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TERPENOIDS FROM *CROTON CAJUCARA*

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Key Word Index—*Croton cajucara*; Euphorbiaceae; clerodane diterpenes; *t*-cajucarin B; sacacarin; acetyl aleuritolic acid.

Abstract—The bark of *Croton cajucara* afforded two novel clerodane-type furano-diterpenes, *t*-cajucarin B and sacacarin, in addition to the previously isolated *nor*-clerodane diterpenes *t*-crotonin, *t*-dehydrocrotonin, cajucarin B and cajucarinolide. The triterpene acetyl aleuritolic acid, was also obtained. Structure elucidation was achieved by spectroscopic measurements including 2D-NMR experiments.

INTRODUCTION

The *Croton cajucara* Benth occurs widely in the Amazon region of northern Brazil, where it is popularly known as "sacaca" and has a history of safe use in folk medicine [1–3]. We are undertaking an extensive phytochemical study involving all parts of *C. cajucara*, from the roots to the leaves, and here report about the bark, which contains several *nor*-clerodane diterpenes [4–8]. The clerodane group of diterpenes include more than 800 isolated compounds [9] and a significant number of these compounds show biological activity such as insect antifeedants, antimicrobial, antiviral, piscicidal, psychotropic, antiulcer and antitumor [10–15]. Our work showed that only the bark of this plant is a rich source of clerodanes, where the major components are the known *t*-dehydrocrotonin **(1)** [5, 6, 8] and the triterpene acetyl aleuritolic acid **(2)** [16–20] and, as minor constituents two novel clerodane-type furano-diterpenes named *t*-cajucarin B **(3)** and sacacarin **(4)**. Among minor constituents the known clerodanes *t*-crotonin **(5)** [6], cajucarin B **(6)** [7] and cajucarinolide **(7)** [8] were also isolated.

RESULTS AND DISCUSSION

Fractionation of the hexane and methanol extracts of the bark of "sacaca" has led to the isolation and characterization of the known terpenoids **(1, 2, 5, 6, 7)** and two new diterpenes **3** and **4**. The infrared spectra of compounds **3** and **4** showed the presence of an α,β-unsaturated ketone [1661 cm^{-1} **(3)** and 1667 cm^{-1} **(4)**] and of a furyl group [1505; 875 cm^{-1} **(3)** and 1511; 874 cm^{-1} **(4)**] confirmed by a positive Ehrlich test [21]. The absorptions at 1720 cm^{-1} **(3)** and 1725 cm^{-1} **(4)** suggested the presence of a lactone carbonyl or a methoxycarbonyl group [7]. The presence of a methoxycarbonyl group in compound **3** was revealed by a singlet signal at δ 3.66 (3H) in the ^1H NMR spectrum. The absence of this signal in the ^1H NMR spectrum of **4** allowed attribution of the absorption at 1725 cm^{-1} to a lactone ring. Further analysis of the ^1H NMR spectrum indicated for both **3** and **4** the presence of a secondary methyl group [δ 0.91 (3H, *d*, $J=6.1$ Hz) **(3)** and 1.00 (3H, *d*, $J=6.5$ Hz) **(4)**], a methyl group attached to sp^2 carbon [δ 1.94 (3H, *br s*) **(3)** and 2.00 (3H, *d*, $J=1.3$ Hz) **(4)**] and a β-substituted furyl group [δ 6.24 (1H, *dd*, $J=0.8$ and 1.7 Hz), 7.20 (1H, *t*, $J=0.7$), 7.32 (1H, *t*, $J=1.7$ Hz) **(3)** and 6.28 (1H, *dd*, $J=0.8$ and 1.6 Hz), δ 7.25 (1H, *m*), δ 7.36 (1H, *t*, $J=1.6$) **(4)**]. Comparative analysis of the proton noise decoupled (PND) and distortionless enhancement by polarization transfer ^{13}C NMR spectra (DEPT) was used to obtain the number of bound hydrogens for each carbon signal (Tables 1, 2, 3 and 4). This analysis in combination with the indications obtained from the heteronuclear ^1H-^{13}C-COSY-$^1J_{CH}$ ($n=1$; $n=2$ and $n=3$, COLOC) 2D shift-correlated spectra allowed us to postulate that **3** was 19-*nor*-clerodane, with a *trans*-A/B ring junction indicated by the coupling constant observed in the signal of the allylic H-5 [δ 2.98 (1H, *br t*, $J=10.7$ Hz)] and **4** was a clerodane-type diterpene with a C-20-C-19 lactone

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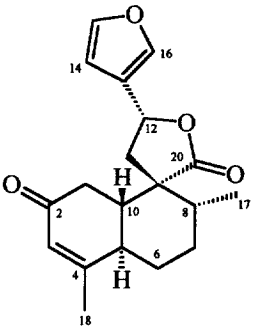

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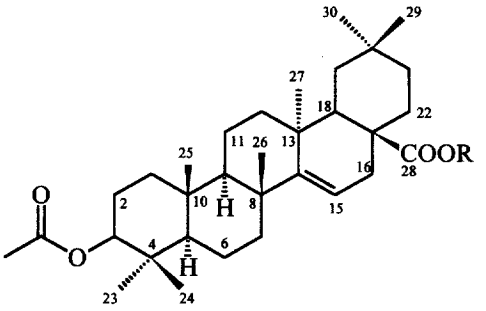

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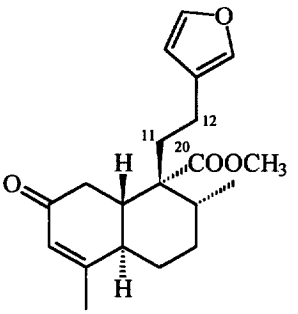

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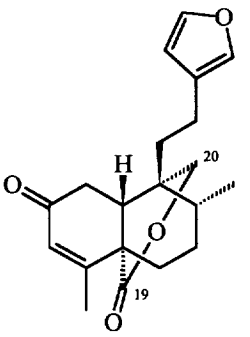

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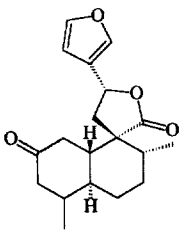

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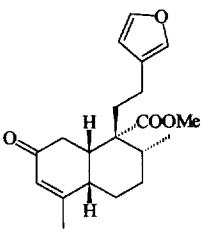

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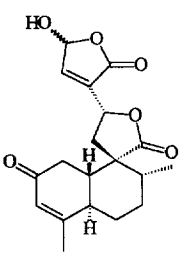

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ring, suggested by the absence of H-5 or a substitute group at the position C-5.

The molecular formula of compound **3**, $C_{20}H_{26}O_4$ was determined by high resolution mass spectrometry [M^+. obs. 330.1834 (27%), calc. 330.1831]. The major fragmentations of both compounds **3** and **6** were identical, a difference was only observed in the relative intensity of the peaks. The dominant fragmentation of the molecular ion of both compounds **3** and **6** gave the ions at *m/z* 121 and 81 as the base peaks of **3** and **6**, respectively. The functional groups of **3** were also identical to those of compound **6**. However, the ^1H NMR and ^{13}C NMR spectra of the decalin moiety of compound **3** were quite similar in appearance to those of *trans*-dehydrocrotonin **1**. This suggested that **3** was a 19-*nor*-clerodane epimer at C-5 of cajucarin B **(6)**. The ^{13}C NMR signals at δ 39.64 C-1, 29.43 C-6, 31.15 C7, 35.66 C-8, 43.41 C-10, and 31.51 C-11 of compound **3** and the ^1H NMR (spectrum recorded at 400 MHz [7]) signal at δ 2.40 H-5 (*dt*, $J = 12.5$ and 3.7 Hz) of compound **6**, revealed the differences between the compounds **3** and **6**. Compound **6** showed upfield shifts at δ 37.46 C-1, 21.03 C6, 27.58 C7, 31.72 C-8 and 38.56 C10 and a downfield shift at δ 37.75 C-11.

The name cajucarin B, that was given to compound **6** [7], could be confused with *t*-cajucarin B **(3)**. Thus, we propose the name *c*-cajucarin B for **6**, which clearly indicates the *cis*-A/B ring junction. Once the structure of **3** was established, analysis of the spectral data of **4** was relatively simple. The molecular formula $C_{20}H_{24}O_4$ was determined by high resolution mass spectrometry [M^+. obs. 328.1665 (36%), calc. 328.1674]. Its ^1H NMR and ^{13}C NMR spectra were

Table 1. ^{1}H NMR (300 MHz) HETCOR and COLOC data for compounds **3**

H	**3** ($CDCl_3$)	**3** (Benzene-d_6)	Correlated carbon	
			HETCOR	COLOC
1	1α 2.13 *dd* (16.0, 14.3)	2.37 *dd* (15.9, 14.3)	39.64	C-2, C-3
	1β 2.50 *dd* (16.0, 3.2)	2.85 *dd* (15.9, 2.8)		
3	5.85 *t* (1.0)	6.11 *br s*	127.15	C-18
5	2.98 *br t* (10.7)	3.04 *br t* (10.6)	40.63	
6	6α 2.37†		29.43	C-8
	6β 1.12†			
7	7α 1.87†		31.15	
	7β 1.64†			
8	1.73†		35.66	
10	1.83†		43.41	C-20
11	2.11†		31.51	
12	2.37†		18.77	
14	6.24 *dd* (1.7, 0.8)	6.21 *dd* (1.7, 0.8)	111.38	C-16
15	7.35 *t* (1.7)	7.29 *dd* (3.3, 1.7)	143.48	C-14
16	7.20 *t* (0.7)	7.16 *br s*	139.25	C-13, C-15
17	0.91 *d* (6.1)	0.98 *d* (6.6)	17.67	C-9
18	1.92 *br s*	1.60 *t* (1.2)	22.50	C-3, C-4
MeO	3.66 *s*	3.36 *s*	51.69	C-20

Solution in $CDCl_3$ referenced to $CHCl_3$ at δ 7.26 ppm. Benzene-d_6, TMS as internal standard. Values in parentheses are coupling constants (Hz).

† Values deduced through homonuclear ^{1}H × ^{1}H-COSY and heteronuclear ^{1}H × ^{13}C-COSY-$^n J_{CH}$ ($n=1$; $n=2$ and 3, COLOC) 2D shift-correlated NMR spectra.

Table 2. ^{13}C NMR (75.4 MHz) data for compound **3** (δ ppm)

C	**3**	**DEPT**
1	39.64	CH_2
2	199.32	C
3	127.15	CH
4	166.71	C
5	40.63	CH
6	29.43	CH_2
7	31.15	CH_2
8	35.66	CH
9	52.94	C
10	43.41	CH
11	31.51	CH_2
12	18.77	CH_2
13	124.97	C
14	111.38	CH
15	143.48	CH
16	139.25	CH
17	17.67	CH_3
18	22.50	CH_3
20	174.95	C
MeO	51.69	

Solution in $CDCl_3$ referenced to $CHCl_3$ at δ 77.23 ppm.

similar regarding the decalin and furyl moieties of compounds **1** and **3**. In fact, the observed modifications were in agreement with the existence of a δ-lactone ring involving the carbon atoms C-19 and C-20: 19,20-epoxy-19-*oxo* or 19,20-epoxy-20-*oxo*. The 2D NMR technique heteronuclear ^{1}H × ^{13}C-COSY-$^n J_{CH}$ ($n=2$ and 3, COLOC), coupling via two and three bonds, was used to define the alternative 19,20-epoxy-19-*oxo*. Compound **4** clearly showed the carbon atom (δ 35.22) coupled through three-bonds to the 2H-20 (δ 4.43). The new position C-20 of the methylene group of the lactone ring of compound **4**, revealed an unusual diterpenoid, sacacarin **4**, present in the natural occurring of clerodane diterpenoids series. This may be of chemotaxonomic significance since the C-20-C-19 lactone ring in previously isolated clerodane diterpenes always had the methylene group at the position-19 [12, 15, 22–25]. The ^{1}H NMR spectrum of previous compounds, where the methylene group is at position C-19 of the C-20-C-19 lactone ring, exhibited two doublets due to H-19A and H-19B [6, 22–25] but the signal due to the methylene group (H-20A and H-20B) of the C-20-C-19 lactone ring of compound **4**, showed a singlet. Although the downfield shifted methylene group (2H-20) and lactone carbonyl group (C-19) of compound **4**, appeared at the same region as in the previous cases [12, 15, 22–25]: ^{1}H NMR and ^{13}C NMR, $CDCl_3$: δ 4.21 *d*, H-19A; δ 4.39 *d*, H-19B and δ 173.5 C-20, as an example from literature [22] and ^{13}C NMR, $CDCl_3$: δ 4.43 *s*, H-20 and δ 171.6 C-19, from compound **4**. It is noteworthy that the expected doublets of H-20 from compound **4**, were obtained in a benzene-d_6 solution [H-20A δ 3.74 (1H, *d*, $J=11.9$) and H-20B δ 3.83 (1H, *dd*, $J=11.9$ and 2.4 Hz)]. With respect to stereochemistry, the decalin moiety of sacacarin is believed to have the

Table 3. ^{1}H NMR (300 MHz), HETCOR and COLOC data for Compound **4**

H	CDCl3	Benzene-d_6	Correlated carbon	
			HETCOR	COLOC
1	1α 2.42-2.32†	1.99 *dd* (16.4, 14.4)	36.69	C-2, C-9
	1β 2.67†	2.69 *dd* (16.4, 3.2)		
3	5.96 *d* (1.2)	5.86 *br s*	128.28	C-1, C-18
6	6α 2.47†		29.08	C-19
	6β 1.75†			
7	7α 1.28†		29.45	
	7β 1.97†			
8	1.97†		36.34	
10	2.42−2.32†		43.22	C-2
11	2.31−1.68†		35.22	
12	2.31−2.22†		17.10	
14	6.28 *dd* (1.6, 0.8)	6.21 *t* (0.8)	110.70	
15	7.36 *t* (1.6)	7.29 *m*	143.07	
16	7.25 *m*	7.29 *m*	138.71	C-13
17	1.00 *d* (6.5)	1.01 *d* (6.0)	16.05	
18	1.96 *d* (1.3)	1.28 *d* (1.3)	20.58	C-3, C-4
20	4.43 *s*	20A 3.74 *d* (11.9)	74.45	C-11
		20B 3.83 *dd* (11.9, 2.4)		

Solution in $CDCl_3$ referenced to $CHCl_3$ at δ 7.26 ppm. Benzene-d_6, TMS as int. standard.
Values in parentheses are coupling constants (Hz).
† Values deduced through homonuclear ^{1}H × ^{1}H-COSY and heteronuclear ^{1}H × ^{13}C-COSY-$^n J_{CH}$ ($n=1$; $n=2$ and 3, COLOC) 2D shift-correlated NMR spectra.

Table 4. ^{13}C NMR (75.4 MHz) data for compound **4**

C	**4** (δ ppm)	**DEPT**
1	36.69	CH_2
2	195.78	C
3	128.28	CH
4	163.52	C
5	49.34	C
6	29.08	CH_2
7	29.45	CH_2
8	36.34	CH
9	38.41	C
10	43.22	CH
11	35.22	CH_2
12	17.10	CH_2
13	123.76	C
14	110.70	CH
15	143.07	CH
16	138.71	CH
17	16.05	CH_3
18	20.58	CH_3
19	171.67	C
20	74.45	CH_2

Solution in $CDCl_3$ referenced to $CHCl_3$ at δ 77.23 ppm.

configuration depicted in formula **4**, like the other known *trans*-clerodane diterpenoids in which the three one-carbon substituents at C-5, C-8 and C-9 are *cis*- to one another [12, 15]. In the sequence of names of clerodane diterpenes isolated from *C. cajucara* [4–8] we propose the name sacacarin for compound **4**, which is correlated with "sacaca".

EXPERIMENTAL

Mps: uncorr.; ^{1}H and ^{13}C NMR: 300 and 75 MHz, respectively; IR and UV; $CHCl_3$ and MeOH, respectively. Plant material was collected in April 1994 in Jacundá, state of Pará (Amazon region-Brazil) and identified by Nelson A. Rosa. A voucher specimen (no. 247) has been deposited in Herbarium of the Museu Paraense Emílio Goeldi (Belém-Brazil).

Isolation

The extraction of the powdered bark (6 kg) was carried out with hexane and MeOH in a Soxhlet apparatus for 48 hr. After evaporation of the solvent, the hexane extract (471.8 g) was filtered over a silica gel (900 g) column affording three frs eluted with hexane (fr A), CH_2Cl_2 (fr B) and MeOH (fr C). Fraction B was submitted to chromatography on a silica gel column eluted with mixtures of hexane-CH_2Cl_2-MeOH of increasing polarity giving 37.2 g of **1**, 4.5 g of **2**, 0,308 g of **3**, 0,151 g of **5**, and 0,064 g of **6**. Fraction C using a similar technique afforded 22.3 g of **1**, 0,101 g of **2**, 0,029 g of **4**, and 0,020 g of **7**. The MeOH extract (202.0 g) was also filtered over a silica gel (400 g) column eluted with hexane-EtOAc at different ratios of increasing polarity and gave 26.3 g of **1**, 0,290 g of **2**, and 0,072 g of **4**.

Compound **1**. Colourless crystals, mp 139–140°, $[\alpha]_D$ +10.6° ($CHCl_3$, *c* 0.6). **IR** $\nu_{max}^{CHCl_3}$ cm^{-1}: 3120, 2959, 2859, 1748, 1666, 1504, 873. ^1H NMR, $CDCl_3$: δ 2.15 (H-1α), 2.51 (H-1β, *dd*, *J* = 15.6, 2.7 Hz), 5.86 (H-3, *br s*, *J* = 1.2 Hz), 3.14 (H-5, *ddd*, *J* = 11, 10.5, 1 Hz), 2.24 (H-6 α), 1.17 (H-6β, *dq*, *J* = 12.8, 3.4 Hz), 1.85 (H-7 α), 1.60-1.72 (H-7 β), 1.60–1.72 (H-8), 1.77 (H-10), 2.33–2.40 (H-11), 5.40 (H-12, *dd*, *J* = 8.6 Hz), 6.37 (H-14, *dd*, *J* = 0.9 Hz), 7.42 (H-15, *m*), 7.42 (H-16, *m*), 1.12 (H-17, *d*, *J* = 5.8 Hz) and 1.93 (H-18, *br s*, *J* = 1.2 Hz). ^{13}C NMR, $CDCl_3$: 39.7 C1, 197.5 C2, 126.7 C3, 165.7 C4, 39.5 C5, 28.2 C6, 30.1 C7, 41.7 C8, 51.4 C9, 46.1 C10, 40.5 C11, 72.3 C12, 125.0 C13, 107.9 C14, 144.2 C15, 139.3 C16, 17.5 C17, 21.8 C18, 176.9 C20.

Compound **2**. White needles, mp 302–303°, $[\alpha]_D$ +21 ($CHCl_3$, *c* 0.1). **IR** $\nu_{max}^{CHCl_3}$ cm^{-1}: 3414, 2935, 2862, 1732, 1686, 1458, 1370, 1297, 1246, 1028, 770. ^1H NMR, $CDCl_3$: δ 4.47 (H-3, *dd*, *J* = 9.3, 6.3 Hz), 1.03 (H-5, *dd*, *J* = 13.4, 3.5 Hz), 5.52 (H-15, *dd*, *J* = 8.0, 3.3 Hz), 2.37 (H-16α, *dd*, *J* = 14.4, 8.0 Hz), 1.92 (H-16β, *dd*, *J* = 14.4, 3.3 Hz), 2.27 (H-18, *dd*, *J* = 13.8, 2.8 Hz), 0.95–0.85 (7 × CH_3-23-27,29,30) and 2.04 (CH_3COO-, *br s*).

Compound **2a**. Obtained by methylation of compound **2**. Colourless crystals, mp 144–145°. **IR** $\nu_{max}^{CHCl_3}$ cm^{-1}: 2936, 1729, 1590, 1467, 1375, 1244, 1168, 1025, 596. ^1H NMR, $CDCl_3$: δ 4.44 (H-3, *dd*, *J* = 9.0, 6.6 Hz), 1.02 (H-5, *dd*, *J* = 13.0, 3.1 Hz), 1.93 (H-7β, *ddd*, *J* = 12.0, 6.8, 3.7 Hz), 5.48 (H-15, *dd*, *J* = 8.0, 3.4 Hz), 1.91 (H-16β, *dd*, *J* = 14.2, 3.4 Hz), 3.57 (-$COOCH_3$, *d*, *J* = 8.2 Hz) and 2.04 (CH_3COO-, *d*, *J* = 8.2 Hz).

Compound **3**. Colourless oil, $[\alpha]_D$-10.2 ($CHCl_3$, *c* 1.6). **IR** $\nu_{max}^{CHCl_3}$ cm^{-1} : 2920, 2850, 1720, 1661, 1505, 1460, 1377, 1151, 875. **UV** λ_{max}^{MeOH} nm: 222.9. **MS** *m/z* (rel. int.): 330 $[M]^+$ (27), 271 (8), 248 (41), 217 (20), 204 (12), 189 (20), 161 (19), 147 (15), 134 (97), 121 (100), 109 (40),95 (56), 82 (66), 81 (80), 71 (48), 57 (96). ^1H NMR and ^{13}C NMR: see Tables 1 and 2.

Compound **4**. Amorphous solid, mp 142.5–144.5°, $[\alpha]_D$ +12.9 ($CHCl_3$, *c* 1.3). **IR** $\nu_{max}^{CHCl_3}$ cm^{-1}: 3131, 2923, 2853, 1725, 1667, 1511, 874. **UV** λ_{max}^{MeOH} nm: 236.8. **MS** *m/z* (rel. int.): 328 $[M]^+$ (36), 284 (5), 282 (7), 275 (5), 247 (16), 245 (4), 234 (29), 216 (31), 189 (18), 175 (17), 161 (26), 162 (6), 137 (19), 135 (28), 121 (39), 122 (58), 95 (100), 81 (42), 67 (14). ^1H NMR and ^{13}C NMR: see Tables 3 and 4.

Compound **5**. Colourless crystals, mp 130–132°, $[\alpha]_d$ +1.5 ($CHCl_3$, *c* 0.8). **Ir** $\nu_{max}^{CHCl_3}$ cm^{-1}: 3139, 2965, 2921, 2883, 1756, 1704, 1505, 873. ^1H NMR, $CDCl_3$: δ 2.44 (H-1β, *tt*, *J* = 12.9, 2.6 Hz), 2.07–2.39 (H-1α), 2.07–2.39 (H-3α), 2.07–2.39 (H-3β), 1.30–1.48 (H-4), 2.00 (H-5, *dddd*, *J* = 11.0, 10.7, 10.6, 3.7 Hz), 2.07–2.39 (H-6α), 0.97–0.83 (H-6β), 1.76 (H-7α, *dddd*, *J* = 12.7, 12.5, 12.3, 3.2 Hz), 1.57 (H-7β), 1.44 (H-8, *m*), 1.30–1.48 (H-10), 2.07–2.39 (H_2-11), 5.37 (H-12, *t*, *J* = 8.6 Hz), 7.40 (H-15, *m*), 7.40 (H-16, *m*), 6.34 (H-14, *t*, *J* = 1.38 Hz), 1.10 (H-17, *d*, *J* = 6.5 Hz) and 1.01 (H-18, *d*, *J* = 6.4 Hz).

Compound **6**. Colourless oil, $[\alpha]_D$-13.1 ($CHCl_3$, *c* 1.7), **IR** $\nu_{max}^{CHCl_3}$ cm^{-1}: 3132, 2934, 2869, 1724, 1664, 1499, 874. **EIMS** *m/z* (rel. int.): 330 $[M]^+$ (28), 271 (7), 248 (23), 217 (14), 204 (18), 189 (31), 161 (26), 147 (17), 134 (61), 121 (80), 109 (34),95 (70), 82 (44), 81 (100), 67 (26),56 (67), 55 (19). ^1H NMR, $CDCl_3$: δ 2.57 (H-1α), 2.63 (H-1β), 5.85 (H-3, *br s*), 2.49 (H-5), 1.72 (H-6α, *dq*, *J* = 14, 3.9, 3.7 Hz), 1.62 (H-6β), 1.56–1.65 (H-7α), 1.84–2.08 (H-7β), 2.18–2.30 (H-8), 2.38 (H-10), 1.84–2.08 (H_2-11), 2.18–2.30 (H_2-12), 6.20 (H-14, *dd*, *J* = 1.7, 0.7 Hz), 7.32 (H-15, *t*, *J* = 1.7 Hz), 7.17 (H-16, *t*, *J* = 1.2 Hz), 1.12 (H-17, *d*, *J* = 7.1 Hz), 1.96 (H-18, *br s*, *J* = 1.2 Hz) and 3.64 (-$COOCH_3$, *s*). ^{13}C NMR, $CDCl_3$: 37.4 C1, 197.5 C2, 126.1 C3, 165.6 C4, 39.0 C5, 21.0 C6, 27.5 C7, 31.7 C8, 52.5 C9, 38.5 C10, 37.7 C11, 19.9 C12, 124.3 C13, 110.7 C14, 142.8 C15, 138.6 C16, 18.3 C17, 22.7 C18, 174.7 C20, 51.3 OMe.

Compound **7**. Colourless needles, mp 202–204°. **IR** $\nu_{max}^{CHCl_3}$ cm^{-1}: 3273, 2978, 1752, 1662, 1617, 1477, 879. ^1H NMR, $CDCl_3$: δ 2.07 (H-1α, *t*, *J* = 14.7 Hz), 2.49 (H-1β, *br d*), 5.94 (H-3, *br s*), 3.07 (H-5, *t*, *J* = 11.6 Hz), 2.25 (H-6α, *dq*, *J* = 12.6, 3.5, 3.5 Hz), 1.19 (H-6β), 1.85 (H-7α), 1.67 (H-7β), 1.70-1.65 (H-8, *m*), 1.82 (H-10), 2.66 (H-11A, *dd*, *J* = 14.8, 9.8 Hz), 2.25 (H-11B), 5.21 (H-12, *tdt*, *J* = 9.2, 8.7, 1.5 Hz), 7.11 (H-14, *t*, *J* = 1.5, 1.4 Hz), 6.17 (H-15, *br s*), 1.10 (H-17, *d*, *J* = 6.5 Hz) and 1.98 (H-18, *br s*, *J* = 1.2 Hz).

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