Using Scalarane Sesterterpenes To Examine a Sponge Taxonomic Anomaly

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A parallel study was conducted on two Indo-Pacific foliose sponges. The first specimen contains 3-hydroxy-20,22-dimethyl-20-deoxoscalarin (**2**), while the second contains 3-oxo-20,22-dimethyl-20-dioxoscalarin 8 (**3**). The physical properties as well as X-ray results confirming the structure and stereochemical features of these compounds are presented first. The difficulty we encountered in the taxonomic identification of these species is also discussed. One of our specimens is identical to material considered by different taxonomists as either *Phyllospongia vermicularis* or *Dysidea vermicularis.* The other is identified as *Carteriospongia* sp. We outline that the parallel chemistry of these two specimens suggests that they are closely related taxonomically.

Introduction

The collection and chemical study of fan-shaped or foliose sponges of the family Spongiidae (order Dictyoceratida) is not always straightforward. Careful scrutiny is required to differentiate amongst genera including *Phyllospongia, Carteriospongia,* and *Strepsichordaia.* Likewise, in our experience, distinguishing some members of the former genus from *Dysidea herbacea* (family Dysideidae) can be problematic. Yet, each of these spongiid genera are common throughout the Indo-Pacific, and many of their species have been thoroughly described taxonomically.[1] Central among their metabolites are alkylated scalarane sesterterpenes.[2,3] Such compounds, often called homoscalaranes, can be further divided into four frameworks consisting of two monoalkylated (C_{26}) and two bis-alkylated (C_{27}) forms.[4] The 20-homosesterterpenes are abundant in the chemistry of both *Lendenfeldia dendyi*[5] *(Phyllospongia dendyi,* jr. synonym)[1a] and *Lendenfeldia frondosa*,[4,6] while 20,22-bishomosesterterpenes have been repeatedly reported from *Phyllospongia*,[7] *Carteriospongia*,[8] and *Strepsichordaia*.[9] Each of these genera are from the Spongiidae family (order Dictyoceratida). Illustrating the continuing taxonomic confusion associated with this group are some recent chemistry publications that treat *Phyllospongia* and *Carteriospongia* as being synonymous.[10,11] It has also been noted that many genera of the order Dictyoceratida may appear to be superficially similar, which can perpetuate errors.[12] As another caveat, 20,-22-bishomosesterterpenes have also been reported from *Dysidea* sponges,[13,14] which are placed in the family Dysideidae.[12] Conflicting observations of this kind prompted our study of two apparently unrelated Indo-Pacific sponges preliminarily identified as being of the *Dysidea* and *Carteriospongia* genera, respectively. Each organism yielded closely related 20,22-bishomosesterterpenes, even though they were obtained on separate expeditions from quite different locales. In this paper, we will first describe the characterization of the sesterterpenes and then comment on the taxonomic properties of their source organisms.

Results and Discussion

The first sponge examined in this study (coll. no. 94028), obtained in the Solomon Islands, was initially identified as *Dysidea vermicularis*. It was quite different in appearance than most of the common foliose sponges we have encountered as it consisted of thin, slender fronds as shown in Figure 1. An uneventful purification of the crude extract yielded a colorless solid, designated here as compound **2**, in which seven methyl groups were observable in the ^{13}C NMR spectrum. The environment of these methyls could be further specified from the ^{1}H NMR data as four singlets, one doublet, one triplet ascribed to an ethyl group, and one acetate. A substructural search of these features in our personal database[15] revealed several 20-homoscalarans having many of these features. Other compounds containing the 20,22-bishomoscalarane framework were pinpointed in a second substructure search using the isolated ethyl group observed by $^{1}H-^{1}H$ COSY NMR. Additional information was provided by the ^{13}C APT NMR count of $C_{29}H_{44}$ made up of six quaternary carbons, nine methines, seven methylenes, and seven methyls. It was soon apparent that the ^{13}C NMR properties of **2** were quite parallel to those of 12-deacetyl-20-methyl-12-*epi*-20-deoxoscalarin (**1**)[16] as can be seen in Table 1. These data indicated an analogous substitution pattern within their BCDE rings especially for the acetate group, the trisubstituted double bond, and the hemiacetal functionality. The unusually low-field ^{13}C NMR signal at δ 81.0 (d) revealed an additional secondary oxygenated carbon in **2**, not present in **1**. A different discrepancy, not immediately resolved, was that the NMR-derived formula of $C_{29}H_{44}O_5H_2$ did not agree with the formula of $C_{29}H_{44}O_4$ obtained from the highest EIMS peak at *m/z* 456.3249 (Δ 1.0 mmu of calcd). In hindsight, the facile dehydration commonplace for a scalarin hemiac-

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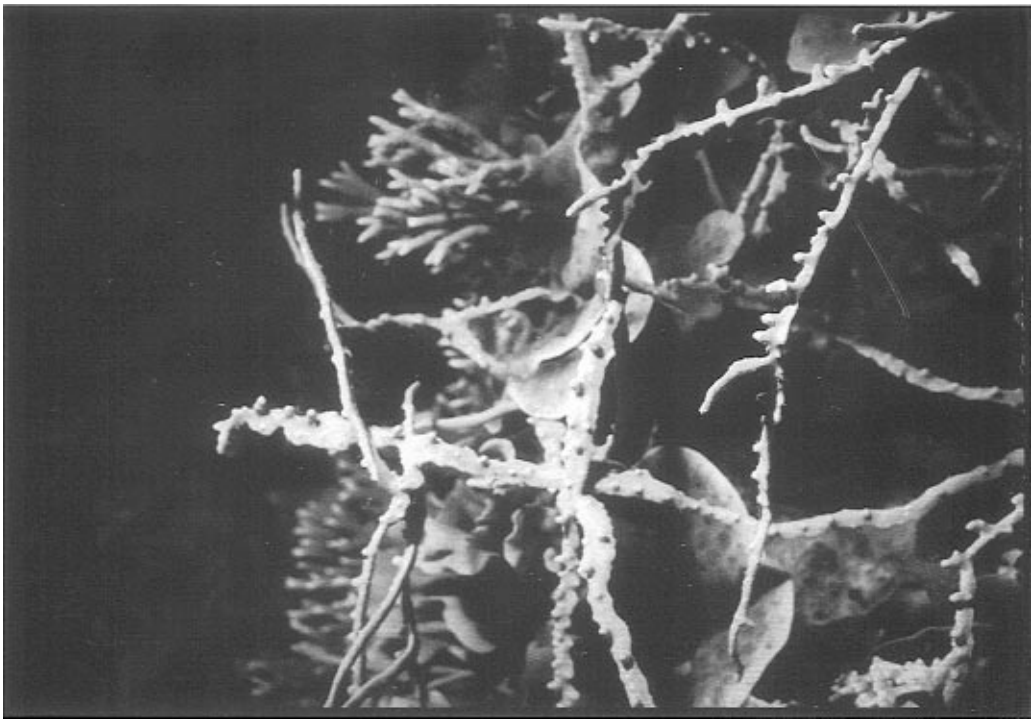
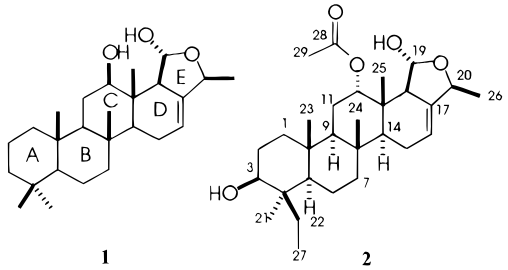


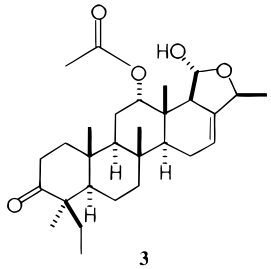
Figure 1. Underwater photograph of coll. no. 94028.

etate residue[16,17] easily explained this difference and suggested the proper MF was $C_{29}H_{46}O_5$.



1

2



3

The NMR assignments of **2** shown in Table 1 were derived from HMQC[18] and HMBC[19] results, and these data were used to assign several stereochemical features. The α-OAc in **2** was established by comparing the NMR *J*'s and shift at H12 (δ 4.90) of **2** to that of scalarin (H12 δ 4.69).[17] Likewise, a C3 β-oxygen was evident from the large ^{1}H *J*'s to H3 (dd = 12.0, 3.5 Hz) plus the 2D NMR correlations (Table 1), establishing the C2−C3(O−)−C4−(C21−C22)−C5 array. Assignment of the C4 ethyl group stereochemistry was also based on analogy to prior models. Both β[9,10,11,20] and α[6] C4 ethyl groups have been reported in the past for 20,22-bishomoscalarins. When no substituent is present at C3 the methylene carbon shift of the C4 scalarin ethyl group is diagnostic: δ_{axial} = 24.5, δ_{equat} = 36.3.[20] The slight upfield shift of C22 (δ 22.4, t) in **2** was consistent with an axial ethyl group slightly shielded by the C3 equatorial oxygen substituent.[21] Repurification of **2** in preparation for an NOE study yielded crystalline material that was immediately subjected to single-crystal X-ray analysis. The computer-generated drawing of the X-ray results appears in Figure 2 and verifies that the highest MS *m/z* peak observed was an $[M - H_2O]^+$. Each of the six-membered rings of **2** are *trans*-fused, and each adopts a regular chair conformation. All of the elements of stereochemistry assigned from the NMR data were also fully confirmed by the X-ray results. Finally, investigation of the bioactivity of **2** revealed a mild response as a GI_{50} = 3.5 μM was observed against the T-47D breast cancer cells, while no activity was registered against leukemia cells in the NCI's 60-cell panel.[22]

The second dictyoceratid sponge (coll. no. 94515), obtained in Indonesia, was being examined in parallel with the above work. It was initially identified as *Carteriospongia* sp.[1] owing to its fanlike shape plus the external and skeletal morphology characteristic of this genus, as shown in Figure 3. As above, one major metabolite was present in the crude oil, and a routine purification yielded **3** as a colorless oil. The resemblance of the ^{1}H and ^{13}C NMR spectral data between **2** and **3** was startling as can be seen in Table 1. A ^{13}C NMR APT formula of $C_{29}H_{43}$ was initially deduced for **3**, and it was expanded to $C_{29}H_{43}O_5H$ on the basis of the presence of five oxygenated functionalities that included a ketone, an acetate, and a hemiacetal. Analogous to the situation above, the FABMS showed a highest *m/z* 455.3157 for $C_{29}H_{43}O_4$ (Δ 0.4 mmu of calcd). This suggested an $[M - H_2O]^+$ further consistent with the hemiacetal moiety. Another immediately obvious parallel between **2** and **3** was the nearly identical ^{13}C NMR shifts of their seven methyl groups. Also, δ 26 for the methylene C22 carbon was similar to that of **2**. Consequently, the location and stereochemistry of all other oxygen substituents and double bonds were proposed as identical between **2** and **3**. It should be noted that the NMR assignments of **3** were confirmed

Table 1. NMR Data ($CDCl_3$) of **1** and at 500/125 MHz of **2** and **3**

	1	**2**			**3**		
atom no.	^{13}C	^{13}C	^1H (δ, mult, *J*, Hz)	HMBC	^{13}C	^1H (δ, mult, *J*, Hz)	HMBC
1	39.9	38.8 t	1.6 m		40.2 t	1.88 m,	H2, H23
1′			0.76 m			1.18 dt, 14.5, 14.5, 3.5	
2	18.1[a]	22.9 t	1.63 m	H3	34.9 t	2.65 dt, 14.5, 14.5, 5.5	
2′			1.46 m			2.21 dt, 14.5, 3.5, 3.0	
3	41.6[b]	81.0 d	3.20 dd, 12, 3.5	H21	215.7 s		H2, H21, H22
4	33.3	41.4 s		H21, H27	52.7 s		H6
5	56.5	57.1 d	1.3−1.5 m	H21, H23	58.7 d	1.28 dd, 12.5, 3.0	H21, H23
6	18.6[a]	18.8 t	1.6 m	H5	18.8 t	1.61 dq, 12.5, 12.5, 12.5, 3.5	
6′			1.58 m			1.52 brd, 12.5	
7	42.1[b]	41.8 t	1.67 m	H24	41.5t	1.78 dt, 12.5, 3.5, 3.5	H24
7′			0.92 m			1.06 dt, 12.5, 12.5, 3	
8	37.4	37.6 s		H24	37.7 s		H9, H24
9	58.9	52.9 d	1.20 dd, 13, 2.5	H12, H23, H24	52.7 d	1.35 brd, 12.5	H10, H24
10	37.4	37.1 s		H23	36.7 s		H6, H23
11	25.9	26.8 t	1.63 m		22.9 t	1.85 brt, 14.5, 14.5	
11′			1.53 m			1.7, brd, 14.5	
12	81.2	74.8 d	4.90 t, 3	H25	74.4 d	4.96 t, 3	H25
13	39.9	36.7 s		H18, H19	37.1 s		H25
14	53.2	50.2 d	1.54 m	H12, H16, H24, H25	50.0 d	1.62 d, 11	H24, H25
15	22.0	22.2 t	2.20 m		23.1 t	2.14 dq, 17, 3, 3, 3	
15′			1.86 m			1.93 m	
16	116.4	114.3 d	5.28 t, 3	H15, H18	114.3 d	5.34 t, 3	
17	140.2	141.5 s		H18, H26	141.3 s		H26
18	61.4	54.9 d	2.77 bs	H16, H25	54.8 d	2.84 bs	H14, H25
19	97.8	96.7 d	5.15 d, 3.5	H18	96.7 d	5.21 d, 3	
20	74.5	73.8 d	4.47 bs	H19	73.9 d	4.62 bs	H19, H26
Me21	33.3	23.4 q	0.96 s		20.4 q	1.05 s	
22	21.3	22.4 t	1.86 m	H21, H27	26.0 t	1.86 dq, 12, 7	H21, H27
22′			1.35 dq, 12, 7			1.39 dq, 12, 7	
Me23	16.6[c]	16.5 q	0.79 s	H1	16.5 q	1.13 s	
Me24	17.0[c]	15.6 q	0.86 s		15.9 q	0.97 s	H14
Me25	8.7	14.9 q	0.71 s	H12, H18	14.8 q	0.79 s	
Me26	19.3	17.7 q	1.20 d, 5.5		17.6 q	1.26 d, 6	
Me27		11.5 q	0.88 t, 7.5		9.1 q	0.68 t, 7.5	H22
Me28		171.0 s		H12, H29	170.9 s		H29
Me29		21.5 q	2.04 s		21.4 q	2.06 s	

[a−c] Values with the same superscript can be interchanged.

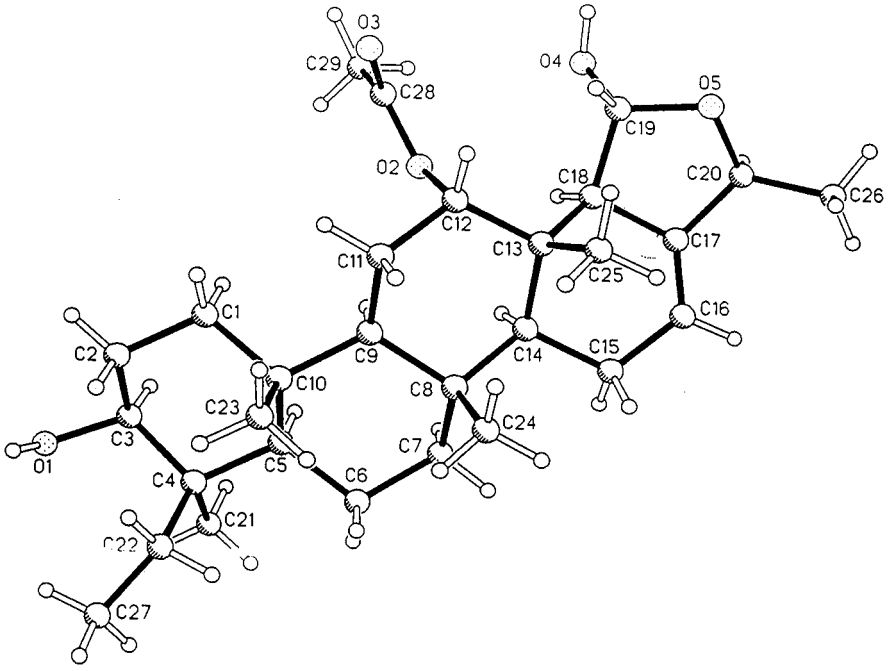


Figure 2. Computer-generated X-ray structure of **2**.

by the use of HMBC results, and the correlations from the ketone carbon (δ 215.7) to protons H2, H21, and H22 supported its assignment at C3. The observed downfield shift for both C2 and C4 of ~9 ppm compared to **2** has precedent in the data reported for penasterone.[23] After completion of the structure elucidation of **3**, we noticed that it had been reported, without supporting physical or taxonomic properties, and the source was stated to be *D. herbacea*.[14]

The chemical versus taxonomic results we obtained above required further analysis. The closely related 20,-22-bishomosesterterpenes **2** and **3** were apparently

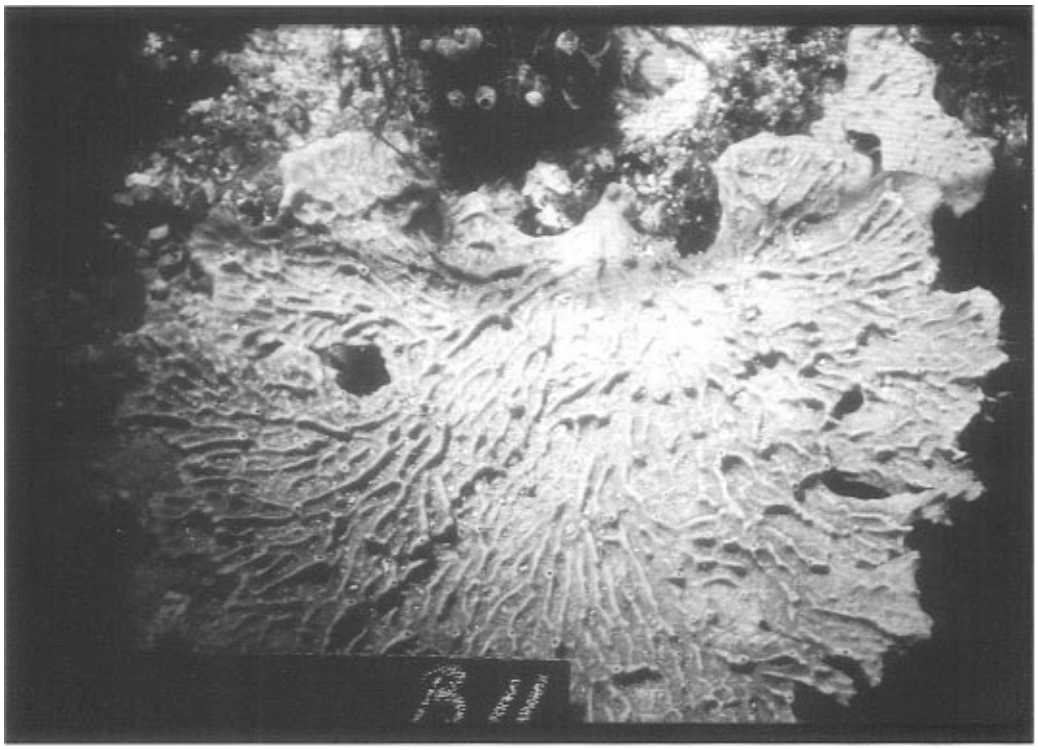


Figure 3. Underwater photograph of coll. no. 94515.

obtained from different families of sponges.[24] Either there is ambiguity in the properties used in the sponge characterization or these results may constitute an anomaly in the relationships expected between sesterterpene chemistry and sponge taxonomy.[25] The basis for our taxonomic identification (see Experimental Section) was next carefully reexamined.

The situation with coll. no. 94028 is the most complex because of the uncertainty about the taxonomic designation for the species *vermicularis*. Dictyoceratid and dendroceratid sponges are characterized by the construction and arrangement of spongin fibers and the morphology of their choanocyte chambers.[1,24] Dictyoceratids (*i.e.*, Spongiidae and Thorectidae) have diplodal choanocyte chambers,[1] which are spherical and small in size[24] (34−42 μm in diameter, 20 600−38 800 μm^3 in volume). Dendroceratids (*i.e.*, Dysideidae and Aplysillidae) have eurypylous choanocyte chambers,[1] which are oval and larger in size[24] (50−105 × 78−175 mm in diameter; 206 200−750 200 μm^3 in volume). The original descriptions of *Phyllospongia vermicularis* by Lendenfeld[26] matches many of the properties of our sample so we conclude that they are the same. However, more recently, Bergquist[1] concluded, after the examination of recollected material, that "(*vermicularis*) is not a *Phyllospongia* but a member of the Family Dysideidae." In part, the confusion arises because the skeleton of *vermicularis* described as fibroreticulate, profusely cored with sand, resembles that of *Dysidea*. However, at this point, no clear case can be made about its genus placement because the choanocyte chamber morphology of *vermicularis* is unknown. On the other hand, the presence of **2** in this sponge certainly suggests a strong relationship to the *Phyllospongia*−*Carteriospongia* group. Additional details about the ultrastructural properties of our voucher appear in the Experimental Section. Fortunately, the examination of the second sample, coll. no. 94515, was rather straightforward. The details in the Experimental Section provide the justification of its assignment as possibly an undescribed species of *Carteriospongia*.

Conclusions

We have examined two morphologically distinct sponge taxa that both contain the same type of 20,22-bishomosesterterpene. This compound class is not widely distributed and might represent an ideal marker for the foliose dictyoceratid sponges of the family Spongiidae. The parallel chemical results described above suggest that the two different sponges examined in this study are closely related. The complete listing of physical properties of these bishomosesterterpenes in Table 1 should make it easy for others to rapidly pinpoint this class of metabolites when making chemical comparisons between sponge taxa. Underway in our lab is a study of the secondary metabolites from a large number of Indo-Pacific foliose dictyoceratid sponges. Our goal is to conduct a parallel examination of their chemistry and biological properties in order to test the possiblility that foliose dictyoceratid sponges are chemically distinct from the other members of the Spongiidae.

Experimental Section

Collection and Identification. The first sponge (coll. no. 94028) was collected in the Solomon Islands at a depth of 40 ft and is shown in Figure 1. The sponge consists of a densely packed mass of thin finger-like projections, 1−2 mm thick and up to 12 cm high. The color alive was gray-lavender, and the smooth surface possesses small round oscules, approximately 1 mm in diameter, distributed on the upper side of branches. The skeleton consists of a rectangular to oval reticulation (meshes 100−600 μm in diameter) of mainly primary

fibers (40−60 μm thick) that are heavily cored with sand. However, toward the interior of the sponge there are a few fibers without sand. The surface is heavily loaded with sand, and the level of skeletal sand incorporation is consistent with the properties of *Dysidea*. However, this species was originally described as *P. vermicularis*.[27] A precise genus assignment for this species requires both the examination and comparison of its choanocyte chambers with those of the main fan or foliose Dictyoceratid genera. Unfortunately, the manner used to preserve the voucher did not allow such an examination to be conducted.

The second sponge (coll. no. 94515), obtained at depths of 20−40 ft from Indonesia, is shown in Figure 3. It was identified as *Carteriospongia* sp. (Spongiidae, Dictyoceratida) with the morphologically closest species being *Carteriospongia contorta*.[1] The specimen was formed by flat, cylindrical branches (1 cm thick) giving the specimen a branched-fan appearance. The color was brownish-red both internally and externally. The surface was profusely ornamented by variously shaped contorted elevations (1−2 mm thick, 2−5 mm high). Small oscules (1−2 mm wide) were observed on the upper side of the fan. The skeleton of this sponge corresponds to that previously described for *Carteriospongia*,[1] with a dense reticulation of predominant primaries (24−40 μm in diameter), irregularly cored with sand, and variously shaped meshes (20−100 μm wide).

Extraction and Isolation. Both sponges were preserved in the field according to our previously outlined methods[27] and then transported to the home laboratory at ambient temperature. Each collection was separately extracted with MeOH (3×), after which the solvent was removed and the resulting oil partitioned between water and CH_2Cl_2. The organic phase was again reduced to an oil, and this was partitioned between hexanes and 10% aqueous MeOH to remove unwanted lipids and steroid components. The MeOH layer was adjusted to 50% aqueous MeOH and extracted with CH_2Cl_2. The CH_2Cl_2 fraction from coll. no. 94028 (0.9 kg, wet) was subjected to chromatography on Sephadex LH-20 (1:1 MeOH:CH_2Cl_2), yielding a fraction (600 mg) that was then passed through silica (2:3 EtOAc:hexanes) to afford a new fraction (227 mg) that after HPLC (ods, 10% aqueous MeOH) gave **2** (5 mg). Similarly, the CH_2Cl_2 partition fraction (1.08 g) was obtained from coll. no. 94515 (0.1 kg, wet). A portion of it (200 mg) was subjected to Sephadex LH-20 chromatography followed by HPLC (ods, 20% aqueous MeOH) to give **3** (5.1 mg).

3-Hydroxy-20,22-dimethyldeoxoscalarin (2): colorless solid; $[\alpha]_D = 51.9°$ (*c* 1.5, CH_2Cl_2); ^1H and ^{13}C NMR in Table 1; LREIMS (70 eV) (*m*/*z*) 456 (100), 428 (15), 381 (20) 256 (10), 203 (20), 146 (38).

Single-Crystal Analysis of 3-Hydroxy-20,22-dimethyl-20-deoxoscalarin (2). A small (0.03 × 0.08 × 0.40 mm[1]) crystal of **2** was used for data collection on a R3m Siemens diffractometer using graphite-monochromated Cu Kα radiation (λ = 1.5418 Å). The crystal belongs to the orthorhombic space group $P2_12_12_1$ with unit cell dimensions of a = 6.285(3) Å, b = 17.728(7) Å, c = 50.63(2) Å. The cell volume is 5641(4) Å^3 with a calculated crystal density of 1.172 g/cm^3, Z = 8, or two molecules per asymmetric unit. Intensities of 4122 diffraction maxima were collected in the range 3° < 2θ < 110° using variable speed (1.5−29°/m) ω-scans. The crystal diffracted weakly, and the completeness of the high-resolution data was less than 20%. Only 1811 out of 4117 independent reflection had $F > 4\sigma(F)$ (44%). Lorentz and polarization but not absorption corrections were applied. Three standard reflections monitored every 97 reflections indicated no significant intensity variation.

The structure was solved by direct methods (SHELX-86).[28] Hydrogen atoms were placed at geometrically calculated sites. The structure was refined by full-matrix least-squares methods on F^2 (SHELX-93)[28,29] using anisotropic thermal parameters for all non-hydrogen atoms and riding hydrogens. The refinement converged to R_1 = 8.4%, wR_2 = 18.6%, GOF = 0.972, and a final difference map revealed no peaks greater than 0.27 e/Å.[1] The final model was judged acceptable in view of the limited high-resolution data and large number of atoms.[30]

3-Keto-20,22-dimethyl-20-deoxoscalarin (3): colorless oil; ^1H and ^{13}C NMR data in Table 1; LRFABMS (*m*/*z*) 471 (5), 455 (20), 411 (7), 395 (100), 161 (15), 135 (24), 119 (30).

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(30) Atomic coordinates, bond distances and angles, and torsional angles for **2** have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from Dr. Olga Kennard, University Chemical Laboratory, 12 Union Road, Cambridge CB2 1EZ, UK.

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