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# Revised Constitution of Sclerophytins A and B

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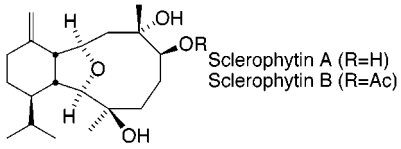
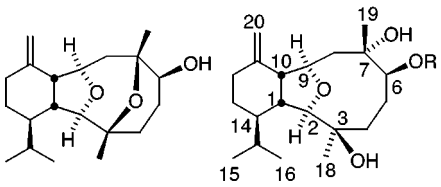
## ABSTRACT




**Spectroscopic reevaluation of sclerophytin B, the acetate of sclerophytin A, has demonstrated unequivocally that these coral metabolites are not composed of two ether bridges.**

Contrary to our expectations, a stereodirected synthesis of **1**, the most stable diastereomer of sclerophytin A,[2] resulted in the acquistion of a substance distinctively different in $^1$H and $^{13}$C NMR detail, polarity, and other spectroscopic parameters from the natural coral metabolite.[3] Herein we detail the results of a global reevaluation of sclerophytin B and demonstrate unequivocally that it and the related alcohol are not composed of two ether bridges as originally formulated, but share the structural features depicted as **2**.




**1** **2a**, R=H (sclerophytin A)
**b**, R=Ac (sclerophytin B)

The structural connectivity in **2b** can be derived from careful examination of the $^1$H, $^{13}$C/DEPT, DQF−COSY, HMQC, and HMBC data obtained in $CDCl_3$ solution (Table 1).[4] These data reveal a total of 36 protons and 22 carbons instead of the $C_{22}H_{34}O_4$ formulation earlier advanced. Of the correct grand total, 34 protons are directly attached to carbon (seven CH, six $CH_2$, five $CH_3$, with the balance comprised of four quaternary carbons), and two "exchangeable" protons that lack correlations in the HMQC spectrum and are therefore necessarily bonded to oxygen. In $CDCl_3$ solution, these two protons show chemical exchange with the $H_2O$ resonance ($\delta_H$ 1.57 s) in the NOESY (exchange correlations in-phase with the diagonal) and NOED (cosaturation upon preirradiation of $H_2O$ resonance) spectra. The infrared spectrum recorded on an extensively dried sample of authentic sclerophytin B exhibited strong hydroxyl absorption at 3500−3300 cm$^{-1}$.

• The following structural fragments are immediately obvious from diagnostic $^1$H and $^{13}$C shifts and multiplicities in conjunction with the connectivities apparent from the DQF−COSY and HMBC data:

• one exocyclic methylene group ($\delta_H$ 4.65 dd, 4.62 dd; $\delta_C$ 147.9 s, 109.3 t, both $^1J_{CH}$ = 155 Hz)

• one isopropyl group ($\delta_H$ 1.73 dqq, 0.96 d, 0.78 d; $\delta_C$ 29.0 d, 21.9 q, 15.6 q)

• one secondary acetate group ($\delta_H$ 5.63 m, 2.08 s; $\delta_C$ 171.9 s, 85.1 d, 21.5 q)

• two tertiary hydroxyl groups ($\delta_H$ 2.30 s, 0.97 s; $\delta_C$ 75.9

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(4) These data were acquired on Varian Unity-400 and UnityPlus-500 systems, using a 400 MHz $^1$H[$^{15}$N−$^{13}$C] Indirect-Detection probe and a 500 MHz $^1$H[$^{13}$C, $^{15}$N] Triple-Resonance PFG probe, respectively.

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**Table 1.** $^1$H and $^{13}$C NMR Data for Sclerophytin B (400 MHz, $CDCl_3$, 28 °C)[a]

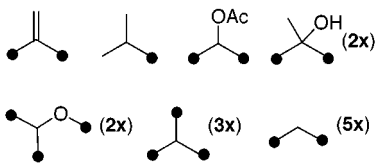
| position | $^1$H NMR data (from high-resolution 1D, DQF−COSY, and selected NOED spectra) $\delta_H$ | $J_{HH}$ [Hz] | $^1$H,$^1$H through-bond correlations (from DQF−COSY)[b] | $^{13}$C shifts (assignments from HMQC and HMBC): $\delta_C$ ($^1J_{CH}$) | $^1$H,$^{13}$C long-range correlations (from 60 and 80 ms HMBC) |
|---|---|---|---|---|---|
| 1*β* | 2.11 dd | 11, 7.5 | 10*β*, 14α | 45.5 d (130) | C-9, C-10, C-14, C-17 |
| 2α | 3.69 s | – | **3*β*-OH** | 90.5 d (**150**) | C-1, C-3, C-9, C-10, C-14, C-18 |
| 3 | – | – | – | 74.9 s (- -) | – |
| 3*β*-**OH** | 0.97 s | – | **2**α | – | C-2, C-3, C-4 |
| 4α | 2.10 m[c] | – | 4*β* | 39.8 t (130) | C-3,[e] C-5, C-6[e] |
| 4*β* | 1.69 m[c] | – | 4α, 5α | 39.8 t (125) | C-2, C-3, C-5, C-6, C-18 |
| 5α | 1.39 m[c] | – | 4*β*, 5*β*, 6α | 28.1 t (125) | C-3, C-4, C-6, C-7 |
| 5*β* | 2.13 m[c] | – | 5α, 6α | 28.1 t (125) | C-3,[e] C-4, C-6[e] |
| 6α | 5.63 m[c] | 5 | 5α, 5*β* | 85.1 d (**145**) | C-4, C-5, C-7, C-19, O**CO**$CH_3$ |
| 7 | – | – | – | 75.9 s (−) | – |
| 7α-**OH** | 2.30 s | – | – | – | C-6, C-7, C-8, C-19 |
| 8α | 1.76 dd | 14.5, 3.5 | 8*β*, 9α | 45.4 t (125) | C-7, C-19 |
| 8*β* | 2.26 dd | 14.5, 11 | 8α, 9α | 45.4 t (125) | C-9, C-10 |
| 9α | 4.13 ddd | 11, 7, 3.5 | 8α, 8*β*,10*β* | 78.0 (**155**) | C-2, C-10, C-11 |
| 10*β* | 3.02 dd | 7.5, 7 | 1*β*, 9α, **12*β***, **20*Z*** | 53.2 d (130) | C-1/8,[f] C-9, C-11, C-12, C-14, C-20 |
| 11 | – | – | – | 147.9 s (−) | – |
| 12α | 2.04 m | – | 12*β*, **20*E***, **20*Z*** | 31.6 t (125) | – |
| 12*β* | 2.25m | – | **10***β*, 12α, 13α, 13*β* | 31.6 t (130) | C-11, C-13, C-20 |
| 13α | 1.70 m | – | 12α, 12*β*, 13*β*, 14α[d] | 24.8 t (125) | C-11, C-12 |
| 13*β* | 1.00 dddd | 13, 13, 13, 3 | 12α, 12*β*, 13α, 14α | 24.8 t (125) | C-12, C-14 |
| 14α | 1.30 m | – | 1*β*, 13α/17,[d] 13[b] | 43.6 d (125) | C-12 |
| 15 | 0.78 d (3H) | 7 | 17 | 15.6 q (125) | C-14, C-16, C-17 |
| 16 | 0.96 d (3H) | 7 | 17 | 21.9 q (125) | C-14, C-15, C-17 |
| 17 | 1.73 dqq | 2,7,7 | 14α,[d] 15, 16 | 29.0 d (120) | C-1, C-13, C-14, C-15, C-16 |
| 18 | 1.14 s (3H) | – | – | 30.3 q (125) | C-2, C-3, C-4, **C-5** |
| 19 | 1.23 s (3H) | – | – | 23.7 q (125) | C-6, C-7, C-8 |
| 20*E* | 4.65 dd | 2.5, 1.5 | **12**α, 20*Z* | 109.3 t (**155**) | **C-9**, C-10, C-11, C-12 |
| 20*Z* | 4.62 dd | 2.5, 1 | **10***β*, **12**α, 20*E* | 109.3 t (**155**) | **C-9**, C-10, C-11, C-12 |
| OCO**CH**$_3$ | 2.08 s (3H) | – | – | 21.5 q (130) | O**CO**$CH_3$ |
| O**CO**$CH_3$ | – | – | – | 171.9 s (- -) | – |

[a] HMQC, HMBD, and NOESY data obtained at 500 MHz. [b] Boldface entries indicate long-range correlations ($^nJ_{HH}$ with $n > 3$). [c] H-4α/*β*, H-5α/*β* and H-6α are higher-order multiplets due to near-coincidence of H-4α and H-5*β*. [d] Unresolved correlations of H-14α/13α and/orH-14α/H17. [e] Unresolved correlations of C-3 and C-6 with H-4α and/or H5*β*. [f] Unresolved correlation to C-1 and/or C-8.

s, 74.9 s), each of which is situated geminally to a tertiary methyl group ($\delta_H$ 1.23 s, 1.14 s; $\delta_C$ 30.3 q, 23.7 q)

• two methines that are each connected to a heteroatom, presumably oxygen, as judged from the $^{13}$C chemical shifts ($\delta_H$ 3.69 s and $\delta_C$ 90.5 d with $^1J_{CH}$ = 150 Hz; $\delta_H$ 4.13 s and $\delta_C$ 78.0 d with $^1J_{CH}$ = 155 Hz).

On the basis of their chemical shifts and one-bond $^1$H,$^{13}$C coupling constants, the remaining $^1$H and $^{13}$C resonances represent three methine and five methylene fragments which are purely aliphatic ($^1J_{CH}$ = 120−130 Hz). Therefore, the structure of **2b** has to be assembled from the following fragments:




Further examination of the DQF−COSY and HMBC data allows unambiguous construction of the remaining connectivities between these fragments. In this process, the formulation of an ether bridge (but not two) between the two downfield methine fragments is supported by three-bond correlations via the ether oxygen in the HMBC spectrum ($\delta_H$ 3.69 s with $\delta_C$ 78.0 d, and $\delta_H$ 4.13 dd with $\delta_C$ 90.5 d). Similar examination of the $^1$H, DQF−COSY, HMQC, and HMBC data obtained in DMSO-$d_6$ (Table 2) is facilitated by the fact that the compound has an entirely first-order $^1$H NMR spectrum in this solvent, and leads to the identical conclusion regarding the constitution of the molecule.

The NMR-derived molecular formula of **2b** is $C_{22}H_{36}O_5$ (MW = 380), in agreement with the following mass spectroscopy data. The CI($CH_4$) mass spectrum showed a base peak at *m*/*z* 321 (100%), $[M + H - HOAc]^+$ in addition to weaker ions at *m*/*z* 363 (40%), $[M + H - H_2O]^+$; 379 (20%), $[M + H - H_2]^+$; and 381 (10%), $[M + H]^+$. LC-MS with ESI-TOF detection showed a single chromatographic component which yielded four significant ions at *m*/*z* 783 (13%), $[2M + Na]^+$; 444 (12%), $[M + Na + CH_3CN]^+$; 403 (15%), $[M + Na]^+$; and 321 (100%), $[M + H - HOAc]^+$. High-resolution peak-matching of these ions, using

**Table 2.** $^1$H and $^{13}$C NMR Data for Sclerophytin B (500 MHz, DMSO-$d_6$, 25 °C)

| position | $^1$H NMR data (from high-resolution 1D and DQF−COSY) $\delta_H$ | $J_{HH}$ [Hz] | $^1$H,$^1$H through-bond correlations (from DQF−COSY)[a] | $^{13}$C shifts (from HMQC and HMBC): $\delta_C$ | $^1$H,$^{13}$C long-range correlations (from 60 ms HMBC) | $^1$H,$^1$H through-space correlations (from NOESY)[b] |
|---|---|---|---|---|---|---|
| 1*β* | 2.14 dd | 11, 7.5 | 2α, 10*β*, 14α | 44 | C-3, C-9, C-10, C-14, C-17 | 2α, 3*β*-OH, 10*β*, **13***β*, 14α, 15, 17, 18 |
| 2α | 3.50 s | – | 1*β*, **3*β*-OH** | 90.5 | C-3, C-9, C-10, C-14, C-18 | 1*β*, 4α, **9**α, 14, 17, **18** |
| 3 | – | – | – | 72.5 (HMBC) | – | – |
| 3*β*-**OH** | 4.38 s | – | **2**α, **18** | – | C-2, C-3, C-4 | 1*β*, 4*β*, **5***β*, **10***β*, 18 |
| 4α | 1.84 dd | 14,11 | 4*β*, 5α, 5*β* | 39 | C-5, C-6 | 2α, 4*β*, 6α |
| 4*β* | 1.50 dd | 14, 8.5 | 4α, 5α, 5*β* | 39 | C-2, C-3, C-5, C-6, C-18 | 3*β*-OH, 4α, 5α, 18 |
| 5α | 1.10 m | – | 4α, 4*β*, 5*β*, 6α | 28 | C-3, C-4, C-6 | 4*β*, 5*β*, 6α |
| 5*β* | 2.03 ddd | 16, 11, 6.5 | 4α, 4*β* 5α, 6α | 28 | C-7 | **3*β*-OH**, 5α, **8***β* |
| 6α | 5.46 d | 6.5 | 5α, 5*β* | 92.5 | C-4, C-5, C-7, C-19, O**CO**$CH_3$ | 4α, 5α, 7α−OH, **9**α, 19, Ac |
| 7 | – | – | – | 73.5 (HMBC) | – | – |
| 7α-**OH** | 4.29 s | – | **8***β* | – | C-6, C-7, C-8, C-19 | 6α, **8**α, **9**α, 19, Ac |
| 8α | 1.44 dd | 14.5, 3.5 | 8*β*, 9α | 45 | C-6, C-7, C-19 | 7α-OH, 8*β*, 9α, 10, 20*Z* |
| 8*β* | 2.27 dd | 14.5, 11 | **7**α-**OH**, 8α, 9α | 45 | C-9, C-10 | **5***β*, 8α, 10*β*, 19 |
| 9α | 3.92 ddd | 11, 7, 3.5 | 8α, 8*β*,10*β*, **12***β* | 77.5 | – | **2**α, **6**α, 7α-OH, 8α, 10*β*, **12**α, **14**α, 20*Z* |
| 10*β* | 2.92 dd | 7.5, 7 | 1*β*, 9α | 52 | C-8, C-9, C-11, C-12, C-14, C-20 | 1*β*, **3*β*-OH**, 8*β*, 9α, 20*Z* |
| 11 | – | – | – | 148 (HMBC) | – | – |
| 12α | 1.95 m | – | 12*β*, 13α, 13*β* | 31 | C-11 | **9**α, 12*β*, **14**α |
| 12*β* | 2.22 dm | 13.5 | **9**α, 12α, 13α, 13*β* | 31 | C-14 | 12α, 13α, 13*β*, 20*E* |
| 13α | 1.66 dm | 12.5 | 12α, 12*β*, 13*β*, 14α | 24 | – | 12*β*, 13*β*, 14α, 16 |
| 13*β* | 0.90 m | – | 12α, 12*β*, 13α, 14α | 24 | – | **1***β*, 12*β*, 13α, 15 |
| 14α | 1.14 m | –- | 1*β*, 13α, 13*β*, 17 | 43 | – | 1*β*, 2α, **9**α, **12**α, 13α, 16, 17 |
| 15 | 0.75 d (3H) | 7 | 17 | 15 | C-14, C-16, C-17 | 1*β*, 13*β*, 16, 17, 18 |
| 16 | 0.93 d(3H) | 7 | 17 | 21.5 | C-14, C-15, C-17 | 13α, 14α, 15, 17 |
| 17 | 1.74 dqq | 2,7,7 | 14α, 15, 16 | 28 | C-13, C-14, C-15, C-16 | 1*β*, 2α, 14α, 15, 16, 18 |
| 18 | 0.99 s (3H) | – | **3*β*-OH** | 29 | C-2, C-3, C-4 | 1*β*, **2**α, 3*β*-OH, 4*β*, 15, 17 |
| 19 | 1.09 s (3H) | – | – | 23.5 | C-6, C-7, C-8 | 6α, 7α-OH, **8**α, **8***β* |
| 20*E* | 4.63 dd | 2.5, 1.5 | **12**α, 20*Z* | 108.5 | C-10, C-12 | 12*β*, 20*Z* |
| 20*Z* | 4.56 br s | – | **12**α, 20*E* | 108.5 | C-10, C-12 | 8α, 9α, 10*β*, 20*E* |
| OCO**CH**$_3$ | 1.95 s (3H) | – | – | 21 | O**CO**$CH_3$ | 6α, 7α-OH |
| O**CO**$CH_3$ | – | – | – | 170.5 (HMBC) | – | – |

[a] Boldface entries indicate long-range correlations ($^nJ_{HH}$ with $n > 3$). [b] Boldface entries indicate correlations which are particularly important for assignment of relative stereochemistry.

a linear calibration based on caffeine ($C_8H_{10}N_4O_2$, $MH^+ = 195.0882$) and erythromycin ($C_{37}H_{67}N_1O_{13}$, $MH^+ = 734.4690$) standards, showed reasonable agreement with the theoretical masses: 783.5025 (calcd for $[C_{44}H_{72}O_{10} + Na]^+$: 783.50235), 444.2700 (calcd for $[C_{22}H_{36}O_5 + Na + CH_3CN]^+$: 444.27262), 403.2455 (calcd for $[C_{22}H_{36}O_5 + Na]^+$: 403.24608), 321.2396 (calcd for $[C_{22}H_{36}O_5 + H - CH_3COOH]^+$: 321.24297).

Stereochemical assignments for **2b** can be derived from 500 MHz NOESY data acquired in DMSO-$d_6$, as compiled in Table 2. 400 MHz NOESY and NOED data acquired in $CDCl_3$ are more difficult to interpret due to resonance overlap, but are consistent with the 500 MHz DMSO-$d_6$ data. The presence of H-12α/H-14α, H-12α/H-9α, and H-14α/H-9α NOE's indicates that these three protons are located on the same face of the molecule. The presence of these NOE's has several implications. First, it requires axial orientation of H-12α and H-14α in the six-membered ring. This is in agreement with the H-12*β*/H-20*E*, H-12*β*/H-13α, and H-12*β*/H-13*β* NOE's, which indicate the situation involving H-12*β* in the six-membered ring to be equatorial and gauche to both H-13α and H-13*β*. Furthermore, the presence of a H-12α/H-9α NOE requires not only α-orientation of H-9, but at the same time *β*-orientation of H-10. The existence of a H-13α/H-14α NOE agrees with H-13α being equatorial and gauche to H-14α, while a H-13*β*/H-1*β* NOE indicates *β*-orientation of H-1, syn to an axial H-13*β*. A strong H-1*β*/H-10*β* NOE, although not conclusive by itself, is consistent with this assignment. The presence of H-2α/H-9α and H-10*β*/3*β*-OH NOE's defines relative stereochemistry at C-2 and C-3. These NOE's require H-2 to be located on the same face of the molecule as H-9, since *β*-orientation of H-2 would preclude both of these NOE's entirely. A strong

H-18/H-2α NOE, although not conclusive by itself, is consistent with the C-3 stereochemical assignment.

Assignment of relative stereochemistry at C-6 and C-7 is primarily based on the presence of H-9α/H-6α and H-9α/7α-OH NOE's. In addition, NOE's observed between H-19 and both H-8α and H-8*β*, but between 7α-OH and H-8α only, further support the C-7 stereochemical assignment. The relative orientation of the H-8 protons is defined by strong H-9α/H-8α and H-10*β*/H-8*β* NOE's. Several further supportive NOE's that are internally consistent with these stereochemical assignments include H-2α/H-4α, 3*β*-OH/H-4*β*, H-6α/H-4α, H-6α/H-5α, 3*β*-OH/H-5*β*, H-8*β*/H-5*β*, and H-10*β*/H-5*β*.

On the basis of the above observations, the revised structures **2a** and **2b** are formulated for sclerophytins A and B. It is entirely possible that other closely related diterpenoids have been misformulated. The methyl ether of sclerophytin F (**2**, R = Me) has previously been isolated and characterized by X-ray crystallography.[5] The corresponding ethyl ether (**2**, R = Et), named patagonicol, has likewise been subjected to diffraction analysis.[6] On this basis, the associated structural assignments and those for eunicellin dibromide,[7] acetoxycladiellin,[8] caledoniol,[9] and sclerophytin C[10] can be considered secure. The spectral data for **2b** are very similar to the $^{1}H$ and $^{13}C$ NMR features reported for a 6-acetoxycladiellene-3,7-diol exhibiting $[\alpha]^{26}_{D}$ +38.[11] However, the structure proposed has the (3*R*,6*S*,7*R*) configuration according to the abstract and discussion, but the structural formula shown is the (3*R*,6*S*,7*S*) diastereomer. The claim is made that the spectral properties compare to those of sclerophytin F (this is not the case) and that $LiAlH_4$ reduction produced sclerophytin F (no supporting data provided). Alam reported the isolation of scelophytin F.[10] His structural assignment is identical to that now proposed for sclerophytin A. Examination of his spectral data indicate that this formulation is also incorrect, since the chemical shift of C-3 clearly indicates that it is acylated, albeit not with an acetate as sclerophytin E is.

These issues are presently under evaluation and will be expounded upon in a full paper.

**Acknowledgment.** We thank Prof. K. Euler (University of Houston) for providing us with a sample of natural sclerophytin B, and Dr. Jeffrey Dage (Aventis Pharmaceuticals) for providing mass spectroscopy data.

**Supporting Information Available:** Copies of $^{1}H$, $^{13}C$, and mass spectra recorded for **2b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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