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Stereocontrolled synthesis of the C79–C96 fragment of symbiodinolide

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ABSTRACT

The stereoselective synthesis of the C79–C96 fragment of symbiodinolide is described in which the spiroacetalization and Kotsuki coupling are the key steps.

Marine organisms produce various secondary metabolites that exhibit remarkable biological activities and chemical structures.[1] In particular, huge polyol and polyether compounds, such as palytoxins, brevetoxins, halichondrins, and maitotoxin are some of the most attractive molecules in natural products chemistry.[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 (Fig. 1).[4,5]

Symbiodinolide (**1**), a novel polyol macrolide with a molecular weight of 2859 mu, exhibits a voltage-dependant N-type Ca^{2+} channel-opening activity at 7 nM and COX-1 inhibitory effect at 2 nM. The planar structure and partial stereochemistries of **1** were elucidated by spectroscopic analysis and chemical degradations.[4] Herein, as a part of our structural study and synthetic study on **1**, we describe the enantio- and stereocontrolled synthesis of the C79–C96 fragment of **1** by using the spiroacetalization and Kotsuki coupling as key steps.

Scheme 1 shows the retrosynthetic analysis of the C79–C96 fragment **2**. The carbon framework of **2** would be constructed via the coupling of alkynyllithium reagent derived from **3**, and triflate **4** under Kotsuki conditions.[6] The spiroacetal **4** would be synthesized through the stereoselective spiroacetalization of the dihydroxyketone **5**, which can be broken down into the alkyne **6** (C79–C85) and the epoxide **7** (C86–C92).

Synthesis of the alkyne **13** (C79–C85) is shown in Scheme 2. Treatment of the aldehyde **8**[7] with the lithium acetylide, prepared from trimethylsilyl acetylene and *n*-BuLi, afforded the corresponding propargylic alcohol. Subsequent TPAP oxidation[8] provided the α,β-ynone **9**. Asymmetric reduction of **9** was performed by using chiral Ru(II) catalyst **10** and *i*-PrOH as the hydrogen donor[9] to give the optically pure propargylic alcohol **11** in 98%. The TMS group was removed with K_2CO_3 in MeOH to give the alkyne **12**, and then the hydroxy group was protected with TBSOTf/2,6-lutidine to afford the silyl ether **13**.

Next, we investigated the stereoselective construction of the spiroacetal moiety (Scheme 3). The ester **14**[10] was converted to the iodide **15** through the two-step sequence; DIBALH reduction and iodination. Treatment of **15** with allyltributylstannane and AIBN gave the alkene **16** in 82% yield.[11] Treatment of **16** with *m*CPBA provided the epoxide **17** as a diastereomixture. The epoxide **17** reacted with the acetylide, prepared from **13** and *n*-BuLi, to give the coupling product **18** in 75% yield.[12] Hydrogenation of **18** followed by TPAP oxidation[8] afforded the ketone **19**. Deprotection of TBS groups and subsequent spiroacetalization were performed by using catalytic CSA in MeOH to result in the formation of the spiroacetal **20** as the sole product.[13]

With the spiroacetal **20** in hand, remaining task was the stereoselective construction of the C93–C96 side chain (Scheme 4). The alcohol **20** was converted to the triflate **21** by the standard procedure in 89% yield. Coupling of **21** with the acetylide, derived from the alkyne **22**[14] and *n*-BuLi, under the Kotsuki conditions gave the desired product **23** in 83% yield.[6] The TBDPS group was removed with TBAF, and the resulting alcohol was protected with TIPSCl/imidazole to give **24**. The alkyne **24** was

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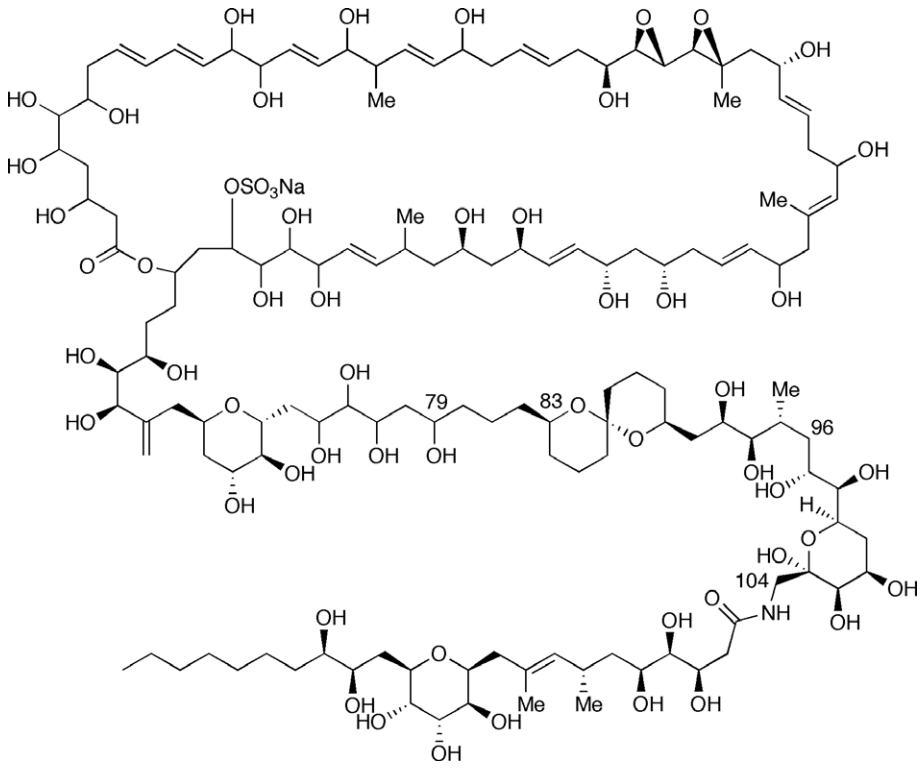
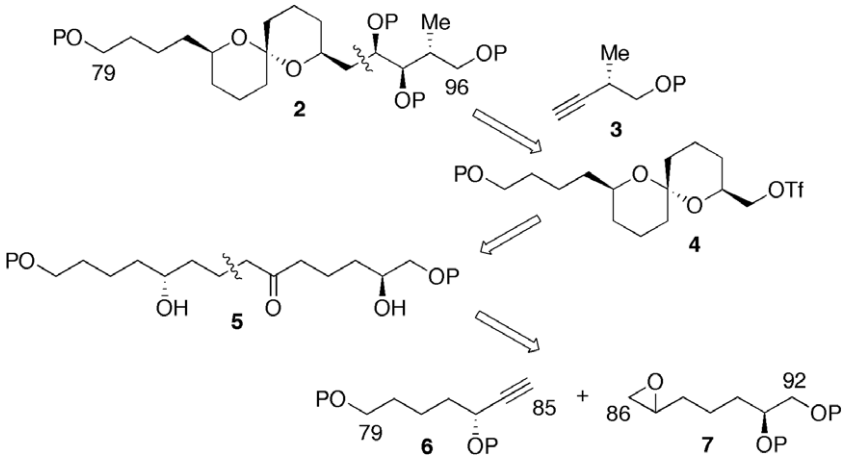
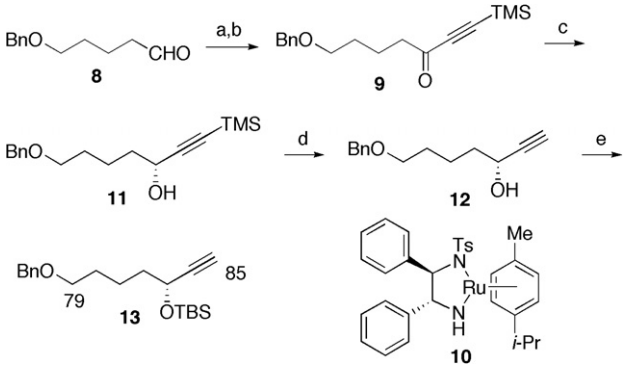


Figure 1. Structure of symbiodinolide (**1**).



Scheme 1. Retrosynthetic analysis of **2**. P = protecting group.

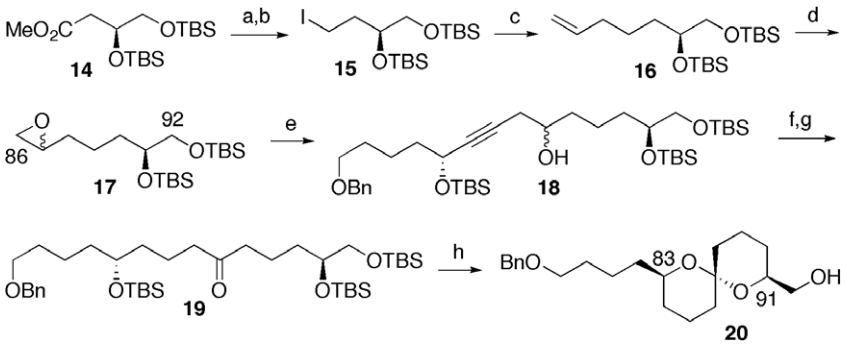


Scheme 2. Reagents and conditions: (a) trimethylsilyl acetylene, *n*-BuLi, THF, −7-8 °C; then **8**, −78 °C, 92%; (b) TPAP, NMO, MS4A, CH_2Cl_2, rt, 72%; (c) **10**, *i*-PrOH, rt, 98%, >99% ee; (d) K_2CO_3, MeOH, rt, 97%; (e) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, quant.

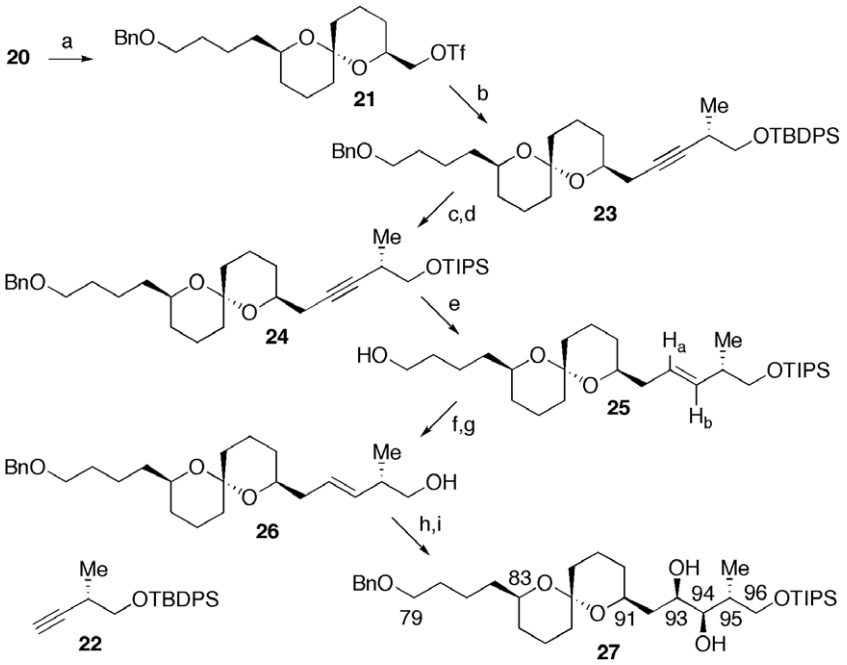
subjected to the Birch reduction conditions to afford the *trans*-alkene **25**, in which the benzyl protecting group was removed.[15] Benzyl protection of **25** followed by removal of the TIPS group gave the alcohol **26**. Sharpless AD[16] and subsequent selective protection of the primary hydroxy group with TIPSCl resulted in the formation of the desired C79–C96 fragment **27**[17,18] as a single stereoisomer.

Table 1 shows the ^{1}H NMR data of symbiodinolide (**1**)[4] and synthetic C79–C96 fragment **27**. The chemical shifts for both compounds are in excellent accordance. Thus, it can be said that the proposed relative stereochemistries in C83–C95 moiety were validated.

In conclusion, we have synthesized the C79–C96 fragment of **1** through the stereoselective spiroacetalization and Kotsuki coupling as key steps. Further synthetic study and structural study on **1** are underway in our laboratory.



Scheme 3. Reagents and conditions: (a) DIBALH, hexane, −78 °C, 77%; (b) I_2, PPh_3, imidazole, Et_2O–CH_3CN (3:1), reflux, 76%; (c) allyltributylstannane, AIBN, benzene, reflux, 82%; (d) *m*CPBA, CH_2Cl_2, 0 °C, 83%; (e) **13** (2.0 equiv), *n*-BuLi (2.2 equiv), THF, −78 °C; then $BF_3{\cdot}OEt_2$ (1.5 equiv), **17** (1.0 equiv), −78 °C, 75%; (f) H_2, Pd-C, Et_3N, EtOAc, rt, 95%; (g) TPAP, NMO, MS4A, CH_2Cl_2, rt, 96%; (h) CSA, MeOH, rt, 96%.



Scheme 4. Reagents and conditions: (a) Tf_2O, 2,6-lutidine, CH_2Cl_2, −78 °C, 89%; (b) **22** (2.5 equiv), *n*-BuLi (2.5 equiv), THF, −78 °C to 0 °C; then **21** (1.0 equiv), DMPU, −10 °C, 83%; (c) TBAF, THF, rt, 98%; (d) TIPSCl, imidazole, DMAP, DMF, rt, quant.; (e) Li, liq. NH_3, *t*-BuOH, THF, −78 °C, 95%; (f) BnBr, NaH, TBAI, THF, 40 °C; (g) TBAF, THF, rt, 78% (two steps); (h) AD-mix-β, $CH_3SO_2NH_2$, *t*-BuOH–H_2O (1:1), 0 °C to rt; (i) TIPSCl, imidazole, DMAP, CH_2Cl_2, rt, 51% (two steps), dr = >99:1.

Table 1
Selected ^1H NMR chemical shifts of symbiodinolide and synthetic fragment **27** in CD_3OD

Position	Symbiodinolide	**27**	$\Delta\delta$[a]
83	3.75	3.72	+0.03
91	3.95	3.90	+0.05
93	4.05	3.96	+0.09
94	3.12	3.27	−0.15
95	2.06	1.88	+0.18
C95-Me	1.03	0.98	+0.05

[a] $\Delta\delta = \delta$symbiodinolide $- \delta$**27** in ppm.

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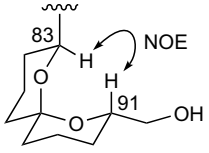

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18. Compound **27**: R_f = 0.20 (hexane/EtOAc, 4:1); $[\alpha]_D^{25}$ +18.1 (*c* 0.09, $CHCl_3$); IR (neat) 3465, 2938 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.31–7.24 (m, 5H), 4.48 (s, 2H), 3.96 (dt, *J* = 9.8, 2.7 Hz, 1H), 3.92–3.87 (m, 2H), 3.75–3.68 (m, 2H), 3.49 (t, *J* = 6.1 Hz, 2H), 3.27 (dd, *J* = 9.8, 2.7 Hz, 1H), 1.94–1.81 (m, 3H), 1.68–1.05 (m, 41H), 0.98 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 140.0, 129.5, 128.9, 128.7, 97.2, 79.0, 74.0, 71.7, 70.5, 69.5, 67.3, 42.3, 40.1, 37.7, 36.9, 33.2, 32.8, 31.2, 23.8, 20.5, 20.2, 18.8, 18.8, 15.2, 13.4; HRMS (ESI TOF MS), calcd for $C_{35}H_{62}O_6SiNa$ $(M+Na)^+$: 629.4213, found: 629.4220.