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Stereoselective synthesis of the C14–C24 degraded fragment of symbiodinolide

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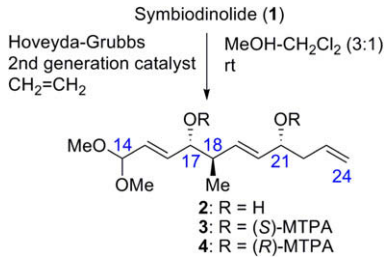
ABSTRACT

Symbiodinolide is a polyol macrolide isolated from the marine dinoflagellate *Symbiodinium* sp. in 2007. The C14–C24 fragment of symbiodinolide possessing the 17*R*/18*R*/21*R* absolute configuration, which was obtained as one of the degraded products of symbiodinolide, was synthesized stereoselectively from *cis*-2-butene-1,4-diol. The detailed comparison of the synthetic product with the degraded product in the spectroscopic data confirmed that the stereostructure of the C14–C24 fragment was 17*R*, 18*R*, and 21*R*.

Symbiodinolide (**1**), a novel polyol compound, has been recently isolated from the marine dinoflagellate *Symbiodinium* sp., which exhibits a voltage-dependant N-type Ca^{2+} channel-opening activity at 7 nM and COX-1 inhibitory effect at 2 μM (Fig. 1).[1] The planar structure and partial stereochemistry of **1** were elucidated by spectroscopic analysis[1] and chemical synthesis.[2] Previously, we degraded **1** via the cross-metathesis with ethylene using Hoveyda–Grubbs second generation catalyst[3] to give the C14–C24 fragment **2** (Scheme 1).[4] The absolute stereochemistries at C17 and C21 positions were determined to be 17*R* and 21*R* by applying the modified Mosher method[5] to bis-(*S*) and (*R*)-MTPA esters **3** and **4** derived from the degraded product **2**. The absolute configuration at C18 position was assigned to be 18*R* on the basis of *J*-based configuration analysis[6] and NOE correlations in **1**. Herein, we report the stereoselective synthesis of (17*R*,18*R*,21*R*)-diol possessing the proposed stereostructure of the degraded product **2**, which has resulted in the confirmation of the absolute configuration of the C14–C24 fragment.

The asymmetric aldol reaction of known aldehyde **5**, which was easily prepared from *cis*-2-butene-1,4-diol,[7] and propionyl oxazolidinethione **6** was performed to give Evans type *syn* aldol adduct **7** as a single stereoisomer (Scheme 2).[8] The absolute stereochemistry of the resulting chiral center at the C17 position was determined by the modified Mosher method.[5] Alcohol **7** was transformed to lactone **9** for the elucidation of the absolute configuration at the C18 position. Thus, reduction of **7** with DIBALH followed by Wittig reaction with $Ph_3P{=}CHCO_2Me$ gave α,β-unsaturated ester **8**. Two double bonds of **8** were hydrogenated with Pd-C, and subsequent DIBALH reduction provided the corresponding diol. Treatment of the diol with TEMPO/NaClO afforded lactone **9**.[9] The observed NOEs H-17/H-20α and CH_3-18/H-20β as shown with the arrows confirmed the absolute stereochemistry at the C18 position of **9** to be *R*. Therefore, the absolute configuration of **7** was elucidated to be 17*R* and 18*S*.

Further transformation of **7** to the (17*R*,18*R*,21*R*)-diol **2** is described in Scheme 3. Removal of the oxazolidinethione chiral auxiliary of **7** by transamination with Me_3Al/MeO(Me)NH·HCl[10] followed by Dess–Martin oxidation[11] and the diastereoselective reduction[12] yielded alcohol **10** as a sole product.[13] The resulting hydroxy group of **10** was protected with TBSOTf/2,6-lutidine to give the corresponding silyl ether. Reduction of the resulting amide to aldehyde with DIBALH and subsequent two-carbon Wittig homologation with $Ph_3P{=}CHCO_2Me$ afforded α,β-unsaturated ester **11** in 93% yield by three steps. Reduction of **11** to allylic alcohol with DIBALH followed



Scheme 1. Cross-metathesis degradation of symbiodinolide (**1**) with ethylene.

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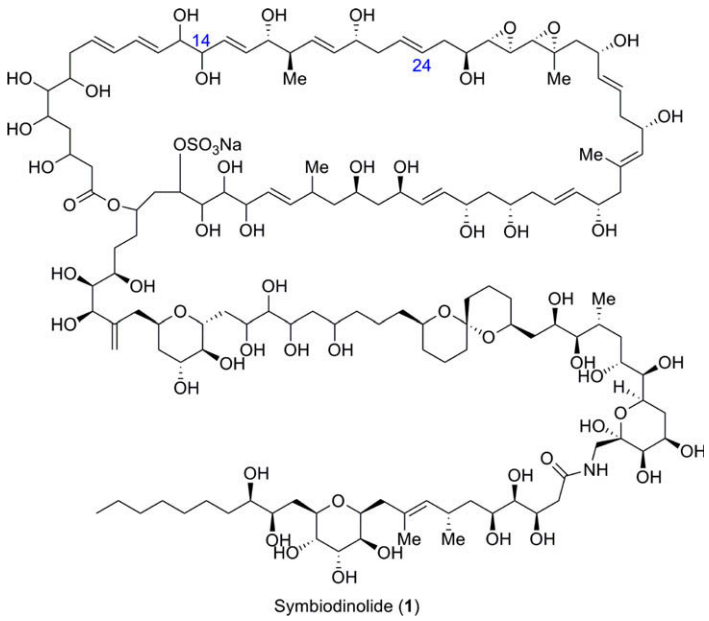
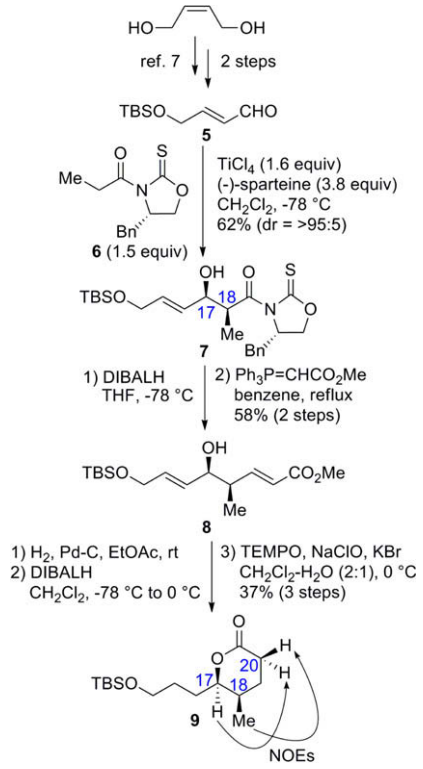
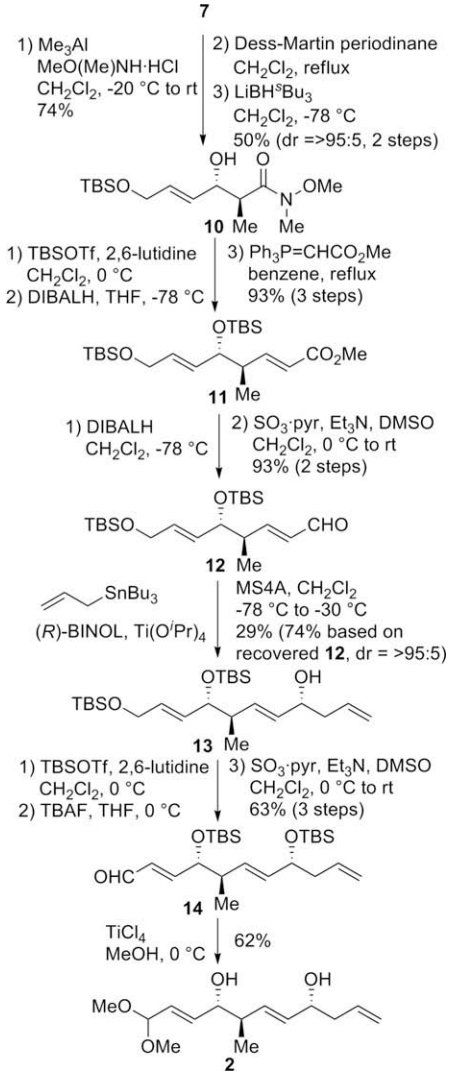


Figure 1. Structure of symbiodinolide (**1**).

by Parikh–Doering oxidation[14] gave aldehyde **12**. Aldehyde **12** was subjected to the asymmetric allylation reported by Keck et al.[15] to provide homoallylic alcohol **13** as a sole product.[13] Treatment of **13** with TBSOTf/2,6-lutidine gave the corresponding silyl ether, followed by selective removal of the primary TBS moiety to yield the corresponding allylic alcohol. Parikh–Doering oxidation[14] of the allylic alcohol gave α,β-unsaturated aldehyde **14**. Methyl acetalization and deprotection of the silyl protective groups in one-pot were



Scheme 2. Synthesis and structural determination of **7**.



Scheme 3. Synthesis of **2**.

achieved with $TiCl_4$ in MeOH to provide (17*R*,18*R*,21*R*)-diol **2**.[16] The spectroscopic data of the synthetic product **2** was identical to those of the degraded C14–C24 fragment reported previously.[4b,17]

In conclusion, we synthesized (17*R*,18*R*,21*R*)-diol **2** in 16 steps from commercially available *cis*-2-butene-1,4-diol. The spectroscopic data of the synthetic product **2** matched those of the degraded C14–C24 fragment obtained from symbiodinolide (**1**), which confirmed that the absolute stereochemistry of the C14–C24 fragment was 17*R*, 18*R*, and 21*R*. Further structural and synthetic studies on **1** are underway in our laboratories.

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17. *The synthetic product* **2**: colorless oil; R_f = 0.30 (hexane/EtOAc, 1:3); $[\alpha]_D^{23}$ −27.4 (*c* 0.13, CH_3OH); IR (neat) 3399, 2925 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.86 (dd, *J* = 15.6, 6.0 Hz, 1H), 5.83–5.76 (m, 1H), 5.68 (dd, *J* = 15.6, 4.8 Hz, 1H), 5.61–5.59 (m, 2H), 5.16–5.12 (m, 2H), 4.81 (d, *J* = 4.8 Hz, 1H), 4.19–4.16 (m, 1H), 3.95 (t, *J* = 6.6 Hz, 1H), 3.32 (s, 3H), 3.32 (s, 3H), 2.36–2.27 (m, 3H), 1.02 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.3, 134.3, 134.1, 132.4, 128.3, 118.2, 102.4, 75.2, 71.5, 52.8, 52.7, 42.7, 42.0, 16.4; HRMS (ESI-TOF) calcd for $C_{14}H_{24}O_4Na$ $(M+Na)^+$ 279.1572, found 279.1591.