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Serrulatin A and B, New Diterpene Polyesters from *Euphorbia serrulata*

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Abstract—Two new diterpene polyesters, serrulatin A (**1**) and B (**2**), were isolated from an *n*-hexane extract of the whole, undried plant of *Euphorbia serrulata*. The structures were elucidated by various spectroscopic methods, including ESI-MS, IR, UV, 1D and 2D NMR techniques and X-ray crystallography. Serrulatin A contains a hitherto unknown heterocyclic ring system, while serrulatin B is a diterpene, which can be formally derived from **1** by ring opening.

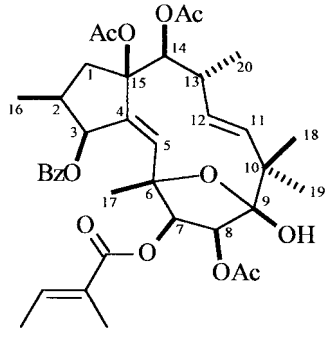
Introduction

The widespread genus *Euphorbia* (Euphorbiaceae) is the source of a large number of biologically active compounds. Besides the well-known skin irritant and tumor-promoting tigliane, ingenane and daphnane diterpenes, considerable attention has been paid to the macrocyclic diterpenes because of their high chemical diversity and therapeutically relevant bioactivity. Macrocyclic diterpenes from *Euphorbia* species have been found to possess various vascular effects, and also cytotoxic, antitumor, antibacterial and HIV-1 reverse transcriptase-inhibiting activities.[1–6] In recent years, investigations on *Euphorbias* have resulted in the discovery of several new classes of diterpenes.[7–11] The genus *Euphorbia* in Hungary consists of about 37 species.[12] In the course of our ongoing studies on biologically active secondary metabolites from the plants of Hungarian Euphorbiaceae, we earlier reported a number of new diterpene polyesters from *Euphorbia* species.[13–15] We now report the isolation and structure elucidation of two new diterpenes (**1**, **2**) from the *n*-hexane-soluble extract of *E. serrulata* Thuill. (nom. illegit. *E. stricta* L.), which is a glabrous annual plant widely distributed in the southern, central and western parts of Europe.[16] Its chemical constituents have not been investigated previously.

Results and Discussion

The *n*-hexane phase of a methanolic extract of the fresh, whole plant of *E. serrulata* was subjected to polyamide CC, silica gel flash chromatography and HPLC to afford crystals of two new optically active compounds (**1**: $[\alpha]_D^{28.5}=+135$, *c*, 0.05, $CHCl_3$, **2**: $[\alpha]_D^{28}=+25$, *c*, 0.055, $CHCl_3$), named serrulatin A (**1**) and B (**2**).

Serrulatin A exhibited IR absorption bands at 3447, 1745, 1740, 1721, 1649, 1459 and 711 cm^{-1} and UV maxima at 223.5, 273.5 and 282 nm, characteristic of hydroxy, ester and phenyl groups. Its molecular formula was assigned as $C_{38}H_{48}O_{12}$ via HRFAB-mass spectrum (M^++Na: *m/z* 721.2815) and detailed NMR investigations. In the ESI-MS spectrum, fragment ions were observed at *m/z* 659, 537, 477 and 377 indicating the sequential loss of acetic, benzoic and a pentenoic acid from the parent ion $[M+Na]^+$ at *m/z* 719.



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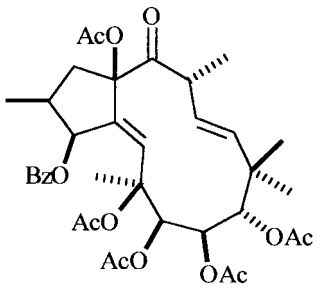

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The ^{1}H NMR and JMOD (*J*-Modulated Spin Echo Experiment) spectra revealed the presence of one benzoyl, three acetyl and one tigloyl groups (Table 1). Additionally, the spectra contained resonances of skeletal carbons and protons, which were assigned on the basis of interpretation of the ^{1}H–^{1}H COSY and HMQC spectra. The proton and carbon connectivities detected here demonstrated that a 20 carbon-containing tricyclic diterpene core is present, consisting of three tertiary and two secondary methyls, one methylene, four oxygen-substituted and two alkyl-substituted methines, three tertiary unsaturated carbons and five quaternary carbons, including one alkyl, one single unsaturated and three oxygen-substituted ones. The ^{1}H–^{1}H COSY spectrum indicated three structural fragments of correlated protons: δ_H 2.56 dd, 1.76 dd, 2.45 m, 0.93 d and 6.23 brd [–CH_2–$CH(CH_3)$–CH(OR)– (R=acyl)] (A); δ_H 5.79 d and 5.59 d [–CH(OR)– CH(OR)–] (B); δ_H 5.41 d, 5.27 dd, 3.15 m, 0.96 d and 4.96 d [–CH=CH–$CH(CH_3)$–CH(OR)] (C). Further, in the ^{1}H–^{1}H COSY spectrum weak ^4J coupling was detected between the protons at δ_H 6.23 and 5.41 d (J=1.7 Hz), indicating their close proximity.

Table 1. NMR data on serrulatin A (**1**) [500 MHz, $CDCl_3$, δ (ppm) (J=Hz)]

Atom	^{1}H	^{13}C	HMBC (H no.)
1α	2.56 dd (13.8, 12.2)	37.7	2, 3, 16
1β	1.76 dd (12.2, 5.5)		
2	2.45 m	35.6	1α, 16
3	6.23 brd (5.5)	73.3	1β, 5, 16
4	–	133.5	1β, 5
5	5.41 d (1.7)	140.5	3, 17
6	–	82.7	5, 7, 17
7	5.79 d (3.7)	73.8	5, 8, 17
8	5.59 d (3.7)	71.5	7, 9-OH, Ac δ 2.08[a]
9	–	105.5	7, 8, 9-OH, 18, 19
10	–	42.8	8, 9-OH, 11, 12, 18, 19
11	5.41 d (16.1)	139.7	12, 18, 19
12	5.27 dd (16.1, 9.3)	135.3	11, 14, 20
13	3.15 m	39.2	11, 12, 14, 20
14	4.96 d (9.7)	76.1	1α, 1β, 13, 20
15	–	91.5	1α, 1β, 3, 5, 14, Ac δ 2.21[a]
16	0.93 d (6.5)	14.4	1β. 2
17	1.13 s	21.5	–
18	1.18 s	24.3	11, 19
19	0.91 s	21.1	11, 18
20	0.96 d (6.9)	20.6	13
9-OH	3.34 s	–	–
3-OBz			
CO	–	166.0	3, 2′, 6′
1′	–	130.9	3′, 5′
2′, 6′	8.09 ‘d’ (7.1)	130.6	2′-6′
4′	7.49 ‘t’ (7.4)	133.2	2′, 6′
3′, 5′	7.39 ‘t’ (7.6)	128.8	3′, 5′
7-OTig			
1″	–	165.8	7, 3″, 4″
2″	–	128.4	4″, 5″
3″	6.70 dq (7.2, 1.6)	138.8	4″, 5″
4″	1.71 m	12.9	3″
5″	1.71 m	15.1	3″
8-OCO*Me*	2.08 s	21.4	–
8-O*C*OMe	–	170.2	8
14-OCO*Me*	2.16 s	21.3	–
14-O*C*OMe	–	171.3	14
15-OCO*Me*	2.21 s	23.3	–
15-O*C*OMe	–	169.1	–

[a] $^4J_{C-H}$ couplings.

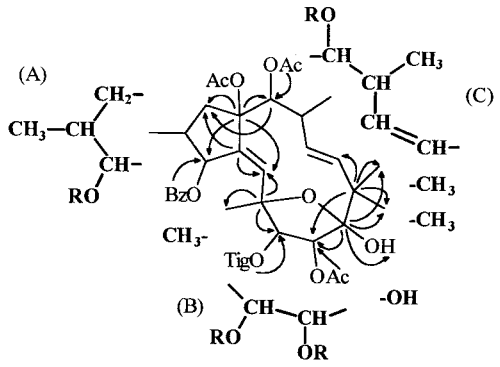

Figure 1. Connection of partial structures of **1** via HMBC correlations (C→H).

The sequences A, B and C, tertiary methyls and quaternary carbons were connected by means of an HMBC experiment (Fig. 1). The long-range correlations of the quaternary carbons at δ_C 91.5 (C-15) and 133.5 (C-4) with the proton signals at δ_H 2.56, 1.76 (H-1α, β), 6.23 (H-3) and 5.41 (H-5) revealed that structural element A, together with two

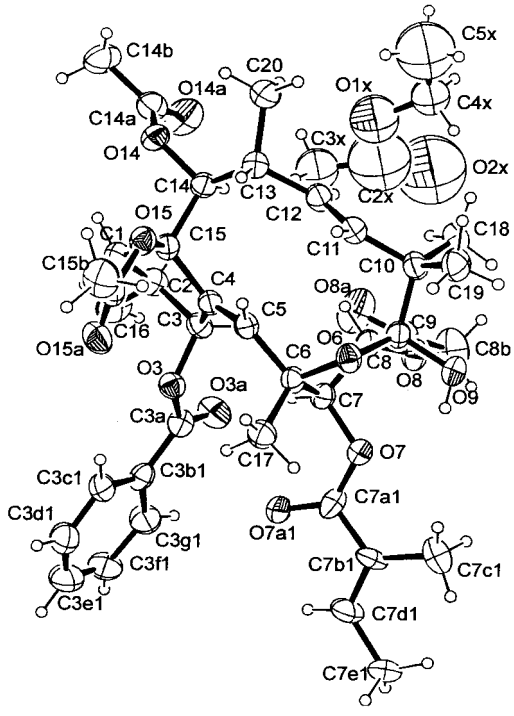

Figure 2. Perspective view of **1**, using thermal ellipsoids with a 30% probability level.

Table 2. NMR data on serrulatin B (**2**) [500 MHz, $CDCl_3$, δ (ppm) (J=Hz)]

Atom	^1H	$^1H^a$	^{13}C	$^{13}C^a$	HMBC (H no.)
1α	2.70 dd (13.4, 6.7)	2.75 dd (13.2, 6.5)	40.3	41.4	2, 3, 16
1β	2.02 t (13.4)	2.13 t (13.2)			
2	2.33 m	2.45 ddq (13.2, 6.8, 6.5)	40.2	41.3	1β, 16
3	5.75 dd (4.5, 1.5)	6.33 brd (4.4)	77.4	78.6	1α, 2, 5, 16
4	–	–	137.5	139.0	1α, 5
5	5.90 d (1.5)	6.53 d (1.6)	138.4	140.0	3, 17
6	–	–	81.8	83.0	5, 17, Ac δ 2.15[b]
7	5.25 d (3.0)	5.67 d (2.9)	76.0	77.1	5, 9, 17, Ac δ 2.04[b]
8	5.37 d (3.0)	5.71 d (2.9)	67.8	69.2	7, 17[b], Ac δ 2.07[b]
9	5.41 s	5.76 s	73.1	74.2	7, 11, 18, 19, Ac δ 2.12[b]
10	–	–	42.1	43.0	8, 11, 12, 18, 19
11	5.42 d (16.3)	5.61 d (16.3)	141.5	142.2	9, 13, 18, 19
12	5.75 dd (16.3, 9.0)	5.67 dd (16.3, 7.8)	127.1	128.7	11, 13, 20
13	3.72 dq (9.0, 6.7)	3.68 dq (7.8, 6.7)	43.0	44.1	11, 12, 20
14	–	–	204.0	204.6	12, 13, 20
15	–	–	90.6	91.4	1α, 3, 5, Ac δ 2.11[b]
16	1.45 d (6.9)	1.69 d (6.8)	17.2	18.2	1β, 2, 3
17	1.48 s	1.81 s	24.1	25.1	5, 7
18	0.90 s	0.95 s	26.4	27.4	9, 11, 19
19	0.85 s	0.90 s	18.1	19.1	9, 11, 18
20	1.26 d (6.7)	1.47 d (6.7)	18.7	19.8	13
3-OBz					
CO	–	–	165.6	166.7	3, 2′, 6′
1′	–	–	130.3	131.6	2′, 6′, 3′, 5′
2′, 6′	8.07 ‘d’ (7.1)	8.28 dd (6.8, 1.5)	129.9	131.1	2′-6′
4′	7.54 ‘t’ (7.4)	7.06 m	133.0	133.7	2′, 6′
3′, 5′	7.42 ‘t’ (7.7)	7.06 m	128.4	129.3	3′, 5′
6-OCO*Me*	2.15 s	1.99 s	21.9	22.3	–
6-O*C*OMe	–	–	169.7	170.9	–
7-OCO*Me*	2.04 s	1.64 s	20.5	20.9	–
7-O*C*OMe	–	–	169.7	170.2	7
8-OCO*Me*	2.07 s	1.82 s	21.0	21.4	–
8-O*C*OMe	–	–	170.4	171.2	8
9-OCO*Me*	2.12 s	1.76 s	20.9	21.1	–
9-O*C*OMe	–	–	169.2	169.4	9
15-OCO*Me*	2.11 s	1.63 s	21.0	21.1	–
15-O*C*OMe	–	–	171.0	171.5	–

[a] In C_6D_6.
[b] $^4J_{C-H}$ couplings.

quaternary carbons, forms a methyl-substituted five-membered ring, present in many types of Euphorbiaceae diterpenes. HMBC cross-peaks between the signals at δ_C 82.7 (C-6) and δ_H 5.41 (H-5), 5.79 (H-7) and 1.13 (H-17) indicated the linkage of structural part B and one methyl group, as depicted in Fig. 1.

The couplings $^2J_{C-H}$ and $^3J_{C-H}$ of the carbons at δ_C 105.5 (C-9) and 42.8 (C-10) and the protons at δ_H 5.59 (H-8), 5.41 (H-11), 5.27 (H-12), 1.18 (H-18) and 0.91 (H-19) clearly suggested that the molecular moieties B and C and two methyl groups are connected through quaternary carbons. Inspection of the correlations between δ_C 91.5 (C-15) and δ_H 4.96 (H-14) and between δ_C 76.1 (C-14) and δ_H 2.56, 1.76 (H-1α,β) revealed that the full structure involved a jatrophane carbon skeleton. The positions of the ester groups were also determined via the HMBC experiment by evaluation of the couplings $^3J_{C-H}$ between the oxymethine protons and the carbonyl carbons. The position of the hydroxy group was evident from the cross-peak between the signals at δ_C 105.5 (C-9) and δ_H 3.34 (OH).

The acetyl group (δ_H 2.21), which did not exhibit any C*H*–O–*C*OR correlations, must be situated on one of the quaternary carbons (C-6, C-9 or C-15). The –*C*–O–CO–C*H*$_3$ couplings ($^4J_{C-H}$=2.1±0.1 Hz) observed in the HMBC spectrum recorded at 60 ms fixed the location of this acetyl group at C-15, and of necessity ethereal functions (deduced from the molecular formula) were sited at positions C-6 and C-9.

The stereochemistry and absolute configuration of serrulatin A were determined by means of X-ray diffraction (Fig. 2) as (2*S*,3*S*,6*R*,7*S*,8*S*,9*S*,13*R*,14*S*,15*S*)-8,14,15-triacetoxy-3-benzoyloxy-6,9-epoxy-9-hydroxy-7-tigloyloxyjatropha-4*Z*,11*E*-diene (**1**).

Serrulatin B displayed IR absorptions of ester (1740 cm^{-1}) and ketone (1720 cm^{-1}) groups and UV maxima (230, 273.5 and 280 nm) of a phenyl group. ESI-MS and extensive NMR studies established the molecular formula $C_{37}H_{46}O_{13}$, with the parent ion $[M+Na]^+$ at *m/z* 721. The ^1H and ^{13}C NMR spectra indicated the presence of five acetate and one benzoate groups (Table 2). Apart from the signals of the ester moieties, the ^1H NMR and JMOD spectra showed signals for three tertiary and two secondary methyls, one methylene, four oxymethines, two alkyl-substituted methines, one trisubstituted olefin, one disubstituted olefin and four quaternary carbons including one ketone (Table 2). The unequivocal assignment of the signals of serrulatin B

was possible by virtue of the information afforded by $^1H-^1H$ COSY, HMQC and HMBC experiments. The long-range $^1H-^{13}C$ correlations detected in the HMBC spectrum yielded the connectivity of the structural fragments around each quaternary carbons. Diagnostic couplings $^2J_{C-H}$ and $^3J_{C-H}$ between the carbons and protons (C-4 and H-1α, H-5; C-6 and H-5, H-17; C-10 and H-9, H-11, H-18, H-19; C-14 and H-13, H-20; and C-15 and H-1α, H-3, H-5) led to the conclusion that the parent skeleton involved jatrophane-4,11-diene functionalized at C-3, C-5, C-6, C-7, C-8, C-9, C-14 and C-15. The locations of the ester groups on C-3, C-7, C-8 and C-9 were confirmed through the observation of HMBC cross-peaks between the carbonyl carbons and the ester-bearing protons. Two acetyl groups situated on quaternary carbons (C-6 and C-15) were allocated via the $-C-O-CO-CH_3$ couplings $^4J_{C-H}$, similarly as in the case of **1**. The HMBC couplings between the signals of δ_C 204.0 and H-12, H-13 and H-20 placed the keto group on C-14. The stereochemical aspects were investigated by means of a NOESY experiment. Because of overlapping signals in the ^1H NMR spectrum recorded in $CDCl_3$, the solvent was changed to benzene-d_6. Diagnostic NOE interactions were detected between H-1α and H-2, between H-2 and H-3, and between H-3 and H-7, H-8 and H-17, proving their α position, and between H-1β and H-16 and H-13, and between 6-OAc and H-9, indicating their β stereochemistry. The NOE effects observed between H-19 and H-7 and between H-8 and H-7 demonstrated the α position of H-19, while the NOE of H-18 and H-9 were indicative of the β position of H-18. The β orientation of 15-OAc followed from the NOESY correlations between 15-OAc and H-16 and the *ortho*- and *meta*-benzoyl protons. NOESY cross-peaks of H-5 with H-8, H-9, H-11 and H-12 pointed to the same stereochemistry of the C-4–C-5 olefin bond as that found in **1**. The *trans* geometry of the C-11–C-12 olefin was concluded from the coupling constant $J_{11,12}$=16.3 Hz. All of the above data are compatible with the structure of serrulatin B as **2**.

Jatrophane diterpenoids are rare in the plant kingdom: their occurrence is limited to merely several species of Euphorbiaceae. Serrulatin A and B (**1**, **2**) are the first compounds of this group that are unsaturated at position C-4–C-5; moreover, **1** has a hitherto unknown heterocyclic ring system because of the C-6–C-9 ethereal function. Biogenetically, a relationship can be postulated between **1** and **2**, with the supposition that **2** originated from **1** by opening of the furan ring.

Experimental

General

Melting points are uncorrected. ESIMS measurements were carried out on a Hewlett–Packard 5989B MS Engine mass spectrometer equipped with an atmospheric pressure ionization electrospray (API-ES) interface (HP 59987A). Samples were introduced into the API-ES ion source by using a Harvard type 22 syringe pump. FAB mass spectrum was measured on a VG ZAB2-SEQ spectrometer. NMR spectra were recorded on a Bruker Avance DRX 500 spectrometer at 500 MHz (^1H) and 125 MHz (^{13}C). The signals of the deuterated solvents were taken as the reference. Two-dimensional experiments were performed with standard Bruker software. IR spectra of KBr discs were run on a Perkin–Elmer Paragon 1000 PC FTIR instrument. Optical rotations were determined in MeOH by using a Perkin–Elmer 341 polarimeter. The UV spectra were recorded on a Shimadzu UV-2101 PC spectrometer. For column chromatography, polyamide (ICN) and silica gel (Kieselgel GF_{254} 15 μm, Merck) were used. HPLC was carried out on a Waters Millipore instrument, with detection at 254 nm on LiChrospher Si 100 and LiChrospher RP-18 (5 μm, 200×4 mm) columns.

Plant material

E. serrulata Thuill. was collected in June 1998 from the hillcountry, near Iklódbördöce, Country Zala, Hungary, and identified by Tamás Rédei (Department of Taxonomy and Ecology, Eötvös Lóránd University, Budapest, Hungary). A voucher specimen (No. 510) has been deposited in the Herbarium of the Department of Pharmacognosy, Albert Szent-Györgyi Medical University, Szeged.

Extraction and isolation

The fresh plant material (2400 g) was percolated with MeOH (19 l) at room temperature. The crude extract was concentrated in vacuo to 500 ml and exhaustively extracted with *n*-hexane (1800 ml). On evaporation, the organic phase gave a residue (16 g), which was chromatographed on a polyamide column (72 g) with mixtures of MeOH–H_2O (3:2 and 4:1) as eluents. The fractions obtained with MeOH–H_2O (3:2) were subjected to silica gel (60 g) flash chromatography, using a gradient system of petroleum ether–EtOAc (49:1, 9:1, 4:1, 7:3 and 1:1). Fractions 35–47 eluted with petroleum ether–EtOAc (7:3) were subjected repeatedly to silica gel flash chromatography, using benzene–$CHCl_3$–diethyl ether mixtures of increasing polarity. Fractions 3–7 obtained with the first eluent (10:5:1) were further fractionated by normal-phase HPLC with *n*-hexane–EtOAc–EtOH 70:10:1 as eluent at a flow rate of 0.5 ml/min. The compound observed at a retention time of 21.2 min yielded **1** (9.9 mg), and the compound at a retention time 30.8 min after RP-HPLC purification with acetonitrile–H_2O (4:1) afforded **2** (38.8 mg).

Serrulatin A (1)

Colourless prisms; mp 137–139°; $[\alpha]_D^{28.5}$=+135 (*c* 0.05, $CHCl_3$); IR ν_{max} (KBr) cm^{-1}: 3447, 2967, 1745, 1740, 1721, 1649, 1459, 1372, 1230, 1063, 1024, 711; UV λ_{max} (log ϵ) (MeOH): 223,5 (4.18), 273.5 (2.94), 282 (2.85); ESI-MS: *m/z* 719 $[M+Na]^+$, 659 $[M+Na-AcOH]^+$, 537 $[M+Na-AcOH-BzOH]^+$, 477 $[M+Na-2\times AcOH-BzOH]^+$, 377 $[M+Na-2\times AcOH-BzOH-TigOH]^+$; ^1H and ^{13}C NMR data, see Table 1.

Serrulatin B (2)

Amorphous solid; mp 193–196°; $[\alpha]_D^{28}$=+25 (*c* 0.055, $CHCl_3$); IR ν_{max} (KBr) cm^{-1}: 2975, 1740, 1720, 1451, 1372, 1235, 1068, 1050, 716; UV λ_{max} (log ϵ) (MeOH):

Table 3. Crystal data and structure refinement for serrulatin A (**1**).

Empirical formula	$C_{38}H_{48}O_{12}+0.5\times C_4H_8O_2$
Formula weight	740.82
Temperature	293(2) K
Wavelength	$\lambda=1.54180$ Å
Crystal system	Tetragonal
Space group	$P4_12_12$
Unit cell dimensions	$a=10.905(1)$ Å
	$c=67.282(6)$ Å
Volume	8001.1(13) Å^3
Z	8
Density (calculated)	1.230 Mg/m^3
Absorption coefficient	0.758 mm^{-1}
F(000)	3168
Psi-scan absorption correction	Max.: 0.9418, min.: 0.7030
Theta range for data collection	$4.83°\leq\theta\leq75.03°$
Index ranges	$-13\leq h\leq13$; $-13\leq k\leq=13$; $-84\leq l\leq84$
Reflections collected	18799
Completeness to 2 θ	0.970
Independent reflections	8014 [R(int)=0.0538]
Reflections $I\geqslant2\sigma(I)$	5061
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	8014/380/599
Goodness-of-fit on F^2	0.923
Final R indices [$I\geqslant2s(I)$]	$R1=0.0450$, $wR2=0.1116$
R indices (all data)	$R1=0.0724$, $wR2=0.1271$
Absolute structure parameter	0.18(18)
Max. and mean shift/esd	0.018, 0.001
Extinction coefficient	0.00124(11)
Largest diff. Peak and hole	0.162 and $-0.260e$ Å^{-3}

230 (4.05), 273.5 (2.94), 280 (2.86); HRFABMS: *m/z* 721.2815 $[M+Na]^+$ (calcd for $C_{37}H_{46}O_{13}Na$, $\Delta=2.9$ mmu); ESI-MS: *m/z* 721 $[M+Na]^+$, 737 $[M+K]^+$, 639 $[M+H-AcOH]^+$, 457 $[M+H-2\times AcOH-BzOH]^+$, 397 $[M+H-3\times AcOH-BzOH]^+$; ^1H and ^{13}C NMR data, see Table 1.

X-Ray crystallographic study on 1[†]

A summary of the crystallographic data, data collection parameters and details of the structure refinement for compound **1** are given in Table 3. A crystal with approximate dimensions of 0.50×0.38×0.08 mm was mounted on an Enraf-Nonius CAD4 diffractometer equipped with a graphite monochromator. Reflections were collected by using Cu Kα radiation and the ω–θ scan mode. The structure was solved by direct methods (SHELXS-97)[17] and refined by full-matrix least-squares (SHELXL-97).[18] The atoms of the substituents at C-3 and C-7 (benzoyloxy and tigloyloxy groups) and the ethylacetate solvate proved to be disordered. Thermal vibrations for non-hydrogen atoms were assumed to be anisotropic, except for the atoms in the solvate. Hydrogen atoms were introduced with isotropic temperature factors in calculated positions.

[†] Crystallographic data for structure **1** reported in this paper have been deposited at the Cambridge Crystallographic Data Center (deposition number CCDC 139767).

Acknowledgements

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