Tetrahedron Letters 50 (2009) 863–866

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis and structural determination of the C33–C42 fragment of symbiodinolide

Hiroyoshi Takamura [a,*], Yuichiro Kadonaga [a], Yoshi Yamano [b], Chunguang Han [b], Yoko Aoyama [b], Isao Kadota [a,*], Daisuke Uemura [b,c]

[a] Graduate School of Natural Science and Technology, Okayama University, 3-1-1 Tsushimanaka, Okayama 700-8530, Japan
[b] Graduate School of Science, Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-8602, Japan
[c] Faculty of Science and Technology, Keio University, 3-14-1 Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan

ARTICLE INFO

Article history:
Received 20 October 2008
Revised 14 November 2008
Accepted 17 November 2008
Available online 20 November 2008

Keywords:
Polyol macrolide
Symbiodinolide
Absolute configuration
Cross-metathesis degradation
Chemical synthesis

ABSTRACT

Symbiodinolide (**1**) is a polyol macrolide with a molecular weight of 2859 mu. As one of the degradation reactions, cross-metathesis of **2**, which is a methyl ester of **1**, with ethylene was performed to give the C33–C42 degraded fragment **4**. The absolute configuration of **4** was estimated to be (36*S*,40*S*) by Mosher method. Stereoselective synthesis of **4** was achieved in 14 steps from L-aspartic acid. Synthetic bis-(*S*)- and (*R*)-MTPA esters exhibited the spectroscopic data identical with those of bis-(*S*)- and (*R*)-MTPA esters derived from the degraded fragment **4**. Thus, the absolute stereochemistry of **4** was elucidated to be (36*S*,40*S*).

Symbiodinolide (**1**), isolated from the marine dinoflagellate *Symbiodinium* sp. in 2007, is a polyol macrolide with a molecular weight of 2859 mu which exhibits a voltage-dependant N-type Ca^{2+} channel-opening activity at 7 nM and COX-1 inhibitory effect at 2 nM.[1,2] The planar structure and partial stereochemistry of **1** were elucidated by spectroscopic analysis[1] and chemical synthesis.[3] Herein, we describe the structural elucidation and stereocontrolled synthesis of the C33–C42 fragment **4**, a degraded product obtained from **1**, as a part of structural analysis and synthetic study of **1** (Fig. 1).

Olefin cross-metathesis is utilized as one of the efficient degradation methods of natural products.[1,4] In order to obtain the degraded product of **1**, we carried out cross-metathesis with ethylene. Thus, treatment of **1** with Et_3N in MeOH provided the methyl ester **2**, which was then subjected to cross-metathesis with ethylene using Hoveyda-Grubbs 2nd generation catalyst **3**[5] to give the C33–C42 fragment **4** as one of the degraded products (Scheme 1).[6] The planar structure of **4** was confirmed by the analyses of 2D NMR spectra and HR-ESIMS [*m*/*z* 205.1206, Δ +0.2 mmu for $(M+Na)^+$].

The absolute stereochemistry of **4** was determined by Mosher method.[7,8] Figure 2 shows the selected $\Delta\delta_{S-R}$ values of the corresponding bis-(*S*)- and (*R*)-MTPA esters derived from **4** by the standard procedures (MTPACl/Et_3N/DMAP).[9] The signs at the C33, C34, and C35 positions showed negative, and those of the C41 and C42 positions exhibited positive. Therefore, we assigned the absolute configuration of **4** to be (36*S*,40*S*) as shown in Figure 2.

We next examined the stereocontrolled synthesis of (36*S*,40*S*)-diol **4** to confirm the assigned absolute structure (Scheme 2). The synthesis started from L-aspartic acid which was converted to (*R*)-epoxide **5** by the known procedure.[10] The epoxide **5** was reacted with lithium acetylide, prepared from ethyl propiolate and *n*-BuLi, to give homopropargylic alcohol **6** in 96% yield.[11,12] The alcohol **6** was protected with TBSOTf/2,6-lutidine to yield the bis-TBS ether **7**. Conjugate addition of the thiolate anion, derived from thiophenol and NaOMe, provided (*Z*)-α,β-unsaturated ester **8**. Thioether **8** was reacted with MeMgBr and CuI to give (*E*)-α,β-unsaturated ester **9** with complete retention of the olefinic configuration.[13] The observed NOE between H-37 and H-39 clearly indicates the (*E*)-configuration of **9**. Reduction of the ester **9** with DIBALH followed by Parikh–Doering oxidation[14] gave α,β-unsaturated aldehyde **10**. The aldehyde **10** was subjected to asymmetric allylation developed by Keck et al.[15] to give homoallylic alcohol **11** in 41% yield (91% based on recovered starting material) with 82% diastereomeric excess (de).[16] Protection of the alcohol **11** with TBDPSCl/imidazole followed by selective deprotection of the TBS moiety provided alcohol **12**. Treatment of **12** with *o*-nitrophenyl

* Corresponding authors. Tel.: +81 86 251 7839; fax: +81 86 251 7836 (H.T.).
E-mail address: takamura@cc.okayama-u.ac.jp (H. Takamura).

0040-4039/$ - see front matter © 2009 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2008.11.056

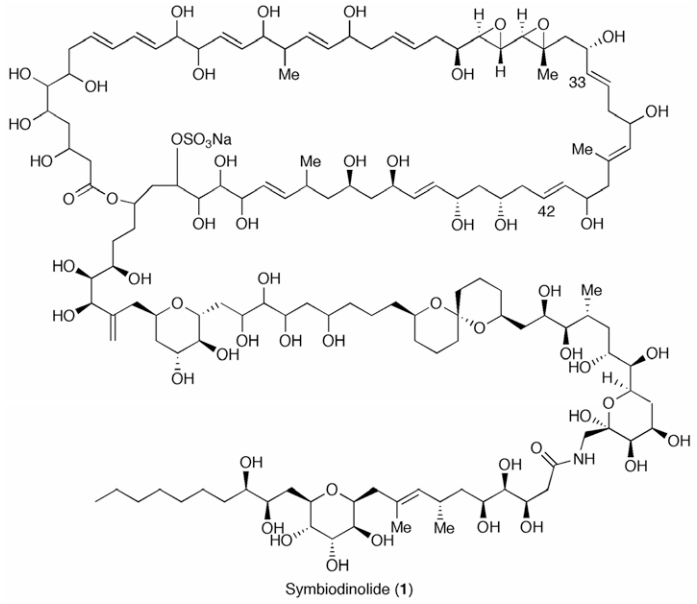
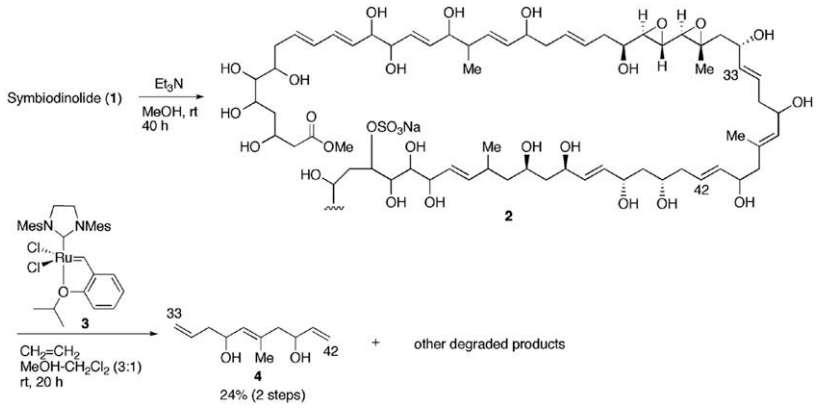


Figure 1. Structure of symbiodinolide (**1**).



Scheme 1. Cross-metathesis degradation with ethylene.

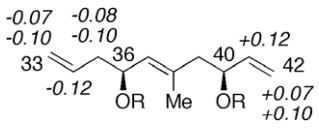
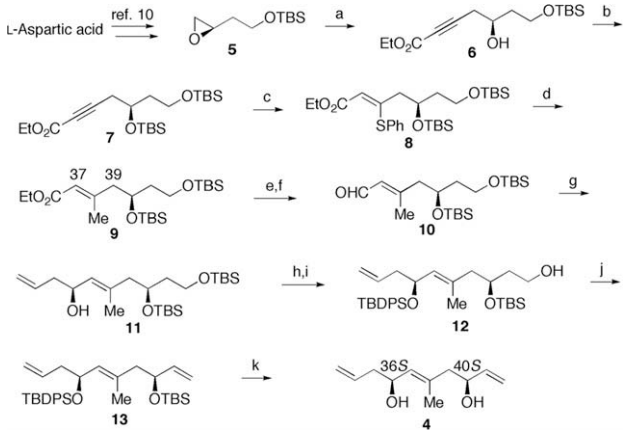


Figure 2. Chemical shift differences ($\Delta\delta_{S-R}$) of bis-MTPA esters derived from **4**. R = MTPA. MTPA = α-methoxy-α-(trifluoromethyl)phenylacetyl.

selenocyanate/*n*-Bu_3P/pyridine followed by oxidative workup afforded alkene **13**.[17] Removal of the silyl protecting groups with TBAF provided the diol **4**. The ^1H NMR spectrum of the synthetic **4** was identical with that of the degraded product **4** obtained from **1**.[18]

Furthermore, to confirm the absolute stereochemistries at C36 and C40 positions of the degraded product **4**, we prepared the bis-(*S*)- and (*R*)-MTPA esters from the synthetic **4**, and compared the spectroscopic data of the synthetic MTPA esters with those of the MTPA esters derived from natural **1**. As shown in Figure 3, the spectra of the synthetic bis-MTPA esters are identical with those of the bis-MTPA esters derived from the degraded product **4** (a to b, c to d), respectively. Therefore, we concluded that the absolute configuration of the C33–C42 fragment was (36*S*,40*S*).



Scheme 2. Reagents and conditions: (a) ethyl propiolate, *n*-BuLi, THF, −78 °C, then $BF_3{\cdot}OEt_2$, **5**, −78 °C to 0 °C, 96%; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 78%; (c) PhSH, NaOMe, MeOH, rt; (d) MeMgBr, CuI, THF, −78 °C to rt; (e) DIBALH, CH_2Cl_2, −78 °C, 77% (3 steps); (f) $SO_3{\cdot}$pyr, Et_3N, DMSO, CH_2Cl_2, 0 °C, 94%; (g) allyltributylstannane, $Ti(Oi\text{-}Pr)_4$, (*S*)-BINOL, CF_3SO_3H, MS4A, CH_2Cl_2, −78 °C to −20 °C, 41% (91% based on recovered starting material), 82% de; (h) TBDPSCl, imidazole, CH_2Cl_2, rt, 95%; (i) CSA, CH_2Cl_2–MeOH (2:1), 0 °C, 56%; (j) *o*-$NO_2PhSeCN$, *n*-Bu_3P, pyridine, THF, rt, then H_2O_2, rt; (k) TBAF, THF, 40 °C, 65% (2 steps). BINOL = 1,1′-bi-2,2′-naphthol, CSA = camphorsulfonic acid, DIBALH = diisobutylaluminum hydride, DMAP = 4-dimethylaminopyridine, DMSO = dimethyl sulfoxide, TBAF = tetrabutylammonium fluoride.

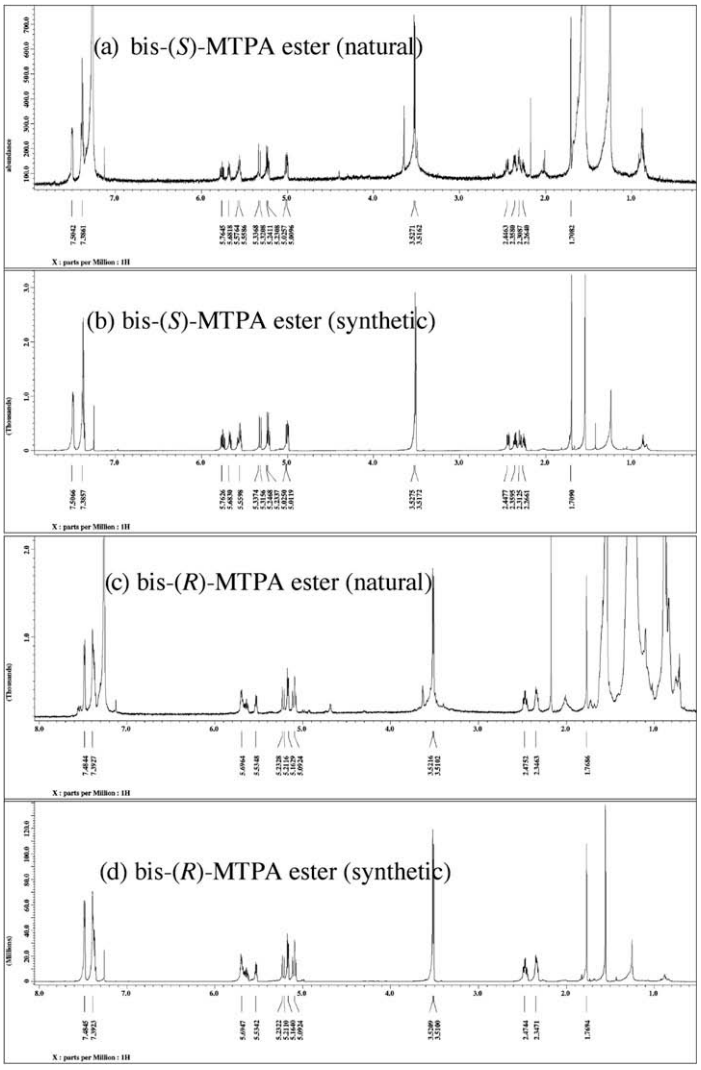


Figure 3. 800 MHz ^{1}H NMR spectra of bis-MTPA esters in $CDCl_3$: (a) bis-(*S*)-MTPA ester derived from natural **1**, (b) synthetic bis-(*S*)-MTPA ester, (c) bis-(*R*)-MTPA ester derived from natural **1**, (d) synthetic bis-(*R*)-MTPA ester.

In conclusion, we obtained the C33–C42 fragment **4** by cross-metathesis degradation of **2** with ethylene. The absolute stereochemistry of **4** was estimated by Mosher method. The proposed structure including absolute configuration was unambiguously confirmed by the enantio- and stereocontrolled synthesis of **4** in 14 steps from L-aspartic acid. Further structural and synthetic studies on **1** are underway in our laboratories.

Acknowledgments

We thank Okayama Foundation for Science and Technology and The Naito Foundation for their financial supports. This research was partially supported by Grant-in-Aid for Scientific Research from MEXT, Japan.

References and notes

1. Kita, M.; Ohishi, N.; Konishi, K.; Kondo, M.; Koyama, T.; Kitamura, M.; Yamada, K.; Uemura, D. *Tetrahedron* **2007**, *63*, 6241.
2. 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.
3. Takamura, H.; Ando, J.; Abe, T.; Murata, T.; Kadota, I.; Uemura, D. *Tetrahedron Lett.* **2008**, *49*, 4626.
4. For some examples of the degradation of natural products by cross-metathesis, see: (a) Ratnayake, A. S.; Hemscheidt, T. *Org. Lett.* **2002**, *4*, 4667; (b) Niggemann, J.; Bedorf, N.; Flörke, U.; Steinmetz, H.; Gerth, K.; Reichenbach, H.; Höfle, G. *Eur. J. Org. Chem.* **2005**, 5013; (c) Williams, P. G.; Miller, E. D.; Asolkar, R. N.; Jensen, P. R.; Fenical, W. *J. Org. Chem.* **2007**, *72*, 5025.
5. Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.
6. Structural determination of other degraded products obtained by cross-metathesis will be reported in the near future.
7. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.
8. For determination of the absolute stereochemistry of secondary/secondary diols by Mosher method, see: Freire, F.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **2005**, *70*, 3778.
9. *Bis-(S)-MTPA ester*: ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.50 (m, 4H, Ph), 7.39 (m, 6H, Ph), 5.76 (ddd, *J* = 17.0, 10.6, 7.3 Hz, 1H, H41), 5.68 (dt, *J* = 8.7, 6.4 Hz, 1H, H36), 5.58 (m, 1H, H34), 5.56 (m, 1H, H40), 5.33 (d, *J* = 17.0 Hz, 1H, H42a), 5.24 (d, *J* = 10.6 Hz, 1H, H42b), 5.23 (m, 1H, H37), 5.01 (dt, *J* = 17.0, 1.4 Hz, 1H, H33a), 5.00 (m, 1H, H33b), 3.53 (s, 3H, OCH_3), 3.52 (s, 3H, OCH_3), 2.45 (dd, *J* = 13.3, 6.0 Hz, 1H, H39a), 2.36 (m, 1H, H35a), 2.31 (dd, *J* = 13.3, 7.8 Hz, 1H, H39b), 2.26

(m, 1H, H35b), 1.71 (d, J = 1.4 Hz, 3H, C38-CH_3). *Bis-(R)-MTPA ester*: ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.48 (m, 4H, Ph), 7.39 (m, 6H, Ph), 5.70 (m, 1H, H36), 5.69 (m, 1H, H34), 5.64 (m, 1H, H41), 5.53 (m, 1H, H40), 5.22 (d, J = 17.0 Hz, 1H, H42a), 5.17 (d, J = 10.1 Hz, 1H, H42b), 5.17 (m, 1H, H37), 5.10 (d, J = 17.5 Hz, 1H, H33a), 5.09 (d, J = 10.6 Hz, 1H, H33b), 3.52 (s, 3H, OCH_3), 3.51 (s, 3H, OCH_3), 2.48 (dd, J = 14.7, 6.4 Hz, 1H, H39a), 2.45 (dd, J = 14.7, 6.9 Hz, 1H, H35a), 2.34 (m, 1H, H35b), 2.34 (m, 1H, H39b), 1.77 (d, J = 1.4 Hz, 3H, C38-CH_3).

10. Donner, C. D. *Tetrahedron Lett.* **2007**, *48*, 8888.
11. Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391.
12. Absolute stereochemistry of **6** was confirmed by Mosher method.
13. (a) Hollowood, C. J.; Yamanoi, S.; Ley, S. V. *Org. Biomol. Chem.* **2003**, *1*, 1664; (b) Ding, F.; Jennings, M. P. *Org. Lett.* **2005**, *7*, 2321.
14. Parikh, J. R.; Doering, W. von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.
15. Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467.
16. Absolute stereochemistry of the resulting chiral center in the allylation of **10** was determined by Mosher method.
17. Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.
18. The diol possessing (36*R*,40*S*) absolute stereochemistry was synthesized from the aldehyde **10**. The ^{1}H NMR spectrum of (36*R*,40*S*)-diol was different from that of the degraded product **4**. Details will be discussed in the full account.