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FULL PAPER

Stereodivergent Synthesis and Stereochemical Reassignment of the C79–C104 Fragment of Symbiodinolide

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

Abstract: We first synthesized eight possible diastereomers of the C79–C97 fragment **3a**–**3h** in a stereodivergent manner by utilizing a dithiane addition to the aldehyde as a key step. Comparing the ^{13}C NMR chemical shifts between the natural product and the synthetic products **3a**–**3h** indicated that the relative stereostructure of this fragment is that represented in **3a** or **3f**. We next stereodivergently synthesized eight possible diastereomers of the C94–C104 fragment **4a**–**4h** and compared their ^{13}C NMR chemical shifts with those of the natural product, which established the relative stereochemistry of this fragment to be that described in **4a** or **4e**. By combining the stereostructural outcomes of the C79–C97 fragment (**3a** or **3f**) and C94–C104 fragment (**4a** or **4e**), we proposed four candidate compounds of the C79–C104 fragment **2a**–**2d**. We next synthesized **2a** and **2b** (**2a** in the preceding article) by a Julia–Kocienski olefination and **2c** and **2d** by a Wittig reaction, respectively. Finally, by comparing the ^{13}C NMR chemical shifts of natural symbiodinolide (**1**) with those of the synthetic products **2a**–**2d**, the stereostructure of the C79–C104 fragment of **1** was reassigned to be that depicted in **2b**.

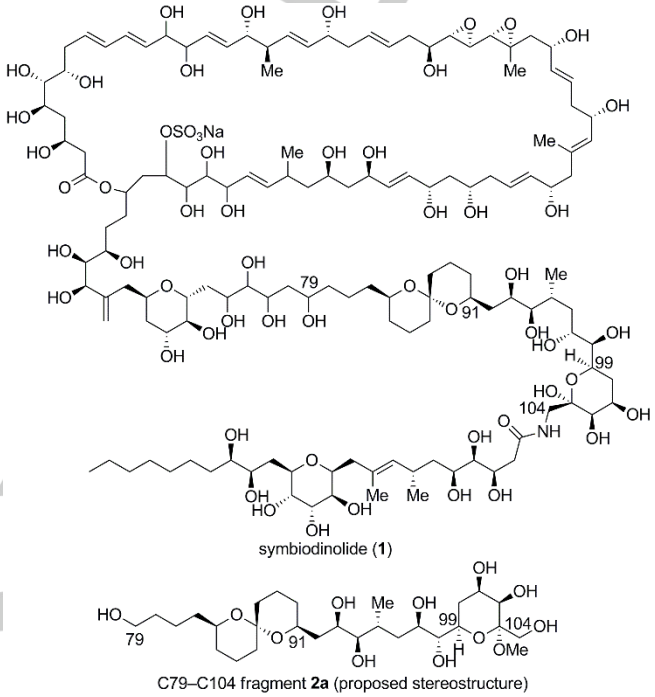

Figure 1. Structures of symbiodinolide (**1**) and the proposed C79–C104 fragment **2a**.

Introduction

In the preceding article,[1] we described the stereoselective synthesis of the C79–C104 fragment **2a** bearing the originally proposed stereochemistry of symbiodinolide (**1**, Figure 1). In addition, we discussed comparison of the ^{13}C NMR chemical shifts between the natural product and the synthetic **2a**, which indicated that the stereostructure of the C91–C99 carbon chain domain of **1** should be reinvestigated. In this article, we report our synthetic approach toward the stereochemical elucidation of the C91–C99 moiety, which led to the stereostructural reassignment of the C79–C104 fragment of symbiodinolide (**1**).

Results and Discussion

Strategy for the stereostructural elucidation of the C79–C104 fragment

In the C91–C99 moiety, there are seven stereogenic centers. Therefore, the number of the possible diastereomers of this domain is $2^6 = 64$.[2] If we could synthesize all 64 possible diastereomers corresponding to the C79–C104 fragment, we could next compare the NMR data between natural symbiodinolide (**1**) and the synthesized products, and then elucidate the stereostructure of the C79–C104 fragment. This approach toward the configurational determination of this moiety is undoubtedly reliable, however, the supply of 64 possible diastereomers by chemical synthesis would require a substantial amount of work. Therefore, we deeply considered more efficient and practical method for the structural elucidation of the C79–C104 fragment. After the consideration, we decided to divide the C79–C104 fragment **2** into two fragments, C79–C97 fragment **3** and C94–C104 fragment **4** (Scheme 1). With regard to the C79–C97 fragment **3**, there are three stereocenters in the carbon chain portion (C93, C94, and C95), therefore, the number of the possible diastereomers of this fragment is eight. We planned to synthesize these eight diastereomers in a stereodivergent manner. If we could obtain all eight diastereomers, we would propose the candidate compound possessing the stereochemistry corresponding to the natural product by comparing the NMR data between natural symbiodinolide (**1**) and the supplied eight diastereomers. Since three stereogenic centers are involved in the acyclic portion of the C94–C104 fragment **4** (C95, C97, and C98), there are also eight possible diastereomers of this fragment. In a similar way to the case of the C79–C97

[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)

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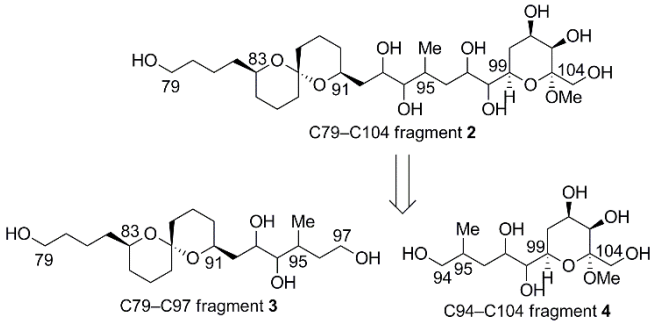
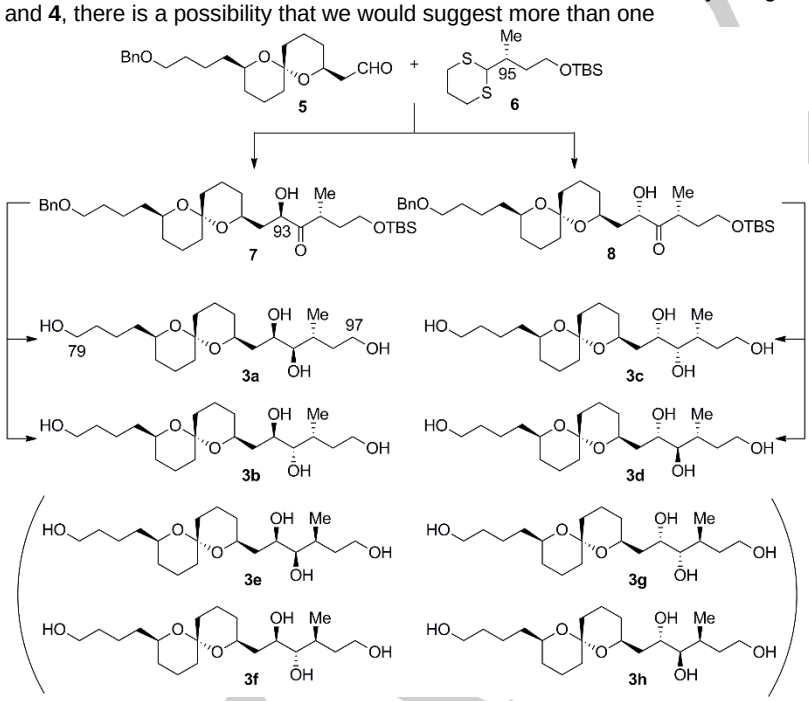


Scheme 1. Strategy for the stereostructural elucidation of **2**.

fragment **3**, the NMR data comparison between the natural product and the eight synthetic products would submit the C94–C104 candidate compound. Because the chiral center at the C95 position is contained in both the C79–C97 fragment **3** and the C94–C104 fragment **4**, the relative stereostructures of **3** and **4** could be connected by the C95 stereochemistry. Finally, we could propose the relative configuration of the C79–C104 fragment **2**. At the stage of the structural determination of each fragment **3** and **4**, there is a possibility that we would suggest more than one candidate compound for **3** and **4**, respectively, because there would be no significant difference in the NMR data among the diastereomers for each of **3** and **4**. In that case, we would synthesize possible diastereomers of the C79–C104 fragment **2** which would come from the combination of the stereostructures of **3** and **4**. Furthermore, comparing the NMR data of these synthetic products with those of natural symbiodinolide (**1**) would establish the stereostructure of the C79–C104 fragment **2**.

Stereodivergent synthetic plan of the C79–C97 fragment

Our stereodivergent synthetic plan of eight possible diastereomers of the C79–C97 fragment **3a**–**3h** is outlined in Scheme 2.[3] Two α-hydroxy ketones **7** and **8**, which have the epimeric relationship at the C93 position with each other, could be synthesized by addition of dithiane **6** to aldehyde **5**. Diastereoselective reduction of the protected compound, which could be prepared from the alcohol **7**, under the control of a Felkin–Anh model[4] effected by the C93 stereogenic center would afford *syn*-diol **3a**. In contrast, chelation-controlled diastereoselective reduction of **7** would provide *anti*-diol **3b**. In the similar way, *syn*-diol **3c** and *anti*-diol **3d** could be synthesized from α-hydroxy ketone **8**. The other four possible diastereomers **3e**–**3h**, which are the C95-epimers of **3a**–**3d**, could be supplied by using the enantiomer of the dithiane **6** as a coupling precursor.

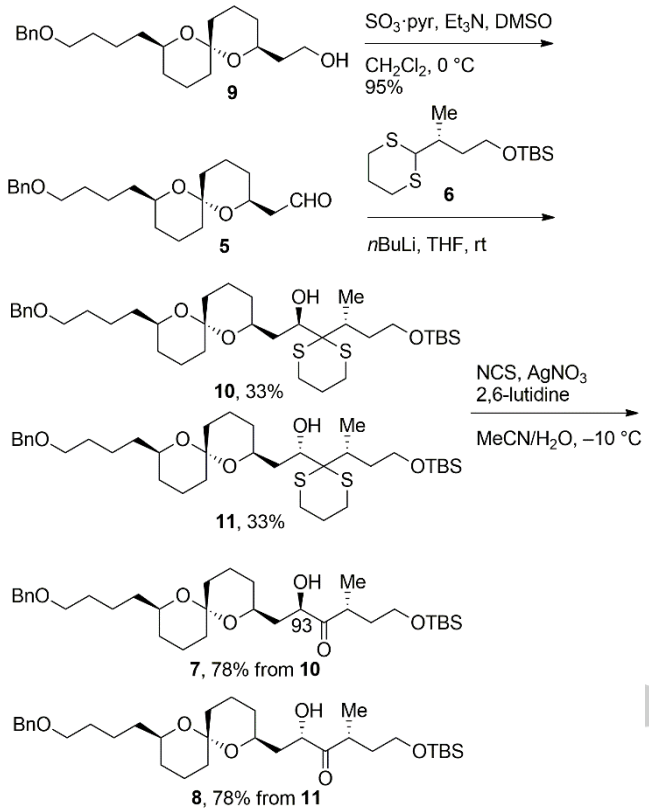


Scheme 2. Stereodivergent synthetic plan of **3a**–**3h**. Bn = benzyl, TBS = *tert*-butyldimethylsilyl.

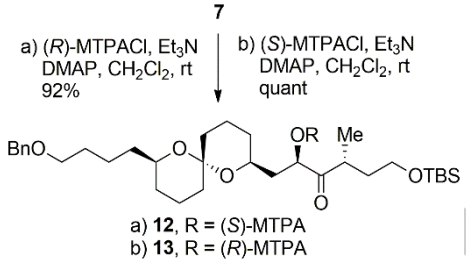
Synthesis of 3a–3d

We first examined the synthesis of the C79–C97 fragment **3a**. Alcohol **9**, which was reported in the preceding paper,[1] was oxidized with SO_3·pyr[5] to give aldehyde **5** (Scheme 3). Deprotonation of dithiane **6**[6] with *n*BuLi and subsequent reaction with the aldehyde **5** furnished the desired two alcohols **10** and **11** in 33% yields, respectively. Hydrolysis of the dithiane moieties of **10** and **11** with *N*-chlorosuccinimide (NCS)/$AgNO_3$/2,6-lutidine[7] provided α-hydroxy ketones **7** and **8**.[8] The absolute configuration at the C93 position of **7** was determined by the modified Mosher method.[9] Thus, treatment of **7** with α-methoxy-β-(trifluoromethyl)phenylacetyl chloride (MTPACl)/Et_3N/4-dimethylaminopyridine (DMAP) yielded MTPA esters **12** and **13** (Scheme 4). The chemical shift differences ($\Delta\delta_{S-R}$) of **12** and **13** in the ^{1}H NMR data were calculated and the results are summarized in Figure 2. The signs at the left side of the C93

position were positive and those at the right side were negative. Therefore, the absolute configuration at the C93 position of **7** was elucidated.



Scheme 3. Synthesis of **7** and **8**. pyr = pyridine, DMSO = dimethylsulfoxide, THF = tetrahydrofuran, rt = room temperature, NCS = *N*-chlorosuccinimide.



Scheme 4. Synthesis of **12** and **13** for the stereochemical determination. MTPA =α-methoxy-β-(trifluoromethyl)phenylacetyl, DMAP = 4-dimethylaminopyridine, quant = quantitative.

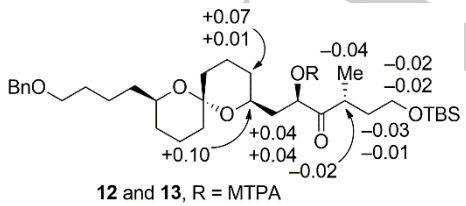
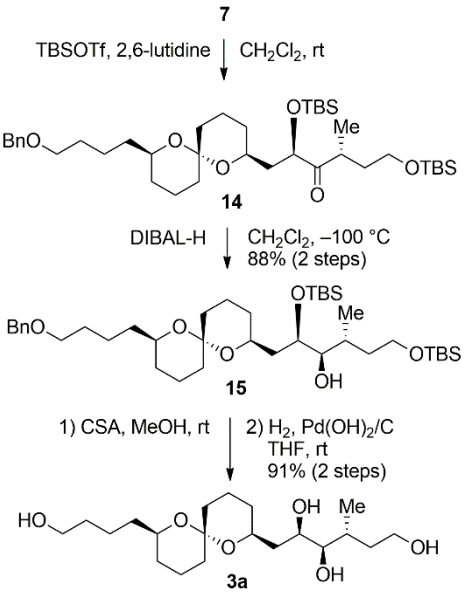


Figure 2. Chemical shift differences ($\Delta\delta_{S-R}$) of **12** and **13**.

After the alcohol **7** was converted to *tert*-butyldimethylsilyl (TBS) ether **14**, we examined the diastereoselective reduction of **14** (Scheme 5). As shown in Table 1, reduction of **14** with $NaBH_4$ proceeded smoothly at –78 °C to 0 °C, however, the diastereomeric ratio of the desired alcohol **15** and the undesired alcohol **16** was 1.2 to 1 (entry 1).[10] Changing the reducing reagent to L-Selectride, more bulky reagent, decreased both of the chemical yield and the diastereomeric ratio, and the starting material **14** was recovered in 69% yield (entry 2). When we treated **14** with diisobutylaluminum hydride (DIBAL-H) at –100 °C, we could obtain **15** quantitatively as a single diastereomer (entry 3). The stereochemical outcome of the formation of **15** could be rationalized by the Felkin–Anh model[4] induced by the C93 configuration. By using the conditions of entry 3, the alcohol **15** was obtained in 88% yield in two steps of TBS protection and DIBAL-H reduction, as described in Scheme 5. Finally, removal of two TBS moieties of **15** with camphorsulfonic acid (CSA) and the benzyl group by the hydrogenation conditions furnished the tetraol **3a**.



Scheme 5. Synthesis of **3a**. Tf = trifluoromethanesulfonyl, DIBAL-H = diisobutylaluminum hydride, CSA = camphorsulfonic acid.

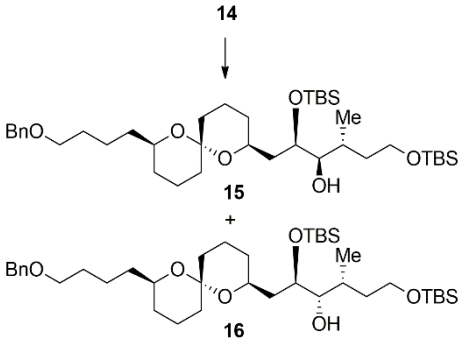


Table 1. Diastereoselective reduction of **14**.

Entry	Conditions	Yield[a]	Ratio (**15**:**16**)[b]
1	$NaBH_4$, MeOH, –78 to 0 °C	quant	1.2:1
2[c]	L-Selectride, CH_2Cl_2, –78 to 0 °C	25%	1:3.2
3	DIBAL-H, CH_2Cl_2, –100 °C	quant	>20:1

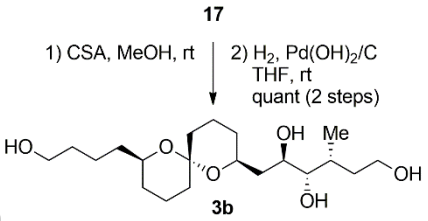
[a] Isolated yield. [b] Based on the isolation. [c] 69% Recovery of **14**.

We next investigated the diastereoselective reduction of the α-hydroxy ketone **7** leading to *anti*-diol **17** and further transformation to the tetraol **3b**. As shown in Table 2, the chelation-controlled reduction of **7** with $Zn(BH_4)_2$[11] provided the expected *anti*-diol **17** and *syn*-diol **18** at a 1.6:1 diastereomeric ratio in 87% combined yield (entry 1). This unsatisfactory result of the diastereoselectivity prompted us to explore the use of a chelating reagent as an additive. After the investigation of reaction conditions, it was proven that the use of L-Selectride as a reducing reagent and $ZnCl_2$ as a chelating reagent was effective[12] and the diol **17** was obtained in 83% yield at a 9.4:1 diastereomeric ratio (entry 2). When the reaction was carried out at –100 °C to 0 °C, the chemical yield and the diastereoselectivity were improved to 86% and >20:1, respectively (entry 3). The TBS and benzyl protective groups of **17** were removed to give the tetraol **3b** quantitatively in two steps (Scheme 6).[13]

Table 2. Diastereoselective reduction of **7**.

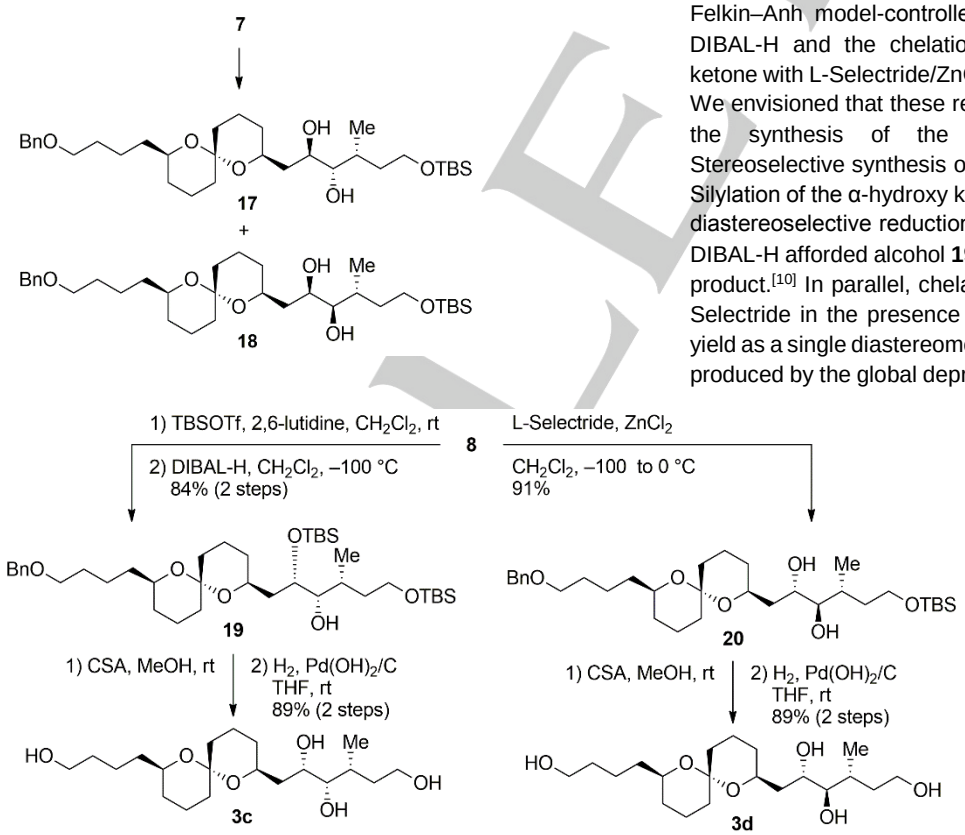
Entry	Conditions	Yield[a]	Ratio (**17**:**18**)[b]
1	$Zn(BH_4)_2$, Et_2O, –78 to 0 °C	87%	1.6:1
2	L-Selectride, $ZnCl_2$, CH_2Cl_2, –78 to 0 °C	83%	9.4:1
3	L-Selectride, $ZnCl_2$, CH_2Cl_2, –100 to 0 °C	86%	>20:1

[a] Isolated yield. [b] Based on the isolation.



Scheme 6. Synthesis of **3b**.

From the results of the synthesis of **3a** and **3b**, it was found that we could synthesize the C93,94-*syn*-diol and the *anti*-diol by the Felkin–Anh model-controlled reduction of α-siloxy ketone with DIBAL-H and the chelation-controlled reduction of α-hydroxy ketone with L-Selectride/$ZnCl_2$, respectively and stereoselectively. We envisioned that these reaction conditions could be applied to the synthesis of the other target molecules **3c**–**3h**. Stereoselective synthesis of **3c** and **3d** is depicted in Scheme 7. Silylation of the α-hydroxy ketone **8** with TBSOTf and subsequent diastereoselective reduction of the resulting α-siloxy ketone with DIBAL-H afforded alcohol **19** in 84% yield in two steps as the sole product.[10] In parallel, chelation-controlled reduction of **8** with L-Selectride in the presence of $ZnCl_2$[12] gave *anti*-diol **20** in 91% yield as a single diastereomer. Finally, the tetraols **3c** and **3d** were produced by the global deprotection of **19** and **20**, respectively.[14]

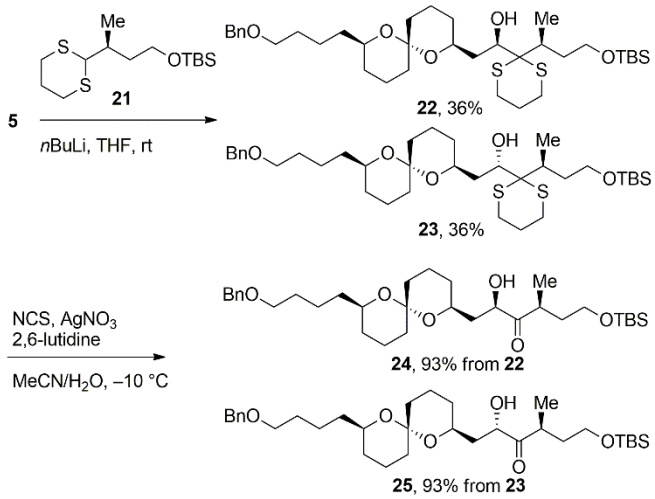


Scheme 7. Synthesis of **3c** and **3d**.

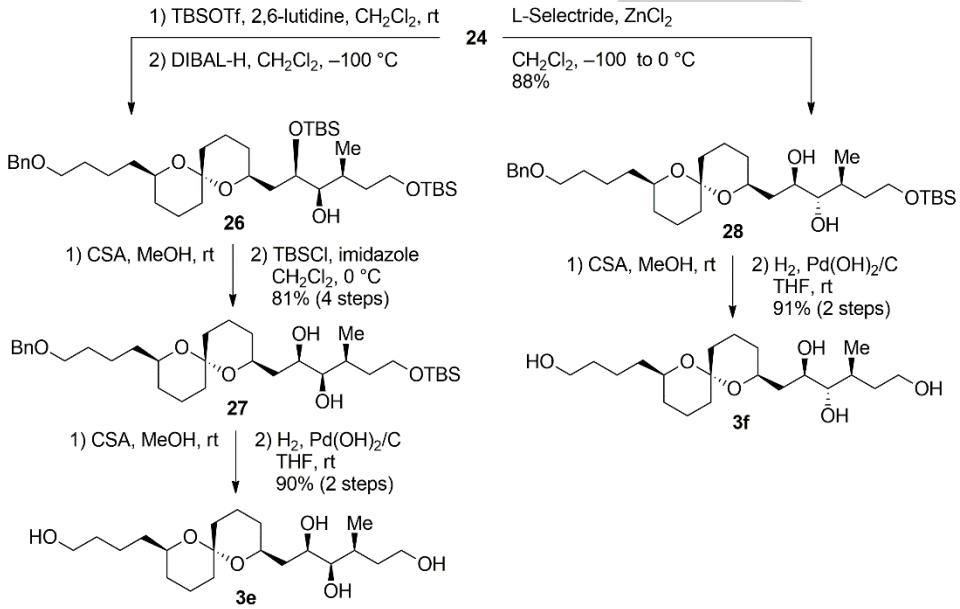
Synthesis of 3e–3h

Having synthesized four possible diastereomers **3a**–**3d** with the (*R*)-configuration at the C95 position, we next tried to synthesize the other four possible diastereomers **3e**–**3h**, the C95-epimers of **3a**–**3d**, by using dithiane **21**[6] and the similar transformation to that for **3a**–**3d**. Thus, coupling of the aldehyde **5** and the dithiane **21** with *n*BuLi gave alcohols **22** and **23** in 36% yields, respectively (Scheme 8). Treatment of **22** and **23** with NCS/$AgNO_3$/2,6-lutidine in aqueous MeCN[7] afforded α-hydroxy ketones **24** and **25**.

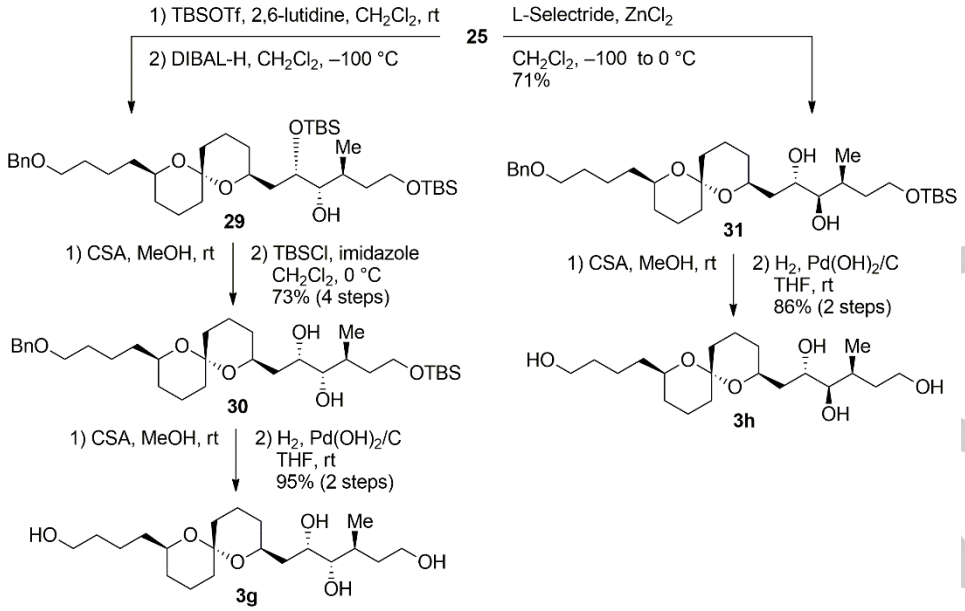
Synthetic transformation from **24** to **3e** and **3f** is illustrated in Scheme 9. Protection of **24** with TBSOTf followed by diastereoselective reduction with DIBAL-H afforded alcohol **26** as a single diastereomer. Removal of the two TBS moieties of **26** and selective silylation of the primary alcohol provided diol **27**,[15,16] which was deprotected to furnish the tetraol **3e**. Treatment of the α-hydroxy ketone **24** with L-Selectride/$ZnCl_2$[11] afforded *anti*-diol **28** in 88% yield as the sole diastereomer.[10] Removal of the TBS and benzyl protective groups of **28** gave the tetraol **3f**. Synthesis of **3g** and **3h**, which are the C93-epimers of **3e** and **3f**, is shown in Scheme 10. The alcohol **25** was transformed to diol **30**[10] by the following four-step sequence: (1) TBS protection, (2) diastereoselective reduction with DIBAL-H, (3) deprotection of the bis-TBS ether, and (4) selective TBS protection of the primary alcohol. Removal of the protective groups of **30** afforded the tetraol **3g** in 95% in two steps. The α-hydroxy ketone **25** was reacted with L-Selectride/$ZnCl_2$[12] to produce *anti*-diol **31**,[10] which was converted to the tetraol **3h** by the deprotection.



Scheme 8. Synthesis of **24** and **25**.



Scheme 9. Synthesis of **3e** and **3f**.



Scheme 10. Synthesis of **3g** and **3h**.

Relative configuration of the C79–C97 fragment

With all of the eight possible diastereomers of the C79–C97 fragment **3a**–**3h** in hand, these were subjected to the 2D NMR analysis. Figure 3 displays graphically deviations of the ^{13}C NMR chemical shifts at the C91, C93, C94, and C95 positions between symbiodinolide (**1**) and the synthetic **3a**–**3h**.[17] From the results of Figure 3, it was found that the chemical shift characteristics of the two diastereomers **3a** and **3f** were more similar to those of the natural product than those of the other six diastereomers. Therefore, we judged the relative configuration of the C79–C97 fragment to be that described in **3a** or **3f**.

Figure 3. Differences of the ^{13}C NMR chemical shifts between natural symbiodinolide (**1**) and the synthesized products **3a**–**3h** ($\Delta\delta = \delta_1 - \delta_3$ in ppm). The x- and y-axes represent the carbon number and $\Delta\delta$, respectively.

Synthesis of 4a–4d

There are eight possible diastereomers of the C94–C104 fragment as shown in Figure 4. As in the case of the C79–C97 fragment, we investigated the stereodivergent synthesis of all possible diastereomers **4a**–**4h**. First, the hexaol **4a** was synthesized through the removal of *p*-methoxybenzyl (PMB) group by hydrogenation and acetonide and TBS moieties with CSA in MeOH from **32**, which was reported in the preceding

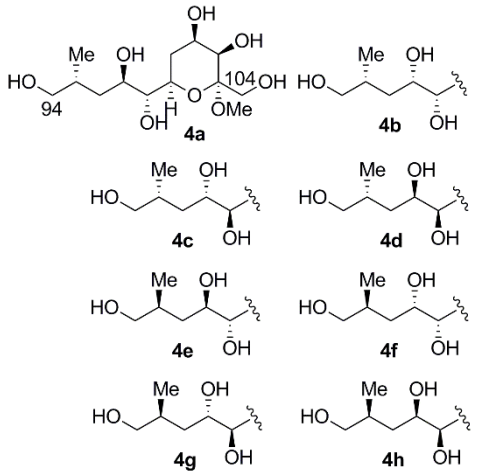
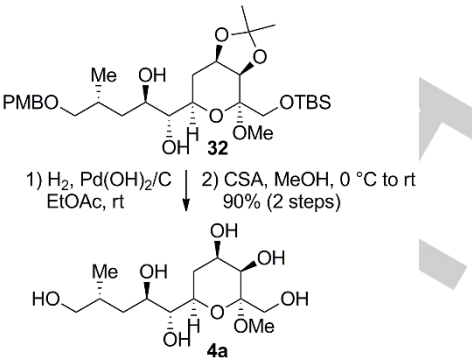


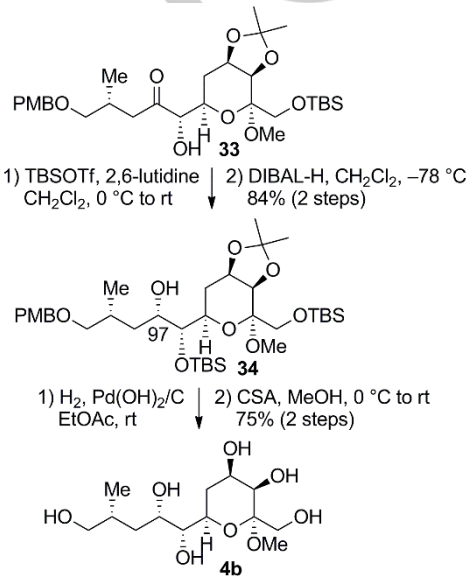
Figure 4. Eight possible diastereomers of the C94–C104 fragment **4a**–**4h**.

article (Scheme 11).[1] The hexaol **4b**, which is the C97-epimer of **4a**, was synthesized by utilizing the diastereoselective reduction of the α-siloxy ketone. Thus, after alcohol **33**[1] was silylated to give the corresponding TBS ether, treatment of the α-siloxy ketone with DIBAL-H provided the desired alcohol **34** in 84% yield in two steps as a single diastereomer (Scheme 12).[10] Diastereoselective reduction by a Felkin–Anh model[4] with DIBAL-H, which was utilized in the synthesis of the C79–C97 fragment, was also effective for introduction of the stereogenic center at the C97 position. Complete deprotection of **34** furnished the hexaol **4b** in 75% yield in two steps.

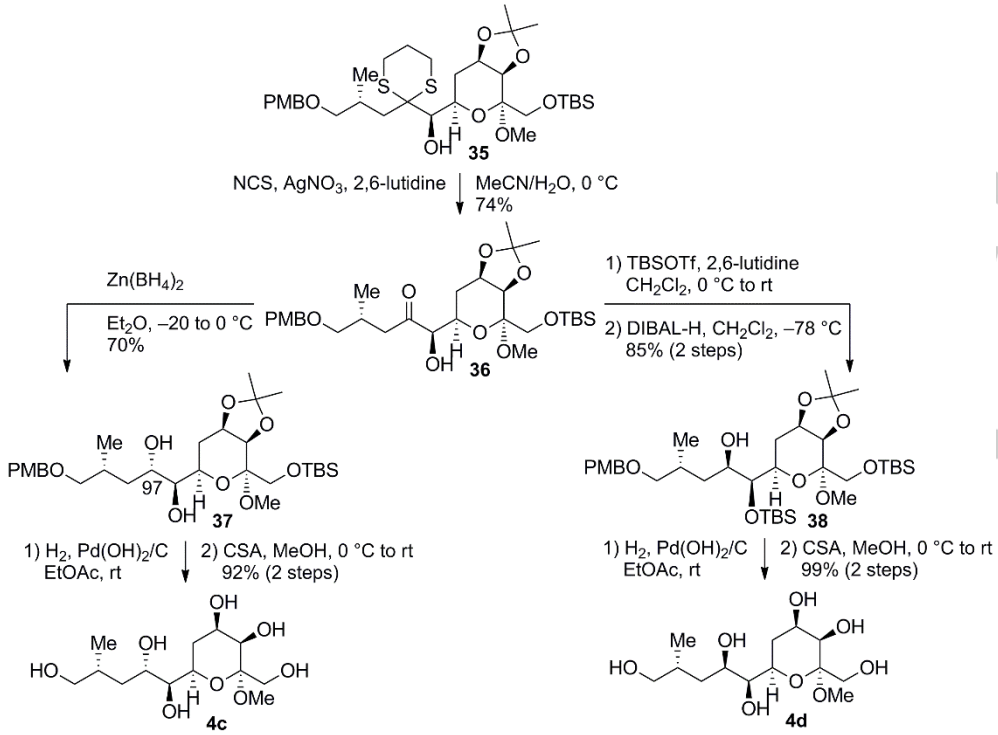
We next tried to synthesize the hexaols **4c** and **4d**, which are the C98-epimers of **4a** and **4b**. As shown in Scheme 13, hydrolysis of the dithiane moiety[7] of **35**[1] followed by chelation-controlled diastereoselective reduction of α-hydroxy ketone **36** with $Zn(BH_4)_2$[11] provided the desired *anti*-diol **37**.[18] In contrast, the α-siloxy ketone derived from **36** was reduced with DIBAL-H to yield alcohol **38** as a single diastereomer.[10] Finally, deprotection of **37** and **38** afforded the hexaols **4c** and **4d**, respectively.



Scheme 11. Synthesis of **4a**. PMB = *p*-methoxybenzyl.



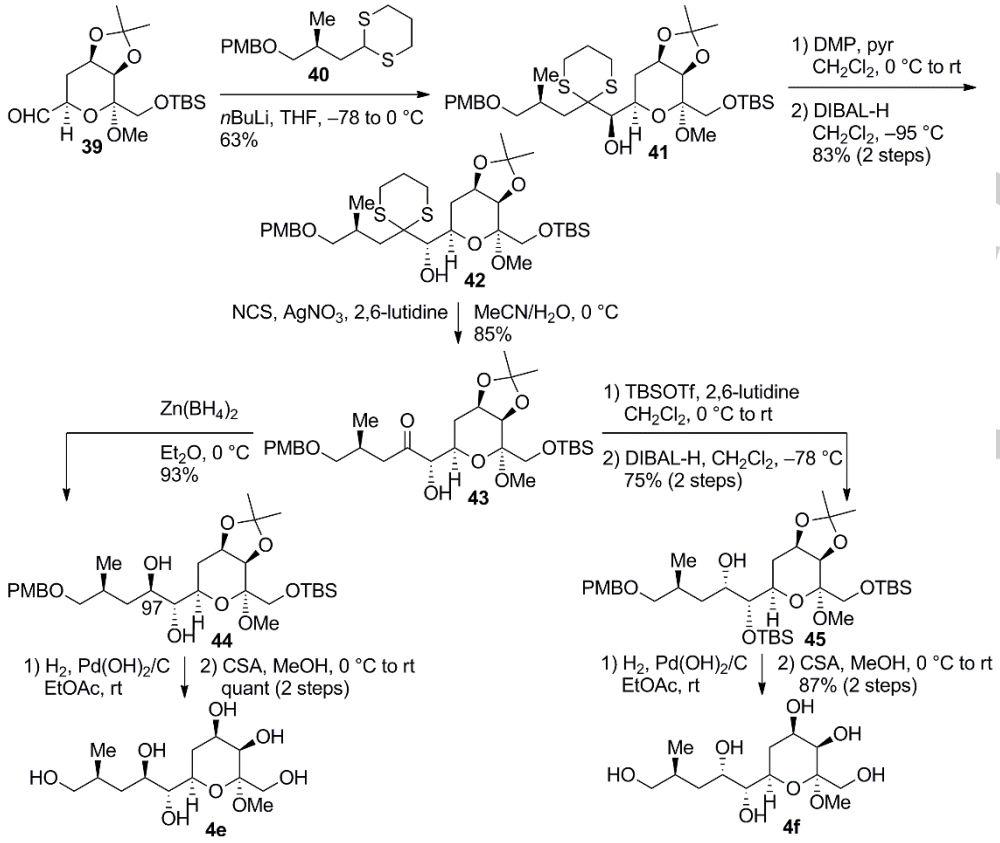
Scheme 12. Synthesis of **4b**.



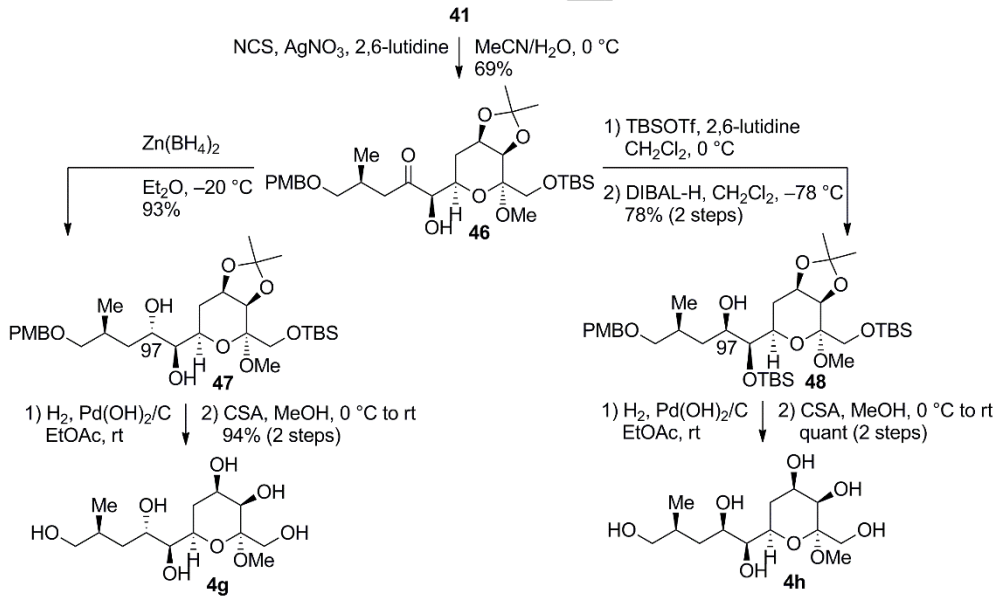
Scheme 13. Synthesis of **4c** and **4d**.

Synthesis of 4e–4h

We next examined the synthesis of **4e**–**4h**, which are the C95-epimers of **4a**–**4d**. Stereoselective synthesis of **4e** and **4f** is described in Scheme 14. Aldehyde **39**[1] was reacted with the anion prepared from dithiane **40**[19] to produce alcohol **41** as a single diastereomer.[10] Oxidation of **41** with Dess–Martin periodinane (DMP)[20], reduction with DIBAL-H, and hydrolysis of the dithiane group[7] afforded α-hydroxy ketone **43**, which is the common synthetic intermediate toward **4e** and **4f**. The α-hydroxy ketone **43** was derivatized to diol **44**[21] by chelation-controlled reduction with $Zn(BH_4)_2$[11] and alcohol **45**[10] by silylation and subsequent Felkin–Anh type[4] reduction with DIBAL-H, stereodivergently and stereoselectively. Global removal of the protective groups of **44** and **45** gave the hexaols **4e** and **4f**. The hexaols **4g** and **4h** were synthesized in the similar sequence to that toward **4e** and **4f**. Thus, the dithiane **41** was hydrolyzed to give α-hydroxy ketone **46**.[7] The key synthetic intermediate **46** was transformed to the tetraols **4g** and **4h** by the diastereoselective reduction with the appropriate reagent, $Zn(BH_4)_2$ and DIBAL-H, and subsequent complete deprotection.[22]



Scheme 14. Synthesis of **4e** and **4f**. DMP = Dess–Martin periodinane.



Scheme 15. Synthesis of **4g** and **4h**.

Relative configuration of the C94–C104 fragment

Having completed stereodivergent synthesis of all of the eight possible diastereomers of the C94–C104 fragment **4a**–**4h**, as in the case of the C79–C97 fragment, we submitted these synthetic products to the 2D NMR analysis and compared their ^{13}C NMR characteristics with those of natural symbiodinolide (**1**). Deviations of the ^{13}C NMR chemical shifts at the C95, C97, C98, and C99 positions between the natural product and the synthetic diastereomers **4a**–**4h** are depicted graphically in Figure 5.[17] As a result of the comparison among all of the eight diastereomers, the

chemical shift differences of **4a** and **4e** were found to be smaller than those of the other six diastereomers. Therefore, we judged the relative stereochemistry of the C94–C104 fragment to be that drawn in **4a** or **4e**.

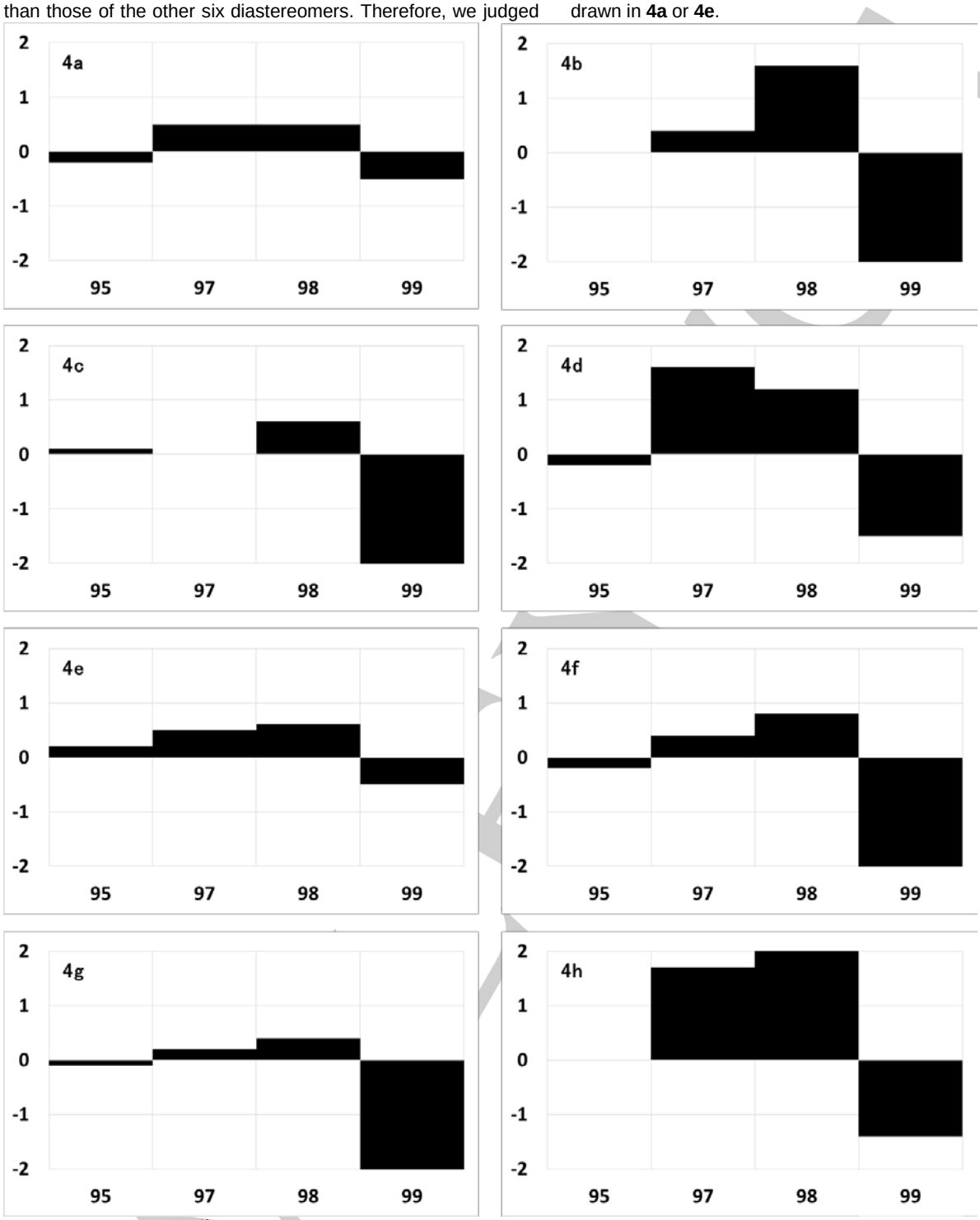
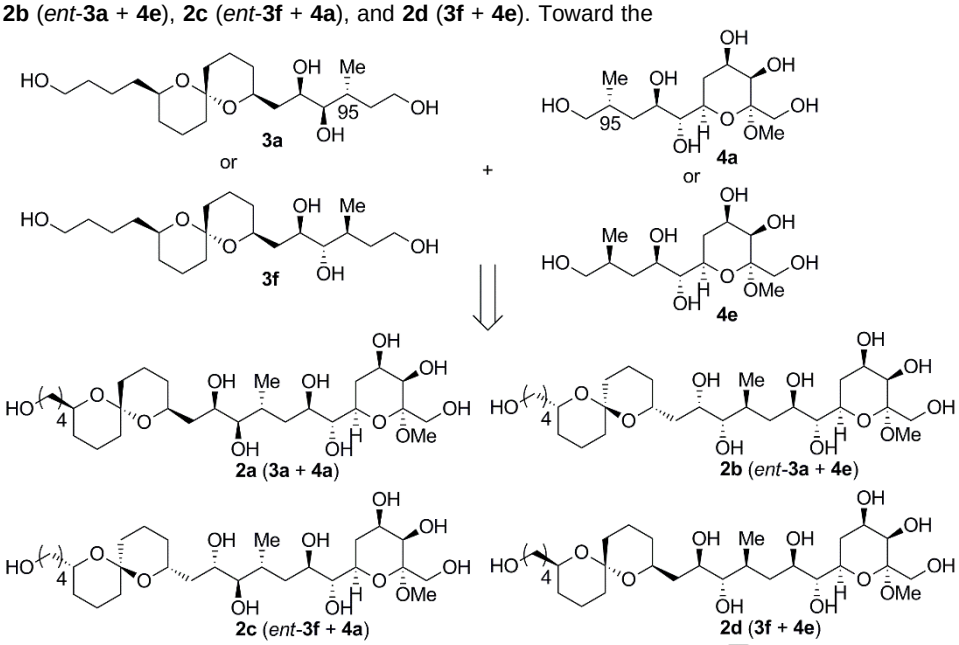


Figure 5. Differences of the ^{13}C NMR chemical shifts between natural symbiodinolide (**1**) and the synthesized products **4a**–**4h** ($\Delta\delta = \delta_1 - \delta_4$ in ppm). The x- and y-axes represent the carbon number and $\Delta\delta$, respectively.

Possible stereostructures of the C79–C104 fragment

We could propose the candidate compounds for each C79–C97 fragment (**3a** and **3f**) and C94–C104 fragment (**4a** and **4e**) by the stereodivergent synthesis of all possible diastereomers and comparison of their ^{13}C NMR chemical shifts with those of the natural product (Scheme 16). Therefore, by connecting the

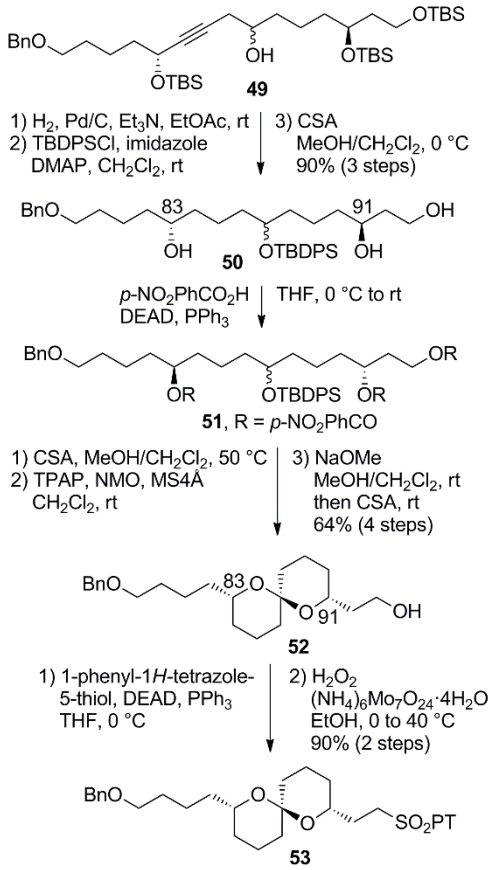
relative configuration of these two fragments through the C95 stereogenic center, the possible relative stereostructures of the C79–C104 fragment were suggested as shown in **2a** (**3a** + **4a**), **2b** (*ent*-**3a** + **4e**), **2c** (*ent*-**3f** + **4a**), and **2d** (**3f** + **4e**). Toward the stereostructural elucidation of the C79–C104 fragment, we next tried to synthesize these four diastereomers **2a**–**2d** in an unified manner.[23]



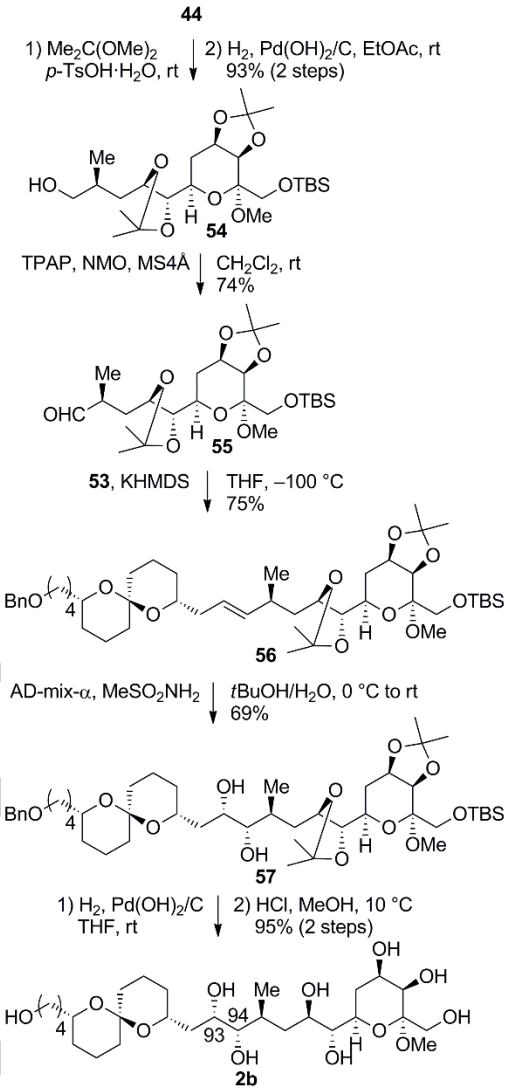
Scheme 16. Four possible diastereomers of the C79–C104 fragment **2a**–**2d**.

Synthesis of 2b–2d

We first examined the stereocontrolled synthesis of alcohol **52** bearing the enantiomeric relationship at the spiroacetal C83–C91 moiety of **3a** and **3f**, which is called for the synthesis of **2b** and **2c**. We tried to synthesize **52** by the Mitsunobu reaction[24] with stereoinversion from the compound prepared in the preceding paper. Thus, hydrogenation of alkyne **49**[1] followed by protection as the *tert*-butyldiphenylsilyl (TBDPS) ether and selective removal of the three TBS groups with CSA afforded triol **50** in 90% yield in three steps (Scheme 17). Two stereochemistries at the C83 and C91 positions of **50** were inverted under the Mitsunobu conditions[24] with *p*-nitrobenzoic acid/ diethyl azodicarboxylate (DEAD)/PPh_3[25] to provide tris-*p*-nitrobenzoate **51**. Deprotection of the TBDPS ether **51** with CSA and oxidation of the resulting alcohol with tetra-*n*-propylammonium perruthenate (TPAP)[26] furnished the corresponding ketone. Hydrolysis of the three *p*-nitrobenzoate groups with NaOMe and subsequent spiroacetalization of the resulting trihydroxyketone with CSA were performed in one-pot to produce the desired product **52** in 64% yield in four steps as a single diastereomer. Stereochemical inversion in the Mitsunobu reaction from **50** to **51** was confirmed at this stage. Thus, the ^1H and ^{13}C NMR data of **52** were identical to those of the alcohol **9**,[1] which is the enantiomer of **52**, and the specific rotation of **52** was $[\alpha]_D^{23}$ –52.4 (*c* 1.02, $CHCl_3$).[27] The optical purity (>95%) of **52** was determined by derivatization of **52** to its (*S*)- and (*R*)-MTPA esters and comparison of their ^1H NMR spectra. The alcohol **52** was transformed to 1-phenyl-1*H*-tetrazol-5-yl (PT)-sulfone **53** by sulfenylation and subsequent oxidation with H_2O_2/Mo^{VI}.[28]



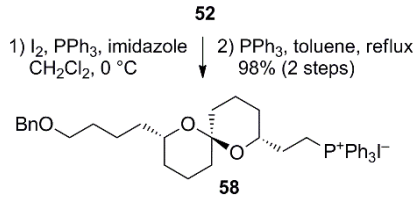
Scheme 17. Synthesis of **53**. TBDPS = *tert*-butyldiphenylsilyl, DEAD = diethyl azodicarboxylate, TPAP = tetra-*n*-propylammonium perruthenate, NMO = *N*-methylmorpholine oxide, MS = molecular sieves, PT = 1-phenyl-1*H*-tetrazol-5-yl.



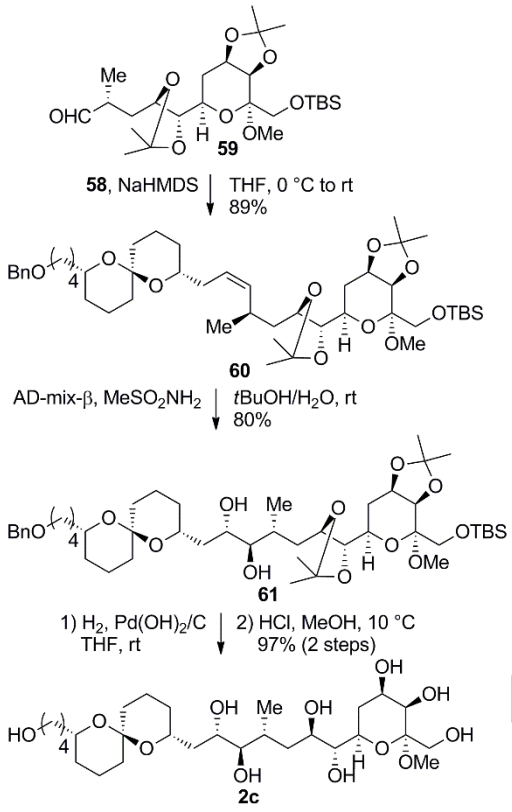
Scheme 18. Synthesis of **2b**. KHMDS = potassium hexamethyldisilazide.

With the coupling precursor **53** in hand, we next tried to synthesize the C93,94-*syn*-diol **2b** by using the similar transformation to that used for the synthesis of **2a**, the combination of a Julia–Kocienski olefination and Sharpless asymmetric dihydroxylation.[1] Acetonide protection of the diol **44** and removal of the PMB moiety gave alcohol **54**, which was oxidized to aldehyde **55** (Scheme 18). The PT-sulfone **53** and the aldehyde **55** were successfully connected via Julia–Kocienski olefination[29] under the conditions optimized in the synthesis of **2a**[1] to give the desired (*E*)-alkene **56** in 75% yield as the sole diastereomer. The alkene **56** was subjected to the Sharpless asymmetric dihydroxylation[30] with AD-mix-α to afford *syn*-diol **57** with the desired stereochemistries.[10] Debenzylation of **57** by hydrogenation and subsequent removal of the acetonide and TBS portions with HCl in MeOH furnished **2b**.

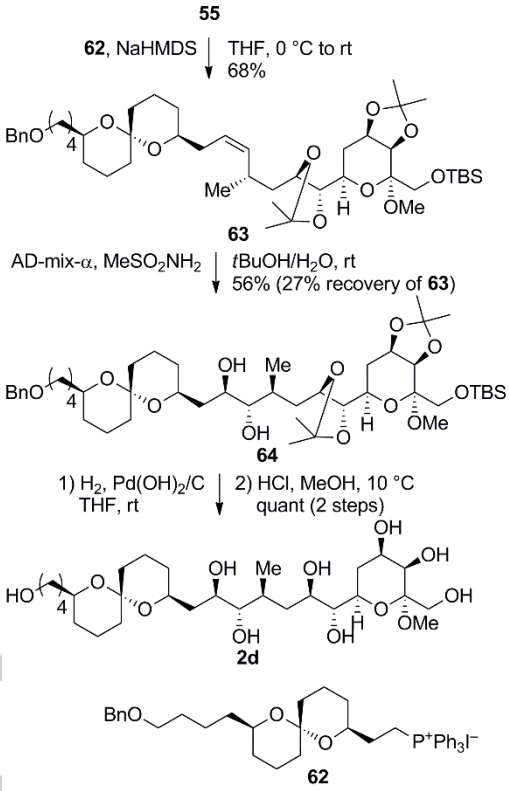
Remaining task was the synthesis of **2c** and **2d** possessing the C93,94-*anti*-configurations. We planned to introduce the C93,94-*anti*-stereochemistries of **2c** and **2d** by dihydroxylation of the corresponding (*Z*)-alkenes. Phosphonium salt **58**, which is the coupling precursor for the synthesis of **2c**, was prepared from the alcohol **52** by iodination followed by reaction with PPh_3 (Scheme 19). Deprotonation of the phosphonium salt **58** with sodium hexamethyldisilazide (NaHMDS) and subsequent Wittig reaction with the aldehyde **59** were successfully performed to afford the desired (*Z*)-alkene **60** in 89% yield as a single diastereomer (Scheme 20). As a result of detailed investigation on the dihydroxylation of **60**, it was proven that the dihydroxylation of (*Z*)-alkene **60** with AD-mix-β provided the desired *anti*-diol **61** in 80% yield.[10,31] Removal of the benzyl, acetinide, and TBS protective groups of **61** produced **2c** in 97% yield in two steps. Stereoselective synthesis of **2d** is illustrated in Scheme 21. The aldehyde **55** was coupled with phosphonium salt **62**,[32] which is the enantiomer of **58**, to furnish (*Z*)-alkene **63** in 68% yield as the sole diastereomer. Treatment of the alkene **63** with AD-mix-α afforded the desired *anti*-diol **64** in 56% yield along with 27% recovery of the starting material **63**.[10,33] Complete deprotection of **64** produced **2d**, quantitatively.



Scheme 19. Synthesis of **58**.



Scheme 20. Synthesis of **2c**. NaHMDS = sodium hexamethyldisilazide.



Scheme 21. Synthesis of **2d**.

Relative configuration of the C79–C104 fragment

With all of the four suggested diastereomers **2a**–**2d** in hand,[23] we next analyzed their 2D NMR spectra carefully and compared their ^{13}C NMR chemical shifts with those of natural symbiodinolide (**1**). As shown in Figure 6, only the diastereomer **2b** was found to exhibit similar NMR characteristics to those of the natural product.[17] In the case of **2a**, **2c**, and **2d**, significant differences were detected, especially in the C91–C99 carbon chain domain. Therefore, we concluded that symbiodinolide (**1**) has the relative stereostructure in the C79–C104 fragment as represented in **2b**.

Conclusions

Toward the stereostructural reassignment of the C79–C104 fragment of symbiodinolide (**1**), which was suggested in the preceding paper,[1] we have carried out a two-phase approach: (1) stereostructural elucidation of the respective C79–C97 and C94–C104 fragments and (2) stereostructural determination of the C79–C104 fragment by using the results obtained in the first phase. Thus, we first synthesized all of the eight possible diastereomers of the C79–97 fragment **3a**–**3h** by using the dithiane addition to the aldehyde and diastereoselective reduction as the key transformations in the unified route. Comparison of the ^{13}C NMR chemical shifts between the natural **1** and the synthetic **3a**–**3h** proposed **3a** and **3f** to be the candidate compounds of the C79–C97 fragment. Next, all of the eight possible diastereomers of the C94–C104 fragment **4a**–**4h** were stereodivergently synthesized and comparison of their ^{13}C NMR data with those of the natural product led to the proposal of **4a** and **4e** as the candidate compounds of this fragment. In addition, all four possible diastereomers of the C79–C104 fragment **2a**–**2d**, which were raised by the combination of **3a**/**3f** and **4a**/**4e**, were synthesized by the Julia–Kocienski and Wittig olefination and subsequent Sharpless asymmetric dihydroxylation (**2a** in the preceding paper). In the comparison of the ^{13}C NMR chemical shifts between of the natural product and the synthesized products **2a**–**2d**, only the diastereomer **2b** displayed the similar NMR characteristics to those of the natural product. Therefore, the relative configuration of the C79–C104 fragment of symbiodinolide (**1**) was reassigned to be that depicted in **2b**. Our results obtained in this work indicate that the C91–C99 carbon chain portion of **1** does not possess the zigzag conformation,

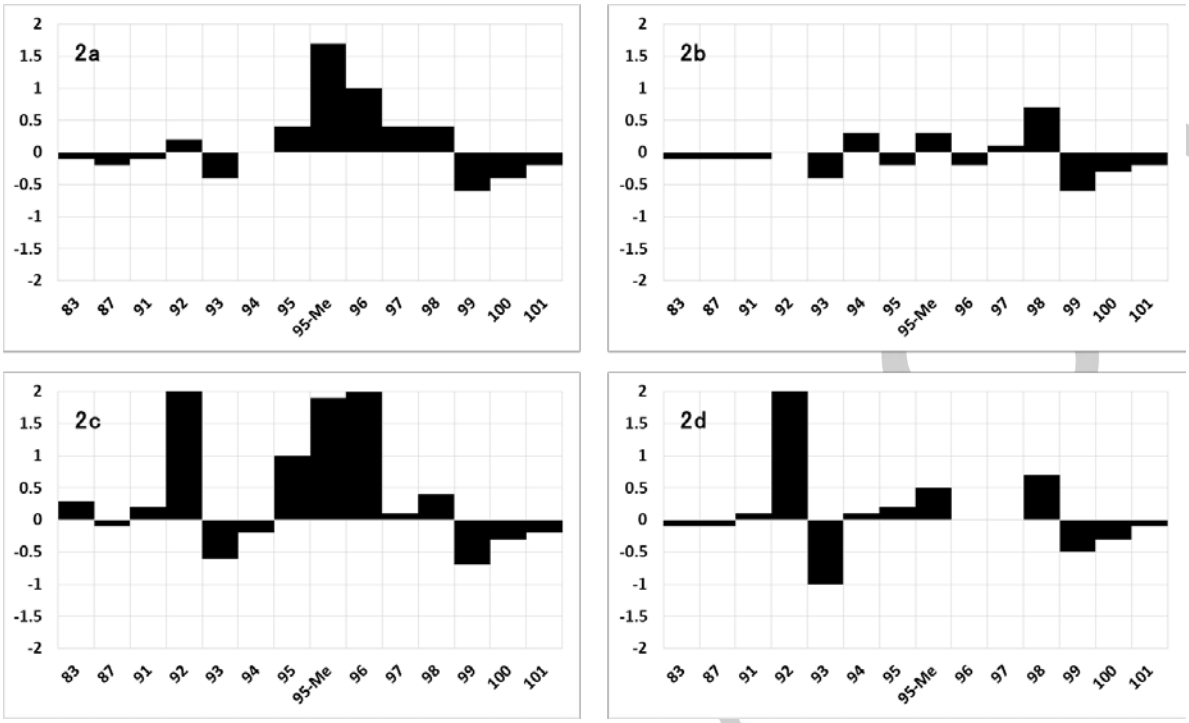


Figure 6. Differences of the ^{13}C NMR chemical shifts between natural symbiodinolide (**1**) and the synthesized products **2a**–**2d** ($\Delta\delta = \delta_1 - \delta_2$ in ppm). The x- and y-axes represent the carbon number and $\Delta\delta$, respectively.

which was proposed in our original report of the structural determination of **1**.[34] Since there are seven stereogenic centers in the C91–C99 carbon chain moiety, the number of the possible diastereomers for this portion is 64. It is noteworthy that the relative stereostructure of the C79–C104 fragment was elucidated by synthesizing only 20 diastereomers instead of 64, that is, eight diastereomers possible for the C79–C97 fragment, eight diastereomers possible for the C94–C104 fragment, and four diastereomers possible for the C79–C104 fragment. Further synthetic study toward the complete structural elucidation of symbiodinolide (**1**) is currently underway and will be reported in due course.

Experimental Section

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

Acknowledgements

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

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

[2] As mentioned in the preceding article, we judged that the stereochemical determination of the two cyclic domains (C83–C91 and C99–C104) is reasonable and there is no need to synthesize the stereoisomers of these two portions.

[3] For selected recent examples on the stereodivergent synthesis of natural products toward the structural elucidation, see: a) T. Kotaki, T. Shinada, K. Kaihara, Y. Ohfune, H. Numata, *Org. Lett.* **2009**, *11*, 5234–5237; b) B. Sui, E. A.-H. Yeh, D. P. Curran, *J. Org. Chem.* **2010**, *75*, 2942–2954; c) S. Tamura, T. Ohno, Y. Hattori, N. Murakami, *Tetrahedron Lett.* **2010**, *51*, 1523–1525; d) D. Urabe, H. Todoroki, K. Masuda, M. Inoue, *Tetrahedron* **2012**, *68*, 3210–3219; e) H. Takamura, H. Wada, M. Ogino, T. Kikuchi, I. Kadota, D. Uemura, *J. Org. Chem.* **2015**, *80*, 3111–3123.

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

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

[6] The enantiomer of **6** is the known compound. See: J. L.-Y. Cheng, M. A. Brimble, *J. Org. Chem.* **2011**, *76*, 9417–9428.

[7] 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.

[8] We obtained **10** and **11** as an inseparable diastereomeric mixture. The α-hydroxy ketones **7** and **8**, transformed from **10** and **11**, were separated by silica gel column chromatography.

[9] I. Ohtani, T. Kusumi, Y. Kashman, H. Kakisawa, *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.

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

[11] 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.

[12] J. Robertson, W. P. Unsworth, S. G. Lamont, *Tetrahedron* **2010**, *66*, 2363–2372.

[13] The stereochemistry at the C94 position of **17**, which was introduced in the reduction of **7**, was determined by the difference of ^{1}H NMR spectra between **3a** and **3b**.

[14] The stereochemistry at the C94 position of **20** was determined by the discrepancy of ^{1}H NMR spectra between **3c** and **3d**.

[15] Actually, we obtained **22** and **23** as an inseparable diastereomeric mixture and proceeded further transformation as the diastereomixture. In the synthesis of **3e** and **3g**, the alcohols **26** and **29** were transformed to **27** and **30** because of the chromatographical separation at this stage. In the synthesis of **3f** and **3h**, two diastereomers were separated at the stage of **28** and **31**.

[16] The stereochemistries at the C93 and C94 positions of **27** were determined because the ^{1}H NMR spectrum of **3e** was different from those of **3f**, **3g**, and **3h**.

[17] See the Supporting Information for details.

[18] The stereochemistry at the C97 position of **37** was determined by the difference of ^{1}H NMR spectra between **4c** and **4d**.

[19] 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.

[20] 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.

[21] The absolute configuration of the resulting C97 stereogenic center of **44** was confirmed by the ^{1}H NMR spectral difference between **4e** and **4f**.

[22] For the stereochemical determination at the C97 position of **48**, see the Supporting Information. The absolute stereochemistry of the C97 sterecenter of **47** was confirmed by the discrepancy of ^{1}H NMR spectra between **4g** and **4h**.

[23] For the synthesis of **2a**, see reference 1.

[24] For reviews on Mitsunobu reaction, see: a) O. Mitsunobu, *Synthesis* **1981**, 1–28; b) K. C. K. Swamy, N. N. B. Kumar, E. Balaraman, K. V. P. P. Kumar, *Chem. Rev.* **2009**, *109*, 2551–2651.

[25] S. F. Martin, J. A. Dodge, *Tetrahedron Lett.* **1991**, *32*, 3017–3020.

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

[27] The alcohol **9**: $[\alpha]_D^{24}$ +50.5 (*c* 1.00, $CHCl_3$).

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

[29] 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.

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

[31] The *anti*-diol, which is the diastereomer of **61**, was obtained in 12% yield. When the alkene **60** was treated with AD-mix-α, the diol **61** and its diastereomer with the C93,94-*anti*-stereochemistries were obtained in 50% and 17% yields, respectively.

[32] The phosphonium salt **62** was prepared from the alcohol **9** by the same transformation as that used from **52** to **58**.

[33] The *anti*-diol, which is the diastereomer of **64**, was obtained in 9% yield. Treatment of the alkene **63** with AD-mix-β gave the diol **64** and its diastereomer with the C93,94-*anti*-configurations in 27% and 16% yields, respectively.

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

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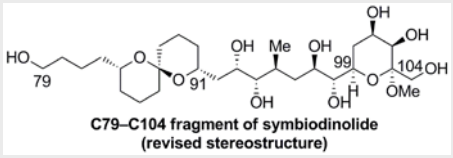

C79–C104 fragment of symbiodinolide
(revised stereostructure)

Structural revision: Stereodivergent synthesis of eight possible diastereomers corresponding to the C79–C97 and C94–C104 fragments resulted in the proposal of two candidate stereostructures, respectively. The synthesis of the four possible diastereomers of the C79–C104 fragment and comparison of their ^{13}C NMR data with those of the natural product allowed stereostructural revision of this fragment of symbiodinolide.

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

Page No. – Page No.

Stereodivergent Synthesis and Stereochemical Reassignment of the C79–C104 Fragment of Symbiodinolide