

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/326394561>

Cytotoxic Sesterterpenoids from Bornean Sponge *Spongia* sp.

Article in *Records of Natural Products* · November 2018

DOI: 10.25135/rnp.69.18.01.209

CITATIONS

4

READS

61

4 authors, including:



Chin-Soon Phan

Hokkaido University

33 PUBLICATIONS 80 CITATIONS

SEE PROFILE



Charles S VAIRAPPAN

Universiti Malaysia Sabah (UMS)

165 PUBLICATIONS 1,946 CITATIONS

SEE PROFILE

Some of the authors of this publication are also working on these related projects:



Soft Coral View project



Laurencia View project

Cytotoxic Sesterterpenoids from Bornean Sponge *Spongia* sp.

Chin-Soon Phan¹, Takashi Kamada², Toshiyuki Hamada³ and
Charles S. Vairappan^{1*}

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

²Laboratory 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

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

(Received January 21, 2018; Revised April 05, 2018; Accepted April 10, 2018)

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 12 α -OAc and 12 β -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. © 2018 ACG Publications. All rights reserved.

1. Sample Source

One population of Bornean sponge *Spongia* sp. was collected at 06°12'073''N, 115°36'062''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.

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 °C). After 5 days of soaking, the resulting MeOH was filtered, concentrated and partitioned between two immiscible solvents EtOAc and H₂O. Further partition between H₂O 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 elution 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 CHCl₃-EtOAc (9:1). Fraction 4 (64.0 mg) was subjected to repeated preparative TLC with toluene-EtOAc (8:2), CHCl₃-EtOAc (85:15) and toluene-EtOAc (7:3) to obtain methyl 18-hydroxy-19-norscalar-16-en-20-carboxylate (**4**, 1.1 mg) [1]. While, scalarolide (**2**, 1.5 mg) [2] was afforded from fraction 6 (47.0 mg) via repeated preparative TLC using toluene-EtOAc (7:3) and CHCl₃-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 C₂₇H₄₀O₄ 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 C₂₅H₃₈O₃ 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 C₂₆H₄₀O₄ 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 C₂₅H₄₀O₄ from FABMS *m/z* (rel. int.): 405 ([M + H]⁺, 32.2 %), 387 ([M + H - H₂O]⁺, 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 10⁴ cells/well in 96-well plate along with the compound which later incubated at 37°C with 5% CO₂ 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 12 β -OAc in **1** and 12 α -OAc sesterterpenes. The acetoxy-bearing methine H-12 α (δ_{H} 4.92, dd, $J = 10.9, 4.8$ Hz) in **1** was not consistent to those of acetoxy-bearing methine H-12 β 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 12 α -acetoxy-13 β ,18 β -cyclobutane-20,24-dimethyl-24-oxoscalar-16-en-25 α -ol (δ_{H} 5.66, t, $J = 3.0$ Hz) [4,10,11]. Other 12 β -OAc sesterterpenes such as 12 β -acetoxy,16 β -methoxy,20 α -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 12 β -OAc bearing methine has a smaller $^3J_{\text{HH}}$ compared to those of 12 α -OAc bearing methine. This deduction was also consistent in 12 β -OH and 12 α -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].

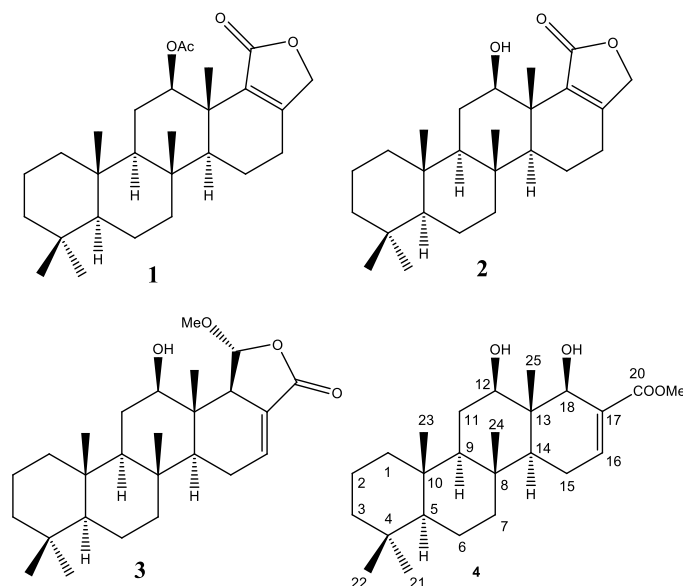


Figure 1. Structures of **1-4**.

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/H-18; 12-OH/18-OH; and 18-OH/H₃-25 (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 IC₅₀ 5.16, 3.93 and 2.31 $\mu\text{g/mL}$, 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.

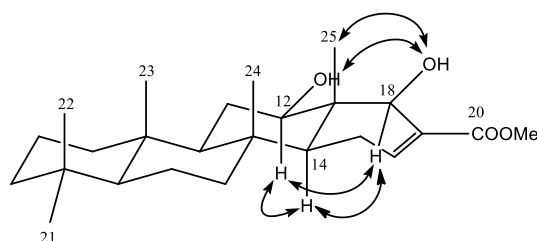


Figure 2. The key NOE correlations of **4**.

Acknowledgments

This work was supported financially by the Sabah Biodiversity Centre [Grant No. GL0070]. The authors would also like to acknowledge Prof. Dr. Naomichi Arima (Kagoshima University) for providing ATL cancer cell line, S1T.

Supporting Information

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

ORCID

Chin-Soon Phan: [0000-0002-6500-696X](https://orcid.org/0000-0002-6500-696X)

Takashi Kamada: [0000-0002-2886-4623](https://orcid.org/0000-0002-2886-4623)

Toshiyuki Hamada: [0000-0002-7631-7974](https://orcid.org/0000-0002-7631-7974)

Charles S. Vairappan: [0000-0001-7453-1718](https://orcid.org/0000-0001-7453-1718)

References

- [1] P.R. Bergquist, R.C. Cambie and M.R. Kernan (1990). Scalarane sesterterpenes from *Collospongia auris*, a new thorectid sponge, *Biochem. Syst. Ecol.* **18**, 349-357.
- [2] R.P. Walker, J.E. Thompson and D.J. Faulkner (1980). Sesterterpenes from *Spongia idia*, *J. Org. Chem.* **45**, 4976-4979.
- [3] S.J. Nam, H. Ko, M.K. Ju, H. Hwang, J. Chin, J. Ham, B. Lee, J. Lee, D.H. Won, H. Choi, J. Ko, K. Shin, T. Oh, S. Kim, J.R. Rho and H. Kang (2007). Scalarane sesterterpenes from a marine sponge of the genus *Spongia* and their FXR antagonistic activity, *J. Nat. Prod.* **70**, 1691-1695.
- [4] C.J. Hernández-Guerrero, E. Zubía, M.J. Ortega and J.L. Carbollo (2006). Sesterterpene metabolites from the sponge *Hyatella intestinalis*, *Tetrahedron.* **62**, 5392-5400.
- [5] H.J. Li, T. Amagata, K. Tenney and P. Crews (2007). Additional scalarane sesterterpenes from the sponge *Phyllospongia papyracea*, *J. Nat. Prod.* **70**, 802-807.
- [6] V. Kulcički, N. Ungur, M. Gavagnin, F. Castelluccio and G. Cimino (2007). Ring B functionalization of scalarane sesterterpenes by radical relay hydrogenation. *Tetrahedron.* **63**, 7617-7623.
- [7] K.P. Lutta, B. Christine, A.A. Teresa and W.W. Cornelius (2008). Antimicrobial marine natural products from the sponge, *Axinella infundibuliformis*, *Rec. Nat. Prod.* **2**, 116-127.
- [8] N. Aktas, Y. Genc, B. Gozcelioglu, B. Konuklugil and U.S. Harput (2013). Radical scavenging effect of different marine sponges from Mediterranean Coasts, *Rec. Nat. Prod.* **7**, 96-104.
- [9] F.C. Özkaya, E. Bedir and E.E. Hameş (2015). A new siderophore from sponge associated *Pseudomonas fluorescens* 4.9.3, *Rec. Nat. Prod.* **9**, 509-517.
- [10] A. Rueda, E. Zubía, M.J. Ortega, J.L. Carbollo and J. Salvá (1997). New cytotoxic metabolites from the sponge *Cacospongia scalaris*, *J. Org. Chem.* **62**, 1481-1485.
- [11] H.J. Li, T. Amagata, K. Tenney and P. Crews (2007). Additional scalarane sesterterpenes from the sponge *Phyllospongia papyracea*, *J. Nat. Prod.* **70**, 802-807.

- [12] S.S. Elhady, A.M. Al-abd, A.M. El-Halawany, A.M. Alahdal, H.A. Hassanean and S.A. Ahmed (2016). Antiproliferative scalarane-based metabolites from the Red Sea sponge *Hyrtios erectus*, *Mar. Drugs*. **14**, 130-143.
- [13] S. Tang, R. Xu, W. Lin and H. Duan (2012). Jaspiferin A and B: two new secondary metabolites from the South China Sea sponge *Jaspis stellifera*, *Rec. Nat. Prod.* **6**, 398-401.
- [14] I.E. Orhan, B. Ozcelik, B. Konuklugil, A. Putz, U.G. Kaban and P. Proksch (2012). Bioactivity screening of the selected Turkish marine sponges and three compounds from *Agelas oroides*, *Rec. Nat. Prod.* **6**, 356-367.
- [15] M. Nakagawa, Y. Hamamoto, M. Ishihama, S. Hamasaki and M. Endo (1987). Pharmacologically active homosesterterpenes from Palauan sponges, *Tetrahedron Lett.* **28**, 431-434.
- [16] A. Fontana, E. Mollo, J. Ortea, M. Gavagnin and G. Cimino (2000). Scalarane and homoscalarane compounds from the nudibranchs *Glossodoris sedna* and *Glossodoris dalli*: Chemical and biological properties, *J. Nat. Prod.* **63**, 527-530.
- [17] Y. Sera, K. Adachi and Y. Shizuri (1999). A new epidioxysterol as an antifouling substance from a Palauan marine sponge, *Lendenfeldia chondrodes*. *J. Nat. Prod.* **62**, 152-154.
- [18] J.C. Braekman, D. Daloz, M. Kaisin and B. Moussiaux (1985). Ichthyotoxic sesterterpenoids from the Neo Guinean sponge *Carteriospongia foliascens*, *Tetrahedron* **41**, 4603-4614.
- [19] J. Song, W. Jeong, N. Wang, H.S. Lee, C.J. Sim, K.B. Oh and J. Shin (2008). Scalarane sesterterpenes from the sponge *Smenospongia* sp., *J. Nat. Prod.* **71**, 1866-1871.
- [20] C.S. Phan, T. Kamada, K. Kobayashi, T. Hamada and C.S. Vairappan (2018). 15-Deoxy-isoxeniolide-A, new diterpenoid from a Bornean soft coral, *Xenia* sp., *Nat. Prod. Res.* **32**, 202-207.
- [21] C.S. Phan, T. Kamada, T. Ishii, T. Hamada and C.S. Vairappan (2017). 12-Epi-9-deacetoxyxenicin, new cytotoxic diterpenoid from a Bornean soft coral, *Xenia* sp. *Nat. Prod. Res.* 1-6. doi: 10.1080/14786419.2017.1410812
- [22] G. Cimino, S. De Stefano and A. Di Luccia (1979). Further sesterterpenes from the sponge *Spongia nitens*: 12-epi-scalaradial and 12,18-diepi-scalaradial, *Experientia*. **35**, 1277-1278.
- [23] Z.L. Wang, Z.G. Zhang, H.C. Li and W.P. Deng (2011). Concise stereoselective synthesis of marine sesterterpene, 16-deacetoxy-12-epi-scalarafuran acetate and its 14-epimer via intramolecular Diels-Alder addition, *Tetrahedron* **67**, 6939-6943.
- [24] F.A. Proietti, A.B. Carneiro-Proietti, B.C. Catalan-Soares and E.L. Murphy (2005). Global epidemiology of HTLV-I infection and associated diseases, *Oncogene* **24**, 6058-6068.

A C G
publications

© 2018 ACG Publications