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MERODITERPENES FROM *CYSTOSEIRA AMENTACEA* VAR. *STRICTA* COLLECTED OFF THE MEDITERRANEAN COASTS

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Key Word Index—*Cystoseira amentacea* var. *stricta*; Cystoseiraceae; brown algae; meroditerpenes; chemotaxonomy.

Abstract—In addition to the meroditerpenes cystoketal and cystoketal derivatives previously described, three new metabolites have been isolated from the brown alga *Cystoseira amentacea* var. *stricta*: 4′-methoxy-(2*E*)-bifurcarenone and its chromene derivative from a specimen collected off the French Riviera coast and 2,12-diepineobalearone from another one collected off the Galite islands coast (Tunisia). Their structures have been established by means of spectral methods, and the results were discussed with data in the literature on the same species collected from Sicily (Italy).

INTRODUCTION

In the course of our continuing phytochemical investigation of the marine family Cystoseiraceae [1–6], we have recently investigated the less polar fraction of the lipid extract of *Cystoseira amentacea* var. *stricta* collected on the western part of the French Riviera, leading to the isolation of two new cystoketal derivatives [7]. We now report the isolation and structure elucidation of two new meroditerpenes (**1**, **2**) obtained on the reinvestigation of this extract, and of a third metabolite (**3**) obtained from the lipid extract of the alga collected off the Galite islands coast. Compounds **1** and **2** are derivatives of 2(*E*)-bifurcarenone (**4**), whereas **3** is a diasteroisomeric form of neobalearone (**5**). Compounds **4** and **5** have been previously described from the same species collected off the Sicily coast [8, 9]. The quantitative determination of **1**, **3** and **5** is also reported from a chemotaxonomic point of view, along with the antimitotic activity of **1**.

RESULTS AND DISCUSSION

The reinvestigation of the lipid extract of *C. amentacea* var. *stricta* collected on the western part of the French Riviera in June 1992 revealed the presence of two new components (**1**, **2**), in addition to sterols and the previously described meroditerpenes cystoketal and cystoketal derivatives [7, 10]. In the same way, the lipid extract of the same alga collected off the coast of the Galite islands (1.27% dry wt of the alga in June 1992) revealed the presence of a minor component (**3**) in addition to sterols.

Compound **1**, $C_{28}H_{40}O_5$ (HRMS), was an optically active oil whose identity was readily settled by comparison of its spectral properties with those of 2(*E*)-bifurcarenone (**4**) and its derivatives [8]. In particular, the *E*-geometry of the double bond at C-2 was indicated by the high-field position of the resonance of the vinyl methyl at C-3 in the ^{13}C NMR spectrum (Table 1) [11, 12]. The main difference from compound **4** in the ^1H NMR spectrum was a 3H singlet at δ 3.74 (Table 2) indicating that **1** was a phenolic monomethyl ether of **4**. Location of the methoxyl group in position 4′ instead of 1′ was deduced firstly from the value of its chemical shift (δ 55.6 in $CDCl_3$) in the ^{13}C NMR spectrum which agrees with a series of closely related compounds [13], and secondly by the formation of the ion at *m/z* 189 in the mass spectrum [14]. These data showed that **1** was 4′-methoxy-2(*E*)-bifurcarenone. The assignment of carbon and proton signals (Tables 1 and 2, respectively) was confirmed by means of homonuclear (COSY) and heteronuclear (HCCORR and HMBC) 2D NMR experiments. In particular, some ^{13}C NMR signals which can be interchanged in ref. [8], such as C-3 and C-6′, C-8 and C-10, C-18 and C-19, 6′-Me and C-20, were precisely located for **1**

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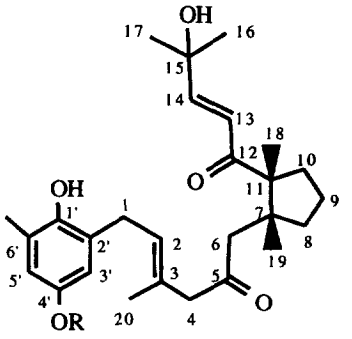

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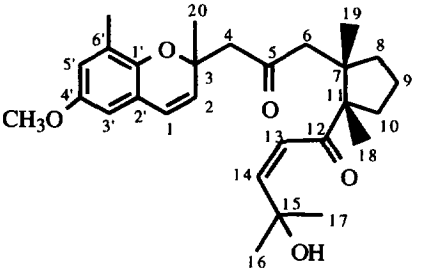

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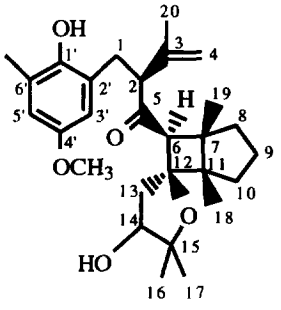

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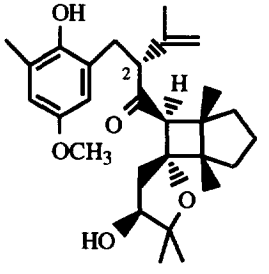

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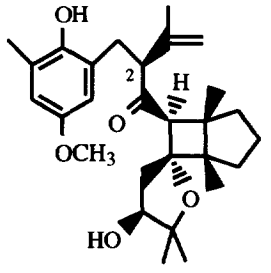

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(Table 1). Moreover, the correlations observed in the ^{1}H–^{13}C long range by inverse detection (HMBC), led us to confirm that C-3′ resonates at a higher field position than C-5′ in the ^{13}C NMR spectrum of **1**.

Compound **2**, $C_{28}H_{38}O_5$ (HRMS), was obtained as an epimeric mixture at C-3. The IR spectrum revealed the presence of ketone (1710 and 1675 cm^{-1}), and olefin (1600 and 1590 cm^{-1}) functionalities, while UV absorption at 265 (ε 5600), 272 (ε 5300) and 330 nm (ε 3100) were indicative of a chromene chromophore [15]. In the same way, the mass spectrum indicated a chromene ring with the fragment at *m/z* 189 (base) resulting from cleavage of the C-3/C-4 bond [13, 16].

The most characteristic features of the ^{1}H NMR spectrum of **2** in C_6D_6 (Table 2) compared with those of **1**, were the upfield shift of the aromatic proton H-3′ (δ 6.42, *d*, $J = 3$ Hz) and the replacement of the signals pertaining to the benzylic methylene and to the adjacent vinyl proton in **1** by an AB system (δ 6.13 and 5.75 each *d*, $J = 10$ Hz) assignable to the olefin protons at C-1 and C-2. The observed doubleting of the signals belonging to Me-3 (δ 1.48 and 1.50, double singlets), Me-6′ (δ 2.30 and 2.32, double singlets) and H-2 (δ 5.72 and 5.75, *dd*) is caused by stereoisomerism about the chiral centre at C-3. All these data showed that **2** was a mixture of the two C-3 epimers of the chromene derivative of **1**. The assignment of carbon and proton signals (Tables 1 and 2, respectively) was confirmed by means of homonuclear (COSY) and heteronuclear (HCCORR) 2D NMR experiments.

The third metabolite (**3**), $C_{28}H_{40}O_5$ (HRMS), was an optically active oil whose spectral properties showed that it was a diastereoisomer of neobalearone (**5**), [9]. The main differences were observed in some of proton resonances. In particular, the ^{1}H NMR spectrum of **3** (Table 3) contains a hydroxymethyne proton resonance (H-14) with a high value of δ 2.20 (in $CDCl_3$), while a resonance assignable to the tertiary methyl at C-7 appears at a normal value (δ 0.84, instead of δ 0.25 for **5**). The exceptional high-field value of the chemical shift for H-14 is due to the shielding effect of the aromatic ring in **3**, while that of the Me-7 in **5** is due to the shielding effect of the double bond at C-3. These data agree with the inversion of the configuration at the chiral centre C-2, as described for 2-*epi*neobalearone (**6**), [9]. Two differences from the proton resonances of **6**, were that Me-7 resonated at δ 0.84, instead of δ 0.96, and that H-16 resonated at δ 1.26, instead of δ 0.72. This led us to propose that **3** was 2,12-di*epi*neobalearone. This hypothesis was confirmed by a ^{1}H–^{1}H NOE difference spectroscopy experiment which showed an enhancement between

Table 1. ^{13}C NMR spectral data for compounds **1**, **2** and **4** (TMS as int. standard)*

	1 (100 MHz)			**2** (100 MHz)		**4** (100 MHz)†	
C	$CDCl_3$	C_6D_6	DEPT	C_6D_6	DEPT	$CDCl_3$	DEPT
1′	146.5	147.3	C	144.6	C	149.8	C
2′	130.6	130.7	C	121.5	C	131.1[a]	C
3′	113.0	113.7	CH	109.4	CH	115.4	CH
4′	153.1	154.0	C	154.1	C	145.4	C
5′	114.1	114.5	CH	116.8	CH	113.1	CH
6′	126.2	126.5	C	127.1	C	127.9[a]	C
1	30.6	31.0	CH_2	123.2	CH	28.6	CH_2
2	127.8	128.4	CH	130.0	CH	127.8	CH
3	128.1	128.7	C	71.1	C	125.8[a]	C
4	55.7	55.8	CH_2	55.1	CH_2	56.6	CH_2
5	209.2	208.5	C	206.9	C	209.6	C
6	47.3	47.5	CH_2	47.0	CH_2	46.4	CH_2
7	46.8	47.1	C	50.4	C	46.9	C
8	34.3	34.8	CH_2	37.1	CH_2	36.6[b]	CH_2
9	20.0	20.5	CH_2	20.1	CH_2	20.0	CH_2
10	36.8	37.4	CH_2	34.6	CH_2	34.2[b]	CH_2
11	60.0	60.1	C	60.0	C	60.2	C
12	204.7	204.3	C	203.0	C	205.9	C
13	122.6	123.1	CH	128.6	CH	122.6	CH
14	152.9	153.3	CH	152.6	CH	153.6	CH
15	71.0	70.8	C	70.5	C	71.2	C
16	29.4	29.5	CH_3	29.6	CH_3	29.3	CH_3
17	29.4	29.4	CH_3	29.5	CH_3	29.3	CH_3
18	21.2	21.4	CH_3	21.3	CH_3	21.1[c]	CH_3
19	20.2	20.3	CH_3	20.3	CH_3	20.2[c]	CH_3
20	16.7	16.9	CH_3	26.1	CH_3	16.2[d]	CH_3
Me-6′	16.5	16.7	CH_3	15.9	CH_3	16.3[d]	CH_3
OMe-4′	55.6	55.3	CH_3	54.5	CH_3	—	CH_3

* Multiplicities were obtained with DEPT sequences.
† ^{13}C NMR data of ref. [8] added for comparison.
[a–d] Values with identical superscripts within the compound **4** column can be interchanged.

H-13 and H-6 (12%), but no NOE effect between H-13 and H-18. The assignment of proton and carbon signals (Tables 3 and 4, respectively) was confirmed by means of homonuclear (COSY) and heteronuclear (HCCORR and HMBC) 2D NMR experiments.

Quantitative analysis—chemotaxonomy

To complete the phytochemical study of *C. amentacea* var. *stricta* started in our previous paper on this topic [7], we determined the concentration of all the meroditerpenes in its lipid extract. For this purpose, the alga was collected from Marseille (Sausset les Pins) to Saint-Raphaël (Le Trayas) at separate locations (western part of the French Riviera) and from one location at the Galite islands (Tunisia). The different collections were treated and extracted in an identical fashion and each ether extract was analysed by normal-phase HPLC (ethyl acetate–isooctane, 1:4).

In addition to cystoketal and cystoketal derivatives which were present in each collection studied and regarded as chemotaxonomic markers of the species [7], two other structures 4′-methoxybifurcarenone (**1**) and neobalearone (**5**), seem to be representative of two 'chemical types' of *C. amentacea* var. *stricta*, respectively. Type 1, with **1** as the main meroditerpene, was obtained from two zones of collection: Toulon and Boulouris-Le Trayas (Saint-Raphaël); while type 2, with **5** as the main meroditerpene, was obtained from the Sausset (Marseille) and Saint-Aygulf zones. With 2,12-di*epi*neobalearone (**3**), a diepimer of (**5**), as the main meroditerpene, the species collected at the Galite islands could be included in chemical type 2.

Cytotoxic activity

Sea-urchin egg development is frequently used as a pharmacological screen for compounds that inhibit cell division [17]. One of the new compounds isolated

Table 2. ^{1}H NMR spectral data of compounds **1**, **2** and **4** (TMS as int. standard)*

H	**1** (400 MHz)		**2** (400 MHz)	**4** (300 MHz)†
	$CDCl_3$	C_6D_6	C_6D_6	$CDCl_3$
3′	6.54 } AB (3)	6.64 } AB (3.1)	6.42 } AB (3)	6.50 } AB (3)
5′	6.60 }	6.69 }	6.69 }	6.40 }
1	3.36 *d* (7)	3.35 *d* (7)	6.13 } AB (10)	3.29 *d* (7)
2	5.34 *t* (6.4)	5.32 *t* (6.1)	5.72/5.75 }	5.35 *t* (7)
4	3.04 *s* (br)	2.75 *s* (br)	2.76 *s* (br)	3.00 *s* (*br*)
6	2.26 } AB (15.6)	2.24 } AB (16)	2.53 } AB (16)	2.30 } AB (16)
	2.44 }	2.45 }	2.72 }	2.44 }
8	1.7–1.9 *m*	1.3–1.5 *m*	} 2.4 *m*	1.9 *m*
9	1.7 *m*	1.6 *m*		1.7 *m*
10	1.5–2.2 *m*	2.0–2.3 *m*		1.5 *m*
13	6.65 } AB (15.2)	6.77 } AB (15.1)	6.73 } AB (15)	6.59 } AB (16)
14	6.88 }	7.03 }	7.01 }	6.85 }
16	1.37 *s*	1.17 *s*	1.32 *s*	1.30 *s*
17	1.36 *s*	1.17 *s*	1.32 *s*	1.28 *s*
18	1.17 *s*	1.18 *s*	1.22 *s*	1.15 *s*
19	1.16 *s*	1.05 *s*	1.07 *s*	1.14 *s*
20	1.72 *s*	1.62 *s*	1.48/1.50 *s*	1.68 *s*
Me-6′	2.27 *s*	2.29 *s*	2.30/2.32 *s*	2.17 *s*
OMe-4′	3.74 *s*	3.47 *s*	3.38 *s*	—
OH	—	—	—	7.36 *s*
OH	5.60 *s*	5.90 *s*	5.65 *s*	5.18 *s*

* Chemical shifts are δ values; coupling constants (J in parentheses) are given in Hz; assignments were confirmed by decoupling and 2D NMR experiments (COSY ^{1}H–^{1}H, HCCORR and HMBC).

† ^{1}H NMR data of ref. [8] added for comparison.

(**1**) has a cytotoxic activity close to that of bifurcarenone (**4**) [18], and mediterraneols [19]. Its ED_{50} value inhibiting the development of the fertilized eggs of the common sea-urchin *Paracentrotus lividus* was 12 μg ml^{-1}.

EXPERIMENTAL

General. MS: direct inlet, 70 eV; ^{1}H NMR: 400 MHz; ^{13}C NMR: 100 MHz. Chemical shifts are quoted in ppm (δ) relative to TMS and coupling constants are in Hertz. Final purification of all metabolites was achieved by HPLC on silica gel (Intersphere Si-60, 5 μm), with RI monitoring.

Plant material. Cystoseira amentacea Bory var. *stricta* Montagne was collected in June 1992 at Le Brusc (Toulon, France) for isolation of compounds **1** and **2**, at the Galite islands (Tunisia) for compound **3** and at Saint-Aygulf (France) for compound **5**. A voucher specimen of this species (from each collection) is deposited in Dr Pellegrini's herbarium: Laboratoire de Biologie Marine Fondamentale et Appliquée, University of Marseille II, France.

Extraction and purification. The shade-dried material collected at Le Brusc (Toulon, France) (242.1 g) was ground and extracted with Et_2O at room temp. After filtration and evapn of solvent, 640 mg of crude extract were obtained and subjected to CC on silica gel eluted with a solvent gradient from hexane to Et_2O. Compounds **1** and **2** were eluted with hexane–Et_2O (4:1). They were subsequently purified by semi-prep. normal phase HPLC (EtOAc–isooctane, 1:4) to give 272 mg of **1** and 32 mg of **2**. In the same way, the shade dried material collected at the Galite islands (19.7 g) gave 250 mg of crude extract and 27 mg of **3**, while the shade-dried material (96.2 g) collected at Saint-Aygulf (France) gave 298 mg of crude extract and 25 mg of **5**. Compound **5** was identified by comparison of its spectral properties (IR, UV, MS, ^{1}H and ^{13}C NMR) and optical rotation with those of a reference sample available from previous work on *C. amentacea* var. *stricta* collected off the Sicilian coast [10].

Table 3. ^{1}H NMR spectral data of compounds **3**, **5** and **6** (TMS as int. standard)*

H	**3** (400 MHz) $CDCl_3$	**3** (400 MHz) C_6D_6	**5** (250 MHz)† $CDCl_3$	**6** (250 MHz)† $CDCl_3$
3′	6.46 *d* (3)		6.41 *d* (3)	6.46 *d* (3)
		6.59 *s*		
5′	6.56 *d* (3)		6.54 *d* (3)	6.56 *d* (3)
1	3.30 *m*	3.30 *m*	3.19 *m*	3.22 *dd* (13.5–11.3)
		2.35 *m*	2.39 *dd* (11–1.6)	2.37 *dd* (13.5–2.3)
2	3.25 *m*	3.29 *s*	3.21 *m*	3.34 *dd* (11.3–2.3)
4	5.05 *s*	4.78 *s*	5.02 *s*	5.05 *s*
	4.89 *s*	4.72 *s*	4.89 *s*	4.89 *s*
6	3.09 *s*	3.43 *s*	3.12 *s*	3.08 *s*
8	—	1.19 *m*	1.30 *m*	1.17 *m*
		1.32 *s*	1.65 *m*	1.51 *m*
9	—	1.34 *m*	1.75 *m*	1.64 *m*
		2.00 *m*		
10	—	1.83 *m*	1.10 *m*	1.09 *m*
		2.33 *m*	2.30 *m*	2.22 *m*
13	—	2.54 *m*	3.04 *dd* (12–6)	2.13 *dd* (11.3–6.8)
		1.16 *m*	1.82 *dd* (12–9)	1.68 *dd* (11.3–10.0)
14	2.20 *dd* (9–6)	2.52 *m*	3.90 *dd* (9–6)	2.20 *dd* (10.0–6.8)
16	1.26 *s*	1.06 *s*	1.10 *s*	0.72 *s*
17	0.98 *s*	1.09 *s*	1.03 *s*	0.84 *s*
18	0.85 *s*	0.83 *s*	0.79 *s*	0.64 *s*
19	0.84 *s*	1.07 *s*	0.25 *s*	0.96 *s*
20	1.76 *s*	1.45 *s*	1.76 *s*	1.76 *s*
Me-6′	2.26 *s*	2.40 *s*	2.21 *s*	2.25 *s*
OMe-4′	3.71 *s*	3.42 *s*	3.72 *s*	3.70 *s*
OH	—	7.67 *s*	7.10 *s*	7.40 *s*

*Chemical shifts are δ values; coupling constants (J in parentheses) are given in Hz; assignments were confirmed by decoupling and 2D NMR experiments (COSY ^{1}H–^{1}H, HCCORR and HMBC).

†^{1}H NMR data of ref. [9] added for comparison.

Compound **1**. Oil; $[\alpha]_D^{25} = 10.7°$ (EtOH; *c* 1.5); IR ν_{max}^{film} cm^{-1}: 3400, 2900, 1710, 1675, 1600, 1440, 1200, 1150, 1070, 980, 850; UV λ_{max}^{EtOH} nm (ε): 220 (18000), 287 (5300); HRMS: [M]$^+$ 456.2871 (calc. for $C_{28}H_{40}O_5$, 456.2875); EIMS (70 eV) *m/z* (rel. int.): 456 (18), 438 (48), 420 (20), 288 (21), 233 (57), 206 (23), 205 (23), 191 (23), 189 (56), 167 (25), 156 (25), 151 (27), 150 (100), 149 (28), 137 (39), 113 (41), 95 (76), 84 (68), 71 (47), 60 (56), 49 (87), 43 (47); ^{13}C and ^{1}H NMR: Tables 1 and 2, respectively.

Compound **2**. Oil: IR ν_{max}^{film} cm^{-1}: 3400, 2900, 1710, 1675, 1600, 1590, 1440, 1200, 1160, 1080, 980, 850; UV λ_{max}^{EtOH} nm (ε): 265 (5600), 272 (5300), 330 (3100); HRMS: [M]$^+$ 454.2714 (calc. for $C_{28}H_{38}O_5$, 454.2719); EIMS (70 eV) *m/z* (rel. int.): 454 (14), 436 (46), 231 (55), 203 (20), 189 (100), 113 (40), 60 (53); ^{13}C and ^{1}H NMR: Tables 1 and 2, respectively.

Compound **3**. Oil; $[\alpha]_D^{25} = -109.8°$ (EtOH; *c* 1.3); IR ν_{max}^{film} cm^{-1}: 3470, 2900, 1685, 1605, 1460, 1200, 1090, 980; UV λ_{max}^{EtOH} nm (ε): 220 (10500), 287 (3300); HRMS: [M]$^+$ 456.2870 (calc. for $C_{28}H_{40}O_5$, 456.2875); EIMS (70 eV) *m/z* (rel. int.): 457 (2) [M–H]$^+$, 439 (18), 360 (8), 342 (5), 288 (12), 273 (7), 246 (12), 233 (15), 232 (31), 228 (16), 206 (8), 205 (6), 191 (9), 190 (18), 189 (16), 168 (26), 155 (100), 151 (43), 150 (85), 138 (13), 137 (50), 123 (13), 113 (21), 109 (15), 96 (18), 95 (28), 91 (14), 83 (10), 81 (20), 79 (10), 71 (47), 69 (38), 43 (60), 41 (19); ^{1}H and ^{13}C NMR: Tables 3 and 4, respectively.

HPLC analysis of compounds **1**, **3** *and* **5**. The method previously described for the determination of sterols and diterpenoids from Cystoseiraceae [1] was used with RI monitoring and 2-methylbutan-2-ol (for **1**) or 4-methoxyacetophenone (for **3** and **5**) as internal standard.

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Table 4. ^{13}C NMR spectral data for compounds **3**, **5** and **6** (TMS as int. standard)*

	3 (100 MHz)			**5** (62.5 MHz)†		**6** (62.5 MHz)†	
	$CDCl_3$	C_6D_6	DEPT	$CDCl_3$	DEPT	$CDCl_3$	DEPT
1′	147.0	147.2	C	146.4	C	146.5	C
2′	128.2	127.8	C	127.0	C	127.6	C
3′	113.6	113.7	CH	113.2	CH	113.2	CH
4′	154.0	154.0	C	153.2	C	153.4	C
5′	114.9	114.5	CH	114.9	CH	114.5	CH
6′	128.7	128.5	C	127.5	C	127.9	C
1	30.3	29.9	CH_2	30.0	CH_2	29.8	CH_2
2	67.6	62.9	CH	64.8	CH	66.9	CH
3	141.7	141.4	C	142.4	C	141.3	C
4	116.3	115.6	CH_2	115.5	CH_2	115.5	CH_2
5	211.5	211.1	C	211.7	C	210.8	C
6	63.0	67.5	CH	60.1	CH	62.5	CH
7	45.2	44.8	C	47.4	C	44.6	C
8	41.7	41.4	CH_2	40.9	CH_2	41.2	CH_2
9	24.8	24.6	CH_2	24.9	CH_2	24.2	CH_2
10	36.5	35.1	CH_2	35.6	CH_2	36.0	CH_2
11	53.4	53.1	C	52.9	C	52.9	C
12	83.0	80.4	C	81.1	C	82.5	C
13	35.0	36.2	CH_2	35.9	CH_2	34.6	CH_2
14	77.4	77.2	CH	78.4	CH	76.7	CH
15	80.3	82.9	C	79.8	C	79.0	C
16	27.8	27.7	CH_3	27.6	CH_3	27.2	CH_3
17	22.3	22.3	CH_3	22.3	CH_3	21.7	CH_3
18	19.4	19.0	CH_3	18.8	CH_3	18.7	CH_3
19	17.5	17.2	CH_3	15.4	CH_3	17.2	CH_3
20	21.3	20.2	CH_3	20.9	CH_3	20.7	CH_3
Me-6′	17.4	17.1	CH_3	16.7	CH_3	16.7	CH_3
OMe-4′	56.1	55.3	CH_3	55.8	CH_3	55.6	CH_3

* Multiplicities were obtained with DEPT sequences.
† ^{13}C NMR data of ref. [9] added for comparison.

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