

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/10746517>

New Sesquiterpene Quinols from a Micronesian Sponge, Aka sp.

ARTICLE *in* JOURNAL OF NATURAL PRODUCTS · JUNE 2003

Impact Factor: 3.8 · DOI: 10.1021/np0205506 · Source: PubMed

CITATIONS

18

READS

29

6 AUTHORS, INCLUDING:



Venugopal J. Mukku

University of Minnesota Crookston

19 PUBLICATIONS 254 CITATIONS

SEE PROFILE



Ruangelie Edrada-Ebel

University of Strathclyde

149 PUBLICATIONS 3,034 CITATIONS

SEE PROFILE



Doriano Fabbro

Novartis

107 PUBLICATIONS 8,264 CITATIONS

SEE PROFILE

New Sesquiterpene Quinols from a Micronesian Sponge, *Aka* sp.

Venugopal J. R. V. Mukku,[†] Ru A. Edrada,[†] Francis J. Schmitz,^{*,†} Michelle Kelly Shanks,[‡] Babathosh Chaudhuri,[§] and Dorian Fabbro[§]

Department of Chemistry and Biochemistry, University of Oklahoma, Norman, Oklahoma 73019, National Institute of Water and Atmospheric Research, Taihoro Nukurangi, Private Bag 109-695 Newmarket, Auckland, New Zealand, and Novartis Pharmaceuticals, Basel, Switzerland

Received November 27, 2002

Three new sesquiterpene quinols (**1**, **2**, and **5**) and two known ones (**3** and **4**) were isolated along with halistanol sulfate (**6**) from a marine sponge of the genus *Aka* collected from Yap Island, Federated States of Micronesia. Their structures were determined from spectral data, and the structure of siphonodictyal C (**3**) was revised. Sulfates **3** and **6** inhibit CDK4/cyclin D1 complexation, whereas **1** and **4** do not.

Cyclin-dependent kinase 4 (CDK4) plays an important role in the G1/S transition phase in the cell cycle.¹ It is inactive in its native form and requires activation by complexation with cyclin D1. The CDK4/cyclin D1 complex phosphorylates the retinoblastoma protein (pRb), which then releases the transcription factors (E2F) that are essential for DNA synthesis. In healthy cells this process is negatively regulated by a family of proteins designated the p16^{INK} proteins. It has been observed that in about 60% of cancers one of these p16 proteins, INK4, is either inactivated or absent, resulting in unregulated phosphorylation of pRb and consequent uncontrolled cell growth. In such p16-deficient, but pRb positive cells, it should be possible to stop the cell cycle by blocking the CDK4/cyclin D1 complex with a small molecule; this constitutes a potential target for drug discovery.

There have been a few reports of natural products exhibiting CDK4/cyclin D1 complex inhibitory activity.² Fascaplysin, a marine natural product isolated from a *Didemnum* tunicate, showed significant and selective in vitro inhibition of CDK4/cyclin D1 activity.³ Using a high throughput screening assay to search for additional inhibitors of CDK4/cyclin D1 phosphorylation, we found that the butanol solubles from a solvent partition of the methanolic extract of a sponge, *Aka* sp. (syn *Siphonodictyon*), showed significant inhibitory activity. A literature search revealed that several groups have studied a related sponge, *Siphonodictyon coralliphagum*,⁴ and reported the isolation of a variety of sesquiterpene quinols. An examination of the ¹H NMR spectrum of the crude active fraction from the *Aka* sp. indicated the presence of similar compounds. We describe herein the isolation and characterization of three new sesquiterpene quinols (**1**, **2**, **5**). Also isolated were the known quinol siphonodictyal C, for which the revised structure **3** is proposed, siphonodictyal A (**4**), and halistanol sulfate (**6**). The results of testing of four of the compounds for inhibiting CDK4/cyclin D1 activity are also reported.

The molecular formula of compound **1**, designated akaol A, was fixed as C₂₃H₃₄O₃ on the basis of HRESIMS and ¹³C NMR data, revealing seven degrees of unsaturation. Its ¹H NMR spectrum in CD₃OD showed signals for the following groups: four tertiary methyls (δ 0.38, 0.78, 0.88, and 1.14), a benzylic methylene [δ 2.67 (1H, d, J = 16 Hz)

Table 1. ¹³C NMR Data for Compounds **1**–**3**, **5**, and **9**^a

C no.	1 ^{b,c}	2 ^{b,c}	3 ^{c,e}	5 ^{c,e,f}	9 ¹³
1	42.1 (t)	41.9 (t)	40.9 (t)	40.7 (t)	39.5
2	19.5 (t)	19.5 (t)	19.9 (t)	20.0 (t)	18.9
3	43.2 (t)	43.3 (t)	43.5 (t)	43.6 (t)	42.2
4	34.0 (s)	34.0 (s)	33.9 (s)	34.0 (s)	33.0
5	54.9 (d)	54.4 (d)	51.7 (d)	51.8 (d)	50.2
6	21.0 (t)	20.9 (t)	24.8 (t)	24.8 (t)	23.8
7	36.6 (t)	36.6 (t)	122.9 (d)	122.5 (d)	122.4
8	50.0 (s)	50.3 (s)	136.6 (s)	137.2 (s)	135.4
9	64.4 (d)	64.3 (d)	56.5 (d)	55.7 (d)	55.4
10	38.6 (s)	38.9 (s)	38.0 (s)	37.9 (s)	36.9
11	22.5 (q)	22.4 (q)	22.4 (q)	22.4 (q)	21.9
12	34.1 (q)	34.1 (q)	33.8 (q)	33.9 (q)	33.2
13	33.3 (q)	32.7 (q)	22.7 (q)	22.7 (q)	22.2
14	15.8 (q)	15.9 (q)	14.4 (q)	14.4 (q)	13.8
15	28.8 (t)	29.9 (t)	27.3 (t)	27.4 (t)	25.9
16	132.1 (s)	134.8 (s) ^d	130.5 (s)	129.8	130.3
17	143.9 (s) ^d	140.5 (s) ^d	149.3 (s)	144.2	124.1
18	141.8 (s) ^d	148.8 (s)	116.6 (s)	133.2	122.6
19	117.3 (d)	117.1 (d)	144.8 (s)	107.4	111.7
20	124.0 (s)	136.6 (s)	143.8 (s)	^g	142.5
21	142.5 (s)	142.1 (s)	123.4 (d)	133.4	147.2
22	73.7 (t)	62.4 (t)	198.1 (d)		169.5
23	57.5 (q)				

^a Spectra were recorded in CD₃OD at 125 MHz, reference to CD₃OD (δ 49.0). ^b Assignments made by HMQC and HMBC experiments. ^c Multiplicities were implied from DEPT experiments (C = s, CH = d, CH₂ = t, CH₃ = q). ^d May be interchanged. ^e Assignments are by analogy only, due to lack of sample for assignment experiments. ^f Assignments of the aromatic carbons are based on calculations.^{9,10} ^g Not observed.

and 2.80 (1H, dd, J = 16, 7.5 Hz)] adjacent to a methine (δ 1.61), an isolated, deshielded methylene [AB quartet (δ 4.27 and 4.40, J = 11 Hz)], and an aromatic proton (δ 6.51, s). The ¹³C NMR data (Table 1) of **1**, including DEPT and HMQC results, revealed the presence of a pentasubstituted aromatic ring, four tertiary methyls, a methoxyl (δ 57.5), seven methylene, and two aliphatic methine groups. The ¹H NMR signal corresponding to the methoxyl group inferred from ¹³C NMR data was not readily observed, as it was masked by the residual solvent signal. However, an ¹H NMR spectrum taken in pyridine-*d*₅ confirmed the presence of the methoxyl group.

The aromatic ring accounts for four of the seven degrees of unsaturation, suggesting that the sesquiterpene unit is tricyclic. Owing to the nature of the co-occurring metabolites, a decalin system was suspected, and this suspicion was supported by comparison of the ¹³C NMR data with that of **3** and **4**. Although limited structural sequence

* To whom correspondence should be addressed. Tel: (405) 325-5581. Fax: (405) 325-6111. E-mail: fjschmitz@ou.edu.

[†] University of Oklahoma.

[‡] National Institute of Water and Atmospheric Research.

[§] Novartis Pharmaceuticals.

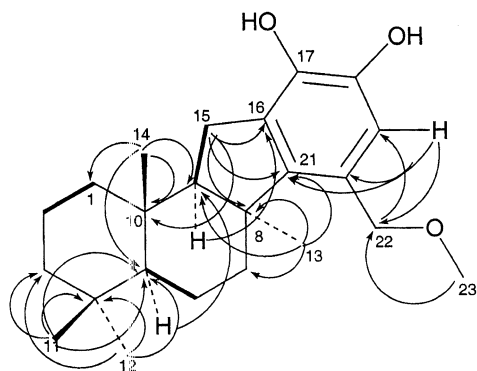


Figure 1. HMBC (curved arrows) and ^1H – ^1H COSY (solid bold lines) correlations for **1**.

information could be gleaned from the COSY spectrum due to minimal signal dispersion, a large portion of the carbon skeleton could be confidently deduced from HMBC data (Figure 1). Those elements of rings A, B, and C not established directly from HMBC data were identified as follows. First, the H-1 and H-5 ^1H NMR signals were each identified through their HMQC correlations to carbons that in turn were assigned from HMBC data. COSY correlations discerned for each of these proton signals enabled us to in turn identify C-2 and C-6 from the HMQC spectrum. This enabled us to account for all the carbons comprising rings A, B, and C. Closure of the bonds between C-2/C-3 and C-6/C-7 was made on biogenetic grounds and by analogy to **3** and **4**. The C-9/C-15 connection was established from the H-9/H-15 coupling seen in the COSY spectrum. Connection of the sesquiterpene skeleton to the aromatic ring to form a five-membered ring was deduced from the HMBC data (Figure 1), in particular the H-13/C-21 correlation. The locations of the methoxymethylene group and the sole aromatic proton were also revealed by HMBC data, especially the H-13 and H-22 correlations to a common aromatic carbon signal at δ 142.5 (C-21) and H-19 to C-22. By default, the hydroxyl groups were assigned to C-17 and C-18, thus completing the planar structure of **1**. The carbon skeleton of **1** is the same as that of pelorol (**7**), which was recently reported by König and Wright^{5a} and ourselves^{5b} and was the first compound reported to have this skeleton. The stereochemistry of **1** was determined as follows. An A/B trans arrangement was assigned due to the general agreement of the ^{13}C NMR chemical shifts for the A/B rings of **1** with those of **7** and **4** and the C-10 methyl shift of δ 15.8, which is characteristic of trans 10-methyl decalins.⁶ The B/C ring junction was assigned as cis with an 8α -methyl group on the basis of the following NMR data. The ^{13}C NMR chemical shift of the C-8 methyl (δ 34.1) is consistent with an equatorial methyl group attached to a cyclohexane ring.⁷ The proton chemical shift of the C-10 methyl group is δ 0.38, noticeably upfield from the corresponding methyl of pelorol, but is consistent with that expected⁸ for an axial methyl shielded by an axial phenyl group. The 8α , 9α stereochemistry is the only B/C ring fusion arrangement that accounts for these data.

Compound **2**, akaol B, has the molecular formula $\text{C}_{22}\text{H}_{31}\text{O}_6\text{SNa}$, which was derived from a combination of HRESIMS and ^{13}C NMR data. A difference of 46 mass units between the pseudo molecular ions in the positive and negative ESIMS spectra strongly suggested the presence of a sodium atom in the molecule and a sulfate group was inferred. The ^{13}C NMR spectrum showed all 22 carbons, and a DEPT spectrum established their multiplicities (4 CH_3 , 7 CH_2 , 3 CH , and 8 C).

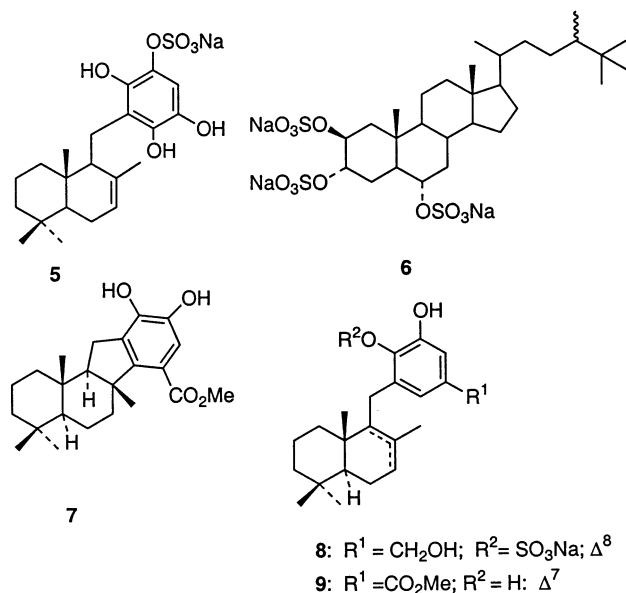
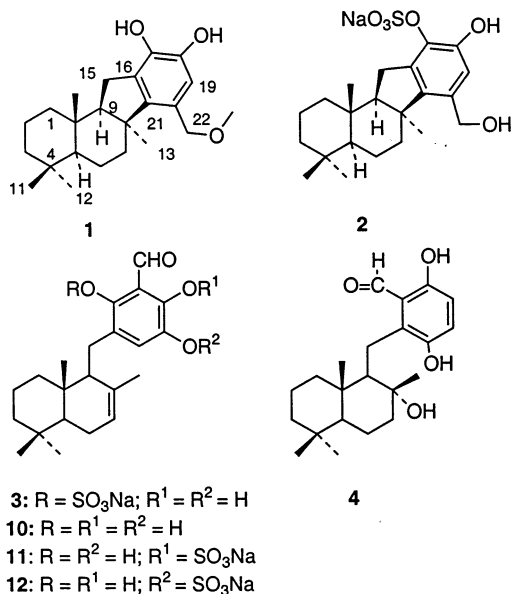
The ^1H NMR spectrum of **2** was similar to that of **1** except for the following differences. The methoxymethylene group signals in **1** were replaced by those of a hydroxyl-methylene group (δ 4.62 and 4.68, J = 13 Hz). Signals for the benzylic methylene and the aromatic proton appeared slightly farther downfield (δ 2.95, d, J = 16 Hz and 3.01, dd, J = 16, 10 Hz) and at δ 6.76, respectively). The chemical shifts of the sesquiterpene part of the molecule were identical with those of compound **1**, suggesting identical skeletons and stereochemistry. However, the ^{13}C chemical shifts of the aromatic carbons of **2** differed from those of **1** owing to the absence of the methoxyl group and the presence of the sulfate. HMBC correlations (see Experimental Section) confirmed most of the same connectivities seen in compound **1**, and hence the same relative placement of the substituents was implied. An HMBC correlation was observed between one of the H-15 resonances and the carbon signal at δ 140.5 (C-17).

The remaining problem was to locate the sulfate group on one of the three oxygen atoms. Placement of the sulfate group at C-22 was ruled out because the C-22 chemical shift of **2** (δ 62.4) was very similar to that of the corresponding benzylic methylene group of siphonodictyal H (**8**, δ 65.2) and quite different from that of C-22 in **1** (δ 73.7), where the benzylic oxygen is substituted. Of the remaining two possible sites, C-17 is preferred over C-18, because if it were to be situated at C-18, a large chemical shift difference (about -6.8 ppm) would have been expected⁹ for C-19 relative to that observed for **1**, but a difference of only 0.02 ppm is observed between these carbon chemical shifts in **1** and **2**. Also, the calculated chemical shifts^{9,10} for all the aromatic carbons fit better for the location of the sulfate group at C-17 rather than C-18.¹¹

The molecular formula for compound **3** was established as $\text{C}_{22}\text{H}_{29}\text{O}_7\text{SNa}$ by a combination of HRESIMS and ^{13}C NMR data. The presence of a sulfate group and the counterion was determined as for compound **2**. The ^{13}C NMR spectrum showed all the carbons and the multiplicities were determined by a DEPT spectrum (4 CH_3 , 5 CH_2 , 5 CH , and 8 C). The ^1H NMR spectrum exhibited signals for three tertiary methyl groups (δ 0.88, 0.92, and 0.92), an olefinic methyl (δ 1.42), a benzylic methylene [δ 2.47 (1H, d, J = 14 Hz) and δ 2.73 (1H, dd, J = 16, 7 Hz)], a proton on a trisubstituted double bond [δ 5.22 (1H, d, J = 4 Hz)], an aromatic proton (δ 6.94), and an aldehyde proton (δ 10.1, s). Five of the oxygen atoms were thus accounted for, one in the aldehyde function and four in the sulfate group. As no signals attributable to oxygen-desielded aliphatic carbons were observed in the ^{13}C NMR spectrum, the remaining two oxygen atoms were assumed to be present as phenolic OH groups, and this was consistent with the occurrence of ^{13}C NMR signals (δ 144.8, 143.8) attributable to oxygenated aromatic carbons.

A desulfated, but otherwise identical compound, siphonodictyal C (**10**), was reported by Sullivan et al. from *Siphonodictyon coralliphagum*.^{4a} The ^1H and ^{13}C NMR data of compound **3** and siphonodictyal C are nearly identical, a fact that is inconsistent for a free phenol and a sulfated analogue. In an effort to resolve this inconsistency, we recorded the mass spectrum using ESI, FAB, and EI modes and observed that the sulfate group is lost during the ionization process using EI, but not using the other analysis modes. Since Sullivan et al. reported EIMS data for **10**, we assume that they inadvertently missed the presence of the sulfate moiety in **10**. The location of the sulfate in **3** could not be ascertained with the available spectral data. Therefore expected chemical shifts of the aromatic carbons

were calculated for all three possible structures, **3**, **11**, and **12**. The calculated shifts^{9,10,12} for the isomer with the sulfate group located at C-17 fit the observed values best and are also consistent with the location of the sulfate group in related sesquiterpene quinols.^{4a} We propose that the structure of siphonodictyal C be revised from **10** to **3**. The ¹³C NMR shifts of the sesquiterpene part were assigned by comparing the chemical shifts observed for **3** with those assigned for **9**.¹³ The stereochemistry remains as assigned earlier.^{4a}



The molecular formula for compound **4** was established as C₂₂H₃₂O₄ by HRESIMS (positive mode). The ¹H NMR spectrum showed signals for four tertiary methyl groups (δ 0.81, 0.83, 1.04, and 1.20). The lowest field of these was indicative of a methyl group geminal to a hydroxyl (δ 1.20). Two mutually coupled doublets at δ 6.62 and 6.98 (*J* = 9 Hz) suggested the presence of two ortho protons on a benzene ring. A singlet at δ 10.6 was assigned to an aldehyde proton, and a corresponding carbon signal was present in the ¹³C NMR spectrum (see Experimental Section). The ¹³C NMR spectrum was weak due to the small amount of sample available, and signals for only 19 carbons were observed. However, most of these could be assigned

(see Experimental Section) from HMQC and HMBC data, and a comparison of the ¹H NMR and observable ¹³C NMR data of **4** with those reported for siphonodictyal A^{4d} isolated from *Siphonodictyon coralliphagum* strongly indicates that **4** is siphonodictyal A.

The molecular formula of compound **5** was determined to be C₂₁H₂₉O₇Na by HRESIMS and NMR data. The sulfate nature of the compound was determined as before. The ¹³C NMR spectrum showed signals for 20 carbons instead of 21, and seven of these are in the olefinic and aromatic region. We conclude that one of the aromatic quaternary carbons could not be detected owing to the small amount of sample. Its ¹H NMR spectrum possessed signals for three tertiary methyls (δ 0.92, 0.89, and 0.87) and an olefinic methyl (δ 1.42) similar to compound **3**. One signal was observed at δ 5.31 (br s), which was assigned to a proton on a trisubstituted double bond. In addition, a signal observed at δ 6.31 was reminiscent of an aromatic proton flanked by two phenolic groups. Benzylic methylene protons were observed at δ 2.75 (1H, dd, *J* = 16, 9 Hz) and 2.58 (1H, dd, *J* = 16, 2.5 Hz).

The ¹³C data of the sesquiterpene part of **5** matched that of compound **3** very well and suggested that all the oxygen atoms are directly or indirectly attached to the aromatic group. The sulfate group accounts for four oxygens, and the remaining three were present in three phenolic hydroxyls. Thus the benzene ring bears a methylene, a proton, a sulfate group, and three hydroxyl groups. The substitution pattern could not be ascertained from the available spectroscopic data. 2D NMR data could not be obtained, as the compound was unstable. The probable substitution pattern was determined by calculation^{9,10,14} (for 10 possible substitution patterns) assuming that the proton is situated between two hydroxyl groups because of its chemical shift. This resulted in the tentative assignment of structure **5** for this compound, for which we suggest the name siphonodictyal I.

Compound **6** was identified as halistanol sulfate on the basis of comparison of its characteristic ¹H and ¹³C NMR spectral data with that reported in the literature.¹⁵

Of the six compounds isolated, **1**, **3**, **4**, and **6** were tested in the CDK4/cyclin D1 assay. The nonsulfated compounds **1** and **4** did not inhibit complex formation at a concentration of 10 μg/mL, whereas the sulfated ones, **3** and **6**, inhibited complexation with IC₅₀'s of 9 and 9.5 μg/mL, respectively. The sulfate group may be acting as a phosphate mimic for binding to the cyclin complex.

Experimental Section

General Experimental Procedures. Optical rotations were measured on a Rudolph Autopol III automatic polarimeter. All NMR spectra were recorded on a Varian VXR-500 MHz spectrometer with a switchable 3 mm probe. FABMS and ESIMS were measured on VG ZAB-E and Micromass Q-TOF mass spectrometers, respectively. EIMS was measured on a Finnigan Polaris/GCQ plus spectrometer. RP VLC was carried out using LRP-2 C₁₈ gel (Whatman Inc.). Preparative HPLC was performed using an RI detector and a Phenomenex ODS column (250 × 10 mm).

Animal Material. The sponge was collected at depths of ~10–20 m in Yap Archipelago, Micronesia, in 1995 and frozen for shipment and storage. It forms firm, relatively thick-walled tubes above coral, the base of which is inside cavities in living coral. The oscular tubes are often multiple, having two or more smooth branches, and are blunt at the apex. The parts of the sponge that are visible are bright, dark yellow; the interior is a duller yellow. The choanosome interior of the sponge emits copious amounts of mucus. The sponge exterior is tough, the interior softer. The ectosomal skeleton is tangential, forming

a regular round-meshed reticulation of angular hastate oxeas, and the choanosome is mushy and pulpy with scattered oxeas. The sponge is an undescribed species of *Aka de Laubenfels* (order Haplosclerida, family Niphatidae). A voucher is retained at the University of Oklahoma (34YA95), and a part of this has been deposited at the Natural History Museum, London, United Kingdom (BMNH 2001.19.7.1).

Extraction and Isolation. Frozen specimens were cut into small pieces and freeze-dried. The dry specimen (19.2 g) was extracted with MeOH (300 mL \times 2) followed by DCM–MeOH (300 mL \times 2). Combined extracts were concentrated to dryness and subjected to Kupchan partitioning.¹⁶ The butanol extract (1.09 g) from the Kupchan partition showed activity and was chromatographed on a RP C₁₈ VLC column using a step gradient beginning with H₂O and progressing in 20% increments to MeOH (100%), and the fractions were coded F008 (767 mg), F009 (56 mg), F010 (37 mg), F011 (25 mg), F012 (78 mg), and F013 (14 mg), respectively. Activity was detected in a variety of fractions. Fractions F009–F012 were chosen for further study based on ¹H NMR spectra.

Each of the four fractions was first separated on RP HPLC using MeOH–0.01 M Na₂SO₄ (8:2), and the subfractions were subsequently purified using different MeOH–H₂O mixtures to obtain compounds **2–4**.

Compounds **1**, **2**, **5**, and **6** were obtained from another portion of the butanol extract by chromatography over Sephadex LH-20, followed by preparative RP HPLC using various MeOH–H₂O ratios.

Akaol (1): [α]_D –12 (c 0.15, MeOH); ¹H NMR (CD₃OD) δ 6.51 (1H, s, H-19), 4.40 (1H, d, J = 11 Hz, H-22), 4.27 (1H, d, J = 11 Hz, H-22'), 3.32 (3H, s, OCH₃), 2.80 (1H, dd, J = 16, 7.5 Hz, H-15), 2.67 (1H, d, J = 16 Hz, H-15'), 2.60, 1.56 (2H, m, H-7), 1.77, 0.94 (2H, m, H-1), 1.61 (1H, m, H-9), 1.58, 1.39, 1.32 (4H, m, H-2, H-6), 1.42, 1.19 (2H, m, H-3), 1.14 (3H, s, 13-CH₃), 1.00 (1H, m, H-5), 0.88 (3H, s, 12-CH₃) 0.78 (3H, s, 11-CH₃), 0.38 (3H, s, 14-CH₃); ¹³C NMR, see Table 1; HRESIMS m/z 357.2430 [M – H][–] (calcd for C₂₃H₃₃O₃, 357.2430).

Akaol (2): [α]_D –36.0 (c 0.05, MeOH); ¹H NMR (CD₃OD) δ 6.76 (1H, s, H-19), 4.68 (1H, d, J = 13 Hz, H-22), 4.62 (1H, d, J = 13 Hz, H-22'), 3.01 (1H, dd, J = 16, 10 Hz, H-15), 2.95 (1H, d, J = 16 Hz, H-15'), 2.63 (1H, m, H-7), 1.80, 0.93 (2H, m, H-1), 1.62 (1H, m, H-9), 1.18 (3H, s, 13-CH₃), 0.88 (3H, s, 12-CH₃), 0.80 (3H, s, 11-CH₃), 0.42 (3H, s, 14-CH₃); ¹³C NMR, see Table 1; HMBC H11/C-3, C-4, C-5; H-12/C-3, C-4, C-5; H13/C-7, C-8, C-9, C-21; H14/C-1, C-5, C-9, C-10; H15/C-17; H19/C-20, C-21; HRESIMS m/z 423.1812 [M – Na][–] (calcd for C₂₂H₃₁O₆–SNa, 423.1841).

Siphonodictyal C (3): [α]_D –13.1 (c 0.19, MeOH); ¹H NMR (CDCl₃+CD₃OD) δ 10.1 (1H, s, –CHO), 6.94 (1H, s, H-21), 5.17 (1H, d, J = 4 Hz, H-7), 2.73 (1H, dd, J = 16, 7 Hz), 2.47 (1H, d, J = 14 Hz), 1.42 (3H, s, 13-CH₃), 0.92 (3H, s), 0.92 (3H, s), 0.88 (3H, s); ¹³C NMR, see Table 1; HRESIMS m/z 437.1629 [M – Na][–] (calcd for C₂₂H₂₉O₇S, 437.1634).

Siphonodictyal A (4): ¹H NMR (CD₃OD) δ 10.6 (1H, s, –CHO), 6.95 (1H, d, J = 9 Hz, H-19), 6.62 (1H, d, J = 9 Hz, H-20), 3.35, 3.07, 1.90, 1.28, 1.08, 0.85, 0.82; ¹³C NMR (CD₃OD) (assigned signals are based on HMQC and/or HMBC data; a few signals were not detected in any spectra due to small sample size) δ 196.0 (C-22), 145.9, 126.6 (C-20), 116.2 (C-19),

74.2 (C-8; observed only in HMBC spectrum), 64.6 (C-9), 57.6 (C-5), 45.2 (C-7), 42.8 (C-3), 41.6 (C-1), 41.3, 34.1 (C-12), 34.0, 24.2 (C-13), 20.8 (C-15), 19.4 (C-11), 15.9 (C-14); HRESIMS m/z 383.2245 [M + Na]⁺ (calcd for C₂₂H₃₄O₄Na, 383.2198).

Siphonodictyol I (5): ¹H NMR (CD₃OD) δ 6.31 (1H, s, H-18), 5.31 (1H, br s, H-7), 2.75 (1H, dd, J = 16, 9 Hz, H-15), 2.58 (1H, dd, J = 16, 2.5 Hz, H-15), 1.42 (3H, s, H-13), 0.92 (3H, s), 0.89 (3H, s), 0.87 (3H, s); ¹³C NMR (see Table 1); HRESIMS m/z 425.1699 [M – Na][–] (calcd for C₂₁H₂₉O₇S, 425.1634).

Acknowledgment. This work was supported by NCIGrant CA 52955. We thank C. Arneson and L. Sharon and the Coral Reef Research Foundation for assistance in collecting specimens, and Dr. J. H. Kwak for assistance with some of the NMR experiments. We thank the Government of Yap, Federated States of Micronesia, for permission to collect specimens.

Supporting Information Available: Tables of calculated vs observed ¹³C NMR data for compounds **2** (S1), **3**, **11**, **12** (S2), and **5** [vs nine alternate aromatic substitution patterns (S3)]; chart of alternative structures for **5** (chart S1). This material is available free of charge via the Internet at <http://pubs.acs.org>.

References and Notes

- (a) Collins, K.; Jacks, T.; Pavletich, N. P. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 2776–2778. (b) Sherr, C. J. *Science* **1996**, *274*, 1672–1677. (c) Pavletich, N. P. *J. Mol. Biol.* **1999**, *287*, 821–828.
- (a) Kobayashi, J.; Suzuki, M.; Tsuda, M. *Tetrahedron* **1997**, *53*, 15681–15684. (b) Sung, N. D.; Kim, M. R.; Ha, J. H.; Kwon, B. M.; Chung, H. W.; Ahn, B. T.; Ryu, S. Y. *Han'guk Nonghwa Hakhoes* **2000**, *43*, 174–178.
- Soni, R.; Muller, L.; Furet, P.; Schoepfer, J.; Stephen, C.; Zumstein-Mecker, S.; Fretz, H.; Chaudhuri, B. *Biochem. Biophys. Res. Commun.* **2000**, *275*, 877–884.
- (a) Sullivan, B. W.; Faulkner, D. J.; Matsumoto, G. K.; Cun-heng, H.; Clardy, J. *J. Org. Chem.* **1986**, *51*, 4568–4573. (b) Killday, K. B.; Wright, A. E.; Jackson, R. H.; Sills, M. A. *J. Nat. Prod.* **1995**, *58*, 958–960. (c) Chan, J. A.; Freyer, A. J.; Carte, B. K.; Hemling, M. E.; Hofmann, G. A.; Mattern, M. R.; Mentzer, M. A.; Westley, J. W. *J. Nat. Prod.* **1994**, *57*, 1543–1548. (d) Sullivan, B.; Djura, P.; McIntyre, D. E.; Faulkner, D. J. *Tetrahedron* **1981**, *37*, 979–382.
- (a) Goclik, E.; Konig, G. M.; Wright, A. D.; Kaminsky, R. *J. Nat. Prod.* **2000**, *63*, 1150–1152. (b) Kwak, J. H.; Schmitz, F. J.; Kelly, M. J. *J. Nat. Prod.* **2000**, *63*, 1153–1156.
- (a) Ayer, W. A.; Browne, L. M.; Fung, S.; Stothers, J. B. *Org. Magn. Reson.* **1978**, *11*, 73–80. (b) Browne, L. M.; Klinck, R. E.; Stothers, J. B. *Org. Magn. Reson.* **1979**, *12*, 561–568.
- Crews, P.; Rodriguez, J.; Jaspars, M. *Organic Structure Analysis*; Oxford University Press: New York, 1998; p 79.
- Molinski, T. F.; Faulkner, D. J. *J. Org. Chem.* **1987**, *52*, 296–298, and references therein.
- Ragan, M. A. *Can. J. Chem.* **1978**, *56*, 2681–2685.
- Wehrli, F. W.; Wirthlin, T. *Interpretation of Carbon-13 NMR Spectra*; Heyden: London, 1978.
- See Table S1 of Supporting Information.
- See Table S2 of Supporting Information.
- Rodriguez, J.; Quinoa, E.; Riguera, R.; Peters, B. M.; Abrell, L. M.; Crews, P. *Tetrahedron* **1992**, *48*, 6667–6680.
- The possible structures and a table of calculated values along with the observed values are in Table S3 of Supporting Information.
- Fusetani, N.; Matsunaga, S.; Konosu, S. *Tetrahedron Lett.* **1981**, *22*, 1985–1988.
- Kupchan, S. M.; Britton, R. W.; Ziegler, M. F.; Siegel, C. W. *J. Org. Chem.* **1973**, *38*, 178–179.

NP0205506