

Article

# Sangiangols A and B, Two New Dolabellanes from an Indonesian Marine Soft Coral, *Anthelia* sp.

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**Abstract:** A new, rare trinor-dolabellane diterpenoid, sangiangol A (**1**), and one new dolabellane diterpenoid, sangiangol B (**2**), together with known cembranes and dolabellanes (**3–8**), were isolated from the ethyl acetate layer of an extract of an Indonesian marine soft coral, *Anthelia* sp. Compounds **1–8** exhibited moderate cytotoxicity against an NBT-T2 cell line (0.5–10 µg/mL). The structures of the new compounds were determined by analyzing their spectra and a molecular modelling study. A possible biosynthetic pathway for sangiangols A (**1**) and B (**2**) is presented. Cytotoxicity requires two epoxide rings or a chlorine atom, as in **4** (stolonidiol) and **5** (clavinflol B).

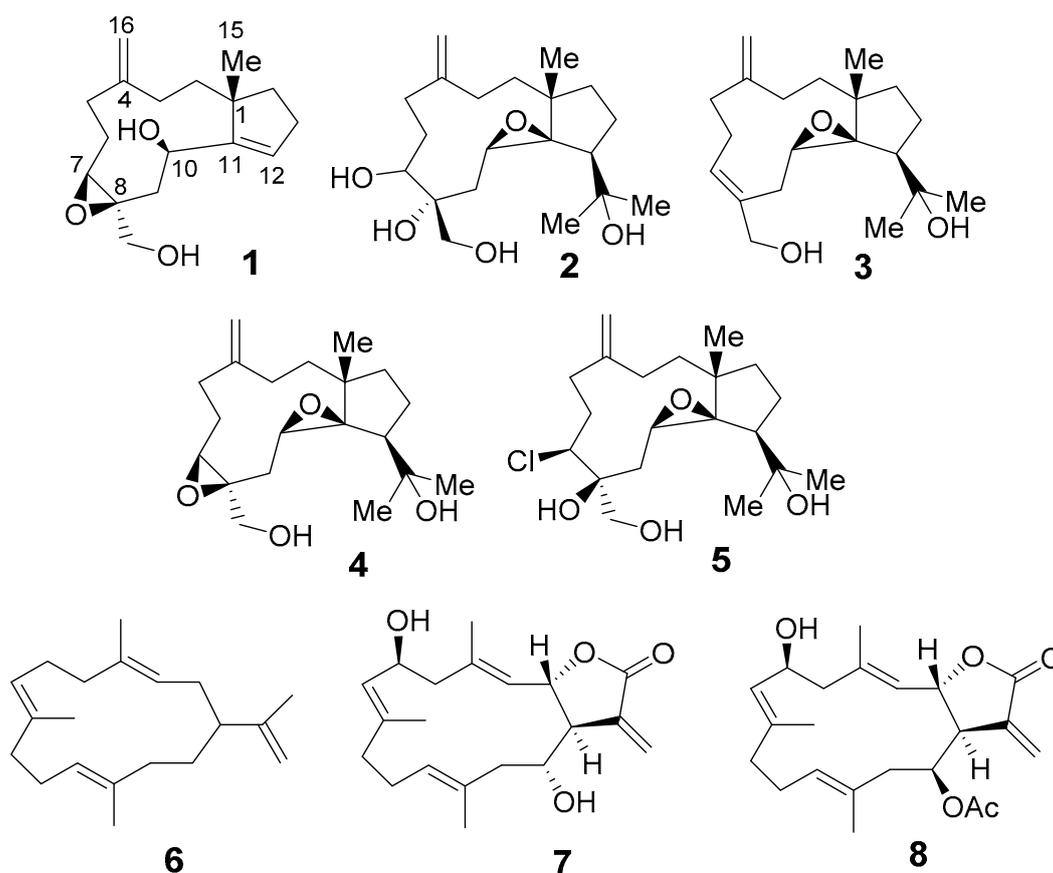
**Keywords:** soft coral; dolabellane; cytotoxicity; NMR; molecular modelling

## 1. Introduction

Soft corals produce numerous, structurally diverse, biologically active terpenoids [1]. More specifically, Indonesian alcyonaceans are rich sources of diterpenoids with a variety of molecular skeletons. From 1970–2017, eight diterpenoid skeletons (briarane, cladiellane, *seco*-cladiellane, cembrane, *nor*-cembrane, dolabellane, flexibilane, and xenicane) were discovered in 11 genera of Indonesian alcyonaceans [2]. Among them, cembrane and briarane skeletons comprise a majority of the known diterpenoids in soft corals globally [2,3]. To date, soft corals of the genus *Anthelia*, family Xenidae, have been shown to contain one type of sesquiterpenoid [4], three types of diterpenoids (xenicane [5], dolabellane [6], a C<sub>24</sub>-acetoacetylated diterpenoid [7,8]), and one type of steroid [9] with cytotoxic activity against various cell lines [4–9]. Moreover, the dolabellane stolonidiol (**4**), was identified as a promising candidate against Alzheimer's disease after its mode of action in HEK293 cells was determined [10]. In our continuing study of metabolites of Indonesian *Anthelia* [4,6], we isolated known diterpenoids **3–8** and new dolabellanes, named sangiangols A (**1**) and B (**2**), the structures of which are the subject of this article.

## 2. Results and Discussion

A sample of the soft coral *Anthelia* sp., collected at Banten (BTN) in northwestern Java, was thoroughly extracted with acetone. After concentration, the residue was partitioned between EtOAc and H<sub>2</sub>O. The EtOAc extract showed significant cytotoxicity against NBT-T2 cells at 1 µg/mL. Thus, it was chromatographed on silica gel, followed by normal or reversed phase HPLC to afford two new molecules, **1** and **2**, along with known compounds **3–8** (Figure 1).



**Figure 1.** Chemical structures of dolabellane-type molecules (1–5) and cembrane-type molecules (6–8).

Sangiagnol A (**1**) was obtained as an optically active oil,  $[\alpha]_D^{27} + 20$ . Its molecular formula is  $C_{17}H_{26}O_3$  by HRESIMS and NMR (Table 1), indicating five degrees of unsaturation. Two compounds were identified as olefins ( $\delta_C$  153.0 (C); 127.0 (CH) ( $\delta_H$  5.88 brt,  $J = 2.5$ ); 150.1 (C); 111.4 (CH<sub>2</sub>) ( $\delta_H$  4.70 s, 4.76 s)) and three others were assigned to a trisubstituted epoxide ( $\delta_C$  61.3 (CH) ( $\delta_H$  3.06 t,  $J = 6.5$ );  $\delta_C$  63.7 (C)) and a bicyclic structure. IR absorption at  $3310\text{ cm}^{-1}$  and at  $1714$  and  $1040\text{ cm}^{-1}$  suggested the presence of hydroxy and exomethylene groups, respectively.

Four spin systems **i–iv** (**1a**; Figure 2) were disclosed by inspecting  $^1\text{H}-^1\text{H}$  COSY cross peaks: (**i**) a trisubstituted double bond next to two methylenes ( $\delta_H$  5.88, 2.31, 2.10, 1.84, 1.63; H-12 to H-14), (**ii**) an oxymethine connected to a methylene ( $\delta_H$  2.20, 4.40; H-9 to H-10), (**iii**) the epoxide methine next to two methylenes ( $\delta_H$  2.42, 2.22, 1.73, 3.06; H-5 to H-7), and (**iv**) two methylenes ( $\delta_H$  1.63, 1.50, 2.10, 1.73; H-2 to H-3). A small coupling ( $^4J_{\text{H-H}}$  1.3 Hz) between H-10 and H-12 with a COSY cross peak supported the presence of an allylic alcohol in Figure 2 (**1a**). HMBC correlations for H-10/C-8, 9, 11, 12 and H-12/C-1, 10, 11, 13, 14 confirmed the connection of spin systems **i** and **ii**. The trisubstituted epoxide was placed at C-7 and C-8, connecting spin systems **ii**, **iii**, and a primary alcohol ( $\delta_H$  3.38, 4.07) by observing HMBC correlations for H-7/C-6, 17; H-10/C-8; H-9/C-7, 8, 17; H-17a,b/C-7, 8, 9. Spin systems **iii** and **iv** were connected through an exomethylene ( $\delta_H$  4.70 s, 4.76 s;  $\delta_C$  153.0, 111.4) placed at C-4, as HMBC correlations H-16a,b/C-3, 4, 5 were observed. Finally, correlations from H<sub>3</sub>-15 to C-1, 2, 11, 14 supported the connection of spin systems **i** and **iv**, confirming the planar structure of **1** as a trinor-dolabellane diterpenoid.

Table 1.  $^1\text{H}$  NMR data for compounds 1 and 2 in  $\text{CDCl}_3$ .

Position	Sangiagnol A (1)				Sangiagnol B (2)			
	$\delta_{\text{C}}$ *	mult.	$\delta_{\text{H}}$ **	$J$ in Hz	$\delta_{\text{C}}$ *	mult.	$\delta_{\text{H}}$ **	$J$ in Hz
1	50.2	C			44.7	C		
2a	38.4	$\text{CH}_2$	1.63	m ***	42.8	$\text{CH}_2$	1.97	m
2b			1.50	ddd (14.4, 11.6, 7.2)			1.25	m ***
3a	29.6	$\text{CH}_2$	2.10	m ***	25.0	$\text{CH}_2$	2.09	dt (15.4, 10.0)
3b			1.73	m ***			1.64	dd (13.3, 10.0)
4	150.1	C			149.3	C		
5a	30.8	$\text{CH}_2$	2.42	dt (14.6, 5.4)	34.3	$\text{CH}_2$	2.45	td (13.6, 4.6)
5b			2.22	dd (14.6, 7.7)			2.29	brdd (13.6, 4.6)
6a	24.4	$\text{CH}_2$	1.73	m ***	27.4	$\text{CH}_2$	1.79	m
6b			1.73	m ***			1.50	m
7	61.3	CH	3.06	t (6.5)	72.9	CH	3.56	d (11.4)
8	63.7	C			75.3	C		
9a	36.0	$\text{CH}_2$	2.20	dd (15.7, 3.0)	33.6	$\text{CH}_2$	1.95	dd (4.5, 2.7)
9b			2.00	dd (15.7, 6.3)			1.92	dd (5.5, 1.6)
10	65.1	CH	4.40	dd (6.3, 1.3)	54.5	CH	3.02	dd (5.4, 2.7)
11	153.0	C			76.7	C		
12	127.0	CH	5.88	brt (2.5)	50.2	CH	2.18	d (10.8, 2.0)
13a	29.7	$\text{CH}_2$	2.31	m ***	27.8	$\text{CH}_2$	1.89	m
13b			2.10	m ***			1.60	m
14a	36.7	$\text{CH}_2$	1.84	ddd (12.7, 9.0, 7.1)	39.0	$\text{CH}_2$	1.79	m
14b			1.63	m ***			1.74	m
15	27.4	$\text{CH}_3$	1.09	s	24.0	$\text{CH}_3$	0.84	s
16a	111.4	$\text{CH}_2$	4.76	s	112.7	$\text{CH}_2$	4.96	s
16b			4.70	s			4.79	s
17a	67.2	$\text{CH}_2$	4.07	d (12.2)	67.2	$\text{CH}_2$	3.89	d (11.4)
17b			3.38	d (12.2)			3.52	d (11.4)
18					75.2	C		
19					29.6	$\text{CH}_3$	1.21	s
20					26.0	$\text{CH}_3$	1.26	s

\* Assigned by DEPT and 2D NMR (HSQC and HMBC) experiments. \*\* Assigned by 2D NMR (COSY, HSQC, and HMBC) experiments. \*\*\* Overlapping signals.

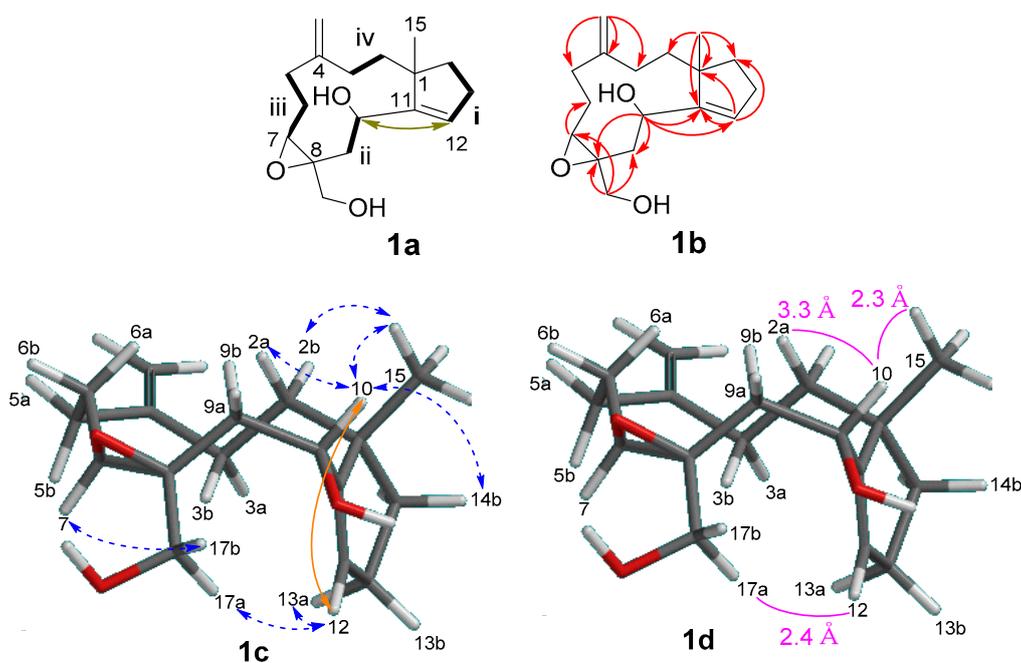
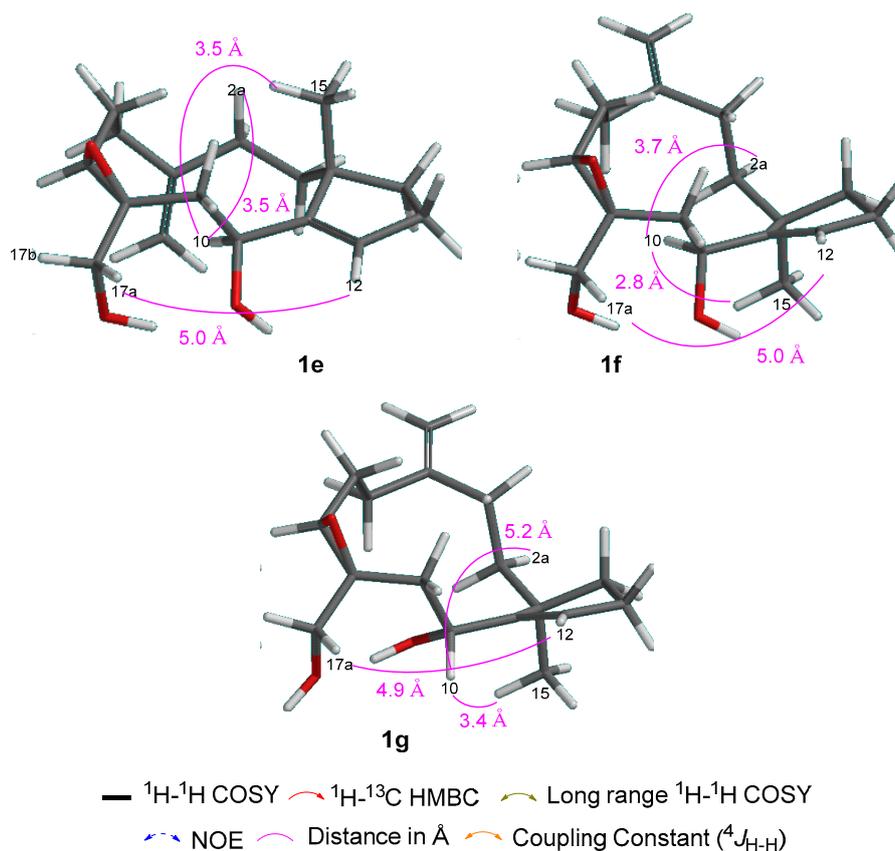


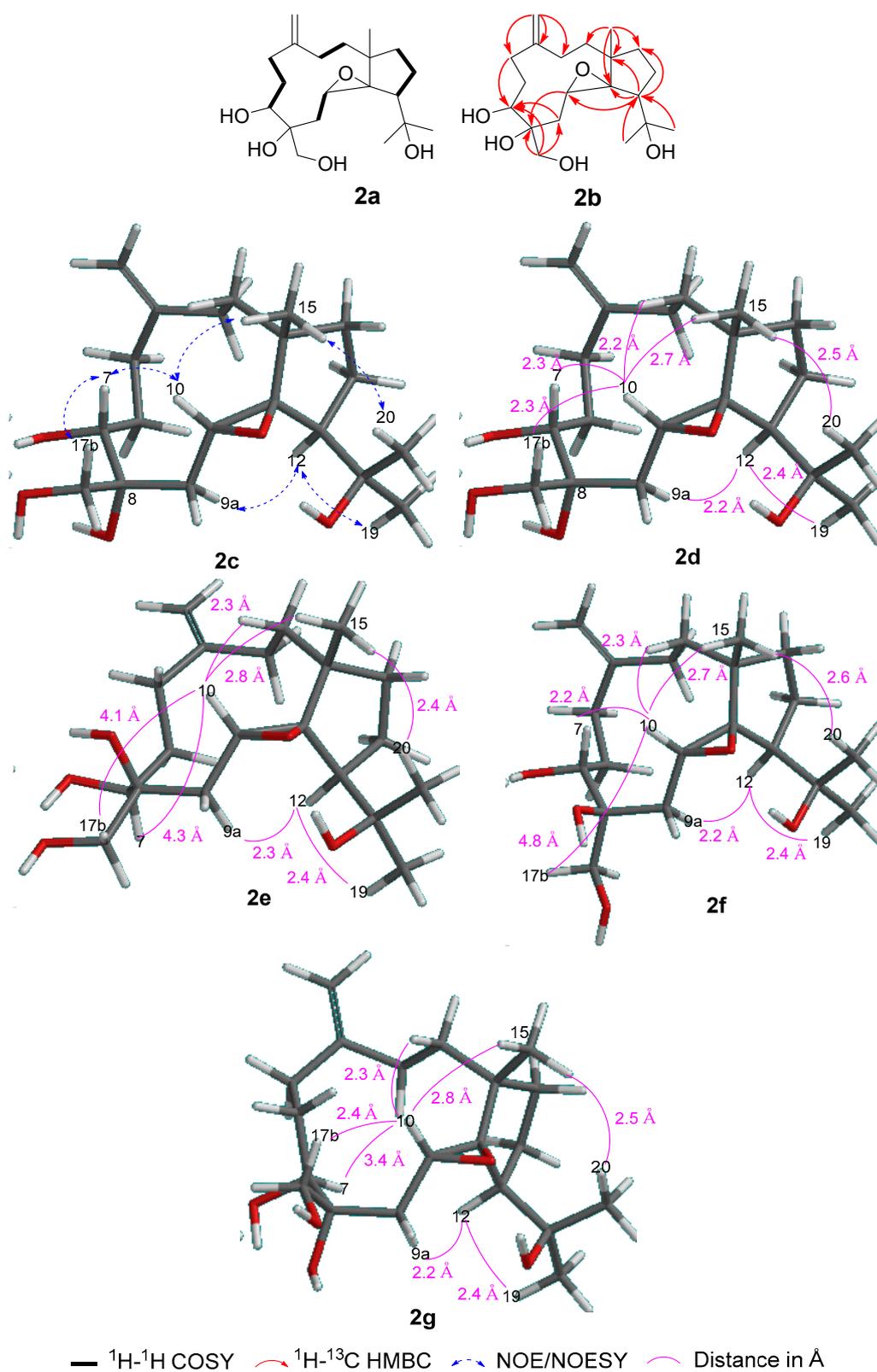
Figure 2. Cont.



**Figure 2.** Key: COSY (**1a**), HMBC (**1b**), NOE (**1c**), correlations and a long-range coupling constant ( $^4J_{H-H}$ ), as well as the distance between atoms (**1d**), with a computer-generated model of **1** (energy minimized:  $1S^*$ ,  $7S^*$ ,  $8S^*$ ,  $10R^*$  for (**1c**);  $1S^*$ ,  $7S^*$ ,  $8S^*$ ,  $10S^*$  for (**1e**);  $1R^*$ ,  $7S^*$ ,  $8S^*$ ,  $10S^*$  for (**1f**);  $1R^*$ ,  $7S^*$ ,  $8S^*$ ,  $10R^*$  for (**1g**), obtained from calculations with molecular mechanics MMFF).

The relative stereochemistry of **1** was tentatively assigned as follows, based on positive NOEs (**1c**; Figure 2). By observing a strong NOE between H-7 and H-17b (**1c**; Figure 2), chirality at the epoxide was revealed to be  $7S^*$ ,  $8S^*$ , as in similar structural units [6,11]. Therefore, four possible stereoisomers—**1c** ( $1S^*$ ,  $7S^*$ ,  $8S^*$ ,  $10R^*$ ), **1e** ( $1S^*$ ,  $7S^*$ ,  $8S^*$ ,  $10S^*$ ), **1f** ( $1R^*$ ,  $7S^*$ ,  $8S^*$ ,  $10S^*$ ), and **1g** ( $1R^*$ ,  $7S^*$ ,  $8S^*$ ,  $10R^*$ )—were further considered. Figure 2 shows the energy-minimized conformations of **1c** and **1e–1g** after molecular mechanics (MMFF) calculation. Of four possibilities, **1c** was the most likely structure because a positive NOE was observed between H-17a and H-12 within a reasonable distance (Figure 2), while other candidates were expected to have longer distances ( $\sim 5$  Å). The angular methyl H-15 at  $\delta_H$  1.09 partially supported this conformation, showing NOEs for H-15/H-2b, 10 (Figure 2). The more downfield-shifted signal for the C-15 ( $\delta$  1.09) of **1** compared to that ( $\delta$  0.85) of the stolonidiol of **4** [6,11] may be due to the absence of the epoxide ring and the presence of an olefin at the ring junction.

Using HRESIMS and NMR, it was determined that sangiangol B (**2**),  $[\alpha]_D^{27} + 15$ , has the molecular formula  $C_{20}H_{34}O_5$ , with an additional oxygen and two hydrogen atoms compared to stolonidiol (**4**). Furthermore, four degrees of unsaturation in **2** indicated a similarity to claviflrol B (**5**) [6,12], a chlorohydrin analog. A detailed 2D NMR (Figure 3) analysis of **2** revealed that the major differences between **2**, **4**, and **5** were the chemical shifts at C-7 ( $\delta_H$  3.56, d (11.4);  $\delta_C$  72.9 for **2** and  $\delta_H$  3.96, d (11.5);  $\delta_C$  67.2 for **5**) [6,12] and at C-8 ( $\delta_C$  75.3 for **2** and 63.2 for **4**) [6,11] (Figure 4). With the NMR chemical shifts and high-resolution mass spectrometry (HRMS) data, compound **2** contained 1,2-diol at C-7 and C-8 for an epoxide in stolonidiol (**4**) or for a chlorohydrin in claviflrol B (**5**) [6,12]. Key HMBC correlations for H-7/C-8, 17; H-17/C-7, 8; H-9/C-7; H-10/C-8 further confirmed the position of the diol, establishing the planar structure.



**Figure 3.** Key: COSY (**2a**), HMBC (**2b**), NOE (**2c**), correlations and distance between atoms (**2d**) with a computer-generated model of **2** (energy-minimized 1S, 7R, 8R, 10R, 11R, 12S for (**2c**); 1S, 7S, 8S, 10R, 11R, 12S for (**2e**); 1S, 7R, 8S, 10R, 11R, 12S for (**2f**); 1S, 7S, 8R, 10R, 11R, 12S for (**2g**), obtained from calculations with MMFF).

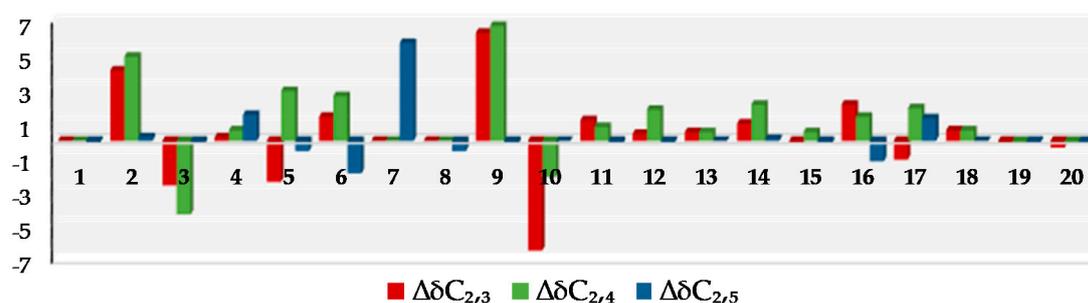


Figure 4. Comparative analysis of  $^{13}\text{C}$  chemical shifts between 2 and 3, 4, 5.

Of the six stereocenters of sangiangol B (2), three can be confirmed as 1*S*, 11*R*, and 12*S* by comparing the  $^{13}\text{C}$ -NMR data for the cyclopentane moiety (C-1, C-11~14) with those of 3, 4, and 5 (Figure 4) [6,11,12] and by observing the rotation value  $[\alpha]_{\text{D}}^{-37.9}$  of co-isolated stolonidiol (4) and the value  $[\alpha]_{\text{D}}^{-31}$  of that reported in 4, the absolute stereochemistry of which was established by X-ray crystallography [11]. Chirality at C-10 was shown to have the same *R* configuration as stolonidiol (4), based on a positive NOE between H-10 and H-15. Among the four possible structures—2*d*: 7*R*,8*R*, 2*e*: 7*S*,8*S*, 2*f*: 7*R*,8*S*, and 2*g*: 7*S*,8*R*—the distances for H-10/H-7 and H-10/H-17b with energy-minimized conformations were compared, as in Figure 3. Both 2*e* and 2*f* were eliminated due to the relatively long distances of H-10/H-17b. However, as two candidates, 2*d* and 2*g*, accorded with the spectral data, the configuration at C-8 was then revealed, while only C-7 remained to be solved.

Furthermore, the biosynthesis of stolonidiol-related molecules can be proposed, as in Figure 5. Geranylgeranyl pyrophosphate (GGPP) is a well-known starting material for diterpenoids [13]. Sangiangol A (1) could be derived from stolonidiol (4) through a series of degradation and epoxide ring-opening reactions, while sangiangol B (2) could be derived from sangiangol C (3) through an epoxidation reaction. Moreover, sangiangol C (3) could be the precursor of stolonidiol (4). Unfortunately, attempts to prepare  $\alpha$ -methoxy- $\alpha$ -trifluoromethylphenylacetic acid (MTPA) esters for the determination of the absolute configurations of both molecules failed because of their instability and the small quantities of these compounds available.

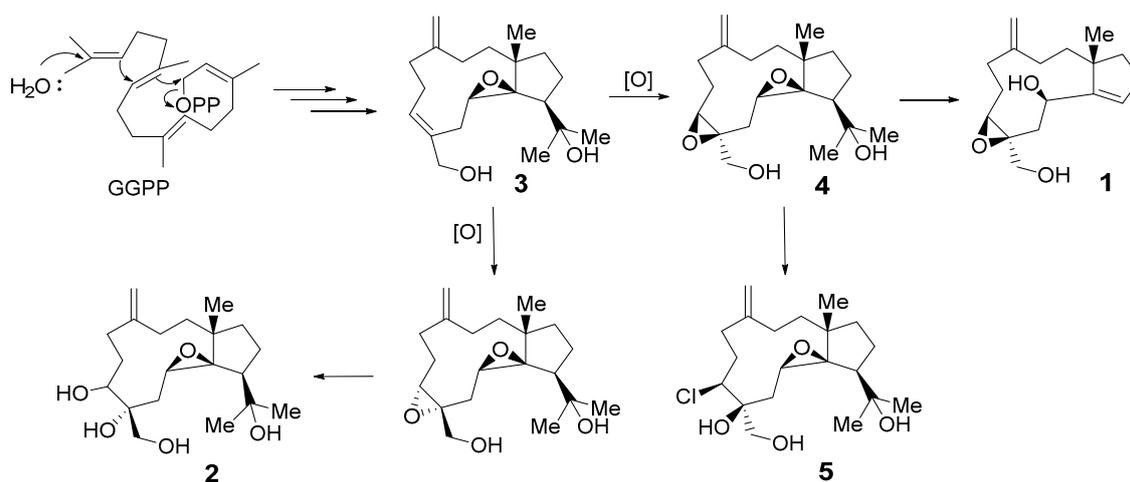


Figure 5. A possible biosynthetic pathway for sangiangols A (1) and B (2).

All isolated compounds (1–8) were evaluated for cytotoxicity against NBT-T2 rat bladder epithelial cells (Table 2). New entities 1 and 2 showed weak toxicity at 5 and 10  $\mu\text{g}/\text{mL}$ , respectively, while known molecules 3–8 showed moderate and weak toxicity at 10, 1, 0.5, 10, 1, and 10  $\mu\text{g}/\text{mL}$ , respectively. From the structure–activity relationship of stolonidiol derivatives, two epoxide rings or a chlorine atom are required for their cytotoxicity, as in 4 (stolonidiol) and 5 (clavinflol B).

**Table 2.** Cytotoxicity of compounds 1–8 against NBT-T2 rat bladder epithelial cells.

Compound	Concentration ( $\mu\text{g/mL}$ )
1	5
2	10
3	10
4	1
5	0.5
6	10
7	1
8	10

### 3. Materials and Methods

#### 3.1. General Methods

The optical rotations were obtained with a JASCO P-1010 digital polarimeter. The  $^1\text{H}$  and  $^{13}\text{C}$ -NMR spectra were recorded on a JEOL  $\alpha$  500 FT NMR spectrometer. The chemical shifts were expressed in  $\delta$  (ppm) and the coupling constants ( $J$ ) in Hz. The electrospray ionization mass spectrometry (ESIMS) data were obtained on a PE QSTAR mass spectrometer and the infrared (IR) spectra were recorded on a DR 8020 Shimadzu spectrophotometer. The HPLC was performed on a Hitachi L-6000 pump equipped with a Shodex RI-101 monitor and a Hitachi L-4000 UV detector, using a Cosmosil 5C<sub>18</sub>AR-II (5  $\mu\text{m}$ ) or a Mightysil RP-18 (5  $\mu\text{m}$ ) column. Merck silica gel 60 (0.063–0.20 mm) was used for column chromatography. The analytical thin layer chromatography (TLC) was performed on commercial silica gel 60 F<sub>254</sub> visualized with vanillin–EtOH–1% H<sub>2</sub>SO<sub>4</sub>. All solvents used were reagent grade.

#### 3.2. Animal Material

A marine soft coral (AA-C31) was collected from Krakatau Island, Banten, Indonesia at 10–15 m depth by hand, while scuba diving. It was then stored in EtOH. The specimen was identified as *Anthelia* sp. by one of us (J.T.).

#### 3.3. Extraction and Isolation

The fresh soft coral specimen (wet weight, 121 g) stored in EtOH was extracted four times using Me<sub>2</sub>CO (4  $\times$  150 mL). The four solutions were pooled and concentrated under vacuum, and the resulting residue was partitioned between EtOAc and H<sub>2</sub>O to obtain a cytotoxic lipophilic extract (1.57 g, NBT-T2 1  $\mu\text{g/mL}$ ). The whole extract was separated on a Si gel 60 column by eluting stepwise with hexane–EtOAc–MeOH to afford 19 fractions. The second fraction (9.7 mg) was further separated using normal phase silica HPLC (hexane 100%) to give cembrane A (6) [13] (2.3 mg). The eighth fraction was purified on reversed phase HPLC to give sangiangol C (3) [14] (1.0 mg). The ninth fraction was repeatedly separated by HPLC (first, reversed-phase C<sub>18</sub> (RP<sub>18</sub>), MeOH–H<sub>2</sub>O, 5:2; second, Si 60, CH<sub>2</sub>Cl<sub>2</sub>–EtOAc, 7:3) to afford kericembrenolide E (7) [15] (2.7 mg), stolonidiol (4) [6,11] (3.5 mg), and clavinflol B (5) [6,12] (1.3 mg). The tenth fraction was subfractionated on RP<sub>18</sub> HPLC to give cembrenolide (8) [16] (1.7 mg), sangiangol A (1) (1.3 mg), and stolonidiol (4) (103.7 mg). Finally, the most polar fraction was repeatedly separated on reversed-phase HPLC (first, RP<sub>18</sub>: MeOH–H<sub>2</sub>O, 2:1 second, RP<sub>18</sub>, MeOH–H<sub>2</sub>O, 4:5) to give sangiangol B (2) (1.4 mg).

##### 3.3.1. Sangiangol A (1)

Colorless oil;  $[\alpha]_{\text{D}}^{27} + 20$  ( $c$  0.09, CHCl<sub>3</sub>); IR (KBr)  $\nu_{\text{max}}$  3418, 2965, 1683, 1645, 1456, 1378, 1168, 1064  $\text{cm}^{-1}$ ;  $^1\text{H}$  and  $^{13}\text{C}$ -NMR (see Tables 1 and 2); HRESIMS  $m/z$  301.1658  $[\text{M} + \text{Na}]^+$  (calculated (calcd) for C<sub>17</sub>H<sub>26</sub>O<sub>3</sub>Na 301.1779).

### 3.3.2. Sangiangol B (2)

Colorless oil;  $[\alpha]_D^{27} + 15$  (c 0.14, CHCl<sub>3</sub>); IR (KBr)  $\nu_{\max}$  3418, 2965, 1645, 1456, 1378, 1168, 1064 cm<sup>-1</sup>; <sup>1</sup>H and <sup>13</sup>C-NMR (see Tables 1 and 2); HRESIMS  $m/z$  377.2230 [M + Na]<sup>+</sup> (calcd for C<sub>20</sub>H<sub>34</sub>O<sub>5</sub>Na 377.2304).

### 3.4. Cytotoxicity Assay

NBT-T2 rat bladder epithelial cells (BRC-1370) purchased from RIKEN (Tsukuba, Ibaraki, Japan) were cultured under a standard protocol using Dulbecco's modified Eagle's medium (DMEM). The cells were seeded in 1 mL of modified Eagle's media supplemented with 10% heat-inactivated fetal bovine serum, streptomycin, amphotericin B, and glutamic acid. The cells were exposed to graded concentrations of the new and known compounds, as well as their fractions at 37 °C, for 72 h and observed under a microscope to observe the effects at 48 and 72 h.

**Author Contributions:** Conceptualization, N.H., A.M. and J.T.; methodology, N.H., A.M. and J.T.; validation, N.H., A.M. and J.T.; investigation, N.H., A.M. and J.T.; data curation, N.H., A.M. and J.T.; writing—original draft preparation, N.H., A.M. and J.T.; writing—review and editing, N.H., A.M. and J.T. All authors have read and agreed to the published version of the manuscript.

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**Conflicts of Interest:** The authors declare no conflict of interest.

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