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ent-Kaurane diterpenoids from the plant *Wedelia trilobata*

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Abstract: Four new *ent*-kaurane diterpenoids, namely, 3*α*-tigloyloxypterokaurene L_3 (**1**), *ent*-17-hydroxy-kaura-9(11),15-dien-19-oic acid (**2**), and wedelobatins A (**3**) and B (**4**), together with 11 known *ent*-kaurane diterpenoids (**5**–**15**), were isolated from the ethanol extract of *Wedelia trilobata*. All the structures of **1**–**15** were elucidated on the basis of spectroscopic studies.

Keywords: ent-kaurane diterpenoids, *Wedelia trilobata*, phytochemical investigation

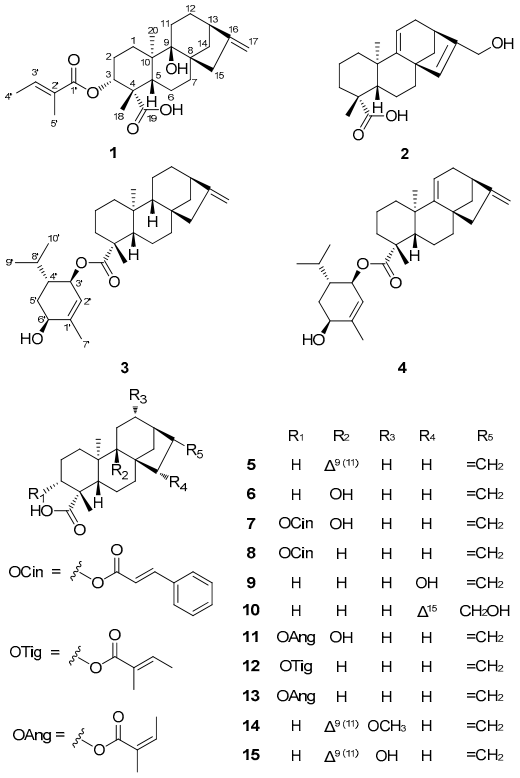
Introduction

Wedelia trilobata has been used as a traditional herbal medicine for the treatment of fever and malaria in Vietnam and also for the treatment of backache, stubborn wounds, sores, and arthritic pain in the Caribbean and Central America.[1,2] Previous phytochemical studies showed that the plants of this genus are a rich source of *ent*-kaurane diterpenoids.[3–5]

As part of our efforts to assemble a large scale natural product library with thousands of compounds derived from plants and micro-organisms, phytochemical investigation on *W. trilobata* led to the isolation of four new *ent*-kaurane diterpenoids, namely, 3*α*-tigloyloxypterokaurene L_3 (**1**), *ent*-17-hydroxykaura-9(11),15-dien-19-oic acid (**2**), and wedelobatins A (**3**) and B (**4**), together with 11 *ent*-kaurane derivatives, grandiflorenic acid (**5**),[6] pterokaurene L_3 (**6**),[7] 3*α*-cinnamoyloxy-pterokaurene L_3 (**7**),[3] *ent*-3*β*-cinnamoyloxykaur-16-en-19-oic acid (**8**),[4] grandifloric acid (**9**),[8] *ent*-17-hydroxykaur-15-en-19-oic acid (**10**),[3] 3*α*-angeloyloxypterokaurene L_3 (**11**),[3] *ent*-3*β*-tigloyloxykaur-16-en-19-oic acid (**12**),[10] *ent*-3*β*-angeloyloxykaur-16-en-19-oic acid (**13**),[3,10] 12*α*-methoxygrandiflorenic acid (**14**),[11] and 12*α*-hydroxygrandiflorenic acid (**15**).[12] This paper herein describes the isolation and structural elucidation of these new compounds.

Results and Discussion

3*α*-Tigloyloxypterokaurene L_3 (**1**), was obtained as a white amorphous powder, with its molecular formula determined as



	R_1	R_2	R_3	R_4	R_5
5	H	$\Delta^{9(11)}$	H	H	=CH_2
6	H	OH	H	H	=CH_2
7	OCin	OH	H	H	=CH_2
8	OCin	H	H	H	=CH_2
9	H	H	H	OH	=CH_2
10	H	H	H	Δ^{15}	CH_2OH
11	OAng	OH	H	H	=CH_2
12	OTig	H	H	H	=CH_2
13	OAng	H	H	H	=CH_2
14	H	$\Delta^{9(11)}$	OCH_3	H	=CH_2
15	H	$\Delta^{9(11)}$	OH	H	=CH_2

$C_{25}H_{36}O_5$ on the basis of HREIMS, showing a molecular ion peak at *m/z* 416.2554 (calcd for $C_{25}H_{36}O_5$, 416.2563). The IR spectrum revealed absorption bands of hydroxyl (3513 cm^{-1}), carbonyl (1701 cm^{-1}), and double bond (1652 cm^{-1}) groups. In the ^1H NMR spectrum (Table 1), the downfield olefinic proton

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Table 1. NMR data of compounds 1 and 2 (^{13}C NMR, 100 MHz, ^{1}H NMR, 600 MHz; $CDCl_3$)

	1		2	
positon	δ_C, type	δ_H (J in Hz)	δ_C, type	δ_H (J in Hz)
1	30.6, CH_2	2.03, td (13.1, 4.1); 1.63[a]	39.8, CH_2	1.86[a]; 1.22, td (13.9, 3.3)
2	23.8, CH_2	2.40, dddd (13.5, 13.1, 12.1, 4.1); 1.79[a]	20.0, CH_2	1.86[a]; 1.48[a]
3	78.7, CH	4.60, dd (12.1, 4.5)	38.2, CH_2	2.13, br. d (13.2); 1.01[a]
4	48.0, C		44.9, C	
5	49.2, CH	1.79[a]	47.2, CH	1.48[a]
6	21.4, CH_2	1.86, m; 1.70, m	18.4, CH_2	2.44, br. q-*like* (11.5); 1.96, m
7	35.9, CH_2	1.84, m; 1.28[a]	27.1, CH_2	1.86[a]; 1.48[a]
8	49.0, C		45.9, C	
9	77.3, C		157.2, C	
10	43.7, C		38.1, C	
11	30.0, CH_2	1.99, br. dd (14.9. 5.6); 1.24, m	113.5, CH	5.00, dd (3.7, 3.1)
12	34.4, CH_2	1.64[a]; 1.58, m	27.9, CH_2	2.27, ddd (18.1, 5.0, 3.1); 1.92, br. dd (18.1, 3.7)
13	42.1, CH	2.62, br. s	38.8, CH	2.69, dd (5.0, 4.8)
14	40.3, CH_2	2.13, dd (11.9, 2.4); 1.27[a]	49.2, CH_2	1.63, br. d (9.2); 1.82, dd (9.2, 4.8)
15	43.7, CH_2	1.80[a]; 2.70, br. d (17.8)	137.2, CH	6.01, s
16	154.6, C		143.4, C	
17	103.4, CH_2	4.81, br. s; 4.78, br. s	60.7, CH_2	4.25, dd (14.1, 1.4); 4.21, dd (14.1, 0.9)
18	24.1, CH_3	1.27, s	28.3, CH_3	1.24, s
19	180.2, C		183.6, C	
20	17.3, CH_3	1.16, s	23.0, CH_3	1.01, s
1′	167.7, C			
2′	128.8, C			
3′	137.2, CH	6.86, br. q (7.1)		
4′	14.4, CH_3	1.77, br. d (7.1)		
5′	12.0, CH_3	1.82, br. s		

[a]signal overlapped

at δ_H 6.86 (br. q, J = 7.1 Hz) and two methyl signals at δ_H 1.77 (br. d, J = 7.1 Hz) and 1.82 (br. s), was indicated by the presence of a tigloyloxy group in **1**.[10] Apart from the five carbon signals assigned to the tigloyloxy group (δ_C 167.7, 128.8, 137.2, 14.4, and 12.0),[10] the ^{13}C NMR (DEPT) spectrum (Table 1) of **1** also exhibited 20 carbons composed of two methyls, nine methylenes, three methines (one oxygenated), and six quaternary carbons, which were consistent with a skeleton of an *ent*-kauranoid.[7] In particular, the NMR spectroscopic features of **1** are similar to those of **6** (pterokaurene L_3), which only differed in the appearance of a tigloyloxy group at C-3 in **1**. It was also confirmed by the chemical shift value of C-3 (δ_C 78.7, CH), C-9 (δ_C 77.3, C) and the HMBC correlations (Figure 1) from H-3 (δ_H 4.60, dd, J = 12.1, 4.5 Hz) to C-1′ (δ_C 167.7, C), C-1 (δ_C 30.6, CH_2), and C-18 (δ_C 24.1, CH_3) as well as the correlations from Me-20, H-12, and H-15 to C-9, and from the methyl at C-4 (Me-18) to a downfield quaternary carbon (C-19) at δ_C 180.2. The β-orientation of the hydroxy group at C-9 in **1** was based on the downfield shift of H-15β (δ_H 2.70) and upfield shift of C-15 (δ_C 43.7) for the γ-steric compression effect in **1** from the hydroxyl group at C-9 to H-15β as evidenced in pterokaurene L_3 (**6**).[7] Furthermore, the ROESY correlations (Figure 2) of H-3 with H-5 and Me-18 suggested that the tigloyloxy was α-orientated. Consequently, the structure of **1** was finally determined as *ent*-3β-tigloyloxy-9α-hydroxykaur-16-en-19-oic acid, and given the name as 3α-tigloyloxypterokaurene L_3.

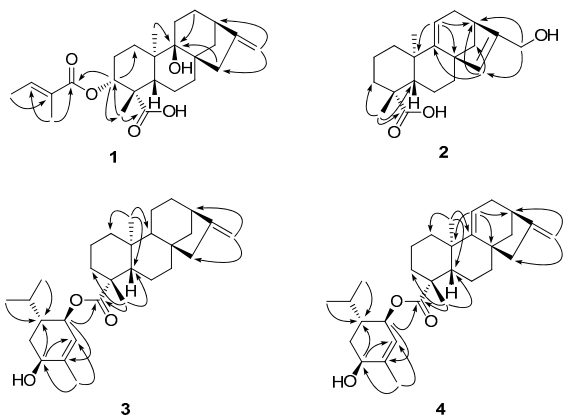

Figure 1. Key HMBC correlations of compounds **1–4**

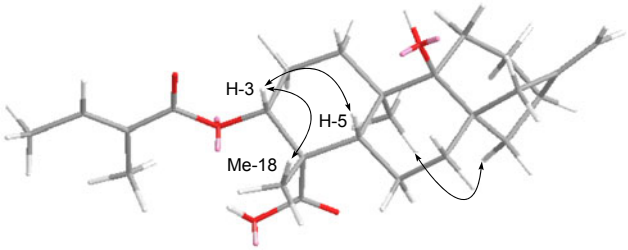

Figure 2. Key ROESY correlations of compound **1**

ent-17-Hydroxykaura-9(11),15-dien-19-oic acid (**2**), was obtained as a white, amorphous powder, with a molecular formula of $C_{20}H_{28}O_3$ on the basis of HREIMS, showing a molecular ion peak at *m/z* 316.2028 (calcd for $C_{20}H_{28}O_3$, 316.2038). The IR spectrum indicated the presence of hydroxyl (3427 cm^{-1}), carbonyl (1693 cm^{-1}), and double bond (1639 cm^{-1}) groups. The ^{13}C NMR (DEPT) spectrum (Table 1) revealed 20 carbons including three sp^3 quaternary carbons, three sp^2 quaternary carbons (one carboxylic acid carbonyl), two sp^3 methines, two sp^2 methines, eight sp^3 methylenes (one oxygenated), and two methyl groups. Its ^{1}H NMR spectrum (Table 1) showed two olefinic protons at δ_H 6.01 (s) and 5.00 (dd, J = 3.7, 3.1 Hz), two AB double doublets assigned to the protons of a hydroxymethyl group at δ_H 4.25 (dd, J = 14.1, 1.4 Hz) and 4.21 (dd, J = 14.1, 0.9 Hz), and two methyl signals at δ_H 1.24 and 1.01 (each 3H, s). These spectroscopic features

suggested that the structure of **2** was similar to that of **10** (*ent*-17-hydroxykaur-15-en-19-oic acid),[3] and only differed in appearance as a double bond between C-9 (δ_C 157.2, C) and C-11 (δ_C 113.5, CH) in **2**. It was confirmed by, the HMBC correlations from H-11 (δ_H 5.00, dd, J = 3.7, 3.1 Hz) to C-8 (δ_C 45.9, C), C-10 (δ_C 38.1, C), and C-13 (δ_C 38.8, CH), as shown in Figure 1. The α-orientation of the carboxylic acid group at C-4 was inferred from the ^{13}C NMR chemical shift of the methyl group at C-4 by comparing those of related *ent*-kaurane diterpenoids, in which the methyl group with β-orientation resulted in resonance of approximately δ_C 29, as opposed to resonance of approximately δ_C 16 when the methyl group was in the α-orientation.[7,13,14] Accordingly, the structure of compound **2** was elucidated as *ent*-17-hydroxykaura-9(11),15-dien-19-oic acid.

Wedelobatin A (**3**), was obtained as a colorless oil, which has a molecular formula of $C_{30}H_{46}O_3$ on the basis of HREIMS, showing a molecular ion peak at *m/z* 454.3454 (calcd for $C_{30}H_{46}O_3$, 454.3447). The IR spectrum suggested the presence of hydroxyl (3428 cm^{-1}), carbonyl (1719 cm^{-1}), and double bond (1657 cm^{-1}) groups. In the ^{13}C NMR (DEPT) spectrum (Table 2), 20 carbon signals including two methyl carbons, nine methylenes, three methines, four quaternary carbons, and two carbons of one double bond, suggested the presence of an *ent*-kaurene skeleton, which was confirmed by the typical ^{1}H NMR signals (Table 2) of *ent*-kaurene as follows: δ 4.79 (1H, br. s), 4.73 (1H, br. s), 2.63 (1H, br. s), 1.18 (3H, s), and 0.91 (3H, s). Particularly, the NMR signals of the *ent*-kaurane moiety were in accordance with those of *ent*-kaurenoic acid.[7] On the other hand, the remaining carbon signals were composed of two olefinic carbons of a trisubstituted double bond, three methyl carbons, one methylene, and four methines (two oxygenated), together with the ^{1}H NMR signals at δ 5.43 (1H, br. s), 5.15 (1H, br. d, J = 8.4 Hz), 4.02 (1H, t, J = 3.3 Hz), 1.81 (3H, s), 0.96, and 0.83 (each 3H, d, J = 6.8 Hz), resembled those of (3*R*,4*R*,6*S*)-3,6-dihydroxymenth-1-ene.[15,16] As shown in Figure 3, the cyclohexene ring in the monoterpene moiety should have half chair configuration. The coupling constant of H-3′ (br. d, J = 8.4 Hz) indicated a *trans* pseudo-diaxial relationship for H-3′ and H-4′ while those of H-6′ (t, J = 3.3 Hz) suggested an equatorial orientation. Consequently, H-3′, H-4′, and H-6′ were determined to be α-, β-, and α-oriented, respectively. The observation of the HMBC correlation (Figure 1) from H-3′ to C-19 as well as the down-field chemical shift of H-3′ at δ_H 5.15 and the upfield chemical shift of C-19 at δ_C 177.4, indicated the linkage between the two moieties at C-3′ and C-19 via an ester connection. Therefore, the structure of wedelobatin A was elucidated, as shown in Figure 1.

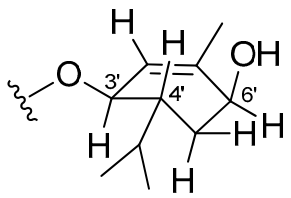

Figure 3. Configuration of the monoterpene moiety

Wedelobatin B (**4**), was obtained as a colorless oil, and determined molecular formula of $C_{30}H_{44}O_3$ on the basis of HREIMS, showing a molecular ion peak at *m/z* 452.3283 (calcd for $C_{30}H_{44}O_3$, 452.3290). The IR spectrum suggested the presence of hydroxyl (3429 cm^{-1}), carbonyl (1716 cm^{-1}), and double bond (1654 cm^{-1}) groups. The ^{1}H and ^{13}C NMR data (Table 2) of **4** were similar to those of **3**. The major difference found was the presence of one more olefinic proton at δ_H 5.23 (dd, J = 3.5, 2.7 Hz) and two olefinic carbons of a trisubstituted double bond in **4**. The double bond was located at C-9 based on the HMBC correlations from H-11 to C-8, C-10, and C-13, which was confirmed by the fact that the NMR data of the *ent*-kaurene moiety were consistent with those of **5**. Hence, the structure of wedelobatin B was determined, as shown in Figure 1.

Experimental Section

General Experimental Procedures. Optical rotations were measured on a Jasco P-1020 polarimeter. IR spectra were obtained by using a Bruker Tensor 27 FT-IR spectrometer with KBr pellets. NMR spectra were acquired with a Bruker AVANCE Ⅲ-600, Bruker DRX-500 or Bruker AV-400 instrument at room temperature. ESIMS and HREIMS were recorded on a Bruker HCT/Esquire and Waters AutoSpec-P776 mass spectrometers. Silica gel (200–300 mesh, Qingdao Marine Chemical Co., Ltd., China), MCI gel CHP-20P (75–150 μm, Mitsubishi Chemical Corporation, Japan), Sephadex LH-20 (Amersham Biosciences, Sweden) and Chromatorex C-18 (40–75 μm, Fuji Silysia Chemical Ltd., Japan) were used for normal pressure column chromatography. MPLC was performed on a Büchi Sepacore System including pump manager C-615, pump modules C-605, and fraction collector C-660 (Büchi Labortechnik AG, Switzerland) and columns were packed with Chromatorex C-18 (40–75 μm, Fuji Silysia Chemical Ltd., Japan). Preparative HPLC was performed on an Agilent 1200 liquid chromatography apparatus with a Zorbax SB-C18 column (5 μm, 9.4 mm × 150 mm). Fractions were monitored and analyzed by TLC (Qingdao Marine Chemical Co., Ltd., China) and spots were visualized by heating silica gel plates immersed in vanillin–H_2SO_4 in EtOH.

Plant Material. The whole plants of *W. trilobata* were collected in Pu'er City of Yunnan Province, China, in November 2010, and identified by Mr. Yu Chen of Kunming Institute of Botany, Chinese Academy of Sciences. The voucher specimen (BBP0311) was deposited at BioBioPha Co., Ltd.

Extraction and Isolation. The air-dried, powdered whole plants of *W. trilobata* (10.0 kg) were extracted with 95% ethanol at room temperature. The alcohol extract was concentrated to derive a residue (1180 g), which was fractionalized by silica gel column chromatography eluted with a solvent system of petroleum ether (PE)-acetone and then MeOH to yield fractions 1–6. Fraction 1 (30 g), eluted with 10% acetone, was further isolated and purified by recrystallization from PE-acetone to afford **5** (17.5 mg). Fraction 2 (48 g), eluted with 15% acetone, was further separated by silica gel column ($CHCl_3$-acetone, 60:1), and then by preparative HPLC (CH_3CN-H_2O, 50%→70%, 10 mL/min) to derive **3** (4 mg), **4** (4 mg), **12** (48 mg), and **13** (8 mg). Fraction 3 (28 g), was eluted using 20% acetone, and

Table 2. NMR data of compounds 3 and 4 (^{13}C NMR, 100 MHz, ^{1}H NMR, 500 MHz; $CDCl_3$)

	3		4	
positon	δ_C, type	δ_H (*J* in Hz)	δ_C, type	δ_H (*J* in Hz)
1	40.7, CH_2	1.84[a]	40.8, CH_2	1.92[a]
		0.79[a]		1.24[a]
2	19.4, CH_2	1.81[a]; 1.41[a]	20.4, CH_2	1.80[a]; 1.48[a]
3	38.0, CH_2	2.17, br. d (13.6); 0.99[a]	38.6, CH_2	2.15, br. d (13.4); 0.99[a]
4	44.1, C		45.1, C	
5	57.2, CH	1.02[a]	46.8, CH	1.65[a]
6	21.9, CH_2	1.84[a]; 1.80[a]	18.6, CH_2	2.52, br. q-*like* (11.5); 1.85[a]
7	41.3, CH_2	1.50, m; 1.43[a]	29.7, CH_2	1.97[a]; 1.46[a]
8	44.2, C		42.3, C	
9	54.9, CH	1.06[a]	156.1, C	
10	39.58, C		38.8, C	
11	18.4, CH_2	1.52–1.60 (2H, m)	114.8, CH	5.23, dd (3.5, 2.7)
12	33.1, CH_2	1.60[a]; 1.46, m	38.0, CH_2	2.42, ddd (17.0, 4.4, 2.7); 1.98, m
13	43.8, CH	2.63, br. s	41.3, CH	2.77, br. s
14	39.57, CH_2	1.95, dd (11.4, 1.3); 1.13, dd (11.4, 4.9)	45.0, CH_2	1.60[a]; 1.51, m
15	49.0, CH_2	2.05 (2H, m)	50.3, CH_2	2.61, br. d (15.6); 2.18, dt (15.6, 2.4)
16	155.9, C		158.6, C	
17	102.9, CH_2	4.79, br. s; 4.73, br. s	105.4, CH_2	4.91, 4.79, br. s
18	29.4, CH_3	1.18, s	28.6, CH_3	1.19, s
19	177.4, C		177.2, C	
20	16.2, CH_3	0.91, s	24.2, CH_3	0.99, s
1′	138.7, C		138.7, C	
2′	124.9, CH	5.43, br. s	125.1, CH	5.43, br. s
3′	71.3, CH	5.15, br. d (8.4)	71.4, CH	5.17, br. d (8.4)
4′	39.2, CH	1.83[a]	39.2, CH	1.84[a]
5′	29.8, CH_2	1.83[a]; 1.60[a]	30.0, CH_2	1.84[a]; 1.59[a]
6′	67.7, CH	4.02, t (3.3)	67.7, CH	4.02, t (3.5)
7′	20.4, CH_3	1.81, s	20.3, CH_3	1.80, s
8′	26.4, CH	1.87[a]	26.4, CH	1.85[a]
9′	17.1, CH_3	0.83, d (6.8)	17.1, CH_3	0.81, d (6.7)
10′	20.9, CH_3	0.96, d (6.8)	20.9, CH_3	0.96, d (6.7)

[a]signal overlapped

subsequently subjected to a silica gel column with a gradient elution (PE-acetone, 40:1→15:1) to yield fractions 3a–3c. Fraction 3a (6.5 g) yielded **6** (40 mg) and **8** (166 mg) after passing over a MCI gel (MeOH, 100%) and MPLC (MeOH-H_2O, 75%→82%, 10 mL/min). **1** (24 mg) and **11** (70 mg) were purified from fraction 3b (7.8 g) through a silica gel column (PE-acetone, 8:1). Fraction 3c (8.5 g) was further separated by silica gel (PE-acetone, 8:1), RP-18 (MeOH-H_2O, 70%), and silica gel-$AgNO_3$ (PE-acetone, 3:1→2:1) to yield **2** (16 mg), **7** (170 mg), **9** (25 mg), and **10** (9 mg). Fraction 5 (4.2 g), was eluted using 30% acetone, and purified using a silica gel column (PE-EtOAc, 4:1→3:1) to afford **14** (8 mg) and **15** (22 mg).

3*α*-Tigloyloxypterokaurene L_3 (1): amorphous powder; $[\alpha]_D^{19}$ − 72.9 (*c* 0.24, $CHCl_3$); IR (KBr) ν_{max} 3513, 2943, 2933, 2859, 1701, 1652, 1450, 1380, 1274, 1258, 1209, 1170, 1152, 1133, 1041, 970 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Table 1; ESIMS (pos.) *m/z* 439 $[M + Na]^+$; HREIMS *m/z* 416.2554 (calcd for $C_{25}H_{36}O_5$, 416.2563).

***ent*-17-Hydroxykaura-9(11),15-dien-19-oic acid (2):** amorphous powder; $[\alpha]_D^{19}$ − 43.6 (*c* 0.25, $CHCl_3$); IR (KBr) ν_{max} 3427, 3031, 2928, 2969, 1693, 1639, 1464, 1377, 1228, 1158, 1118, 1003, 988 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Table 1; ESIMS (neg.) *m/z* 315 $[M - H]^-$, HREIMS *m/z* 316.2028 (calcd for $C_{20}H_{28}O_3$, 316.2038).

Wedelobatin A (3): oil; $[\alpha]_D^{22}$ − 121.8 (*c* 0.41, $CHCl_3$); IR (KBr) ν_{max} 3428, 2956, 2929, 2872, 2853, 1719, 1657, 1465, 1447, 1386, 1369, 1227, 1149, 1015 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Table 2; ESIMS (pos.) *m/z* 477 $[M + Na]^+$, HREIMS *m/z* 454.3454 (calcd for $C_{30}H_{46}O_3$, 454.3447).

Wedelobatin B (4): oil; $[\alpha]_D^{21}$ − 29.2 (*c* 0.31, $CHCl_3$); IR (KBr) ν_{max} 3429, 2957, 2929, 2870, 1716, 1654, 1464, 1377, 1219, 1144, 1045, 1015, 985 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Table 2; ESIMS (pos.) *m/z* 475 $[M + Na]^+$, HREIMS *m/z* 452.3283 (calcd for $C_{30}H_{44}O_3$, 452.3290).

Electronic Supplementary Material

Supplementary material is available in the online version of this article at http://dx.doi.org/10.1007/s13659-013-0029-4 and is accessible for authorized users.

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