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Inhibitory effects of sesquiterpene lactones from the Indonesian marine sponge *Lamellodysidea* cf. *herbacea* on bone morphogenetic protein-induced osteoblastic differentiation

Satoshi Ohte [a,j,*], Hiroyuki Yamazaki [b,j], Ohgi Takahashi [b], Henki Rotinsulu [b,c], Defny S. Wewengkang [b,c], Deiske A. Sumilat [b,d], Delfly B. Abdjul [b,e], Wilmar Maarisit [b,f], Magie M. Kapojos [b,g], Huiping Zhang [h], Fumiaki Hayashi [h], Michio Namikoshi [b], Takenobu Katagiri [i], Hiroshi Tomoda [a], Ryuji Uchida [b,*]

[a] Graduate School of Pharmaceutical Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641, Japan
[b] Faculty of Pharmaceutical Sciences, Tohoku Medical and Pharmaceutical University, Sendai 981-8558, Japan
[c] Faculty of Mathematic and Natural Sciences, Sam Ratulangi University, Kampus Bahu, Manado 95115, Indonesia
[d] Faculty of Fisheries and Marine Science, Sam Ratulangi University, Kampus Bahu, Manado 95115, Indonesia
[e] North Sulawesi Research and Development Agency, 17 Agustus Street, Manado 95117, Indonesia
[f] Faculty of Mathematics and Natural Sciences, Christian University of Indonesia, Tomohon 95362, Indonesia
[g] Faculty of Nursing, University of Pembangunan Indonesia, Kampu, Manado 95115, Indonesia
[h] SR Science and Development Division, RIKEN SPring-8 Center, 1-7-22 Suehiro-cho, Tsurumi-ku, Yokohama, Kanagawa 230-0045, Japan
[i] Division of Biomedical Sciences, Research Center for Genomic Medicine, Saitama Medical University, 1397-1 Yamane, Hidaka, Saitama 350-1241, Japan

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ABSTRACT

A new unique sesquiterpene lactone, bicyclolamellolactone A (**1**), was isolated together with two known monocyclofarnesol-type sesquiterpenes, lamellolactones A (**2**) and B (**3**), from the Indonesian marine sponge *Lamellodysidea* sp. (cf. *L. herbacea*). The planar structure of **1** was assigned based on its spectroscopic data (1D and 2D NMR, HRESIMS, UV, and IR spectra). The relative and absolute configuration of **1** was determined by comparison of its calculated and experimental electronic circular dichroism spectra in combination with NOESY correlations. Compounds **1**–**3** inhibited bone morphogenetic protein (BMP)-induced alkaline phosphatase activity in mutant BMP receptor-carrying C2C12 cells with IC_{50} values of 51, 4.6, and 20 μM, respectively.

Fibrodysplasia ossificans progressiva (FOP) is a rare genetic skeletal disorder that causes progressive heterotopic ossification (HO) in the skeletal muscle, tendons, fascia, and ligaments,[1–3] which occurs in approximately one out of every 2 million people.[4] In 2006, a recurrent mutation R206H within ACVR1/ALK2, which is one of the bone morphogenetic protein (BMP) type I receptors, was identified in FOP patients.[5] It was later revealed that the induction of HO is caused by the activation of intracellular BMP signaling induced by the ALK2 mutant.[2,6] Based on this finding, suppression of BMP signaling has been under development as a promising therapeutic strategy;[7] however, no products have yet been approved as FOP therapeutics. Therefore, the discovery of novel pharmaceutical leads for the treatment of FOP are still needed.

In the course of our screening for inhibitory substances of BMP-induced alkaline phosphatase (ALP) activity (BMP signaling inhibitors) using a stable ALK2(R206H)-expressing C2C12 cell line [abbreviated as C2C12(R206H)],[8] we reported several small molecule inhibitors, such as trichocyalides, lucilactaenes, 5-prenyltriptophol, and scopranones, from terrestrial microorganisms.[8–11] Moreover, we recently started to screen marine-derived samples such as marine sponges, ascidians, and marine-derived microorganisms and discovered protuboxepin K from the culture broth of marine-derived *Aspergillus* sp. BFM-0085.[12] With continuous efforts, we found that the EtOH extract of the marine sponge *Lamellodysidea* sp. (cf. *L. herbacea*), collected in Manado, Indonesia, inhibited BMP-induced ALP activity in C2C12 (R206H) cells. The bioassay-guided separation of this extract led to the isolation of a new sesquiterpene lactone, named bicyclolamellolactone A

* Corresponding authors.
E-mail addresses: ohtes@pharm.kitasato-u.ac.jp (S. Ohte), uchidar@tohoku-mpu.ac.jp (R. Uchida).
[j] These authors contributed equally to this work.

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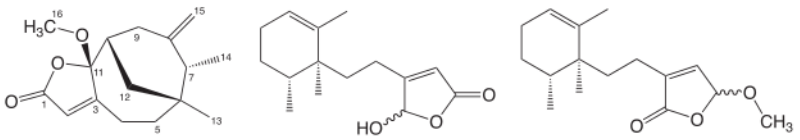

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Fig. 1. Structures of compounds **1**–**3** obtained from the Indonesian marine sponge *Lamellodysidea* cf. *herbacea*.

Table 1
^{13}C (200 MHz) and ^{1}H (800 MHz) NMR data for **1** in CD_3OD.

No.	**1**	
	δ_C	δ_H, mult. (*J* in Hz)
1	173.0	
2	120.6	5.73, dd (2.0, 1.4)
3	172.6	
4a	26.6	2.52, dddd (2.0, 4.6, 5.9, 18.5)
4b		2.87, dddd (1.4, 4.8, 11.4, 18.5)
5a	40.1	1.55, dddd (1.5, 4.8, 5.9, 14.6)
5b		1.79, m
6	37.2	
7	47.8	2.19, q (7.2)
8	151.6	
9a	30.2	2.01, dd (2.0, 13.8)
9b		2.43, m
10	40.0	2.42, m
11	113.9	
12	32.5	1.78, m
13	31.1	0.89, s
14	17.9	1.05, d (7.2)
15a	112.9	4.49, dd (2.2, 2.6)
15b		4.79, dd (1.9, 2.6)
16	50.6	3.16, s

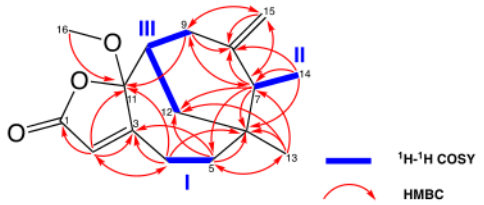

Fig. 2. ^{1}H-^{1}H COSY and HMBC correlations for **1**.

(**1**), possessing a rare bicyclo[4.3.1]decane skeleton, together with two known monocyclofarnesol-type sesquiterpenes,[13] lamellolactones A (**2**) and B (**3**) (Fig. 1).

We herein describe the isolation, structural elucidation, and biological properties of compounds **1**–**3**.

A small part of the Indonesian marine sponge *L.* cf. *herbacea* was extracted by EtOH, and the extract (50 μg/mL) exhibited 86% inhibition against BMP-induced ALP activity in the screening assay using C2C12 (R206H) cells. The rest of the sponge (619.7 g wet weight) was minced and soaked in EtOH. After evaporation, the obtained water residue was purified with an ODS column and repeated HPLC to yield compounds **1** (0.7 mg), **2** (1.4 mg), and **3** (0.6 mg).[14] Compounds **2** and **3** were identified as lamellolactones A and B, respectively, by comparing their spectroscopic data with those previously reported.[13]

The molecular formula of bicyclolamellolactone A (**1**)[15] was assigned to be $C_{16}H_{22}O_3$ from its HRESIMS (*m/z* 263.1641 $[M + H]^+$, Δ –0.6 mmu) and NMR data (Table 1). The ^{1}H and ^{13}C NMR spectra of **1** (in CD_3OD) indicated 22 proton and 16 carbon signals, which were classified into two methyls, one oxygenated methyl, four sp^3 methylenes, two sp^3 methines, one sp^3 quaternary carbon, one acetal carbon, one sp^2 methylene, one sp^2 methine, two sp^2 quaternary carbons, and one carbonyl carbon from the analysis of HSQC data (Table 1). Three partial structures (I–III) were elucidated from the ^{1}H-^{1}H COSY spectrum of **1**, as shown by blue bold lines in Fig. 2. HMBC correlations from H_2-4 (δ_H 2.52 and 2.87) to C-6 (δ_C 37.2), from H_2-5 (1.55 and 1.79) to C-6, C-12 (32.5), and C-13 (31.1), from H_3-13 (0.89) to C-5 (40.1), C-6, C-7 (47.8), and C-12, from H_3-14 (1.05) to C-6, C-7, and C-8 (151.6), and from H_2-15 (4.49 and 4.79) to C-7, C-8, and C-9 (30.2) connected partial structures I–III to form a six-membered ring. The presence of an α,β-unsaturated-γ-lactone ring was determined from the ^{13}C NMR signal at δ_C 173.0 and IR absorption at 1630 cm^{-1} in addition to HMBC correlations from H-2 (5.73) to C-1 (173.0), C-3 (172.6), and C-11 (113.9). The remaining HMBC data from H-2 to C-4 (26.6), from H_2-4 to C-2 (120.6), C-3, and C-11, from H_2-5 to C-3, and from H_2-9 (2.01 and 2.43) to C-11 established the bicyclo[4.3.1]decane framework with the α,β-unsaturated-γ-lactone ring

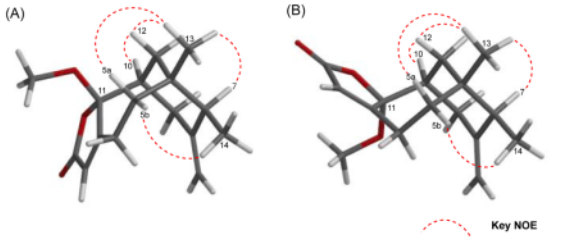

Fig. 3. Key NOE correlations of **1** for the most stable conformers calculated for the two possible stereostructures A (11*R*) and B (11*S*).

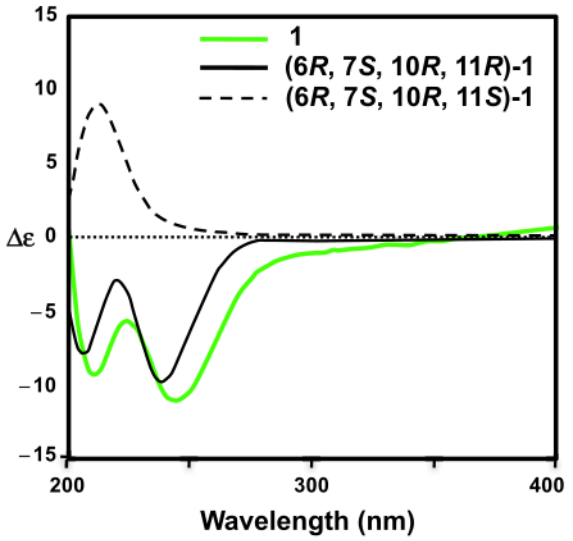

Fig. 4. Experimental ECD spectrum of **1** (green line) and calculated ECD spectra of (6*R*, 7*S*, 10*R*, 11*R*)-**1** (black line) and (6*R*, 7*S*, 10*R*, 11*S*)-**1** (dashed line).

Table 2
Effects of compounds **1–3** on osteoblastic differentiation and their cytotoxicity.

Compound	IC_{50} (μM)	
	ALP[a]	Cytotoxicity (C2C12)
1	51	> 76
2	4.8	> 40
3	20	> 38

[a] ALP: alkaline phosphatase.

(Fig. 2). Additionally, an OCH_3 residue at δ_H 3.16 (δ_C 50.6) was located at the C-11 position by the HMBC correlation between H_3-16 (δ_H 1.16) and C-11. Consequently, the skeletal structure of **1** was assigned as shown in Fig. 2.

The relative configuration of **1** was elucidated by analysis of the NOESY data in CD_3OD (Fig. 3). NOESY correlations between H-5a (δ 1.55)/H_3-13 (0.89), H-5b (1.79)/H_3-14 (1.05), H-7 (2.19)/H_3-13, H-10 (2.42)/H_2-12 (1.78), and H_2-12/H_3-13 gave two possible stereostructures, A and B, as shown in Fig. 3. However, the stereochemistry at C-11 could not be determined due to a lacking key NOESY correlation. The most stable conformers of the 11*R* and 11*S* isomers (A and B) were calculated using Spartan'14 and Monte Carlo conformational analysis with the MMFF94 force field,[16] which was consistent with the NOE data for **1** (Fig. 3).

In order to confirm the absolute structure of **1**, including the C-11 configuration, the electronic circular dichroism (ECD) spectra of the two possible isomers, (6*R*, 7*S*, 10*R*, 11*R*)- and (6*R*, 7*S*, 10*R*, 11*S*)-**1** were calculated using the energy-minimized structures based on the NOE data[16] and compared with the experimental ECD spectrum of **1** (Fig. 4). The experimental ECD of **1** (green line) coincided with the calculated ECD spectrum of the (6*R*, 7*S*, 10*R*, 11*R*)-isomer (solid line). Close inspections of the computational results revealed that the all electronic transitions responsible for the peaks in the ECD spectra of the two isomers are to the LUMO. In the both isomers, the LUMO is essentially a π* orbital of the α, β-unsaturated carbonyl (C═C–C═O) moiety at C-1–C-3, which is directly connected to C-11. For (6*R*, 7*S*, 10*R*, 11*S*)-**1**, the positive Cotton effect around 210 nm is due to a π → π* transition in the C═C–C═O moiety. The electronic transitions responsible for the spectrum of (6*R*, 7*S*, 10*R*, 11*R*)-**1** are much more complicated, although the Boltzmann-averaged spectrum mainly reflects the spectrum by the most stable conformer. The electrons excited include the π electrons of the exocyclic double bond at C-8–C-15, the π electrons of the double bond at C-2–C-3, the lone-pair electrons of the oxygen in the methoxy group, and the lone-pair electrons of the oxygen in the carbonyl group (it should be noted that, in (6*R*, 7*S*, 10*R*, 11*R*)-**1**, the exocyclic double bond is spatially in close contact with the double bond at C-2–C-3). Therefore, the characteristics of the calculated ECD spectra reflects the configurational difference at C-11 between (6*R*, 7*S*, 10*R*, 11*S*)- and (6*R*, 7*S*, 10*R*, 11*R*)-**1**. Taken together, the absolute configuration of **1** was assigned as shown in Fig. 1.

The effects of compounds **1–3** on osteoblastic differentiation and cytotoxicity in C2C12(R206H) cells were measured by previously described methods,[8–12,17] and their IC_{50} values are summarized in Table 2. Compound **1** inhibited BMP-induced ALP activity, a typical marker of osteoblastic cells, with an IC_{50} value of 51 μM. Since the ALP inhibitory activity of **2** (IC_{50} = 4.6 μM) showed potency that was approximately four greater than that of **3** (IC_{50} = 20 μM), the direction and methylation of their lactone moieties are important for activity. The biological activities of **2** and **3**, originally isolated from the marine sponge *Lamellodysidea* sp. in our previous study,[13] have not been reported. Therefore, this is the first report that **2** and **3** showed inhibitory effects on BMP-induced osteoblastic differentiation. None of the compounds **1–3** showed cytotoxicity against C2C12(R206H) cells up to 38–76 μM in the MTT assay[17] (Table 2).

In conclusion, a new sesquiterpene lactone, bicyclolamellolactone A (**1**), was obtained along with lamellolactones A (**2**) and B (**3**) from the EtOH extract of the marine sponge *L.* cf. *herbacea* collected in Indonesia. Compound **1** possesses a rare bicyclo[4.3.1]decane-containing butenolide skeleton. Although five congeners have been reported from marine sponges and nudibranches,[18–21] marked biological activities of the natural products in this class have been unknown. In this study, **1** was found to inhibit BMP-induced ALP activity without cytotoxicity. Further investigations will provide more details on the mode of action of **1**.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmcl.2021.127783.

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14 The marine sponge was collected by scuba diving in the coral reef at Manado, North Sulawesi, Indonesia, in December 2013 and identified as *Lamellodysidea* sp. (cf. *L. herbacea*). The shape, appearances, and spicles and filaments detected under

microscope were very similar to those of the authentic specimen.[13] A voucher specimen was deposited at the Faculty of Mathematic and Natural Sciences, Sam Ratulangi University as 13-12-10=1-2.The marine sponge (619.7 g, wet weight) was cut into small pieces and soaked in EtOH (1.5 L) on the boat immediately after its collection. After filtration, the EtOH solution was evaporated in vacuo to give the water residue (40 mL). The crude mixture was subjected to an ODS flash column (i.d. 28 mm × 100 mm) and divided into five fractions (Frs. 1–5) with the stepwise elution of 0%. 40%, 60%, and 80% CH_3CN in H_2O and 100% CH_3CN (25 mL each). Compounds **1** (0.7 mg), **2** (1.4 mg), and **3** (0.6 mg) were isolated from Fr. 4 (80% CH_3CN eluate; 19.2 mg) by preparative HPLC [column, Pegasil ODS SP100 (Senshu Co., Ltd., Tokyo, Japan), i.d. 10 mm × 250 mm; solvent, 60% CH_3CN in H_2O; flow rate, 3.0 mL/min; detection, UV 210 nm].

15 Bicyclolamellolactone A (**1**): white solids; $[\alpha]^{24}_D$ –214.2 (c 0.01, CH_3OH); IR (KBr) ν_{max} 1630, 1400, 1063, 670 cm^{-1}; UV (CH_3OH) λ_{max} (log ε) 216 (3.7) nm (shoulder); ECD (7.6 × 10^{-5} M, CH_3CN) λ_{max} (Δε) 243 (–10.8), 211 (–9.1) nm; ESIMS m/z 263 $[M + H]^+$; HRESIMS m/z 263.1641 $[M + H]^+$ (calcd for $C_{16}H_{22}O_3$, 263.1647); ^1H and ^{13}C NMR (CD_3OD), see Table 1.

16 Conformational analyses of (6*R*, 7*S*, 10*R*, 11*R*)- and (6*R*, 7*S*, 10*R*, 11*S*)-**1** in the gas phase were performed using the MMFF force field. The conformers obtained were further optimized in the gas phase by the density functional theory (DFT) method with the B3LYP functional and the 6-31G(d) basis set. Single-point calculations of solvation Gibbs energies in CH_3OH and in CH_3CN were then performed for the gas-phase optimized geometries by the SM8 continuum model using the same DFT method as above. The energy order was not changed from that in the gas phase both in CH_3OH and in CH_3CN. These calculations were performed using Spartan'14 (Wavefunction, Inc., Irvine, CA, USA). The ECD spectra of (6*R*, 7*S*, 10*R*, 11*R*)- and (6*R*, 7*S*, 10*R*, 11*S*)-**1** in CH_3CN were calculated using Gaussian 16 (Gaussian, Inc., Wallingford, CT, USA) by the time-dependent DFT (TDDFT) method with the CAM-B3LYP functional and the 6-311+G(d,p) basis set; the solvent effect was introduced by the polarizable continuum model (PCM). For (6*R*, 7*S*, 10*R*, 11*R*)-**1**, the predicted three lowest-energy conformers were included in Boltzmann averaging using the relative energies calculated by the SM8 model. These three conformers lie within 4.5 kJ/mol of each other, the fourth conformer being 7.5 kJ/mol higher than the most stable one. For (6*R*, 7*S*, 10*R*, 11*S*)-**1**, no Boltzmann averaging was performed since the second conformer was energetically separated from the most stable one by 9.3 kJ/mol. Ten low-lying excited states were calculated for each conformer, corresponding to the wavelength region down to about 170 nm, and the calculated spectra were displayed using GaussView 5.0.9 (Semichem, Inc., Shawnee Mission, KS, USA) with the peak half-width at half height being 0.333 eV. The Boltzmann-averaged spectrum of (6*R*, 7*S*, 10*R*, 11*R*)-**1** at 298.15 K were produced by using Excel 2016 (Microsoft Co., Redmond, WA, USA).

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