Four New Neoclerodane Diterpenoids from *Ajuga decumbens*

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Four new neoclerodane diterpenoids, 15-epilupulin A (**1**), 6-*O*-deacetylajugamarin (**2**), and ajugadecumbenins A (**3**) and B (**4**), were isolated from the whole plants of *Ajuga decumbens*. Their structures were elucidated on the basis of spectroscopic data and chemical correlations.

Introduction. – *Ajuga decumbens* THUNB. (family Labiatae) is a common perennial plant growing in China, Korea, and Japan. The whole herb of *A. decumbens*, has been used for the treatment of sore throat, removing phlegm, and alleviating fever as a folkloric crude drug [1][2]. Up to the present, several kinds of compounds have been isolated from *A. decumbens* and their structures have been characterized as neoclerodane diterpenoids [1–10], phytoecdysones [11–14], and iridoid glycosides [15], showing activities as insect antifeedants, insect-molting inhibitors, and bitter principles. As part of our ongoing research on the biologically active constituents of traditional Chinese herbal medicine [16–18], we investigated the chemical constituents of the plant *A. decumbens*, and four new neoclerodane diterpenoids, namely 15-epilupulin A[1]) (**1**), 6-*O*-deacetylajugamarin[1]) (**2**), and ajugadecumbenins A[1]) (**3**) and B[1]) (**4**), were isolated from the EtOH extract of the plant. The present paper describes the isolation and structural elucidation of these new compounds.

The plant *A. decumbens* was exhaustively extracted with 95% EtOH, and the EtOH extract was divided into Et_2O-, BuOH- and H_2O-soluble portions. The Et_2O-soluble portion was repeatedly subject to column chromatography (silica gel, petroleum ether/AcOEt gradients) to afford pure compounds **1**–**3**, while pure **4** was obtained by further HPLC purification (*C18*).

Results and Discussion. – The diterpenoid 15-epilupulin A[1]) (**1**) was obtained as colorless needles. The HR-EI-MS of **1** established a molecular formula $C_{30}H_{46}O_{11}$ (*m*/*z* 582.3068 (M^+). On the basis of some ^{1}H-NMR data (*Table 1*), the presence of a clerodane diterpene skeleton as that of lupulin A (**5**) [19] could be easily deduced. In fact, the ^{1}H- and ^{13}C-NMR spectra (*Table 1*) of **1** showed essentially the same signals as those present in the spectra of lupulin A. Further NMR data, including NOESY data (*Figure*), and their comparison with those of hativene A (**6**) [20] suggested that

[1]) Trivial atom numbering; for systematic names, see *Exper. Part.*

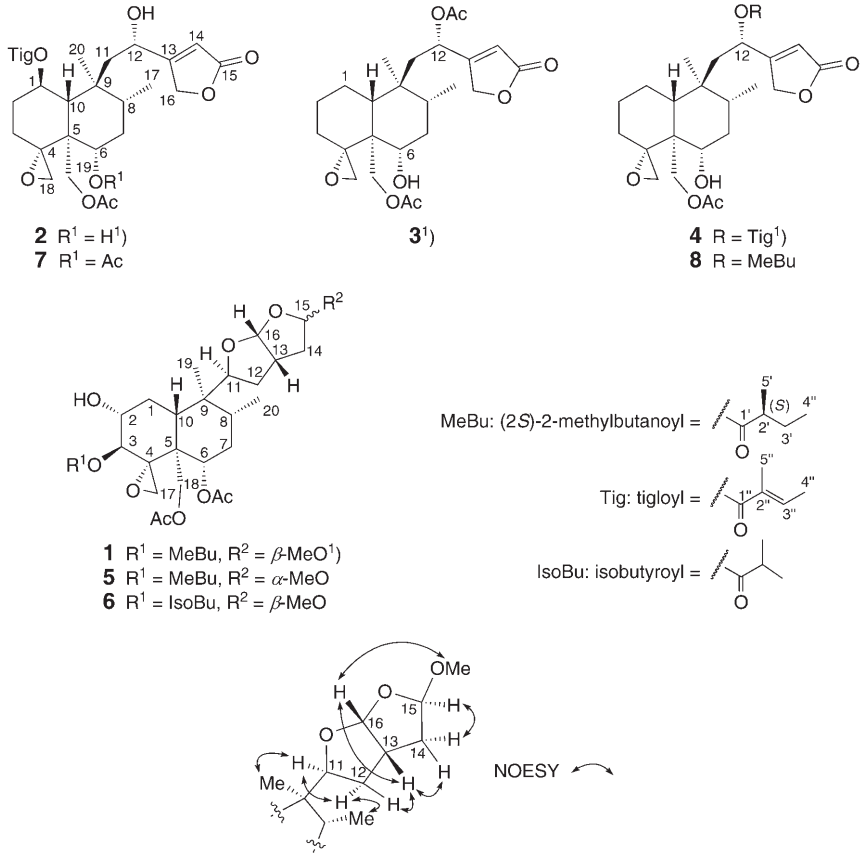

Figure. *Selected NOE correlations of the hexahydrofurofuran ring moiety of* **1**

MeO–C(15) of lupulin A (**5**) most likely should have α-configuration instead of the reported β one [19], and the structure of **1** was thus determined to be 15-epilupulin A.

The ^{1}H-NMR spectrum of **1** showed two acetate Me groups (δ 2.12 and 1.93), a MeO group (δ 3.32), and a 2-methylbutanoic acid ester functionality (2 Me groups at δ 0.89 (*t*, $J = 7.5$ Hz) and 1.11 (*d*, $J = 7.0$ Hz)). In addition, a characteristic Me *s* at δ 0.95 (*s*, Me(19)) and Me *d* at δ 0.87 (*d*, $J = 7.7$ Hz, Me(20)) were also observed. Likewise, the presence of a hexahydrofurofuran-ring moiety was suggested by the signals at δ 5.74 (*d*, $J = 5.5$ Hz, H–C(16)), 5.10 (*d*, $J = 4.8$ Hz, H–C(15)), 4.01 (*dd*, $J = 4.4$, 11.8 Hz, H–C(11)), and 3.00–3.02 (*m*, H–C(13)). These data were very similar to those of lupulin A (**5**) [19]. The observed differences between **1** and **5** were found mainly in the chemical shifts of H–C(11) ($\Delta\delta$ -0.36 ppm), H–C(13) ($\Delta\delta + 0.19$ ppm), and H–C(15) ($\Delta\delta$ -0.07 ppm) and in the coupling constant of H–C(15) ($J(14\alpha,15)$ 4.8 Hz in **1** and 5.6 Hz in **5**, suggesting that **1** is the C(15) epimer of lupulin A. The NOESY data (*Figure*) of **1** revealed the correlations MeO–C(15)/H–C(16), H–C(16)/H–C(13), H–C(13)/H_β–C(14) and H–C(15)/H_α–C(14), in accord with the β configuration of MeO–C(15). The chemical shift and coupling pattern of H–C(15) of **1**, including the NOESY data, were closely comparable to the H–C(15) signal of hativene A (**6**) (δ 5.08 (*d*, $J = 4.7$ Hz)) [20], further confirming the β configuration of MeO–C(15).

Table 1. *^{1}H- and ^{13}C-NMR Data*[a]) *of Compound* **1**. δ in ppm, J in Hz. Trivial atom numbering.

	δ(H)	δ(C)		δ(H)	δ(C)
H_α–C(1)	1.79–1.81 (*m*)	30.3 (*t*)	H_β–C(14)	2.20 (*dd*,	–
H_β–C(1)	2.63 (*ddd*,	–		*J* = 9.6, 12.9)	
	J = 2.6, 5.6, 13.7)		H–C(15)	5.10 (*d*, *J* = 4.8)	104.9 (*d*)
H_β–C(2)	3.64–3.65 (*m*)	71.8 (*d*)	H–C(16)	5.74 (*d*, *J* = 5.5)	107.3 (*d*)
H_α–C(3)	5.23 (*d*, *J* = 9.8)	72.4 (*d*)	H_a–C(17)	2.55 (*d*, *J* = 4.2)	42.5 (*t*)
C(4)	–	62.9 (*s*)	H_b–C(17)	2.78 (*d*, *J* = 4.2)	–
C(5)	–	45.6 (*s*)	H_a–C(18)	4.40 (*d*, *J* = 12.5)	61.5 (*t*)
H_β–C(6)	4.69 (*dd*, *J* = 11.5, 4.4)	71.2 (*d*)	H_b–C(18)	4.79 (*d*, *J* = 12.5)	–
H_α–C(7)	1.61–1.63 (*m*)	33.3 (*t*)	Me(19)	0.95 (*s*)	13.8 (*q*)
H_β–C(7)	1.50–1.51 (*m*)	–	Me(20)	0.87 (*d*, *J* = 7.7)	16.5 (*q*)
H_β–C(8)	1.44–1.46 (*m*)	35.9 (*d*)	C(1′)=O	–	175.6 (*s*)
C(9)	–	40.0 (*s*)	H–C(2′)	2.32–2.41 (*m*)	41.2 (*d*)
H–C(10)	1.67–1.69 (*m*)	43.7 (*d*)	H_a–C(3′)	1.42–1.44 (*m*)	26.7 (*t*)
H–C(11)	4.01 (*dd*, *J* = 4.4, 11.8)	83.0 (*d*)	H_b–C(3′)	1.60–1.63 (*m*)	–
H_α–C(12)	1.47–1.49 (*m*)	32.5 (*t*)	Me(4′)	0.89 (*t*, *J* = 7.5)	11.2 (*q*)
H_β–C(12)	1.71–1.73 (*m*)	–	Me(5′)	1.11 (*d*, *J* = 7.0)	16.3 (*q*)
H–C(13)	3.00–3.02 (*m*)	40.1 (*d*)	*Ac*O–C(6)	1.93 (*s*)	21.0 (*q*),
*Me*O–C(15)	3.32 (*s*)	54.7 (*q*)			170.0 (*s*)
H_α–C(14)	1.66–1.68 (*m*)	38.1 (*t*)	*Ac*O–C(18)	2.12 (*s*)	21.1 (*q*),
					170.1 (*s*)

[a]) Assignments made by DEPT, ^{1}H,^{1}H-COSY, HMQC, HMBC, and ROESY experiments.

Compound **2**, 6-*O*-deacetylajugamarin[1]), was obtained as colorless needles. The molecular formula of **2** was inferred as $C_{27}H_{38}O_9$ from the HR-EI-MS data (*m*/*z* 506.2530 (M^+)). The ^{1}H- and ^{13}C-NMR data (*Table 2*) of **2** were very similar to those of ajugamarin (**7**) [21]. In fact, **2** differs from **7** only by bearing a OH group instead of an AcO group at C(6). Due to the deacetyl effect, the O-bearing methine proton H–C(6) (δ 3.61 (*dd*, *J* = 4.4, 10.8 Hz)) of **2** was obviously upfield shifted with respect to H–C(6) of **7** (δ 4.8–4.6). The molecular mass of **2**, *i.e.*, 42 mass units lower than that of **7**, further supported structure **2** for this isolate. Compound **2** was, therefore, determined as the 6-*O*-deacetylajugamurin.

Ajugadecumbenin A[1]) (**3**) was obtained as colorless needles. The ESI-MS of **3** prominently showed a quasimolecular-ion peak at *m*/*z* 923.0 ($[2M + Na]^+$), and its molecular formula was inferred as $C_{24}H_{34}O_8$ from the HR-ESI-MS data (*m*/*z* 450.2269 (M^+). It was immediately apparent from the ^{1}H- and ^{13}C-NMR data (*Table 2*) of **3** that it shared the same molecular-skeleton with **2**. Further spectral data established that **3** is the 12-*O*-acetyl-1-de(tigloyloxy) derivative of **2**, named ajugadecumbenin A.

Two acetate Me signals (δ 2.07 and 2.10) in the ^{1}H-NMR spectrum suggested that **3** had an additional AcO group as compared to **2**. On the other hand, the signals for the tigloyloxy functionality and the downfield signal of H–C(1) of **2** were not observed in **3** indicating that there is no tigloyloxy group at C(1) of **3**. Moreover, the downfield-shifted broad *d* of H–C(12) (δ 5.80 (br. *d*, *J* = 9.0 Hz)) with respect to that of **2** suggested clearly that the OH group at C(12) of **2** (δ 4.71–4.73 (*m*, H–C(12))) was acetylated in **3**. The presence of an acetate group at C(12) was confirmed by the HMBC cross-peak between H–C(12) and the O-bearing ester carbonyl group (δ 169.5).

Table 2. *^{1}H- and ^{13}C-NMR Data*[a]) *of Compounds* **2**–**4**. δ in ppm, J in Hz. Trivial atom numbering.

	2		**3**		**4**	
	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)
H_α–C(1)	5.81 (*ddd*, *J* = 11.1, 11.1, 4.9)	71.3 (*d*)	1.56 (*dd*, *J* = 13.5, 2.1)	21.2 (*t*)	1.57–1.59 (*m*)	21.3 (*t*)
H_β–C(1)	–	–	1.78 (*d*, *J* = 13.5)	–	1.77 (*d*, *J* = 7.0)	–
H_α–C(2)	1.60–1.62 (*m*)	32.0 (*t*)	1.29–1.31 (*m*)	24.8 (*t*)	1.26–1.28 (*m*)	25.0 (*t*)
H_β–C(2)	2.17–2.19 (*m*)	–	2.02–2.04 (*m*)	–	2.06–2.07 (*m*)	–
H_α–C(3)	2.37–2.38 (*m*)	30.1 (*t*)	2.08–2.09 (*m*)	31.8 (*t*)	2.05–2.08 (*m*)	31.9 (*t*)
H_β–C(3)	1.17–1.19 (*m*)	–	1.09–1.11 (*m*)	–	1.10–1.12 (*m*)	–
C(4)	–	66.2 (*s*)	–	66.7 (*s*)	–	66.9 (*s*)
C(5)	–	46.1 (*s*)	–	45.3 (*s*)	–	45.4 (*s*)
H_β–C(6)	3.61 (*dd*, *J* = 4.4, 10.8)	73.0 (*d*)	3.53 (*dd*, *J* = 4.1, 11.1)	73.0 (*d*)	3.55 (*dd*, *J* = 4.5, 11.0)	72.9 (*d*)
CH_2(7)	1.59–1.61 (*m*)	33.8 (*t*)	1.51–1.52 (*m*)	33.7 (*t*)	1.58–1.59 (*m*)	33.8 (*t*)
H_β–C(8)	1.59–1.62 (*m*)	34.9 (*d*)	1.60–1.63 (*m*)	35.2 (*d*)	1.63–1.65 (*m*)	35.3 (*d*)
C(9)	–	39.6 (*s*)	–	39.5 (*s*)	–	39.6 (*s*)
H_β–C(10)	2.57 (*d*, *J* = 11.3)	50.2 (*d*)	1.37 (*dd*, *J* = 2.8, 12.3)	47.8 (*d*)	2.37 (*d*, *J* = 3.5)	47.9 (*d*)
H_α–C(11)	2.01 (*d*, *J* = 11.0, 16.0)	43.1 (*t*)	2.05–2.08 (*m*)	40.7 (*t*)	2.07–2.09 (*m*)	40.8 (*t*)
H_β–C(11)	1.55–1.57 (*m*)	–	1.56–1.58 (*m*)	–	1.56–1.58 (*m*)	–
H–C(12)	4.71–4.73 (*m*)	65.8 (*d*)	5.80 (*d*, *J* = 9)	66.3 (*d*)	5.72 (br. *d*, *J* = 8.7)	66.3 (*d*)
C(13)	–	170.5 (*s*)	–	168.2 (*s*)	–	168.1 (*s*)
H–C(14)	5.86 (*dd*, *J* = 1.7, 3.3)	114.5 (*d*)	5.92 (*dd*, *J* = 1.8, 3.1)	116.0 (*d*)	5.93 (br. *s*)	116.1 (*s*)
C(15)	–	173.7 (*s*)	–	172.3 (*s*)	–	171.7 (*s*)
H_α–C(16)	4.77 (*d*, *J* = 1.8)	70.9 (*t*)	4.71 (*dd*, *J* = 1.8, 17.6)	70.3 (*t*)	4.72 (*dd*, *J* = 1.9, 17.6)	70.4 (*t*)
H_β–C(16)	4.77 (*d*, *J* = 1.8)	–	4.82 (*dd*, *J* = 1.8, 17.6)	–	4.83 (*dd*, *J* = 1.9, 17.6)	–
Me(17)	0.86 (*d*, *J* = 6.7)	15.5 (*q*)	0.84 (*d*, *J* = 6.6)	15.5 (*q*)	0.85 (*d*, *J* = 6.5)	15.5 (*q*)
H_a–C(18)	2.55 (*d*, *J* = 3.4)	49.6 (*t*)	2.38 (*d*, *J* = 3.4)	48.3 (*t*)	2.40 (*d*, *J* = 3.6)	48.4 (*t*)
H_b–C(18)	3.33 (*dd*, *J* = 3.4, 2.2)	–	3.16 (*dd*, *J* = 3.4, 2.1)	–	3.19 (br. *s*)	–
H_a–C(19)	4.54 (*d*, *J* = 12.4)	62.3 (*t*)	4.49 (*d*, *J* = 12.0)	61.8 (*t*)	4.54 (*d*, *J* = 12.1)	61.8 (*t*)
H_b–C(19)	4.73 (*d*, *J* = 12.4)	–	4.54 (*d*, *J* = 12.0)	–	4.56 (*d*, *J* = 12.1)	–
Me(20)	0.82 (*s*)	17.7 (*q*)	0.71 (*s*)	17.3 (*q*)	0.74 (*s*)	17.3 (*q*)
C(1″)=O	–	166.1 (*s*)	–	–	–	168.2 (*s*)
C(2″)	–	129.1 (*s*)	–	–	–	128.5 (*s*)
H–C(3″)	6.72 (*dq*, *J* = 1.4, 6.9)	138.6 (*d*)	–	–	6.99 (*q*, *J* = 7.2)	138.0 (*d*)
Me(4″)	1.80 (br. *d*, *J* = 7.0)	12.7 (*q*)	–	–	1.79 (*d*, *J* = 7.2)	12.0 (*q*)
Me(5″)	1.85 (*s*)	14.5 (*q*)	–	–	1.85 (*s*)	14.5 (*q*)
*Ac*O–C(12)	–	–	2.07 (*s*)	20.9 (*q*), 169.5 (*s*)	–	–
*Ac*O–C(19)	2.12 (*s*)	21.1 (*q*), 170.9 (*s*)	2.10 (*s*)	21.1 (*q*), 171.0 (*s*)	2.11 (*s*)	21.1 (*q*), 171.0 (*s*)

[a]) Assignments made by DEPT, ^{1}H,^{1}H-COSY, HMQC, HMBC, and ROESY experiments.

Ajugadecumbenin B[1]) (**4**) was obtained as amorphous powder. The molecular formula of **4** was determined to be $C_{27}H_{38}O_8$ (HR-EI-MS: *m/z* 490.2551 (M^+)), with two H-atoms less than that of ajugamarin F_3 (**8**) [22]. Careful comparison of the ^{1}H- and ^{13}C-NMR data (*Table 2*) of **4** and **8** revealed that the only difference between those two compounds resided in the substitutents at C(12) (tigloyloxy in **4** and 2-methylbutanoyloxy in **8**).

In the ^{1}H-NMR spectrum of **4**, the signals due to two olefinic Me groups Me(4″) and Me(5″), replacing the Me signals of the 2-methylbutanoyl group of **8**, appeared as a *d* ($J = 7.2$ Hz) at δ 1.79 and a broad *s* at δ 1.85, resp. The presence of the 12-(tigloyloxy) group was further confirmed by comparison of the NMR data of **4** with those of the related compound ajugatakasin A [9].

The absolute configurations of compounds **1**–**4** including the configuration at C(2′) of the 2-methylbutanoyl group of **1** and **4** were not ascertained. However, biogenetic consideration led to the conclusion that these new diterpenoids had the same absolute structure as other neoclerodane-type diterpenoids isolated from *Ajuga* species whose absolute configurations have been established by X-ray diffraction analysis [23–26].

All the new compounds were evaluated for their inhibitory activity against hPTP1B (human protein tyrosine phosphatase 1B), a key target for the treatment of type-II diabetes and obesity [27], as well as cytotoxicity against several tumor cell lines. Unfortunately, the results indicated that all compounds were inactive. Other bioassays, such as antibacterial and anti-inflammatory activities, are currently ongoing.

Experimental Part

General. TLC: precoated silica gel plates (*Yan Tai Zi Fu Chemical Group Co.*; *G60*, *F-254*). Column chromatography (CC): commercial silica gel (*Qing Dao Hai Yang Chemical Group Co.*; 200–300 mesh) and *Sephadex LH-20* (*Amersham Biosciences*). Reversed-phase HPLC: *Agilent-1100* instrument for liquid chromatography, with a *VWD-G1314A* detector at 210 nm; semi-prep. *ODS-HG-5* (5 μm, 10 mm (i.d.) × 25 cm) column. M.p.: *X-5* apparatus; uncorrected. Optical rotations: *Perkin-Elmer 341* polarimeter. UV Spectra: *756-CRT* spectrophotometer; λ_{max} (log ε) in nm. IR Spectra: *Nicolet Magna-FT-IR-750* spectrophotometer; $\tilde{\nu}_{max}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: *Varian Mercury-400* spectrometer (^{1}H at 400 MHz and ^{13}C at 100 MHz); chemical shifts δ in ppm, with residual $CHCl_3$ (δ(H) 7.26, δ(C) 77.0) or CD_3OD (δ(H) 3.30, δ(C) 49.5) as internal standard, coupling constants *J* in Hz. ESI- and HR-ESI-MS: *Q-TOF-Micro* LC-MS/MS spectrometer; in *m/z*.

Plant Material. Plant material was purchased from *Shanghai Huayu Pharm. Co.* and identified as *A. decumbens* by Assoc. Prof. *J.-G. Shen* of the Shanghai Institute of Materia Medica, Chinese Academy of Sciences. A voucher specimen (P-21) is available for inspection at the Herbarium of the Shanghai Institute of Materia Medica, CAS.

Extraction and Isolation The dried whole plants (5.0 kg) of *A. decumbens* were powdered and exhaustively extracted with EtOH. The extract was concentrated, and the resulting residue was dissolved in H_2O and partitioned with Et_2O and BuOH resp. The Et_2O-soluble portion was repeatedly subjected to CC (silica gel, increasing amounts of AcOEt in petroleum ether): **1** (5.7 mg), **2** (18.0 mg), and **3** (41.0 mg). The fraction eluting with AcOEt/petroleum ether 9:1 was repeatedly subjected to CC (silica gel) and further purified by semi-prep. HPLC (*C18 TSK ODS* (5 μm), 45% aq. MeCN, flow rate 2.5 ml/min, detection at 210 nm): **4** (3.7 mg, t_R 42.7 min).

15-Epilupulin A (=*(2*S*)-2-Methylbutanoic Acid (1*R,*2*S,*3*R,*4a*R,*5*S,*6*R,*8*S,*8a*R*)-8-(Acetyloxy)-8a-[(acetyloxy)methyl]-5-[(2*S,*3a*S,*5*R,*6a*R*)-hexahydro-5-methoxyfuro[2,3-*b*]furan-2-yl]octahydro-3-hydroxy-5,6-dimethylspiro[naphthalene-1(2*H*),2′-oxiran]-2-yl Ester*; **1**): Colorless needles. M.p. 133–135°. $[\alpha]_D^{20} = -85$ ($c = 1.14$, $CHCl_3$). UV (MeOH): 218 (4.3). IR (KBr): 3450, 3025, 1729, 1644, 1391,

1251,1124. ^{1}H- and ^{13}C-NMR: *Table 1*. ESI-MS: 605.3 ($[M + Na]^+$). HR-EI-MS: 582.3068 (M^+, $C_{30}H_{46}O_{11}^+$; calc. 582.3096).

6-O-Deacetylajugamarin (*=(2*E*)-2-Methylbut-2-enoic Acid (1*R*,4*R*,4a*R*,5*S*,6*R*,8*S*,8a*R*)-8a-[(Acetyloxy)methyl]-5-[(2*S*)-2-(2,5-dihydro-5-oxofuran-3-yl)-2-hydroxyethyl]octahydro-8-hydroxy-5,6-dimethylspiro[naphthalen-1(2*H*),2′-oxiran]-4-yl Ester*; **2**): Colorless needles. M.p. 127–128°. $[\alpha]_D^{20} = +10$ ($c =$ 0.4, $CHCl_3$). UV (MeOH): 217 (4.2). IR (KBr): 3539, 3479, 1774, 1743, 1716, 1695, 1458, 1367, 1269, 1238, 1136, 1086, 883, 739. ^{1}H- and ^{13}C-NMR: *Table 2*. ESI-MS: 529.3 ($[M + Na]^+$). HR-EI-MS: 506.2530 (M^+, $C_{27}H_{38}O_9^+$; calc. 506.2544).

Ajugadecumbenin A (*=(1*R*,4a*R*,5*S*,6*R*,8*S*,8a*R*)-8a-[(Acetyloxy)methyl]-5-[(2*S*)-2-(acetyloxy)-2-(2,5-dihydro-5-oxofuran-3-yl)ethyl]-5,6-dimethylspiro[naphthalen-1(2*H*),2′-oxiran]-8-ol*; **3**): Colorless needles. M.p. 156–158°. $[\alpha]_D^{20} = 0$ ($c = 0.3$, $CHCl_3$). UV (MeOH): 217 (4.4). IR (KBr): 3477, 1778, 1747, 1643, 1367, 1261, 1229, 1036, 883. ^{1}H- and ^{13}C-NMR: *Table 2*. ESI-MS: 473.1 ($[M + Na]^+$), 923.0 ($[2M + Na]^+$). HR-EI-MS: 450.2269 (M^+, $C_{24}H_{34}O_8^+$; calc. 450.2284).

Ajugadecumbenin B (*=(2*E*)-2-Methylbut-2-enoic Acid (1*S*)-2-{(1*R*,4a*R*,5*S*,6*R*,8*S*,8a*R*)-8a-[(Acetyloxy)methyl]octahydro-8-hydroxy-5,6-dimethylspiro[naphthalene-1(2*H*),2′-oxiran]-5-yl}-1-(2,5-dihydro-5-oxofuran-3-yl)ethyl Ester*; **4**): Amorphous powder. $[\alpha]_D^{20} = +6$ ($c = 0.64$, $CHCl_3$). UV (MeOH): 218 (4.3). IR (KBr): 3483, 1778, 1743, 1718, 1700, 1468,1366, 1270, 1137, 1088, 886, 739. ^{1}H- and ^{13}C-NMR: *Table 2*. HR-EI-MS: 490.2551 (M^+, $C_{27}H_{38}O_8^+$; calc. 490.2535).

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