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THE STRUCTURES AND STEREOCHEMISTRY OF CYTOTOXIC SESQUITERPENE QUINONES FROM *DACTYLOSPONGIA ELEGANS*

*Jaime Rodríguez°+, Emilio Quiñoá°+, Ricardo Riguera°, Barbara M. Peters+, Leif M. Abrell+, and Phillip Crews+**

°Departamento de Química Orgánica, Facultad de Química, Universidad de Santiago de Compostela, Santiago 15706, España; +Department of Chemistry and Biochemistry and Institute of Marine Sciences, University of California, Santa Cruz, CA 95064, USA

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Abstract. The cytotoxicity of a crude extract from *Dactylospongia elegans* stimulated a search for the active constituents. The structures and absolute stereochemistry are elucidated for four new, **9**, **11**, **18**, **19**, and thirteen previously described compounds, **3**, **4**, **6a**, **7**, **8**, **10**, **12** - **17**, **21**. These compounds were isolated from collections of *D. elegans* obtained from three different Indo-Pacific regions, Fiji, Papua New Guinea, and Thailand. This species appears to elaborate a broader range of the mixed biogenesis sesquiterpene-hydroquinone (-quinone) metabolites in comparison to those of other sponges or seaweeds. Three compounds, **4**, **9**, and **13**, were potent (IC_{50}'s were less than 1 μg/mL). The quinone ring appears to be essential for this *in vitro* activity.

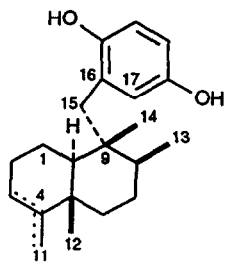
INTRODUCTION

Many terpene-hydroquinone (and -quinone) marine natural products have been described in the literature.[1] An especially notable terpene-hydroquinone family is that headed by avarol (**1**) and arenarol (**2**) but there has been much controversy surrounding some of the biological properties and stereo structures reported for these and related compounds. Unfortunately, a tantalizing report that avarol inhibits replication of the HIV virus[2] has not withstood subsequent scrutiny.[3] Opposite absolute configurations appear in the literature for closely related compounds including: (+) (**1**),[4] (+) (**2**),[5] (-) ilimaquinone (**3**),[6] (+) epi-ilimaquinone (**4**),[7] and (+) isospongiaquinone (**5**).[8] At one time (+) (**1**)[4] and (-) (**3**)[6] were considered to be enantiomeric at C-5/C-8/C-9/C-10, but in 1987 Capon[9] reversed the absolute stereochemistry of (-) **3** placing (+) **1** and (-) **3** in the same 8*S*,9*R* absolute stereochemical series as shown here. Schmitz,[10] building on Capon's conclusions, assumed an 8*S*,9*R* stereochemistry for (+) **2**. This same absolute stereochemistry is present in (+) **5** based on its chemical correlation to (-) **3**,[11] and it may also apply to (+) **4** which occurs as a mixture with (-) **3**.[7] Astonishingly, enantiomeric absolute configurations have been recently proposed for the pair (+) smenospondiol (**6a**)[12] and (+) dictyoceratin A (**6b**)[13] even though both have been isolated from Dictyoceratid sponges; the former is redrawn here to reflect the current correct (-) **3** absolute stereochemistry used as a basis for their proposed stereochemisty.

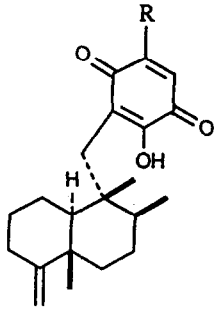
Our interest in the above family of metabolites arose when the crude extract of *Dactylospongia elegans* (collection no. 90169) obtained from Papua New Guinea showed *in vitro* activity (IC_{50} = 5 μg/mL) against P388 cells. Solvent partitioning accompanied by additional assay data indicated that cytotoxins were present. Activity levels of the CCl_4 partition fractions were slightly enhanced and varied from IC_{50}'s = 1-2 μg/mL against three

non-leukemia cell lines which included human breast (A549), human colon (HT-29), or mouse melanoma (B16/F10). Initially the sponge was identified as *Smenospongia* sp. but eventually this was revised to *Dactylospongia*, thus illustrating how these two sponges can be confused in spite of the different appearance of their type specimens and their placement in separate orders (see Table 3).[14]

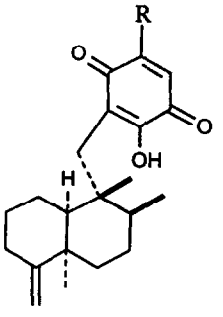
Early in this study a search of our "sponge" database[15] focused attention on publications by Faulkner[16] and of Guyot[12,17,18] reporting members of the avarol-arenarol family. Purification efforts were launched on a cytotoxic active extract and were rapidly expanded to six other collections of *Dactylospongia elegans* housed in our repository and obtained from Indo-Pacific stations in the Fiji Islands or Phuket Island, Thailand. The seventeen compounds we isolated can be divided into new metabolites **9**, **11**, **18**, **19**, and previously reported compounds **3**, **4**, **6a**, **7**,[17] **8**,[18] **10**,[18] **12**,[19] **13** - **16**,[16] **17**,[20] and **21**.[21] Although it was not possible to subject this entire list to follow-up bioassay analysis, compounds **4**, **9**, and **13**, showed cytotoxicity (IC_{50}'s < 1 μg/mL). Their cytotoxic properties and the absolute stereochemistry assigned for these new structures are disclosed below. Comments will also be offered on a fascinating chemotaxonomic pattern that is now emerging for this class of sesquiterpene-hydroquinones (-quinones).



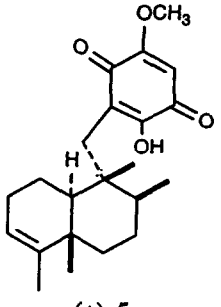
(+) **1** Δ^3
(+) **2** Δ^4



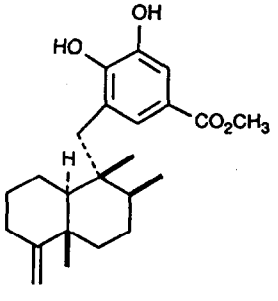
(-) **3** R = OCH_3
7 R = NH_2
8 R = NH-*i*Bu
10 R = $NHCH_2CH_2Ph$



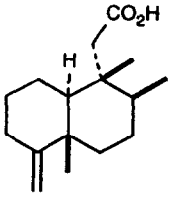
(+) **4** R = OCH_3
(+) **9** R = NH-*i*Bu
(+) **11** R = $NHCH_2CH_2Ph$



(+) ***5***



(+) **6a** smenospondiol
(+) **6b** dictyoceratin A



(-) ***12***

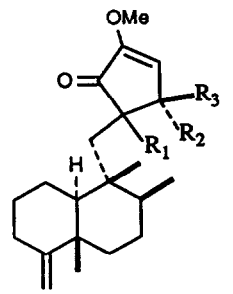
RESULTS AND DISCUSSIONS

A chemotaxonomic view of the *Smenospongia*[12,17,18,21,22] and *Dactylospongia*[16] literature indicated that terpene-quinones ought to be isolated which contained 4,9 friedodrimane (**A, B**) or drimane (**C**) skeletons. The Me ^{13}C NMR shifts accompanying **A - C** (Chart 1) are diagnostic of the equatorial or axial stereochemistry shown and are often used as reliable indicators of stereochemical variations[23] within parallel structural sets. Consequently, such data were initially sought in NMR spectra of crude extract fractions or pure compounds.

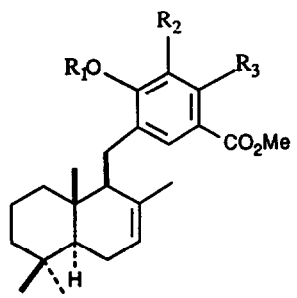
Three metabolites with **B**-type sesquiterpene substructures were isolated from the hexanes and CCl_4 solvent partition fractions of the Papua New Guinea collection no. 90169. The known compound (+) **4** was accompanied by two new metabolites, (+) epi-smenospongiarine (**9**) $C_{26}H_{39}NO_3$ FABMS MH^+ = 414 and (+) epi-smenospongidine (**11**) $C_{29}H_{37}NO_3$ FABMS MH^+ = 448. Both of these latter compounds had the **B** array attached to a quinone ring bearing an -NHR group at C-20. These respective features were assigned from the characteristic ^{13}C NMR C-4/11/12/15 shifts (Table 1) as well as the sensitivity of the quinone ring NMR shifts at C-19/20 to the nature of the C-20 substituent including -OR (δ102/162 in **4**) versus -NHR (96/151 in **7**).[17] The *p*-quinone ring substitution pattern of **9** was easily established using $^2J_{C\text{-}H}$ and $^3J_{C\text{-}H}$ correlations. Proton H-19 correlated to C-17 and C-21; H_2-15 correlated to C-16, C-17 and C-21. All of the ^{13}C NMR shifts of **9** are similar to those of its epimer **8**[18] excepting the values at C-4, C-11 and C-12, and the same was true for the ^{13}C NMR shifts of **11** as compared to those of its epimer **10** and of **3** versus those of its epimer **4** (Table 1).

The investigation conducted on material collected from Fiji (collection no. 89135) included subjecting both CCl_4 and hexanes solvent partition fractions to extensive chromatographic purifications. Seven compounds containing fragment **A**, as recognized from diagnostic ^{13}C NMR shifts, as noted above, were isolated. Six of these, smenospondiol (**6a**), smenospongine (**7**), and dactylospongenones A - D (**13 - 16**), have been previously isolated. The other compound, smenospongic acid (**12**), was identified straightforwardly as substructure **A** (Table 1) plus a CO_2H.[19]

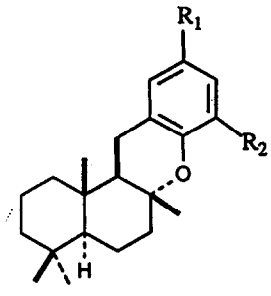
A very different compound, (-) smenodiol (**17**) $C_{23}H_{32}O_4$ (positive ion HREIMS 372.2290, Δ 1.0 mmu of calcd), was isolated from a Thailand collection (no. 88035). The structure was identified by considering several types of NMR



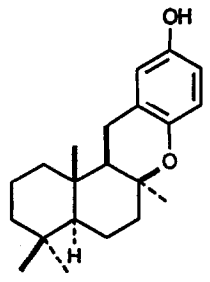
	R_1	R_2	R_3
13	αH	OH	CO_2Me
13a	αH	OAc	CO_2Me
14	βH	CO_2Me	OH
15	αH	CO_2Me	OH
16	βH	OH	CO_2Me



	R_1	R_2	R_3
(-) **17**	H	OH	H
17a	CH_3	OCH_3	H
17b	Ac	OAc	H
(-) **18**	H	H	H
18a	Ac	H	H
(-) **19**	H	OH	OH
19a	CH_3	OH	OH
19b	Ac	OH	OH



	R_1	R_2
(-) **20**	CO_2Me	OH
20a	CO_2Me	OCH_3
20b	CO_2Me	OAc
(+)**21a**	OH	H
(-) **21b**	enantiomer of **21a**	



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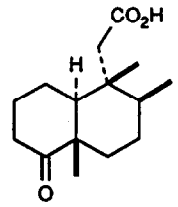
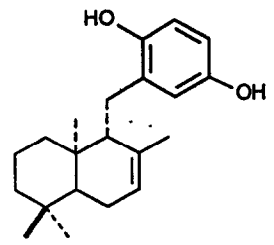


(-) **22**



(+) **23**

data[24] and was confirmed by Faulkner's subsequent report of this compound isolated from *Smenospongia* sp.[20] Methylation and acetylation of **17** gave the corresponding disubstituted derivatives **17a** and **17b**. Acid promoted cyclization[20] of **17** yielded product **20**,[25] $C_{23}H_{32}O_4$ (HREIMS *m/z* M^+ 372.2295, Δ 0.5 mmu of calcd). The most significant features of the ^{13}C NMR of **20** are the absence of the Δ^7 olefinic function, the presence of an upfield quaternary carbon signal for C-8 (δ 79.6), and the additional shielding (Δ = -2.4 ppm, alkylation effect) at C-21 consistent with the cyclization of **17** taking place between C-21 and C-8. Methylation or acetylation of **20** afforded monosubstituted derivatives **20a** or **20b** respectively. The relative stereochemistry at C-5/8/9/10 in **20** was assigned based on the characteristic shifts of Me-13 and Me-14, the ^{13}C shifts at the AB ring sites which were nearly identical with those of chromazonarol (**21b**)[21] and the NOE observed between H_2-15 and Me-11.

A mixture of quinones and quinols with A or C residues was isolated from the other Thailand collection (no. 88006). The major component (-) **17**, as described above, was accompanied by additional new compounds. These were (-) dactylosponol (**18**), $C_{23}H_{32}O_3$ (HREIMS 356.2350, Δ 0.1 mmu of calcd) and (-) dactylospontriol (**19**), $C_{23}H_{32}O_5$. Their structures were both established once the ^{13}C NMR data were compared to those of **17**. In addition, both **18** and **19** were smoothly converted into their corresponding methyl ethers and/or acetates. Also accompanying these former compounds were four known compounds: (-)**3**, **8**, **10** and **21**.

Absolute stereochemical correlations. Capon's 8*S*,9*R*,10*S* stereo assignment for (-) ilimaquinone (**3**)[9] was an important cornerstone to the analysis of the absolute stereochemistry of the compounds we isolated. A primary assumption made here is that mixtures of metabolites whose structures incorporate moieties A - C isolated from an individual sponge collection should all belong to the same podal series.[26] Of immediate significance is the isolation of (-) **3** from all three of the geographical areas sampled. The relevant collections and the α's of **3** are: Fiji (no. 85020, $[\alpha]_{589}$ = -19.5°), Papua New Guinea (no. 90177, $[\alpha]_{589}$= -27.6°), and Thailand (no. 88006, [α] = -23°). Separate ozonolysis of (-) **3** and (+) **6a** gave (-) **22** whose spectral properties

Table 1. ^{13}C NMR (ppm; $CDCl_3$) data of compounds containing substructures A, B and C.

Atom	3[b]	4[c]	8[d]	9[c]	10[c]	11[c]	12[c]	17[c]	18[c]	19[c]	20[c]
1	23.2	22.5	23.2	22.5	23.4	22.5	22.5	39.5	39.4	39.5	39.2
2	28.7	25.0	28.0	25.0	27.8	25.0	27.4	18.9	18.9	18.9	18.4
3	33.0	32.0	33.0	32.8	33.7	32.8	33.0	42.2	42.2	42.2	40.9
4	160.5	153.4[a]	160.3	153.6	161.9	153.6	160.0	33.0	33.0	33.0	33.2
5	40.5	39.5	40.4	39.5	41.3	39.5	40.2	50.2	50.2	50.3	56.1
6	36.7	37.9	36.8	37.9	37.8	37.9	36.9	23.8	23.8	23.8	19.7
7	28.7	27.9	28.6	27.9	30.4	27.9	28.3	122.4	122.8	122.8	41.8
8	38.2	39.5	38.0	39.3	38.3	39.3	37.9	135.4	135.1	135.0	79.6
9	43.3	44.9	42.9	44.4	43.3	44.5	41.5	55.4	53.7	53.3	51.8
10	50.2	48.5	50.0	48.3	-	48.3	49.9	36.9	37.0	36.8	37.0
11	102.6	105.7	102.4	105.7	102.6	105.7	102.9	21.9	21.9	21.9	21.5
12	20.6	33.2	20.5	33.2	21.0	33.2	20.8	33.2	33.2	33.2	33.4
13	17.9	18.7	17.8	18.7	18.7	18.7	16.4	22.2	22.4	22.4	21.1
14	17.3	18.3	17.2	18.4	17.7	18.4	17.3	13.8	13.9	13.7	14.9
15	32.4	32.7	32.6	32.0	34.0	32.0	42.6	25.9	26.0	24.5	21.8
16	117.4	117.7	113.5	113.8	-	114.0	176.3	130.3	-	120.1	-
17	153.4	153.5[a]	157.1	157.3	155.3	157.0		124.1	131.8	121.0	123.8
18	182.4	182.5	178.0	178.2	-	178.4		122.6	129.9	108.4	122.1
19	102.1	102.0	91.5	91.5	91.7	91.9		111.7	128.7	144.9	113.0
20	161.8	161.7	150.2	150.6	154.7	150.1		142.5	115.1	122.5	144.5
21	182.0	182.1	182.8	182.9	184.3	182.8		147.2	157.4	146.1	144.8
22	56.8	56.8						167.9	169.5	170.4	167.2
1′			44.1	41.2	44.6	44.1		52.1	53.7	52.1	52.1
2′			36.7	36.9	34.0	34.3					
3′			25.9	26.0	139.1	137.5					
4′			22.2	22.4	129.5	128.6					
5′			22.2	22.4	129.5	129.0					
6′					127.5	127.1					

[a] May be reversed
[b] Ref. 6.
[c] This work
[d] Ref. 18.

were identical to literature data.[6] Collectively, these findings intimate that all A-substructure metabolites isolated possess *8S,9R* stereochemistry. A reasonable extension of this conclusion is that the literature structures including smenospondiol (**6a**) ($\alpha = +13°$[12] or $\alpha = +12°$, our data) and dictyoceratin A (**6b**) ($\alpha = +6°$[13]) are not enantiomers but are both members of the *8S,9R* podal series. The absolute stereochemistry of (+) epi-ilimaquinone (**4**) has

not been definitively determined[7] but can be assumed to be as shown here. In view of the isolation of (-) **3** accompanied by (+) **4**, (+) **9** and (+) **11** from the same Papua New Guinea collections, we propose that the latter three have an 8*S*,9*R* **B** substructure. To date, all the hydroquinones with a substructure **C** isolated from sponges, headed by ent-chromazonarol (**21a**),[27] appear to have 9*R*,10*S* stereochemistry. This is enantiomeric to parallel compounds, headed by chromazonarol (**21b**), isolated from brown alga.[28] Consistent with this view are the antipodal rotations of **18** ([α] = -14°) isolated here versus that reported for the seaweed metabolite isozonoral (**23**) ([α] = +30°)[29,47] which has been reported with a 9*S*,10*R* C-type ring system.[30] In view of these relationships it seems reasonable to assume that **17** - **20** are all in the *ent*-chromazonarol (**21a**) series. Also consistent with this picture is Ireland's[31] recent report of the sponge-derived quinone sesquiterpene (-) mamanuthaquinone which contains the **D** substructure having 8S,9R,10S stereochemistry.

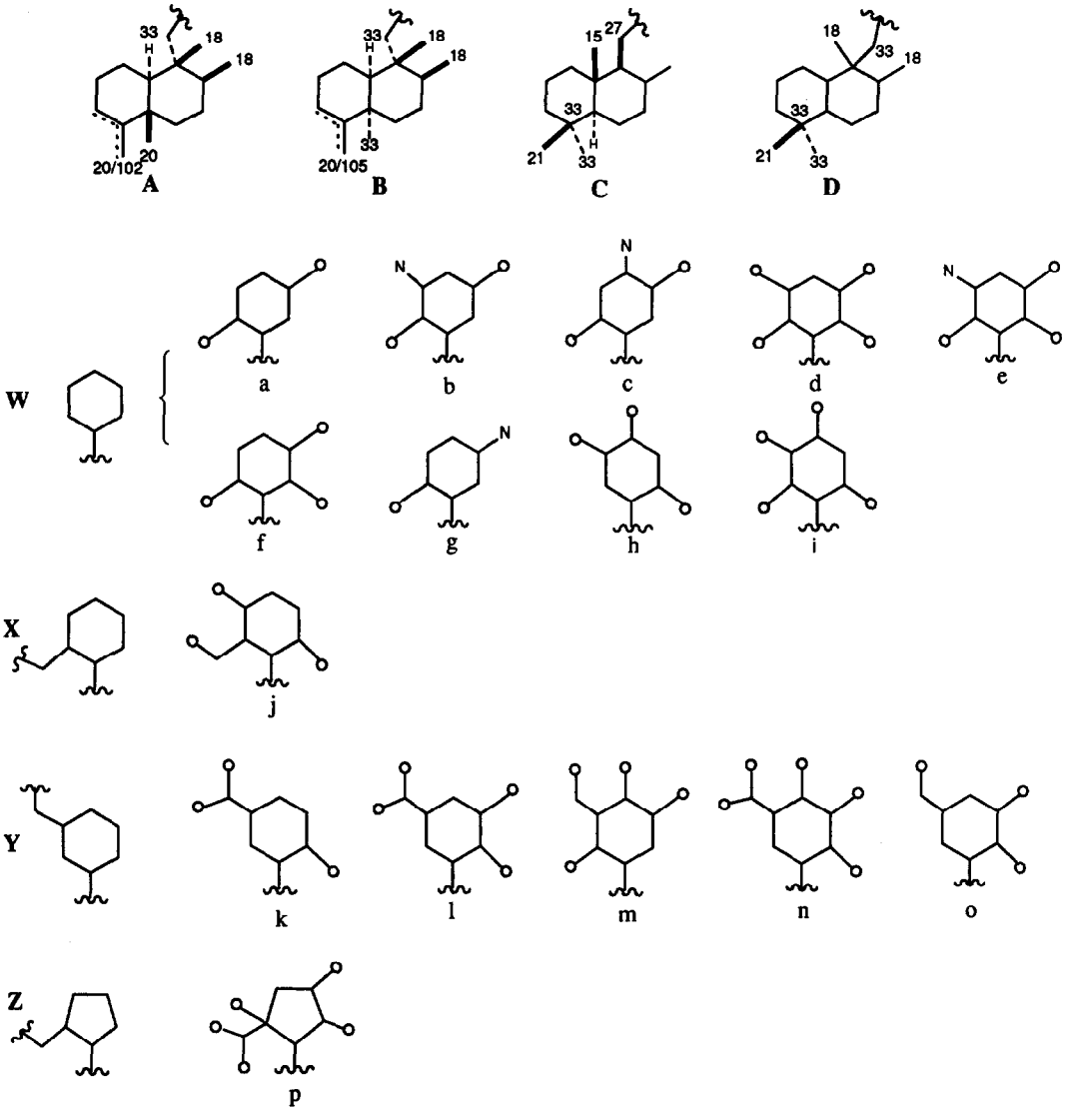
Biological activity. Müller has previously evaluated the *in vitro* and *in vivo* antileukemic activity of avarol and related compounds.[32] The most active was avarone which exhibited a 70% *in vivo* curative effect against L5178Y mouse Leukemia cells at doses of 10 mg/kg. Diminished *in vitro* potency was reported for aminated derivatives as shown by the following ED_{50}'s (μM) of avarone (0.6), avarol (**1**) (0.9), 3,4-dihydroavarol (1.3), 19-*N*-Me avarone (4.2), and 20-*N*-Me avarone (10).[32] Table 2 summarizes our *in vitro* results against both Leukemia (P388) and important solid tumor models (A549, HT-29 and B-16/F10). These data provide an interesting contrast to those reported by Müller. The most active compounds against the Leukemia targets were the aminoquinone **9** and the non-quinone containing derivative **13**. The quinone ring appears to be essential for *in vitro* activity against the solid tumors as exhibited by the potency of **4** and **9**, and the inactivity of **13** - **16**.[33]

Table 2. *In vitro* cytotoxicity of selected compounds (IC_{50}'s μg/mL)

Compound	A549	HT-29	B16/F10	P388
4	0.9	3.4	1.1	2.2
7	5.7	4.0	4.1	2.6
9	0.8	0.9	0.6	0.7
11	3.9	2.4	1.9	1.9
13	NA	NA	2.1	0.6
14	NA	NA	NA	NA
15 & 16	NA	NA	NA	NA

Chemotaxonomical considerations. The possibility that bicyclic quinone (hydroquinone) sesquiterpenoids, such as those considered in this study, are restricted to a narrow range of taxa was considered. A literature search commenced and was focused on compounds with terpene substructures **A** - **D** and benzenoid derived substructures **W** - **Z**. The **W** - **Z** subset can be further subdivided into groups as a function of the heteroatom substitution and presence (or absence) of an additional carbon. The large number of possible structural permutations that have been observed are summarized in Chart 1. The terpenoid portion of these mixed biogenesis products isolated thus far most often has substructure **A** or **C**, while only four examples of partial structure **D** have been reported. Interestingly, our work substantially adds to the known numbers of compounds with substructure **B**. A view based on the benzenoid-

Chart 1. Summary of sesquiterpene-hydroquinone (-quinone) substructures.*



* Absolute stereochemistry is not implied.

derived part of these compounds presents a much wider filter because the four substructures W - Z can each be subdivided into as many as 9 unique observed substituent and substitution patterns, exemplified by a - i under W, j under X, k - o under Y, or p under Z. Hydroquinone, quinone, and phenol residues occur among type W - Y substructures, with moiety Z representing a ring contraction product of W. Overall, the benzenoid residues W and Y have been reported most frequently.

Table 3 classifies these biosynthetic products in accordance with their structure type and the corresponding marine source. As can be seen, all the sponge derived compounds reported emanate from three Families (Spongiidae, Thorectidae, Dysideidae) of the Order Dictyoceratida and one Family (Niphatidae) of the Order Haplosclerida. Our work elevates *D. elegans* to a position as being a species yielding the largest variety of structures, comprising three terpene skeletons (A, B, C) and three different benzenoid-derived types (W, Y, Z). One alga *Dictyoteris undulata* (= *zonaroides*) has also been reported as a source of compounds with terpenoid

Table 3. Reported sesquiterpenes from sponges and algae.

Source (Order, Family, *Genus*)	Type of Compounds
SPONGES	
Dictyoceratida	
Dysideidae	
Dysidea avara	AWabcd[34,35,36]
Dysidea arenaria	BWa[5]
Dysidea cinerea	AWadfhi[37]
Dysidea pallescens	CWa[27]
Dysidea sp.	AWa[38]
Dysidea sp.	BWbg[39]
Dysidea sp.	AWah[40]
Thorectidae	
Hyrtios (= *Inodes*) *eubamma*	CWh[41]
Smenospongia sp.	AWde[17,18]
	AYl[12]
	CYl[20]
Smenospongia aurea	CWa[21]
	DWa[21,22]
Fasciospongia sp.	DWd[31]
Spongiidae	
Dactylospongia sp.	AWd[16]
	AYkl[16]
	AZp[16]
Dactylospongia elegans	AWde*
	AYl*
	AZp*
	BWde*
	CYkln*
	CWa*
Heteronema sp.	CWh[42]
Hippospongia metachromia	AWd[6]
Hippospongia sp.	AYln[12]
	AWd[12]
Hyatella sp.	DWd[43]
	AWd[43]
Stelospongia canalis	AWd[44]
	CWd[44]
Stelospongia conulata	AWd[8]
	CWd[8]
Haplosclerida	
Niphatidae	
Siphonodictyon coralliphagum	DYm[45]
	CYmo[45]
	AYlo[45]
	CXj[46]
ALGAE	
Dictyotales	
Dictyotaceae	
Dictyopteris undulata (= *zonaroides*)	CWa[28,30,47,48]
	CYk[47,48]

* This work.

moiety C but, as noted above, this substructure is enantiomeric to that observed from sponges. To the extent that the compounds of Chart 1 are products of *de novo* biosynthesis, then both the sponges and alga noted in Table 3 have a parallel but antipodal enzymic apparatus to cyclize and arylate farnesane type precursors.

EXPERIMENTAL SECTION

The NMR spectra were recorded at 250 MHz for ^1H, and 62.5 MHz for ^{13}C. Multiplicities of ^{13}C NMR resonances were determined from APT, DEPT, or ^{13}C-^1H COSY NMR data. Low resolution positive ion electron impact mass spectrometry data were obtained on a quadrupole instrument at UCSC or on a high resolution magnetic sector spectrometer at the University of Santiago (Spain), the positive ion FAB mass spectral data were measured at UCSC.

Collection. All *Dactylospongia elegans* specimens were collected by the UCSC group using SCUBA at the stations (collection no.) indicated: Similani Is., Phuket, Thailand (88006, 88035), Fiji (85020, 89135, 89169), Papua New Guinea (90169, 90177).

Identification. The sponge (collection no. 90169) *Dactylospongia elegans* (Thiele, 1899) (Family Thorectidae, Order Dictyoceratida) whose voucher specimens and underwater photo are available (from P.C.) was identified by Ms. M. C. Diaz (UCSC, Institute of Marine Sciences) and Dr. R. W. M. van Soest (Univ. of Amsterdam, Holland). This organism can be regularly collected from shallow reefs (-20 to -30 feet) in Fiji and Papua New Guinea. All voucher specimens were carefully examined and no. 90169 is representative and exhibits the following characteristics: color - yellow-brownish (alive) which turns from dark brown to purple in alcohol; shape - massive-amorphous flat encrusting sometimes with creeping branches; consistency - easy to tear; surface - blunt to finely ramified conules regularly distributed; ectosome - very rough, conulose; choanosome - predominant fibers of a similar diameter (30 - 70 mm); spicules - none; fibers - clear brown-yellow showing some stratification in some specimens.

Extraction and Purification. Representative protocols are as follows. The sponges were stored in methanol. The methanol was decanted from the sponge and conc. *in vacuo*. This was repeated twice and the extracts were combined. This was then partitioned between water and CH_2Cl_2 and the organic fraction was conc. *in vacuo*. This was partitioned between 10% aqueous MeOH and hexane (3x50 mL), the aqueous portion was made 20% aqueous and extracted with CCl_4 (3x50 mL), the aqueous portion was made 40% aqueous and extracted with CH_2Cl_2 (3x50 mL). The extracts were conc. *in vacuo*. THAILAND. Work-up of #88035 yielded sesquiterpene, **17** (11 mg), from the CCl_4 fraction after HPLC on silica using ether/hexane (3:1) as eluant. The 88006 collection yielded 4.7 g of a crude viscous oil. The dry extract was chromatographed on a Sephadex LH20 ($CHCl_3$/MeOH, 4:3) column to afford three main fractions. The second fraction was rechromatographed on a silica gel flash column eluting with CH_2Cl_2/MeOH (95:5) giving compounds **19** (5 mg), **3** (12 mg), **8** (36 mg), and **10** (24 mg). The third fraction was eluted with CH_2Cl_2/MeOH mixtures on a flash silica gel column; elution with 3% MeOH gave compound **17** (26 mg) and a mixture of sesquiterpenes that was submitted to reverse phase HPLC (ODS, MeOH:H_2O, 83:17) affording **17** (10 mg), **18** (6 mg), and **21** (27 mg). FIJI. The 89135 collection (101.92 g dried weight) yielded 5.2 g of crude extract. The hexane and CCl_4 fractions yielded **12** (9 mg), **6a** (66 mg), **7** (1 mg), a mixture of **13** and **14** (19 mg) which was partially acetylated to give **13a** (14 mg) and **14** (3 mg), and an inseparable mixture of **15** and **16**. The 90169 collection (87.45 g dried weight) yielded 7.4 g of a crude viscous oil and purification as above yielded **4** (107 mg), **9** (36 mg) and **11** (13 mg). The spectral data for the known compounds matched that reported in the literature, but α's could not be reliably measured for **7**, **8**, **10**, **13** - **16**, because the solutions were so highly colored.

Epi-ilimaquinone (4): $[\alpha]_{589}$ = +29.8° (*c* 0.004 g/mL, $CHCl_3$); IR ($CHCl_3$): 3685, 1645, 1611 cm^{-1}; ^{13}C NMR ($CDCl_3$): see Table 1; ^1H NMR ($CDCl_3$) [atom number]: δ [11] 4.66 (ds), [12] 1.04 (s), [13] 0.92 (d, J = 6.1 Hz), [14] 0.86 (s), [15] 2.53 (AB system, J_{AB} = 13.7 Hz), [19] 5.86 (s), [22] 3.86 (s).

Smenospondiol (6a): $[\alpha]_{589}$ = +11.2° (*c* 0.006 g/mL, $CHCl_3$); IR ($CHCl_3$): 3533 (w), 3209 (br w), 2929 (m), 2861 (w), 1708 (m), 1602 (m), 1440 (s), 1384 (w), 1304 (s), 1220 (s), 1214 (s), 1210 (s), 1099 (w), 1011 (m), 896 (w) cm^{-1}; EIMS, *m/z* (relative intensity

%): 372 (M^+, 1), 191 (51), 182 (24), 175 (8), 153 (6), 135 (12), 121 (15), 109 (21), 95 (100), 81 (12); ^{13}C NMR ($CDCl_3$) [atom number]: δ [1] 23.2 (t), [2] 27.9 (t), [3] 33.1 (t), [4] 160.2 (s), [5] 40.2 (s), [6] 36.6 (t), [7] 27.7 (t), [8] 36.4 (d), [9] 42.2 (s), [10] 48.1 (d), [11] 102.8 (t), [12] 20.6 (q), [13] 17.6 (q), [14] 17.6 (q), [15] 37.0 (t), [16] 125.2 (s), [17] 127.4 (d), [18] 120.3 (s), [19] 114.0 (d), [20] 142.5 (s), [21] 148.9 (s), [22] 167.8 (s), [-OCH_3] 52.1 (q); ^1H NMR ($CDCl_3$) [atom number]: δ [1, 3] 2.09 (br d, J = 13.2 Hz), [1, 2, 6, 7, 8] 1.61-1.15 (m), [2] 1.93-1.84 (m), [3] 2.34 (dt, J = 14.5, 5.1 Hz, H_{ax}), [10] 0.96 (dd, J = 12.0, 1.5 Hz), [11] 4.41 (s), 4.36 (s), [12] 1.06 (s), [13] 1.03 (d, J = 6.3 Hz), [14] 0.87 (s), [15] 2.66 (s), [17] 7.51 (d, J = 1.2 Hz), [19] 7.38 (d, J = 0.9 Hz), [OH] 6.73 (br s), [OH] 6.01 (s), [-OCH_3] 3.86 (s).

Smenospongine (7): EIMS, *m/z* (relative intensity %): 343 (M^+, 1), 344 ($(M + H)^+$, 1), 191 (6), 153 (100), 135 (6), 109 (11), 107 (5), 95 (59), 79 (3), 69 (3); ^{13}C NMR ($CDCl_3$) [atom number]: δ [1] 23.3 (t), [2] 28.0 (t), [3] 33.0 (t), [4] 160.5 (s), [5] 40.5 (s), [6] 36.7 (t), [7] 28.7 (t), [8] 38.0 (d), [9] 43.0 (s), [10] 50.0 (d), [11] 102.6 (t), [12] 20.6 (q), [13] 17.9 (q), [14] 17.3 (q), [15] 32.5 (t), [17] 156.0 (s), [19] 95.7 (d), [20] 150.7 (s); ^1H NMR ($CDCl_3$) [atom number]: δ [1, 3] 2.15-2.03 (m), [1, 2, 6, 7, 8] 1.52-1.25 (m), [2] 1.85 (m), [3] 2.33 (dt, J = 13.5, 5.4 Hz, H_{ax}), [10] 0.78 (dd, J = 12.0, 1.0 Hz), [11] 4.44 (br s), [12] 1.05 (s), [13] 0.97 (d, J = 6.2 Hz), [14] 0.84 (s), [15] 2.51 (d), 2.40 (d) (AB system, J_{AB} = 13.9 Hz), [19] 5.63 (s), [NH_2] 5.55 (br s), [OH] 8.13 (br s).

Smenospongiarine (8): mp: 170-172 °C; IR (KBr): 3400, 3200, 1640 cm^{-1}; UV [λ_{max}] (MeOH): 210, 325; EIMS *m/z* (relative intensity %): 413 (4), 400 (3), 356 (3), 277 (2), 257 (7), 223 (100), 209 (15), 191 (7), 152 (18), 95 (37); ^{13}C NMR ($CDCl_3$): see Table 1; ^1H NMR ($CDCl_3$) [atom number]: δ [11] 4.43 (br s), [12] 1.04 (s), [13, 4′, 5′] 0.95 [3 d's overlapped), [14] 0.83 (s), [15] 2.70 (m), 2.31 (m), [19] 5.41 (br s), [1′] 3.43 (m), [2′] 2.87 (m), [OH] 8.41 (br s), [NH] 6.41 (br t).

Epi-smenospongiarine (9): oil; $[\alpha]_{589}$ = +96.7° (*c* 0.0012 g/mL, $CHCl_3$); ^{13}C NMR ($CDCl_3$): see Table 1; ^1H NMR ($CDCl_3$) [atom number]: δ [11] 4.70 (ds), [12] 1.06 (s), [13, 4′, 5′] 0.95 (3 d's overlapped), [14] 0.86 (s), [15] 2.50 (AB system, J_{AB} = 14.2 Hz), [19] 5.39 (s), [1′] 3.20 (q, J = 7.5 Hz), [2′] 2.95 (t, J = 6.25 Hz), [NH] 6.50 (br d); FABMS: *m/z* 414.

Smenospongidine (10): oil; IR (KBr): 3400, 3200, 1650 cm^{-1}; UV [λ_{max}] (MeOH): 210, 330; EIMS *mz* (relative intensity %): 447 (2), 412 (1), 269 (1), 257 (79), 192 (30), 191 (26), 166 (33), 149 (41), 107 (45), 91 (43), 81 (70), 69 (58); ^{13}C NMR ($CDCl_3$): see Table 1; ^1H NMR ($CDCl_3$) [atom number]: δ [11] 4.45 (br s), [12] 1.05 (s), [13] 0.77 (d), [14] 0.82 (s), [15] 2.48 (m), [2′] 2.95 (m), [4′, 5′, 6′] 7.27 (m), [NH] 6.53 (br s), [OH] 5.41 (s).

Epi-smenospongidine (11): oil; $[\alpha]_{589}$ = +37.5° (*c* 0.0016 g/mL, $CHCl_3$); ^{13}C NMR ($CDCl_3$): see Table 1; ^1H NMR ($CDCl_3$) [atom number]: δ [11] 4.70 (ds), [12] 1.06 (s), [13] 0.92 (d, J = 6.2 Hz), [14] 0.87 (s), [15] 2.50 (AB system, J_{AB} = 13.8 Hz), [19] 5.42 (s), [1′] 3.44 (q, J = 6.4 Hz), [2′] 2.96 (t, J = 7.3 Hz), [4′, 5′, 6′] 7.26 (m), [NH] 6.50 (br s); FABMS: *m/z* 448.

Smenospongic acid (12): $[\alpha]_{589}$ = -53.8° (*c* 0.003 g/mL, $CHCl_3$); ^{13}C NMR ($CDCl_3$): see Table 1; ^1H NMR ($CDCl_3$) [atom number]: δ [1] 0.95 (m, H_{eq}), [1] 0.80 (t, J = 9.0 Hz, H_{ax}), [2] 1.49-1.40 (m), [3] 1.61-1.55 (m), [6] 2.31-2.24 (m, H_{eq}), [6] 2.10 (br d, J = 11.7 Hz, H_{ax}), [7] 1.89-1.80 (m), [8] 1.79-1.70 (m), [10] 1.31-1.25 (m), [11] 4.50 (br s), [12] 1.04 (s), [13] 0.90 (d, J = 6.6 Hz), [14] 0.80 (s), [15] 2.40 (d), 2.28 (d) (AB system, J_{AB} = 13.5 Hz).

Dactylospongenone A acetate (13a) and Dactylospongenone B (14): **13a**: ^{13}C NMR ($CDCl_3$) [atom number]: δ [1] 22.2 (t), [2] 27.7 (t), [3] 33.0 (t), [4] 159.2 (s), [5] 40.0 (s), [6] 37.0 (t), [7] 28.3 (t), [8] 37.1 (d), [9] 40.2 (s), [10] 49.1 (d), [11] 102.4 (t), [12] 20.5 (q), [13] 16.3 (q), [14] 17.6 (q), [15] 32.9 (t), [16] 53.1 (d), [17] 196.4 (s), [18] 160.7 (s), [19] 119.4 (d), [20] 85.7 (s), [21] 170.5 (s), [acetate -O_2C] 168.8 (s), [-OCH_3] 57.4 (q), [-OCH_3] 52.0 (q), [-OAc] 21.5 (q); ^1H NMR ($CDCl_3$) [atom number]: δ [11] 4.47 (s), [12] 1.06 (s), [13] 0.80 (d, J = 6.4 Hz), [14] 0.75 (s), [16] 2.77 (br s), [19] 6.69 (s), [-OCH_3] 3.75 (s), [-OCH_3] 3.70 (s), [-OAc] 2.15 (s), 2.32 (m, 5H), 1.90-1.30 (m, 8H); and **14**: ^{13}C NMR ($CDCl_3$) [atom number]: δ [1] 22.1 (t), [2] 27.7 (t), [3] 33.6 (t), [4] 158.9 (s), [5] 39.7 (s), [6] 36.9 (t), [7] 28.1 (t), [8] 37.1 (d), [9] 40.0 (s), [10] 48.3 (d), [11] 102.8 (t), [12] 20.3 (q), [13] 16.7 (q), [14] 17.8 (q), [15] 32.9 (t), [16] 54.7 (d), [17] 198.5 (s), [18] 160.0 (s), [19] 121.4 (d), [20] 80.6 (s), [21] 175.0 (s), [-OCH_3] 57.3 (q), [-OCH_3] 53.6 (q); ^1H NMR ($CDCl_3$) [atom number]: δ [11] 4.48 (s), [12] 1.03 (s), [13] 1.00 (d, J = 6.3 Hz), [14] 0.74 (s), [15] 1.87 (dd, J = 15.4, 5.1 Hz), [16] 2.65 (m), [19] 5.92 (s), [OH] 3.82 (s), [-OCH_3] 3.75 (s), [-OCH_3] 3.74 (s), 2.30 (m, 1H), 2.13 (m, 2H), 1.52-1.23 (m,

6H), 1.11 (m, 1H), 1.08 (m, 1H).

Dactylospongenone C (15) and Dactylospongenone D (16): **15** (major component): ^{13}C NMR ($CDCl_3$) [atom number]: δ [1] 21.9 (t), [2] 27.7 (t), [3] 33.1 (t), [4] 157.8 (s), [5] 39.5 (s), [6] 37.3 (t), [7] 28.4 (t), [8] 38.2 (d), [9] 40.1 (s), [10] 49.1 (d), [11] 102.4 (t), [12] 20.4 (q), [13] 16.7 (q), [14] 17.7 (q), [15] 32.5 (t), [16] 49.7 (d), [17] 201.7 (s), [18] 160.8 (s), [19] 123.3 (d), [21] 175.9 (s), [-OCH_3] 57.4 (q), [-OCH_3] 53.8 (q), (one signal obscured by solvent); **16** (minor component): ^{13}C NMR ($CDCl_3$) [atom number]: δ [1] 21.9 (t), [2] 27.6 (t), [3] 33.0 (t), [4] 157.9 (s), [5] 40.0 (s), [6] 37.1 (t), [7] 27.9 (t), [8] 37.7 (d), [9] 40.3 (s), [10] 48.2 (d), [11] 102.3 (t), [12] 20.3 (q), [13] 16.4 (q), [14] 17.7 (q), [15] 32.8 (t), [16] 49.9 (d), [17] 201.8 (s), [18] 160.6 (s), [19] 123.6 (d), [21] 175.8 (s), [-OCH_3] 57.4 (q), [-OCH_3] 53.9 (q), (one signal obscured by solvent).

Smenodiol (17): mp: 164-166 °C; $[\alpha]_{546}$ = -46.7° (*c* 0.003 g/mL, CH_2Cl_2); IR (KBr): 3500, 3360, 1700, 1630, 1610 cm^{-1}; UV [λ_{max}] (MeOH): 254, 280; (MeOH+NaOH): 244, 328; EIMS *m/z* (relative intensity %): 372.2290 (16) [M^+ calc. for $C_{23}H_{32}O_4$ 372.2300], 357 (5), 341 (7), 248 (16), 233 (36), 219 (9), 191 (100), 181 (33); ^{13}C NMR ($CDCl_3$): see Table 1; ^1H NMR ($CDCl_3$) [atom number]: δ [7] 5.39 (br s), [9] 2.41 (m), [11] 0.91 (s), [12] 0.88 (s), [13] 1.44 (br s), [14] 0.90 (s), [15] 2.66 (m), [17] 7.58 (d, J = 1.8 Hz), [19] 7.46 (d, J = 1.8 Hz), [-OH] 5.97 (br s), [-OCH_3] 3.89 (s); **17a**: $[\alpha]_{546}$ = -15° (*c* 0.002 g/mL, CH_2Cl_2); IR (KBr): 1690, 1630, 1610 cm^{-1}; EIMS *m/z* (relative intensity %): 400 (10), 385 (5), 369 (3), 191 (100); ^1H NMR ($CDCl_3$) [atom number]: δ [7] 5.41 (br s), [9] 2.11 (m), [11] 0.89 (s), [12] 0.90 (s), [13] 1.41 (br s), [14] 0.84 (s), [15] 2.69 (m), [17] 7.61 (d, J = 1.7 Hz), [19] 7.41 (d, J = 1.7 Hz), [-OCH_3] 3.96 (s), [-OCH_3] 3.86 (s), [-OCH_3] 3.81 (s); **17b**: $[\alpha]_{546}$ = -10° (*c* 0.001 g/mL, CH_2Cl_2); IR (KBr): 1700, 1630, 1610 cm^{-1}; EIMS *m/z* (relative intensity %): 456 (5), 441 (3), 425 (2), 413 (10), 397 (2), 370 (3), 355 (3), 191 (100); ^1H NMR ($CDCl_3$) [atom number]: δ [7] 5.40 (br s), [11] 0.91 (s), [12] 0.89 (s), [13] 1.38 (br s), [14] 0.86 (s), [15] 2.40-2.50 (m), [17] 7.95 (d, J = 1.6 Hz), [19] 7.71 (d, J = 1.6 Hz), [-OCH_3] 3.91 (s), [-OAc] 2.29 (s), [-OAc] 2.17 (s).

Dactylosponol (18): mp: 145-147 °C; $[\alpha]_{546}$ = -14° (*c* 0.0005 g/mL, CH_2Cl_2); IR (KBr): 3500-3300, 1700, 1600 cm^{-1}; UV [λ_{max}]: (MeOH) 254, 284; (MeOH+NaOH): 242, 296, 324; EIMS *m/z* (relative intensity %): 356.2350 (11) [M^+ calc. for $C_{23}H_{32}O_3$ 356.2351], 341 (6), 313 (11), 232 (19), 217 (53), 191 (100), 165 (30); ^{13}C NMR ($CDCl_3$): see Table 1; ^1H NMR ($CDCl_3$) [atom number]: δ [7] 5.40 (br s), [9] 2.45 (m), [11] 0.92 (s), [12] 0.93 (s), [13] 1.43 (br s), [14] 0.90 (s), [15] 2.74 (dd, J = 15.4, 9.2 Hz), [15] 2.59 (dd, J = 15.4, 2.9 Hz), [17] 7.95 (d, J = 1.8 Hz), [19] 7.76 (dd, J = 8.4, 1.8 Hz), [20] 6.75 (d, J = 8.4 Hz), [-OCH_3] 3.86 (s); **18a**: EIMS *m/z* (relative intensity %): 398 (6), 383 (5), 367 (4), 355 (2), 339 (6), 207 (3), 191 (100); ^1H NMR ($CDCl_3$) [atom number]: δ [7] 5.40 (br s), [9] 2.35 (m), [11] 0.89 (s), [12] 0.92 (s), [13] 1.37 (br s), [14] 0.88 (s), [15] 2.51 (m), [17] 8.06 (d, J = 1.8 Hz), [19] 7.85 (dd, J = 8.4, 1.8 Hz), [20] 7.07 (d, J = 8.4 Hz), [-OCH_3] 3.92 (s), [-OAc] 2.35 (s).

Dactylospontriol (19): mp: 167-169 °C; $[\alpha]_{546}$ = -18° (*c* 0.001 g/mL, CH_2Cl_2); IR (KBr): 3500-3300, 1690, 1600 cm^{-1}; UV [λ_{max}] (MeOH): 256, 300; (MeOH+NaOH): 252, 300, 325, 344; EIMS *m/z* (relative intensity %): 388 (1), 373 (3), 357 (5), 191 (100), 181 (18); ^{13}C NMR ($CDCl_3$): see Table 1; ^1H NMR ($CDCl_3$) [atom number]: δ [7] 5.41 (br s), [9] 2.34 (m), [11] 0.88 (s), [12] 0.91 (s), [13] 1.45 (br s), [14] 0.85 (s), [15] 2.64 (dd, J = 15.6, 9.1 Hz), [15] 2.47 (dd, J = 15.6, 3.3 Hz), [17] 7.14 (s), [-OH] 10.58 (s), [-OH] 5.67 (s), [-OCH_3] 3.92 (s); **19a**: EIMS *m/z* (relative intensity %): 402 (2), 387 (3), 371 (3), 191 (100), 181 (18); ^1H NMR ($CDCl_3$) [atom number]: δ [7] 5.40 (br s), [9] 2.30 (m), [11] 0.88 (s), [12] 0.91 (s), [13] 1.41 (br s), [14] 0.85 (s), [15] 2.60 (m), [17] 7.21 (s), [-OCH_3] 3.88 (s), [-OCH_3] 3.85 (s); **19b**: $[\alpha]_{546}$ = -9° (*c* 0.001 g/mL, CH_2Cl_2); EIMS *m/z* (relative intensity %): 430 (2), 415 (1), 399 (3), 387 (20), 191 (100), 181 (18); ^1H NMR ($CDCl_3$) [atom number]: δ [7] 5.43 (br s), [9] 2.34 (m), [11] 0.89 (s), [12] 0.91 (s), [13] 1.51 (br s), [14] 0.86 (s), [15] 2.72 (dd, J = 15.6, 9.1 Hz), [15] 2.52 (dd, J = 15.6, 2.1 Hz), [17] 7.38 (s), [-OCH_3] 3.83 (s), [-OAc] 2.36 (s).

Preparation of 20. A solution of **17** (14 mg) in 4 mL of EtOH containing one drop of concentrated HCl was heated at reflux for 10 h. Concentration *in vacuo* gave 8 mg of **20**: $[\alpha]_{546}$ = -9° (*c* 0.002 g/mL, CH_2Cl_2); IR (KBr): 3500-3300, 1700, 1610 cm^{-1}; UV [λ_{max}] (MeOH): 250, 305; (MeOH+NaOH): 246, 270, 337; EIMS *m/z* (relative intensity %): 372.2295 (10) [M^+ calc. for $C_{23}H_{32}O_4$ 372.2300], 357 (4), 341 (5), 248 (3), 233 (6), 219 (10), 191 (100), 181 (18); ^{13}C NMR ($CDCl_3$): see Table 1; ^1H NMR ($CDCl_3$) [atom number]:

δ [9] 2.16 (m), [11] 0.89 (s), [12] 0.91 (s), [13] 1.22 (s), [14] 0.85 (s), [15] 2.63 (m), [17, 19] 7.39 (s), [-OH] 5.51 (br s), [-OCH_3] 3.85 (s); **20a**: UV [λ_{max}] (MeOH): 270, 283, 300; EIMS *m/z* (relative intensity %): 386 (26), 371 (8), 335 (7), 195 (30), 191 (100); ^{1}H NMR ($CDCl_3$) [atom number]: δ [9] 2.23 (m), [11] 0.90 (s), [12] 0.89 (s), [13] 1.23 (s), [14] 0.85 (s), [15] 2.66 (m), [17] 7.47 (d, J = 1.7 Hz), [19] 7.36 (d, J = 1.7 Hz), [-OCH_3] 3.88 (s), [-OCH_3] 3.82 (s); **20b**: UV [λ_{max}] (MeOH): 250, 277; EIMS *m/z* (relative intensity %): 414 (9), 399 (8), 383 (5), 371 (10), 355 (1), 191 (100); ^{1}H NMR ($CDCl_3$) [atom number]: δ [9] 2.03 (m), [11] 0.90 (s), [12] 0.89 (s), [13] 1.19 (s), [14] 0.84 (s), [15] 2.70 (m), [17] 7.69 (d, J = 1.7 Hz), [19] 7.52 (d, J = 1.7 Hz), [-OCH_3] 3.85 (s), [-OAc] 2.28 (s).

Derivatization of compounds 17 - 20. A solution of the sesquiterpene (3 mg) in pyridine (0.5 mL) and acetic anhydride (0.1 mL) was stirred at room temperature overnight. The excess reagents were removed *in vacuo* to give the acetylated compounds. A solution of sesquiterpene (3 mg) in DMF (0.3 mL) and methyl iodide (0.3 mL) was stirred at room temperature for 20 h. The residue was filtered, washed with H_2O (3x2 mL), and dried with anhyd. Na_2SO_4 to give the methylated compounds.

8-Epi-chromazonarol (21): EIMS *m/z* (relative intensity %): 314 (M^+, 69), 299 (4), 191 (100), 161 (42), 123 (61); ^{13}C NMR ($CDCl_3$) [atom number]: δ [1] 40.1 (t), [2] 18.2 (t), [3] 40.7 (t), [4] 33.0 (s), [5] 55.4 (d), [6] 18.3 (t), [7] 41.9 (t), [8] 75.5 (s), [9] 49.6 (d), [10] 38.3 (s), [11] 21.8 (q), [12] 33.7 (q), [13] 27.1 (q), [14] 14.2 (q), [15] 22.9 (t), [16] 123.7 (s), [17] 114.8 (d), [18] 148.8 (s), [19] 117.6 (d), [20] 113.9 (d), [21] 148.7 (s); ^{1}H NMR ($CDCl_3$) [atom number]: δ [5] 1.42 (m), [11] 0.80 (s), [12] 0.90 (s), [13] 1.14 (s), [14] 0.76 (s), [15] 2.86 (dd, J = 16.0, 8.0 Hz), [15] 2.69 (dd, J = 16.0, 3.0 Hz), [17, 19, 20] 6.59 (m).

Preparation of 22: A solution of ilimaquinone (8.3 mg) in dry acetone (3 mL) was saturated with ozone at -78 °C for 1 h. After excess ozone was removed by a nitrogen stream, 8N Jones reagent (16 drops) was added and the mixture was stirred at 0 °C for 1.5 h then diluted with water and extracted with CH_2Cl_2 (3x25 mL). The organic extracts were combined and extracted with 10% aqueous $NaHCO_3$ solution (3x25 mL). The aqueous extracts were combined, made acidic with 1N HCl, and then extracted with CH_2Cl_2 (3x50 mL). The organic extracts were combined, dried ($MgSO_4$) and conc. *in vacuo* to give a mixture of acids. This was dissolved in 10% methanolic ether and treated with an excess of diazomethane at room temperature for 2 h. This was concentrated *in vacuo* and separated by flash chromatography (EtOAc:Hex 1:4) to give the methyl ester **22** (2.5 mg, 43%) [α] = -23° (*c* = 0.0025 g/mL).

In the same manner, **6a** (3.0 mg) was converted to the methyl ester **22** (1.1 mg, 53%). [α] = -18° (*c* = 0.0011 g/mL).

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