New Cytotoxic Sesterterpenes from the Sponge *Sarcotragus* Species

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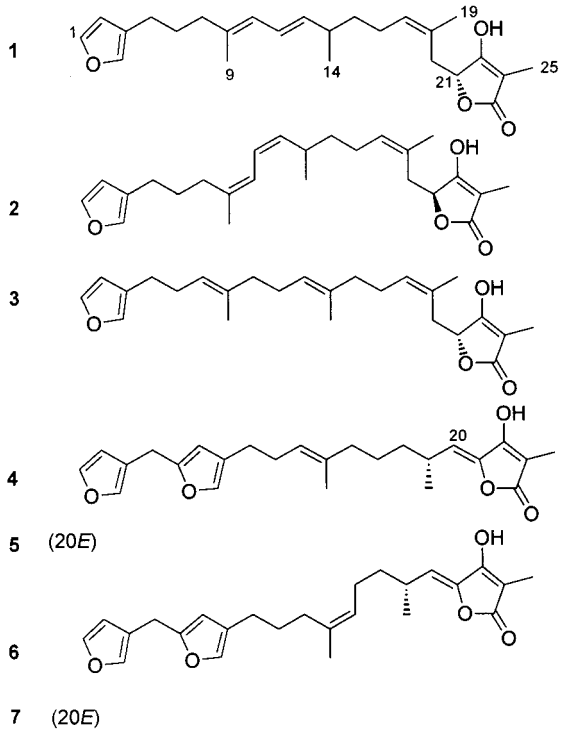
Five new (**1**−**3**, **5**, and **7**) and two known (**4**, **6**) furanosesterterpene tetronic acids were isolated from the marine sponge *Sarcotragus* sp. by bioactivity-guided fractionation. These compounds showed cytotoxicity against a panel of five human tumor cell lines. The gross structures were established on the basis of NMR and MS analyses. The compounds showed interesting variations of geometry and absolute configuration.

The sponge *Sarcotragus* is a genus of the order Dictyoceratida. Marine sponges of the order Dictyoceratida have been the source of a wide variety of linear sesterterpenes,[1] many of which contain both the furan ring and the tetronic acid moiety, while others are degradation products of these. Sponges of the genus *Sarcotragus* are reported to contain compounds such as variabilin,[2] (7*E*,12*E*,20*E*)-variabilin, (7*E*,12*Z*,20*Z*)-variabilin, 8-hydroxy-(12*E*, 20*Z*)-variabilin, 14-furan-3-yl-3,7,11-trimethyltetradeca-7,11-dienoic acid,[3] octa- and nonaprenylhydroquinone sulfate,[4] and geranylfarnesylacetone.[5]

In our study of the cytotoxic compounds from marine sponges, five new furanosesterterpene tetronic acids (**1**−**3**, **5**, and **7**) along with two known congeners, ircinin-1 (**4**)



and ircinin-2 (**6**),[6,7] have been isolated from a *Sarcotragus* sp. collected from Korean waters. Compounds **1**−**3** possess an unconjugated tetronic acid moiety, while **5** and **7** possess a conjugated tetronic acid moiety and are the geometric isomers of ircinin-1 (**4**) and ircinin-2 (**6**), respectively. The gross structures of the compounds were elucidated by the aid of COSY, HMQC, and HMBC experiments, while the geometries of the double bonds were determined based on ^{1}H−^{1}H coupling constants or ^{13}C NMR data. The absolute configurations were defined by optical rotation or circular dichroism spectroscopy. In this paper, the isolation, structure elucidation, and biological activity of the new furanosesterterpene tetronic acids are described.

Results and Discussion

The methanol extract of the sponge displayed cytotoxicity against five human tumor cell lines and showed toxicity to brine shrimp larvae (LD_{50}, 93 μg/mL). Guided by the brine shrimp assay, the methanol extract was successively fractionated employing reversed-phase flash column chromatography, ODS HPLC, and CN HPLC to afford compounds **1**−**7** as the causative components. Compounds **1**−**3** were chemically unstable, and they slowly degraded on storing.

Compound **1** was isolated as a light yellow oil. A β-substituted furan unit was recognized from the broad singlets at δ_H 7.36, 7.24, and 6.28 in the ^{1}H NMR spectrum (Table 1). The presence of an unconjugated tetronic acid moiety was established with the aid of COSY, HMQC, and HMBC experiments. A characteristic vinylic methyl singlet at δ_H 1.64 which was correlated to a carbon at δ_C 6.0 (C-25) and the appearance of an oxymethine proton resonance at δ_H 4.75 coupled to a carbon at δ_C 78.8 (C-21) were consistent with the tetronic acid functionality not being further conjugated. Furthermore, the multiplicity of this oxymethine proton (dd, J = 8.5, 3.4 Hz) together with its demonstrated coupling to the allylic methylene protons (δ_H 2.63, dd, J = 14.3, 3.4 Hz, and δ_H 2.27, dd, J = 14.3, 8.5 Hz) supported the structural unit C-18−C-25. Assignment of an unconjugated tetronic acid terminus was also confirmed by spectroscopic correlation to that of the known sesterterpene tetronic acid palinurin,[8] which incorporated the same structural features except the geometry at C-17. Two vinylic methyl singlets at δ_H 1.70 and 1.75 (δ_C 16.5 and 24.4, respectively) and a secondary methyl doublet at δ_H 0.98 (J = 6.8 Hz, δ_C 21.5) were present in the carbon chain linking the tetronic acid moiety to the furan unit. The ^{1}H NMR spectrum also featured the presence of a trisubstituted olefin (δ_H 5.29, H-17) and a 1,1,4-trisubsti-

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Table 1. ^{1}H NMR Data of Compounds **1**−**7** (CD_3OD, 600 MHz)[a]

position	1	2	3	4	5	6	7
1	7.36 (brs)	7.37 (brs)	7.36 (brs)	7.39 (brs)	7.40 (brs)	7.39 (brs)	7.39 (brs)
2	6.28 (brs)	6.29 (brs)	6.29 (brs)	6.30 (brs)	6.29 (brs)	6.31 (brs)	6.31 (brs)
4	7.24 (brs)	7.25 (brs)	7.24 (brs)	7.31 (brs)	7.31 (brs)	7.31 (brs)	7.31 (brs)
5	2.37 (t, 7.6)	2.39 (t, 7.4)	2.44 (t, 7.7)	3.69 (s)	3.68 (s)	3.70 (brs)	3.70 (brs)
6	1.66 (m)	1.67 (m)	2.24 (m)				
7	2.05 (t. 7.7)	2.10 (t, 7.3)	5.17 (t, 7.1)	5.90 (brs)	5.90 (brs)	5.89 (brs)	5.89 (brs)
9	1.70 (s)	1.71 (s)	1.58 (s)	7.09 (brs)	7.10 (brs)	7.10 (brs)	7.10 (brs)
10	5.75 (d, 10.7)	6.04 (d, 11.4)	1.99 (m)	2.36 (t, 7.5)	2.35 (t, 7.5)	2.29 (t, 7.5)	2.29 (t, 7.5)
11	6.18 (dd, 15.1, 10.7)	6.12 (t, 11.0)	2.08 (m)	2.20 (q, 7.0)	2.19 (q, 7.0)	1.55 (q, 7.5)	1.56 (q, 7.5)
12	5.37 (dd, 15.1, 8.3)	5.09 (t, 10.3)	5.12 (t, 6.9)	5.13 (t, 6.5)	5.13 (t, 7.5)	1.98 (m)	2.01 (m)
13	2.15 (m)	2.62 (m)					
14	0.98 (d, 6.8)	0.94 (d, 6.7)	1.59 (s)	1.51 (s)	1.52 (s)	1.64 (s)	1.64 (s)
15	1.34 (m)	1.38 (m)	1.99 (m)	1.95 (m)	1.98 (m)	5.11 (t, 7.5)	5.13 (t, 8.0)
16	1.99 (m)	1.99 (m)	2.10 (q, 6.8)	1.38 (m)	1.38 (m)	1.90 (m)	1.90 (m)
17	5.29 (t, 6.9)	5.25 (t, 6.8)	5.28 (t, 7.4)	1.29 (m)	1.28 (m)	1.40 (m)	1.40 (m)
						1.34 (m)	1.34 (m)
18				2.69 (m)	3.41 (m)	2.70 (m)	3.41 (m)
19	1.75 (s)	1.75 (s)	1.75 (s)	1.02 (d, 7.0)	1.01 (d, 6.5)	1.02 (d, 6.5)	1.01 (d, 6.5)
20	2.63 (dd, 14.3, 3.4)	2.55 (dd, 14.6, 2.9)	2.64 (dd, 14.2, 2.4)	5.19 (d, 10.0)	5.22(d, 10.5)	5.20 (d, 10.0)	5.22 (d, 10.5)
	2.27 (dd, 14.3, 8.5)	2.17 (dd, 14.6, 9.6)	2.23 (m)				
21	4.75 (dd, 8.5, 3.4)	4.43 (dd, 9.6, 2.9)	4.63 (dd, 6.3, 2.4)				
25-CH_3	1.64 (s)	1.57 (s)	1.61 (s)	1.66 (s)	1.67 (s)	1.65 (s)	1.67(s)

[a] Multiplicities and coupling constants in parentheses. Compounds **4**−**7** were measured at 500 MHz.

Table 2. ^{13}C NMR Data of Compounds **1**−**7** (CD_3OD, 50 MHz)[a]

position	1	2	3	4	5	6	7
1	143.9	143.9	143.7	144.0	144.1	144.1	144.1
2	111.9	111.9	112.0	112.1	112.2	112.2	112.2
3	126.2	124.8	126.2	123.0	123.1	123.1	123.1
4	140.1	140.1	140.0	140.9	140.9	140.9	140.9
5	25.2	25.2	25.9	24.7	24.8	24.8	24.8
6	29.5	29.5	29.6	155.4	155.4	155.6	155.6
7	40.3	40.6	125.5[b]	108.2	108.3	108.1	108.1
8	136.7	138.5	136.6	127.0	127.1	127.1	127.1
9	16.5	16.3	16.1[c]	138.6	138.6	138.7	138.6
10	126.5[b]	121.8	40.7	26.1	26.1	25.7	25.7
11	126.6[b]	121.8	27.7[d]	29.5	29.5	29.5	29.5
12	139.1	137.1	125.1[b]	125.2	125.2	32.2	32.2
13	38.0	32.5	135.8	136.6	136.8	136.3	136.1
14	21.5	21.8	16.0[c]	15.9	15.9	23.6	23.6
15	38.2	38.8	40.7	40.5	40.7	126.3	126.5
16	27.0	26.9	27.5[d]	26.8	26.8	26.9	26.8
17	130.5[c]	129.5[b]	129.6[e]	37.8	38.6	38.8	39.4
18	130.6[c]	132.1[b]	131.2[e]	31.6	30.1	31.5	30.4
19	24.4	24.3	24.4	21.2	22.1	21.2	21.9
20	35.4	35.9	35.5	113.3	118.5	112.9	119.9
21	78.8	78.7	79.7	147.9	147.7	148.4	148.2
22	177.2	182.3	180.2	173.7	173.5	175.0	172.6
23	96.8	90.4	92.9	94.0	98.1	93.3	97.3
24	178.1	189.2	184.0	176.7	175.3	177.3	176.0
25	6.0	6.0	5.9	5.9	5.9	6.0	6.0

[a] Compounds **1**, **4**, and **6** were measured at 75 MHz. [b−e] Assignments with the same superscript in the same column may be interchanged.

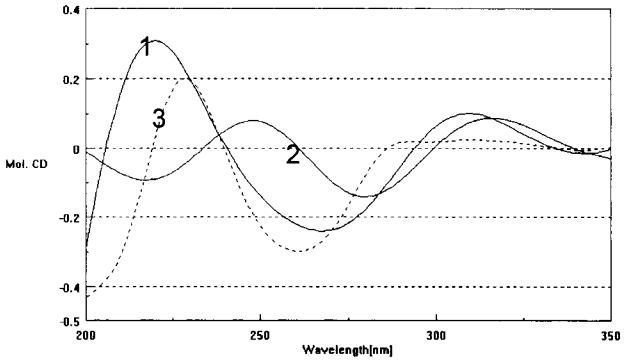

Figure 1. CD spectra of compounds **1**−**3**.

tuted diene (δ_H 6.18, H-11; 5.75, H-10; 5.37, H-12). The ^{13}C NMR data (Table 2) were in accordance with the values reported for the similar types of compounds.[8]

The *E* geometry of the trisubstituted double bond (C-8) was assigned on the basis of the upfield resonance (δ_C16.5, C-9) of the vinylic methyl carbon,[9] while the geometry of the disubstituted double bond (C-11) was determined to be *E* on the basis of the coupling constants of the respective protons (J = 15.1 Hz). The carbon chemical shift of the C-19 methyl (δ_C 24.4) indicated the *Z* geometry of this trisubstituted double bond, which was also supported by an upfield shift of the C-20 signal (δ_C 35.4) compared to that of palinurin (δ_C 41.6, C-20).[8−11] The low-resolution FABMS spectrum of **1** showed an $[M + Na]^+$ ion at *m*/*z* 421 and a characteristic $[M + 2Na - H]^+$ ion at *m*/*z* 443, which might be produced by an exchange of the acidic hydrogen with Na^+ followed by complexation with a second Na^+. The molecular ion was detected at *m*/*z* 398 in EIMS. The absolute configuration of the α,β-unsaturated γ-lactone was determined by CD spectroscopy. The CD spectrum of **1** showed a positive Cotton effect at 221 nm ($\pi-\pi^*$) and a negative Cotton effect at 268 nm ($n-\pi^*$), indicating the absolute configuration of C-21 to be *R* (Figure 1).[12−14] The absolute configuration of C-13 remains to be determined.

The EIMS spectra of **2** and **3** showed the same $[M]^+$ ion at *m*/*z* 398 as **1**. The ^{1}H and ^{13}C NMR spectra indicated that they were geometric or double bond position isomers of **1**. Both the ^{1}H and ^{13}C NMR spectra of **2** showed a close similarity to those of **1**, with the only difference being in the coupling constant of the disubstituted olefinic protons (J = 11.0 Hz). This confirmed **2** as the 11*Z*-isomer of **1**.[9] The CD spectrum of **2** showed a negative Cotton effect at 218 nm ($\pi-\pi^*$) and a positive Cotton effect at 248 nm ($n-\pi^*$), indicating the absolute configuration of C-21 to be *S*.[12−14]

The ^{1}H NMR spectrum of compound **3** displayed resonances consistent with the presence of three vinylic methyls (δ_H 1.58, 3H, s; 1.59, 3H, s; 1.75, 3H, s) and three trisubstituted double bonds (δ_H 5.28, 1H, t; 5.17, 1H, t; 5.12, 1H, t). The positions of the double bonds were confirmed by the COSY experiment. Examination of the ^{13}C NMR chemical shifts for the vinylic methyl resonance confirmed the geometry of the trisubstituted double bonds as 7*E*,12*E*, and 17*Z*. The assignments of the carbons and protons were supported by COSY and HMBC experiments and were

Table 3. Cytotoxity Data of Compounds **1**−**7**[a]

compound	A549	SK-OV-3	SK-MEL-2	XF498	HCT15
1	29.70	22.06	>30.00	24.83	27.18
2	10.10	11.30	7.78	8.89	8.95
3	16.89	26.84	16.31	20.40	27.49
4	3.72	6.55	8.95	5.42	6.91
5	4.98	9.39	10.18	6.52	9.82
6	3.80	5.90	5.87	3.70	4.74
7	3.80	6.24	8.37	5.00	7.31
cisplatin	0.72	1.23	2.26	1.03	1.10
doxorubicin	0.02	0.11	0.02	0.08	0.04

[a] Data as expressed in ED_{50} values (μg/mL). A549: human lung cancer; SK-OV-3: human ovarian cancer; SK-Mel-2: human skin cancer; XF498: human CNS cancer; HCT 15: human colon cancer.

similar to the literature values of the geometric isomer (7*E*,12*E*,17*E*)-21*R*-palominin.[12] The CD spectrum of **3** showed a positive Cotton effect at 228 nm ($\pi-\pi^*$) and a negative Cotton effect at 261 nm ($n-\pi^*$), indicating the absolute configuration at C-21 to be *R*.[12−14]

The identity of the two known compounds, ircinin-1 (**4**) and ircinin-2 (**6**), was confirmed by comparison of the ^{1}H NMR and ^{13}C NMR data with those reported previously.[6,7] Full assignment of the ^{1}H NMR (Table 1) and ^{13}C NMR (Table 2) was achieved on the basis of the analysis of COSY and HMBC data. These assignments were in agreement with the published data except for the interchange of the assignments of several carbons (Table 2).[6,7] Compounds **4** and **6** showed positive $[\alpha]_D$ values of +32.3° and +34.8°, respectively, which were consistent with an 18*R* configuration. Interestingly, both positive and negative $[\alpha]_D$ values had been assigned for ircinin-1 and ircinin-2, indicating the presence of both enantiomers in nature.[6,7,15,16]

The ^{1}H and ^{13}C NMR spectra of **5** and **7** were very similar to those of ircinin-1 (**4**) and ircinin-2 (**6**), respectively, with the exception of the geometry of the double bond vicinal to the tetronic acid moiety.[3] A downfield shift from δ_H 2.69 to 3.41 of H-18 in **5** as compared to ircinin-1 (**4**) indicated that **5** was the 20*E* isomer of **4**. A downfield shift was also observed for H-20 (Table 1). Similarly, compound **7** showed a downfield shift (from δ 2.70 to 3.41) of H-18 as compared to ircinin-2 (**6**), indicating that **7** was the 20*E* isomer of **6**. ^{13}C NMR chemical shifts of **5** and **7** also featured the corresponding differences as compared to **4** and **6**. Notable downfield shifts of C-20 signals were observed at δ_C118.5 and 119.9, respectively, which indicate 20*E* geometry.[3] The absolute configuration of C-18 was determined to be *R* on the basis of its positive optical rotations.[15,16] The signal assignments of **5** and **7** were supported by COSY and HMBC experiments. The Δ^{20} geometric isomers could be separated to each single component by HPLC, but slowly returned to equilibrium mixture upon standing.

Compounds **1**−**7** were generally unstable. Especially the unconjugated tetronic acid furanosesterterpenes (**1**−**3**) were very unstable, and they easily decomposed even at low temperature when kept in the solid state.

Diverse biological activities such as antibacterial,[3,11−13,17−23] antiviral,[18] antitumor,[3,24−27] antiinflammatory,[28] antispasmodic,[29] brine shrimp lethality,[15,30,31] ichthyotoxicity,[32,33] and inhibitory activities to starfish egg,[10,34,35] sea urchin sperm,[6] and protein phosphatase[36] have been attributed to furanosesterterpene tetronic acids. The tetronic acid functionality was suggested to be essential for antibiotic activity, and the unconjugated tetronic acid furanosesterterpenes were more active than the conjugated counterparts.[13] Compounds **1**−**7** showed cytotoxicity against a small panel of five human tumor cell lines (Table 3). Of the conjugated tetronic acid furanosesterterpenes, the 20*E* isomers (**4**, **6**) were slightly more active than the 20*Z* isomers (**5**, **7**).

Experimental Section

General Experimental Procedures. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC200, DMX600, Varian Unity Plus 300, and Unity INVOA 500 instruments. Chemical shifts were reported with reference to the respective residual solvent peaks (δ_H 3.30 and δ_C 49.0 for CD_3OD). IR spectra were measured using a JASCO FT/IR-410 spectrometer. Optical rotations were obtained using a JASCO DIP-370 digital polarimeter. CD spectra were measured using a JASCO J-715 spectropolarimeter (sensitivity 50 mdeg, resolution 0.2 nm, recorded in MeOH). HRFABMS data were obtained on a JEOL JMS-SX-101A. FAB-CID tandem MS data were obtained using a JEOL JMS-HX110/110A. HPLC was performed with an YMC ODS-H80 (semipreparative, 250 × 10 mm i.d., 4 μm, 80 Å; preparative, 250 × 20 mm i.d., 4 μm, 80 Å) and a YMC-Pack CN (250 × 10 mm i.d., 5 μm, 120 Å) column using a Shodex RI-71 detector.

Animal Material. The sponge was collected in July 1998 (15−25 m depth), off Cheju Island, Korea. This specimen was identified as *Sarcotragus* sp. by Prof. Sim, Hannam University. It was a massive spreading sponge of 4.6 × 11 and 45.3 cm thickness. Oscules are 2−4 mm in diameter, scattered on the face. The surface of the body was dark gray, and the underpart was beige. The texture was elastic and tough. The skeleton has strong fasciculated primary fibers, 280−530 μm in diameter, and uncored. Secondary fibers, 60−330 μm in diameter, are slightly fasciculated and uncored. The endosome skeleton was thick, simple, and dark brown in color. Filaments were very tightly arranged and emerge from the hole of fiber and have a terminal knob, 2.5−5 μm in thickness, 12−15 μm in diameter. A voucher specimen (J98J-5) of this horny sponge (registry No. Por.33) was deposited in the Natural History Museum, Hannam University, Taejon, Korea.

Extraction and Isolation. The frozen sponge (7 kg) was extracted with MeOH at room temperature. The MeOH extract was partitioned between water and CH_2Cl_2. The CH_2Cl_2-soluble portion was further partitioned between 90% MeOH and *n*-hexane to yield 90% MeOH (54 g) and *n*-hexane soluble (13 g) fractions. The 90% MeOH fraction was subjected to reversed-phase flash column chromatography (YMC Gel ODS-A, 60 Å 500/400 mesh), eluting with a solvent system of 25 → 0% H_2O/MeOH, to obtain 20 fractions (Fg1−Fg20). These fractions were evaluated for activity in the brine shrimp assay, and fractions Fg6−Fg9 were found active. These fractions were combined (7.4 g) and further separated by reversed-phase flash column chromatography (YMC Gel ODS-A, 60 Å, 500/400 mesh), eluting with 25 → 0% H_2O/MeOH, to afford 10 fractions. Fractions Fg6-5− Fg6-7 (5.4 g) were combined, and the combined fraction was further separated by a reversed-phase flash column chromatography (YMC Gel ODS-A, 60 Å, 500/400 mesh), eluting with 33 → 0% H_2O/MeCN, to afford 13 fractions. Guided by the brine shrimp assay, the fraction Fg6-5-6 was separated by HPLC (YMC ODS-H80, 250 × 10 mm i.d., S-4 μm), eluting with MeOH/H_2O, 6:1, to afford six fractions. Known compounds ircinin-2 (**6**, 4 mg) and its 20*E* isomer (**7**, 4 mg) were obtained by purification of fraction Fg6-5-6-2 by CN HPLC. Ircinin-1 (**4**, 9 mg) and its 20*E* isomer (**5**, 3 mg) were purified from fraction Fg6-5-6-3 by HPLC (YMC-Pack CN (250 × 10 mm i.d., 5 μm, 120 Å). Compounds **1** (173 mg), **2** (0.8 mg), and **3** (1.5 mg) were obtained upon repeated purification of fractions Fg6-5-6-5, Fg6-5-6-4, and Fg6-5-6-6, respectively.

Sarcotin A (1): light yellow oil; $[\alpha]^{25}_D$ + 67.9° (*c* 0.04, MeOH); IR (film) ν_{max} 3376, 2947, 2834, 1770, 1733, 1029, 668 cm^{-1}; CD (*c* 4 × 10^{-4} M, MeOH), $\Delta\epsilon$, 0 (335.2), +0.1 (308.5), 0 (293.3), −0.24 (268.3), 0 (240.9), +0.31 (220.5), 0 (205.8); ^{1}H NMR data, see Table 1; ^{13}C NMR data, see Table 2; EIMS *m*/*z* 398 $[M]^+$; FABMS *m*/*z* 443 $[M + 2Na - H]^+$ (10), 421 $[M + Na]^+$ (41), 399 $[M + H]^+$(7), 329 (11), 307 (67), 289 (29), 154 (100), 137 (100).

Sarcotin B (2): light yellow oil; ^{1}H NMR data, see Table 1; ^{13}C NMR data, see Table 2; CD (*c* 6 × 10^{-4} M, MeOH), $\Delta\epsilon$, 0 (340.1), +0.09 (315.6), 0 (299.6), −0.15 (279.5), 0 (261.5), +0.08 (247.5), 0 (233.9), 0.10(217.7); EIMS *m*/*z* 398 $[M]^+$; FABMS *m*/*z* 443 $[M + 2Na - H]^+$(3), 421 $[M + Na]^+$(3), 399 $[M + H]^+$(12), 329 (26), 154 (90), 137 (63).

Sarcotin C (3): light yellow oil; ^{1}H NMR data, see Table 1; ^{13}C NMR data, see Table 2; CD (*c* 1.8 × 10^{-3} M, MeOH), $\Delta\epsilon$, 0 (333.5), +0.02 (311.2), 0 (286.9), −0.30 (260.8), 0 (239.7), +0.20 (228.4), 0 (220.1); EIMS *m*/*z* 398 $[M]^+$; FABMS *m*/*z* 443 $[M + 2Na - H]^+$ (55), 421 $[M + Na]^+$ (15), 399 $[M + H]^+$ (1), 326 (18), 173 (30), 153 (5), 92 (18).

Ircinin-1 (4): yellow oil; $[\alpha]^{25}_D$ + 32.3° (*c* 0.05, MeOH), ^{1}H NMR data, see Table 1; ^{13}C NMR data, see Table 2; EIMS *m*/*z* 410 $[M]^+$ (56), 307 (100), 289 (60), 154 (100), 137 (100), 89 (40).

Sarcotin D (5): yellow oil; $[\alpha]^{25}_D$ + 36.1° (*c* 0.05, MeOH); ^{1}H NMR data, see Table 1; ^{13}C NMR data, see Table 2; EIMS *m*/*z* 410 $[M]^+$ (56), 307 (100), 289 (60), 154 (100), 137 (100), 89 (40).

Ircinin-2 (6): yellow oil; $[\alpha]^{25}_D$ + 34.8° (*c* 0.06, MeOH), ^{1}H NMR data, see Table 1; ^{13}C NMR data, see Table 2; EIMS *m*/*z* 410 $[M]^+$(74), 329 (25), 307 (100), 289 (45), 154 (100), 136 (100), 106 (38), 89 (28).

Sarcotin E (7): yellow oil; $[\alpha]^{25}_D$ + 41.6° (*c* 0.06, MeOH); ^{1}H NMR data, see Table 1; ^{13}C NMR data, see Table 2; EIMS *m*/*z* 410 $[M]^+$ (74), 329 (25), 307 (100), 289 (45), 154 (100), 136 (100), 106 (38), 89 (28).

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