Hexaprenoid Hydroquinones from the Sponge *Haliclona* (aka *Adocia*) sp.

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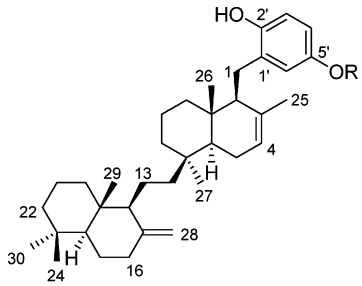
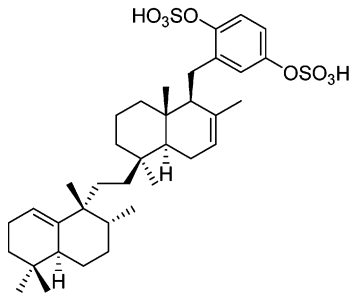
Three new hexaprenoid hydroquinones, adociaquinol (**1**), adociasulfate 11 (**2**), and adociasulfate 12 (**3**), together with the known adociasulfates 2, 4, and 6, were isolated from the marine sponge *Haliclona* (aka *Adocia*) sp. The structures of these compounds were elucidated by interpretation of spectroscopic data.

Merotriterpenes are a relatively rare class of metabolite that have been found to exhibit a variety of interesting biological activities. The shaagrockols, toxicols, and toxiusol isolated from the Red Sea sponge *Toxiclona toxius* were reported to inhibit HIV reverse transcriptase.[1−3] Akaterpin from the marine sponge *Callyspongia* sp. was found to be an inhibitor of phosphatidylinositol-specific phospholipase C.[4] More recently, sponges of the genus *Adocia* (order Haplosclerida, family Chalinidae), collected from Palau and Australia, have produced a series of biologically active hexaprenoid hydroquinone sulfates.[5−8] Adociasulfates 1−6 and 10, reported from a Palauan sponge of this genus, were found to be inhibitors of the kinesin motor protein.[5,9] Independently, adociasulfates 1, 7, and 8, from an unidentified species of *Adocia* collected in Northern Queensland, were found to have H^+-ATPase protein pump activity.[6] In this study further investigation of a Palauan specimen of *Haliclona* (aka *Adocia*) sp. led to the isolation of three new merotriterpenoids, adociaquinol (**1**) and adociasulfates 11 (**2**) and 12 (**3**), and the three known adociasulfates 2, 4, and 6. This paper describes the isolation and structural elucidation of the new compounds.



1 R = H
2 R = SO_3H



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Results and Discussion

The specimen of *Haliclona* (aka *Adocia*) sp. from Palau was kept frozen until being extracted with methanol. The methanolic extract was first fractionated on polymeric HP-20 resin. The 40% acetone in water fraction was further purified by chromatography on size exclusion TSK-HW-40 and reversed-phase HPLC to obtain adociasulfate 11 (**2**). The 60% acetone in water fraction was purified by reversed-phase HPLC to obtain adociaquinol (**1**) and a mixed fraction, which was separated on TSK-HW-40 and HPLC to obtain adociasulfate 12 (**3**) along with the three known compounds, adociasulfates 2, 4, and 6.

Adociaquinol (**1**) was isolated as a colorless oil, $[\alpha]_D$ −45. The molecular formula of adociaquinol (**1**), $C_{36}H_{54}O_2$, which was determined from the HRFABMS of the $[M]^+$ ion at *m*/*z* 518.4112 (Δ −1.2 mmu), required 10 degrees of unsaturation. An initial examination of the ^{13}C NMR data revealed 10 carbons in the aromatic/olefinic region of the spectrum and 26 aliphatic carbons. These data suggested that adociaquinol consisted of an aromatic ring joined to a tetracyclic hexaprenoid containing two olefinic bonds. Analysis of the NMR data (Table 1) revealed that the aromatic portion of the molecule was a monosubstituted hydroquinone. The ^1H NMR spectrum revealed three aromatic proton signals at δ 6.35 (1H, dd, J = 8.5, 3.0 Hz), 6.54 (1H, d, J = 8.5 Hz), and 6.57 (1H, d, J = 3.0 Hz) that showed HSQC correlations to the aromatic carbon signals at δ 112.1 (C-4′), 115.2 (C-3′), and 115.6 (C-6′), respectively. Analysis of the HMBC data, which contained correlations from the phenolic-OH signals at δ 8.57 (OH-2′) to C-1′, C-2′, and C-3′, and from 8.49 (OH-5′) to C-4′, C-5′, and C-6′, confirmed the positions of hydroxyl groups at C-2′ and C-5′. The benzylic protons at δ 2.53 (1H, dd, J = 14.5, 8.0 Hz) and 2.36 (1H, brd, J = 14.5 Hz) at C-1 were coupled to a methine signal at δ 2.25 (1H, brd, J = 8.0 Hz) in a COSY experiment. HMBC correlations from H_2-1 (δ 2.53, 2.36) to C-1′ and C-2′ and a three-bond correlation from H-2 to C-1′ confirmed the connection of C-1 to the C-1′ position on the aromatic ring.

Both the H_2-1 and H-2 signals also showed HMBC correlations to an olefinic signal at δ 135.0 that was assigned to the fully substituted carbon of the trisubstituted olefin (C-3). HMBC correlations from the olefinic methyl signal at δ 1.39 (3H, brs, Me-25) to C-2, C-3, and C-4 and from the methyl signal at δ 0.8 (3H, s, Me-26) to C-2, C-6, C-7, and C-8 indicated that C-2 was flanked by a trisubstituted olefin on one side and a ring junction bearing a methyl group on the other. The COSY spectrum revealed the connectivity between the H-4 signal at δ 5.31 (brs, 1H) through the H_2-5 signal at 1.88 (m, 2H) to the H-6 signal at δ 1.25 (m, 1H), completing the assignment of the ring D. The *cis*-relationship between H-4 and Me-25 was confirmed by an NOE correlation observed in a ROESY experiment. The presence of HMBC correlations from the Me-27 signal at δ 0.86 (s, 3H) to C-6, C-10, C-11, and C-12, together with a detailed analysis of the HSQC

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Table 1. ^{1}H, ^{13}C, and HMBC Data for Adociaquinol (**1**) and Adociasulfate 12 (**3**)

	1[a]			**3**[b]		
C #	δ_C (DEPT)	δ_H, mult. (*J* in Hz)	HMBC	δ_C (DEPT)	δ_H, mult. (*J* in Hz)	HMBC
1	25.5 (CH_2)	2.53 dd (14.5, 8.0) 2.36 brd (14.5)	C-1′, C-2′, C-2, C-3, C-6′ C-1′, C-2′, C-2, C-3, C-6′, C-7	28.0 (CH_2)	2.87 dd (16.0, 10.0) 2.69 brd (16.0)	C-1′, C-2′, C-6′
2	54.5 (CH)	2.25 brd (8.0)	C-1′, C-3	56.3 (CH)	2.38 brd (8.0)	
3	135.0 (C)			136.6 (C)		
4	121.3 (CH)	5.31 s		122.8 (CH)	5.28 brs	
5	22.8 (CH_2)	1.88 m		24.5 (CH_2)	1.87 m	
6	52.2 (CH)	1.25 m	C-5, C-11, C-12, C-16, C-27, C-26	54.1 (CH)	1.35 m	
7	36.4 (C)			38.1 (C)		
8	38.9 (CH_2)	1.90 m 1.09 m		40.8 (CH_2)	1.92 brd (12.0) 1.19 dt (12.0, 5.0)	
9	18.6 (CH_2)	1.41 m		19.8 (CH_2)	1.42 m	
10	36.8 (CH_2)	1.78 m 0.93 m		38.1 (CH_2)	1.72 m 0.96 m	
11	35.6 (C)			36.6 (C)		
12	31.2 (CH_2)	1.76 m 0.89 m		26.7 (CH_2)	1.38 m	
13	17.6 (CH_2)	1.36 m 1.21 m		26.1 (CH_2)	1.57 m 0.95 m	
14	57.2 (CH)	1.52 m	C-12, C-15, C-19, C-28, C-29	43.6 (C)		
15	148.6 (C)			46.3 (CH)	1.28 m	
16	37.8 (CH_2)	2.36 m 1.98 td (12.0, 4.0)	C-17 C-15, C-17, C-28	32.7 (CH_2)	1.53 m 1.48 m	
17	24.0 (CH_2)	1.70 m 1.24 m		31.5 (CH_2)	1.83 dq (11.5, 3.0) 1.10 m	
18	54.7 (CH)	1.11 m	C-14, C-17, C-19, C-23, C-24, C-29, C-30	45.1 (CH)	1.56 m	
19	39.3 (C)			147.6 (C)		
20	38.4 (CH_2)	1.74 m 1.02 m		117.6 (CH)	5.35 m	
21	18.9 (CH_2)	1.48 m		24.3 (CH_2)	2.03 m	
22	41.6 (CH_2)	1.37 m 1.18 m		32.4 (CH_2)	1.40 m 1.10 m	
23	33.2 (C)			32.4 (C)		
24	21.5 (CH_3)	0.79 s	C-18, C-22, C-23, C-30	28.6 (CH_3)	0.93 s	C-18, C-22, C-23, C-30
25	21.8 (CH_3)	1.39 brs	C-2, C-3, C-4	22.9 (CH_3)	1.40 brs	C-2, C-3, C-4
26	14.6 (CH_3)	0.80 s	C-2, C-6, C-7, C-8	15.5 (CH_3)	0.90 s	C-2, C-6, C-7, C-8
27	28.8 (CH_3)	0.86 s	C-6, C-10, C-11, C-12	29.4 (CH_3)	0.84 s	C-6, C-10, C-11, C-12
28	105.4 (CH_2)	4.84 s 4.52 s	C-14, C-15, C-16 C-14, C-16	24.1 (CH_3)	1.01 s	C-13, C-14, C-15, C-19
29	14.4 (CH_3)	0.65 s	C-14, C-18, C-19, C-20	16.9 (CH_3)	0.86 d (7.0)	C-14, C-15, C-16
30	33.4 (CH_3)	0.87 s	C-18, C-22, C-23, C-24	28.5 (CH_3)	0.87 s	C-18, C-22, C-23, C-24
1′	129.9 (C)			139.0 (C)		
2′	146.7 (C)			148.4 (C)		
3′	115.2 (CH)	6.54 d (8.5)	C-1, C-2′	123.3 (CH)	7.35 d (9.0)	C-1′, C-2′, C-4′, C-5′
4′	112.1 (CH)	6.35 dd (8.5, 3.0)	C-2′, C-3′, C-5′	119.8 (CH)	7.05 dd (9.0, 3.0)	C-2′
5′	149.3 (C)			150.5 (C)		
6′	115.6 (CH)	6.57 d (3.0)	C-1′, C-4′, C-5′	123.1 (CH)	7.27 d (3.0)	C-2′, C-4′, C-5′
OH-2′		8.57 s	C-1′, C-2′, C-3′			
OH-5′		8.49 s	C-4′, C-5′, C-6′			

[a] Spectra obtained in DMSO-d_6. [b] Spectra obtained in CD_3OD.

and COSY data, permitted the assignment of the signals in ring C and established the presence of an alkyl chain at C-11, thereby defining the C/D decalin ring system.

A majority of the A/B ring system was elucidated from a series of HMBC correlations from the three methyl signals Me-24, Me-29, and Me-30 (δ 0.79, 0.65, and 0.87) and the exocyclic methylene proton signals H_2-28 (δ 4.84 and 4.52). COSY correlations observed between H_2-16/H_2-17/H-18, and H_2-20/H_2-21/H_2-22, completed the assignment of the A/B decalin ring system. The COSY spectrum also provided evidence of the ethyl linkage (CH_2-12 and CH_2-13) linking the A/B and C/D ring systems.

The relative stereochemistry of adociaquinol (**1**) was determined from NOE enhancements observed in a ROESY experiment. NOE correlations from Me-26 to H_2-5, H_2-1, and H-12a, together with correlations from H-6 to H-2 and Me-27, establish the *trans*-fused nature of the C/D rings and the equatorial geometry of both the benzyl chain at C-2 and the methyl group at C-11. A long-range *W*-coupling between Me-26 and H-2 in the COSY experiment was consistent with the 1,2-diaxial arrangement of these two groups. In a similar fashion, the NOE correlations from Me-29 to Me-24 and H-13b and from H-18 to H-14 and Me-30 establish the *trans*-fused nature of the A/B rings and placed the C-12/C-13 side chain in the equatorial position. Although some ROESY correlations were observed between protons on the A/B ring system and those on the C/D ring system, the overlap of key signals made it impossible to determine the relative stereochemistry of the two decalin ring systems. The stereochemistry of adociaquinol (**1**) is therefore defined as (2*S**,6*S**,7*S**,11*R**,14*S**,18*R**,19*R**) or (2*S**,6*S**,7*S**,11*R**,14*R**,18*S**,19*S**).

Adociasulfate 11 (**2**) was obtained as a colorless oil, $[\alpha]_D$ −18. The molecular formula, $C_{36}H_{54}O_5S$, was determined by high-resolution mass measurement of the $[M - H]^-$ ion at *m*/*z* 597.3624 (Δ +1.0 mmu). The presence of an S═O stretching band at 1210 cm^{-1} in the IR spectrum and a significant [M + 2] peak (11%) in the mass spectrum were consistent with presence of a sulfate group. A comparison of the ^{1}H and ^{13}C NMR data revealed that **2** was identical to adociaquinol (**1**) except that one of the phenolic hydroxyl groups had been replaced by a sulfate. The ^{1}H NMR contained three aromatic proton signals at δ 6.60 (1H, d, J = 8.5 Hz), 6.72 (1H, dd, J = 8.5, 3.0 Hz), and 6.90 (1H, d, J = 3.0 Hz)

that correlated to the carbons δ 114.3 (C-3′), 118.4 (C-4′), and 121.5 (C-6′), respectively. Location of the phenolic group at C-2′ and the sulfate C-5′ was assigned by interpretation of the HMBC experiment, which showed correlations from the phenolic hydroxyl signal at δ 8.98 to the C-1′, C-2′, and C-3′ signals. This assignment was supported by a comparison of the ^{1}H and ^{13}C chemical shifts of the aromatic ring signals in the sulfate **2** with those of the phenol **1**. The observed upfield shift of C-5′ and the downfield shifts of C-4′ and C-6′ in the ^{13}C NMR spectrum and the downfield shifts of the H-4′ and H-6′ in the ^{1}H NMR spectrum were consistent with the replacement of the C-5′ phenol by a sulfate group. The structure of adociasulfate 11 (**2**) was confirmed by acid-catalyzed hydrolysis to obtain adociaquinol (**1**), which was identical in all respects to an authentic sample.

Adociasulfate 12 (**3**) was obtained as a colorless oil, $[\alpha]_D$ −30. The molecular formula, $C_{36}H_{54}O_8S_2$, was determined by HRFABMS of the $[M - 2H + Na]^-$ ion at *m*/*z* 699.2987 (Δ +1.4 mmu). The presence of a strong S═O stretching band in the IR and a significant [M + 2] peak in the ESIMS was consistent with the presence of sulfate groups. Overall, the NMR features of **3** were similar to those of **1** and **2**, except that it lacked the exocyclic methylene signals and the proton and carbon signals of the aromatic ring were further deshielded. Due to the overlap of the methyl signals, the NMR data were obtained in CD_3OD (Table 1). Analysis of the NMR data allowed the proton resonances at δ 7.35 (1H, d, J = 9.0 Hz), 7.27 (1H, d, J = 3.0 Hz), and 7.05 (1H, dd, J = 9.0, 3.0 Hz) and the carbons at δ 150.5 (C-5′), 148.4 (C-2′) 139.0 (C-1′) 123.3 (C-3′), 123.1 (C-6′), and 119.8 (C-4′) to be assigned to a 1-alkyl-2,5-hydroquinone disulfate. Alkyl substitution at C-1′ was confirmed by HMBC correlation from a proton (δ 2.87) of the methylene group at C-1 to C-1′, C-2′, and C-6′. Similar HMBC and COSY correlations established the C/D decalin ring system containing the trisubstituted double bond and allowed its connection to the aromatic moiety. In the A/B decalin ring system of **3**, the exocyclic olefinic methylene group of **1** and **2** was replaced by a trisubstituted double bond (δ 5.35; δ 147.6, 117.6). HMBC correlations from the three methyl signals at Me-24, Me-28, and Me-30 (δ 0.93, 1.01, and 0.87) and the methyl doublet signal at Me-29 (δ 0.8) allowed a major portion of the decalin ring system to be assembled. HMBC correlations from the Me-28 signal to the substituted olefinic carbon at δ 147.6 (C-19), a quaternary carbon at δ 43.6 (C-14), and a methine carbon at δ 46.3 (C-15) established the connection of Me-28 to C-14. The connection of the methyl doublet Me-29 to C-15 was determined from HMBC correlations from Me-29 to C-14, C-15, and a methylene group at C-16. COSY correlations between H-15/H_2-16/H_2-17/H-18 and between the olefinic methine signal H-20/H_2-21/H_2-22, together with a long-range allylic coupling observed between H-20 and H-18, completed the assignment of the A/B ring system. Additional HMBC correlations from Me-28 to the methylene group at C-13 and from Me-27 to C-12, together with COSY correlations between the proton signals of these methylene groups, established the isolated ethyl bridge and linked the A/B and C/D ring systems.

The relative stereochemistry of adociasulfate 12 (**3**) was determined from NOE enhancements observed in a ROESY experiment and ^{1}H−^{1}H coupling constants (Figure 2). Comparison of ROESY correlations to that of **1** and **2** established the *trans*-fusion of the C/D rings with the benzyl chain equatorial and the ethyl bridge in the axial position. The relative stereochemistry of the A/B ring system was made somewhat difficult due to the overlap of the aliphatic signals in the ^{1}H NMR spectrum. NOE correlations observed between Me-24 (δ 0.93) and H_2-21 (δ 2.03) require Me-24 and H-21 to be in a 1,3-diaxial configuration and on the same side of the A/B ring. The 1,3-diaxial arrangement of Me-24 and H-17b (δ 1.10) and the anti-periplanar arrangement of H-17b and H-18 were established from ^{1}H−^{1}H coupling constants and NOE correlations. Homonuclear decoupling of H17b resulted in collapse of H-18 to a broadened singlet, indicating a large coupling between H-17b and H-18. Similarly decoupling of H-17a (δ 1.83, dq, J = 11.5, 3.0 Hz) resulted in collapse of H-18 to a doublet of 13.0 Hz, indicating a small (3.0 Hz) coupling between H-17a and H-18. These data combined with NOE correlations from both Me-24 and Me-30 to H-17b, together with correlation from Me-30 to H-17a and from H-17a to H-18, supported the assignment. The presence of a correlation between H-15 and the axial H-17b in the ROESY experiment established that H-17b and H-15 were on the same side of the molecule and suggested that ring B was in a boat conformation with H-15 in the axial position and the methyl doublet Me-29 equatorial. The axial arrangement of H-15 was supported by homonuclear decoupling of Me-29 in a 1D TOCSY experiment in which Me-29 was irradiated. This resulted in collapse of H-15 from a highly coupled multiplet to a doublet of doublets with coupling constants of 12.0 and 5.0 Hz, indicating one large and one small coupling. This is consistent only with H-15 in the axial position with ring B in a chair conformation. Finally NOE correlations observed from Me-28 to both H-15 and Me-29, together with a strong ROESY correlation to the olefinic proton H-20, established the equatorial arrangement of Me-28, placing the ethyl bridge in the axial position on the underside of the ring as drawn. The stereochemistry of adociasulfate 12 (**3**) is therefore defined as (2*S**,6*S**,7*S**,11*R**,14*R**,15R*,18*S**) or (2*S**,6*S**,7*S**,11*R**,14*S**, 15*S**,18*R**).

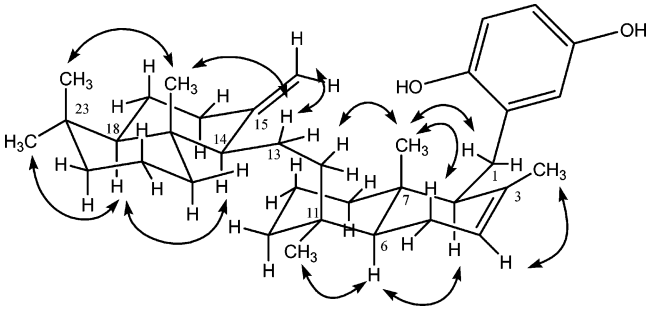

Figure 1. Selected NOE correlations that establish the relative stereochemistry of adociaquinol (**1**).

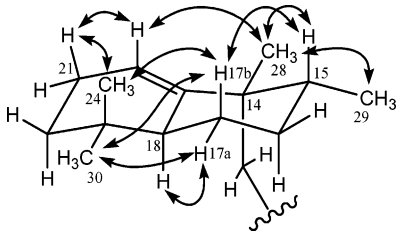

Figure 2. Selected ROESY correlations used to establish the relative stereochemistry of the A/B ring system of adociasulfate 12 (**3**).

All three compounds were evaluated for cytotoxicity in a human colon tumor (HCT-116) cell line and were found to have no significant cytotoxicity.

Experimental Section

General Experimental Procedures. Optical rotations were measured on a Rudolph Research Autopol III polarimeter. IR spectra were recorded on a Perkin-Elmer 1600 FTIR spectrophotometer. UV spectra were recorded on a Lambda 3B instrument. The ^{1}H, ^{13}C, and DEPT spectra were recorded on a Varian Gemini 400 spectrometer. All 2D NMR experiments were performed on a Unity-INOVA 300 spectrometer. All chemical shifts were referenced to the residual solvent peak (DMSO-d_6: ^{1}H, δ 2.39 ppm; ^{13}C, δ 39.5 ppm; MeOD-d_4: ^{1}H, δ 3.30 ppm; ^{13}C, δ 49.5 ppm). The high-resolution MALDI Fourier transform mass spectrum was recorded on an Ionspec FTMS mass spectrometer at the Scripps Research Institute. The HRFABMS measurement

performed on a VG ZAB2SE was obtained from the UC Riverside Regional Facility.

Biological Material. The sponge *Haliclona* (aka *Adocia*) sp. was collected by hand using scuba at a depth of 15 m at Turtle Island Basin, Palau, in 1996. The specimen was immediately frozen and kept at −20 °C until extraction. A voucher specimen has been deposited in the SIO Benthic Invertebrate Collection.

Extraction and Purification. The sponge (320 g wet weight) was extracted with MeOH (2 × 850 mL) for 24 h. The first and then the second extracts were passed through a column of HP20 (5 × 13 cm). The eluent was concentrated to 1 L. The column was eluted with 1 L fractions of (1) H_2O, (2) 20% Me_2CO/H_2O, (3) 40% Me_2CO/H_2O (4) 60% Me_2CO/H_2O, (5) 80% Me_2CO/H_2O, and (6) Me_2CO. Fraction 3 was concentrated to dryness and chromatographed on a TSK HW40 in 50% aqueous MeOH. A late-eluting fraction (40 mg) was subjected to further separation on reversed-phase HPLC (Hamilton PRP-1; 10 × 250 mm; 5 mL/min; 40−75% CH_3CN/H_2O over 45 min) to give adociasulfate 11 (**2**, 16.5 mg, 0.005% wet weight). Fraction 4 from the original HP-20 column was subjected to reversed-phase HPLC (Hamilton PRP-1; 25 × 250 mm; 10 mL/min; 35−50% CH_3CN/H_2O over 40 min, 40−80% CH_3CN/H_2O over 30 min) to afford adociaquinol (**1**, 15.4 mg, 0.005% wet weight) and an inseparable mixture of early-eluting compounds (70.0 mg). This mixture was further chromatographed on a TSK HW40 in 50% aqueous MeOH to give adociasulfates 2 (6 mg, 0.002% wet weight), 4 (15 mg, 0.005% wet weight), and 6 (4 mg, 0.001% wet weight) and a fraction (13 mg) that was rechromatographed on a reversed-phase HPLC (Hamilton PRP-1; 10 × 250 mm; 5 mL/min; 30−50% CH_3CN/H_2O over 50 min) to give adociasulfate 12 (**3**, 2.4 mg, 0.001% wet weight).

Adociaquinol (1): clear oil; $[\alpha]^{20}_D$ −45 (*c* 0.7, MeOH); UV (MeOH) λ_{max} 208 nm (log ϵ) (4.17), 246 (3.55), 296 (3.43); IR (KBr) ν_{max} 3354, 2917, 2845, 1639, 1597, 1504, 1447, 1374, 1364, 1192 cm^{-1}; ^1H and ^{13}C NMR (DMSO-d_6, 300 MHz) see Table 1; HRFABMS *m*/*z* 518.41120 $[M]^+$ (calcd for $C_{36}H_{54}O_2$ 518.41238).

Adociasulfate 11 (2): clear oil; $[\alpha]^{20}_D$ −18 (*c* 2.2, MeOH); UV (MeOH) λ_{max} 208 nm (log ϵ) (4.15), 220 (3.80), 282 (3.22); IR (KBr) ν_{max} 3417, 2925, 2845, 1643, 1505, 1439, 1259, 1210, 1050 cm^{-1}; ^1H and ^{13}C NMR (400 MHz, DMSO-d_6) δ 8.98 (s, 1H, 2′-OH), 6.90 (d, 1H, J = 3.0 Hz, H-6′), 6.72 (dd, 1H, J = 8.5, 3.0 Hz, H-4′), 6.60 (d, 1H, J = 8.5 Hz, H-3′), 5.29 (s, 1H, H-4), 4.82 (s, 1H, H-28a), 4.50 (s, 1H, H-28b), 2.51 (dd, 1H, J = 14.5, 9.0 Hz, H-1a), 2.37 (brd, 1H, J = 14.5 Hz, H-1b), 2.35 (d, 1H, J = 10.0 Hz, H-16a), 2.24 (brd, 1H, J = 9.0 Hz, H-2), 1.95 (dt, 1H, J = 11.0, 5.0 Hz, H-16b), 1.87 (m, 2H, H-5), 1.87 (m, 1H, H-8a), 1.76 (m, 1H, H-12a), 1.76 (m, 1H, H-10a), 1.72 (m, 1H, H-20a), 1.68 (m, 1H, H-17a), 1.57 (m, 1H, H-14), 1.46 (m, 2H, H-21), 1.42 (m, 2H, H-9), 1.35 (s, 3H, Me-25), 1.34 (m, 1H, H-13a), 1.34 (m, 1H, H-22a), 1.26 (m, 1H, H-6), 1.23 (m, 1H, H-17b), 1.21 (m, 1H, H-13b), 1.16 (m, 1H, H-22b), 1.12 (m, 1H, H-18), 1.11 (m, 1H, H-8b), 1.01 (m, 1H, H-20b), 0.91 (m, 1H, H-10b), 0.86 (m, 1H, H-12b), 0.84 (s, 3H, Me-27), 0.84 (s, 3H, Me-30), 0.78 (s, 3H, Me-26), 0.76 (s, 3H, Me-24), 0.63 (s, 3H, Me-29); ^{13}C NMR (100 MHz, DMSO-d_6) δ 150.2 (C-2′), 148.6 (C-15), 145.4 (C-5′), 135.0 (C-3), 129.1 (C-1′), 121.5 (C-6′), 121.4 (C-4), 118.4 (C-4′), 114.3 (C-3′), 105.5 (C-28), 57.3 (C-14), 54.7 (C-18), 54.3 (C-2), 52.0 (C-6), 41.6 (C-22), 39.6 (C-19), 38.9 (C-8), 38.5 (C-20), 37.8 (C-16), 36.7 (C-10), 36.4 (C-7), 35.6 (C-11), 33.4 (C-30), 33.2 (C-23), 31.2 (C-12), 28.7 (C-27), 25.4 (C-1), 24.0 (C-17), 22.8 (C-5), 21.9 (C-25), 21.6 (C-24), 18.9 (C-21), 18.6 (C-9), 17.6 (C-13), 14.6 (C-26), 14.4 (C-29); HRFABMS *m*/*z* 597.36240 $[M - H]^-$ (calcd for $C_{36}H_{53}O_5S$, 597.36159).

Hydrolysis of Adociasulfate 11 (2). *p*-Toluenesulfonic acid (5.0 mg) was added to a solution of **2** (2.0 mg) in Me_2CO (1.5 mL). After 1 h the reaction was quenched with H_2O (500 μL) and passed through a column of HP20ss (1 × 2 cm). The eluent was diluted with H_2O and re-passed through the column. The column was then eluted with 10 mL fractions of (1) 50% Me_2CO/H_2O and (2) Me_2CO. The Me_2CO fraction was concentrated to dryness to afford adociaquinol (**1**) (1.5 mg, 87% yield).

Adociasulfate 12 (3): clear oil; $[\alpha]^{20}_D$ −30 (*c* 0.03, MeOH); UV (MeOH) λ_{max} 210 nm (log ϵ) (3.93), 278 (3.01); IR (KBr) ν_{max} 3405, 2948, 2917, 2855, 1675, 1644, 1483, 1447, 1379, 1255, 1208, 1141, 1037 cm^{-1}; ^1H and ^{13}C NMR (Table 1); HRFABMS *m*/*z* 699.29870 $[M - 2H + Na]^-$ (calcd for $C_{36}H_{52}O_8S_2Na$, 699.30013).

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Supporting Information Available: NMR spectra of **1**, **2**, and **3** are available including ^1H, ^{13}C, DEPT, COSY, HSQC, HMBC, and ROESY. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Issacs, S.; Kashman, Y. *Tetrahedron Lett.* **1992**, *33*, 2227−2230.
(2) Issacs, S.; Hizi, A.; Kashman, Y. *Tetrahedron* **1993**, *49*, 4275−4282.
(3) Loya, S.; Tal, R.; Hizi, A.; Issacs, S.; Kashman, Y.; Loya, Y. J. *Nat. Prod.* **1993**, *56*, 2120−2125.
(4) Fukami, A.; Ikeda, Y.; Kondo, S.; Naganawa, H.; Takeuchi, T.; Furuya, S.; Hirabayashi, Y.; Shimoike, K.; Hosaka, S.; Watanabe, Y.; Umezawa, K. *Tetrahedron Lett.* **1997**, *38*, 1201−1202.
(5) Blackburn, C. L.; Hopmann, C.; Sakowicz, R.; Berdelis, M. S.; Goldstein, L. S. B.; Faulkner, D. J. *J. Org. Chem.* **1999**, *64*, 5565−5570.
(6) Kalaitzis, J. A.; de Almeida Leone, P.; Harris, L.; Butler, M. S.; Ngo, A.; Hooper, J. N. A.; Quinn, R. J. *J. Org. Chem.* **1999**, *64*, 5571−5574.
(7) Kalaitzis, J. A.; Quinn, R. J. *J. Nat. Prod.* **1999**, *62*, 1682−1684.
(8) Blackburn, C. L.; Faulkner, D. J. *Tetrahedron* **2000**, *56*, 8429−8432.
(9) Sakowicz, R.; Berdelis, M. S.; Ray, K.; Blackburn, C. L.; Hopmann, C.; Faulkner, D. J.; Goldstein, L. S. B. *Science* **1998**, *280*, 292−295.

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