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Stereoselective Synthesis and Absolute Configuration of the C1′−C25′ Fragment of Symbiodinolide

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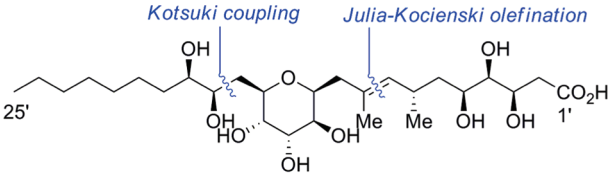

C1'-C25' Fragment of Symbiodinolide

Stereoselective synthesis of the C1′−C25′ fragment of symbiodinolide, which was obtained as a degraded product from symbiodinolide by alkaline hydrolysis, has been accomplished. The synthetic route features Kotsuki coupling and Julia−Kocienski olefination in the introduction of the side chains. This enantio- and stereoselective synthesis has established the absolute configuration of the C1′−C25′ fragment.

Introduction

Various biologically and physiologically active secondary metabolites have been isolated from marine origin.[1] In particular, polyol and polyether compounds with a large molecular weight, such as palytoxins, brevetoxins, and halichondrins, are some of the most attractive molecules for natural product chemists, synthetic chemists, biochemists, and pharmacological scientists.[2] In our continuing search for these types of compounds,[3] we reported the isolation of symbiodinolide (**1**) from the symbiotic marine dinoflagellate *Symbiodinium* sp. in 2007 (Figure 1).[4,5]

Symbiodinolide (**1**), a novel polyol macrolide, exhibits a voltage-dependent N-type Ca^{2+} channel-opening activity at 7 nM and COX-1 inhibitory effect at 2 μM. The planar structure and partial stereochemistry of **1** were elucidated by spectroscopic analysis[4] and chemical synthesis.[6] Previously, we obtained the C1′−C25′ fragment **2** as a degraded product of **1** by alkaline hydrolysis (Scheme 1).[4] Herein, as a part of our structural and synthetic studies of **1**, we describe the enantio- and stereocontrolled synthesis of the C1′−C25′ fragment, thereby establishing that the absolute configuration of this fragment is that described in **2**.

(1) (a) Uemura, D. *Bioorganic Marine Chemistry*; Scheuer, P. J., Ed.; Springer: Berlin, Heidelberg, 1991; Vol. 4, pp 1−31. (b) Shimizu, Y. *Chem. Rev.* **1993**, *93*, 1685. (c) Uemura, D. *Chem. Rec.* **2006**, *6*, 235.

(2) (a) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897. (b) Murata, M.; Yasumoto, T. *Nat. Prod. Rep.* **2000**, *17*, 293 and references therein.

(3) For recent results, see: (a) Washida, K.; Koyama, T.; Yamada, K.; Kita, M.; Uemura, D. *Tetrahedron Lett.* **2006**, *47*, 2521. (b) Kita, M.; Roy, M. C.; Siwu, E. R. O.; Noma, I.; Takiguchi, T.; Itoh, M.; Yamada, K.; Koyama, T.; Iwashita, T.; Uemura, D. *Tetrahedron Lett.* **2007**, *48*, 3423. (c) Kita, M.; Roy, M. C.; Siwu, E. R. O.; Noma, I.; Takiguchi, T.; Yamada, K.; Koyama, T.; Iwashita, T.; Wakamiya, A.; Uemura, D. *Tetrahedron Lett.* **2007**, *48*, 3429.

(4) Kita, M.; Ohishi, N.; Konishi, K.; Kondo, M.; Koyama, T.; Kitamura, M.; Yamada, K.; Uemura, D. *Tetrahedron* **2007**, *63*, 6241.

(5) Symbiodinolide (**1**) is a structural congener of zooxanthellatoxins, which are polyol macrolides isolated from the dinoflagellate *Symbiodinium* sp. For the structural elucidation of zooxanthellatoxins, see: (a) Nakamura, H.; Asari, T.; Murai, A.; Kondo, T.; Yoshida, K.; Ohizumi, Y. *J. Org. Chem.* **1993**, *58*, 313. (b) Asari, T.; Nakamura, H.; Murai, A.; Kan, Y. *Tetrahedron Lett.* **1993**, *34*, 4059. (c) Nakamura, H.; Asari, T.; Murai, A.; Kan, Y.; Kondo, T.; Yoshida, K.; Ohizumi, Y. *J. Am. Chem. Soc.* **1995**, *117*, 550. (d) Nakamura, H.; Asari, T.; Fujimaki, K.; Maruyama, K.; Murai, A.; Ohizumi, Y.; Kan, Y. *Tetrahedron Lett.* **1995**, *36*, 7255. (e) Nakamura, H.; Fujimaki, K.; Murai, A. *Tetrahedron Lett.* **1996**, *37*, 3153. (f) Nakamura, H.; Sato, K.; Murai, A. *Tetrahedron Lett.* **1996**, *37*, 7267. (g) Nakamura, H.; Takahashi, M.; Murai, A. *Tetrahedron: Asymmetry* **1998**, *9*, 2571. (h) Nakamura, H.; Maruyama, K.; Fujimaki, K.; Murai, A. *Tetrahedron Lett.* **2000**, *41*, 1927.

(6) (a) Takamura, H.; Ando, J.; Abe, T.; Murata, T.; Kadota, I.; Uemura, D. *Tetrahedron Lett.* **2008**, *49*, 4626. (b) Takamura, H.; Kadonaga, Y.; Yamano, Y.; Han, C.; Aoyama, Y.; Kadota, I.; Uemura, D. *Tetrahedron Lett.* **2009**, *50*, 863. (c) Murata, T.; Sano, M.; Takamura, H.; Kadota, I.; Uemura, D. *J. Org. Chem.* **2009**, *74*, 4797. (d) Takamura, H.; Kadonaga, Y.; Yamano, Y.; Han, C.; Kadota, I.; Uemura, D. *Tetrahedron* **2009** DOI: 10.1016/j.tet.2009.07.019.

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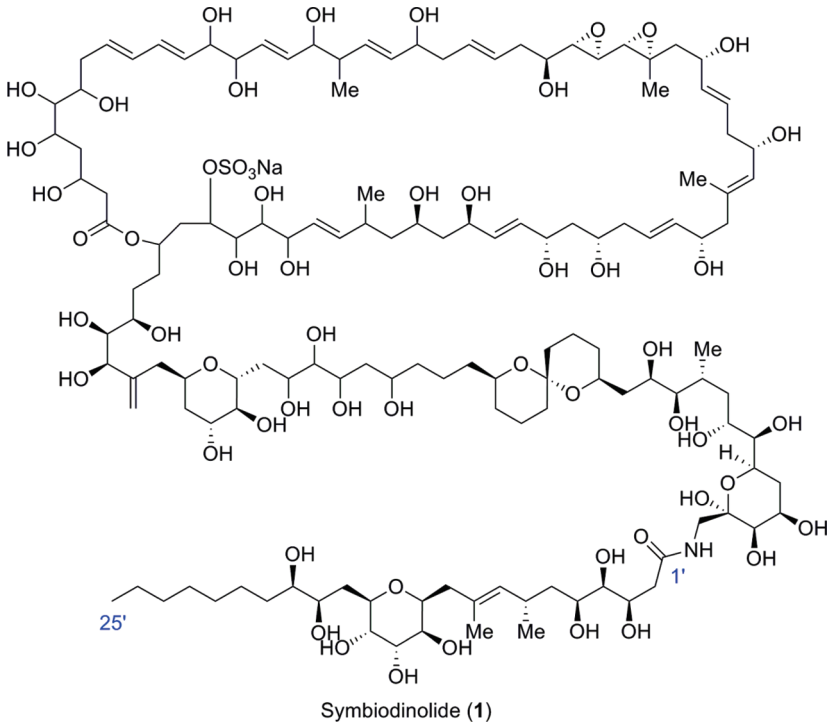
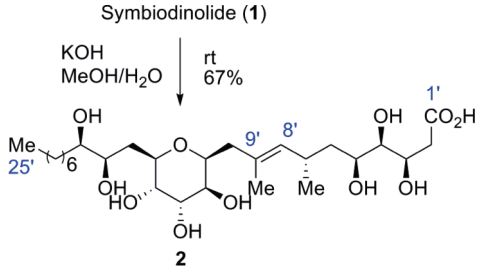


FIGURE 1. Structure of symbiodinolide (**1**).

SCHEME 1. Alkaline Hydrolysis of Symbiodinolide (1)



Retrosynthetic Analysis

Scheme 2 outlines the retrosynthetic analysis of **2**. We planned to synthesize **2** by the construction of C8′−C9′ trisubstituted olefin moiety from left-hand side segment **3** and right-hand side segment **4**. The left side chain of **3** would be introduced via the coupling of alkynyllithium reagent derived from alkyne **5** and triflate **6**.[7] The tetrahydropyran **6** with three contiguous oxygenated functional groups would be provided by the functionalization of dihydropyran **7**. On the other hand, aldehyde **4**, the coupling partner of **3**, would be synthesized via the stereoselective methylation of ester **8**. The ester **8** would be prepared from D-(+)-xylose.

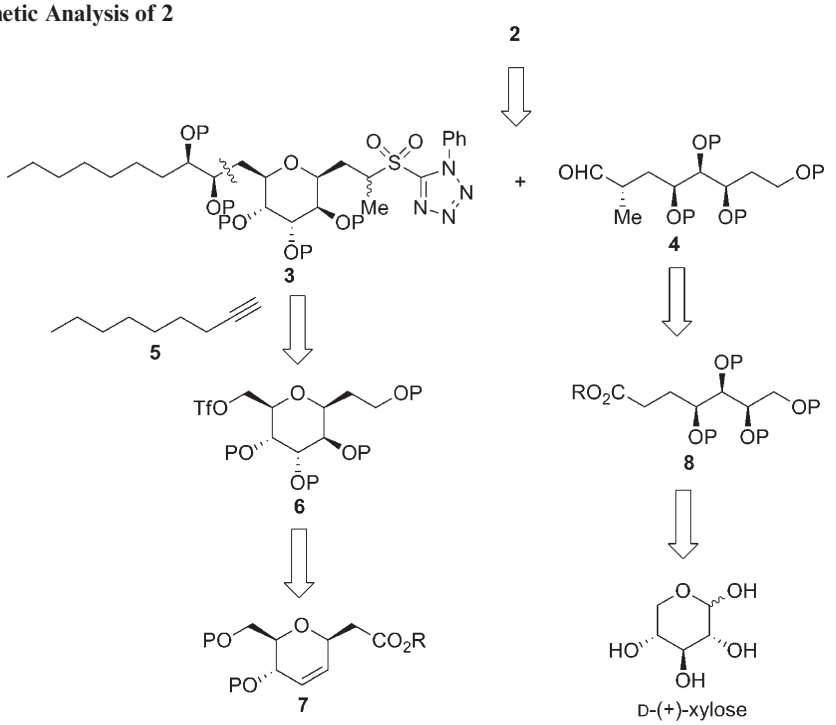
Results and Discussion

Synthesis of the Left-Hand Side Segment. Stereoselective construction of the tetrahydropyran ring moiety is described in Scheme 3. Treatment of allylic alcohol **9**, which can be easily prepared from tri-*O*-acetyl-D-glucal in two steps,[8] with *N*,*N*-dimethylacetamide dimethyl acetal in refluxing xylene formed Eschenmoser−Claisen rearrangement product **10** in 93% yield. Iodolactonization of **10** proceeded smoothly to give iodolactone **11** as a single stereoisomer. The lactone **11** was converted to epoxy ester **12** under the methanolysis conditions.[9] The regio- and stereoselective opening of the epoxide **12** promoted by TFA proceeded at 60 °C to afford trihydroxy lactone **13**.[9,10] Continuous protection of the primary hydroxy group with TBDPSCl/imidazole and the vicinal diol as an acetonide gave silyl ether **14**. The configurational determination of **14** was verified by $^1H-^1H$ coupling constants and NOE correlations. The large magnitude of $J_{14',15'}$ (9.7 Hz) indicated that H14′ and H15′ were in an axial−axial relationship. The moderate magnitude of $J_{13',14'}$ (5.5 Hz) suggested that H13′ and H14′ were oriented in equatorial and axial conformations, respectively. The observed NOEs H11′/H12′ and H11′/H15′ confirmed that they were in *syn* relationships to each other. Reduction of **14** in two-step sequence (DIBALH and $NaBH_4$) followed by protection of the primary hydroxy moiety as TBS ether and the secondary hydroxy group as MOM ether provided protected tetrahydropyran **15**. The TBDPS ether **15** was converted to triflate **16** by the selective deprotection of TBDPS group and triflation.

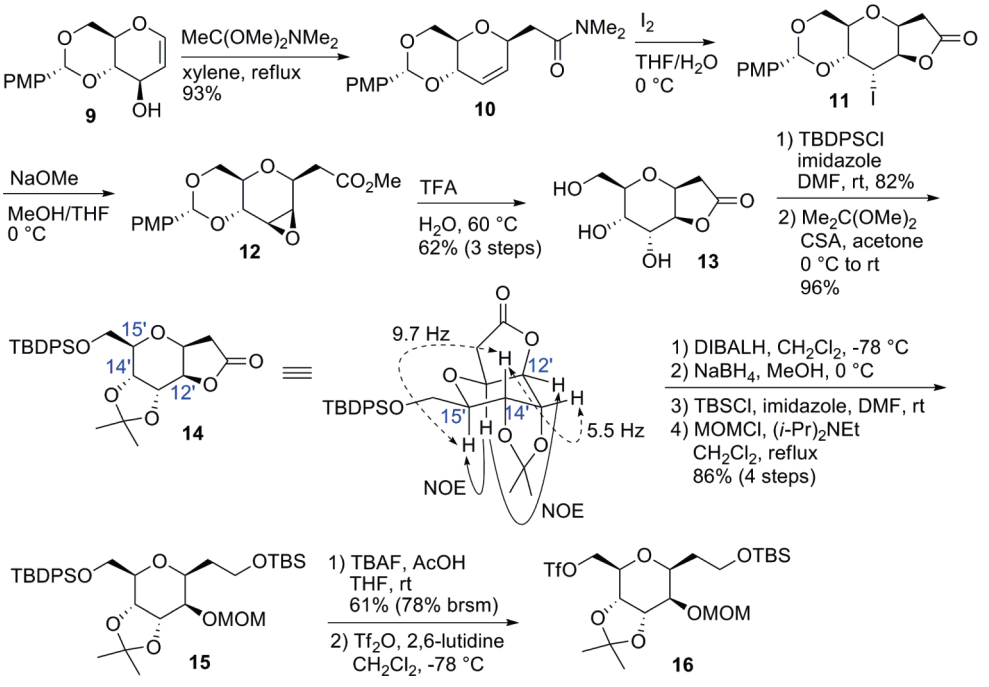
Scheme 4 describes the introduction of the left side chain. Coupling of the triflate **16** with *n*-$C_7H_{15}CCLi$ under Kotsuki conditions[7] gave alkyne **17**. The alkyne **17** was subjected to the Birch reduction conditions to afford *trans*-alkene **18** as a single stereoisomer. The Sharpless AD[11] of **18** proceeded

(7) Kotsuki, H.; Kadota, I.; Ochi, M. *Tetrahedron Lett*. **1990**, *31*, 4609.
(8) Bartolozzi, A.; Pacciani, S.; Benvenuti, C.; Cacciarini, M.; Liguori, F.; Menichetti, S.; Nativi, C. *J. Org. Chem*. **2003**, *68*, 8529.
(9) Colombo, L.; Casiraghi, G.; Pittalis, A. *J. Org. Chem*. **1991**, *56*, 3897.
(10) For the reaction mechanism on lactonization of γ,δ-epoxy esters, see: Wawrzenczyk, C.; Grabarczyk, M.; Bialonska, A.; Ciunik, Z. *Tetrahedron* **2003**, *59*, 6595.
(11) For a review of the Sharpless AD reaction, see: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev*. **1994**, *94*, 2483.

SCHEME 2. Retrosynthetic Analysis of 2



SCHEME 3. Synthesis of 16



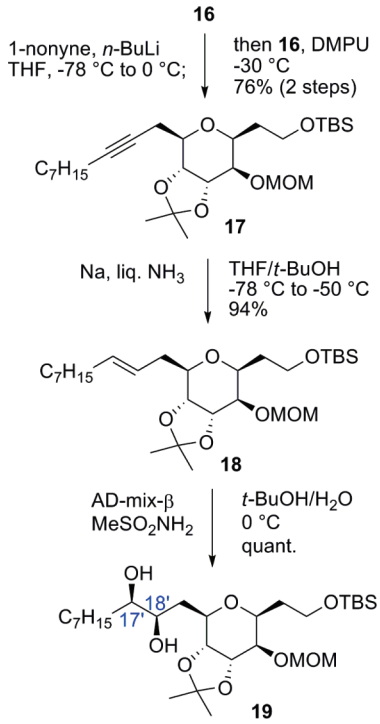
smoothly to provide diol **19** quantitatively as the sole product. The absolute stereochemistry of the resulting chiral centers at C17′ and C18′ positions of **19** were elucidated by modified Mosher method.[12] Figure 2 depicts the $\Delta\delta_{S-R}$ values of bis-MTPA esters (*S*)-**20** and (*R*)-**20**, which were prepared from **19**. The signs at the C17′ and C18′ positions were negative (−0.05 and −0.12, respectively). Therefore, the absolute configurations of the C17′ and C18′ positions were elucidated to be 17′*R* and 18′*R*, respectively.

The next task was the functionalization of the right side chain. Protection of the diol **19** as an acetonide, followed by removal of the TBS protecting group with TBAF, gave alcohol **21** (Scheme 5). The alcohol **21** was converted to the coupling precursor **22** by four-step sequence: (1) Parikh−Doering oxidation,[13] (2) methylation of the resulting aldehyde,

(12) Freire, F.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **2005**, *70*, 3778.

(13) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

SCHEME 4. Synthesis of 19



(3) Mitsunobu reaction of the resulting secondary alcohol with 1-phenyl-1*H*-tetrazole-5-thiol, and (4) oxidation of the resulting sulfide.

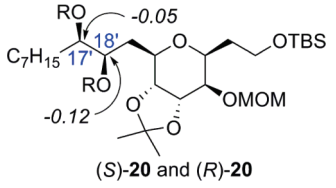
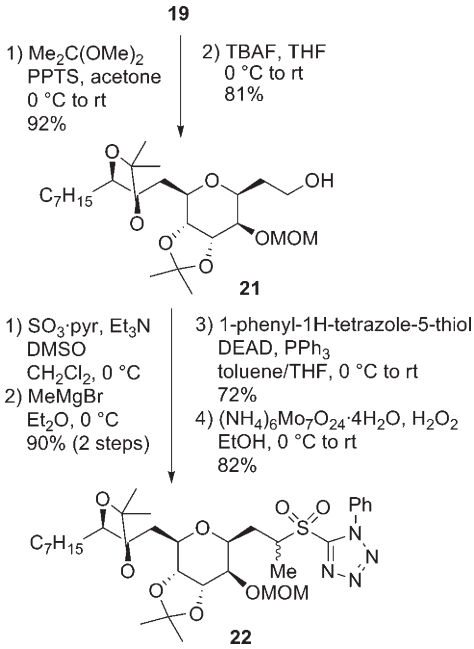


FIGURE 2. Chemical shift differences ($\Delta\delta_{S-R}$) of (*S*)-**20** and (*R*)-**20**. R = MTPA. MTPA = α-methoxy-α-(trifluoromethyl)-phenylacetyl.

Synthesis of the Right-Hand Side Segment. With the left-hand side segment **22** in hand, we next examined the preparation of the right-hand side segment (Scheme 6). One-carbon elongation of the known alcohol **23**,[14] prepared from D-(+)-xylose in 4 steps, was carried out by Parikh−Doering oxidation[13] and subsequent Wittig methylenation to give alkene **24** in 86% yield by 2 steps. Hydroboration of **24** with $BH_3 \cdot SMe_2$ followed by oxidative workup and protection of the resulting alcohol with TBSCl/imidazole provided silyl ether **25**. After hydrolysis of the dithioacetal moiety with $AgNO_3$, Ag_2O, and H_2O,[15] the resulting aldehyde was treated with $Ph_3P{=}CHCO_2Me$ to give α,β-unsaturated ester **26**. Chemoselective hydrogenation of **26** was carried out with H_2 and Pd/C in EtOAc, and ester moiety was saponified with $LiOH \cdot H_2O$ to afford carboxylic acid **27**. The carboxylic acid **27** was converted to imide **28** possessing a chiral oxazolidinone under the mild reaction conditions (PivCl and Et_3N; then LiCl

SCHEME 5. Synthesis of 22



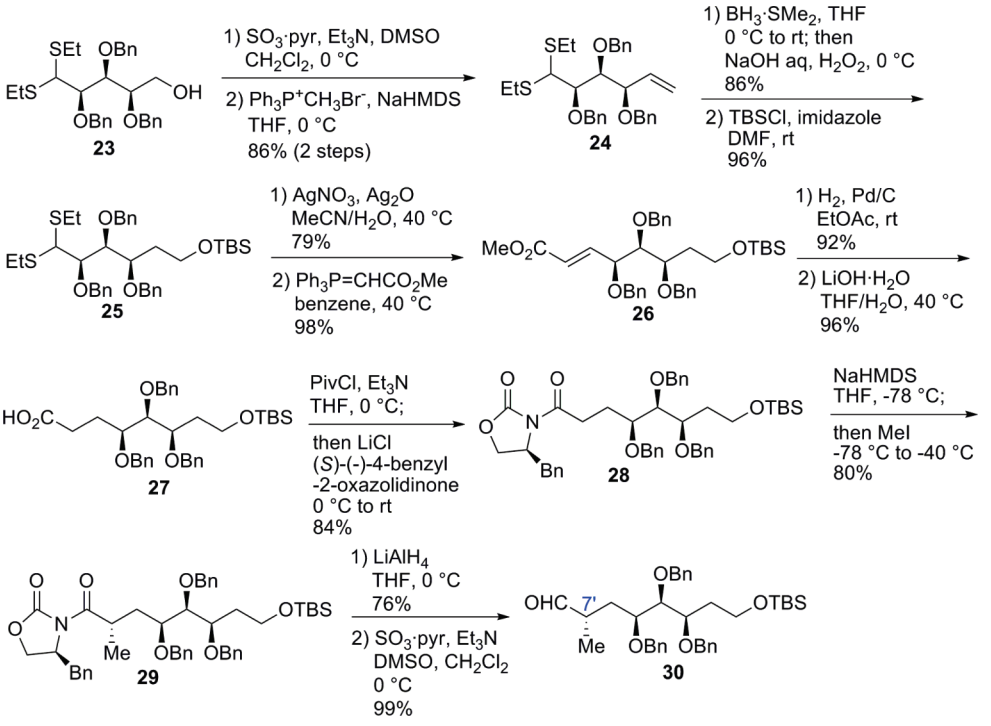
and oxazolidinone).[16] Asymmetric methylation of **28** in accordance with Evans' report[17] proceeded at −78 to −40 °C to give the desired methylated product **29** as a single stereoisomer. The chiral auxiliary was removed by $LiAlH_4$, and Parikh−Doering oxidation[13] of the resulting alcohol provided the right-hand side coupling precursor **30**.

The aldehyde **30** was transformed to lactone **32** for the confirmation of the absolute stereochemistry at the C7′ chiral center, which was introduced by the Evans asymmetric alkylation of **28** (Scheme 7). Pinnic oxidation of **30** gave carboxylic acid **31**. Benzyl protecting groups of **31** were removed, followed by lactonization under the reflux conditions in toluene to provide the lactone **32**. The observed NOE H5′/H7′ of **32** indicated that they were in *syn* relationships to each other. Therefore, it was confirmed that the Evans asymmetric methylation of **28** proceeded in a desired stereoselectivity.

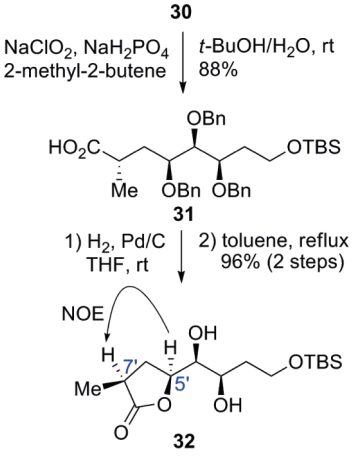
Completion of the Synthesis. Julia−Kocienski coupling[18] of the sulfone **22** and the aldehyde **30** was examined under various conditions, and the results are summarized in Table 1. When **22** was deprotonated with KHMDS or NaHMDS as the base and treated with **30**, only a trace amount of the coupling products was observed (entry 1 and 2). Treatment of **22** with LiHMDS gave the desired *E*-alkene **33** along with the *Z*-alkene **34** at a 1:1 *E*/*Z* diastereomeric ratio in 43% yield (entry 3). When LDA that was prepared from $(i\text{-Pr})_2NH$ and *n*-BuLi was used as the base, diastereoselectivity and chemical yield were improved to 1.5:1 diastereomeric ratio and 61% yield (entry 4). The alkenes **33** and **34** could be easily separated by preparative TLC. Stereostructure of **33** was confirmed by ROESY correlation between Ha and Hb as shown with an arrow. Similarly, the structural determination of **34** was performed by NOE observation

(14) Kireev, A. S.; Breithaupt, A. T.; Collins, W.; Nadein, O. N.; Kornienko, A. *J. Org. Chem.* **2005**, *70*, 742.
(15) Corey, E. J.; Shibasaki, M.; Knolle, J.; Sugahara, T. *Tetrahedron Lett.* **1977**, *18*, 785.
(16) Ho, G.-J.; Mathre, D. J. *J. Org. Chem.* **1995**, *60*, 2271.
(17) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.
(18) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26.

SCHEME 6. Synthesis of 30



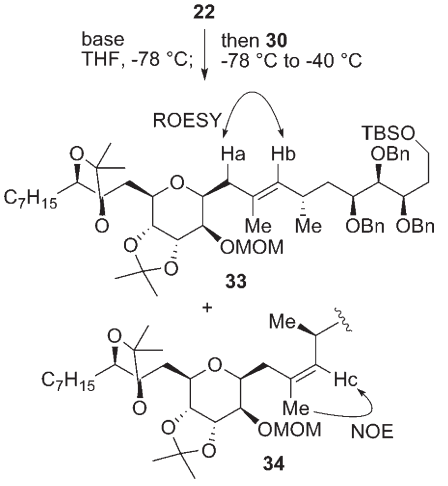
SCHEME 7. Determination of Absolute Configuration at C7′ Position of 30



between the allylic methyl moiety and Hc as described with an arrow.

Remaining tasks were the removal of protecting groups and functionalization at C1′ position. Removal of the TBS protecting group of **33** with TBAF and subsequent stepwise Parikh−Doering oxidation[13] and Pinnick oxidation[19] gave carboxylic acid **35** in 93% yield for 2 steps (Scheme 8). Deprotection of the benzyl moieties under the Birch reduction conditions provided triol **36**. The acetonide and methoxymethyl protecting groups of **36** were removed with TFA to give the carboxylic acid **2** and its corresponding lactone, whose structure was not characterized. Finally, treatment of the mixture obtained above with KOH provided **2**. The synthetic **2** was identical to the degraded C1′−C25′ fragment of symbiodinolide (**1**) in all aspects (^{1}H NMR, HRMS, and optical rotation[20]). Thus, the absolute configuration of the C1′−C25′ fragment was confirmed to be that described in **2**.

TABLE 1. Julia−Kocienski Coupling of 22 and 30



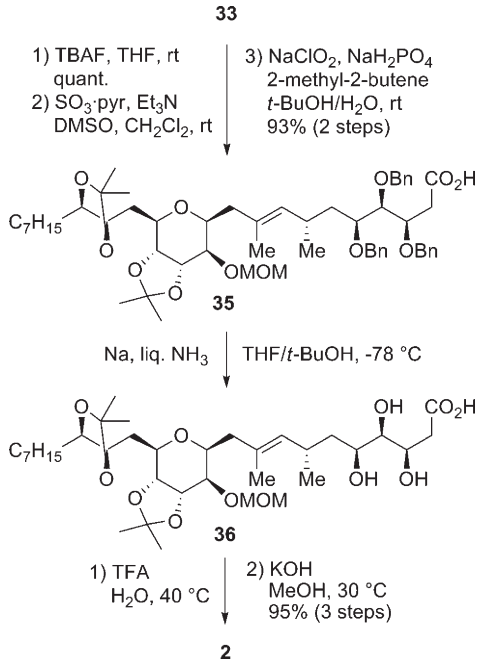
entry	base	**33**:**34**	% yield[a]
1	KHMDS	ND[b]	trace
2	NaHMDS	ND[b]	trace
3	LiHMDS	1:1	43
4	LDA	1.5:1	61

[a]Isolated yields. [b]Not determined.

(19) (a) Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1175. (b) Bal, B. S.; Childers, W. E. Jr; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.

(20) The degraded C1′−C25′ fragment: $[\alpha]^{20}_D = +10.6$ (*c* 0.05, CH_3OH). The synthetic **2**: $[\alpha]^{23}_D = +10.6$ (*c* 0.05, CH_3OH).

SCHEME 8. Completion of the Synthesis of 2



Conclusion

We have synthesized the C1′−C25′ fragment of **1**, which was obtained as a degraded product from **1** by alkaline hydrolysis, via Kotsuki coupling and Julia−Kocienski olefination as key steps from the known alcohol **9** with 2.8% overall yield. On the basis of the spectroscopic data of the synthetic and degraded samples, we concluded that the absolute stereochemistry of this fragment was that depicted in **2**. Further structural and synthetic studies on **1** are underway in our laboratories.

Experimental Section

Alkyne 17. To a solution of TBDPS ether **15** (116 mg, 180 μmol) in THF (3.6 mL) was added TBAF−AcOH (premixed solution, 1.0 M TBAF in THF 5.0 mL + AcOH 0.30 mL, 0.20 mL, 0.188 mmol) at room temperature. The mixture was stirred for 9 h at the same temperature. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over $MgSO_4$. Concentration and column chromatography (hexane/EtOAc, 50:1, 9:1, 1:1) gave the corresponding alcohol (44.7 mg, 61%) and recovered TBDPS ether **15** (25.6 mg, 22%). The corresponding alcohol: colorless oil; R_f = 0.32 (hexane/EtOAc, 1:1); $[\alpha]^{16}_D$ +36.2 (*c* 0.74, $CHCl_3$); IR (neat) 3502, 2930 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.79 (d, *J* = 6.8 Hz, 1 H), 4.66 (d, *J* = 6.8 Hz, 1 H), 4.30 (dd, *J* = 5.1, 2.4 Hz, 1 H), 4.00 (dd, *J* = 9.0, 5.1 Hz, 1 H), 3.89 (ddd, *J* = 9.2, 3.9, 1.5 Hz, 1 H), 3.81 (dd, *J* = 11.7, 2.9 Hz, 1 H), 3,78 (t, *J* = 1.7 Hz, 1 H), 3.76−3.73 (m, 2 H), 3.62 (dd, *J* = 11.7, 6.8 Hz, 1 H), 3.45−3.41 (m, 1 H), 3.41 (s, 3 H), 2.92 (s, 1 H), 1.97−1.89 (m, 1 H), 1.75−1.67 (m, 1 H), 1.48 (s, 3 H), 1.36 (s, 3 H), 0.89 (s, 9 H), 0.05 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.5, 96.8, 78.4, 74.1, 74.0, 71.9, 70.7, 63.5, 59.2, 56.1, 33.9, 28.1, 26.3, 25.9, 18.3, −5.3, −5.4; HRMS (FAB) calcd for $C_{19}H_{38}O_7SiNa$ $(M + Na)^+$ 429.2284, found 429.2268.

To a solution of the alcohol obtained above (694 mg, 1.70 mmol) in CH_2Cl_2 (20 mL) were added 2,6-lutidine (0.40 mL, 3.40 mmol) and Tf_2O (0.34 mL, 2.04 mmol) at −78 °C. After the mixture was stirred for 15 min at the same temperature, the reaction was quenched with saturated aqueous $NaHCO_3$. The resultant mixture was diluted with Et_2O, washed with saturated aqueous $CuSO_4$, H_2O, and brine, and dried over $MgSO_4$. Concentration and column chromatography (hexane/EtOAc, 9:1) gave triflate **16** (915 mg) as a yellow oil, which was used for the next reaction without further purification.

To a solution of 1-nonyne (0.42 mL, 2.56 mmol) in THF (10 mL) was added *n*-BuLi (1.59 M in hexane, 1.6 mL, 2.54 mol) at −78 °C. The mixture was stirred for 30 min at the same temperature, allowed to warm to 0 °C, and stirred for 30 min at the same temperature. The resultant mixture was cooled to −30 °C, then to the mixture were added DMPU (4.0 mL) and triflate **16** obtained above in THF (4.0 mL + 3.0 mL + 3.0 mL). The mixture was stirred for 1 h at the same temperature. The reaction was quenched with saturated aqueous NH_4Cl. The resultant mixture was diluted with Et_2O, washed with H_2O and brine, and dried over $MgSO_4$. Concentration and column chromatography (hexane/EtOAc, 9:1) gave alkyne **17** (661 mg, 76% in two steps): yellow oil; R_f = 0.41 (hexane/EtOAc, 4:1); $[\alpha]^{17}_D$ +23.1 (*c* 1.29, $CHCl_3$); IR (neat) 2930, 1471 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.79 (d, *J* = 7.1 Hz, 1 H), 4.65 (d, *J* = 7.1 Hz, 1 H), 4.27 (dd, *J* = 5.0, 2.4 Hz, 1 H), 3.90 (dd, *J* = 9.2, 5.0 Hz, 1 H), 3.84−3.75 (m, 4 H), 3.40 (s, 3 H), 3.35 (td, *J* = 8.7, 3.4 Hz, 1 H), 2.54 (ddd, *J* = 16.8, 5.6, 2.4 Hz, 1 H), 2.36 (ddt, *J* = 16.8, 8.3, 2.2 Hz, 1 H), 2.14−2.10 (m, 2 H), 1.99−1.91 (m, 1 H), 1.69−1.61 (m, 1 H), 1.45 (s, 3 H), 1.35 (s, 3 H), 1.29−1.20 (m, 10 H), 0.87 (s, 9 H), 0.85 (t, *J* = 7.1 Hz, 3 H), 0.05 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.3, 96.6, 81.4, 77.2, 76.2, 74.4, 74.2, 74.1, 72.3, 59.5, 56.0, 34.2, 31.7, 29.0, 28.8, 28.2, 26.4, 25.9, 23.4, 22.6, 18.9, 18.3, 14.1, −5.3, −5.4; HRMS (FAB) calcd for $C_{28}H_{52}O_6SiNa$ $(M + Na)^+$ 535.3431, found 535.3442.

Alkene 18. To a solution of alkyne **17** (123 mg, 0.240 mmol) in liquid NH_3 (12 mL), THF (6.0 mL), and *t*-BuOH (2.0 mL) was added Na (100 mg, 4.34 mmol) at −78 °C, and the resultant mixture was gradually warmed to −50 °C for 40 min. After the mixture was stirred at the same temperature for 20 min, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with H_2O and Et_2O. The aqueous layer was extracted with Et_2O, and the combined organic layer was washed with H_2O and brine, and dried over Na_2SO_4. Concentration and column chromatography (hexane/Et_2O, 9:1) gave alkene **18** (116 mg, 94%): colorless oil; R_f = 0.62 (hexane/EtOAc, 4:1); $[\alpha]^{25}_D$ +32.5 (*c* 0.76, $CHCl_3$); IR (neat) 2927, 1470 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.52−5.45 (m, 2 H), 4.80 (d, *J* = 7.0 Hz, 1 H), 4.66 (d, *J* = 7.0 Hz, 1 H), 4.26 (dd, *J* = 5.2, 2.2 Hz, 1 H), 3.84 (dd, *J* = 9.2, 5.1 Hz, 1 H), 3.81−3.74 (m, 4 H), 3.40 (s, 3 H), 3.22 (td, *J* = 9.2, 3.3 Hz, 1 H), 2.39−2.33 (m, 1 H), 2.18−2.12 (m, 1 H), 1.98−1.89 (m, 3 H), 1.68−1.63 (m, 1 H), 1.46 (s, 3 H), 1.36 (s, 3 H), 1.35−1.21 (m, 10 H), 0.89 (s, 9 H), 0.87 (t, *J* = 7.0 Hz, 3 H), 0.51 (s, 3 H), 0.47 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.8, 125.9, 109.2, 96.7, 78.6, 74.9, 74.4, 74.3, 72.1, 59.5, 56.1, 36.4, 34.2, 32.7, 31.9, 29.5, 29.2, 28.2, 26.5, 26.0, 22.6, 18.3, 14.1, −5.3, −5.4; HRMS (FAB) calcd for $C_{28}H_{54}O_6SiNa$ $(M + Na)^+$ 537.3587, found 537.3583.

Diol 19. To a solution of alkene **18** (164 mg, 0.319 mmol) in *t*-BuOH (1.5 mL) and H_2O (2.0 mL) were added $MeSO_2NH_2$ (30.0 mg, 0.319 mmol) and AD-mix-β (446 mg) at 0 °C. After the mixture was stirred at the same temperature for 23 h, the reaction was quenched with Na_2SO_3 (500 mg). The mixture was diluted with H_2O and extracted with EtOAc. The organic layer was washed with 2 M aqueous NaOH and brine and dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc, 2:1) gave diol **19** (178 mg, quant.): colorless oil; R_f = 0.31 (hexane/EtOAc, 1:1); $[\alpha]^{25}_D$ +31.4 (*c* 0.63, $CHCl_3$); IR (neat) 3466, 2928 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.81 (d, *J* = 6.8 Hz, 1 H), 4.67 (d, *J* = 6.8 Hz, 1 H), 4.30 (dd, *J* = 5.0, 2.4 Hz, 1 H), 3.95 (dd, *J* = 9.3, 5.1 Hz, 1 H), 3.90−3.85 (m, 1 H),

3.80−3.74 (m, 3 H), 3.67 (ddd, J = 9.0, 5.9, 3.2 Hz, 1 H), 3.53 (td, J = 8.4, 3.9 Hz, 1 H), 3.43−3.42 (m, 1 H), 3.42 (s, 3 H), 1.95−1.85 (m, 2 H), 1.76−1.64 (m, 2 H), 1.49 (s, 3 H), 1.49−1.47 (m, 2 H), 1.38 (s, 3 H), 1.34−1.20 (m, 10 H), 0.90 (s, 9 H), 0.87 (t, J = 7.1 Hz, 3 H), 0.07 (s, 3 H), 0.06 (s, 3 H); ^{13}C (100 MHz, $CDCl_3$) δ 109.5, 96.8, 75.9, 74.6, 74.4, 74.2, 74.0, 72.6, 71.4, 59.4, 56.1, 36.6, 33.6, 33.2, 31.8, 29.6, 29.2, 28.2, 26.4, 25.8, 25.6, 22.6, 18.3, 14.0, −5.3, −5.4; HRMS (FAB) calcd for $C_{28}H_{56}O_8SiNa$ $(M + Na)^+$ 571.3642, found 571.3633.

Alcohol 21. To a solution of diol **19** (178 mg, 0.319 mmol) in 2,2-dimethoxypropane (3.0 mL) and acetone (1.0 mL) was added PPTS (7.5 mg, 30.0 μmol) at 0 °C, then the resultant solution was allowed to warm up to room temperature. After the mixture was stirred at the same temperature for 2 h, the reaction was quenched with Et_3N. Concentration and column chromatography (hexane/EtOAc, 9:1, 4:1) gave the corresponding acetonide (172 mg, 92%): colorless oil; R_f = 0.58 (hexane/EtOAc, 4:1); $[\alpha]^{26}_D$ +50.2 (c 0.71, $CHCl_3$); IR (neat) 2930 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.81 (d, J = 7.0 Hz, 1 H), 4.67 (d, J = 7.0 Hz, 1 H), 4.27 (dd, J = 4.8, 2.4 Hz, 1 H), 3.86−3.73 (m, 6 H), 3.63−3.58 (m, 1 H), 3.53 (brt, J = 9.0 Hz, 1 H), 3.42 (s, 3 H), 1.98−1.89 (m, 1 H), 1.86−1.79 (m, 1 H), 1.73−1.55 (m, 4 H), 1.49 (s, 3 H), 1.37 (s, 3 H), 1.36 (s, 3 H), 1.34 (s, 3 H), 1.31−1.22 (m, 10 H), 0.89 (s, 9 H), 0.87 (t, J = 6.8 Hz, 3 H), 0.06 (s, 3 H), 0.53 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.4, 108.0, 96.8, 81.4, 76.6, 75.1, 74.9, 74.4, 74.3, 72.7, 59.9, 56.2, 37.0, 34.3, 32.7, 31.8, 29.7, 29.2, 28.1, 27.5, 27.4, 26.5, 26.0, 26.0, 22.6, 18.3, 14.1, −5.3; HRMS (FAB) calcd for $C_{31}H_{60}O_8SiNa$ $(M + Na)^+$ 611.3955, found 611.3956.

To a solution of the TBS ether obtained above (172 mg, 0.292 mmol) in THF (3.0 mL) was added TBAF (1.0 M in THF, 0.40 mL, 0.40 mmol) at 0 °C. The mixture was stirred at room temperature for 3 h. The resultant mixture was poured into H_2O and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc, 4:1, 2:1) gave alcohol **21** (112 mg, 81%): colorless oil; R_f = 0.20 (hexane/EtOAc, 2:1); $[\alpha]^{27}_D$ +61.9 (c 0.92, $CHCl_3$); IR (neat) 3500, 2931 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82 (d, J = 7.1 Hz, 1 H), 4.67 (d, J = 7.1 Hz, 1 H), 4.28 (dd, J = 4.9, 2.2 Hz, 1 H), 3.91 (ddd, J = 10.3, 3.2, 1.5 Hz, 1 H), 3.87−3.77 (m, 5 H), 3.65−3.56 (m, 2 H), 3.42 (s, 3 H), 2.08−1.99 (m, 3 H), 1.87−1.81 (m, 1 H), 1.72−1.62 (m, 2 H), 1.50 (s, 3 H), 1.38 (s, 3 H), 1.38 (s, 3 H), 1.36 (s, 3 H), 1.31−1.26 (m, 10 H), 0.87 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.5, 108.2, 96.8, 81.5, 76.7, 75.0, 74.9, 74.7, 74.3 74.0, 60.3, 56.2, 36.0, 32.9, 32.7, 31.8, 29.7, 29.1, 28.2, 27.3, 27.2, 26.4, 25.9, 22.6, 14.1; HRMS (FAB) calcd for $C_{25}H_{46}O_8Na$ $(M + Na)^+$ 497.3090, found 497.3080.

Sulfone 22. To a solution of alcohol **21** (112 mg, 0.235 mmol) in DMSO (2.0 mL) and CH_2Cl_2 (2.0 mL) were added Et_3N (0.33 mL, 2.35 mmol) and SO_3·pry (188 mg, 1.18 mmol) at 0 °C. The mixture was stirred at the same temperature for 2 h. The reaction was quenched with saturated aqueous NH_4Cl, and the mixture was extracted with EtOAc. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated to give the corresponding aldehyde (107 mg) as a colorless oil, which was used for the next reaction without further purification.

To a solution of aldehyde obtained above in Et_2O (2.0 mL) was added MeMgBr (3.0 M in Et_2O, 0.13 mL, 0.352 mmol) at 0 °C. The mixture was stirred at the same temperature for 1 h. The reaction was quenched with saturated aqueous NH_4Cl, and the mixture was extracted with EtOAc. The organic layer was washed with H_2O and brine and dried over $MgSO_4$. Concentration and column chromatography (hexane/EtOAc, 4:1, 2:1, 1:1) gave the corresponding alcohol (104 mg, 90% in two steps) as a 1:1 diastereomeric mixture: colorless oil; R_f = 0.30 (hexane/EtOAc, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82 (d, J = 7.1 Hz, 1 H), 4.81 (d, J = 7.1 Hz, 1 H), 4.67 (d, J = 7.1 Hz, 1 H), 4.66 (d, J = 7.1 Hz, 1 H), 4.30−4.25 (m, 2 H), 4.12−4.03 (m, 2 H), 3.90−3.73 (m, 8 H), 3.65−3.56 (m, 4 H), 3.43 (s, 3 H), 3.42 (s, 3 H), 2.24−2.22 (m, 4 H), 2.04−1.93 (m, 2 H), 1.87−1.80 (m, 2 H), 1.69−1.60 (m, 2 H), 1.56−1.50 (m, 2 H), 1.50−1.21 (m, 50 H), 0.87 (t, J = 5.6 Hz, 3 H), 0.87 (t, J = 5.6 Hz, 3 H); HRMS (FAB) calcd for $C_{26}H_{48}O_8Na$ $(M + Na)^+$ 511.3247, found 511.3246.

To a solution of the alcohol obtained above (216 mg, 0.441 mmol) in toluene (5.0 mL) and THF (1.0 mL) were added 1-phenyl-1H-tetrazole-5-thiol (94.0 mg, 0.530 mmol), PPh_3 (139 mg, 0.530 mmol), and DEAD (2.2 M in toluene, 0.24 mL, 0.530 mmol) at 0 °C. The mixture was stirred at the same temperature for 2 h and a further 2 h at room temperature. The mixture was concentrated and purified by column chromatography (hexane/EtOAc, 9:1, 5:1) to give the corresponding sulfide (205 mg, 72%) as a 1:1 diastereomeric mixture: colorless oil; R_f = 0.44 (hexane/EtOAc, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59−7.51 (m, 10 H), 4.81 (d, J = 7.1 Hz, 1 H), 4.80 (d, J = 7.1 Hz, 1 H), 4.68 (d, J = 7.1 Hz, 1 H), 4.66 (d, J = 7.1 Hz, 1 H), 4.29−4.28 (m, 2 H), 4.24−4.17 (m, 2 H), 3.92 (brd, J = 9.8 Hz, 1 H), 3.86−3.78 (m, 7 H), 3.60−3.51 (m, 4 H), 3.41 (s, 3 H), 3.41 (s, 3 H), 2.40−2.33 (m, 1 H), 2.30−2.21 (m, 1 H), 2.07−1.97 (m, 2 H), 1.85−1.76 (m, 2 H), 1.63−1.19 (m, 56 H), 0.89−0.84 (m, 6 H); HRMS (FAB) calcd for $C_{33}H_{52}N_4O_7SNa$ $(M + Na)^+$ 671.3454, found 671.3463.

To a solution of the sulfide obtained above (205 mg, 0.315 mmol) in EtOH (3.0 mL) were added aqueous H_2O_2 (30%, 0.32 mL, 3.14 mmol) and $(NH_4)_6Mo_7O_{24}$·$4H_2O$ (39.0 mg, 31.5 μmol) at 0 °C. The mixture was stirred at room temperature and extracted with EtOAc. The organic layer was washed with H_2O and brine and dried over $MgSO_4$. Concentration and column chromatography (hexane/EtOAc, 9:1, 5:1) gave sulfone **22** (176 mg, 82%) as a 1:1 diastereomeric mixture: colorless oil; R_f = 0.20 (hexane/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68−7.55 (m, 10 H), 4.81 (d, J = 7.1 Hz, 1 H), 4.81 (d, J = 7.1 Hz, 1 H), 4.66 (d, J = 7.1 Hz, 1 H), 4.65 (d, J = 7.1 Hz, 1 H), 4.30−4.27 (m, 2 H), 4.10−4.05 (m, 2 H), 3.92 (brd, J = 9.0 Hz, 1 H), 3.87−3.77 (m, 7 H), 3.62−3.52 (m, 4 H), 3.40 (s, 3 H), 3.39 (s, 3 H), 2.76−2.69 (m, 1 H), 2.35−2.29 (m, 1 H), 2.17−2.08 (m, 1 H), 1.86−1.77 (m, 3 H), 1.61−1.21 (m, 56 H), 0.88−0.80 (m, 6 H); HRMS (FAB) calcd for $C_{33}H_{52}N_4O_9SNa$ $(M + Na)^+$ 703.3353, found 703.3368.

(*E*)-Alkene 33. To a solution of sulfone **22** (49.8 mg, 73.1 μmol) in freshly distilled THF (1.0 mL) was added LDA (0.5 M in THF, 175 μL, 88 μmol) at −78 °C. After the mixture was stirred at the same temperature for 15 min, to the mixture was added aldehyde **30** (35.9 mg, 61.0 μmol) in THF (0.30 mL + 0.15 mL + 0.15 mL). The mixture was gradually warmed up to −40 °C for 30 min. After the mixture was stirred at the same temperature, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was extracted with EtOAc, and then the organic layer was washed with H_2O and brine and dried over $MgSO_4$. Concentration and purification by preparative TLC (hexane/EtOAc, 6:1) to give (*E*)-alkene **33** (22.8 mg, 36%) and (*Z*)-alkene **34** (16.0 mg, 25%). (*E*)-Alkene **33**: colorless oil; R_f = 0.52 (hexane/EtOAc, 4:1); $[\alpha]^{28}_D$ +36.3 (c 0.61, $CHCl_3$); IR (neat) 2929 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 7.40−7.36 (m, 5 H), 7.22−7.09 (m, 10 H), 5.26 (d, J = 8.8 Hz, 1 H), 4.79 (d, J = 11.3 Hz, 1 H), 4.76 (d, J = 11.7 Hz, 1 H), 4.71 (d, J = 11.7 Hz, 1 H), 4.67−4.64 (m, 2 H), 4.57−4.52 (m, 2 H), 4.48−4.46 (m, 2 H), 4.18 (brt, J = 8.5 Hz, 1 H), 4.11−4.08 (m, 1 H), 4.00−3.97 (m, 2 H), 3.93−3.83 (m, 3 H), 3.80−3.77 (m, 1 H), 3.75−3.71 (m, 1 H), 3.64−3.61 (m, 2 H), 3.16 (s, 3 H), 2.74−2.70 (m, 2 H), 2.20−2.17 (m, 2 H), 2.07 (brt, J = 12.1 Hz, 1 H), 1.93−1.85 (m, 2 H), 1.79−1.76 (m, 1 H), 1.75 (s, 3 H), 1.63−1.58 (m, 3 H), 1.54 (s, 3 H), 1.51 (s, 3 H), 1.46 (s, 3 H), 1.35 (s, 3 H), 1.29−1.24 (m, 10 H), 1.06 (d, J = 6.6 Hz, 3 H), 0.98 (s, 9 H), 0.89 (t, J = 7.0 Hz, 3 H), 0.06 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (150 MHz, C_6D_6);

δ 139.8, 139.7, 139.5, 134.2, 130.7, 128.5, 128.5, 128.5, 128.3, 127.9, 127.7, 127.5, 127.5, 109.4, 108.1, 97.3, 82.9, 81.8, 77.7, 77.1, 76.9, 75.7, 75.4, 75.3, 75.0, 74.6, 74.5, 73.4, 72.4, 59.9, 55.7, 41.5, 38.8, 37.2, 34.9, 33.2, 32.2, 30.1, 29.6, 29.4, 28.6, 27.9, 27.8, 26.8, 26.7, 26.1, 23.0, 21.1, 18.4, 16.1, 14.3, −5.2, −5.2; HRMS (ESI) calcd for $C_{62}H_{96}O_{11}SiNa$ $(M + Na)^+$ 1067.6620, found 1067.6621. (*Z*)-Alkene **34**: colorless oil; R_f = 0.38 (hexane/EtOAc, 4:1); $[\alpha]^{27}_D$ +17.7 (*c* 0.96, $CHCl_3$); IR (neat) 2929 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.41−7.37 (m, 5 H), 7.28−7.08 (m, 10 H), 5.18 (d, *J* = 9.5 Hz, 1 H), 4.81−4.70 (m, 3 H), 4.64 (q, *J* = 5.8 Hz, 1 H), 4.56 (t, *J* = 6.8 Hz, 2 H), 4.51−4.46 (m, 2 H), 4.16 (brt, *J* = 8.6 Hz, 1 H), 4.10−4.05 (m, 1 H), 4.02−3.98 (m, 2 H), 3.93−3.89 (m, 2 H), 3.86−3.78 (m, 2 H), 3.74−3.69 (m, 1 H), 3.66−3.59 (m, 2 H), 3.18 (s, 3 H), 2.77−2.71 (m, 1 H), 2.64 (dd, *J* = 14.0, 9.4 Hz, 1 H), 2.54 (dd, *J* = 14.0, 3.4 Hz, 1 H), 2.20−2.15 (m, 1 H), 2.07 (t, *J* = 12.2 Hz, 1 H), 1.95 (s, 3 H), 1.92−1.74 (m, 3 H), 1.67−1.49 (m, 3 H), 1.52 (s, 3 H), 1.47 (s, 3 H), 1.45 (s, 3 H), 1.34 (s, 3 H), 1.31−1.24 (m, 10 H), 0.98 (s, 9 H), 0.95 (d, *J* = 6.4 Hz, 3 H), 0.89 (t, *J* = 6.4 Hz, 3 H), 0.05 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (100 MHz, C_6D_6); δ 139.8, 139.6, 139.5, 133.8, 132.0, 128.5, 128.5, 128.5, 127.9, 127.7, 127.6, 127.5, 109.4, 108.1, 97.4, 83.4, 81.8, 77.6, 77.2, 77.2, 76.6, 75.7, 75.6, 75.5, 75.4, 74.7, 73.5, 72.6, 60.0, 55.9, 39.1, 37.0, 35.1, 33.8, 33.2, 32.3, 30.2, 29.8, 29.3, 28.6, 27.9, 27.9, 26.9, 26.9, 26.3, 25.0, 23.2, 21.2, 18.6, 14.4, −5.0, −5.0; HRMS (ESI) calcd for $C_{62}H_{96}O_{11}SiNa$ $(M + Na)^+$ 1067.6620, found 1067.6621.

Carboxylic Acid 35. To a solution of TBS ether **33** (15.2 mg, 14.5 μmol) in THF (0.50 mL) was added TBAF (1.0 M in THF, 0.10 mL, 0.10 mmol) at room temperature. After the mixture was stirred at the same temperature for 4 h, the mixture was poured into Et_2O, washed with H_2O and brine, and dried over $MgSO_4$. Concentration and column chromatography (hexane/EtOAc, 3:1) gave the corresponding alcohol (13.6 mg, quant.): colorless oil; R_f = 0.39 (hexane/EtOAc, 2:1); $[\alpha]^{27}_D$ +64.5 (*c* 0.36, $CHCl_3$); IR (neat) 3502, 2930 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37−7.27 (m, 15 H), 4.94 (d, *J* = 9.5 Hz, 1 H), 4.86−4.75 (m, 2 H), 4.69−4.67 (m, 2 H), 4.59 (d, *J* = 3.9 Hz, 1 H), 4.56 (d, *J* = 4.4 Hz, 1 H), 4.43 (d, *J* = 11.7 Hz, 1 H), 4.29 (dd, *J* = 4.9, 2.9 Hz, 1 H), 3.87−3.77 (m, 4 H), 3.69 (dd, *J* = 10.3, 3.2 Hz, 1 H), 3.60−3.36 (m, 7 H), 3.43 (s, 3 H), 2.42 (dd, *J* = 14.2, 9.5 Hz, 1 H), 2.13−2.02 (m, 2 H), 1.81−1.74 (m, 1 H), 1.71−1.63 (m, 1 H), 1.59−1.43 (m, 6 H), 1.57 (s, 3 H), 1.52 (s, 3 H), 1.38 (s, 3 H), 1.37 (s, 3 H), 1.35 (s, 3 H), 1.29−1.22 (m, 10 H), 0.88 (t, *J* = 7.1 Hz, 3 H), 0.75 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.4, 138.4, 133.3, 130.8, 128.7, 128.4, 128.4, 128.4, 128.3, 128.1, 127.7, 127.7, 109.5, 108.0, 97.0, 81.4, 80.6, 78.8, 76.3, 75.9, 74.9, 74.7, 74.7, 74.6, 74.5, 74.5, 73.5, 71.3, 59.9, 56.2, 41.3, 36.7, 36.3, 33.9, 32.6, 31.8, 29.7, 29.1, 28.6, 28.1, 27.5, 27.3, 26.5, 26.0, 22.6, 21.2, 15.9, 14.1; HRMS (ESI) calcd for $C_{56}H_{82}O_{11}Na$ $(M + Na)^+$ 953.5755, found 953.5742.

To a solution of the alcohol obtained above (13.6 mg, 14.6 μmol) in CH_2Cl_2 (0.25 mL) and DMSO (0.25 mL) were added Et_3N (21 μL, 0.154 mmol) and SO_3·pry (12.2 mg, 77 μmol) at room temperature. After the mixture was stirred at the same temperature for 30 min, the mixture was poured into Et_2O, washed with H_2O and brine, and dried over $MgSO_4$. Concentration gave the corresponding aldehyde (15.8 mg) as a pale yellow oil, which was used for the next reaction without further purification.

To a solution of aldehyde obtained above in *t*-BuOH (0.40 mL) and H_2O (0.10 mL) were added 2-methyl-2-butene (32 μL, 0.308 mmol), NaH_2PO_4 (11.1 mg, 92.4 μmol), and $NaClO_2$ (10.4 mg, 92.4 μmol) at room temperature. After the mixture was stirred at the same temperature for 30 min, the mixture was diluted with H_2O and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. Concentration and column chromatography ($CHCl_3$/MeOH, 49:1) gave carboxylic acid **35** (12.8 mg, 93% in two steps): colorless oil; R_f = 0.28 (hexane/EtOAc, 2:1); $[\alpha]^{27}_D$ +41.2 (*c* 0.56, $CHCl_3$); IR (neat) 3030, 1733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.25 (m, 15 H), 4.90 (d, *J* = 9.5 Hz, 1 H), 4.86−4.82 (m, 2 H), 4.69−4.58 (m, 5 H), 4.38 (d, *J* = 12.0 Hz, 1 H), 4.28 (dd, *J* = 4.7, 2.4 Hz, 1 H), 4.07 (dt, *J* = 7.3, 4.6 Hz, 1 H), 3.92 (brt, *J* = 8.8 Hz, 1 H), 3.81−3.78 (m, 2 H), 3.74 (dd, *J* = 7.6, 2.9 Hz, 1 H), 3.49−3.42 (m, 2 H), 3.49−3.44 (m, 2 H), 3.44 (s, 3 H), 2.51 (dd, *J* = 15.6, 5.6 Hz, 1 H), 2.40 (dd, *J* = 14.2, 9.5 Hz, 1 H), 2.09−1.99 (m, 3 H), 1.85−1.72 (m, 2 H), 1.61−1.42 (m, 4 H), 1.58 (d, *J* = 1.0 Hz, 3 H), 1.46 (s, 3 H), 1.39 (s, 3 H), 1.37 (s, 3 H), 1.36 (s, 3 H) 1.29−1.23 (m, 10 H), 0.88 (t, *J* = 6.8 Hz, 3 H), 0.73 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.3, 138.8, 137.8, 137.7, 132.7, 130.0, 129.4, 128.4, 128.2, 128.2, 128.1, 127.9, 127.4, 127.2, 109.3, 107.7, 97.1, 81.4, 77.2, 76.1, 74.9, 74.8, 74.6, 74.4, 73.4, 71.9, 71.1, 71.0, 60.4, 56.1, 40.5, 39.2, 37.5, 36.1, 32.6, 31.8, 29.7, 29.1, 28.5, 28.2, 27.4, 27.4, 26.5, 26.1, 22.6, 21.4, 21.0, 15.0, 14.2, 14.1; HRMS (ESI) calcd for $C_{56}H_{80}O_{12}Na$ $(M + Na)^+$ 967.5547, found 967.5560.

Carboxylic Acid 2. To a solution of tribenzyl ether **35** (15.2 mg, 16.1 μmol) in liquid NH_3 (10 mL), THF (5.0 mL), and *t*-BuOH (1.0 mL) was added Na (181 mg, 7.86 mmol) at −78 °C. After the mixture was stirred at the same temperature for 1 h, the reaction was quenched with saturated aqueous NH_4Cl, and the mixture was allowed to warm to room temperature. The mixture was diluted with H_2O and desalted by passing through the polystyrene gel chromatography (TSK-G3000S, H_2O, aqueous 50% EtOH, EtOH). The aqueous 50% EtOH and EtOH fractions were concentrated to give triol **36** (11.0 mg) as a colorless oil, which was used for the next reaction without further purification.

A solution of triol **36** obtained above in H_2O−TFA (3:1, 0.50 mL) was heated to 40 °C and stirred at the same temperature for 24 h. The mixture was concentrated to give the mixture of carboxylic acid **2** and its corresponding lactone (9.0 mg) as a colorless oil, which was used for the next reaction without further purification.

A solution of the mixture of carboxylic acid **2** and its corresponding lactone obtained above in MeOH (0.60 mL) and aqueous KOH (1.0 M, 0.30 mL) was heated to 30 °C and stirred at the same temperature for 14 h. The resultant mixture was diluted with H_2O and desalted by passing through polystyrene gel column chromatography (TSK-G3000S, H_2O, aqueous 50% EtOH, EtOH), and the aqueous 50% EtOH and EtOH fractions were concentrated. The residue was purified by column chromatography (ODS, aqueous 30% to 50% MeOH) to give carboxylic acid **2** (8.4 mg, 95% in three steps): colorless oil; R_f = 0.32 (ODS, aqueous 70% MeOH); $[\alpha]^{23}_D$ +10.6 (*c* 0.05, CH_3OH); IR (neat) 3406, 2925, 1633, 1576 cm^{-1}; ^1H NMR (800 MHz, CD_3OD) δ 5.08 (d, *J* = 9.2 Hz, 1 H), 4.04 (dd, *J* = 11.5, 6.0 Hz, 1 H), 3.90 (t, *J* = 3.7 Hz, 1 H), 3.89 (t, *J* = 6.9 Hz, 1 H), 3.74 (td, *J* = 10.0, 1.8 Hz, 1 H), 3.71 (ddd, *J* = 10.0, 3.6, 2.8 Hz, 1 H), 3.68 (td, *J* = 6.9, 3.7 Hz, 1 H), 3.56 (d, *J* = 3.7 Hz, 1 H), 3.52 (dd, *J* = 10.0, 2.8 Hz, 1 H), 3.39−3.37 (m, 1 H), 3.25 (dd, *J* = 4.8, 2.8 Hz, 1 H), 2.59−2.53 (m, 1 H), 2.41−2.39 (m, 2 H), 2.26 (dd, *J* = 12.8, 7.4 Hz, 1 H), 2.22 (dd, *J* = 13.8, 6.5 Hz, 1 H), 1.96 (ddd, *J* = 14.4, 10.6, 1.8 Hz, 1 H), 1.68 (s, 3 H), 1.63 (dt, *J* = 13.8, 6.4 Hz, 1 H), 1.54−1.49 (m, 3 H), 1.46−1.41 (m, 2 H), 1.35−1.30 (m, 10 H), 0.96 (d, *J* = 6.4 Hz, 3 H), 0.90 (t, *J* = 6.9 Hz, 3 H); ^{13}C NMR (150 MHz, CD_3OD) δ 180.2, 134.8, 131.5, 76.3, 75.9, 74.2, 73.8, 72.3, 71.9, 71.6, 71.6, 70.1, 42.3, 42.0, 41.7, 37.1, 34.0, 33.1, 30.8, 30.5, 30.1, 27.1, 23.7, 21.4, 16.8, 14.4; HRMS (ESI) calcd for $C_{27}H_{50}O_{11}Na$ $(M + Na)^+$ 573.3251, found 573.3237.

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Supporting Information Available: Additional experimental procedures and spectral and analytical data for new compounds and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.