 $[M+1]^+$ (1.6), 459 $[M-HOAc+1]^+$ (0.5), 403 $[M-C_5H_8O_3+1]^+$ (0.9), 343 [403 − HOAc]$^+$ (3.1), 307 $[M-C_{10}H_{13}O_5]^+$ (2.8), 247 [307 − HOAc]$^+$ (24), 229 [247 − H_2O]$^+$ (30), 117 $[HO-C_5H_7O_2+1]^+$ (85), 99 $[C_5H_7O_2]^+$ (100).

8β-5'-[4'',5''-Dihydroxytigloyl]-4'-hydroxytigloyloxydesacetylzuubergenin (**3**). Pale yellow oil, HPLC R_t 20 min (5.3%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420 (OH), 1730, 1740 (lactone), 1220. Molecular formula: $C_{25}H_{30}O_9$. EIMS *m/z* (rel. int.): no molecular ion was observed, 342 $[M-C_5H_8O_4]^+$ (4.6), 246 $[M-C_{10}H_{14}O_6]^+$ (14.6), 228 [246 − H_2O]$^+$ (100), 228 $[C_{10}H_{13}O_6-1]^+$ (100). CIMS *m/z*: 475 $[M+1]^+$, 357 $[M-C_5H_{10}O_3+1]^+$, 343 $[M-C_5H_8O_4+1]^+$, 229 (see EIMS), 133 $[C_5H_8O_4+1]^+$, 115 $[C_5H_7O_3+1]^+$, 97 $[115-H_2O]^+$.

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