

(S)-2-Hydroxy-3-(((2R,3R,4S,5R,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)propyl (E)-8-Hydroperoxyhexadec-6-enoate

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Short Note

(S)-2-Hydroxy-3-(((2R,3R,4S,5R,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)propyl (E)-8-Hydroperoxyhexadec-6-enoate

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Abstract: A new oxylipin (**1**) was isolated from cyanobacteria collected at Tokyo Bay, Japan. The structure of **1** was elucidated based on spectroscopic data including 1D and 2D NMR, as well as high-resolution mass spectrometry. The structure of **1** was elucidated to be (S)-2-hydroxy-3-(((2R,3R,4S,5R,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)propyl (E)-8-hydroperoxyhexadec-6-enoate.

Keywords: cyanobacteria; marine natural product; structure elucidation; NMR; galactolipid



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1. Introduction

Oxylipins are a class of oxygenated natural products formed from fatty acids by a pathway involving at least one step of dioxygen (O₂)-dependent oxidation [1,2]. It has been revealed that oxylipins have physiologically significant activities in many organisms [3,4]. Recently, our research group has found new oxylipins from the Okinawan cyanobacteria [5,6]. In the present study, further research on the cyanobacteria collected from Tokyo Bay led to the isolation of a new oxylipin ester, (S)-2-hydroxy-3-(((2R,3R,4S,5R,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)propyl (E)-8-hydroperoxyhexadec-6-enoate (**1**; Figure 1).

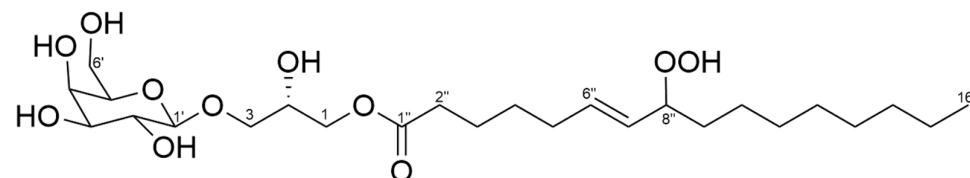


Figure 1. Structure of compound (**1**).

2. Results and Discussion

An HR-ESI-MS analysis of compound (**1**) showed an [M – H][–] ion peak at *m/z* 521.2950 (calcd. for C₂₅H₄₅O₁₁, 521.2967), indicating a molecular formula of C₂₅H₄₆O₁₁ with three degrees of unsaturation. The ¹H and ¹³C-NMR spectra indicated that compound (**1**) was an oxidized derivative of monogalactosyl monoacylglycerol (MGMG). In the ¹³C NMR spectrum, 11 oxygen-bearing carbons including a carbonyl carbon were observed. Overall, 6 of the 11 oxygen-bearing carbons were assigned to a galactose unit (Table 1).

δ_C 62.4, 69.9, 72.5, 74.7, 76.3, 105.2) and a glycerol unit (δ_C 66.1, 69.3, 72.1). The remaining two ^{13}C signals (δ_C 86.6, 173.7) were supposed to belong to a fatty acid moiety.

Table 1. 1H (600 MHz) and ^{13}C NMR (150 MHz) spectroscopic data for compound (1) in acetone- d_6 .

Position	δ_H (ppm, J in Hz)	δ_C , (ppm, Type)
1'	4.26, d (7.2)	105.2, CH
2'	3.53, overlap	72.5, CH
3'	3.51, dd (9.3, 2.8)	74.7, CH
4'	3.88, brs	69.9, CH
5'	3.55, m	76.3, CH
6'	3.76, m	62.4, CH ₂
1	4.12, d (5.4)	66.1, CH ₂
2	3.94, m	69.3, CH
3a	3.66, dd (10.7, 4.8)	72.1, CH ₂
3b	3.82, dd (10.7, 5.5)	
1''		173.7, C
2''	2.33, t (7.4)	34.4, CH ₂
3''	1.62, overlap	25.1, CH ₂
4''	1.44, m	29.3, CH ₂
5''	2.07, overlap	32.6 ^a , CH ₂
6''	5.68, dt (15.4, 6.5)	134.6, CH
7''	5.41, ddt (15.4, 7.9, 1.5)	131.2, CH
8''	4.19, m	86.6, CH
9''a	1.41, m	33.6, CH ₂
9''b	1.63, overlap	
10''	1.23–1.37, m	26.1, CH ₂
11''	1.23–1.37, m	30.0 ^b , CH ₂
12''	1.23–1.37, m	30.3 ^b , CH ₂
13''	1.23–1.37, m	30.4 ^b , CH ₂
14''	1.23–1.37, m	32.7 ^a , CH ₂
15''	1.23–1.37, m	23.3, CH ₂
16''	0.88, t (6.8)	14.4, CH ₃
8''-OOH	10.31, s	

^a chemical shifts are interchangeable. ^b chemical shifts are interchangeable.

The glycerol part—H₂-1 (δ_H 4.12) –H₂-2 (δ_H 3.94) –H₂-3 (δ_H 3.66 and 3.82)—and the galactose part—H-1' (δ_H 4.26) –H-2' (δ_H 3.53) –H-3' (δ_H 3.51) –H-4' (δ_H 3.88) –H-5' (δ_H 3.55) –H₂-6' (δ_H 3.76)—were assigned by the detailed analysis of COSY correlations (Figure 2). The $^3J_{H-1',H-2'}$ (7.2 Hz) and $^3J_{H-3',H-4'}$ (2.8 Hz) confirmed that the sugar was β -galactose. In the fatty acid moiety of 1, the existence of a hydroperoxy group (-OOH) was speculated from unusual oxymethine signals H-8'' (δ_H 4.19) and C-8'' (δ_C 86.6), together with the molecular formula of C₂₅H₄₆O₁₁. A hydroperoxy proton at δ_H 10.31 was also observed [7]. The position of the double bond and the -OOH group was elucidated by the COSY and TOCSY experiments (Figure 2). The COSY correlations of H₂-2'' (δ_H 2.33)

– H₂-3'' (δ_{H} 1.62) – H₂-4'' (δ_{H} 1.44) – H₂-5'' (δ_{H} 2.07) – H-6'' (δ_{H} 5.68) indicated that the double bond was positioned at $\Delta^{6''}$. The olefin protons in **1** were observed at δ_{H} 5.68 (H-6'') and δ_{H} 5.41 (H-7''). The proton coupling constant of 15.4 Hz between H-6'' and H-7'' and the NOE correlation H-6''/H-8'' confirmed the *E* configuration of the double bond $\Delta^{6''}$. Furthermore, the COSY correlation between olefin proton H-7'' (δ_{H} 5.41) and an oxy-proton H-8'' (δ_{H} 4.19) indicated that the hydroperoxy group was substituted on C-8''. These results, along with the HMBC correlation of H-2'' (δ_{H} 2.33)/C-1'' (δ_{C} 173.7), led to the determination of the fatty acid unit as (*E*)-8-hydroperoxyhexadec-6-enoic acid. Moreover, HMBC correlations from H₂-3 (δ_{H} 3.66 and 3.82) to C-1' (δ_{C} 105.2) and H₂-1 (δ_{H} 4.12) to C-1'' (δ_{C} 173.7) confirmed an ether linkage between C-3 and C-1' and an ester linkage between C-1 and C-1'', respectively.

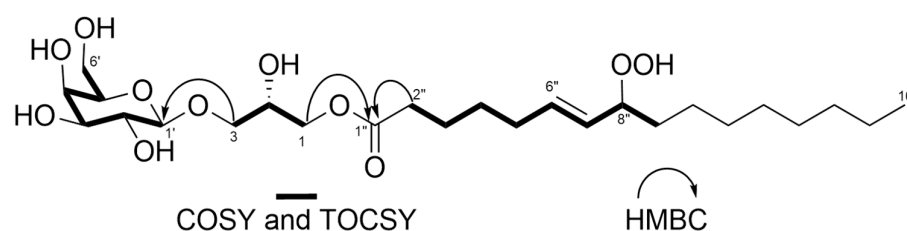


Figure 2. Key COSY and TOCSY (bold line) and HMBC (arrow, H to C) correlations for compound (**1**).

The configuration at C-2 (δ_{C} 69.3) of glycerol in **1** was determined on the basis of the specific rotation of galactosylglycerol [8]. Galactosylglycerol (**2**, Figure 3) obtained by methanolysis of **1** showed a negative specific rotation ($[\alpha]_{\text{D}}^{27} -8.16$ (*c* 0.49, MeOH)), indicating that the configuration at C-2 in galactosylglycerol is *R* [8]. Absolute configuration of the hydroperoxy group at C-8'' could not be determined in this study.

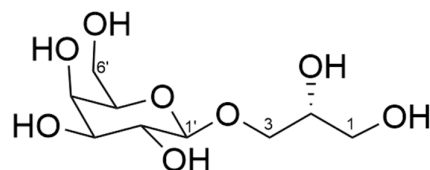


Figure 3. Structure of galactosylglycerol (**2**).

Compound (**1**) is a novel esterified oxylipin which clearly originated from monogalactosylmonoacylglycerol (MGMG).

3. Materials and Methods

3.1. General Procedure and Method

The HR ESI-MS was measured with a micrOTOF-QII (Bruker, Billerica, MA, USA), a quadrupole time-of-flight mass spectrometer (QTOFMS), along with a high-performance liquid chromatograph of UltiMate 3000 Series (Thermo Fisher Scientific, Waltham, MA, USA). The NMR spectra were recorded on a Bruker AVANCE III 600 spectrometer (Bruker Biospin AG, Fällanden, Switzerland) at 300 K and referenced to residual solvent signals (δ_{H} 2.05, δ_{C} 29.84 for acetone-*d*₆). Optical rotations were measured using a JASCO P-2100 (JASCO Co., Tokyo, Japan) with a 10 mm long cell. Bioassay results were recorded on a Model 550 microplate reader (Bio-Rad Co., Hercules, CA, USA).

3.2. Biological Materials

Cyanobacteria were collected at Tokyo Bay (35.58 N, 139.77 E), Japan, in 2016. The 16S rRNA sequence amplicon analysis (Bioengineering Lab. Co., Ltd., Tokyo, Japan) was used to identify the cyanobacteria sample. The results revealed that the cyanobacterium

belonged to Oscillatoriales. A voucher specimen (20160725-a) was deposited at the Tokyo University of Marine Science and Technology.

3.3. Isolation of Compound (1)

The frozen algal sample (wet weight: 5.6 kg) was extracted with methanol (MeOH) thrice. After the elimination of MeOH under reduced pressure, the extracts were partitioned between ethyl acetate (EtOAc) and H₂O. After evaporation of EtOAc, the extract was fractionated by MPLC using ODS gel (Cosmosil 75C18-OPN, Nacalai Tesque Inc., Kyoto, Japan) with stepwise elution with 50%, 70%, 90%, and 100% MeOH [size of the column, 40 × 180 mm; each eluant volume, 700 mL]. The 90% MeOH eluate was subjected to an ODS column (Cosmosil 5C18-AR-II, 20 × 250 mm, Nacalai Tesque Inc., Kyoto, Japan) with 80% MeOH for 10 min, followed by a gradient elution from 80% to 100% MeOH for 50 min [flow rate, 4.0 mL/min; detection at 254 nm]. The fraction was further purified by an ODS column (Cosmosil 5C18-AR-II, 10 × 250 mm, Nacalai Tesque Inc., Kyoto, Japan) with 80% MeOH for 10 min, then a gradient elution from 80% to 100% MeOH for 50 min [flow rate, 2.0 mL/min; detection at 210 nm]. The final purification was performed via recycle HPLC using the reversed-phase column (CAPCELLPAK, 10 × 250 mm, Nacalai Tesque Inc., Kyoto, Japan) with 75% Acetonitrile (MeCN) [flow rate, 2.0 mL/min; detection at 210 nm]. Compound 1 (3.88 mg) was isolated at a retention time of 8.7 min. Compound (1); white solid, $[\alpha]_D^{27} -4.17$ (c 0.72, MeOH).

3.4. Preparation of Compound (2)

A solution of triethylamine/MeOH (1:4) was added to the compound (1, 1.08 mg) and the mixture was stirred at 20 °C for 46 h [9]. The reaction mixture was partitioned between hexane and 80% MeOH. Compound (2, 0.4 mg) was obtained in the aq. MeOH layer.

Supplementary Materials: The following supporting information can be downloaded online: Figure S1: HR-ESI-MS of compound (1) (negative); Figure S2: ¹H-NMR spectrum of compound (1) (acetone-*d*₆, 600 MHz); Figure S3: ¹³C-NMR spectrum of compound (1) (acetone-*d*₆, 150 MHz); Figure S4: ¹H-¹H COSY spectrum of compound (1) (acetone-*d*₆, 600 MHz); Figure S5: HSQC spectrum of compound (1) (acetone-*d*₆, 600 MHz); Figure S6: HMBC spectrum of compound (1) (acetone-*d*₆, 600 MHz); Figure S7: NOESY spectrum of compound (1) (acetone-*d*₆, 600 MHz).

Author Contributions: Conceptualisation, H.N. and M.S.; isolation, M.H.; structure analysis, B.Z., M.H., R.K. and M.S.; MS analysis, H.U.; writing—original draft preparation, M.S., B.Z. and R.K.; writing—review and editing, H.N. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: The spectroscopic data presented in this study are available as Supplementary Materials.

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