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Euryspongins A–C, three new unique sesquiterpenes from a marine sponge *Euryspongia* sp.

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ABSTRACT

Three new unique sesquiterpenes, euryspongins A–C (**1**–**3**), were isolated from a marine sponge *Euryspongia* sp. collected at Iriomote Island, Okinawa, Japan. Compound **1** possessed a bicyclic furanosesquiterpene structure with six- and eight-membered rings, whereas compounds **2** and **3** had an α,β-unsaturated-γ-lactone ring instead of the furan ring in **1**. Only five natural products in this class have been reported, and compounds **1**–**3** are the sixth–eighth examples of natural products. Compounds **1**–**3** had no inhibition effect against PTP1B, an important target enzyme for the treatment of diabetes, while the dehydro derivative of **1** [dehydroeuryspongin A (**4**)] exhibited inhibitory activity (IC_{50} = 3.6 μM).

Marine sponges have been shown to be an important resource for the discovery of bioactive natural products. Many metabolites isolated from marine sponges possess unique structural features and potent biological activities.[1] Sponges of the genus *Euryspongia* have been shown to contain various types of secondary metabolites, including steroidal sulfates,[2] secosteroids,[3] hydroquinones,[4] sesquiterpene quinones,[5] and furanoterpenoids.[6] During our search program for novel and useful metabolites from marine organisms, three new unique sesquiterpenes, named euryspongins A–C (**1**–**3**), were isolated from a marine sponge *Euryspongia* sp. collected at Iriomote Island, Okinawa, Japan (Fig. 1). The structures of **1**–**3** were assigned on the basis of their spectroscopic data as unique sesquiterpenes possessing a six- and eight-membered bicyclic skeleton. Only five compounds, pallescensin B (**5**),[7a] nakafuran-8 (**6**),[7b] 5-hydroxynakafuran-8 (**7**),[7c] 5-acetoxynakafuran-8 (**8**),[7c] and *O*-methyl nakafuran-8 lactone (**9**),[7d] have thus far been reported as natural products in this class (Fig. 1). The natural products **1**–**3** did not show inhibitory activity against protein tyrosine phosphatase 1B (PTP1B), an important target for the treatment of type-II diabetes, while the dehydrated product of **1** [dehydroeuryspongin A (**4**)] inhibited the activity of this enzyme (IC_{50} = 3.6 μM). We describe herein the isolation, structure elucidation including stereochemistry, and biological activity of compounds **1**–**4**.

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The marine sponge (306.6 g, wet weight)[8] was extracted with ethanol, and the extract (1.1 g) was separated by an ODS column (100 g) followed by repeated HPLC to give compounds **1** (12.7 mg), **2** (0.90 mg), and **3** (1.55 mg) as colorless oil.[9]

The molecular formula, $C_{15}H_{20}O_2$, of euryspongin A (**1**)[10] was assigned from HREIMS (*m*/*z* 232.1462 [M]$^+$, Δ −0.1 mmu) and NMR data (Table 1). ^{1}H and ^{13}C NMR spectra of **1** showed 19 proton and 15 carbon signals, which were classified into three methyls, two methylenes, two sp^3 methines, one sp^3 oxygenated methine, one sp^3 quaternary carbon, two sp^2 methines, one sp^2 oxygenated methine, two sp^2 quaternary carbons, and one sp^2 oxygenated quaternary carbon from HMQC data. The presence of an OH group was revealed from IR absorption at 3402 cm^{-1} and the molecular formula of **1**. Three partial structures (I–III), shown as bold lines in Figure 2, were elucidated from the ^{1}H–^{1}H COSY spectrum of **1**. An α,β-disubstituted furan ring in partial structure I was assigned from HMBC correlations from H-1 (δ 7.15) and H-2 (6.37) to C-3 (122.6) and C-10 (150.1) (Fig. 2) and UV absorption at 220 nm.[7b] HMBC correlations from H_3-13 (δ 0.78) to C-11 (44.2), C-12 (33.4), and C-14 (30.1), from H_3-14 (0.90) to C-6 (48.1), C-12, and C-13 (36.3), and from H_3-15 (1.87) to C-6, C-7 (141.5), and C-8 (120.2) connected partial structures II and III by forming a six-membered ring. The connections of a furan ring and, consequently, an eight-membered ring were elucidated from HMBC correlations from H-4 (δ 4.59) to C-3 and C-10, from H_2-5 (2.16 and 2.27) to C-3, from H-9 (3.45) to C-10, and from H_2-11 (1.56 and 1.64) to

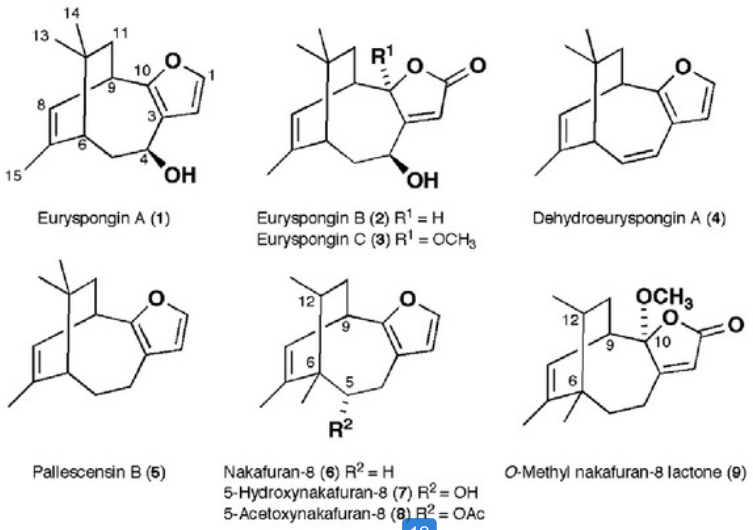

Figure 1. Structures of compounds **1–9**.

Table 1
^{1}H and ^{13}C NMR data for eurypongins A–C (**1–3**) in $CDCl_3$

Position	Eurypongin A (**1**)		Eurypongin B (**2**)		Eurypongin C (**3**)	
	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)
1	138.8	7.15 d (1.9)	172.5	–	166.8	–
2	109.3	6.37 d (1.9)	118.0	6.26 s	119.9	6.30 d (1.0)
3	122.6	–	176.1	–	170.1	–
4	65.9	4.59 dd (11.1, 4.8)	67.0	4.32 dd (10.6, 5.5)	65.7	4.32 ddd (10.0, 5.6, 1.0)
5a	40.8	2.27 ddd (14.0, 9.2, 4.8)	34.9	2.22 ddd (14.1, 8.6, 5.7)	35.6	2.22 ddd (14.0, 8.2, 5.8)
5b		2.16 ddd (13.9, 11.0, 1.1)		1.95 dd (13.9, 10.6)		1.98 dd (14.0, 10.6)
6	48.1	2.08 d (8.7)	47.2	1.89 d (8.8)	47.5	1.90 d (8.7)
	141.5	–	142.5	–	140.4	–
8	120.2	5.74 dq (7.3, 1.4)	118.8	5.61 d (6.6)	119.4	5.60 dq (7.3, 1.0)
	150.1					
9	33.8	3.45 ddd (7.3, 6.0, 2.2)	33.9	2.96 br t	37.2	2.97 br t
10	150.1	–	83.5	4.85 s	109.4	–
11	44.2	1.56 dd (13.3, 6.0)	30.2	1.25 m	33.8	1.25 m
		1.64 dd (13.3, 2.2)		1.35 dd (15.0, 9.5)		1.53 dd (15.5, 10.1)
12	33.4	–	34.0	–	33.1	–
13	36.3	0.78 s	29.3	0.93 s	29.8	0.92 s
14	30.1	0.90 s	33.7	0.95 s	34.7	0.96 s
15	23.5	1.87 d (1.4)	24.0	1.81 s	24.0	1.82 d (1.0)
10-OCH_3					51.1	3.23 s

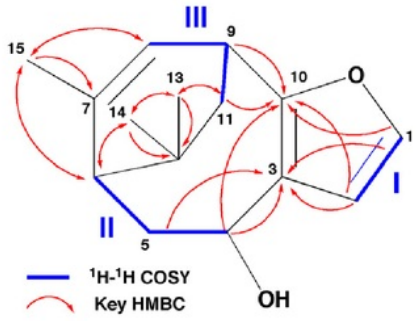

Figure 2. ^{1}H–^{1}H COSY and HMBC correlations for eurypongin A (**1**).

C-10 (Fig. 2). Thus, the skeletal structure of **1** was assigned as shown in Figure 2.

The relative stereochemistry of **1** was elucidated by the analysis of NOESY data ($CDCl_3$) and 1D NOE difference experiments in C_6D_6 (Fig. 3). Correlations between H-4 (δ 4.59)/H_3-15 (1.87), H-5b (2.16)/H_3-13 (0.78), H-6 (2.08)/H_3-14 (0.90), H_3-15/H-8 (5.74), and H-8/H-9 (3.45) were observed in the NOESY spectrum of **1** measured in $CDCl_3$ (Fig. 3). Assignment of the stereochemistry at C-4 to C-6 was also confirmed by NOE difference experiments in C_6D_6 (Fig. 3) because ^{1}H signals were observed closely to each other in $CDCl_3$. NOE difference spectra in C_6D_6 exhibited strong enhancements between H-4 (δ 4.45)/H_3-15 (1.47), H-6 (1.80)/14 (0.78), and H-6/H_3-15. Considering these NOE data, the Monte Carlo conformational analysis was performed with an

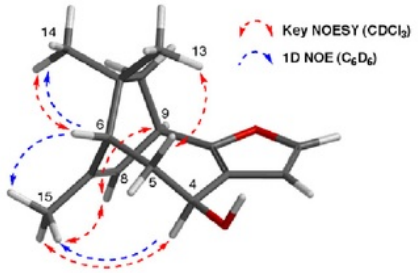

Figure 3. Relative stereochemistry of euryspongin A (**1**).

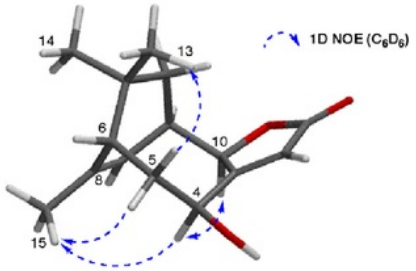

Figure 5. Relative stereochemistry of euryspongin B (**2**).

MMFF94 force field utilizing Spartan'04[11] as shown in Figure 3. The modified Mosher's method[12] was applied to investigate the absolute stereochemistry of **1**, but the reaction of **1** with *S*-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPA-Cl) resulted in the decomposition of **1**. Thus, the absolute stereochemistery of **1** was tentatively assigned by comparing the specific rotation with that of the related compound, 5-hydroxynakafuran-8 (**7**),[7c] since **1** and **7** will plausibly be produced via the identical biosynthetic pathway. The absolute configuration of 5-hydroxynakafuran-8 (**7**) was reported to be (*5S*, *6S*, *9R*, *12R*), and, therefore, the absolute stereochemistry of **1** was suggested to be depicted as shown in Figure 1. However, further study should be necessary to define the assignment.

Euryspongin B (**2**)[13] showed the $[M]^+$ ion at *m*/*z* 248.1401 (Δ −1.1 mmu) in HREIMS, and the molecular formula was determined to be $C_{15}H_{20}O_3$ using NMR data (Table 1). IR absorptions at 3545 and 1746 cm^{-1} indicated the presence of an OH and a carbonyl groups. ^1H and ^{13}C NMR spectra of **2** were similar to those of **1**, except for signals due to the furan ring in **1**. Oxygenated sp^3 methine (δ_H 4.85, δ_C 83.5) and carbonyl (δ_C 172.5) signals were detected in ^1H and ^{13}C NMR spectra of **2** instead of the oxygenated sp^2 signals due to the C-1 (δ_H 7.15, δ_C 138.8) and C-10 (δ_C 150.1) positions in those of **1** as the most remarkable differences between **2** and **1**. The presence of an α,β-unsaturated-γ-lactone in **2** was elucidated by analysis of HMBC data (Fig. 4) together with IR and UV data.[7d,13] Consequently, the structure of **2** was assigned as an α,β-unsaturated-γ-lactone derivative of **1** at the furan ring.

HREIMS (*m*/*z* 278.1509 $[M]^+$, Δ −0.9 mmu) and NMR data (Table 1) for **3** deduced the molecular formula of euryspongin C (**3**)[14] as $C_{16}H_{22}O_4$. The physico-chemical properties of **3** were similar to those of **2**, indicating that they share a similar skeleton.[13,14] Differences in the molecular weight and formula between **2** and **3** (30 mu, CH_2O) were detected in NMR spectra of **2** and **3**. ^1H and ^{13}C NMR spectra of **3** showed an extra OMe signal at δ_H 3.23 (δ_C 51.1) and an acetal carbon signal at δ_C 109.4 instead of an oxygenated methine (δ_H 4.85, δ_C 83.5) at the C-10 position in **2**. An HMBC correlation was observed from the OMe signal at δ_H 3.23 to δ_C 109.4 (C-10). Thus, the structure of euryspongin C (**3**) was assigned as a 10-methoxy derivative of euryspongin B (**2**).

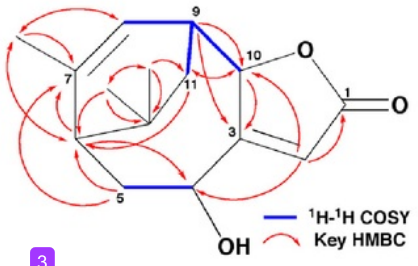

Figure 4. ^1H–^1H COSY and HMBC correlations for euryspongin B (**2**).

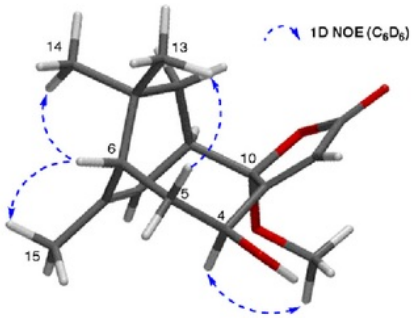

Figure 6. Relative stereochemistry of euryspongin C (**3**).

The relative stereochemistry of compounds **2** and **3** was determined to be the same as that of **1** from analysis of ^1H coupling constants ($CDCl_3$) and NOE data (C_6D_6). ^1H coupling constants measured in $CDCl_3$ and NOE correlation patterns in C_6D_6 of **1**–**3** were very similar to each other. The relative configuration at C-4 and C-10 in **2** and **3** was determined from NOE data. NOE difference spectra of **2** and **3** in C_6D_6 showed enhancements between H-4 (δ 3.57)/H-10 (4.25) in **2** and between H-4 (3.96)/10-OMe (2.89) in **3** (Figs. 5 and 6). Considering these NOE data, the Monte Carlo conformational analyses were performed with an MMFF94 force field utilizing Spartan'04[11] as shown in Figures 5 and 6. Accordingly, the relative stereochemistry of **2** and **3** were assigned as shown in Figure 1. These configurations were supported by the relative stereochemistry of a related lactone derivative, *O*-methyl nakafuran-8 lactone (**9**), determined by X-ray crystallography,[7d] which has the same relative configuration as **3**.

Eurypongins A–C are unique sesquiterpenes possessing a six- and eight-membered skeleton with a furan or γ-lactone ring. Only five natural products in this class, pallescensin B (**5**), nakafuran-8 (**6**), 5-hydroxynakafuran-8 (**7**), 5-acetoxynakafuran-8 (**8**), and *O*-methyl nakafuran-8 lactone (**9**), have thus far been reported.[7] Therefore, we added three more examples (**1**–**3**) to this class of natural products.

Nakafuran-8 (**6**)[15] and *O*-methyl nakafuran-8 lactone (**9**)[7d] were reported to have inhibitory activity against PTP1B. This enzyme plays a major role in dephosphorylation of the insulin receptor and is regarded as a key target for the treatment of type-II diabetes and obesity.[16] Eurypongins A–C (**1**–**3**) were, therefore, tested for their effect against PTP1B activity using our bioassay method described previously.[17] Unfortunately, compounds **1**–**3** did not show apparent activity even at 35–40 μM. In the same bioassay, oleanolic acid,[18] a positive control, inhibited PTP1B activity with an IC_{50} value of 1.1 μM. We presumed that differences in bioactivity between compounds **1**–**3** and two active compounds (**6**[15] and

9[7d]) were attributed to an OH group at C-4 in **1**–**3**, and, then, the activity of a dehydro derivative of **1**, dehydroeuryspongin A (**4**),[19] was examined. As expected, compound **4** showed inhibitory activity against PTP1B with an IC_{50} value of 3.6 μM. Moreover, compounds **1**–**4** did not inhibit cell proliferation of two human cancer cell lines, HCT-15 (colon) and Jurkat (T-cell lymphoma) cells at 45 μM.[20]

Acknowledgments

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8. The marine sponge was collected by scuba diving in the coral reef at Iriomote Island, Okinawa, Japan, in 2010 and identified as *Euryspongia* sp. The voucher specimen was deposited at the Faculty of Pharmaceutical Sciences, Tohoku Pharmaceutical University as 10-10-11=2-2.
9. The frozen sponge (306.6 g, wet weight) was thawed, cut into small pieces, and extracted with ethanol (1.0 L). The ethanol extract was evaporated to dryness (1.1 g) and applied on an ODS column (100 g). The column was eluted stepwise with 0, 50, 60, 70, 80, 90, and 100% CH_3OH in H_2O (each 400 mL). The fraction eluted with 80% CH_3OH (140.8 mg) was purified by preparative HPLC [column, PEGASIL ODS (Senshu Sci. i.d. 10 × 250 mm); solvent, 70% CH_3OH; flow rate, 2.0 mL/min; detection, UV 220 nm] to give euryspongin A (**1**) (t_R = 17.1 min) as a colorless oil (12.7 mg). Euryspongin B (**2**) was isolated as a colorless oil (0.90 mg) by preparative HPLC with 65% CH_3OH (t_R = 23.1 min) from the fraction eluted with 60% CH_3OH (29.5 mg). The fraction eluted with 70% CH_3OH (84.6 mg) was separated by preparative HPLC (70% CH_3OH, t_R = 24.2 min) to yield euryspongin C (**3**) as a colorless oil (1.55 mg).
10. *Euryspongin A* (**1**): A colorless oil; $[\alpha]_D^{20}$ −33.9 (*c* 0.10, $CHCl_3$); IR (KBr) ν_{max} 3402, 2357, 1630, 1385 cm^{-1}; UV (MeOH) λ_{max} 220 (ε 12850), 269 (ε 8630); EIMS *m*/*z* 232 $[M]^+$; HREIMS *m*/*z* 232.1462 ($[M]^+$; calcd for $C_{15}H_{20}O_2$, 232.1463); ^1H NMR (C_6D_6) δ 7.05 (1H, d, *J* = 1.9 Hz), 6.51 (1H, d, *J* = 1.5 Hz), 5.51 (1H, d, *J* = 7.6 Hz), 4.45 (1H, dd, *J* = 10.7, 4.9 Hz), 3.45 (1H, br t, *J* = 7.8 Hz), 2.08 (1H, ddd, *J* = 13.2, 10.7, 1.5 Hz), 1.99 (1H, ddd, *J* = 14.2, 8.8, 4.9 Hz), 1.80 (1H, d, *J* = 8.8 Hz), 1.69 (1H, dd, *J* = 13.4, 1.7 Hz), 1.63 (3H, d, *J* = 1.5 Hz), 1.47 (1H, dd, *J* = 13.2, 6.3 Hz), 0.78 (3H, s), 0.72 (3H, s); ^1H and ^{13}C NMR ($CDCl_3$), see Table 1.
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13. *Euryspongin B* (**2**): A colorless oil; $[\alpha]_D^{20}$ +90.4 (*c* 0.10, $CHCl_3$); IR (KBr) ν_{max} 3545, 1748, 1648, 1424 cm^{-1}; UV (MeOH) λ_{max} 201 (ε 20510), 220 (ε 11310); EIMS *m*/*z* 248 $[M]^+$; HREIMS *m*/*z* 248.1401 ($[M]^+$; calcd for $C_{15}H_{20}O_3$, 248.1412); ^1H NMR (C_6D_6) δ 6.02 (1H, s), 5.02 (1H, d, *J* = 5.3 Hz), 4.25 (1H, s), 3.57 (1H, dd, *J* = 10.1, 5.8 Hz), 2.60 (1H, br t), 1.74 (1H, ddd, *J* = 14.5, 8.7, 5.8 Hz), 1.56 (1H, dd, *J* = 12.6, 10.6 Hz), 1.37 (3H, s), 1.33 (1H, d, *J* = 8.7 Hz), 1.03 (1H, dd, *J* = 15.0, 9.4 Hz), 0.86 (1H, d, *J* = 15.5 Hz), 0.66 (3H, s), 0.65 (3H, s); ^1H and ^{13}C NMR ($CDCl_3$), see Table 1.
14. *Euryspongin C* (**3**): A colorless oil; $[\alpha]_D^{20}$ +52.2 (*c* 0.16, $CHCl_3$); IR (KBr) ν_{max} 3468, 1760, 1647, 1427 cm^{-1}; UV (MeOH) λ_{max} 201 (ε 20600), 220 (ε 11410); EIMS *m*/*z* 278 $[M]^+$; HREIMS *m*/*z* 278.1509 ($[M]^+$; calcd for $C_{16}H_{22}O_4$, 278.1518); ^1H NMR (C_6D_6) δ 6.06 (1H, s), 5.54 (1H, d, *J* = 6.8 Hz), 3.96 (1H, dd, *J* = 10.6, 5.8 Hz), 2.90 (1H, br t), 2.89 (3H, s), 1.72 (1H, m), 1.59 (1H, dd, *J* = 14.1, 10.4 Hz), 1.48 (3H, s), 1.40 (1H, d, *J* = 8.2 Hz), 1.23 (1H, dd, *J* = 15.9, 8.0 Hz), 0.93 (1H, d, *J* = 15.5 Hz), 0.68 (6H, s); ^1H and ^{13}C NMR ($CDCl_3$), see Table 1.
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19. Dehydroeuryspongin A (**4**) was formed in an NMR tube. Three days after measuring 2D NMR spectra of **1** in $CDCl_3$, the ^1H NMR spectrum showed signals due to a dehydro product (**4**). ^1H and ^{13}C NMR spectra of this product revealed that signals due to **1** had disappeared and the purity of **4** was quite high. Compound **4** was recovered by evaporating the solvent. Compound **4**: a pale yellow oil; $[\alpha]_D^{20}$ +55.9 (*c* 0.46, $CHCl_3$); UV (MeOH) λ_{max} 200 (ε 17900), 280 (ε 5480); EIMS *m*/*z* 214 $[M]^+$; HREIMS *m*/*z* 214.1365 ($[M]^+$; calcd for $C_{15}H_{18}O$, 214.1358); ^1H NMR ($CDCl_3$) δ 7.02 (1H, d, *J* = 1.5 Hz), 6.20 (1H, d, *J* = 1.9 Hz), 6.06 (1H, d, *J* = 12.3 Hz), 5.71 (1H, dd, *J* = 12.1, 9.7 Hz), 5.67 (1H, dd, *J* = 7.3, 1.5 Hz), 3.30 (1H, t, *J* = 8.0 Hz), 2.40 (1H, d, *J* = 9.7 Hz), 1.90 (1H, d, *J* = 14.0 Hz), 1.81 (3H, d, *J* = 1.4 Hz), 1.64 (1H, dd, *J* = 14.3, 9.4 Hz), 1.13 (3H, s), 0.97 (3H, s); ^{13}C NMR ($CDCl_3$) δ 161.9, 137.7, 133.0, 130.8, 122.1, 118.2, 114.4, 113.7, 51.7, 41.5, 39.6, 33.2, 32.4, 29.1, 23.4.
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