Spongiapyridine and Related Spongians Isolated from an Indonesian Spongia sp.

Stephen M. Parrish,† Wesley Y. Yoshida,† Tamara P. Kondratyuk,‡ Eun-Jung Park,‡ John M. Pezuzz‡, Michelle Kelly,§ and Philip G. Williams*†

†Department of Chemistry, University of Hawaii at Manoa, Honolulu, Hawaii 96822, United States
‡Daniel K. Inouye College of Pharmacy, University of Hawaii at Hilo, Hilo, Hawaii 96720, United States
§Coasts and Oceans National Centre, National Institute of Water & Atmospheric Research Ltd, 41 Market Place, Auckland Central 1010, New Zealand

Supporting Information

ABSTRACT: New compounds 18-nor-3,17-dihydroxyspongia-3,13(16),14-trien-2-one (1), 18-nor-3,5,17-trihydroxyspongia-3,13(16),14-trien-2-one (2), and spongiapyridine (3) and the known compound 17-hydroxy-4-epi-spongialactone A (4) were isolated from an Indonesian sponge of the genus Spongia. The structures of 1–3 were deduced by analyses of physical and spectroscopic data. Diterpene 3 is unusual, as the D-ring is a pyriddy ring system rather than the standard δ-lactone. The structure elucidation of this compound was complicated by facile exchange of the axial proton at the C-11 methylene with deuterium from methanol-d₄. The isolated compounds were tested for biological activity in a battery of in vitro assays (TNF-α-induced NFκB, LPS-induced iNOS, RXR stimulation, quinone reductase 1 induction, aromatase inhibition, TRPM7 ion channels, and aspartic protease BACE1 inhibition). Norditerpene 2 modestly inhibited aromatase with an IC₅₀ of 34 μM and induced quinone reductase 1 activity with a CD (the concentration needed to double the enzymatic response) of 11.2 μM. The remaining isolates were inactive.

RESULTS AND DISCUSSION

Compound 1 was isolated as a white powder after multiple rounds of chromatography. High-resolution mass spectrometry gave a protonated molecule at m/z 317.1747 [M + H]⁺. This datum is consistent with a molecular formula of C₁₉H₂₄O₄ and indicated eight double-bond equivalents. The carbon spectrum showed seven sp³ carbons, six of which were C=C bonds and one of which was a conjugated carbonyl carbon (δC₂ 195.4). Therefore, the compound had four rings to account for the remaining double-bond equivalents.

The planar structure of 1 was assembled by analyses of COSY and HMBC correlations. Beginning with the tertiary methyl group (H₃-20, 0.88 ppm), the observation of HMBC correlations to two methines, a quaternary carbon, and a methylene (C-1, C-5, C-9, C-10) was critical toward the assembly of fragment 1 (Figure 1). This alkyl chain was assembled by analyses of physical and spectroscopic data. Diterpene 3 is unusual, as the D-ring is a pyriddy ring system rather than the standard δ-lactone. The structure elucidation of this compound was complicated by facile exchange of the axial proton at the C-11 methylene with deuterium from methanol-d₄. The isolated compounds were tested for biological activity in a battery of in vitro assays (TNF-α-induced NFκB, LPS-induced iNOS, RXR stimulation, quinone reductase 1 induction, aromatase inhibition, TRPM7 ion channels, and aspartic protease BACE1 inhibition). Norditerpene 2 modestly inhibited aromatase with an IC₅₀ of 34 μM and induced quinone reductase 1 activity with a CD (the concentration needed to double the enzymatic response) of 11.2 μM. The remaining isolates were inactive.

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amplitude of the order of sp² carbons, creating an αβ-
unsaturated ketone moiety within a six-membered ring.

The two downfield protons at δ₁H-16 7.14 and δ₁H-15 7.17, as
well as four remaining sp² carbons, hinted at the possibility of a
furan moiety (δ₁H from the HMBC data suggested the heteroaromatic
ring was a furan5). With a furan moiety in mind, HMBC correlations
from the proton resonance at δ₁H-16 7.14 to C-14 and C-15, in addition to correlations from
δ₁H-15 7.17 to C-16 and C-13, suggested the furan ring is as
shown in Figure 1.

Fragments 1 and 2 were joined based on HMBC correlations
observed from the methylene proton resonance of the primary
alcohol (δ₁H-16 7.14 and δ₁H-15 7.17, as
well as four remaining sp² carbons, hinted at the possibility of a
heteroaromatic ring. The ¹J_C–H value for position 16 extracted from
the HMBC data suggested the heteroaromatic ring was a furan moiety (¹J_C–H = 201 Hz vs a reference value of 202 Hz in
furan5). With a furan moiety in mind, HMBC correlations from
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shown in Figure 1.

Table 1. NMR Spectroscopic Data (500 MHz, CD₃OD) for 1

| position | δ_C⁸ | δ_H | COSY | HMBC (¹H to ¹³C)⁵⁴ |
|----------|------|-----|------|-------------------|
| a        | 53.3  | 2.73 (16.6) | H-1, H-19 | 2, 3, 5, 6, 9, 10, 20 |
| 1b       | 2.18 (16.6) | H-1 | 2, 3, 5, 6, 9, 10, 20 |
| 2        | 195.4 | 4.94 | H-19a | 2, 3, 5, 6, 9, 10, 20 |
| 3        | 145.7 | 4.94 | H-19b | 2, 3, 5, 6, 9, 10, 20 |
| 4        | 132.9 | 4.94 | H-19c | 2, 3, 5, 6, 9, 10, 20 |
| 5        | 50.1  | 2.62 (5.1) | H-19d | 2, 3, 5, 6, 9, 10, 20 |
| 6a       | 21.7  | 1.91 (6.6) | H-19e | 2, 3, 5, 6, 9, 10, 20 |
| 6b       | 1.62 (6.6) | H-19f | 2, 3, 5, 6, 9, 10, 20 |
| 7a       | 34.9  | 2.53 (6.6) | H-19g | 2, 3, 5, 6, 9, 10, 20 |
| 7b       | 1.41 (6.6) | H-19h | 2, 3, 5, 6, 9, 10, 20 |
| 8        | 40.8  | 1.72 (6.6) | H-19i | 2, 3, 5, 6, 9, 10, 20 |
| 9        | 54.4  | 1.72 (6.6) | H-19j | 2, 3, 5, 6, 9, 10, 20 |
| 10       | 21.7  | 1.72 (6.6) | H-19k | 2, 3, 5, 6, 9, 10, 20 |
| 11a      | 18.9  | 1.72 (6.6) | H-19l | 2, 3, 5, 6, 9, 10, 20 |
| 11b      | 1.72 (6.6) | H-19m | 2, 3, 5, 6, 9, 10, 20 |
| 12a      | 21.1  | 2.80 (16.0, 20.0) | H-19n | 2, 3, 5, 6, 9, 10, 20 |
| 12b      | 2.56 (16.0, 20.0) | H-19o | 2, 3, 5, 6, 9, 10, 20 |
| 13       | 120.8 | 2.56 (16.0, 20.0) | H-19p | 2, 3, 5, 6, 9, 10, 20 |
| 14       | 131.3 | 2.56 (16.0, 20.0) | H-19q | 2, 3, 5, 6, 9, 10, 20 |
| 15       | 139.2 | 2.56 (16.0, 20.0) | H-19r | 2, 3, 5, 6, 9, 10, 20 |
| 16       | 138.3 | 2.56 (16.0, 20.0) | H-19s | 2, 3, 5, 6, 9, 10, 20 |
| 17a      | 62.8  | 2.56 (16.0, 20.0) | H-19t | 2, 3, 5, 6, 9, 10, 20 |
| 17b      | 3.48 (16.0, 20.0) | H-19u | 2, 3, 5, 6, 9, 10, 20 |
| 19       | 13.3  | 1.88 (6.0) | H-19v | 2, 3, 5, 6, 9, 10, 20 |
| 20       | 15.6  | 0.88 (6.0) | H-19w | 2, 3, 5, 6, 9, 10, 20 |

⁴⁵HMBC correlations optimized for ¹J_C–H = 7 Hz. ⁶Numbering is consistent with previously published compounds of this type.¹
alcohol proton in aprotic solvents (CDCl₃ and CD₃CN) and at lower temperatures (down to −20 °C).

Spongiapyridine (3) had an observed HRESI-TOFMS m/z of 342.1701 [M + H]+, being consistent with a molecular formula of C₂₀H₂₃NO₄. Comparison of the NMR data for this compound with those of 1 showed that 3 contained identical features in the A- and B-rings and contained a primary alcohol as well. The C- and D-rings, however, included a nitrogen atom, a second carbonyl carbon (δC-12 199.1), a third aromatic proton, and downfield shifts of the aromatic protons (δH₁₂ 8.71, δH₁₆ 8.58, δH₁₇ 7.82). In contrast to the ¹JCH value observed in 1, the resonance at δH₁₆ 8.58 displayed a ¹JCH value of 182 Hz, which was no longer consistent with a furan moiety. Instead, this one-bond coupling constant was consistent with a carbon adjacent to the nitrogen in a pyridine moiety. Consequently, a ¹H−¹⁵N HMBC experiment was performed to help support this supposition. In this experiment, a correlation was observed from the signal at δH₁₆ 8.58 to a nitrogen resonating at δN−68 (referenced to nitromethane), further supporting the inclusion of a pyridine moiety in 3.

Additional structural modifications were deduced based on HMBC correlations from δH₁₈b 3.74 to δC₁₄ 145.6, which connected the pyridine ring to ring B, and between δH₁₇ 7.82 and δC₁₂ 199.1, indicating the carbonyl was at C-12 (Figure 2). The final structural fragment left unaccounted for in 3, according to a phase-sensitive HSQC experiment, was a putative methine that resonated at δH₁₁b 2.60 and showed a COSY correlation to δH₉ 2.36. However, if a methine was present at C-11, then this would result in a molecular formula inconsistent with the observed MW of 341. Upon closer inspection, 3 was dissolved in CD₃OH.

### Table 2. ¹³C NMR Spectroscopic Data (125 MHz, CD₃OD) for 2−4

| position | 2 δC | 3 δC | 4 δC |
|----------|------|------|------|
| 1        | 50.3 | 51.9 | 46.6 |
| 2        | 194.2| 194.5| 177.0|
| 3        | 143.0| 145.7| 74.8 |
| 4        | 132.9| 131.9| 53.8 |
| 5        | 76.8 | 49.0 | 58.0 |
| 6        | 28.7 | 21.8 | 22.7 |
| 7        | 36.8 | 33.8 | 35.0 |
| 8        | 32.8 | 42.5 | 41.7 |
| 9        | 48.6 | 50.4 | 55.3 |
| 10       | 44.0 | 41.8 | 40.2 |
| 11       | 22.6 | 35.9 | 19.9 |
| 12       | 21.4 | 199.1| 21.6 |
| 13       | 122.4| 139.5| 120.8|
| 14       | 127.0| 145.6| 131.6|
| 15       | 139.9| 149.3| 139.0|
| 16       | 138.1| 148.3| 138.2|
| 17       | 71.0 | 120.3| 62.8 |
| 18       | 10.7 | 13.2 | 14.9 |
| 19       | 18.7 | 14.6 | 17.7 |
| 20       |      |      |      |

*S was dissolved in CD₃OH. Chemical shifts identified via HMBC correlations.

### Table 3. ¹H NMR Spectroscopic Data (500 MHz, CD₃OD) for 2−4

| position | ²δH (J in Hz) | ³δH (J in Hz) | ⁴δH (J in Hz) |
|----------|---------------|---------------|---------------|
| 1        | 2.64, d (17.2)| 2.62, m       | 2.86, m       |
| 2        | 2.57, d (17.2)| 2.20, d (16.4)| 2.84, m       |
| 3        | 4.67, brs     | 3.95, brs     |               |
| 5        | 2.66, d (11.4)*| 2.25, d (11.9)|               |
| 6        | 2.19, ddd (13.4, 10.8, 2.2)| 2.17, brd (10.2)| 1.75, m       |
| 7        | 2.00, m       | 1.74, m       | 1.29, m       |
| 7        | 2.10, dd (12.4, 6.5)| 2.80, brd (9.9)| 2.45, brd (13.0)|
| 9        | 1.78, dddd (11.8, 11.8 3.1, 3.1)| 1.73, m| 1.32, m       |
| 11       | 1.70, brd (13.2)| 2.36, dd (14.5, 4.8)| 1.51, d (10.7)|
| 12       | 1.84, m       | 3.04, dd (18.5, 14.5)| 1.83, dd (13.5, 6.9)|
| 13       | 1.62, ddd (12.8, 12.8, 4.2)| 2.60, m| 1.74, m       |
| 14       | 2.76, ddd (15.2, 3.1, 3.1)| 2.82, m| 2.55, m       |
| 15       | 2.31, dddd (15.2, 12.8, 4.2, 1.9)| 8.71, brs| 7.14, s       |
| 16       | 8.71, brs    | 8.58, d (4.8)| 7.14, s       |
| 17       | 4.01, dd (9.0, 3.1)| 7.82, d (4.8)| 3.88, d (11.0)|
| 18a      | 3.70, dd (9.0, 1.6)| 3.49, d (11.0)|               |
| 18b      | 4.02, d (11.4)| 3.74, d (11.4)|               |
| 19       | 1.83, s       | 1.90, d (1.9)| 1.25, s       |
| 20       | 1.09, s       | 1.06, brs     | 1.03, brs     |

*S was dissolved in CD₃OH. *b* J value extracted from the 1D TOCSY spectrum obtained by irradiating the resonance at 1.75 ppm. 
investigation of the $^{13}$C spectrum, it became clear that the carbon at δ$_{C,11}$ 35.9 was not a singlet, as would be expected in a broad-band-decoupled carbon spectrum, but instead was coupled to another nucleus, displaying a triplet with lines in a ratio of 1:1:1. The multiplicity of this carbon resonance suggested coupling with a nucleus that had a quantum spin number of one. One possible explanation for the observed coupling was that deuterium from the solvent was exchanging with one of the protons alpha to the C-12 ketone. To test this hypothesis of deuterium exchange, 3 was dissolved in CD$_3$OH, and the NMR spectra were rerecorded. The result was the collapse of the carbon triplet into a singlet and the appearance of an additional proton at δ$_{C,11}$ 3.04, showing that C-11 was a methylene. It is interesting to note that only the axial proton adjacent to the ketone, not the equatorial proton, is exchanged, likely due to the well-known stereoelectronic effect, i.e., overlap of the axial C–H bond with the ketone’s p$^\pi$-orbital as documented by Corey and Sneen that favors removal of that proton.

The relative configuration of 3 was determined in a manner similar to that described for 1. An NOE correlation between H$_2$-20 and H$_2$-18 indicated they were syn and axial. H-5 and H-9 had J values of 11.4 and 14.5 Hz, respectively, suggesting they are also axial, resulting in proposed structure 3.

HRESI-LCMS of 4 gave a protonated molecule at m/z 363.1790 [M + H]$^+$, consistent with the molecular formula C$_{26}$H$_{36}$O$_6$. All the major spectral differences were assigned to the A-ring by comparison of the NMR spectra of 1 and 4. These changes were two ester/carboxylic acid functional groups, an oxygenated methylene, and an sp$^3$ quaternary carbon. These changes were at the expense of the $\alpha$$\beta$-unsaturated carbonyl and were satisfied via a seven-membered lactone ring. All of the HMBC correlations from δ$_{H,19}$ 1.25 and also from δ$_{H,4}$ 2.87 supported this structure (Figure 2). An NOE correlation between δ$_{H,19}$ 1.25 and δ$_{H,20}$ 1.03 confirmed the configuration at C-4, indicating that 4 was the known compound 17-hydroxy-4-epi-spongialactone A. This molecule has previously been isolated, but only as the diaecetyl methyl ester derivative by Gunasekera and Schmitz from a Spongia sp. specimen. For this reason, we included its spectroscopic data in this report.

All of the spongian diterpenes for which the absolute configurations have been determined belong to the same enantiomeric series. It is, therefore, believed that compounds 1–4 have the absolute configuration 5R,8S,9R,10R.

A plausible biosynthetic pathway is proposed in Figure 3. From geranylgeraniol, a polyolefin cyclization cascade could give structure 5. After oxidation to yield 6, attack on the carbonyl carbon by the primary alcohol yields 7b. A 1,4-elimination of H$_2$O establishes the furan 8b, which is followed by several oxidations to yield our new compound 1. Similar known structures could also be accounted for by this biosynthetic pathway. For example, oxidation from 7b leads to the known compound zimolactone B, and further oxidation of 7a to a carboxylic acid before cyclization leads to the framework required for zimolactones A and C$\beta$ (not shown). Also, from 8b, partial oxidation may account for spongidiol, spongatriol, and their C-5 epimers.

Compound 7a may feed into an alternative pathway to produce 3. Condensation of 7a with glyline and subsequent cyclization yields 8a. Decarboxylation, oxidation at C-12, and A-ring oxidation yields spongipyridine 3.

There are many strategies for decreasing cancer mortality through chemoprevention, and a variety of assessments were performed with 1–4. Modest inhibition of TNF-α-activated NF-κB activity was observed for all compounds with ED$_{50}$ values around 50 $\mu$M (data not shown). No significant activity was observed for inhibition of iNOS activity in LPS-induced RAW 264.7 murine macrophage cells, and no significant induction occurred in a retinoic X receptor response element luciferase reporter gene assay.

Another approach is the inhibition or down-regulating aromatase. Aromatase, a key cytochrome P450 enzyme, catalyzes the rate-limiting aromatization step in the conversion of androgens (testosterone and androstenedione) to estrogens (estradiol and estrone). Aromatase inhibitors decrease bioavailable estrogen and have shown considerable activity in the prevention of certain breast cancers. Such compounds ultimately reduce estradiol receptor stimulation and reduce the formation of genotoxic estrogen metabolites. Certain non-steroidal aromatase inhibitors are already in clinical use for the treatment of breast cancer, and several naturally occurring nonsteroidal aromatase inhibitors have shown promising chemopreventive activity. In the current investigation, compound 2 inhibited aromatase in a dose-dependent manner with an IC$_{50}$ value of 34.4 $\mu$M. The other compounds did not achieve 50% inhibition at a concentration of 50 $\mu$M.

NAD(P)H:quinone reductase 1, a cytoprotective enzyme, can exhibit cancer protective activity by inhibiting the formation of intracellular semiquinone radicals and by generating $\alpha$-tocopherolhydroquinone, which acts as a chemopreventive agent. Cancer chemoprevention can be achieved by activating QR1. One parameter used to compare the QR1 induction potential of different compounds is the CD value, i.e., the concentration of test compound required to double QR1 activity. With cultured Hepa 1c1c7 cells, 2 demonstrated a CD value of 11.2 $\mu$M, which is similar to the CD value of resveratrol (21 $\mu$M), a weak QR1 inducer.
Lastly, all of our isolated compounds were screened against BACE 1 as part of our ongoing search for drug leads for Alzheimer’s disease (AD). BACE1 is an aspartic protease and one of the major players in the amyloid cascade hypothesis for AD.12,13 All compounds showed no significant activity toward the aspartic protease BACE1 (<100 μM).

**EXPERIMENTAL SECTION**

**General Experimental Procedures.** Optical rotations were measured on a Jasco DIP-370 digital polarimeter at the sodium D-line (589 nm). UV absorbances were measured on a Varian Cary 50 Bio UV–vis spectrophotometer. IR spectroscopy was measured as a thin film on a CaF2 disk using a Shimadzu IRAffinity-1 FTIR. 1H, 13C, and 2D NMR experiments were performed on a Varian Unity Inova 500 MHz spectrometer. NMR spectra were referenced to the appropriate residual solvent signal (δH 3.30, δC 49.1 for MeOH-d4) with chemical shifts reported in δ units (ppm). The HSQC experiments were optimized for 1JCH = 140 Hz and HMBE experiments for 1JCH = 7 Hz. Mixing times for ROESY and NOESY experiments were 500 ms and were generally 80 ms for the 1D TOCSY experiments. High-resolution mass spectrometric data were obtained on an LC-MS-TOF spectrometer using ESI mode.

**Collection and Isolation.** The sponge was collected from Bunaken Marine Park, Sulawesi, Indonesia, in 1992, and freeze-dried and stored at −20 °C. The freeze-dried sponge appears to have come from a cavernous encrusting sponge with surface conules, the color in life appears to be charcoal gray, and the interior is tan. The texture is soft and compressible, tending relatively easily. The skeleton is composed of slightly fasciculated primary fibers cored with foreign spicule detritus, and a light dusting of foreign spicules is found in the collagenous ectosome. The secondary spongin network is well developed. The sponge is most closely comparable to species in the genus *Spongia* (order Dictyoceratida, family Spongiidae) with homogeneous spongin fibers, but the primary fibers are slightly fasciculated as in species of the genus *Cacospongia*. A voucher specimen has been deposited at the Natural Museum, London (NHMUK2012.3.27.3).

The freeze-dried sponge (50 g) was extracted overnight three times with a 1:1 mixture of MeOH and CH2Cl2. The resulting extract (7.4 g) was subjected to a liquid–liquid partitioning protocol between hexanes, CH2Cl2, BuOH, and H2O. The CH2Cl2 partition (2.6 g) was subjected to a liquid partitioning protocol between hexanes, CH2Cl2, BuOH, and H2O. The CH2Cl2 partition (2.6 g) with chemical shifts reported in δ units (ppm). The HSQC experiments were optimized for 1JCH = 140 Hz and HMBE experiments for 1JCH = 7 Hz. Mixing times for ROESY and NOESY experiments were 500 ms and were generally 80 ms for the 1D TOCSY experiments. High-resolution mass spectrometric data were obtained on an LC-MS-TOF spectrometer using ESI mode.

The sponge was subjected to a liquid partitioning protocol between hexanes, CH2Cl2, BuOH, and H2O. The CH2Cl2 partition (2.6 g) was subjected to a liquid partitioning protocol between hexanes, CH2Cl2, BuOH, and H2O. The CH2Cl2 partition (2.6 g) with chemical shifts reported in δ units (ppm). The HSQC experiments were optimized for 1JCH = 140 Hz and HMBE experiments for 1JCH = 7 Hz. Mixing times for ROESY and NOESY experiments were 500 ms and were generally 80 ms for the 1D TOCSY experiments. High-resolution mass spectrometric data were obtained on an LC-MS-TOF spectrometer using ESI mode.

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