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Cytotoxic Sesterterpenoids from Bornean Sponge *Spongia* sp.

Chin-Soon Phan[1], Takashi Kamada[2], Toshiyuki Hamada[3] and Charles S. Vairappan[1*]

[1]*Laboratory of Natural Products Chemistry, Institute for Tropical Biology and Conservation, Universiti Malaysia Sabah, 88400 Kota Kinabalu, Sabah, Malaysia*

2 Laboratory of Natural Products Chemistry, Department of Materials and Life Science, Faculty of Science and Technology, Shizuoka Institute of Science and Technology, 2200-2 Toyosawa, Fukuroi, Shizuoka 437-8555, Japan

[3] *Graduate School of Science and Engineering, Kagoshima University, 1-21-35 Korimoto, Kagoshima 890-0065, Japan*

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Abstract: Four scalarane sesterterpenoids, scalarolide acetate (**1**), scalarolide (**2**), 12-*O*-deacetyl-12-*epi*-19-*O*-methylscalarin (**3**) and methyl 18-hydroxy-19-norscalar-16-en-20-carboxylate (**4**) were isolated from the Bornean sponge *Spongia* sp. The distinction between 12α-OAc and 12β-OAc, and 19-olide and 20-olide in sesterterpenes were revealed as well as previously not assigned relative configuration at 18-OH of **4** is reported herein for the first time. In addition, compounds **1**-**3** showed strong cytotoxic activities against adult T-cell leukemia (ATL), S1T cells. This is the first record of scalarane sesterterpenes from the Bornean sponge.

Keywords: Borneo; sponge; sesterterpenes; adult T-cell leukemia; S1T.

1. Sample Source

One population of Bornean sponge *Spongia* sp. was collected at 06º12’073’’N, 115º36’062’’E, Mengalum Island, Sabah (Malaysia); on the 23th September 2017. The voucher specimen (BORMI0024) is kept at the BORNEENSIS (Institute for Tropical Biology and Conservation) in the Universiti Malaysia Sabah.

2. Previous Studies

Scalarane skeleton is a tetracyclic sesterterpenes of four fused six-membered rings, however, there are exceptions that these sesterterpenoids possessed ring E and formed pentacyclic system [1-4].

* Corresponding author: E-Mail: csv@ums.edu.my ; Phone +60-88-320-000 ext 2397, Fax +60-88-320-291.

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It has been well characterized that both tetra- and pentacyclic system of this skeleton consisted A/B/C/D ring with the conserved *trans*-fused junctions [5]. The structural variety of this compound's family was derived from different oxidation at C-19 and C-20 [6]. In addition, scalarane sesterterpenes are often investigated for their biological activities [1-3,7-19].

3. Present Study

Fresh sponge specimen (800 g wet wt) was macerated in MeOH at room temperature (23 ºC). After 5 days of soaking, the resulting MeOH was filtered, concentrated and partitioned between two immiscible solvents EtOAc and H_2O. Further partition between H_2O and BuOH was performed. A total of 1.5 g of crude EtOAc extract was separated via normal phase silica gel column chromatography via gradient solvent eluation of hexane-EtOAc in an increasing polarity into ten fractions. Scalarolide acetate (**1**, 6.2 mg) [1] was obtained through preparative TLC of fraction 7 (63.0 mg) with toluene-EtOAc (8:2), while the residue was further purified to acquire 12-*O*-deacetyl-12-*epi*-19-*O*-methylscalarin (**3**, 11.0 mg) [3] *via* preparative TLC with $CHCl_3$-EtOAc (9:1). Fraction 4 (64.0 mg) was subjected to repeated preparative TLC with toluene-EtOAc (8:2), $CHCl_3$-EtOAc (85:15) and toluene-EtOAc (7:3) to obtained methyl 18-hydroxy-19-norscalar-16-en-20-carboxylate (**4**, 1.1 mg) [1]. While, scalarolide (**2**, 1.5 mg) [2] was afforded from faction 6 (47.0 mg) *via* repeated preparative TLC using toluene-EtOAc (7:3) and $CHCl_3$-EtOAc (9:1) as solvent system. Compounds **1** and **4** were first isolated from sponge *Collospongia auris* [1], while **2** and **3** were first reported from sponge *Spongia idia* and *Spongia*, respectively [2,3].

Compound **1**; colorless oil; molecular formula of $C_{27}H_{40}O_4$ from FABMS *m/z* (rel. int.): 429 ($[M + H]^+$, 10.1 %), 369 (100.0 %), 370 (27.3 %).

Compound **2**; colorless amorphous solid; molecular formula of $C_{25}H_{38}O_3$ from FABMS *m/z* (rel. int.): 387 ($[M + H]^+$, 72.0 %), 369 (34.9 %), 307 (27.7 %), 289 (15.8 %).

Compound **3**; white amorphous solid; molecular formula of $C_{26}H_{40}O_4$ from FABMS *m/z* (rel. int.): 417 ($[M + H]^+$, 51.6 %), 369 (26.6 %), 307 (27.0 %), 289 (14.4 %).

Compound **4**; colorless needles; molecular formula of $C_{25}H_{40}O_4$ from FABMS *m/z* (rel. int.): 405 ($[M + H]^+$, 32.2 %), 387 ($[M + H - H_2O]^+$, 25.5 %), 355 (23.9 %), 307 (26.9 %), 289 (15.6 %).

Cytotoxic assay: The RPMI-1640 medium supplemented with 10% fetal bovine serum, 100 U/mL penicillin, 100 µg/mL streptomycin and 2 mM L-glutamate was used to culture ATL cell line, S1T. Cytotoxic assay was conducted by loading 1 x 10^4 cells/well in 96-well plate along with the compound which later incubated at 37°C with 5% CO_2 for 72 h. Well with the absence of compound served as negative control, and etoposide as positive control. Assessment of cell viability was carried out using tetrazolium (WST-8) assay kit (Dojindo, Japan) measured at 450 nm with a microplate reader [20,21].

3.1. Structure Significance and Their Cytotoxicity

In the current study, a total of four scalarane sesterterpenoids, scalarolide acetate (**1**), scalarolide (**2**), 12-*O*-deacetyl-12-*epi*-19-*O*-methylscalarin (**3**) and methyl 18-hydroxy-19-norscalar-16-en-20-carboxylate (**4**) have isolated and identified (Figure 1). Thorough study showed sesterterpenes isolated from nature possessed α or β relative configurations for acetate or hydroxyl group at C-12, moreover the α,β-unsaturated γ-lactone motif can be at 19-olide or 20-olide [1-12,16]. Therefore, compound **1** served as model compound for comparison of latter configurations in the scalarane sesterterpenes.

The vicinal proton-proton coupling constants were significantly differed between 12β-OAc in **1** and 12α-OAc sesterterpenes. The acetoxy-bearing methine H-12α (δ_H 4.92, dd, *J* = 10.9, 4.8 Hz) in **1** was not consistent to those of acetoxy-bearing methine H-12β in 12-*epi*-acetylscalarolide (δ_H 5.54, dd, *J* = 2.9, 2.7 Hz), 16-acetylfuroscalarol (δ_H 5.41, dd, *J* = 2.8, 2.8 Hz), hyatelone A (δ_H 5.31, dd, *J* = 3.5, 2.2 Hz), 20-*O*-acetylhyatolide C (δ_H 5.49, dd, *J* = 2.9, 2.3 Hz) and 12α-acetoxy-13β,18β-cyclobutane-20,24-dimethyl-24-oxoscalar-16-en-25α-ol (δ_H 5.66, t, *J* = 3.0 Hz) [4,10,11]. Other 12β-OAc sesterterpenes such as 12β-acetoxy,16β-methoxy,20α-hydroxy-17-scalaren-19,20-olide (δ_H 4.88, dd, *J* = 10.8, 3.6 Hz) and 12-*epi*-scalaradial (δ_H 4.80, dd, *J* = 10.0, 4.0 Hz) were found matching to those of **1** [12,22]. This finding suggested that 12β-OAc bearing methine has a smaller $^3J_{HH}$ compared to those of 12α-OAc bearing methine. This deduction was also consistent in 12β-OH and 12α-OH bearing methine of sesterterpenes. The chemical shifts for α,β-unsaturated γ-lactone unit of 20-olide in **1** (δ_C 171.0, 161.3, 134.4 and 70.1; δ_H 4.55 and 4.47) was significantly differed to those of 19-olide in isomer **1** (δ_C 174.1, 167.3, 125.5 and 68.1; δ_H 4.70 and 4.42) [23].

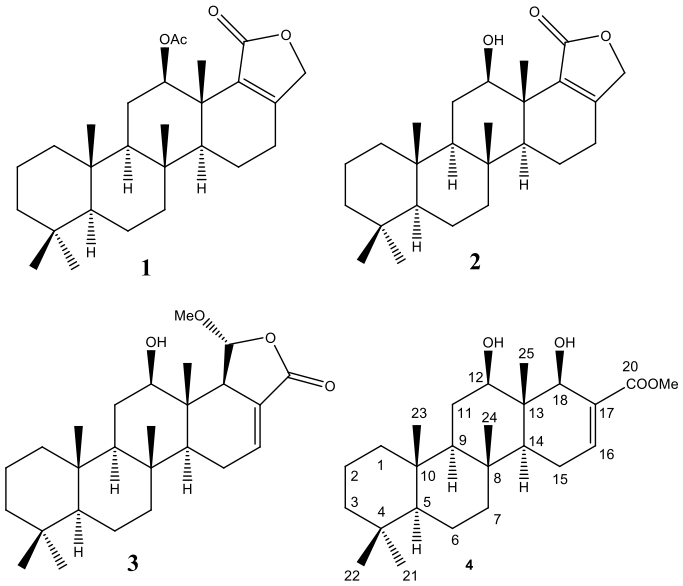

Figure 1. Structures of **1-4**.

The relative configuration of 18-OH of **4** was not assigned when first reported by Bergquist et al. (1990) [1]. In this regard, β relative configuration was assigned on 18-OH based on NOESY cross peaks of H-12/H-18; H-12/H-14; H-14/H18; 12-OH/18-OH; and 18-OH/H_3-25 (Figure 2). The aggressive malignancy on mature activated T-cells due to infection of human T-cell lymphotropic virus type I was characterized as adult T-cell leukemia (ATL) which exclusively found in the areas of South American, Japan, Northern Iran, the Caribbean Basin, Southern India, West-Central Africa and some isolated region in tropics [24]. Compounds **1-3** displayed potent cytotoxicity towards ATL, S1T cell lines with the IC_{50} 5.16, 3.93 and 2.31 ug/mL, respectively. Unfortunately, compound **4** was not evaluated for its biological activities due to its limitation availability. Nevertheless, to the best of our knowledge, this is the first report of sponge-derived secondary metabolites evaluated on ATL cell lines. Previous investigation showed these scalarane sesterterpenes have tested for their antimicrobial [1], and antifeedant activities [2]. Besides that, compound **3** was reported to inhibit the interaction between farnesoid X-activated receptor and coactivator peptide (SRC-1) [3]. In addition, platelet-aggregation inhibitory [15], anti-inflammatory [16], anti-fouling [17], ichthyotoxic [18], and cytotoxic properties [19], were reported from this compound's family. Owing to their intrigued biological activities, these compounds are promising to further investigate for the mechanism of their cytotoxicity towards ATL that involved pro-apoptotic proteins.

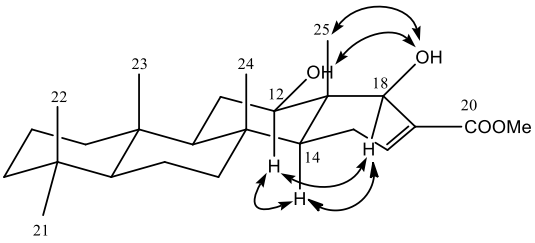

Figure 2. The key NOE correlations of **4**.

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Supporting Information

Supporting Information accompanies this paper on http://www.acgpubs.org/RNP

ORCID
Chin-Soon Phan: 0000-0002-6500-696X
Takashi Kamada: 0000-0002-2886-4623
Toshiyuki Hamada: 0000-0002-7631-7974
Charles S. Vairappan: 0000-0001-7453-1718

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