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Structural Reassignment of a Marine Metabolite from a Binaphthalenetetrol to a Tetrabrominated Diphenyl Ether

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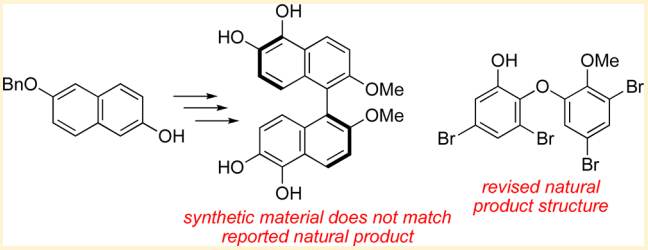
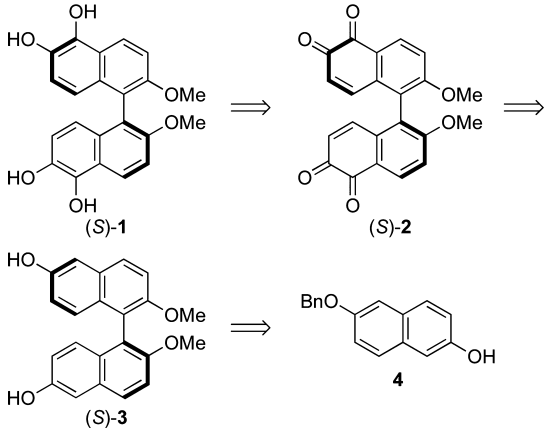
Supporting Information

ABSTRACT: The structure of a reported natural product isolate has been revised from (*S*)-2,2′-dimethoxy-[1,1′-binaphthalene]-5,5′,6,6′-tetraol to a known tetrabrominated diphenyl ether. After total synthesis of the reported binaphthalenetetrol was accomplished via a key reduction of a binaphtho-*ortho*-quinone, comparison of the physical properties and NMR spectroscopic data of the synthetic material indicated that the structure of the natural product isolate was incorrect. Evaluation of the authentic natural product suggested the structure is a tetrabrominated diphenyl ether, likely 3,5-dibromo-2-(3,5-dibromo-2-methoxyphenoxy)phenol.



Over the past several years we have developed and effectively used oxidative asymmetric biaryl coupling to synthesize axially or helically chiral naphthalene-based natural products,[1] including nigerone,[2] cercosporin,[3] hypocrellin A,[4] and other perylenequinones.[5] More recently, we have shown the value of using axially chiral binaphtho-*para*-quinones to synthesize the bisanthraquinone natural product (*S*)-5,5′-bisoranjidiol.[6] During our study of binaphtho-*ortho*-quinone-diols, a new marine natural product was reported that mapped onto this skeleton: (*S*)-2,2′-dimethoxy-1,1′-binaphthyl-5,5′,6,6′-tetraol [(*S*)-**1**, Scheme 1]. Isolated in 2007 from an Indonesian *Lendenfeldia* sp. sponge,[7] this material was reported to significantly inhibit hypoxia-induced and iron-chelator (1,10-phenanthroline)-induced activation of the transcription factor HIF-1 (hypoxia-inducible factor-1) in T47D breast tumor cells. The published structure of (*S*)-**1** was deduced from the analysis of NMR spectroscopic data and the absolute configuration from the CD spectrum.[7] Herein, we describe a total synthesis of the proposed binaphthalenetetrol natural product, (*S*)-**1**. Together with a reanalysis of the natural product isolate, this effort supports reassignment as a tetrabrominated diphenyl ether.

Scheme 1. Retrosynthetic Analysis



RESULTS AND DISCUSSION

Retrosynthetic analysis of (*S*)-**1** revealed that reduction of chiral binaphtho-*ortho*-quinone (*S*)-**2** would readily reveal the proposed natural product. The biquinone (*S*)-**2**, in turn, could be obtained by selective oxidation of (*S*)-**3**. Asymmetric biaryl coupling of **4** with a dinuclear chiral vanadium catalyst,[8] followed by methylation and deprotection, would provide (*S*)-**3**.

Known biaryl (*S*)-**5** was synthesized in 82% yield and 81% ee (enhanced to 98% ee after trituration) from **4** using chiral vanadium catalyst **6** (Scheme 2).[8] Methylation of (*S*)-**5**, followed by removal of the benzyl protecting groups, provided intermediates (*S*)-**7** and (*S*)-**3** in 73% and 99% yields, respectively. Oxidation of binaphthol (*S*)-**3** efficiently provided binaphtho-*ortho*-quinone (*S*)-**2** as an orange solid with very high efficiency (97% yield). A crystal structure of *rac*-**2** secured our structural assignment (Figure 1). Compound *rac*-**2** was prepared in the same manner as (*S*)-**2**, except the achiral catalyst $VO(acac)_2$ was used instead of **6** for the biaryl coupling reaction. Subsequent reduction of (*S*)-**2** with sodium dithionite produced the desired compound synthetic-**1** (Scheme 2).

Surprisingly, both the spectroscopic data and physical properties of synthetic-**1** did not correlate with those reported for the natural product. The synthetic material was unstable in

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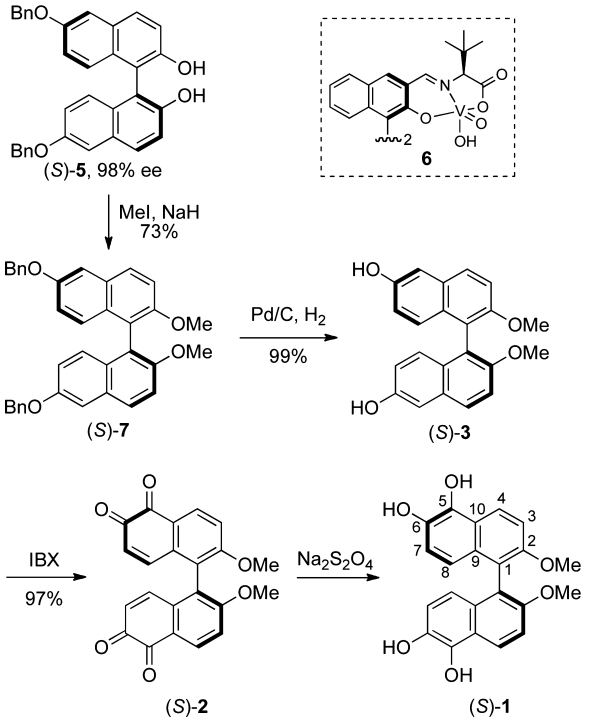
Scheme 2. Synthesis of Reported Natural Product (*S*)-1[a]



[a]Abbreviations: IBX, *o*-iodoxybenzoic acid.

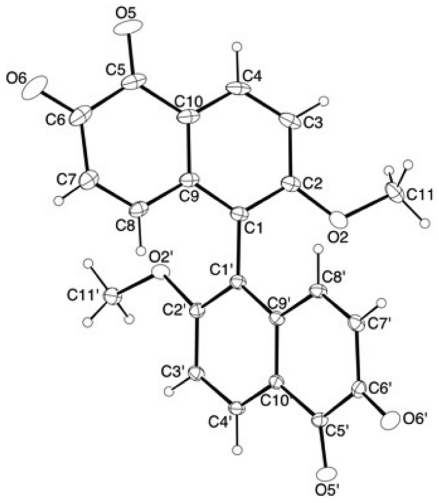


Figure 1. Crystal structure of binaphtho-*ortho*-quinone *rac*-**2**.

air and to silica, readily forming perylenequinone upon standing. In contrast, the natural product was isolated using silica gel column chromatography (2:1 hexanes−EtOAc).[7] In addition, synthetic-**1** was insoluble in $CDCl_3$, the solvent used to obtain the published NMR spectroscopic data. Due to this poor solubility, it was necessary to add EtOAc to $CDCl_3$ in order to obtain a spectrum. A cleaner spectrum was recorded in acetone-d_6. Both the acetone-d_6 and $CDCl_3$ spectra show the expected two pairs of doublets and the two phenol peaks of synthetic-**1** (Table 1).

On the other hand, the ^{1}H NMR data for the reported natural product (Table 1) are missing both phenol peaks and lack any of the expected splitting patterns. Analysis of the original spectrum[9] indicates that it was obtained at high concentration, which could account for the observed broad

Table 1. Comparison of ^{1}H NMR Data for Literature and Synthetic-1

position[b]	literature[a] ($CDCl_3$) δ_H	synthetic ($CDCl_3$ + EtOAc) δ_H	synthetic (acetone-d_6) δ_H (J in Hz)
3	6.70, br s	7.29, d	7.45, d (9.3)
4	7.39, br s	8.13, d	8.25, d (9.3)
7	7.16, br s	6.44, d	6.45, d (9.3)
8	7.32, br s	6.79, d	6.90, d (9.0)
OH		6.98, br s	8.00, s
OH		6.31, br s	7.65, s
OMe	4.02, s	3.62, s	3.68, s

[a]Reference 7. [b]See Scheme 2 for numbering.

peaks and the missing phenol signals. There is also a significant departure between the chemical shifts of synthetic-**1** and the isolated natural product, with all aromatic peaks differing by at least 0.53 ppm. In addition, the OMe is shifted downfield at 4.02 ppm for literature-**1** relative to the synthetic material at 3.62 ppm (Table 1). Due to the instability and solubility problems, obtaining a satisfactory ^{13}C NMR spectrum in $CDCl_3$ was difficult. However, the OMe is visible at 56.9 ppm (Table 2), whereas the OMe for the published material is at 61.5 ppm. The remaining chemical shifts from the ^{13}C NMR spectrum in acetone-d_6 are also quite different.

Table 2. Comparison of ^{13}C NMR Data for Literature- and Synthetic-1

position[b]	literature[a] ($CDCl_3$) δ_C	synthetic (acetone-d_6) δ_C
1	117.4	120.9
2	145.0	139.0
3	118.2	114.6
4	130.2	122.9
5	150.5	154.3
6	138.5	138.5
7	120.2	117.6
8	127.4	119.2
9	119.9	130.9
10	118.5	122.6
OMe	61.5	56.7 (56.9)[c]

[a]Reference 7. [b]See Scheme 2 for numbering. [c]Recorded in $CDCl_3$ + EtOAc.

On the basis of the reported HRESIMS data (m/z 378.1105), which suggested a molecular formula of $C_{22}H_{18}O_6$, and the correlations presented for the NMR spectroscopic data, the structure originally proposed for **1** appears logical.[7] Scrutinizing the data further, however, revealed inconsistencies. From the analysis of the published ^{1}H−^{13}C HMBC correlations, two- and three-bond correlations between C-6/H-7 and C-6/H-8 were not reported (for atom numbering see Scheme 2).[7] After an analysis of the original spectroscopic data,[9] it also appears that there are 13 peaks in the ^{13}C NMR spectrum rather than the 11 published. These two extra peaks are very closely associated with peaks at 117.4 and 150.4 ppm.

These inconsistencies prompted us to conduct our own examination of the natural product isolate.[9] The (−)-HRESIMS spectrum of the metabolite exhibited a cluster of peaks, which indicates four bromines are present and gives a molecular formula of $C_{13}H_8Br_4O_3$ ($[M - H]^-$ m/z 526.7119). Moreover,

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our ^{13}C NMR spectrum was identical to that supplied to us,[9] indicating that there are 13 carbons. The ^{1}H NMR spectrum also revealed small coupling constants consistent with *meta*-protons on an aromatic ring (see Table 3). The COSY correlation data showed that two spin systems were present, with H-2 coupled to H-4 and H-10 coupled to H-12 (Table 3).

Table 3. NMR Spectroscopic Data for Natural Product Isolate[a]

position	δ_C, type	δ_H (J in Hz)	HMBC[b]
1	150.9, C		
2	119.1, CH	6.83, d (2.3)	1, 3, 4, 6
3	117.5, C		
4	130.8, CH	7.46, d (2.2)	3, 6
5	119.2, C		
6	146.2, C		
7	61.8, CH_3	4.03, s	6
8	139.3, C		
9	150.6, C		
10	120.2, CH	7.18, d (2.2)	8, 9, 11, 12
11	120.1, C		
12	127.6, CH	7.35, d (2.2)	8, 10, 13
13	117.4, C		

[a]Recorded in $CDCl_3$, 500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR. [b]HMBC correlations indicate the protons in column 3 coupling to the carbon entry in column 2.

Interpretation of the HSQC and HMBC data (Table 3) revealed a tetrabrominated diphenyl ether with the OMe and OH on separate rings and two bromines on each ring. There are three correlations missing, but eight possible structures could be proposed based on the data (see Figure 2). Comparison of calculated chemical shifts with the observed ^{13}C NMR data (Table 4) of the metabolite highlighted **8** as the closest match and possible identity of the natural product.

A literature search of the molecular formula revealed a few tetrabrominated diphenyl ethers (isolated from marine sponges).[10,11] Of the compounds in Figure 2, however, only **8** has been reported. Comparison of the NMR data from this report and the isolation report[7] with the published data for compound **8** also indicated a reasonable match (Table 5).[12] Further suggestive support for this structure is that **8** was previously isolated from a Palauan collection of another *Lendenfeldia* sponge.[11,13] Overall, the evidence supports structure **8** as the identity of the natural product.

In summary, oxidative naphthol coupling was shown to provide an expeditious entry into more highly oxidized congeners, such as the binaphtho-*ortho*-quinones. Oxidatively sensitive binaphthalenetetrol (*S*)-**1** was efficiently synthesized from a binaphtho-*ortho*-quinone intermediate, the structure of which was confirmed by crystallography. Comparison of the structural data from this synthetic material shows that the reported natural product structure is not (*S*)-2,2′-dimethoxy-[1,1′-binaphthalene]-5,5′,6,6′-tetraol [(*S*)-**1**]. Examination of an authentic sample of the natural product indicates that it is a tetrabrominated diphenyl ether.

EXPERIMENTAL SECTION

General Experimental Procedures. Infrared spectra were recorded on either a Jasco FT/IR-480 Plus spectrometer or an Applied Systems ReactIR 1000. NMR spectra were recorded on 300 and 500 MHz spectrometers. Multiplicity for ^{1}H NMR data is reported as follows: s = singlet, d = doublet, t = triplet, br = broad, m = multiplet. ^{1}H NMR spectra were referenced to the residual solvent peaks: $CDCl_3$ (7.26 ppm), acetone-d_6 (2.05 ppm), and CD_3OD (3.31 ppm). ^{13}C NMR spectra were referenced to $CDCl_3$ (77.16 ppm) and acetone-d_6 (29.8 ppm). High-resolution mass spectra were measured on a Waters LC-TOF mass spectrometer (model LCT-XE Premier). Enantiomeric excesses were determined using analytical HPLC with UV detection at 254 nm. An analytical Chiralpak IA column (4.6 mm × 250 mm, 5 μm) from Daicel was used. All reactions were carried out under an atmosphere of dry argon, unless otherwise noted. When necessary, solvents and reagents were dried prior to use. DMF was distilled from $MgSO_4$. Reactions were all monitored via analytical thin layer chromatography, and visualization was accomplished with UV light. Column chromatography was performed with Silicycle SiliaFlash P60 silica gel (40−63 μm particle size).

(*S*)-6,6′-Bis(benzyloxy)-2,2′-dimethoxy-1,1′-binaphthalene [(*S*)-7]. To a solution of (*S*)-**5**[8] (143 mg, 0.29 mmol, 98% ee) at 0 °C was added NaH (60%, 62.5 mg, 1.56 mmol), followed by MeI (7 μL, 1.1 mmol) after 10 min. After stirring 2 h at room temperature, the mixture was cooled to 0 °C and quenched with H_2O. This mixture was extracted with EtOAc (×2) and washed several times with H_2O, followed by brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed (20% EtOAc/hexanes) to afford (*S*)-7 as a white solid (119 mg, 73%, 98% ee): mp 78−81 °C; IR (film) ν_{max} 2933, 1596, 1504, 1253 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (2H, d, J = 9.0 Hz), 7.48 (4H, d, J = 7.4 Hz), 7.42 (2H, d, J = 9.1 Hz), 7.40 (4H, t, J = 7.5 Hz), 7.34 (2H, t, J = 7.3 Hz), 7.27 (2H, d, J = 2.5 Hz), 7.05 (2H, d, J = 9.3 Hz), 7.0 (2H, dd, J = 9.2 Hz, 2.5 Hz), 5.16 (4H, s), 3.74 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4 (C−O × 2), 153.8 (C−O × 2), 137.3 (C × 2), 130.2 (C × 2), 129.7 (C × 2), 128.7 (CH × 4), 128.2 (CH × 2), 128.1 (CH × 2), 127.7 (CH × 4), 127.1 (CH × 2), 120.3 (C × 2), 119.7 (CH × 2), 115.2 (CH × 2), 107.4 (CH × 2), 70.2 (CH_2 × 2), 57.3 (OCH_3 × 2); HRESIMS m/z 527.2219 $[M + H]^+$ (calcd for $C_{36}H_{30}O_4$, 527.2222).

(*S*)-2,2′-Dimethoxy-[1,1′-binaphthalene]-6,6′-diol [(*S*)-3]. A solution of (*S*)-7 (279 mg, 0.529 mmol) in MeOH/THF (11.2 mL) was evacuated and purged with Ar. To this solution was added Pd/C

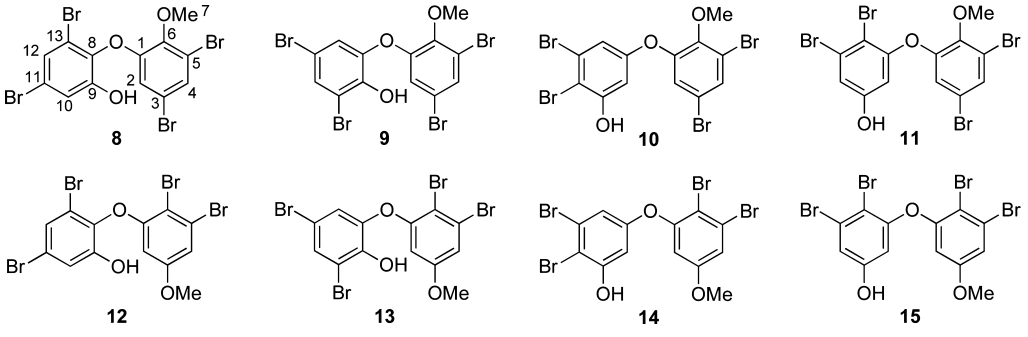

Figure 2. Possible structures of the natural product isolate.

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Table 4. Differences between Observed ^{13}C NMR Data of Natural Product Isolate and Calculated[a] ^{13}C NMR Data of 8−15

		$\Delta\delta_C$							
position	observed δ_C	8	9	10	11	12	13	14	15
1	150.9	0.5	0.5	0.5	0.5	−6.3	−6.3	−6.3	−6.3
2	119.1	3.8	3.8	3.8	3.8	14.3	14.3	14.3	14.3
3	117.5	7.8	7.8	7.8	7.8	6	6	6	6
4	130.8	2	2	2	2	17.9	17.9	17.9	17.9
5	119.2	5.1	5.1	5.1	5.1	−7.4	−7.4	−7.4	−7.4
6	146.2	−1.7	−1.7	−1.7	−1.7	−15.3	−15.3	−15.3	−15.3
7	61.8	0.9	0.9	0.9	0.9	6	6	6	6
8	139.3	0.9	−4.7	−20.3	−20.1	0.9	−4.7	−20.3	−20.1
9	150.6	−1.5	5.6	−7.9	−7	−1.5	5.6	−7.9	−7
10	120.2	2.3	4.5	4.6	5.7	2.3	4.5	4.6	5.7
11	120.1	2.1	10.1	9.4	8.3	2.1	10.1	9.4	8.3
12	127.6	0.6	−1.6	21.2	21.2	0.6	−1.6	21.2	21.2
13	117.4	−1.6	6.3	−9.6	−9.6	−1.6	6.3	−9.6	−9.6

[a]Chemical shifts were calculated using CambridgeSoft ChemBioDraw.

Table 5. Comparison of NMR Data of Natural Product Isolate with Literature for Compound 8

	observed ($CDCl_3$)		original data[a] ($CDCl_3$)		lit.[b] ($CDCl_3$)	lit.[c] (CD_3OD)	observed (CD_3OD)
position	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_H
1	150.9		150.5		152.9		
2	119.1	6.83	118.2	6.70	118.0	6.53	6.50
3	117.5		117.4		117.4		
4	130.8	7.46	130.2	7.40	129.7	7.30	7.39
5	119.2		119.0		119.8		
6	146.2		145.0		147.1		
7	61.8	4.03	61.5	4.01	61.5	3.96	3.99
8	139.3		138.5		140.0		
9	150.6		150.5		153.6		
10	120.2	7.18	120.2	7.16	121.1	7.10	7.13
11	120.1		119.9		120.4		
12	127.6	7.35	127.4	7.33	127.1	7.25	7.34
13	117.4		117.4		119.4		

[a]Values taken from hard copies of spectra; see SI. [b]Reference 11. [c]Reference 10.

(10 wt %, 104 mg), and the mixture evacuated and purged three times with H_2. After stirring under a hydrogen atmosphere overnight, the mixture was filtered through Celite with EtOAc and concentrated. The residue was passed through a short column of silica (30% EtOAc/hexanes) to afford (*S*)-**3** as a white solid (182 mg, 99%): mp >240 °C dec; IR (film) ν_{max} 3366, 1598, 1511, 1256 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 8.33 (2H, s), 7.81 (2H, d, J = 9.0 Hz), 7.46 (2H, d, J = 9.0 Hz), 7.23 (2H, d, J = 2.3 Hz), 6.93 (2H, d, J = 9.1 Hz), 6.89 (2H, dd, J = 9.1 Hz, 2.4 Hz), 3.68 (6H, s); ^{13}C NMR (125 MHz, acetone-d_6) δ 154.3 (C−O × 2), 154.0 (C−O × 2), 131.6 (C × 2), 129.7 (C × 2), 128.1 (CH × 2), 127.6 (CH × 2), 121.0, 119.5, 115.9, 109.8, 57.0 (OCH_3 × 2); HRESIMS m/z 347.1284 $[M + H]^+$ (calcd for $C_{22}H_{18}O_4$, 347.1283).

(*S*)-2,2′-Dimethoxy-[1,1′-binaphthalene]-5,5′,6,6′-tetraone [(*S*)-2]. To a solution of (*S*)-**3** (15.4 mg, 0.044 mmol) in 0.8 mL of DMF was added 2-iodoxybenzoic acid (25.0 mg, 0.089 mmol). The mixture was stirred for 3 h in the dark. Following this time, the mixture was diluted with H_2O and extracted with EtOAc. The organic layer was washed with 25% aqueous $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed (5%−10% EtOAc/CH_2Cl_2) to afford (*S*)-**2** as an orange solid (16.2 mg, 97%): mp 190 °C dec; $[\alpha]^{25}_D$ −42.1 (*c* 0.054, 98% ee, CH_2Cl_2); UV (CH_2Cl_2) λ_{max} (log ε) 388 (6.91), 270 (6.88); IR (film) ν_{max} 2927, 2850, 1661, 1568, 1468, 1274 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.29 (2H, d, J = 8.7 Hz), 7.10 (2H, d, J = 8.7 Hz), 6.97 (2H, d, J = 10.4 Hz), 6.34 (2H, d, J = 10.4 Hz), 3.86 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.2 (C═O × 2), 177.7 (C═O × 2), 163.2 (C−O × 2), 141.5 (CH × 2), 135.6 (C × 2), 133.7 (CH × 2), 129.2 (CH × 2), 125.5 (C × 2), 123.3 (C × 2), 112.0 (CH × 2), 56.7 (OCH_3); HRESIMS m/z 375.0877 $[M + H]^+$ (calcd for $C_{22}H_{14}O_6$, 375.0869).

(*S*)-2,2′-Dimethoxy-[1,1′-binaphthalene]-5,5′,6,6′-tetraol [(*S*)-1]. In a separatory funnel, (*S*)-**2** (16 mg, 0.043) was dissolved in CH_2Cl_2 (2 mL) and diluted with Et_2O (4 mL). Then, an aqueous solution of $Na_2S_2O_4$ (40 mg/6 mL) was added. The mixture was shaken, and additional $Na_2S_2O_4$ (50 mg) was added, followed by shaking until a loss of orange color was observed in the organic layer. After separating the layers, the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated to afford **1** as an air-sensitive, off-white solid (98% ee): IR (film) ν_{max} 3375, 2925, 1600, 1518, 1367, 1259, 1095 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) Table 1; ^{13}C NMR (125 MHz, acetone-d_6) Table 2; compound partially oxidized during ionization: HRESIMS m/z 375.0863 $[M - H]^-$ (calcd for $C_{22}H_{15}O_6$, 375.0869).

Natural product isolate (tetrabrominated diphenyl ether 8): IR (film) ν_{max} 3366, 2930, 1569, 1469, 1393, 1255, 1216, 914 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$ and CD_3OD) Tables 3 and 5; ^{13}C NMR (125 MHz, $CDCl_3$) Table 3; HRESIMS m/z 526.7119 $[M - H]^-$ (calcd for $C_{13}H_7Br_4O_3$, 526.7129).

X-ray Crystallographic Analysis of *rac*-2. Crystals of a racemic sample of **2** were obtained by slow evaporation from CH_2Cl_2. The X-ray intensity data were collected at a temperature of 143(1) K on a Bruker APEXII CCD area detector employing graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). The structure was solved by direct methods (SHELXS-97). There was a region of disordered

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solvent for which a reliable disorder model could not be devised; the X-ray data were corrected for the presence of disordered solvent using SQUEEZE. Refinement was by full-matrix least-squares based on F^2 using SHELXL-97. All reflections were used during refinement. Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were refined using a riding model. The crystallographic data for *rac*-**2** have been deposited at the Cambridge Crystallographic Data Centre with the deposition number 883203. Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB21EZ, UK [fax: +44(0)-1233-336033 or e-mail: deposit@ccdc.cam.ac.uk].

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

1D and 2D NMR spectra and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Kozlowski, M. C.; Morgan, B. J.; Linton, E. C. *Chem. Soc. Rev.* **2009**, *38*, 3193−3207.

(2) (a) DiVirgilio, E. S.; Dugan, E. C.; Mulroony, C. A.; Kozlowski, M. C. *Org. Lett.* **2007**, *9*, 385−388. (b) Kozlowski, M. C.; Dugan, E. C.; DiVirgilio, E. S.; Maksimenka, K.; Bringmann, G. *Adv. Synth. Catal.* **2007**, *349*, 583−594.

(3) (a) Morgan, B. J.; Dey, S.; Johnson, S. W.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2009**, *131*, 9413−9425. (b) Morgan, B. J.; Mulrooney, C. A.; Kozlowski, M. C. *J. Org. Chem.* **2010**, *75*, 44−56.

(4) (a) O'Brien, E. M.; Morgan, B. J.; Kozlowski, M. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 6877−6880. (b) O'Brien, E. M.; Morgan, B. J.; Mulrooney, C. A.; Kozlowski, M. C. *J. Org. Chem.* **2010**, *75*, 57−68.

(5) (a) Mulrooney, C. A.; Morgan, B. J.; Li, X.; Kozlowski, M. C. *J. Org. Chem.* **2010**, *75*, 16−29. (b) Morgan, B. J.; Mulrooney, C. A.; O'Brien, E. M.; Kozlowski, M. C. *J. Org. Chem.* **2010**, *75*, 30−43. (c) O'Brien, E. M.; Li, J.; Carroll, P. J.; Kozlowski, M. C. *J. Org. Chem.* **2010**, *75*, 69−73.

(6) Podlesny, E. E.; Kozlowski, M. C. *Org. Lett.* **2012**, *14*, 1408−1411.

(7) Dai, J.; Liu, Y.; Zhou, Y.-D.; Nagle, D. G. *J. Nat. Prod.* **2007**, *70*, 1824−1826.

(8) (a) Somei, H.; Asano, Y.; Yoshida, T.; Takizawa, S.; Yamataka, H.; Sasai, H. *Tetrahedron Lett.* **2004**, *45*, 1841−1844. (b) Guo, Q.-X.; Wu, Z.-J.; Luo, Z.-B.; Liu, Q.-Z.; Ye, J.-L.; Luo, S.-W.; Cun, L.-F.; Gong, L.-Z. *J. Am. Chem. Soc.* **2007**, *129*, 13927−13938. (c) Takizawa, S.; Katayama, T.; Sasai, H. *Chem. Commun.* **2008**, 4113−4122. (d) Takizawa, S.; Katayama, T.; Somei, H.; Asano, Y.; Yoshida, T.; Kameyama, C.; Rajesh, D.; Onitsuka, K.; Suzuki, T.; Mikami, M.; Yamataka, H.; Jayaprakash, D.; Sasai, H. *Tetrahedron* **2008**, *64*, 3361−3371. (e) Takizawa, S.; Katayama, T.; Kameyama, C.; Onitsuka, K.; Suzuki, T.; Yanagida, T.; Kawai, T.; Sasai, H. *Chem. Commun.* **2008**, 1810−1812.

(9) Copies of the original ^{1}H and ^{13}C NMR spectra and a sample of the natural product isolate were kindly provided by Dr. Nagle (see ref 7).

(10) Norton, R. S.; Croft, K. D.; Wells, R. J. *Tetrahedron* **1981**, *37*, 2341−2349.

(11) Hattori, T.; Konno, A.; Adachi, K.; Shizuri, Y. *Fisheries Sci.* **2001**, *67*, 899−903.

(12) Observed ^{1}H and ^{13}C NMR chemical shifts appear to be concentration dependent.

(13) Compound **8** was reported from the sponge *Phyllospongia dendyi*. This sponge has been taxonomically reclassified as *Lendenfeldia dendyi*: Bergquist, P. R. *New Zeal. J. Zool.* **1980**, *7*, 443−503.