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

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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*-quinonediols, a new marine natural product was reported which 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.

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**

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

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). *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 air and to silica, readily reverting to the bisquinone 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 CDCl₃, the solvent used to obtain the published NMR spectroscopic data. Due to this poor solubility, it was necessary to add EtOAc to CDCl₃ in order to obtain a spectrum. A cleaner spectrum was recorded in acetone-*d*₆. Both the acetone-*d*₆ and CDCl₃ spectra show the expected two pairs of doublets and the two phenol peaks of synthetic-**1** (Table 1).

On the other hand, the ¹H 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 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 ¹³C NMR spectrum in CDCl₃ 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 ¹³C NMR spectrum in acetone-*d*₆ are also quite different.

Based on the reported HRESIMS data (*m/z* 378.1105), which suggested a molecular formula of C₂₂H₁₈O₆, 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 ¹H-¹³C 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 4).⁷ After an analysis of the original spectral data,⁹ it also appears that there are 13 peaks in the ¹³C NMR spectrum rather than the 11 published.

These two extra peaks are very closely associated with peaks at 117.4 ppm 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 indicate four bromines are present and gives a molecular formula of C₁₃H₈Br₄O₃ ([M–H][–] *m/z* 526.7119). Moreover, our ¹³C NMR spectrum was identical to that supplied to us⁹ indicating that there are 13 carbons. The ¹H 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).

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 ¹³C 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 report⁷ 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 MHz and 500 MHz spectrometers. Multiplicity for ¹H NMR data are reported as follows: s = singlet, d = doublet, t = triplet, br = broad, m = multiplet. ¹H NMR spectra were referenced to the residual solvent peaks: CDCl₃ (7.26 ppm), acetone-*d*₆ (2.05 ppm) and CD₃OD (3.31 ppm). ¹³C NMR spectra were referenced to: CDCl₃ (77.16 ppm), 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 MgSO₄. Reactions were all monitored via analytical thin layer chromatography (TLC) 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 H₂O. This mixture was extracted with EtOAc (×2) and washed several times with H₂O, followed by brine. The organic layer was dried over Na₂SO₄, 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; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 (CH₂ ×2), 57.3 (OCH₃ ×2); HRESIMS *m/z* 527.2219 [M+H]⁺ (calcd for C₃₆H₃₀O₄, 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 (10 wt%, 104 mg) and the mixture evacuated and purged three times with H₂. After stirring under 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 decomp; IR (film) $\nu_{\max}$ 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); ¹³C 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 (OCH₃ ×2); HRESIMS *m/z* 347.1284 [M+H]⁺ (calcd for C₂₂H₁₈O₄, 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 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 H₂O and extracted with EtOAc. The organic layer was washed with 25% aqueous NaHCO₃, dried over Na₂SO₄, filtered, and concentrated. The residue was chromatographed (5%–10% EtOAc/CH₂Cl₂) to afford (*S*)-2 as an orange solid (16.2 mg, 97%): mp 190 °C decomp; [α]_D²⁵ –42.1 (c 0.054, 98% ee, CH₂Cl₂); UV (CH₂Cl₂) $\lambda_{\max}$ (log ϵ) 388 (6.91), 270 (6.88); IR (film) $\nu_{\max}$ 2927, 2850, 1661, 1568, 1468, 1274 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 (OCH₃); HRESIMS *m/z* 375.0877 [M+H]⁺ (calcd for C₂₂H₁₄O₆, 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 CH₂Cl₂ (2 mL) and diluted with Et₂O (4 mL). Then, an aqueous solution of Na₂S₂O₄ (40 mg/6 mL) was added. The mixture was shaken and additional Na₂S₂O₄ (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 Na₂SO₄, filtered, and concentrated to afford **1** as an air-sensitive, off-white solid (98% ee): IR (film) $\nu_{\max}$ 3375, 2925, 1600, 1518, 1367, 1259, 1095 cm⁻¹; ¹H NMR (300 MHz, acetone-*d*₆) Table 1; ¹³C NMR (125 MHz, acetone-*d*₆) Table 2; compound partially oxidized during ionization: HRESIMS *m/z* 375.0863 [M–H][–] (calcd for C₂₂H₁₅O₆, 375.0869).

Natural Product Isolate (Tetrabrominated diphenyl ether **8**)

IR (film) $\nu_{\max}$ 3366, 2930, 1569, 1469, 1393, 1255, 1216, 914 cm⁻¹; ¹H NMR (500 MHz, CDCl₃ and CD₃OD) Tables 3 and 5; ¹³C NMR (125 MHz, CDCl₃) Table 3; HRESIMS *m/z* 526.7119 [M–H][–] (calcd for C₁₃H₇Br₄O₃, 526.7129).

X-ray Crystallographic Analysis of *Rac*-2

Crystals of a racemic sample of **2** were obtained by slow evaporation from CH₂Cl₂. 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-K α radiation (λ = 0.71073 Å). The structure was solved by direct methods (SHELXS-97). There was a region of disordered 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 F² 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].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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

Figure 2.
Possible structures of the natural product isolate.

Scheme 1.
Retrosynthetic Analysis

Scheme 2.
Synthesis of Reported Natural Product (*S*)-1
Abbreviations: IBX, *o*-iodoxybenzoic acid

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

Compd 1	Literature ^a (CDCl_3)	Synthetic (CDCl_3 + EtOAc)	Synthetic (acetone- d_6)
position ^b	δ_{H}	δ_{H}	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

^aReference 7.^bSee Scheme 2 for numbering.

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

Compd 1	Literature ^a (CDCl_3)	Synthetic (acetone- d_6)
position ^b	δ_{C}	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

^aReference 7.^bSee Scheme 2 for numbering.^cRecorded in CDCl_3 + EtOAc.

Table 3NMR Spectroscopic Data for Natural Product Isolate^a

position	δ_C , type	δ_H (<i>J</i> 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		

^aRecorded in ¹H NMR and 125 MHz for ¹³C NMR.^bHMBC correlations indicate the protons in CDCl₃, 500 MHz for column 3 coupling to the carbon entry in column 2.

Table 4
Differences between Observed ^{13}C NMR Data of Natural Product Isolate and Calculated ^{13}C NMR Data of **8–15**

position	Observed δ_{C}	$\Delta\delta_{\text{C}}$ between calculated ^a and observed for cmpds 8–15										
		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			

^aChemical shifts were calculated using CambridgeSoft ChemBioDraw.

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

position	Observed (CDCl ₃)		Original Data ^a (CDCl ₃)		Lit. ^b (CDCl ₃)		Lit. ^c (CD ₃ OD)		Observed (CD ₃ OD)	
	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	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					

^aValues taken from hard copies of spectra, see SI.

^bReference 11.

^cReference 10.