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Isolation and Structure Elucidation of a Novel Symmetrical Macrocyclic Phthalate Hexaester

Michiya Kamio [1], Weina Jiang [1], Hiroki Osada [1], Masayuki Fukuoka [1], Hajime Uchida [2], Ryuichi Watanabe [2], Toshiyuki Suzuki [2] and Hiroshi Nagai [1,*]

[1] Department of Ocean Sciences, Tokyo University of Marine Science and Technology, Tokyo 108-8477, Japan; mkamio@kaiyodai.ac.jp (M.K.); jwnkouina@gmail.com (W.J.); zbibaz36@gmail.com (H.O.); 0917mfukuoka@gmail.com (M.F.)

[2] Fisheries Technology Institute, Japan Fisheries Research and Education Agency, Yokohama 236-8648, Japan; huchida@affrc.go.jp (H.U.); rwatanabe@affrc.go.jp (R.W.); tsuzuki@affrc.go.jp (T.S.)

* Correspondence: nagai@kaiyodai.ac.jp

Abstract: A novel symmetrical macrocyclic phthalate hexaester (**1**) and a known macrocyclic phthalate tetraester (**2**) were isolated during a natural product-exploring program on the cyanobacterium *Moorea producens*. Their structures were elucidated based on spectroscopic data, including nuclear magnetic resonance and high-resolution mass spectra. In the antibacterial activity test, compounds **1** and **2** showed no bioactivity at the concentrations tested.

Keywords: phthalate ester; cyanobacterium; *Moorea producens*; isolation; structural elucidation

Citation: Kamio, M.; Jiang, W.; Osada, H.; Fukuoka, M.; Uchida, H.; Watanabe, R.; Suzuki, T.; Nagai, H. Isolation and Structure Elucidation of a Novel Symmetrical Macrocyclic Phthalate Hexaester. *Symmetry* **2021**, *13*, 361. https://doi.org/10.3390/sym13020361

Academic Editor: Miroslav Miletín

Received: 9 February 2021
Accepted: 20 February 2021
Published: 23 February 2021

1. Introduction

The phthalate esters found in the environment can be anthropogenic and petrogenic compounds or natural products. Petrogenic phthalate esters such as di(2-ethylhexyl) phthalate (DEHP), diisononyl phthalate (DINP), diisodecyl phthalate (DIDP), di(2-propylheptyl) phthalate (DPHP), and dibutyl phthalate (DBP) are used as plastic additives or solvents and leach from them into environmental water and sediments [1]. In the ocean, the amount of microplastics that potentially release these phthalate esters is increasing [2]. Thus, the majority of phthalate esters in the ocean are recognized as being anthropogenic. In contrast, phthalate esters have been isolated or detected as natural products from various organisms, including terrestrial bacteria belonging to the genus *Streptomyces* [3–5]; the pathogenic bacteria *Helicobacter pylori* [6]; the terrestrial fungi *Fusarium merismoides* [7]; *Penicillium olsonii* [8]; *Penicillium lanosum*; *Trichoderma asperellum*; *Aspergillus niger* [9]; the terrestrial plants *Aloe vera* [10,11] and *Cardaria draba* [12]; the freshwater cyanobacteria *Anabena flos-aquae*, *Cylindrospermopsis raciborskii*, *Microcystis aeruginosa*, *Oscillatoria* sp. and *Phormidium* sp.; the green algae *Botryococcus braunii*, *Cladophora fracta*, *Chlorella* sp., *Hydrodictyon reticulatum* and *Spirogyra* spp. [13]; the marine red alga *Bangia atropurpurea* [14]; the marine green alga *Ulva* sp.; the marine brown algae *Undaria pinnatifida*; and *Laminaria japonica* [15]. Most recently, a macrocyclic phthalate tetraester (**2**, Figure 1) was reported as a natural product from the scorpion *Liocheles australasiae* [16]. These phthalate esters are consumed by microorganisms including aerobic and anaerobic bacteria [17–20]. Thus, some of the phthalate esters are biologically produced and consumed in the biosphere.

The cyanobacterium *Moorea producens* (formerly *Lyngbya majuscula*) is a species known for producing many bioactive compounds [21]. Some of these compounds have been recognized as potential pharmaceutical compounds [22,23]. *M. producens* has been involved in causing contact dermatitis, also known as "swimmer's itch", in many Pacific areas [24]. The causative agents of this contact dermatitis have been reported to be aplysiatoxins and lyngbyatoxins produced by *M. producens* [25–28]. In addition, it has been reported that food tainted with aplysiatoxins that led to food poisoning was contaminated with

M. producens [29]. Recently, we isolated and reported new toxic constituents from *M. producens* [30–34]. During the exploration of aplysiatoxin-related compounds from the cyanobacterium *M. producens*, we isolated compounds with interesting symmetrical structures: a novel symmetrical macrocyclic hexaester **1** (Figure 1) and a known macrocyclic tetraester **2** (Figure 1). The true origin of the phthalate esters is controversial, as we mentioned above; however, the record of finding of new phthalates is valuable. Thus, here, we report the isolation, structure elucidation and bioactivities of these cyclic phthalate compounds **1** and **2**.

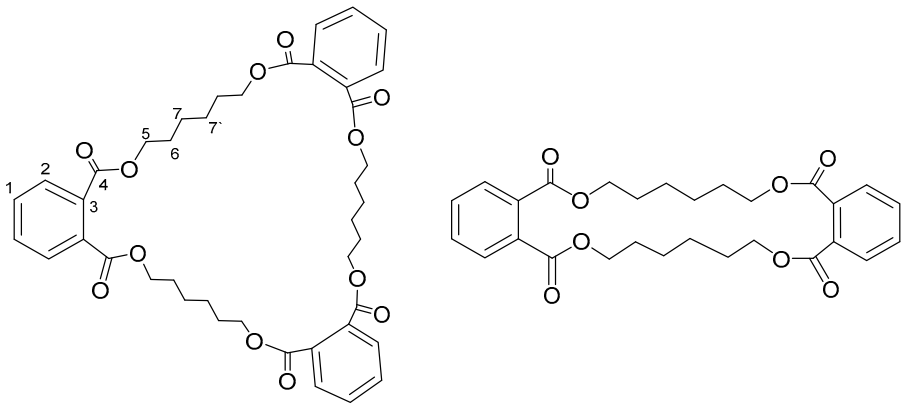

Figure 1. Chemical structures of compound **1** (**left**) and compound **2** (**right**).

2. Materials and Methods

2.1. General Experimental Procedures

Reversed-phase high-performance liquid chromatography (RP-HPLC) was carried out using an HPLC system equipped with a UV-975 Intelligent Ultraviolet-visible (UV/VIS) Detector (JASCO Co., Tokyo, Japan). A HPLC Senshu Scientific SSC-1310 Recycle Unit (Senshu Scientific Co., Tokyo, Japan) was also used, which consisted of a LC-10AD VP pump (SHIMADZU Co., Kyoto, Japan) and a SPD-6AV detector. HR-ESI-MS spectra data were obtained using a Bruker MicrOTOF QII (Bruker Co., Billerica, MA, USA) mass spectrometer. NMR spectra were recorded in CD_3OD at 800 MHz (or 600 MHz) on a Bruker AVANCE III 800 MHz (or 600 MHz, Bruker Co., Billerica, MA, USA) spectrometer. The chemical shifts were reported in δ units (ppm) using CD_3OD solvent (δH at 3.31 ppm and δC at 49.0 ppm) as the internal standard signals. The UV spectra were measured on a HITACHI U-3000 (Hitachi High-Tech Fielding Co., Tokyo, Japan) spectrometer.

2.2. The Cyanobacterium

The cyanobacterium *M. producens* was collected from Kuba Beach, Nakagusuku, Okinawa, Japan, on 13 July 2010. The collected samples were immediately stored in a freezer (−30 °C) without lyophilization. The Okinawan collection was identified as *M. producens*. A voucher specimen (#20100713-a) was also retained.

2.3. Extraction and Isolation

A frozen sample of the cyanobacterium *M. producens* (10.1 kg wet wt.) was lyophilized and then sequentially extracted with ethanol, methanol (MeOH), and acetone at RT. The extracts were combined and evaporated to obtain the residue (492.7 g, dry wt.). Next, the residue was partitioned between 80% MeOH and hexane. After solvent evaporation of the 80% MeOH layer, the condensed fraction was partitioned using distilled water and ethyl acetate (EtOAc). The EtOAc layer was then evaporated to dryness. The EtOAc fraction (4.3 g, dry wt.) was purified using a 40 × 170 mm open glass column filled with ODS resin (Pegasil Prep ODS-7515-12A, Senshu Scientific Co., Tokyo, Japan) with a stepwise increase in aqueous MeOH (30%, 50%, 70%, 85%, and 100%). The 85% MeOH layer (333.3 mg, dry wt.) was purified using reversed-phase HPLC on a 10 × 250 mm column (COSMOSIL

5C18-AR-II, Nacalai Tesque Inc., Kyoto, Japan) under the following conditions: 80% MeOH isocratic for the first 95 min; 100% MeOH isocratic from 95 min to 150 min at 2 mL/min flow rate; UV-Vis detection at 254 nm, with the sample divided into 16 fractions using a fraction collector at 8-min intervals. Fraction 3 (*t*R 16–24 min, 19.1 mg, dry wt.) was then subjected to HPLC using an isocratic system (flow rate: 1 mL/min; detection: 254 nm) on a 10 × 250 mm column (COSMOSIL 5C18-AR-II) with 85% MeOH solvent. The resulting 33 fractions were collected at 2-min intervals using a fraction collector. Finally, a recycling HPLC (column: COSMOSIL C18-AR-II 10 × 250 mm, solvent: 88% MeOH for compound **2** and 82% MeOH for compound **1**, flow rate: 1 mL/min, detection: 210 nm) was performed on fractions 3–19 (*t*R 36–38 min) and fractions 3–18 (*t*R 34–36 min) for the isolation of compound **1** (0.10 mg) and compound **2** (0.16 mg).

2.4. Bioactive Assays

The antibacterial assays of compounds **1** and **2** were carried out using *Escherichia coli* JCM No. 20135 and *Pyricularia oryzae* Ina 86–137. *E. coli* was cultured at 25 °C for 3 days in B-1 medium, consisting of 5.0 g/L Bactom TM Peptone, 3.0 g/L beef extract, 3.0 g/L NaCl, and 15.0 g/L agar powder (Kanto Chemical Co. Inc., Tokyo, Japan). *P. oryzae* was cultured at RT in Ottaviani and Agosti (OA) medium containing 50 g/L of oatmeal, 5 g/L sucrose, and 30 g/L agar powder. Both media were prepared using distilled water. Compounds **1** and **2** were dissolved in MeOH and then absorbed on paper discs (8 mm in diameter). After placing the discs on to the assay plates were incubated at 27 °C for 18 h (*E. coli*) and at RT for 13 days (*P. oryzae*).

3. Results and Discussion

Compound **1** (0.10 mg) and compound **2** (0.16 mg) were isolated during exploring natural products from the Okinawan cyanobacterium *M. producens* (10.1 kg wet wt.). Compound **1** possessed a molecular formula of $C_{42}H_{48}O_{12}$, as shown by the mass spectrum with the $[M + H]^+$ ion peak at *m/z* 745.3222 (calcd. for $C_{42}H_{49}O_{12}$, 745.3219) (Figure S1) and the $[M + Na]^+$ ion peak at *m/z* 767.3042 (calcd. for $C_{42}H_{48}O_{12}Na$, 767.3038). The UV spectral data of compound **1** suggested the existence of a conjugated ring system (UV λ max (ethanol) nm (ε) 225 (27,788), 274 (5686)), the structure of which was predominantly determined by 1D and 2D nuclear magnetic resonance (NMR) spectral analyses. The ^{1}H-NMR spectrum revealed the existence of an ethylene group at H-5 (δH 4.30, dd, *J* = 6.6 Hz, 6.6 Hz) connected to the oxygen of the carboxyl group. The proton signals with chemical shifts of δH 7.60 (H-1, dd, *J* = 3.3 Hz, 5.7 Hz) and δH 7.71 (H-2, dd, *J* = 3.3 Hz, 5.7 Hz) indicated a benzene ring. Furthermore, the existence of two ethylene groups was revealed by the proton signals of δH 1.77 (H-6, m) and δH 1.49 (H-7, m). From the ^{13}C-NMR spectrum, the signals of C-1 (δC 132.3), C-2 (δC 129.9), and C-3 (δC 133.6) confirmed the existence of a benzene ring and identified three methylene groups at C-5 (δC 66.9), C-6 (δC 29.6), and C-7 (δC 26.9).

^{1}H-^{1}H COSY spectrum analysis (Figure S4) revealed the correlation between H-1 and H-2, which further confirmed the existence of a benzene ring. The correlations of H-5/H-6 and H-6/H-7 were also detected. Moreover, the correlations of H-5/C-4, C-6, and C-7; and H-6/C-5 and C-7, were detected from the ^{1}H-^{13}C HMBC spectrum (Figure S6), indicating the partial structure of compound **1** (Figure 2). Furthermore, the molecular weight of compound **1** was detected to be 744 Da, which corresponds to exactly three times of the molecular weight of the partial structure (MW 248 Da, $C_{14}H_{16}O_4$) (Figure 2). Meanwhile, the correlation of H-7/C-7 was detected from the HMBC spectrum (Figure 3), indicating that C-7 was connected to a carbon with the same situation as C-7. Thus, compound **1** was revealed to be a novel macrocyclic hexaester (Figure 1). NMR data are summarized in Table 1.

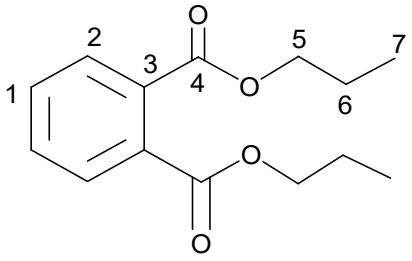

Figure 2. Partial structure of compound **1**.

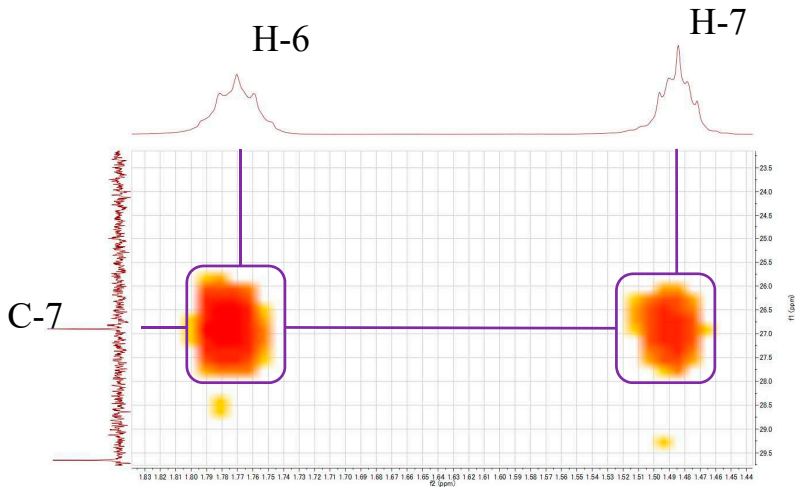

Figure 3. Correlation of H-7/C-7 detected in the ^{1}H-^{13}C HMBC spectrum of compound **1** in CD_3OD.

Table 1. NMR-assigned table for compound **1** in CD_3OD.

Atom	^{13}C [a]	^{1}H, mult, *J* (Hz) [b]	COSY	HMBC (H→C)
1	132.3	7.60, dd (3.3, 5.7 Hz)	H-2	C-2
2	129.9	7.71, dd (3.3, 5.7 Hz)	H-1	C-1, C-3
3	133.6			
4	169.4			
5	66.9	4.30, dd (6.6, 6.6 Hz)	H-6	C-4, C-6, C-7
6	29.6	1.77, m	H-7	C-5, C-7
7	26.9	1.49, m	H-6	C-7

[a] Recorded at 200 MHz; [b] recorded at 800 MHz. Coupling constants (Hz) are in parentheses. Abbreviations: dd, double-doublet; m, multiplet.

Compound **2** possessed a molecular formula of $C_{28}H_{32}O_8$, as shown in the high-resolution electrospray ionization mass spectra (HR-ESI-MS) according to the $[M + H]^+$ ion peak at *m*/*z* 497.2120 (calcd. for $C_{28}H_{33}O8$, 497.2170) and the $[M + Na]^+$ ion peak at *m*/*z* 519.1934 (calcd. for $C_{28}H_{32}O_8Na$, 519.1987). Comparing the ^{1}H-NMR data of compounds **1** and **2**, the proton signals were found to be identical, revealing that compound **1** and **2** had the same partial structure. Furthermore, the molecular weight of compound **2** was measured to be 496 Da, which was exactly twice that of the partial structure (MW 248 Da) of compound **1** (Figure 2), indicating that compound **2** is a macrocyclic tetraester (See Figure 1). Compound **2** was recently reported as a natural compound [16]. Therefore, compounds **1** and **2** are possibly natural products.

Compounds **1** and **2** showed no antibacterial activity against *E. coli* JCM No 20135 and *P. oryzae* Ina 86–137 at the concentrations tested (**1**, 12 µg/disc; **2**, 10 µg/disc; methanol was tested as the control).

A novel symmetrical macrocyclic hexaester (**1**) and a known macrocyclic tetraester (**2**) were isolated during a natural product-exploring program on the cyanobacterium *Moorea producens*. These molecules could be produced by the cyanobacterium. Further study is needed to determine the true origin of these symmetrical compounds.

Supplementary Materials: The following are available online at https://www.mdpi.com/2073-8994/13/2/361/s1, Figure S1. HR-ESI-MS spectrum of compound **1**, Figure S2. ^{1}H-NMR spectrum of compound **1** in CD_3OD, Figure S3. ^{13}C-NMR spectrum of compound **1** in CD_3OD, Figure S4. ^{1}H-^{1}H COSY spectrum of compound **1** in CD_3OD, Figure S5. ^{1}H-^{13}C HSQC spectrum of compound **1** in CD_3OD, Figure S6. ^{1}H-^{13}C HMBC spectrum of compound **1** in CD_3OD.

Author Contributions: H.N. conceived and designed the research. W.J. purified the compound. R.W., T.S. and H.U. performed the spectral measurement. W.J. carried out the structural identification. H.O. performed the antibacterial assay. M.F. taxonomically identified the cyanobacterium. M.K., W.J. and H.N. analyzed the data and wrote the paper. All authors have read and agreed to the published version of the manuscript.

Funding: The authors disclose the receipt of the following financial support for the research, authorship, and/or publication of this article: this work was partly supported by JSPS KAKENHI Grant Number 19K06220 (HN) from the Ministry of Education, Culture, Sport, Science, and Technology, Japan.

Acknowledgments: The authors gratefully acknowledge N. Oshiro, S. Iwanaga, and D. Kamiya of the Okinawa Prefectural Institute of Health and Environment for the cyanobacteria sample collection. The authors would like to thank Microbe Division (RIKEN BRC JCM) for providing *E. coli*, as well as T. Sone of Hokkaido University for providing *P. oryzae* Ina 86–137.

Conflicts of Interest: The authors declare no conflict of interest.

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