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Bridged Tricyclic Sesquiterpenes from the Tubercle Nudibranch *Phyllidia coelestis* Bergh

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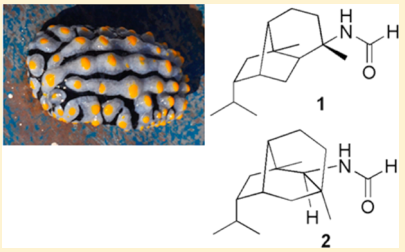
Supporting Information

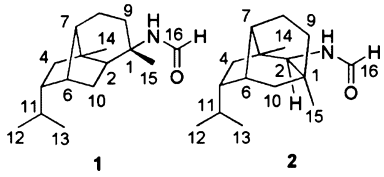
ABSTRACT: A new sesquiterpene, 1-formamido-10(1→2)-abeopupukeanane (**1**), was isolated from the tubercle nudibranch *Phyllidia coelestis* Bergh, along with 2-formamidopupukeanane (**2**), which is reported here as a natural product for the first time. A rearrangement pathway toward the unprecedented tricyclo[4.4.0.0^{2,8}]decane skeleton is proposed. Both compounds showed antiproliferative activity when targeting HeLa, MCF-7, KB, and HT-29 cancer cell lines in the range 0.05−10 μM.



Sea slugs are known for their ability to sequester toxic chemicals from their diets, either as intact chemical structures or with slight transformations, and employ such compounds in their chemical defense.[1] Tubercle nudibranchs of the genus *Phyllidia* graze on sponges and can sequester specific sponge metabolites. For example, it was observed that the slug *P. varicosa* secreted mucus that was lethal to crustaceans living in the same aquarium. The constituent in the slug's mucus was later identified to be 9-isocyanopupukeanane, a metabolite from its sponge prey *Ciocalypta* sp. (ex. *Hymeniacidon* sp.).[2] A number of sesquiterpenes with pupukeanane and related neopupukeanane skeletons have been isolated from specimens of *P. varicosa*, *P. bourguini*, and *P. pustulosa* nudibranchs and also from *Axinyssa*, *Ciocalypta*, and *Phycopsis* sponges,[3] thus implying the close dietary relationship among the nudibranchs and their sponge prey.

In this study, the nudibranch *P. coelestis* Bergh was investigated, leading to the isolation of an unprecedented rearranged bridged sesquiterpene, named 1-formamido-10(1→2)-abeopupukeanane (**1**). Another bridged sesquiterpene, 2-formamidopupukeanane (**2**), is reported here from a natural source for the first time. A rearrangement route for formation of the pupukeanane derivatives and their cytotoxicities are also reported.

Compound **1** forms colorless crystals. The molecular formula of **1** was proposed to be $C_{16}H_{27}NO$, based on the HREI mass at m/z 249.2087 $[M]^+$. The resulting unsaturation degree of 4 comprises one carbonyl (δ_C 160.8, C-16) and three rings. The ^1H and ^{13}C NMR spectra of **1** (500 MHz for ^1H, $CDCl_3$; Table 1) show two sets of signals in a 1:1 ratio. This is due to the *cisoid*/*transoid* formamide rotamers as indicated by the formamide protons at δ 8.20 (d, J = 12.6 Hz) and 8.02 (d, J = 2.1 Hz) for H-16 and at δ 5.58 (br d, J = 12.6 Hz) and 5.15 (br s) for 1-N*H* and by their corresponding carbon resonances at δ 163.2 and 160.8 (C-16). Such an NMR phenomenon of formamide rotamers has been widely recognized and very well reported (for example, see ref 4). For brevity, the discussion described hereafter refers to the conformer corresponding to the signals resonating at 8.02 and 5.15 ppm. The chemical shifts of the other conformer are bracketed in Table 1.



All of the remaining resonances of the aliphatic methylene and methine protons of **1** cluster densely in the high-field region (δ_H 0.75−2.05). COSY correlations (Figure 1) that were unambiguously identified included those between δ_H 8.02 (d, J = 2.1 Hz, H-16) and 5.15 (br s, 1-N*H*), between δ_H 2.02 (br d, J = 8.0 Hz, H-2) and 1.47 (m, H-10), and from δ_H 1.44 (m, H-4a) and 0.91 (m, H-4b) through 1.26 (m, H-5) to 1.94 (dd, J = 5.5, 2.5 Hz, H-6). Except for C-16, all 15 other carbon resonances are also observed in the high-field range (δ_C 19−58). Among these, two quaternary carbons (δ_C 57.8 [C-1] and 45.6 [C-3]) and three methines (δ_C 49.8 [C-2], 49.4 [C-7], and

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Table 1. NMR Data of 1 (500 MHz for ^{1}H, 125 MHz for ^{13}C, $CDCl_3$)

	δ_C,[a] type	δ_H (J in Hz)[a]
1	57.8, C [56.3]	
2	49.8, CH [53.4]	2.02, br d (8.0) [1.51, m]
3	45.6, C [45.7]	
4	45.3, CH_2 [45.3]	(a) 1.44, m [1.44, m]; (b) 0.91, m [0.91 [m]
5	50.2, CH [50.1]	1.26, m [1.26, m]
6	41.3, CH [41.5]	1.94, dd (5.5, 2.5) [1.98, dd (5.5, 2.5)]
7	49.4, CH [49.1]	1.45, m [1.40, m]
8	20.6, CH_2 [20.2]	(a) 1.73, m [1.73, m]; (b) 1.58, m [1.58, m]
9	30.5, CH_2 [31.0]	1.62, 2H, m [1.72, 2H, m]
10	24.5, CH_2 [24.9]	(a) 1.47, m [1.52, m]; (b) 1.22, m [1.24, m]
11	28.8, CH [28.8]	1.42, m [1.42, m]
12	21.6, CH_3 [21.4]	0.80, d (6.5) [0.80, d (6.5)]
13	21.6, CH_3 [21.5]	0.80, d (6.5) [0.80, d (6.5)]
14	19.9, CH_3 [21.2]	1.24, s [1.19, s]
15	25.6, CH_3 [30.3]	1.30, s [1.21, s]
16	160.8, CH [163.2]	8.02, d (2.1) [8.20, d (12.6)]
1-N*H*		5.15, br s [5.58, br d (12.6)]

[a]The chemical shifts of the *transoid* conformer are in brackets.

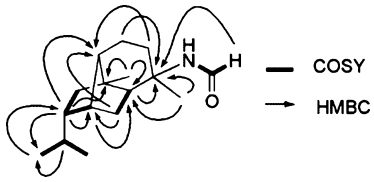

Figure 1. COSY and key HMBC correlations of **1**.

41.3 [C-6]) were deduced as either bridgehead carbons or as part of ring junctions, thus constituting three ring systems.

Crucial HMBC correlations (Figure 1) that allowed the connection of the fragments from COSY correlations with bridgehead carbons listed above were those from δ_H 5.15 (br s, 1-N*H*), 1.73 (m, H-8a), 1.62 (2H, m, H_2-9), 1.58 (m, H-8b), and 1.30 (3H, s, H_3-15) to δ_C 57.8 (C-1); from δ_H 1.94 (dd, J = 5.5, 2.5 Hz, H-6), 1.44 (m, H-4a), 1.30 (3H, s, H_3-15), 1.24 (3H, s, H_3-14), and 0.91 (m, H-4b) to δ_C 49.8 (C-2); from δ_H 2.02 (br d, J = 8.0 Hz, H-2) 1.44 (m, H-4a), 1.26 (m, H-5), 1.24 (3H, s, H_3-14), and 0.91 (m, H-4b) to δ_C 45.6 (C-3); from δ_H 1.47 (m, H-10), 1.42 (m, H-11), and 1.26 (m, H-5) to δ_C 41.3 (C-6); and from δ_H 1.62 (2H, m, H_2-9), 1.47 (m, H-10), and 1.26 (m, H-5) to δ_C 49.4 (C-7), therefore leading to the bridged tricyclic skeleton of **1**. An isopropyl substituent defined by the H-11 methine (δ 1.42, m) and H_3-12 and H_3-13 methyls (both δ 0.80, d, J = 6.5 Hz) was placed at C-5 (δ 50.2). The structure of **1** was confirmed by X-ray crystallographic analysis (Figure 2), allowing **1** to be identified as a rearranged sesquiterpene with an unprecedented tricyclo[4.4.0.0^{2,8}]decane skeleton, named 1-formamido-10(1→2)-abeopupukeanane. The positions shown here are numbered after those given to the pupukeanane skeleton.[2,3]

The crystallographic data provided the complete relative configuration of **1** as 1*S**,2*S**,3*S**,5*S**,6*R**,7*R** (Figure 2); however, the formamide geometry in both the rotameric

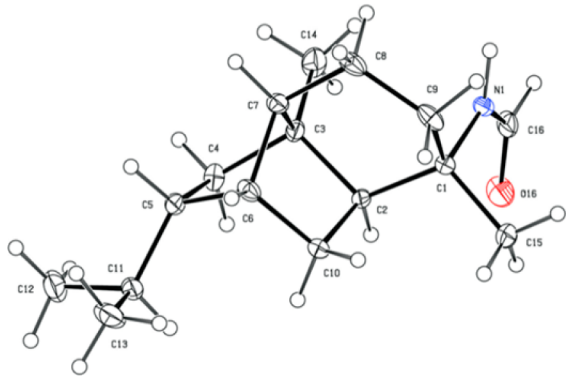

Figure 2. ORTEP drawing for the structure of **1**.

conformers requires a determination through the coupling constants between H-16 and 1-N*H*. All of the resonances that correspond to the signals at δ_H 8.20 and 5.58 (both d, J = 12.6 Hz) belong to the *transoid* conformer, and those to δ_H 8.02 (d, J = 2.1 Hz) and 5.15 (br s) belong to the *cisoid* one. This was confirmed by the NOESY experiment (Figure 3), from which the NOE between H-15 and 1-N*H* (**1a**) was observed with the *cisoid* set of resonances, whereas H-16 of the *transoid* conformer showed dipolar coupling with H-2 (**1b**).

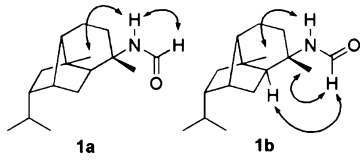

Figure 3. Dipolar couplings observed from the NOESY spectrum of **1** in the *cisoid* (**1a**) and *transoid* (**1b**) conformations.

Compound **2**, possessing the molecular formula $C_{16}H_{27}NO$, is a constitutional isomer of **1**. Similar to **1**, the NMR spectra of **2** (500 MHz for ^{1}H, $CDCl_3$) showed two sets of resonances in a 2:1 ratio, attributed to the rotating formamide moiety. The formamide functionality was observed at δ 8.25 (dd, J = 2.0, 0.5 Hz, H-16) and 5.43 (br s, 2-N*H*) for the major conformer and at δ 7.90 (d, J = 11.9 Hz, H-16) and 5.76 (br s, 2-N*H*) for the minor one. The structure determination of **2** was carried out in the same manner as that for **1** and showed that **2** is a pupukeanane derivative, named 2-formamidopupukeanane. The geometry of the formamide moiety of each conformer was determined using the coupling constants between H-16 and 2-N*H*. The small coupling constant of 2.0 Hz in the major conformer indicates a *cisoid* geometry, whereas the large *transoid* coupling of 11.9 Hz is associated with the minor one. The relative configuration of **2** shown here imitates that of **1** as discussed earlier. The structure of **2** was first reported as a chemically derivatized intermediate formed during the structure determination of 2-isocyanopupukeanane,[2b] but its spectroscopic and physical properties have not been reported. Compound **2** is reported here as a natural product along with its complete spectroscopic data for the first time.

The biogenetic origin of the pupukeanane skeleton has been proposed to arise from amorphene[3a] (Scheme 1). Upon 3→7 cyclization of amorphene, a 4(2→3) shift leads to the pupukeananes, whereas an 8(7→3) shift yields the neo-pupukeanane series. A 10(1→2) shift on the pupukeanane cation intermediate would result in the abeopupukeanane

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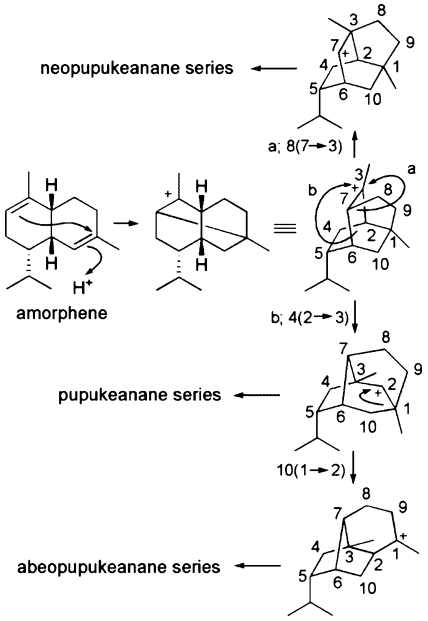
Scheme 1. Proposed Biogenetic Origin of Pupukeanane, Neopupukeanane, and Abeopupukeanane Skeletons



structure. As for the nitrogenated functionalities, it has been demonstrated that the formamide functionality in sponge-derived sesqui- and diterpenes is derived from the isonitrile.[5] However, unlike most nitrogenous natural products, including the majority of alkaloids and amide derivatives, of which nitrogen atoms come from amino acids, the source of the isonitrile in the pupukeananes and related marine-derived terpenes is the inorganic cyanide ion.[5c] For example, it has been demonstrated that the cyanide ion is the nitrogen source of 2-isocyanopupukeanane in the sponge *Ciocalypta* sp.[5] Similar results were reported with the isocyanoterpenes in sponges of other genera, including *Amphimedon*, *Acanthella*, and *Axinyssa*.[5c,6] It is proposed here that the formamide moiety in **1** and **2** may come from the isonitrile in a route similar to that of other pupukeananes and related sponge-derived terpenes, i.e., presumably incorporated as a cyanide ion by the sponges prior to being consumed by the mollusk.

Both compounds were tested for their cytotoxicities against cancer cell lines. The IC_{50}(±SD) values of **1** against HeLa, MCF-7, KB, and HT-29 cells were 0.13(0.012), 0.65(0.29), 2.4(0.32), and 6.8(0.23) μM, respectively, and those of **2** against HeLa, MCF-7, and KB were 0.07(0.008), 8.2(0.29), and 1.2(0.10) μM. As for the HT-29 cells, 35% inhibition was observed at 20 μM **2**. Both compounds weakly inhibited the proliferation of human gingival fibroblast cells (65% and 25% inhibition, each at 20 μM, respectively).

EXPERIMENTAL SECTION

General Experimental Procedures. Melting points were determined on a Fisher-Johns melting point apparatus. Optical rotations were obtained on a Perkin-Elmer341 polarimeter. UV spectra were obtained from a Genesys 6 spectrophotometer. ECD spectra were measured on a Jasco J-715 spectropolarimeter using the same conditions as those for the measurements of the optical rotations. IR spectra were obtained from a Jasco 810 IR spectrophotometer. All the NMR experiments were performed on an FT-NMR Varian Unity Inova 500 spectrometer at 500 MHz for ^{1}H and 125 MHz for ^{13}C, referencing the solvent signals ($CDCl_3$, 7.26 ppm of residual $CHCl_3$ for ^{1}H, 77.0 ppm for ^{13}C). HREI mass spectra were recorded on an MAT95 XL mass spectrometer. HPLC was performed on a Thermo Scientific SCM1000 solvent delivery system, connected to a SPECTRAsystem 1500 diode UV tunable detector and a Rheodyne V77251 injector port. All the chemicals and chromatographic solvents were laboratory grade and were all used as purchased.

Animal Materials. Eight specimens of the nudibranch *Phyllidia coelestis* Bergh were collected manually by scuba diving from Koh-Ha Islets, Krabi Province, Thailand, in February 2010. One specimen (AP10-032-03) was preserved and deposited at the Department of Pharmacognosy and Pharmaceutical Botany, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Songkhla. The taxonomic identification was kindly performed by Assoc. Prof. Suchana Chawanich of the Department of Marine Science, Faculty of Science, Chulalongkorn University, Bangkok.

Extraction and Isolation. The nudibranchs (seven specimens) were chopped, blended in MeOH/EtOAc (1:1), and macerated exhaustively (3 × 20 mL). The concentrated extract (0.7 g), after partitioning in EtOAc to eliminate trace water, was further partitioned with a series of solvents to yield *n*-hexane, $CHCl_3$, and *n*-BuOH extracts (457, 44, and 24 mg, respectively). The hexane extract was fractionated over SiO_2 (Merck; CH_2Cl_2/hexane, 9:1) and Sephadex LH20 (GE-Healthcare; CH_2Cl_2/MeOH, 1:1) columns. The major fraction was pooled and chromatographed over a SiO_2 HPLC column (VertiSep, 10 × 250 mm, 10 mm; 3% *i*-PrOH in hexane) to yield **1** and **2** (2.1 and 1.6 mg, respectively). The fraction that contains **1** was allowed to crystallize in the same chromatographic solvent to yield crystals of **1**.

*1-Formamido-10(1→2)-abeopupukeanane (**1**):* colorless, orthorhombic crystals; mp 152 °C; $[\alpha]_D$ +17.2 (*c* 0.10, MeOH); UV (MeOH) λ_{max} (log ε) 293 (2.18) nm; ECD (*c* 0.10, MeOH) λ_{max} ($\Delta\varepsilon$) 295 (−4.5), 228 (−4.3) nm; (*c* 0.10, $CHCl_3$) λ_{max} ($\Delta\varepsilon$) 230 (−8), 222 (6.5), 215 (−2.5) nm; IR (neat) ν 3290, 2930, 1655 cm^{-1}; ^{1}H and ^{13}C NMR see Table 1; HREIMS *m*/*z* 249.2087 [M]$^+$ (calcd for $C_{16}H_{27}NO$, 249.20926).

*2-Formamidopupukeanane (**2**):* colorless solid; $[\alpha]_D$ −36 (*c* 0.08, MeOH); UV (MeOH) λ_{max} (log ε) 290 (2.08) nm; ECD (*c* 0.08, MeOH) λ_{max} ($\Delta\varepsilon$) 295 (−3.5), 220 (−11) nm; (*c* 0.08, $CHCl_3$) λ_{max} ($\Delta\varepsilon$) 230 (−10.5), 220 (7.5) nm; IR (neat) ν 3300, 2950, 1662 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.25 (1H, dd, *J* = 2.0, 0.5 Hz, H-16) [7.90 (d, *J* = 11.9 Hz)], 5.43 (1H, br d, *J* = 5.9 Hz, 2-N*H*) [5.76 (m)], 3.59 (1H, d, *J* = 10.5 Hz, H-2) [2.73 (d, *J* = 11.0 Hz)], 2.04 (1H, m, H-6) [2.04], 1.92 (1H, m, H-4a) [1.90], 1.67 (1H, m, H-8a) [1.72], 1.52 (1H, m, H-10a) [1.56], 1.46 (1H, m, H-8b) [1.50], 1.45 (1H, m, H-11) [1.48], 1.34 (1H, m, H-4b) [1.90], 1.21 (1H, m, H-10b) [1.16], 1.20 (1H, m, H-9a) [1.30], 1.20 (1H, m, H-7) [1.23], 1.16 (1H, m, H-9b) [1.30], 0.91 (3H, s, H_3-14) [0.91], 0.82 (6H, d, *J* = 6.4 Hz, H_3-12 and H_3-13) [0.83], 0.76 (3H, s, H_3-15) [0.77]; ^{13}C ($CDCl_3$, 125 MHz) δ 161.1 (C, C-16) [164.7], 62.4 (CH, C-2) [68.6], 49.7 (CH, C-5) [49.6], 49.1 (CH_2, C-4) [49.5], 44.1 (CH, C-7) [44.0], 42.4 (C, C-3) [43.2], 38.8 (CH, C-6) [38.2], 33.8 (CH_2, C-9) [33.5], 30.5 (C, C-1) [30.9], 29.3 (CH, C-11) [29.4], 27.6 (CH_2, C-10) [27.5], 25.4 (CH_3, C-15) [22.7], 21.7 (CH_3, C-14) [21.7], 21.6 (2CH_3, C-12 and C-13) [21.6], 17.6 (CH_2, C-8) [17.4]; HREIMS *m*/*z* 249.2087 [M]$^+$ (calcd for $C_{16}H_{27}NO$, 249.20926). Note: The NMR chemical shifts of the minor conformer are bracketed.

Crystallographic Analysis. X-ray diffraction data were obtained on a Bruker-Nonius kappaCCD diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) at 150(2) K. The structure was solved with direct methods by SIR97 and refined with full-matrix least-squares calculations on F^2 using SHELXL-97.[7] Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre under the reference number CCDC 915518. Copies are available free of charge on application to the Director, CCDC, 12 Union Rd., Cambridge, CB2 1EZ, UK (e-mail: deposit@ccdc.cam.ac.uk).

Crystal Data. 1-Formamido-10(1→2)-abeopupukeanane (**1**): $C_{16}H_{27}NO$, orthorhombic, dimensions 0.30 × 0.15 × 0.10 mm^3, *D* = 1.139 g/cm^3, space group $P2_12_12_1$, *Z* = 4, *a* = 7.0316(2) Å, *b* = 9.5125(4) Å, *c* = 21.7347(8) Å, *V* = 1453.79(9) Å^3, reflections

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collected/unique: 8819/3794, number of observations [$>2\sigma(I)$] 3426, final R indices [$I > 2\sigma(I)$] $R_1 = 0.0460$, $wR_2 = 0.1124$.

Antiproliferative Activity. The antiproliferative activity was determined using the SRB colorimetric assay,[8] targeting HeLa, MCF-7, KB, and HT-29 cancer cells and human gingival fibroblasts as normal cells. Camptothecin was used as standard drug (IC_{50}'s 0.13 ± 0.003, $(3.3 \pm 1.1) \times 10^{-3}$, 0.02 ± 0.003, and $(0.7 \pm 0.1) \times 10^{-3}$ μM against HeLa, MCF-7, KB, and HT-29 cancer cells, respectively).

■ ASSOCIATED CONTENT

Supporting Information

ECD, ^{1}H and ^{13}C NMR (1D, COSY, HMQC, HMBC, and NOESY) spectra of **1** and **2**, CIF file for **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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