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Determination of absolute configuration of C14–C23 fragment in symbiodinolide

Chunguang Han [a], Yoshi Yamano [a], Masaki Kita [b], Hiroyoshi Takamura [a], Daisuke Uemura [a,c,*]

[a] Department of Chemistry, Graduate School of Science, Nagoya University, Furo-cho, Chikusa, Nagoya 464-8602, Japan
[b] Department of Chemistry, Graduate School of Pure and Applied Sciences, University of Tsukuba, 1-1-1 Tennodai, Tsukuba 305-8571, Japan
[c] Department of Biosciences and Informatics, Faculty of Science and Technology, Keio University, 3-14-1 Hiyoshi, Yokohama 223-8522, Japan

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ABSTRACT

The degradation product C14–C23 **2** was obtained using ethenolysis with the 2nd-generation Hoveyda-Grubbs catalyst from 62-membered lactone in symbiodinolide (**1**). The absolute configurations of three chiral centers in fragment **2** were assigned as 17*R*, 18*R*, and 21*R* by a combination of *J*-based configuration analysis and the Mosher–Riguera method.

Symbiodinolide (**1**), a unique super-carbon-chain compound (SCC)[1] with a molecular weight of 2860, was isolated from the Okinawan symbiotic dinoflagellate *Symbiodinium* sp. (Fig. 1). Recently, its isolation, structure elucidation, and the partial stereochemistries were reported.[2] In our continuing investigation on the stereochemical assignment of symbiodinolide (**1**), the absolute configurations of three chiral centers (C17, C18, and C21) in degradation product **2** were assigned by a combination of *J*-based configuration analysis (JBCA),[3] ROESY correlations, and the Mosher–Riguera method.[4]

In the course of the further stereochemical analysis of symbiodinolide (**1**), the relative configurations between the vicinal stereocenters C17 and C18 were determined by *J*-based configuration analysis. Two- and three-bond $^{13}C-^{1}H$ coupling constants ($^{2,3}J_{C,H}$) of symbiodinolide were measured in CD_3OD. The small $^{3}J_{C19/H17}$ values (1.1 Hz) indicated that C19 is gauche to H17, and the geminal $^{13}C-^{1}H$ coupling constants ($^{2}J_{C,H}$) also provide conformational information (when an oxygen functionality on a carbon atom is *gauche* to its geminal proton, $^{2}J_{C,H}$ becomes large, and when it is *anti*, the value becomes small), so the large $^{2}J_{C17/H18}$ values (5.5 Hz) identified that 17–OH is gauche to H18. Thereby, three possible conformers A-3 (*threo*), B-1, and B-3 (*erythro*) can be identified in Figure 2.

The ROESY correlations for C18-Me/H17 in symbiodinolide indicated gauche relations for C18-Me and H17 in two conformers A-3 and B-3. Because of anti-relations for C18-Me and H15 in A-3, *erythro* configuration B-3 was finally assigned on the basis of the crucial ROESY correlations for C18-Me/H15 (Fig. 2). The relative configurations of vicinal centers C17 and C18 were concluded as shown in Figure 3.

However, the stereochemical assignment of the other stereocenters in the 62-membered polyunsaturated lactone of **1** could not be completed by spectral analysis due to that the signals are largely overlapping. Thereby, the chemical degradation reaction was essential for symbiodinolide (**1**). Ethenolysis[5] (cross-metathesis with ethene) is an attractive alternative to ozonolysis and periodate oxidation of alkenes because of its wide functional group tolerance, comparatively mild reaction conditions and the degraded products without redundant modification. Here, we carried out an effective ethenolysis with the commercially available 2nd-generation Hoveyda-Grubbs (Hoveyda-Grubbs II) catalyst[6] under ordinary ethene pressure (balloon) at room temperature as described before.[7] As a result, an acetal C14–C23 **2** and two other terminal olefin degradation products (in small amounts, respectively) were successfully obtained from the 62-membered polyunsaturated lactone (Scheme 1). The structure of C14–C23 fragment **2** was confirmed by the analysis of ^{1}H NMR, COSY correlations, and HR MS.[8]

The absolute configurations at two chiral centers (C17 and C21) of 1,5-diol **2** could be determined using the Mosher–Riguera method. A trace diol **2** (~ 0.1 mg) was dissolved in 2% DMAP solution in CH_2Cl_2, and then added Et_3N, and (*R*)-(−)- or (*S*)-(+)-MTPACl. The mixture was stirred at room temperature for 21 h. After the addition of *N*,*N*-dimethyl-1,3-propanediamine, the solvent was

* Corresponding author. Tel./fax: +81 45 566 1842.
E-mail address: uemura@bio.keio.ac.jp (D. Uemura).

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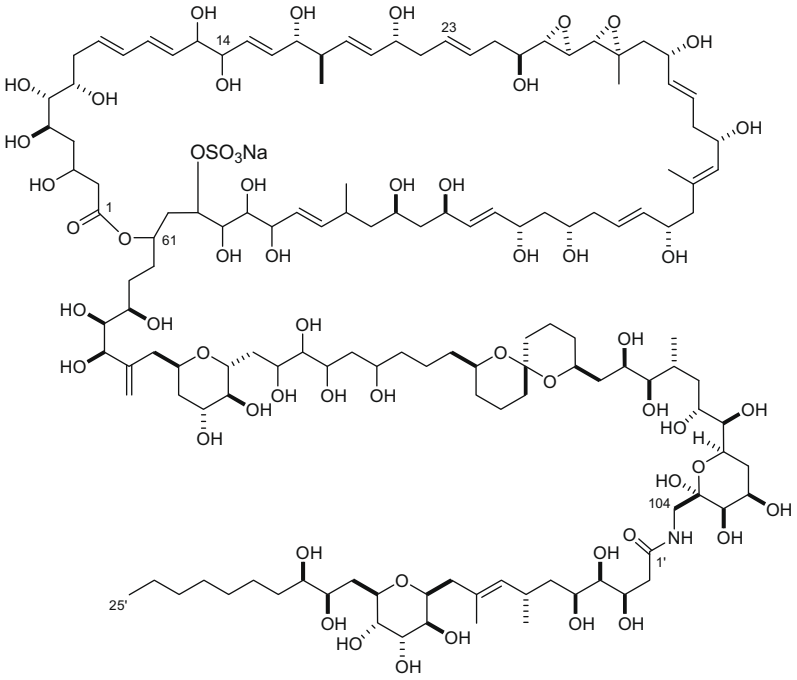

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Figure 1. Structure of symbiodinolide (**1**) with the absolute configurations (17*R*, 18*R*, and 21*R*) in fragment **2** determined in the present study.

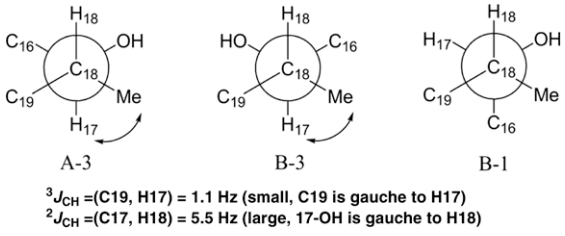


Figure 2. $^{2,3}J_{C,H}$ values were used to assign the relative configurations of C17 and C18 of **1**.

evaporated in vacuo. The residue was purified through a silica gel column, and then HPLC [Develosil ODS-HG-5 (Ø 10 × 250 mm), Nomura Chemical, flow rate 4 ml/min, 80–100% aq MeCN, 40 min, linear gradient] to afford a trace amount of bis-(*S*)- and (*R*)-MTPA esters **2s**[9] and **2r**[10] of **2**, respectively. The ^{1}H NMR data for two bis-MTPA derivatives are assigned by the analysis of COSY correlations. $\Delta\delta$ values ($\Delta\delta = \delta_S - \delta_R$) obtained from the ^{1}H NMR data of **2s** and **2r** showed positive signs for H21 (+0.03), H22 (+0.05), H23 (+0.12), and H24 (+0.09), and negative signs for H17 (−0.06), H16 (−0.11), H15 (−0.08), and H14 (−0.03) shown in Figure 4. These results were consistent with the *syn*-1,5-diols noted by Riguera for acyclic systems (Fig. 5).[4,5b] Thus, suggesting C17 and

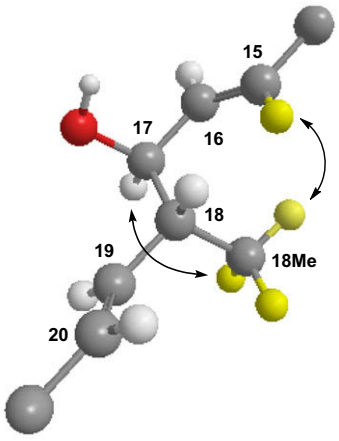
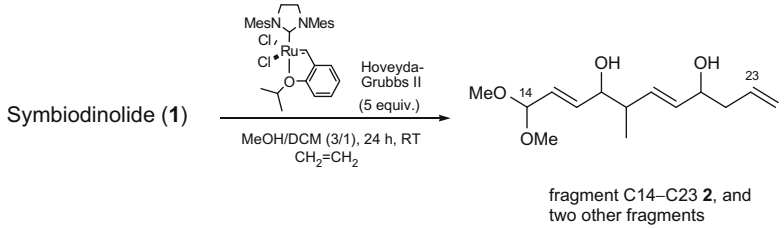


Figure 3. ROESY correlations (black) between C18-Me/H17 and H15 in 3D model.

C21 possessed *R*- and *R*-configurations, respectively. Therefore, the absolute configurations of C14–C23 **2** were assigned as 17*R*, 18*R*, and 21*R*.

In conclusion, an *erythro* configuration was assigned between the vicinal centers C17 and C18 in 62-membered lactone of



Scheme 1. C14–C23 fragment **2** obtained by olefin cross-metathesis with ethene.

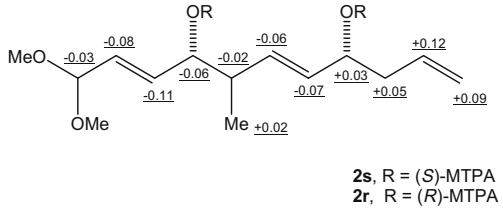


Figure 4. $\Delta\delta_{S-R}$ values for the bis-MTPA derivatives of **2**.

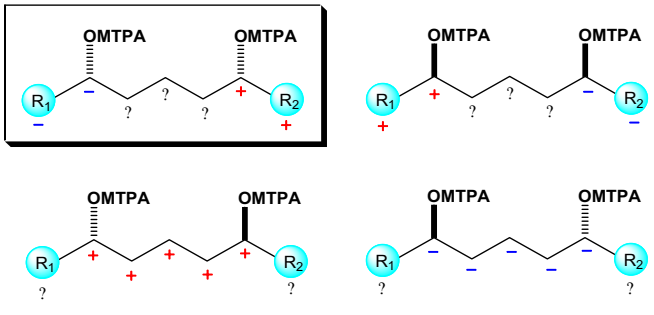


Figure 5. Preditive $\Delta\delta_{S-R}$ (+ or −) patterns for the bis-MTPA esters of acyclic 1,5-diols.

symbiodinolide (**1**) on the basis of *J*-based configuration analysis and ROESY correlations. Using ethenolysis with Hoveyda-Grubbs II catalyst, a degradation product C14–C23 **2** was obtained from **1**, and the absolute configurations of three chiral centers in **2** were assigned as 17*R*, 18*R*, and 21*R* by the Mosher–Riguera method. Further chemical degradation studies in order to obtain the new fragments and a complete assignment of the absolute stereochemistry of symbiodinolide are currently underway.

Acknowledgments

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8. C14–C23 fragment **2**: ^{1}H NMR (800 MHz, $CDCL_3$) δ 5.86 (dd, J = 6.4, 15.8 Hz, 1H, H16), 5.80 (m, 1H, H23), 5.68 (dd, J = 4.6, 15.8 Hz, 1H, H15), 5.61 (m, 2H, H19 and H20), 5.14 (m, 2H, $C23CH_2$), 4.81 (d, J = 4.6 Hz, 1H, H14), 4.18 (m, 1H, H21), 3.96 (m, 1H, H17), 3.33 and 3.32 (s, 6H, C14-OMe × 2), 2.34 and 2.31 (m, 3H, H18 and H22a,b), 1.03 (d, J = 6.9 Hz, 1H, C18-Me); HR ESI-TOF-MS m/z 279.1579 $(M+Na)^+$, calcd for $C_{14}H_{24}O_4Na$: 279.1572.
9. C14–C23 fragment bis-(*S*)-MTPA ester (**2s**): ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.50 (m, 4H, Ph), 7.39 (m, 6H, Ph), 5.70 (m, 1H, H23), 5.68 (dd, J = 5.5, 15.8 Hz, 1H, H16), 5.64 (dd, J = 4.1, 15.8 Hz, 1H, H15), 5.63 (dd, J = 7.8, 15.2 Hz, 1H, H19), 5.46 (m, 2H, H20 and H21), 5.34 (t, J = 5.5 Hz, 1H, H17), 5.10 (m, 2H, $C23CH_2$), 4.74 (d, J = 4.1 Hz, 1H, H14), 3.50 and 3.53 (s, 6H, C14-OMe × 2), 2.54 (m, 1H, H18), 2.39 and 2.43 (m, 2H, H22a,b), 0.97 (d, J = 6.9 Hz, 3H, C18-Me); HR ESI-TOF-MS m/z 711.2262 $(M+Na)^+$, calcd for $C_{34}H_{38}F_6O_8Na$: 711.2369.
10. C14–C23 fragment bis-(*R*)-MTPA ester (**2r**): ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.49 (m, 4H, Ph), 7.38 (m, 6H, Ph), 5.79 (dd, J = 5.5, 15.6 Hz, 1H, H16), 5.72 (dd, J = 4.2, 15.6 Hz, 1H, H15), 5.70 (dd, J = 7.8, 15.6 Hz, 1H, H19), 5.59 (m, 1H, H23), 5.53 (dd, J = 7.4, 15.6 Hz, 1H, H20), 5.44 (m, 1H, H21), 5.40 (t, J = 5.5 Hz, 1H, H17), 5.01 (m, 2H, $C23CH_2$), 4.77 (d, J = 4.2 Hz, 1H, H14), 3.50 and 3.53 (s, 6H, C14-OMe × 2), 2.56 (m, 1H, H18), 2.33 and 2.37 (m, 2H, H22a,b), 0.95 (d, J = 7.4 Hz, 3H, C18-Me); HR ESI-TOF-MS m/z 711.2341 $(M+Na)^+$, calcd for $C_{34}H_{38}F_6O_8Na$: 711.2369.