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1 **Title:**

2 Two new algal bromophenols from *Odonthalia corymbifera*

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14

15 **Abstract**

16 Two new algal bromophenols, odonthalol and odonthadione, were isolated from the
17 alga *Odonthalia corymbifera*. Odonthalol was determined as a trimer of brominated
18 hydroxylated benzyl (BHB) units. Three units were connected via ether and methylene
19 bridges. Odonthadione was identified as a hybrid compound of the BHB unit and a unique
20 cyclopentenedione. The cyclopentenedione unit has not been reported from natural origin.

21

22 **Keywords**

23 Bromophenol; antioxidant; tyrosinase; inhibition

24

Introduction

Algal bromophenols consist of brominated hydroxylated benzyl (BHB) unit. Rhodomelaceae algae contain monomers and dimers of mono- to tribrominated 3,4-dihydroxybenzyl alcohols and alkyl ethers as typical BHB units.¹ Many kinds of the dimers have been reported and constructed with two BHB units via ether and methylene bridges.² However, there are few reports on isolation of bromophenol trimers³⁻⁵ and hybrid bromophenols.⁶⁻⁸ Algal bromophenols have been investigated for various activities such as antioxidant,⁶ enzyme inhibitory,⁹⁻¹⁶ feeding deterrent,¹⁷ antimicrobial^{18,19} and anti-inflammatory³ activities. In the present report, two new algal bromophenols, a trimer of BHB units named odonthalol (**1**) and a hybrid compound of a BHB unit and a cyclopentenedione moiety named odonthadione (**3**), were isolated from the alga *Odonthalia corymbifera* (S. G. Gmelin) Greville (Rhodomelaceae).

Figure 1. Novel algal bromophenols, Odonthalol (**1**) and odonthadione (**3**).

Results and Discussion

The alga *O. corymbifera* (1.8 kg) was collected at the coast of Hakodate city, Japan (May, 2016) and extracted with 95% MeOH. The EtOAc soluble fraction (19.5 g) of MeOH extract was chromatographed over silica gel, RP-18 column chromatography, and Sephadex LH-20. Final purification was performed by RP-18 HPLC (eluted with 70% aqueous MeOH) to obtain compounds **1**²⁰ (2.8 mg) and **3**²¹ (6.5 mg).

Table 1. ¹H (500 MHz) and ¹³C NMR (125 MHz) data of odonthalol (**1**) and its permethylated derivative (**2**) in acetone-*d*₆

Position	1			2			
	δ _C , type	δ _H	HMBC	δ _C , type	δ _H	HMBC	ROESY
1a	130.7 ^a , C			135.7, C			
2a	128.5, C			129.1, C			
3a	115.0 ^b , C			122.7 ^f , C			
4a	144.6 ^c , C			146.9, C			
5a	143.4 ^c , C			153.0, C			
6a	116.2, CH	6.94, s	2a, 4a, 5a, 7a	113.8, CH	7.11, s	1a, 2a, 4a, 5a, 7a	7a, 8a, 5a-OMe
7a	73.1, CH ₂	4.16, brs	ND ^g	73.5, CH ₂	4.35, s	1a, 2a, 6a, 8a	6a, 6b
8a	57.8, CH ₃	3.14, s	7a	58.2, CH ₃	3.22, s	7a	6a, 6b
4a-OMe				60.4, CH ₃	3.75, s	4a	
5a-OMe				56.4, CH ₃	3.88, s	5a	6a
1b	125.5 ^a , C			130.5, C			
2b	143.2 ^d , C			142.6, C			
3b	105.8, C			106.5, C			
4b	142.2 ^d , C			146.9, C			
5b	143.9, C			152.2, C			
6b	114.1, CH	6.08, s	2b, 4b, 5b	112.8, CH	6.39, s	1b, 2b, 4b, 5b, 7b	7a, 8a, 5b-OMe, 5c-OMe
7b	31.7, CH ₂	3.94, brs	ND ^g	32.9, CH ₂	4.07, brs	ND ^g	
4b-OMe				60.8, CH ₃	3.80, s	4b	
5b-OMe				56.5, CH ₃	3.64, s	5b	6b
1c	131.1, C			136.5, C			
2c	117.4, C			116.6, C			
3c	114.0 ^b , C			122.6 ^f , C			
4c	145.6 ^e , C			151.1, C			
5c	145.2 ^e , C			146.9, C			
6c	113.3, CH	6.78, s	2c, 4c, 5c, 7c	113.7, CH	6.71, s	1c, 2c, 4c, 5c,	6b, 7c, 8c, 5c-

7c	75.1, CH ₂	4.37, s	1c, 2c, 6c, 8c	74.9, CH ₂	4.36, s	7c 1c, 2c, 6c, 8c	OMe 6c
8c	58.8, CH ₃	3.29, s	7c	58.6, CH ₃	3.30, s	7c	6c
5c-OMe				61.1, CH ₃	4.06, s	5c	6c

^{a-f}Data are interchangeable within same character.

^gNot detected because of a broad proton signal.

FDHRMS of odonthalol (**1**) suggests to be a tetrabrominated compound and its molecular formula of C₂₃H₂₀Br₄O₈. The ¹H NMR spectrum (Table 1) showed three aromatic, two methylenic, and two methoxy proton signals, along with a broad proton signal (δ_H 3.94). The ¹³C NMR spectrum revealed eighteen aromatic, two methylenic and two methoxy carbon signals (Table 1). These signals were characterized to be an oligomer of BHB units. Unfortunately, HSQC and HMBC correlations of compound **1** were limited within individual two units of 1-methoxymethyl-2,3,4,5-tetrasubstituted benzene moieties. One remaining carbon signal was not determined because no correlation was observed with the broad proton signal of low signal height in HSQC and HMBC experiments. Thus little information of connection among different units was observed.

Compound **1** was converted with trimethylsilyldiazomethane in methanol to permethylated derivative **2**.²² Molecular ion peak of derivative **2** increased 70 mass units compared to that of **1** in FDMS. New five methoxy signals were appeared in NMR spectra of **2** (Table 1). These data suggested presence of five free phenolic hydroxy groups in **1**. Therefore, one remaining oxygen atom would be used to form an ether linkage. The five methoxy groups were completely assigned to individual positions with consideration of HMBC and ROESY correlations (Figure 2). All other proton and carbon signals of derivative **2** except for carbon signals C-3a, C-3b and C-3c were also assigned from the 2D NMR data.

The three aromatic carbons signals at δ_C 122.7, 122.6, and 106.5, showing no correlation with the three aromatic proton signals in the HMBC experiment, are assigned to be the brominated aromatic carbons at *para*-positions (3a, 3b and 3c) of the three respective aromatic protons. Thus the remaining four aromatic carbons at the positions 2a, 2b, 7b, and 4c are suggested to connect among the three BHB units. Their carbon chemical shifts lead to determine combinations of connectivity, that is to say, alkylated aromatic C-2a (δ_C 129.1) is connected with alkylated aromatic C-1b (δ_C 130.5) via a methylene bridge at C-7b (δ_C 32.9). On the other hand, oxygenated aromatic C-2b (δ_C 142.6) is connected with oxygenated aromatic C-4c (δ_C 151.1) via an ether bridge. Thus structures of odonthalol (**1**) and its pentamethylated derivative (**2**) are determined as trimers of bromophenols. Partial structure of units A and B of odonthalol (**1**) had already isolated from the same alga.¹⁶ Connectivity between units B and C of **1** may due to debrominated phenol coupling like the previously isolated bromophenols possessing a diaryl ether bridge.¹⁰ To the best of our knowledge, odonthalol (**1**) is a novel algal bromophenol trimer whose BHB units are uniquely connected via ether and methylene bridges.

Figure 2. Key HMBC (single arrows) and ROESY (double arrows) correlations of compound **2**.

Figure 3. Key HMBC correlations of compound **3**.

Table 2. ^1H (500 MHz) and ^{13}C NMR (125 MHz) data of odonthadione (**3**) in acetone- d_6 and methanol- d_4

Position	δ_{C} in acetone- d_6	δ_{H} (J in Hz)	HMBC	δ_{C} in methanol- d_4	δ_{H} (J in Hz)
1a	131.1			131.0	
2a	116.4			116.6	
3a	113.6			114.2	
4a	144.1			144.7	
5a	145.2			146.0	
6a	118.0	6.89, s	2a, , 4a, 5a, 7a	117.9	6.76, s
7a	34.3	3.09, dd (14.6, 7.0) 3.05, dd (14.6, 7.0)	1a, 2a, 6a, 1b, 2b, 3b	34.9	3.07, dd (14.6, 7.0) 3.06, dd (14.6, 7.0)
1b	201.6			203.4 ^a	
2b	51.3	3.22, t (7.0)	1a, 7a, 1b, 3b	51.8	NO ^b
3b	202.6			203.6 ^a	
4b	166.2			166.7	
5b	143.0	7.10, s	1b	143.5	7.09, s
6b	57.3	4.51, s	3b, 4b, 5b	57.6	4.48, s

^aExchangeable.

^bNot observed.

Odonthadione (**3**) was determined as a dibrominated compound and its molecular formula of $\text{C}_{13}\text{H}_{10}\text{Br}_2\text{O}_5$ based on FDHRMS data. The ^1H NMR spectrum in acetone- d_6 showed a conjugated olefinic proton at δ 7.10, an aromatic proton at δ 6.89, an equivalent methylene at δ 4.51, a non-equivalent methylene at δ 3.09/3.05, and a methine at δ 3.22 (Table 2). The last methine proton signal was disappeared in the ^1H NMR spectrum measured

in methanol- d_4 . The ^{13}C NMR and HSQC spectrum revealed six aromatic, two ketonic, two olefinic, two methylenes, and one methine carbons. Among them, six aromatic and one methylene carbon are typical for the BHB unit. Both the methylene protons in BHB unit and methine proton were correlated not only one another but also with both ketonic carbons in HMBC experiment (Figure 3). However the olefinic and methylene protons were correlated with respective different ketonic carbons. Therefore, remaining structure other than the BHB unit was determined as 4-hydroxymethyl-4-cyclopentene-1,3-dione-2-yl moiety. Odonthadione (**3**) is not optically active under specific rotation measurement. This reason is seemed that compound **3** is racemic mixture because the proton at 2-position in 1,3-diketone moiety was easily exchangeable in protic solvent like the case of ^1H NMR spectrum in methanol- d_4 . The compound **3** is a novel hybrid algal bromophenol, especially this is the first report on a naturally occurring cyclopentenone moiety.

Table 3. Various activity^a of odonthalol and odonthadione

Compound	DPPH EC ₅₀ ^b (μM)	ABTS EC ₅₀ ^b (μM)	CUPRAC EC _{A0.50} ^c (μM)	FRAP EC _{A0.50} ^c (μM)	Cu ²⁺ - chelation EC ₅₀ ^b (μM)	Tyrosinase inhibition IC ₅₀ ^d (μM)
1	13.5 $\pm$ 0.0	6.7 $\pm$ 0.1	7.8 $\pm$ 0.1	10.8 $\pm$ 0.1	74.3 $\pm$ 0.1	31.0 $\pm$ 0.1
3	24.7 $\pm$ 0.0	17.3 $\pm$ 0.1	13.6 $\pm$ 0.1	11.1 $\pm$ 0.1	61.9 $\pm$ 0.1	17.3 $\pm$ 0.1
BHA	34.0 $\pm$ 0.1	10.4 $\pm$ 0.2	16.0 $\pm$ 0.1	8.3 $\pm$ 0.1		
Catechol	16.9 $\pm$ 0.1	7.3 $\pm$ 0.0	25.4 $\pm$ 0.1	9.1 $\pm$ 0.1		
EDTA					31.6 $\pm$ 0.1	
Kojic acid						35.0 $\pm$ 0.0

^a All values are represented as mean $\pm$ standard error (n=3).

^b The half maximal effect concentration.

^c The effective concentration for absorbance of 0.50.

^d The half maximal inhibitory concentration.

The isolated algal bromophenols **1** and **3** were investigated for antioxidant and tyrosinase inhibitory activities by employing free radical scavenging,^{23,24} metal-reducing antioxidant,^{25,26} copper chelation,²⁷ and tyrosinase inhibition²⁸ assays (Table 3). Bromophenols **1** and **3** exhibited almost same antioxidant activities compare with the positive controls examined. Compound **3** displayed two fold stronger tyrosinase inhibitory activities while compound **1** showed slightly higher activity with the positive control kojic acid. This study has disclosed new functionality of naturally occurring bromophenol as a tyrosinase inhibitor.

In conclusion, two new algal bromophenols showing tyrosinase inhibition and antioxidant were isolated from *O. corymbifera*. One is a BHB unit trimer which has an ether linkage. The other is a hybrid of a BHB unit and a unique cyclopentenedione moiety.

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Supplementary Data

Supplementary data associated with this article can be found, in the online version, at XXX.

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171 3838-3851.
- 172 20. Odonthalol (**1**). Brown amorphous solid; UV (CH₃OH) $\lambda_{\max}$ (log ϵ) 210 (4.57), 232 sh
173 (4.00), 290 (3.57) nm; IR (CHCl₃) $\nu_{\max}$ 3528, 3022, 2928, 1718, 1602, 1281 cm⁻¹; ¹H
174 NMR (500 MHz, (CD₃)₂CO) and ¹³C NMR (125 MHz, (CD₃)₂CO), see Table 1;
175 FDMS m/z 740/742/744/746/748 (relative intensity 1:4:6:4:1); HRFDMS m/z
176 739.7888 (calcd for C₂₃H₂₀⁷⁹Br₄O₈, 739.7819).
- 177 21. Odonthadione (**3**). Light brown amorphous solid; $[\alpha]_D^{27}$ 0 (c 2.6, acetone); UV
178 (CH₃OH) $\lambda_{\max}$ (log ϵ) 212 (4.28), 230 sh (3.94), 292 (3.32) nm; IR (CHCl₃) $\nu_{\max}$ 3510,
179 3023, 2928, 2856, 1705, 1602, 1558, 1472 cm⁻¹; ¹H NMR (500 MHz, (CD₃)₂CO)
180 and ¹³C NMR (125 MHz, (CD₃)₂CO), see Table 2; HRFDMS m/z 403.8889 (calcd
181 for C₁₃H₁₀⁷⁹Br₂O₅, 403.8895).
- 182 22. Odonthalol (**1**) in MeOH was quantitatively converted with trimethylsilyldiazomethane
183 in hexane to pentamethyl ether (**2**) at room temperature. Odonthalol pentamethyl ether
184 (**2**). Pale yellow amorphous solid; ¹H NMR (500 MHz, (CD₃)₂CO) and ¹³C NMR
185 (125 MHz, (CD₃)₂CO), see Table 1; FDMS m/z 810/812/814/816/818 (relative
186 intensity 1:4:6:4:1); HRFDMS m/z 809.8691 (calcd for C₂₈H₃₀⁷⁹Br₄O₈, 809.8675).
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R=H Odonthalol (**1**)

R=Me **2**

Odonthadione (**3**)