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Two new luffarin derivatives from the Adriatic Sea sponge *Fasciospongia cavernosa*

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Abstract—Together with the known luffarin V and 6*Z*-luffarin V, two new sesterterpenes (**1a** and **2**), related to luffarins have been isolated from the sponge *Fasciospongia cavernosa*, collected in the Northern Adriatic Sea. The structures of the new compounds were proposed on the basis of spectroscopic data. The absolute stereochemistry of compound **1a** was determined by application of Mosher's method.

1. Introduction

Within the class of terpenoids, the sesterterpenes form a rare group of isoprenoids, which occur in widely differing sources and have been isolated from terrestrial fungi,[1] plants[2] and insects[3] as well as from marine organisms,[4,5] mainly from sponges and nudibranchs. Marine organisms have provided a large number of sesterterpenoids, possessing novel carbon skeletons, which are different from those present in terrestrial species. Several sesterterpenoids isolated from marine organisms have shown biological activity.[6]

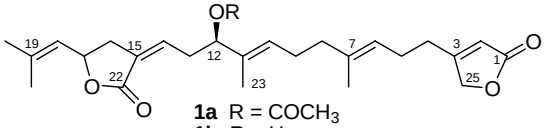
Marine sponges belonging to the family Thorectidae, which includes the genera *Cacospongia*, *Fasciospongia*, *Luffariella* and *Thorecta*, are known[4,5] to be a rich source of novel sesterterpenoids (see above). Some containing a γ-hydroxybutenolide moiety showed strong anti-inflammatory activity, for example, manoalide,[7] the first sesterterpene to be reported from a *Luffariella* sp., has been extensively investigated as a potent inhibitor of phospholipase A_2.[4,5] Subsequently many related metabolites from *Luffariella* sp. were reported.[4,5] Among the manoalide congeners, particularly interesting are cacospongionolides, which exhibit specific inhibition of human phospholipase A_2 and are more stable than manoalide.[6]

Our group has investigated the chemistry of a number of specimens of *Fasciospongia cavernosa* Schmidt (family Thorectidae) collected in the Mediterranean Sea, in order to provide sufficient cacospongionolides. We have reported the isolation of novel related metabolites,[6] including the 6*Z* isomer of luffarin V,[8] a metabolite isolated from the Australian sponge *Luffariella geometrica*.[9] We have isolated two new sesterterpenoids (**1a** and **2**) related to luffarins, from a sample of *F. cavernosa* collected in the Northern Adriatic Sea. The structure determination of these compounds are reported in this paper.

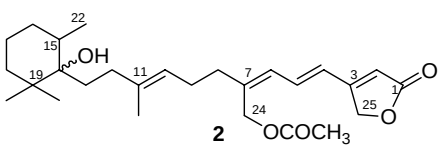
2. Results and discussion

The Et_2O-soluble fraction of the Me_2CO extract of *F. cavernosa* was chromatographed on Si gel, followed by reverse HPLC, to give compounds **1a** and **2**, together with two, their relatives luffarin V[9] and its 6*Z* isomer.[8]

The spectral data of luffarin V and (6*Z*)-luffarin V[10] were in excellent agreement with those reported in the literature. Furthermore, (6*Z*)-luffarin V was identified by comparison with an authentic sample.



1a R = $COCH_3$
1b R = H
1c R = (*R*)-MTPA
1d R = (*S*)-MTPA



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Keywords: Luffarins; *Fasciospongia cavernosa*; Sesterterpenoids.
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Table 1. NMR spectral data of **1a**

Position	^{13}C	^{1}H multiplicity (J in Hz)	HMBC ($J_{C-H}=10$ Hz)
1	174.0s	—	5.82 (H-2), 4.72 (H-25)
2	115.5d	5.82tt (1.7, 1.6)	4.72 (H-25), 2.44 (H-3)
3	170.2s	—	5.82 (H-2), 4.72 (H-25), 2.44 (H-4), 2.27 (H-5)
4	28.6t	2.44 br t (7.2)	5.82 (H-2), 2.27 (H-5)
5	25.6t	2.27dt (7.1, 7.2)	—
6	122.3d	5.07 br t (7.1)	2.44 (H-4), 2.27 (H-5), 2.00 (H-8), 1.59 (H-24)
7	136.8s	—	2.44 (H-4), 2.27 (H-5), 2.00 (H-8), 1.59 (H-24)
8	38.9t	2.00 br t (7.3)	5.07 (H-6), 2.08 (H-9), 1.59 (H-24)
9	25.8t	2.08 br dt (6.5, 7.3)	2.00 (H-8)
10	127.8d	5.40 br t (6.5)	5.19 (H-12), 2.08 (H-9), 1.60 (H-23)
11	132.9s	—	2.08 (H-9), 1.60 (H-23)
12	77.9d	5.19m[a]	6.05 (H-14), 5.40 (H-10), 1.60 (H-23)
13a	31.1t	3.08m[a]	6.05 (H-14)
13b		3.02m[a]	6.05 (H-14)
14	137.5d	6.05ddt (7.3, 2.5, 2.0)	5.19 (H-12), 3.08 (H-13a), 3.02 (H-13b)
15	126.9s	—	2.99 (H16a), 2.56 (H-16b)
16a	36.4t	2.99ddd (15.6, 7.0, 2.0)	5.20 (H-18)
16b		2.56ddd (15.6, 6.7, 2.5)	5.20 (H-18)
17	74.1d	5.11	2.56 (H-16b)
18	123.2d	5.20m[a]	5.11 (H-17), 1.74 (H-20), 1.71 (H-21)
19	139.8s	—	5.11 (H-17), 1.74 (H-20), 1.71 (H-21)
20	25.6q	1.74d (1.2)	5.20 (H-18), 1.71 (H-21)
21	18.3q	1.71d (1.2)	5.20 (H-18), 1.74 (H-20)
22	169.5s	—	6.05 (H-14), 2.99 (H-16a)
23	12.0q	1.60s	5.40 (H-10), 5.19 (H-12)
24	16.1q	1.59s	5.07 (H-6), 2.00 (H-8)
25	73.1d	4.72d (1.7)	5.82 (H-2), 2.44 (H-4)
26	170.2s	—	2.02 (H-27), 5.19 (H-12)
27	25.7q	2.02s	—

[a] Overlapped signals.

Compound **1a** had $[\alpha]_D$ −34.6 and a molecular formula $C_{27}H_{36}O_6$, as derived by HRMS. The UV absorption at 220 nm and IR bands at 1778, 1744, 1672, 1625 and 1240 cm^{-1}, suggested the presence of two γ-butenolide moieties and an acetate function in the molecule. The analysis of the NMR data (Table 1) established the presence of a β-substituted α,β-unsaturated γ-butenolide moiety [^1H NMR δ 5.82 (1H, tt, $J=1.7$, 1.6 Hz, H-2) and 4.72 (2H, d, $J=1.7$ Hz, H-25); ^{13}C NMR δ 174.0 (s, C-1), 170.2 (s, C-3), 115.5 (d, C-2), 73.1 (t, C-25)], two trisubstituted double bonds [δ 5.40 (1H, t, $J=6.5$ Hz, H-10), 5.07 (1H, t, $J=7.1$ Hz, H-6); 136.8 (s, C-7), 132.9 (s, C-11), 127.8 (d, C-10), 122.3 (d, C-6)] along with associated methyls [δ 1.60 (3H, s, H-23), 1.59 (3H, s, H-24); 16.1 (q, C-24), 12.0 (q, C-24)] indicating an *E* geometry, and a terminal trisubstituted double bond [δ 5.20 (1H, H-18); 139.8 (s, C-19), 123.2 (d, C-18)] along with two olefinic methyls [δ 1.74 (3H, d, $J=1.2$ Hz, H-20), 1.71 (3H, d, $J=1.2$ Hz, H-21); 25.6 (q, C-20), 18.3 (q, C-21)]. The COSY spectrum indicated that the oxymethine proton at δ 5.19 (H-12) was coupled to the non-equivalent methylene protons at δ 3.08 and 3.02 (H-13a, H-13b), which in turn were coupled with an olefinic proton at δ 6.05 (H-14). These data, together with the HMBC correlation of the oxymethine proton at δ 5.19 (H-12) with the carbonyl at δ 170.2 (C-26) allowed us to locate the second butenolide functionality and the acetate group in the C-12/C-18 portion of the molecule, defining the structure of compound **1a**. The location of the acetyl functionality at C-12 was also supported by chemical shift of C-23, which appeared as an upfield carbon shifted to δ 12.0 ppm. The geometry of Δ^{14} was assigned as *Z* on the basis of a comparison of the NMR data with those of an authentic sample of (6*Z*)-luffarin V[8] and related compounds.[9]

The absolute stereochemistry of compound **1a** was determined by application of modified Mosher's method,[11] to the deacetyl derivative **1b**, which was obtained by treatment of **1a** with MeOH saturated with Na_2CO_3. The alcohol **1b** was treated with *S*-(−)- and *R*-(+)-α-methoxy-α-(trifluromethyl)phenylacetyl chloride (MTPA-Cl) to yield the corresponding *R*- and *S*-MTPA esters (**1c** and **1d**, respectively). The proton chemical shifts of both diastereoisomers **1c** and **1d** were carefully assigned by analysis of their COSY spectra. From the MTPA determination rule,[11] the positive and negative $\Delta\delta$ ($\delta_{S\text{-MTPA ester}}-\delta_{R\text{-MTPA ester}}$) value observed for signals protons were located on the right and on the left side of the MTPA plane, respectively, showing clearly that the absolute configuration at C-9 is *R*.

Compound **2** had $[\alpha]_D$ −5.07 and a molecular formula $C_{27}H_{40}O_5$, as derived by HRMS. IR bands at 3300, 1778, 1744, 1672, 1240, 1233 and 1050 cm^{-1} indicated the presence of ester, γ-butenolide, and hydroxyl functions in the molecule. The UV absorption at 257 nm and ^1H NMR resonances at δ 6.86 (1H, dd, $J=15.6$, 11.3 Hz, H-5), 6.47 (1H, br d, $J=15.6$ Hz, H-4), 6.13 (1H, br d, $J=11.3$ Hz, H-6), 5.93 (1H, br s, H-2) and 5.01 (2H, br s, H-25) confirmed the presence of a diene conjugated with a β-substituted α,β-unsaturated γ-butenolide moiety. Furthermore, the ^1H NMR spectrum (Table 2) of **2** showed resonances due to one secondary, two tertiary and one olefinic methyl groups [δ 0.94 (3H, d, $J=7.0$ Hz), 0.95 (3H, s), 0.97 (3H, s) and 1.64 (3H, br s)], an oxymethylene [δ 4.76 (2H, s)], and an olefinic proton [δ 5.15 (br t, $J=6.9$ Hz)]. ^{13}C NMR resonances observed at δ 137.4 (s), 122.6 (d), 76.5 (s) and 61.4 (t) confirmed the presence of a trisubstituted double bond and of an oxymethylene, and

Table 2. NMR spectral data of **2**

Position	^{13}C	^{1}H multiplicity (J in Hz)	HMBC ($J_{C-H}=10$ Hz)
1	173.5s	—	5.93 (H-2), 5.01 (H-25)
2	115.3d	5.93 br s	6.47 (H-4), 5.01 (H-25)
3	161.7s	—	6.86 (H-5), 6.47 (H-4), 5.93 (H-2), 5.01 (H-25)
4	122.6d	6.47 br d (15.6)	6.13 (H-6), 5.93 (H-2), 5.01 (H-25)
5	131.9d	6.86dd (11.3, 15.6)	6.13 (H-6)
6	128.5d	6.13 br d (11.3)	6.86 (H-25), 6.47 (H-4), 4.76 (H-24), 2.27 (H-8)
7	143.5s	—	6.86 (H-25), 4.76 (H-24), 2.27 (H-8), 2.19 (H-9)
8	35.8t	2.27t (7.3)	6.13 (H-6), 4.76 (H-24), 2.19 (H-9)
9	26.4t	2.19dd (6.9, 7.3)	5.15 (H-10), 2.27 (H-8)
10	122.6d	5.15 br t (6.9)	2.19 (H-9), 2.07 (H-12), 1.64 (H-23)
11	137.4s	—	2.19 (H-9), 2.07 (H-12), 1.64 (H-23)
12	34.7t	2.07m[a]	5.15 (H-10), 1.64 (H-23), 1.60 (H-13)
13	28.8t	1.60m[a]	2.07 (H-12)
14	76.5s	—	1.60 (H-13), 0.95 (H-20), 0.94 (H-22)
15	37.5d	1.87m[a]	1.60 (H-13, H-16), 1.46 (H-17), 1.17 (H-16)
16	30.9t	1.60m,[a] 1.17m	1.46 (H-17), 0.94 (H-22)
17	20.3t	1.46m	1.36 (H_1-18)
18	37.5t	1.87m,[a] 1.36m	1.46 (H-17), 0.97 (H-21), 0.95 (H-20)
19	39.2s	—	1.60 (H-13), 1.46 (H-17), 0.97 (H-21), 0.95 (H-20)
20	25.0q	0.95s	0.97 (H-21)
21	23.2q	0.97s	0.95 (H-20)
22	16.1q	0.94d (7.0)	—
23	16.1q	1.64 br s	5.15 (H-10), 2.07 (H-12)
24	61.4t	4.76s	6.13 (H-6), 2.27 (H-8)
25	70.4t	5.01 br s	6.47 (H-4), 5.93 (H-2)
26	170.5s	—	4.76 (H-24), 2.07 (H-12)
27	20.9q	2.09s	—

[a] Overlapped signals.

showed the presence of a tertiary alcohol. An HMBC correlation observed between the H-6 proton (δ 6.13) and the carbon triplet at δ 61.4 located the oxymethylene on C-24. Furthermore, HMBC correlation between H-24 and the carbonyl of the acetate group at δ 170.5 located the acetoxy group at C-24. The COSY spectrum indicated that the H-6 proton (δ 6.13) had a long-range coupling to the methylene protons at δ 2.27 (t, $J=7.3$ Hz, H-8). This was further coupled to the methylene double doublet observed at δ 2.19 (dd, $J=7.3$, 6.9 Hz, H-9), which in turn was coupled with the olefinic proton at δ 5.15 (H-10). This latter olefinic proton had in turn a long-range coupling to the olefinic methyl at δ 1.64 (H-23) and with methylene at δ 2.07 (H-12). This was in turn coupled with the methylene protons at δ 1.60 (H-13). The remaining COSY data allowed for the definition of the spin system delineated by H-16/H-17/H-18/H-19/H-20. Taking into account the molecular formula and the data discussed thus far, the molecule of **2** must possess a carbo-monocyclic skeleton. Further interpretation of the COSY, HMQC and HMBC data allowed us to assign all the chemical shifts in the ^{1}H and ^{13}C NMR spectra and to define the presence of a 1-hydroxy-2,6,6-trimethylcyclohexane moiety connected to C-13 [δ 1.60 (m); 28.8 (t)].

The (4*E*,6*Z*,10*E*)-stereochemistry was determined from $J_{4,5}=15.6$ Hz, by the presence of a NOE between the H-5 and the oxymethylene protons at δ 4.76 (H-24), and by the upfield ^{13}C NMR chemical shift for the olefinic methyl (16.1 ppm). It was not possible to ascertain the absolute configuration of C-14 and C-15 from the very small amount of compound isolated.

The carbon skeleton of compound **2** resembles those of luffarin-P[9] and manoalide diol.[12]

The isolation of several related constituents from individual specimens of *F. cavernosa* confirms the peculiarity of the sponges belonging to the family Thorectidae. Similar variation of related metabolites were observed for the sponges *L. geometrica*,[9] *L. variabilis*,[13] and *Thorectandra excavatus*.[14]

3. Experimental

3.1. General experimental procedures

UV spectra were obtained on a Varian DMS 90 spectrophotometer. IR spectra were recorded on a Bio-Rad FTS-7 FT-IR spectrometer. Optical rotations were measured on a Jasco DIP 370 polarimeter, using a 10-cm microcell. Mass spectra were recorded on an AEI MS-50 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, on a Bruker Avance-400 spectrometer, using an inverse probe fitted with a gradient along the *Z*-axis, in $CDCl_3$, using the solvent signal as an internal standard. The 2D NMR spectra were obtained using Bruker's microprograms. Si gel chromatography was performed using pre-coated Merck F_{254} plates and Merck Kieselgel 60 powder.

3.2. Animal material

The sponge *F. cavernosa* (order Dictyoceratida; family Thorectidae) was collected by dredging (−25 m) in May 2002 at Rovinj (Croatia). It was frozen at −20° until extracted and identified by Prof. R. Pronzato of Dip.Te.Ris. dell'Università di Genova, Italy. A voucher specimen is maintained in the Pozzuoli institute collection (voucher No. S6R/02).

3.3. Extraction and isolation

The frozen sponge (102.3 g dry wt after extraction) was extracted with acetone and, after elimination of the solvent under reduced pressure, the aqueous residue was extracted with diethyl ether. The ethereal extract was evaporated under reduced pressure to obtain brown oil (4.2 g), which was applied on a column of Si gel. The column was eluted with a solvent gradient system from petroleum ether (40–70°) to AcOEt.

Fractions eluted with petroleum ether–AcOEt (6/4) was purified by preparative HPLC (Kromasil C18; CH_3CN/H_2O, 94:6; flow 3 ml/min) yielding luffarin V (2.1 mg), (6*Z*)-luffarin V (3.7 mg), compound **1a** (45.7 mg) and compound **2** (1.3 mg).

3.3.1. Luffarin V. $[\alpha]_D$ −29.8 (*c* 0.02, $CHCl_3$); UV, IR, MS, and ^1H, ^{13}C NMR data are in agreement with those reported in literature.[9]

3.3.2. (6*Z*)-Luffarin V. $[\alpha]_D$ −17.8 (*c* 0.03, $CHCl_3$); UV, IR, MS, and ^1H, ^{13}C NMR data are in agreement with those of authentic sample.

3.3.3. Compound 1a. Amorphous solid; $[\alpha]_D$ −34.6 (*c* 0.2, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 220 (3.64) nm; IR ($CHCl_3$) ν_{max} 1778, 1744, 1672, 1625, 1240, 1055 cm^{-1}; NMR data see Table 1; EIMS (70 eV) *m/z* (%) $[M]^+$ 456.2515 ($C_{27}H_{36}O_6$ requires 456.2512) (2), $[M-CH_3CO_2H]^+$ 396 (13), 378 (60), 249 (100), 213 (90), 166 (95), 121 (60).

3.3.4. Compound 2. Amorphous solid; $[\alpha]_D$ −5.1 (*c* 0.01, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 257 (3.76) nm; IR ($CHCl_3$) ν_{max} 3300, 1778, 1744, 1672, 1240, 1233, 1050 cm^{-1}; NMR data see Table 2; cross peaks were observed in a NOESY spectrum between the following signals (only cross peaks not sensitive to strong filtering are reported): δ 6.13–2.27 (H-6, H-8), 5.15–2.27 (H-10, H-8), 6.86–5.01 (H-5, H-25), 6.86–4.76 (H-5, H-24); EIMS (70 eV) *m/z* (%) $[M]^+$ 444.2678 ($C_{27}H_{40}O_5$ requires 444.2676) (5), $[M-H_2O]^+$ 426 (3), 382 (10), 341 (8), 279 (20), 267 (28), 195 (50), 167 (50), 149 (100), 123 (80), 121 (65).

3.4. Alkaline hydrolysis of compound 1a

Compound **1a** (10 mg) was dissolved in 3 ml of MeOH saturated with Na_2CO_3, and the solution was kept at room temperature for 18 h. After neutralization the reaction mixture was extracted with EtOAc. The EtOAc extract was purified on Si gel column using Et_2O as eluent to obtain **1b** (6 mg).

3.4.1. Compound 1b. Amorphous solid; UV (MeOH) λ_{max} (log ε) 222 (3.60) nm; IR ($CHCl_3$) ν_{max} 3350 (br), 1778, 1672, 1625, 1233 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.29 (1H, ddt, *J*=7.8, 2.4, 2.2 Hz, H-14), 5.85 (1H, tt, *J*=1.7, 1.6 Hz, H-2), 5.38 (1H, br t, *J*=6.7 Hz, H-10), 5.22 (1H, m, H-18), 5.18 (1H, ddd, *J*=7.1, 6.8, 1.7 Hz, H-17), 5.09 (1H, br t, *J*=6.9 Hz, H-6), 4.73 (2H, d, *J*=1.7 Hz, H-25), 4.10 (1H, br t, *J*=6.5 Hz, H-12), 3.06 (1H, dddd, *J*=15.9, 7.1, 2.4, 1.7 Hz, H-16a), 2.92 (2H, m, H-13), 2.61 (1H, dddd, *J*=15.9, 6.8, 2.4, 2.2 Hz, H-16b), 2.46 (2H, br t, *J*=7.2 Hz, H-4), 2.31 (2H, dt, *J*=7.2, 6.9 Hz, H-5), 2.12 (2H, m, H-9), 2.05 (2H, m, H-8), 1.77 (3H, d, *J*=1.2 Hz, H-20), 1.74 (3H, d, *J*=1.2 Hz, H-21), 1.77 (3H, d, *J*=1.2 Hz, H-20), 1.65 (3H, br s, H-23), 1.62 (3H, br s, H-24); ^{13}C NMR ($CDCl_3$): δ 174.1 (s, C-1), 170.3 (s, C-3), 169.7 (s, C-22), 139.8 (s, C-19), 139.2 (d, C-14), 136.9 (s, C-7), 135.7 (s, C-11), 126.8 (s, C-15), 125.1 (d, C-10), 123.3 (d, C-18), 122.4 (d, C-6), 115.6 (d, C-2), 76.6 (d, C-12), 74.4 (d, C-17), 73.2 (t, C-25), 39.1 (t, C-8), 36.5 (t, C-16), 33.7 (t, C-13), 28.6 (t, C-4), 25.9 (t, C-9), 25.6 (t, C-5), 25.5 (q, C-20), 18.4 (q, C-21), 15.9 (q, C-24), 12.3 (q, C-23); EIMS (70 eV) *m/z* (%) $[M]^+$ 414 (5), $[M-H_2O]^+$ 396 (15), 378 (55), 249 (100), 213 (85), 166 (95), 121 (55).

3.5. Preparation of *R*- and *S*-MTPA esters of compound 1b

S-(−)-MTPA chloride (Aldrich) (20 µl) was added to a solution of compound **1b** (2 mg) in dry pyridine (0.5 ml) and the resulting mixture was kept at room temperature for 2 h. After the removal of the solvent under reduced pressure the residue was subjected to preparative TLC on Si gel plate (petroleum ether/Et_2O; 4:1) to give *R*-MTPA ester **1c** (1.5 mg) of compound **1b**. The *S*-MTPA ester **1d** (1.3 mg) was obtained in the same manner, starting from *R*-(+)-MTPA chloride. Only chemical shifts of the C-12 region are reported because all other are remote from the MTPA group, so that their $\Delta\delta$ values are zero, and their chemical shifts were reported before.

3.5.1. (*R*)-MTPA esters 1c. ^1H NMR ($CDCl_3$): δ 6.06 (1H, ddt, *J*=7.8, 2.4, 2.2 Hz, H-14), 5.55 (1H, t, *J*=6.5 Hz, H-12), 5.39 (1H, br t, *J*=6.7 Hz, H-10), 3.28 (1H, m, H-13a), 3.21 (1H, m, H-13b), 2.98 (1H, dddd, *J*=15.9, 7.1, 2.4, 1.7 Hz, H-16a), 2.56 (1H, dddd, *J*=15.9, 6.8, 2.4, 2.2 Hz, H-16b), 2.09 (2H, m, H-9), 2.02 (2H, m, H-8), 1.60 (3H, br s, H-23).

3.5.2. (*S*)-MTPA esters 1d. ^1H NMR ($CDCl_3$): δ 5.89 (1H, ddt, *J*=7.8, 2.4, 2.2 Hz, H-14), 5.56 (1H, t, *J*=6.5 Hz, H-12), 5.46 (1H, br t, *J*=6.7 Hz, H-10), 3.09 (2H, m, H-13), 2.90 (1H, dddd, *J*=15.9, 7.1, 2.4, 1.7 Hz, H-16a), 2.55 (1H, dddd, *J*=15.9, 6.8, 2.4, 2.2 Hz, H-16b), 2.13 (2H, m, H-9), 2.05 (2H, m, H-8), 1.65 (3H, br s, H-23).

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