WILEY-VCH

FULL PAPER

Stereoselective Synthesis of the Proposed C79–C104 Fragment of Symbiodinolide

Hiroyoshi Takamura,*[a] Takayuki Fujiwara,[a] Yohei Kawakubo,[a] Isao Kadota,[a] and Daisuke Uemura[b]

Abstract: Stereoselective and streamlined synthesis of the proposed C79–C104 fragment **2** of symbiodinolide (**1**), a polyol marine natural product with a molecular weight of 2860, was achieved. In the synthetic route, the proposed C79–C104 fragment **2** was synthesized by utilizing a Julia–Kocienski olefination and subsequent Sharpless asymmetric dihydroxylation as key transformations in a convergent manner. Detailed comparison of the ^{13}C NMR chemical shifts between the natural product and the synthetic C79–C104 fragment **2** revealed that the stereostructure at the C91–C99 carbon chain moiety of symbiodinolide (**1**) should be reinvestigated.

Introduction

A variety of biologically active secondary metabolites have been isolated from marine origin.[1] Among them, polyether and polyol marine natural products, such as brevetoxins, ciguatoxins, halichondrins, and palytoxins, are the attractive molecules in natural product chemistry, synthetic chemistry, and medicinal chemistry due to their extraordinary structures and potent biological activities.[2] Their structural feature is a long carbon backbone which is highly functionalized by oxygen atom.

We previously reported the isolation of symbiodinolide (**1**, Figure 1) from the symbiotic marine dinoflagellate *Symbiodinium* sp. in 2007.[3] Symbiodinolide (**1**) is a 62-membered polyol macrolide with a molecular weight of 2860 and 61 stereogenic centers. This natural product displays voltage-dependent N-type Ca^{2+} channel-opening activity at 7 nM and COX-1 inhibitory effect at 2 μM (65% inhibition). In addition, **1** ruptures the tissue surface of the acoel flatworm *Amphiscolops* sp. at 2.5 μM. The gross structure of **1** was established by the extensive 2D NMR analysis[3] and partial stereochemistries of **1** were elucidated by the degradation of the natural product[3,4] and chemical synthesis of each fragment[5] by our group. However, the complete configurational elucidation of **1** remains to be unsolved issue because of its huge and complicated molecular structure. In the C91–C99 carbon chain moiety, the stereochemistries were determined by the analysis of $^{3}J_{H,H}$ coupling constants and nuclear Overhauser effect (NOE) observations.[3] In this article, we first describe the stereoselective synthesis of the C79–C104 fragment **2** possessing the proposed stereostructure. Furthermore, the ^{13}C NMR chemical shifts were compared between the natural product and the synthetic product **2**, which indicates that the stereochemical determination of the C91–C99 carbon chain domain of **1** needs to be reexamined.[6]

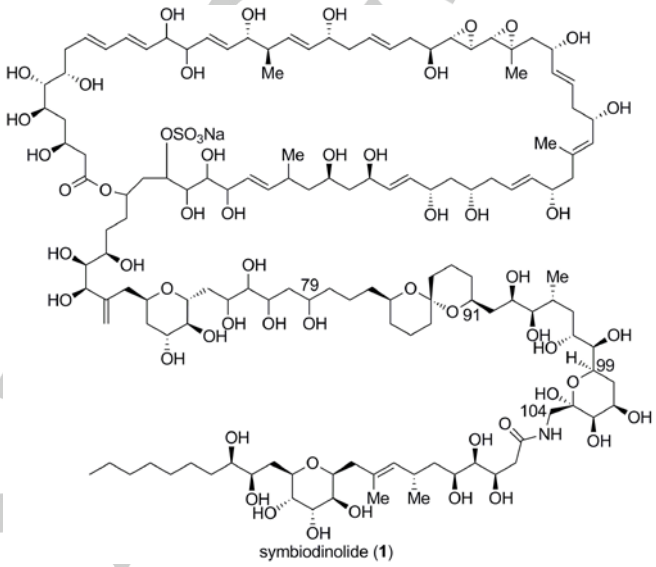


Figure 1. Structure of symbiodinolide (**1**).

Results and Discussion

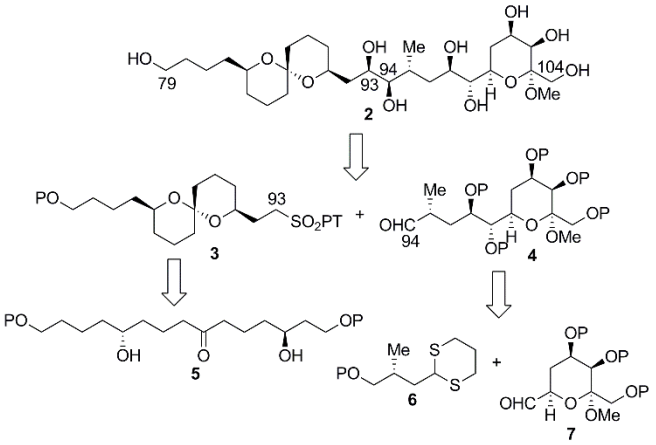
Retrosynthetic analysis of 2

Our retrosynthetic analysis of the proposed C79–C104 fragment **2** is shown in Scheme 1. We envisioned that the target molecule **2** could be synthesized by the Julia–Kocienski olefination[7] between 1-phenyl-1*H*-tetrazol-5-yl (PT)-sulfone **3** and aldehyde **4** and subsequent stereoselective introduction of the *syn*-diol moiety at the C93 and C94 positions utilizing Sharpless asymmetric dihydroxylation.[8] The carbon framework of the coupling precursor **3** could be stereoselectively constructed through the thermodynamic-controlled spiroacetalization of dihydroxyketone **5**. On the other hand, tetrahydropyran fragment

[a] Prof. Dr. H. Takamura, T. Fujiwara, Y. Kawakubo, Prof. Dr. I. Kadota
Department of Chemistry, Graduate School of Natural Science and Technology, Okayama University
3-1-1 Tsushimanaka, Kita-ku, Okayama 700-8530 (Japan)
E-mail: takamura@cc.okayama-u.ac.jp
[b] Prof. Dr. D. Uemura
Department of Chemistry, Faculty of Science, Kanagawa University
2946 Tsuchiya, Hiratsuka 259-1293 (Japan)

Supporting information for this article is given via a link at the end of the document.

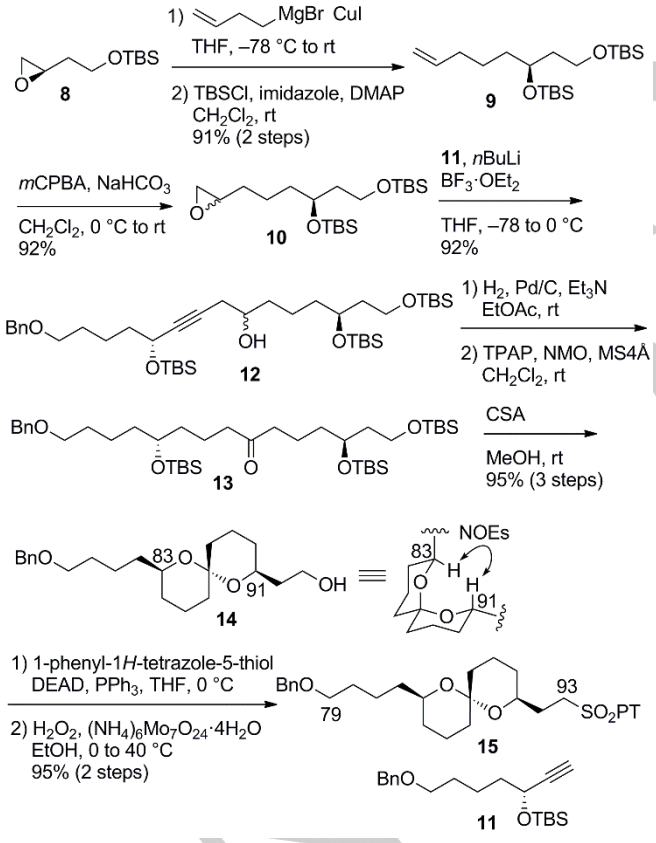
4 could be synthesized via the reaction of dithiane **6** and aldehyde **7**.



Scheme 1. Retrosynthetic analysis of **2**. P = protective group. PT = 1-phenyl-1*H*-tetrazol-5-yl.

Synthesis of PT-sulfone 15

First, we investigated the stereoselective synthesis of the C79–C93 fragment PT-sulfone **15**.[9] The synthesis commenced from optically pure epoxide **8**, which was prepared from L-aspartic acid by the known procedure (Scheme 2).[10] The epoxide **8** was treated with 3-butenylmagnesium bromide/CuI[11] to afford the desired secondary alcohol. The resulting alcohol was protected with *tert*-butyldimethylsilyl chloride (TBSCl) to provide silyl ether **9**. The alkene **9** was oxidized with *m*-chloroperbenzoic acid (*m*CPBA) to give terminal epoxide **10** as a 1:1 diastereomeric mixture. The coupling between the epoxide **10** and alkyne **11**[5a,12] with *n*BuLi/BF_3·OEt_2[13] proceeded smoothly to produce alcohol **12** in 92% yield. Hydrogenation of the alkyne **12** followed by tetra-*n*-propylammonium perruthenate (TPAP) oxidation[14] of the resulting alcohol gave ketone **13**. Global deprotection of the three TBS groups of **13** and spiroacetalization with camphorsulfonic acid (CSA) in MeOH were performed in one-pot to provide alcohol **14** in 95% yield in three steps as a single stereoisomer.[15] The absolute configuration of **14** was unambiguously established by the NOE correlations between H-83 and H-91. The stereochemical outcome in the spiroacetalization can be rationalized by the thermodynamic stability of **14** due to its double anomeric effect. Treatment of the alcohol **14** with 1-phenyl-1*H*-tetrazole-5-thiol/diethyl azodicarboxylate (DEAD)/PPh_3 and subsequent oxidation of the resulting PT-sulfide with H_2O_2/Mo^{VI}[16] furnished PT-sulfone **15** in 95% yield in two steps.

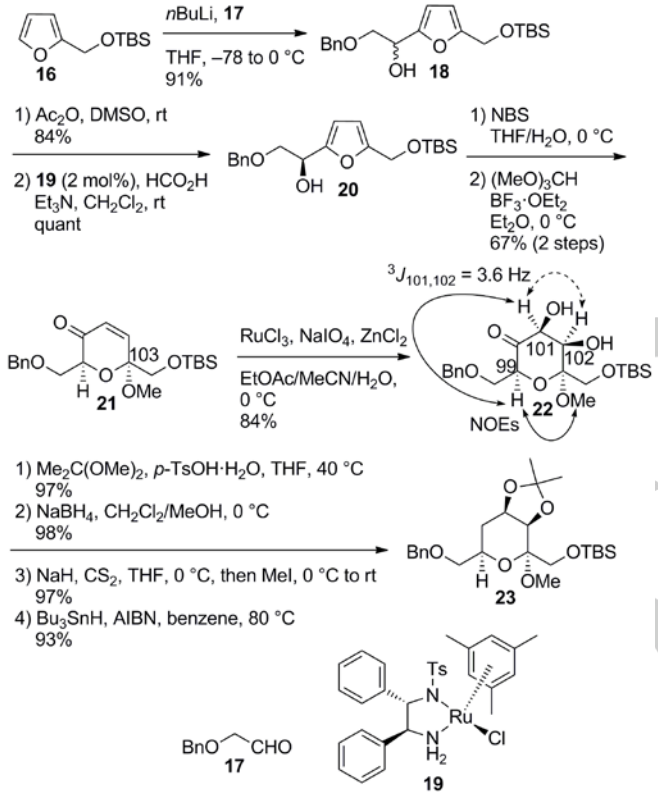


Scheme 2. Synthesis of **15**. THF = tetrahydrofuran, rt = room temperature, TBS = *tert*-butyldimethylsilyl, DMAP = 4-dimethylaminopyridine, *m*CPBA = *m*-chloroperbenzoic acid, Bn = benzyl, TPAP = tetra-*n*-propylammonium perruthenate, NMO = *N*-methylmorpholine oxide, MS = molecular sieves, CSA = camphorsulfonic acid, NOE = nuclear Overhauser effect, DEAD = diethyl azodicarboxylate.

Synthesis of aldehyde 29

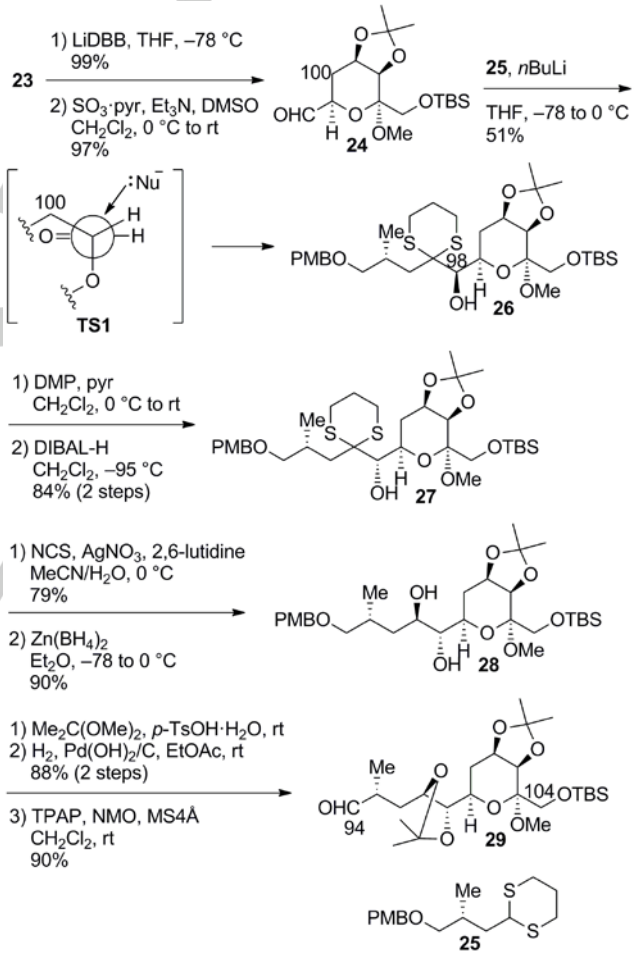
With the coupling precursor **15** in hand, we next examined the stereocontrolled synthesis of the C94–C104 fragment aldehyde **29**,[17] which is the coupling partner of **15**. We first investigated the stereoselective construction of the tetrahydropyran moiety. Thus, deprotonation of furan **16**[18] with *n*BuLi and subsequent reaction with aldehyde **17**[19] gave racemic furyl alcohol **18** (Scheme 3). Oxidation of the alcohol **18** with Ac_2O/dimethylsulfoxide (DMSO)[20] followed by asymmetric transfer hydrogenation of the resulting furyl ketone using HCO_2H/Et_3N as the hydrogen source in the presence of 2 mol% of (*S*,*S*)-ruthenium catalyst **19**[21] provided optically active furyl alcohol **20** quantitatively as a single stereoisomer.[22] Achmatowictz rearrangement[23] of **20** was initiated with *N*-bromosuccinimide (NBS) in aqueous THF at 0 °C to yield the corresponding hemiacetals as a 1:1 diastereomeric mixture at the C103 position, which were quite unstable, therefore, reacted immediately with $(MeO)_3CH$/BF_3·OEt_2 in Et_2O at 0 °C to afford the desired methyl acetal **21** and its 103-epimer in 67% and 10% yields in two steps, respectively. Next, the stereoselective introduction of the vicinal diol moiety at the C101 and C102 positions was examined. We first carried out the OsO_4-catalyzed dihydroxylation of enone **21**, however, unfortunately, the reaction did not proceed at all and the enone **21** was recovered quantitatively. Plietker et al. reported that RuO_4-catalyzed dihydroxylation in the presence of a Lewis acid was efficient for the electron-deficient alkenes.[24] Therefore, according to their protocol, the enone **21** was treated with $RuCl_3$/$NaIO_4$ in the presence of $CeCl_3$ as a Lewis acid to produce the desired diol **22** in 51% yield. After the detailed investigation, the use of $ZnCl_2$ as a Lewis acid was found to be effective to furnish **22** in 84% yield as the sole product. The stereostructure of the diol **22** was elucidated by the NMR spectroscopy. Thus, the stereochemistry at the C103 position resulting in the transformation from **20** to **21**

was verified by the NOE correlations between H-99 and OCH_3-103. The NOE observations of H-99/H-101 and the small magnitude of the coupling constant ($^3J_{101,102}$ = 3.6 Hz) confirmed that H-99, H-101, and H-102 were oriented in the *syn* relationship to each other. Although the detailed conformational analysis of **21** was not carried out, the 103-methoxy group seems to sterically prevent the RuO_4-approaching from the α-face. After the diol **22** was protected with $Me_2C(OMe)_2$, the resulting ketone was reduced with $NaBH_4$ to produce the corresponding β-alcohol, presumably due to the steric repulsion between the acetonide moiety and the reagent. The absolute configuration at the C100 position of the resulting β-alcohol was determined by the $^3J_{99,100}$ coupling constant (5.5 Hz). The hydroxy moiety at the C100 position was removed via Barton–McCombie deoxygenation[25] by way of the *S*-methyl dithiocarbonate to afford tetrahydropyran **23**.



Scheme 3. Synthesis of **23**. Ac = acetyl, DMSO = dimethylsulfoxide, Ts = toluenesulfonyl, quant = quantitative, NBS = *N*-bromosuccinimide, AIBN = 2,2'-azobisisobutyronitrile.

We next turned our attention to the introduction of the C94–C97 moiety. Thus, deprotection of the benzyl group of **23** with lithium 4,4'-di-*t*-butylbiphenylide (LiDBB)[26] followed by Parikh–Doering oxidation[27] gave aldehyde **24** (Scheme 4). Deprotonation of dithiane **25** with *n*BuLi, which was synthesized from commercially available (*S*)-3-hydroxy-2-methylpropionate by the known procedure,[28] and addition of the aldehyde **24** led to the formation of alcohol **26** as a single stereoisomer.[22] The stereoselective addition of the anion, which was formed from **25**, to the aldehyde **24** is understandable by a Felkin–Anh model[29] as shown in **TS1**. Unfortunately, the stereochemistry at the C98 position was undesired, therefore, the stereoinversion at the C98 position of **26** was performed by Dess–Martin oxidation[30] and subsequent diastereoselective reduction with diisobutylaluminum hydride (DIBAL-H) at –95 °C to furnish alcohol **27** bearing the desired configuration in 84% yield in two steps as the sole product. After the hydrolysis of the dithiane moiety of **27** with *N*-chlorosuccinimide (NCS)/$AgNO_3$/2,6-lutidine in aqueous MeCN,[31] the resulting α-hydroxy ketone was reduced diastereoselectively with $Zn(BH_4)_2$ through the chelated transition state[32] to afford the desired *anti*-diol **28** as a single diastereomer.[22] Acetonide protection of **28**, removal of the *p*-methoxybenzyl (PMB) group by hydrogenation, and TPAP oxidation[14] provided the aldehyde **29**.



Scheme 4. Synthesis of **29**. DBB = 4,4'-di-*t*-butylbiphenylide, pyr = pyridine, PMB = *p*-methoxybenzyl, DMP = Dess–Martin periodinane, DIBAL-H = diisobutylaluminum hydride, NCS = *N*-chlorosuccinimide.

Synthesis of the proposed C79–C104 fragment 2.

Having synthesized both coupling precursors **15** and **29**, we next focused on the connection of these two fragments by the Julia–Kocienski olefination (Table 1).[7] When we treated the PT-sulfone

15 with lithium diisopropylamide (LDA) as a base and reacted with the aldehyde **29**, the (*E*)- and (*Z*)-alkenes **30** and **31** were obtained in 95% combined yield as an inseparable mixture at a 2.8:1 diastereomeric ratio (entry 1).[33] The resulting configuration at the C93 and C94 positions were verified by the $^3J_{93,94}$ coupling constants, respectively (15.3 Hz in **30** and 10.2 Hz in **31**). Although we obtained the desired coupling product **30**, *E*/*Z* selectivity was quite low. When we used potassium hexamethyldisilazide (KHMDS) as the base, the *E*/*Z* ratio was increased to 8:1 (entry 2). Finally, lowering the reaction temperature to –100 °C, we could obtain the (*E*)-alkene **30** in 70% yield as a single diastereomer (entry 3).

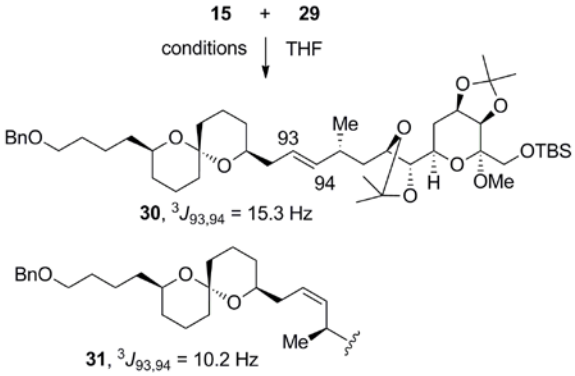


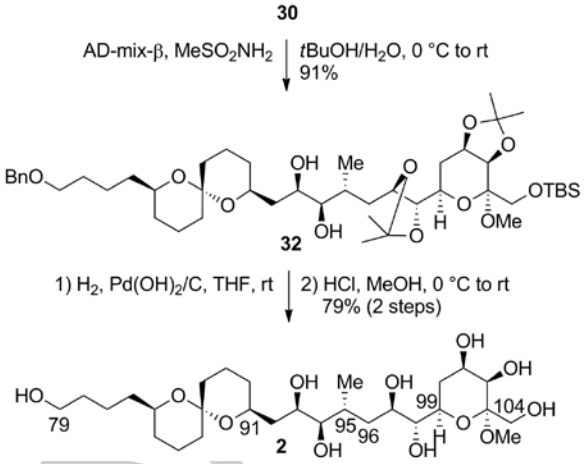
Table 1. Julia–Kocienski olefination between **15** and **29**.

Entry	Conditions[a]	Yield (%)[b]	Ratio (**30**:**31**)[c]
1	LDA, –78 to 0 °C	95	2.8:1
2	KHMDS, –78 °C	80	8:1
3	KHMDS, –100 °C	70	>20:1

[a] LDA = lithium diisopropylamide, KHMDS = potassium hexamethyldisilazide. [b] Isolated yield. [c] Determined by analysis of the ^{1}H NMR spectra.

Further transformation from **30** to the target molecule **2** is depicted in Scheme 5. The alkene **30** was exposed to the Sharpless asymmetric dihydroxylation[8] with AD-mix-β to produce diol **32** possessing the expected and desired stereochemistries.[22] Finally, deprotection of the benzyl group by hydrogenation followed by simultaneous removal of the acetonide and TBS moieties with HCl in MeOH furnished the proposed C79–C104 fragment **2** in 79% yield in two steps.

Next, we compared the ^{13}C NMR data of the synthetic product **2** with those of the corresponding moiety of natural symbiodinolide (**1**).[34] The ^{13}C NMR chemical shifts and their deviations of **1** and **2** are summarized in Table 2. Unexpectedly, the ^{13}C NMR chemical shifts of the synthetic **2** did not match those of the natural product. Especially, their chemical shift deviation was critical at the C95-Me group. These findings clearly indicate that the stereostructure at the C91–C99 carbon chain region of symbiodinolide (**1**) should be resurveyed.[35]



Scheme 5. Synthesis of **2**.

Table 2. ^{13}C NMR chemical shifts and their deviations of natural symbiodinolide (**1**) and the synthetic product **2**.[a]

Position	**1**[b]	**2**[c]	$\Delta(\delta_1-\delta_2)$[d]
83	70.3	70.4	–0.1
87	97.0	97.2	–0.2
91	67.1	67.2	–0.1
92	42.0[e]	41.8	+0.2
93	68.7	69.1	–0.4
94	80.9	80.9	0.0
95	33.5	33.1	+0.4
95-Me	19.0	17.3	+1.7
96	38.7	37.7	+1.0
97	70.5	70.1	+0.4
98	78.5	78.1	+0.4
99	68.8	69.4	–0.6
100	30.7	31.1	–0.4
101	67.1	67.3	–0.2

[a] Chemical shifts are reported in ppm with reference to the internal residual solvent (CD_3OD, 49.0 ppm). [b] Data from reference 3. Recorded at 200 MHz. [c] Recorded at 150 MHz. [d] δ_1 and δ_2 are chemical shifts of natural symbiodinolide (**1**) and the synthetic product **2**, respectively. [e] We previously reported the C92 chemical shift (46.4 ppm) in reference 3. In this work, after the careful and detailed reinvestigation of the ^{13}C NMR data, we have revised the chemical shift assignment (42.0 ppm).

Conclusions

Stereoselective and streamlined synthesis of the C79–C104 fragment **2** with the originally assigned stereostructure of symbiodinolide (**1**) was examined. Acid-catalyzed thermodynamic-controlled spiroacetalization was used as a key step to afford stereoselectively the coupling precursor **15**. The other coupling precursor **29** was synthesized by utilizing the Achmatowicz reaction for the tetrahydropyran construction and the dithiane addition to the aldehyde for the introduction of the C94–C97 moiety. The PT-sulfone **15** and the aldehyde **29** were coupled via Julia–Kocienski olefination and subsequent Sharpless asymmetric dihydroxylation produced the target molecule **2**. In addition, comparison of the ^{13}C NMR chemical shifts between the natural product and the synthesized **2** suggests that the relative configuration at the C91–C99 region of symbiodinolide (**1**) needs to be reinvestigated. Further our effort toward the stereostructural elucidation of this moiety of **1** will be reported in the following article.[36]

Experimental Section

Experimental details, compound data, and copies of NMR spectra of new compounds can be found in the Supporting Information.

Acknowledgements

We are grateful to Division of Instrumental Analysis, Okayama University, for the NMR measurements. We appreciate JGC-S Scholarship Foundation, The Naito Foundation, The Sumitomo Foundation, and The Uehara Memorial Foundation for their financial supports. This research was supported by a Grant-in Aid for Scientific Research (No. 24710250) from the Japan Society for the Promotion of Science (JSPS).

Keywords: natural products • macrocycles • polyols • structure elucidation • stereoselective synthesis

[1] a) D. Uemura in *Bioorganic Marine Chemistry*, *Vol. 4* (Ed.: P. J. Scheuer), Springer, Berlin, Heidelberg, **1991**, pp. 1–31; b) Y. Shimizu, *Chem. Rev.* **1993**, *93*, 1685–1698; c) D. Uemura, *Chem. Rec.* **2006**, *6*, 235–248.

[2] a) T. Yasumoto, M. Murata, *Chem. Rev.* **1993**, *93*, 1897–1909; b) M. Murata, T. Yasumoto, *Nat. Prod. Rep.* **2000**, *17*, 293–314; c) M. Kita, D. Uemura, *Chem. Rec.* **2010**, *10*, 48–52.

[3] M. Kita, N. Ohishi, K. Konishi, M. Kondo, T. Koyama, M. Kitamura, K. Yamada, D. Uemura, *Tetrahedron* **2007**, *63*, 6241–6251.

[4] a) C. Han, D. Uemura, *Tetrahedron Lett.* **2008**, *49*, 6988–6990; b) C. Han, Y. Yamano, M. Kita, H. Takamura, D. Uemura, *Tetrahedron Lett.* **2009**, *50*, 5280–5282; c) C. Han, Y. Yamano, F. Kakiuchi, K. Nakamura, D. Uemura, *Tetrahedron* **2011**, *67*, 9622–9626.

[5] a) H. Takamura, J. Ando, T. Abe, T. Murata, I. Kadota, D. Uemura, *Tetrahedron Lett.* **2008**, *49*, 4626–4629; b) T. Murata, M. Sano, H. Takamura, I. Kadota, D. Uemura, *J. Org. Chem.* **2009**, *74*, 4797–4803; c) H. Takamura, T. Murata, T. Asai, I. Kadota, D. Uemura, *J. Org. Chem.* **2009**, *74*, 6658–6666; d) H. Takamura, Y. Kadonaga, Y. Yamano, C. Han, Y. Aoyama, I. Kadota, D. Uemura, *Tetrahedron Lett.* **2009**, *50*, 863–866; e) H. Takamura, Y. Kadonaga, Y. Yamano, C. Han, I. Kadota, D. Uemura, *Tetrahedron* **2009**, *65*, 7449–7456; f) H. Takamura, Y. Kadonaga, I. Kadota, D. Uemura, *Tetrahedron Lett.* **2010**, *51*, 2603–2605; g) H. Takamura, Y. Kadonaga, I. Kadota, D. Uemura, *Tetrahedron* **2010**, *66*, 7569–7576; h) H. Takamura, K. Tsuda, Y. Kawakubo, I. Kadota, D. Uemura, *Tetrahedron Lett.* **2012**, *53*, 4317–4319; i) H. Takamura, T. Fujiwara, I. Kadota, D. Uemura, *Beilstein J. Org. Chem.* **2013**, *9*, 1931–1935; j) H. Takamura, H. Wada, M. Ogino, T. Kikuchi, I. Kadota, D. Uemura, *J. Org. Chem.* **2015**, *80*, 3111–3123.

[6] For reviews on the structural elucidation of natural products by the chemical synthesis, see: a) K. C. Nicolaou, S. A. Snyder, *Angew. Chem.* **2005**, *117*, 1036–1069; *Angew. Chem. Int. Ed.* **2005**, *44*, 1012–1044; b) M. E. Maier, *Nat. Prod. Rep.* **2009**, *26*, 1105–1124; (c) T. L. Suyama, W. H. Gerwick, K. L. McPhail, *Bioorg. Med. Chem.* **2011**, *19*, 6675–6701.

[7] a) P. R. Blakemore, W. J. Cole, P. J. Kocieński, A. Morley, *Synlett* **1998**, 26–28; b) P. R. Blakemore, *J. Chem. Soc. Perkin Trans. 1* **2002**, 2563–2585; c) C. Aïssa, *Eur. J. Org. Chem.* **2009**, 1831–1844.

[8] For a review, see: H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483–2547.

[9] For our preliminary communication on the synthesis of the C79–C93 fragment, see reference 5i.

[10] C. D. Donner, *Tetrahedron Lett.* **2007**, *48*, 8888–8890.

[11] I. Paterson, E. A. Anderson, S. M. Dalby, J. H. Lim, P. Maltas, O. Loiseleur, J. Genovino, C. Moessner, *Org. Biomol. Chem.* **2012**, *10*, 5861–5872.

[12] For the preparation of **11**, see the Supporting Information.

[13] M. Yamaguchi, I. Hirao, *Tetrahedron Lett.* **1983,** *24*, 391–394.

[14] For a review, see: S. V. Ley, J. Norman, W. P. Griffith, S. P. Marsden, *Synthesis* **1994**, 639–666.

[15] For reviews on the spiroacetal, see: a) F. Perron, K. F. Albizati, *Chem. Rev.* **1989**, *89*, 1617–1661; b) J. E. Aho, P. M. Pihko, T. K. Rissa, *Chem. Rev.* **2005**, *105*, 4406–4440.

[16] H. S. Schultz, H. B. Freyermuth, S. R. Buc, *J. Org. Chem.* **1963**, *28*, 1140–1142.

[17] For our preliminary communication on the synthesis of the C94–C104 fragment, see reference 5h.

[18] S. Celanire, F. Marlin, J. E. Baldwin, R. M. Adlington, *Tetrahedron* **2005**, *61*, 3025–3032.

[19] N. Nishizono, Y. Akama, M. Agata, M. Sugo, Y. Yamaguchi, K. Oda, *Tetrahedron* **2011**, *67*, 358–363.

[20] J. D. Albright, L. Goldman, *J. Am. Chem. Soc.* **1965**, *87*, 4214–4216.

[21] a) A. Fujii, S. Hashiguchi, N. Uematsu, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1996**, *118*, 2521–2522; b) R. Noyori, S. Hashiguchi, *Acc. Chem. Res.* **1997**, *30*, 97–102.

[22] For the stereochemical determination, see the Supporting Information.

[23] O. Achmatowicz Jr., P. Bukowski, B. Szechner, Z. Zwierzchowska, A. Zamojski, *Tetrahedron* **1971**, *27*, 1973–1996.

[24] B. Plietker, M. Niggemann, *J. Org. Chem.* **2005**, *70*, 2402–2405.

[25] D. H. R. Barton, S. W. McCombie, *J. Chem. Soc. Perkin Trans. 1* **1975**, 1574–1585.

[26] a) P. K. Freeman, L. L. Hutchinson, *J. Org. Chem.* **1980**, *45*, 1924–1930; b) R. E. Ireland, M. G. Smith, *J. Am. Chem. Soc.* **1988**, *110*, 854–860.

[27] J. R. Parikh, W. v. E. Doering, *J. Am. Chem. Soc.* **1967**, *89*, 5505–5507.

[28] a) R. D. Walkup, P. D. Boatman Jr., R. R. Kane, R. T. Cunningham, *Tetrahedron Lett.* **1991**, *32*, 3937–3940; b) J. B. Shotwell, W. R. Roush, *Org. Lett.* **2004**, *6*, 3865–3868.

[29] a) A. Mengel, O. Reiser, *Chem. Rev.* **1999**, *99*, 1191–1223; b) D. A. Evans, S. J. Siska, V. L. Cee, *Angew. Chem.* **2003**, *115*, 1803–1807; *Angew. Chem. Int. Ed.* **2003**, *42*, 1761–1765.

[30] a) D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155–4156; b) D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.

[31] a) E. J. Corey, B. W. Erickson, *J. Org. Chem.* **1971**, *36*, 3553–3560; b) A. V. R. Rao, G. Venkatswamy, S. M. Javeed, V. H. Deshpande, B. R. Rao, *J. Org. Chem.* **1983**, *48*, 1552–1554.

[32] a) T. Nakata, T. Tanaka, T. Oishi, *Tetrahedron Lett.* **1983**, *24*, 2653–2656; b) T. Oishi, T. Nakata, *Acc. Chem. Res.* **1984**, *17*, 338–344.

[33] We did not observe the epimerization at the C95 position of the aldehyde **29** in our investigation of the Julia–Kocienski olefination between **15** and **29**.

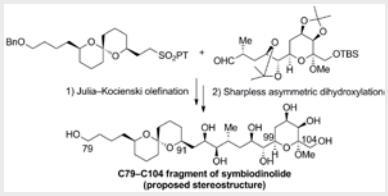
[34] For some examples on comparing the NMR data between model compounds and the natural product toward the structural elucidation, see: a) W. Zheng, J. A. DeMattei, J.-P. Wu, J. J.-W. Duan, L. R. Cook, H. Oinuma, Y. Kishi, *J. Am. Chem. Soc.* **1996**, *118*, 7946–7968; b) T. Oishi, M. Kanemoto, R. Swasono, N. Matsumori, M. Murata, *Org. Lett.* **2008**, *10*, 5203–5206; c) H. Fuwa, K. Ishigai, T. Goto, A. Suzuki, M. Sasaki, *J. Org. Chem.* **2009**, *74*, 4024–4040; d) E. Fleury, M.-I. Lannou, O. Bistri, F. Sautel, G. Massiot, A. Pancrazi, J. Ardisson, *J. Org. Chem.* **2009**, *74*, 7034–7045; e) K. C. Nicolaou, C. F. Gelin, J. H. Seo, Z. Huang, T. Umezawa, *J. Am. Chem. Soc.* **2010**, *132*, 9900–9907.

[35] The relative configurations of the two cyclic moieties (C83–C91 and C99–C104 domains) were determined by $^{3}J_{H,H}$ coupling constants and NOE experiments in reference 3. In addition, the ^{13}C NMR chemical shift differences of these two domains between the natural **1** and the synthetic **2** were not significant. From these two results, we judged that the stereochemical elucidation of these two cyclic domains was reliable.

[36] H. Takamura, T. Fujiwara, Y. Kawakubo, I. Kadota, D. Uemura, The following article.

FULL PAPER

Structural doubt: Stereoselective and streamlined synthesis of the C79–C104 fragment of symbiodinolide, a polyol marine natural product with a molecular weight of 2860, revealed that the stereochemistry of the C91–C99 carbon domain of this natural product needs to be reassigned.



C79–C104 fragment of symbiodinolide
(proposed stereostructure)

H. Takamura, T. Fujiwara, Y. Kawakubo, I. Kadota, D. Uemura*

Page No. – Page No.

Stereoselective Synthesis of the Proposed C79–C104 Fragment of Symbiodinolide