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DIACETOXY-SUBSTITUTED POLYACETYLENES FROM *ATRACTYLODES LANCEA*

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Key Word Index—*Atractylodes lancea*; Asteraceae; rhizomes; *Cang-zhu*; polyacetylenes; *threo-erythro*-isomerism.

Abstract—Six new polyacetylenes have been isolated from the rhizomes of *Atractylodes lancea*. Besides 1-(2-furyl)-(7*E*)-nonene-3,5-diyne-1,2-diacetate, a new natural compound, two further vicinal diacetoxyalkenynes were postulated as *erythro*- and *threo*-forms of (1,5*E*, 11*E*)-tridecatriene-7,9-diyne-3,4-diacetate in comparison with similar structures in the literature. Three other constituents turned out to be (3*E*,5*E*,11*E*)-tridecatriene-7,9-diyne-1,2-diacetate together with its (3*Z*)- and (5*Z*)-isomers. All structures were established by UV, EI-mass spectrometry, 1D and 2D NMR experiments. © 1997 Elsevier Science Ltd

INTRODUCTION

In traditional Chinese medicine, *Cang-zhu* (the rhizomes of *Atractylodes lancea* (Thunb.) DC. and *A. chinensis* (DC.) Koidz., has been used to treat rheumatic diseases, digestive disorders, mild diarrhoea and influenza, and is said to be a diaphoretic [1]. Previous phytochemical investigations showed the presence of the polyacetylenes, atractylodin, atractylodinol and acetylatractylodinol [2, 3]. Several reports deal with the composition of the essential oil [4–6]. We now report on the isolation and structural elucidation of six new polyacetylenes (**1–6**) obtained in the course of our search for the antiinflamatory active principle of *A. lancea* rhizomes.

RESULTS AND DISCUSSION

The *n*-hexane extract of rhizomes was subjected to silica gel column chromatography (CC). Further purification of the CC fractions by middle pressure liquid chromatography (MPLC) led to the isolation of three polyacetylenes (**1–3**) while modified separation on silica gel CC yielded three additional acetylenic compounds (**4–6**). Compounds **1**, **2**, **4** and **5** were obtained in a pure and crystalline state; **3** was oily and very unstable. Compound **6** could not be separated from **4** and had to be analysed from a mixture (3:2) with the latter. The characteristic UV absorption maxima of **1** at 284, 268, 245, 241, 215 and 208 nm indicated an ene-diyne-chromophore [7]. Compounds **2** and **3** showed the UV-spectrum of an ene-diyne-ene-chromophore ($\lambda_{max\ of\ 2\ and\ 3}$ = 313, 295, 277, 263, 247, 236, 231 and 218 nm) and **4–6** were observed to have the UV absorption maxima at 337, 316, 296, 280, 267, 251 and 208 nm, typical for a diene-diyne-ene-chromophore [7]. In the EI-mass spectrum of **1**, the $[M]^+$ occurred at *m/z* 300, in the mass spectra of the other acetylenes at *m/z* 286. The base, peak at *m/z* 43 in all mass spectra and a fragment at *m/z* 258 (**1**) or 244 (**2–6**), respectively, indicated at least one acetyl group in the molecules $[M\text{-}H_2C{=}C{=}O]^+$. The molecular structures of the acetylenes were determined by ^1H and ^{13}C NMR spectroscopy using COSY and HETCOR experiments. Chemical shift parameters and assignments of **2–6** are summarized in Tables 1 (protons) and 2 (carbons). The ^1H NMR spectra (300 MHz, **4** in addition: 500 MHz, $CDCl_3$, TMS) of the six acetylenes revealed in each case the presence of a terminal methyl group at $\delta \approx 1.8$ (J = 1.9 and 6.9 Hz) coupling with two *trans*-configurated olefinic protons at $\delta \approx 6.4$ (*dq*, $J \approx 6.9$ and ≈ 15.8 Hz) and at δ 5.5–5.6 (*dq*, J = 1–1.9 and ≈ 15.8 Hz). In the ^1H NMR spectra of all six compounds, two singlets (of three protons each) at $\delta \approx 2.1$ were also observed, which—with regard to the mass spectral observations—indicated diacetoxy-substituted acetylenes. ^1H NMR data of **1** differed from the others by the occurrence of three multiplets (δ = 6.51, 1H, *dt*, J = 3.3 and 0.7 Hz; δ = 6.37, 1H, *dd*, J = 3.3 and 1.9 Hz, and δ = 7.42, 1H, *dd*, 1.9 and 0.8 Hz) that

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Table 1. ^{1}H NMR chemical shift assignments and coupling constant data for acetylenes **2–6** (in $CDCl_3$/TMS, 300 MHz, except **4**: 500 MHz)

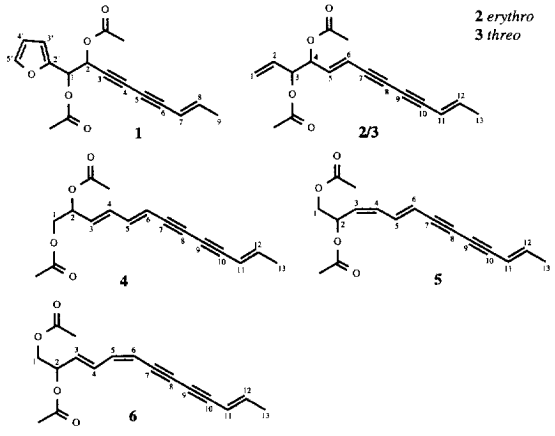
Proton	**2**	**3**	**4**	**5**	**6**
1a	5.32 *dt* (10.5, 1.2)	5.31 *dt* (10.5, 1.1)	4.10 *dd* (11.8, 6.9)	4.10 *dd* (11.8, 7.1)	4.15 *dd* (11.8, 6.8)
1b	5.34 *dt* (17.3, 1.2)	5.34 *dt* (17.3, 1.2)	4.25 *dd* (11.8, 3.8)	4.21 *dd* (11.7, 4.2)	4.28 *dd* (11.8, 3.8)
2	5.75 *ddd* (17.3, 10.5, 6.4)	5.73 *ddd* (17.3, 10.5, 6.1)	5.54 *dt* (6.7, 3.8)	5.86 *dddd* (8.7, 7.4, 4.1, 1.1)	5.6 *m*
3	5.42 *ddt* (6.4, 3.9, 1.1)	5.38 *tt* (6.1, 1.1)	5.74 *dd* (15.2, 6.6)	5.44 *t* (9.9)	5.83 *dd* (15.4, 6.8)
4	5.46 *ddd* (6.6, 3.9, 1.3)	5.45 *ddd* (6.3, 6.0, 1.3)	6.36 *dd* (15.6, 10.9)	6.22 *t* (11.3)	6.83 *ddt* (15.4, 11.1, 1.0)
5	6.16 *dd* (15.9, 6.6)	6.13 *dd* (15.9, 6.3)	6.65 *dd* (15.5, 10.9)	7.07 *ddd* (15.1, 11.7, 1.1)	6.47 *t* (11.0)
6	5.82 *dt* (15.9, 1.1)	5.82 *dt* (15.9, 1.1)	5.73 *d* (15.2)	5.76 *d* (15.6)	5.59 *d* (10.5)
11	5.58 *ddq* (15.7, 1.8, 0.9)	5.57 *ddq* (15.8, 1.8, 0.9)	5.59 *dq* (15.8, 0.9)	5.60 *dq* (15.8, 0.9)	5.61 *dq* (15.8, 1.0)
12	6.34 *dq* (15.7, 6.9)	6.34 *dq* (15.8, 6.9)	6.34 *dq* (16.1, 6.8)	6.35 *dq* (15.6, 6.9)	6.36 *dq* (15.8, 6.9)
13a,b,c	1.83 *dd* (6.9, 1.8)	1.83 *dd* (6.9, 1.8)	1.83 *dd* (6.9, 1.7)	1.84 *dd* (6.9, 1.7)	1.85 *dd* (6.9, 1.8)
$OCOCH_3$	2.08 *s* 2.09 *s*	2.090 *s* 2.094 *s*	2.07 *s* 2.10 *s*	2.07 *s* 2.08 *s*	2.08 *s* 2.12 *s*

Table 2. ^{13}C NMR chemical shift values of acetylenes **2**–**6** (75 MHz, in $CDCl_3$/TMS)

C-atom	2		3		4		5		6	
1	120.0		119.9		64.6		64.6		64.6	
2	131.2		131.5		71.3		68.0		71.4	
3	74.4		74.0		130.0		127.4		130.8	
4	73.6		73.2		132.9		132.2		131.0	
5	138.5		138.9		142.6		138.3		141.3	
6	113.7		113.5		112.3		113.9		110.2	
7, 8, 9, 10	71.9		71.9		72.3		72.3		72.2	
	76.1		76.2		77.7		78.4		77.3	
	77.7		77.7		79.5		79.5		81.0	
	81.4		81.4		82.2		82.6		82.8	
11	109.7		109.7		109.8		109.8		109.8	
12	144.2		144.3		144.0		144.1		144.0	
13	19.0		19.0		19.0		19.0		19.0	
$O\underline{C}OCH_3$	169.7	169.9	169.58	169.7	170.0	170.6	70.0	170.6	170.2	170.7
$OCO\text{-}\underline{C}H_3$	20.9	21.0	20.86	20.9	20.8	21.1	20.8	21.0	20.8	21.1

indicated a substituted furyl ring system, also present in the known compound, atractylodin [2]. One clue to determine the linkage of the furyl ring to the carbon chain was that the signal of H-3′ at δ 6.51 appeared as a doublet of triplets, demonstrating the presence of a long-range coupling ($\approx$0.6 Hz) with the proton at C-1 (δ 6.10, 1H, *bd*, J = 5.5 Hz). This proton and its vicinal coupling partner at δ 5.94 (1H, *dd*, J = 5.5 and 0.8 Hz) are both attached to the acetoxyl-bearing carbons. The latter showed a long-range coupling to the olefinic proton at C-7 (J = 0.8 Hz). Thus, polyacetylene **1** was determined to be 1-(2-furyl)-(7*E*)-nonene-3,5-diyne-1,2-diacetate, which is a new natural compound.

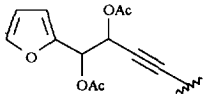
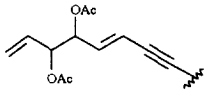
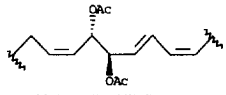
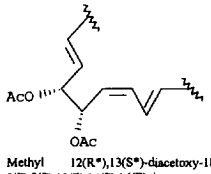
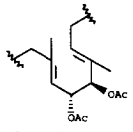
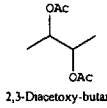
Compound **2** showed signals for two terminal vinylic protons at δ = 5.34 and 5.32 (H-1a,b) with a geminal coupling constant of J = 1.2 Hz and a vicinal coupling J = 10.5 or 17.3 Hz, respectively, to a one proton signal at δ 5.75 (H-2) that itself coupled with another proton (H-3) attached to the first acetoxyl-bearing carbon (δ = 5.42, 1H, *ddt*; J = 1.1, 3.9 and 6.4 Hz). The carbon chain is continued by a second acetoxyl-bearing carbon with a proton-signal (H-4) at



δ 5.46 (*ddd*, J = 1.3, 3.9 and 6.6 Hz). The latter coupled with two *trans*-configurated olefinic protons at δ 6.16 (*dd*, J = 6.6 and 15.9 Hz) and δ 5.82 (*dt*, J = 1.1 and 15.9 Hz), which form the beginning of the ene-diyne-ene-chromophore attached to a terminal olefinic methyl group, as mentioned above. From these spectral data, the structure of **2** was elucidated as (1,5*E*,11*E*)-tridecatriene-7,9-diyne-3,4-diacetate, a constituent already known from *Dahlia* species [8], but new for the genus *Atractylodes*.

So far, the configuration of carbon atoms 3 and 4 in compound **2** have not been assigned—theoretically, two *threo*- and two *erythro*-enantiomers are possible. By highfield NMR, compound **3** was shown to be an isomer of compound **2**, that in all spectral data only differed significantly from **2** in the magnitude of the coupling H-3–H-4; J(H-3/H-4) of **2** was 3.9 Hz, J(H-3/H-4) of **3** was 6.0 Hz. Comparison with similar compounds in the literature (Table 3), like sargatriol triacetate [11] with the *threo*-configuration (J = 8 Hz) or methyl-(12*R*,13*S*)-diacetoxy-18-keto-(5*Z*,8*Z*,10*E*,14*Z*,16*E*)-eicosapentaenote (J = 4 Hz, *erythro*-configuration) [10], led us to the conclusion that polyacetylene **2** must have the *erythro*-form of (1,5*E*,11*E*)-tridecatriene-7,9-diyne-3,4-diacetate; **3** is therefore its *threo* isomer. From this point of view, acetylene **1** that contains the same partial structure with a coupling constant of J = 5.5 Hz has to be considered as the *threo*-form. An explanation for the larger coupling constants of the vicinal protons in the *threo*-compounds and for the fact that the isomers show only small chemical shift differences in ^1H and ^{13}C NMR spectra, can be found in the conformational consequences [13] of the gauche-effect implying the preference for the gauche-conformation [14]. Neglect of this effect—that comes into operation in case of very electronegative substituents—can lead to erroneous configurational assignments ([9], see Table 3).

Table 3. Coupling constants of protons attached to vicinal diacetoxy substituted carbons for compounds **1–3** and model compounds

Compounds	$^3J_{H/H}$ erythro	$^3J_{H/H}$ *threo*	Reference
 **1**		5.5	This paper
 **2/3**	3.9(**2**)	6.0(**3**)	This paper
 Methyl-12(R),13(S)-diacetoxy 5(Z),8(Z),10(E),14(Z)-icosatetraenoic acid	3.7		*Structure revised*:[10]
 Methyl 12(R*),13(S*)-diacetoxy-18-keto-5(Z),8(Z),10(E),14(Z),16(E)eicosapentaenoate	4.0		[10]
 Sargatriol triacetate		8.0	[11]
 2,3-Diacetoxy-butane	3.5 (*meso*)	5.1 (*racemic*)	[12]

Polyacetylenes **4–6** seemed to have a common skeleton that only differed in the configuration of the double bonds. The M_r and mass spectral fragments, the chromophore and the NMR shifts and assignments—the latter could even be determined for compound **4** in a mixture with **6**—gave evidence that the basic structure was tridecatriene-7,9-diyne-1,2-diacetate, a polyacetylene first isolated from *Centaurea ruthenica* without assignment of the double bond configuration [15]. The coupling constants of the olefinic protons of polyacetylenes **4–6** showed that all the double bonds of **4** are *trans*-configurated, while **5** and **6** represent the 3(*Z*)- and 5(*Z*)-isomers, respectively. Interestingly, the main compound of these isomers in the rhizomes of *A. lancea* was the very unstable 3(*Z*),5(*E*),11(*E*)-isomer, **5**.

The six new acetylenes were subjected to cyclooxygenase (COX-1) and 5-lipoxygenase inhibition assays but did not show any significant inhibitory activity on both enzymes. Further results on antiinflammatory active compounds of *Cang-zhu* are in progress.

EXPERIMENTAL

Plant material. Provided by the TCM-hospital in Kötzting, Germany. A voucher specimen is deposited at the Institute of Pharmaceutical Biology, Düsseldorf. NMR spectra were recorded at 300 MHz (^{1}H) and 75 MHz (^{13}C) on a Varian VXR-300 (^{1}H NMR of **4** on a Bruker DRX 500) in $CDCl_3$. Chemical shifts are expressed in δ values from TMS as int. standard, coupling constants are given in Hz. δ were recorded at 70 eV from HPLC GC/EI-MS. UV spectra were taken on-line. CC was carried out on silica gel (230–400 mesh, Merck) and on Sephadex LH 20 (Pharmacia). MPLC columns were filled with RP-18 silica

gel (25–40 μm, Merck). After every evapn step, the residue was flushed with N_2. Cyclo-oxygenase and 5-lipoxygenase assays were performed as described previously [16, 17].

Extraction and isolation. Dried rhizomes (570 g) were extracted in a soxhlet apparatus with *n*-hexane for 150 hr. The extract was evapd to an oily mass (46 g). Continuous flash CC with *n*-hexane, then *n*-hexane–EtOAc mixts, on silica gel afforded a fr. (*n*-hexane–EtOAc, 8:2, 3 g) that was separated further by CC on silica gel with the same eluents. *n*-Hexane–EtOAc (91:9) yielded three impure frs containing **1** and **2** (160 mg), **3** (115 mg) and **4–6** (320 mg). Further purification was achieved on RP-18 material using MPLC with MeOH–H_2O gradients and afforded **1** (10 mg), **2** (16 mg) and **3** (6 mg). Acetylenes **4–6** were purified on a silica gel column using toluene with an increasing percentage of EtOAC as the mobile phase. One of the obtained frs consisted of **5** (22 mg). **4** (2 mg) recrystallized from another fr. Efforts were made to separate **6** and **4** from a third fr. (15 mg) by RP-18 MPLC—the peaks were separated in the chromatogram—after evaporation, however, every fr. contained again **4** and **6** in the same ratio (*ca* 3:2). Therefore, NMR spectra were taken of the mixt.

1-(2-*Furyl*)-(*E*)-*nonene*-3,5-*diyne*-1,2-*diacetate* (**1**). White crystals. $[\alpha]_D^{23°} = +29.2°$ (EtOH; *c* 0.13). UV λ_{max} nm: 284, 268, 254, 241, 215, 208. IR ν_{max} cm^{-1}: 2920, 2840, 2220 (-C≡C-), 1740 and 1360 (-$OCOCH_3$), 1220, 1210, 1020 (-C=C-), 940 (*trans*-C=C-), 740. EI-MS *m/z* (rel int.): 300 $[M]^+$ (<1), 258 $[M-H_2C=C=O]^+$ (8), 139 (38), 119 (39), 97 (85), 43 $[H_3C\text{-}C=O]^+$ (100). ^1H NMR (300 MHz, $CDCl_3$): δ 6.10 (1 H, *bd*, *J* = 5.5 Hz, C-1), 5.94 (1H, *dd*, *J* = 5.5, 0.8 Hz, C-2), 5.52 (1H, *ddq*, *J* = 15.8, 1.9, 0.8 Hz, C-7), 6.37 (1H, *dq*, *J* = 15.8, 6.9 Hz, C-8), 1.83 (3H, *dd*, *J* = 6.9, 1.9 Hz, C-9), 6.51 (1H, *dt*, *J* = 3.3, 0.7 Hz, C-3′), 6.37 (1H, *dd*, *J* = 3.3, 1.9 Hz, C-4′), 7.42 (1H, *dd*, *J* = 1.9, 0.8 Hz, C-5′), 2.06 and 2.14 (each 3H, *s*, -$OCOCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 68.24 (C-1), 64.00 (C-2), 71.28, 71.83, 74.37 and 78.40 (C-3,4,5,6), 109.25 (C-7), 145.08 (C-8), 18.99 (C-9), 148.08 (C-2′), 110.36 (C-3′), 110.48 (C-4′), 143.17 (C-5′), 169.19 and 169.65 (-$\underline{C}OOCH_3$), 20.64 and 20.84 (-$COO\underline{C}H_3$).

erythro-(1,5*E*,11*E*)-*Tridecatriene*-7,9-*diyne*-3,4-*diacetate* (**2**). White crystals. $[\alpha]_D^{23°} = +44.2°$ (EtOH; *c* 0.44). UV λ_{max} nm: 313, 295, 277, 263, 247, 236, 231, 218 nm. IR ν_{max} cm^{-1}: 2920, 2850, 2200 (-C≡C-), 1740 and 1370 (-$OCOCH_3$), 1220, 1020 (-C=C-), 940 (*trans*-C≡C-). EI-MS *m/z* (rel int.): 286 $[M]^+$ (<1), 244 $[M-H_2C=C=O]^+$ (<1), 145 (64), 115 (49), 43 $[H_3C\text{-}C=O]^+$ (100). ^1H NMR (300 MHz, $CDCl_3$): Table 1. ^{13}C NMR (75 MHz, $CDCl_3$): Table 2.

threo-(1,5*E*,11*E*)-*Tridecatriene*-7,9-*diyne*-3,4-*diacetate* (**3**). Yellow oil. $[\alpha]_D^{23°} = -18.7°$ (EtOH; *c* 0.13). UV λ_{max} nm: 313, 295, 277, 263, 247, 236, 231, 218 nm. IR ν_{max} cm^{-1}: 2920, 2850, 2200 (-C≡C-), 1740 and 1370 (-$OCOCH_3$), 1220, 1020 (-C=C-), 940 (*trans*-C=C-). EI-MS *m/z* (rel int.): 286 $[M]^+$ (<1), 244 $[M-H_2C=C=O]^+$ (<1), 145 (73), 115 (30), 43 $[H_3C\text{-}C=O]^+$ (100); ^1H NMR (300 MHz, $CDCl_3$): Table 1; ^{13}C NMR (75 MHz, $CDCl_3$): see Table 2.

(3*E*,5*E*,11*E*)-*Tridecatriene*-7,9-*diyne*-1,2-*diacetate* (**4**). White crystals. UV λ_{max} nm: 337, 316, 296, 280, 267, 251, 208. IR ν_{max} cm^{-1}: 2910, 2840, 2190 (-C≡C-), 1730 and 1360 (-$OCOCH_3$), 1220, 1120 (-C=C-), 1020, 980, 940 (*trans*-C=C-). EI-MS *m/z* (rel int.): 286 $[M]^+$ (<1), 244 $[M-H_2C=C=O]^+$ (<1), 184 $[M-H_3C\text{-}COOH\text{-}H_2C=C=O]^+$ (62), 115 (38), 93 (47), 43 $[H_3C\text{-}C=O]^+$ (100). ^1H NMR (500 MHz, $CDCl_3$): Table 1. ^{13}C NMR (75 MHz, $CDCl_3$): Table 2.

(3*Z*,5*E*,11*E*)-*Tridecatriene*-7,9-*diyne*-1,2-*diacetate* (**5**). White crystals. UV λ_{max} nm: 337, 316, 296, 280, 267, 251, 208. EI-MS *m/z* (rel int.): 286 $[M]^+$ (<1), 244 $[M]-H_2C=C=O]^+$ (<1), 184 $[M-H_3C\text{-}COOH\text{-}H_2C=C=O]^+$ (77), 115 (70), 93 (78), 43 $[H_3C\text{-}C=O]^+$ (100). ^1H NMR (300 MHz, $CDCl_3$): Table 1. ^{13}C NMR (75 MHz, $CDCl_3$): Table 2.

(3*E*,5*Z*,11*E*)-*Tridecatriene*-7,9-*diyne*-1,2-*diacetate* (**6**). Oily in a mixt. with (**4**), yellow-brownish. UV λ_{max} nm: 337, 316, 296, 280, 267, 251, 208. EI-MS *m/z* (rel int.): 286 $[M]^+$ (<1), 244 $[M-H_2C=C=O]^+$ (<1), 184 $[M-H_3C\text{-}COOH\text{-}H_2C=C=O]^+$ (65), 115 (41), 93 (53), 43 $[H_3C\text{-}C=O]^+$ (100). ^1H NMR (300 MHz, $CDCl_3$): Table 1. ^{13}C NMR (75 MHz, $CDCl_3$): Table 2.

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