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Stereoselective synthesis and absolute configuration of the C33–C42 fragment of symbiodinolide

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ABSTRACT

Cross-metathesis of methyl ester which was prepared from symbiodinolide with ethylene was performed to give the C33–C42 degraded fragment. This fragment was estimated to be (36*S*,40*S*)-diol by the modified Mosher method. Stereoselective synthesis of the (36*S*,40*S*)-diol and its diastereomer (36*R*,40*S*)-diol was achieved from L-aspartic acid. Synthetic bis-(*S*)- and (*R*)-MTPA esters which were derivatized from the (36*S*,40*S*)-diol exhibited spectroscopic data identical with those of bis-(*S*)- and (*R*)-MTPA esters derived from the degraded product. Thus, the absolute stereochemistry of the C33–C42 fragment was elucidated to be (36*S*,40*S*).

1. 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 chemist, biochemists, and pharmacological scientists.[2] Previously, one of the authors (D. U.) reported the isolation of symbiodinolide (**1**) from the symbiotic marine dinoflagellate *Symbiodinium* sp. (Fig. 1).[3,4] 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[3] and chemical synthesis.[5] Herein, we describe the cross-metathesis degradation with ethylene and stereoselective synthesis of the C33–C42 fragment (36*S*,40*S*)-diol **14** and its diastereomer (36*R*,40*S*)-diol **19**, which has resulted in the unambiguous structural determination of the C33–C42 fragment.[6]

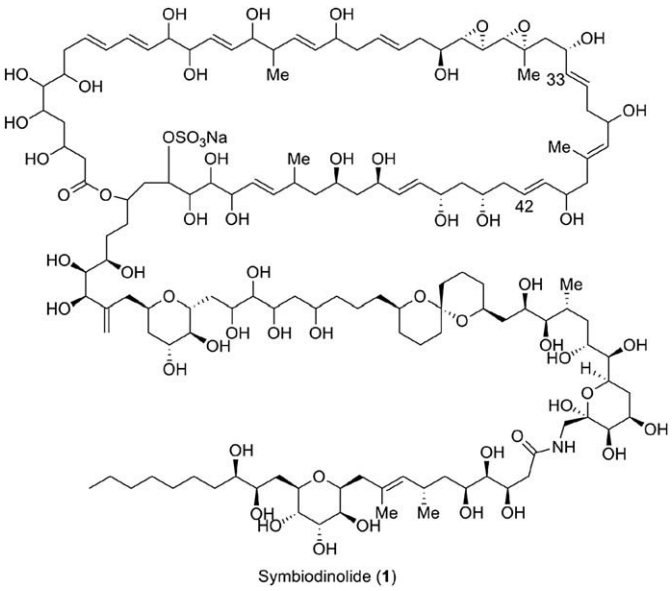

Figure 1. Structure of symbiodinolide (**1**).

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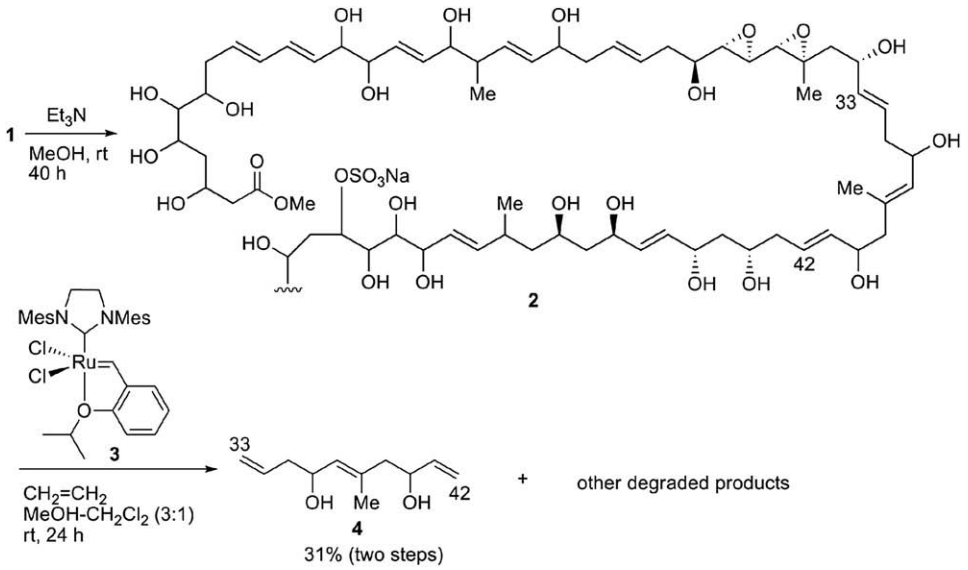


Scheme 1. Cross-metathesis degradation with ethylene.

2. Results and discussion

2.1. Cross-metathesis degradation with ethylene

Olefin cross-metathesis is one of the efficient degradation methods of natural products.[7] To obtain the degraded product of **1**, we carried out cross-metathesis with ethylene. Thus, treatment of **1** with Et_3N in MeOH provided methyl ester **2**, which was then subjected to cross-metathesis with ethylene using Hoveyda–Grubbs second generation catalyst **3**[8] to give the C33–C42 fragment **4** as one of the degraded products (Scheme 1).[9] The planar structure of **4** was confirmed by the analyses of 2D NMR spectra and HR-ESIMS.

The absolute stereochemistry of **4** was estimated by the modified Mosher method.[10,11] 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). 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.

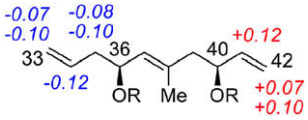
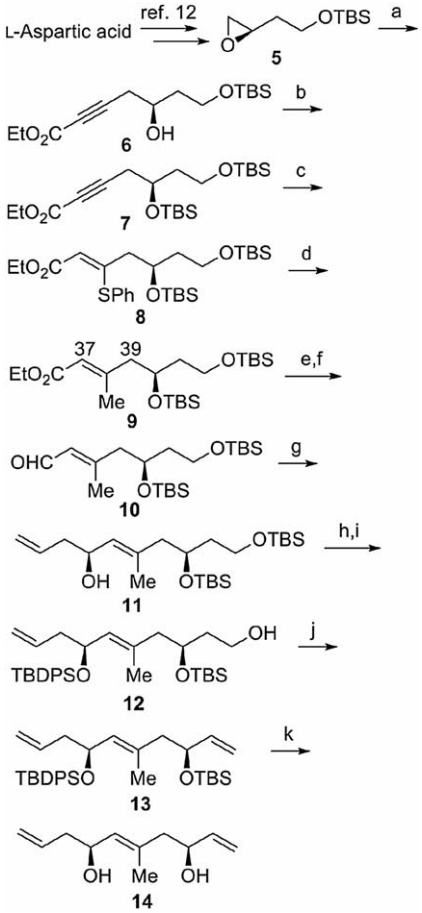


Figure 2. Chemical shift differences ($\Delta\delta_{S-R}$) of bis-MTPA esters derived from **4**. R=MTPA. MTPA=α-methoxy-α-(trifluoromethyl)phenylacetyl.

2.2. Synthesis of (36*S*,40*S*)-diol 14

We next investigated the stereoselective synthesis of the (36*S*,40*S*)-diol **14** to confirm the assigned stereostructure (Scheme 2). The starting material L-aspartic acid was transformed to epoxide **5** by the known procedure.[12] Treatment of **5** with the lithium acetylide, derived from ethyl propiolate, gave acetylenic alcohol **6**.[13,14] The alcohol **6** was protected with TBSOTf/2,6-lutidine to provide TBS ether **7**. Conjugate addition of benzenethiol to **7** provided (*Z*)-thioether **8**, which was reacted with MeMgBr and CuI to give (*E*)-α,β-unsaturated ester **9** with the complete configurational retention at the alkene.[15] The observed NOE between H37 and H39 clearly indicated the (*E*)-configuration of **9**. Reduction of **9** with DIBALH followed by Parikh–Doering oxidation[16] gave α,β-unsaturated aldehyde **10**. The aldehyde



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, 95%; (c) PhSH, NaOMe, MeOH, rt; (d) MeMgBr, CuI, THF, −78 °C to rt; (e) DIBALH, CH_2Cl_2, −78 °C, 77% (three steps); (f) $SO_3\cdot$pyr, Et_3N, DMSO, CH_2Cl_2, 0 °C, 94%; (g) allyltributylstannane, Ti(O*i*-Pr)$_4$, (*S*)-BINOL, TfOH, 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, 36% (82% based on recovered starting material); (j) *o*-NO_2PhSeCN, *n*-Bu_3P, pyridine, THF, rt, then H_2O_2, rt; (k) TBAF, THF, 40 °C, 65% (two steps). BINOL=1,1′-bi-2,2′-naphthol, CSA=camphorsulfonic acid, DIBALH=diisobutylaluminum hydride, DMAP=4-dimethylaminopyridine, DMSO=dimethyl sulfoxide, MS=molecular sieves, TBAF=tetrabutylammonium fluoride, TBDPS=*t*-butyldiphenylsilyl, TBS=*t*-butyldimethyllsilyl, Tf=trifluoromethanesulfonyl.

10 was subjected to asymmetric allylation developed by Keck et al.[17] to give homoallylic alcohol **11** in 41% yield (91% based on recovered starting material) with 82% diastereomeric excess (de).[18] Protection of **11** with TBDPSCl/imidazole followed by selective deprotection of the TBS moiety provided alcohol **12**. Treatment of **12** with *o*-nitrophenyl selenocyanate/*n*-Bu_3P/pyridine followed by oxidative work-up afforded alkene **13**.[19] Final desilylation with TBAF provided the (36*S*,40*S*)-diol **14**. The ^{1}H NMR spectrum of the synthetic product **14** was identical to that of the degraded product **4** obtained from **1** (Fig. 3a and b). However, there have been a number of reported examples where two diastereomers with the remote stereogenic centers exhibit the indistinguishable spectral data.[7d,20] Therefore, we next examined the stereoselective synthesis of the (36*R*,40*S*)-diol **19** which was the diastereomer of **14**.

2.3. Synthesis of (36*R*,40*S*)-diol 19

The synthesis of the (36*R*,40*S*)-diol **19** started from the aldehyde **10** which was the synthetic intermediate toward **14** (Scheme 3). Treatment of **10** with allylmagnesium bromide and subsequent oxidation with Dess–Martin periodinane[21] gave ketone **15**. The stereoselective reduction of **15** was performed by CBS reduction conditions[22] to afford allylic alcohol **16** as a sole product in 80% yield. Further transformation toward **19** was similar to that toward **14**. The alcohol **16** was protected as TBDPS ether to give silyl ether **17**. Selective removal of TBS moiety of **17** gave alcohol **18**. Terminal alkene moiety was introduced by Grieco–Nishizawa conditions,[19] followed by deprotection of silyl groups to provide the (36*R*,40*S*)-diol **19**. The distinguishable differences between the degraded product **4** and the synthetic product **19** in the ^{1}H NMR spectra were observed. Therefore, the relative configuration of the degraded product **4** was elucidated to be (36*S**,40*S**).

2.4. Determination of the absolute configuration

To confirm the absolute configuration of the degraded product **4**, we prepared the bis-(*S*)- and (*R*)-MTPA esters from the synthetic (36*S*,40*S*)-diol **14**, and compared the spectroscopic data of the

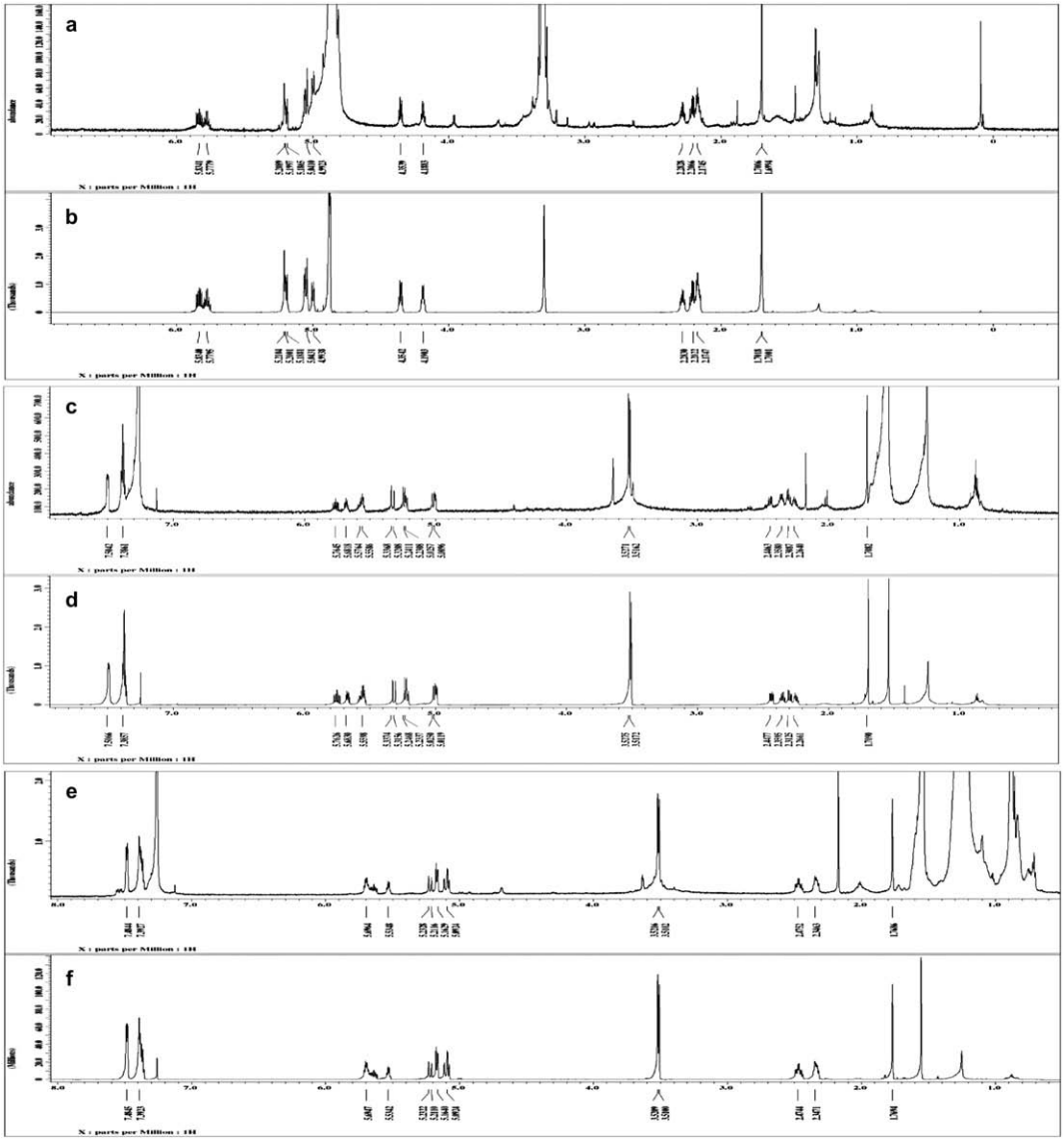
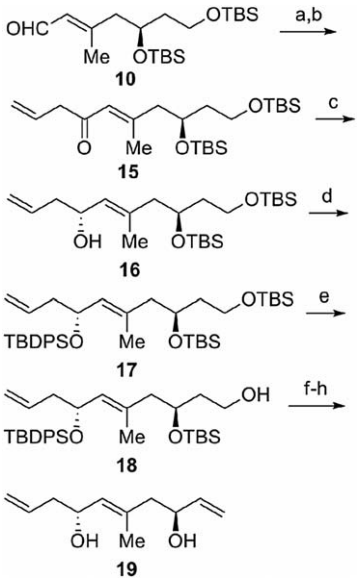


Figure 3. 800 MHz ^{1}H NMR spectra of diols and bis-MTPA esters: (a) the degraded product **4** (CD_3OD), (b) the synthetic product **14** (CD_3OD), (c) bis-(*S*)-MTPA ester derived from the degraded product **4** ($CDCl_3$), (d) bis-(*S*)-MTPA ester prepared from the synthetic product **14** ($CDCl_3$), (e) bis-(*R*)-MTPA ester derived from the degraded product **4** ($CDCl_3$), (f) bis-(*R*)-MTPA ester prepared from the synthetic product **14** ($CDCl_3$).



Scheme 3. Reagents and conditions: (a) allylmagnesium bromide, THF, 0 °C; (b) Dess–Martin periodinane, pyridine, CH_2Cl_2, rt, 77% (two steps); (c) (*S*)-2-methyl-CBS-oxazaborolidine, $BH_3{\cdot}SMe_2$, toluene, −78 °C to −30 °C, 80%; (d) TBDPSCl, imidazole, CH_2Cl_2, rt, 98%; (e) CSA, CH_2Cl_2–MeOH (2:1), 0 °C, 31% (64% based on recovered starting material); (f) *o*-NO_2PhSeCN, *n*-Bu_3P, pyridine, THF, rt; (g) H_2O_2, THF, rt; (h) TBAF, THF, 40 °C, 68% (three steps).

synthetic MTPA esters with those of the MTPA esters derived from the degraded product **4**. As shown in Figure 3, the spectra of the synthetic bis-MTPA esters prepared from the synthetic diol **14** were identical with those of the bis-MTPA esters derived from the degraded product **4** (c and d, e and f), respectively. Therefore, we concluded that the absolute configuration of the C33–C42 fragment was (36*S*,40*S*).

3. Conclusion

In conclusion, we obtained the C33–C42 fragment **4** via cross-metathesis degradation of **2** with ethylene. We synthesized the (36*S*,40*S*)-diol **14** and the (36*R*,40*S*)-diol **19**, and then compared their ^{1}H NMR spectra to that of the degraded product **4**, which resulted in the determination of the relative configuration of the C33–C42 fragment. The ^{1}H NMR spectra of the synthetic bis-MTPA esters prepared from **14** were identical with those of the bis-MTPA esters derived from **4**, which elucidated that the absolute configuration was (36*S*,40*S*).

4. Experimental section

4.1. General

All reactions were carried out under an atmosphere of argon. All reaction solvents were purchased as dehydrated solvents and stored with active molecular sieves 4 Å. All solvents for work-up procedure were used as received. Reactions were monitored by thin layer chromatography (Merck silica gel plate $60F_{254}$). Column chromatography was performed with Kanto Chemical silica gel (60 N, spherical, neutral, particle size 63–210 μm). Chemical shifts in nuclear magnetic resonance (NMR) data are indicated in parts per million (ppm) downfield from tetramethylsilane (TMS, δ=0.00) with residual undeuterated solvent peaks as internal reference, for ^{1}H NMR $CHCl_3$ (7.26) or CHD_2OD (3.31) and deuterated solvent peaks shifts for ^{13}C NMR $CDCl_3$ (77.0) or CD_3OD (49.0). Multiplicities are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad) or combinations of those. Coupling constants (*J*) are in hertz.

4.2. Degraded product 4

To a solution of symbiodinolide (**1**) (10.0 mg, 3.50 μmol) in MeOH (13 mL) was added Et_3N (4.0 mL) at room temperature. The mixture was stirred at room temperature for 40 h. Concentration gave methyl ester **2** (10.0 mg), which was used in the next reaction without further purification.

A solution of methyl ester **2** (10.0 mg) obtained above in MeOH (0.8 mL) was degassed three times and then replaced with ethylene gas. To the resulting solution was added Hoveyda–Grubbs second generation catalyst **3** (5.2 mg, 8.30 μmol) in CH_2Cl_2 (0.24 mL) at room temperature. The mixture was stirred at room temperature for 24 h. After being diluted with ethyl vinyl ether (0.20 mL), the mixture was stirred at room temperature for 1 h and then concentrated. The residue was purified by ODS column chromatography (aqueous 50% MeOH) and then applied to Develosil HG-5 reversed-phase HPLC column (ϕ 10.0×250 mm, Nomura Chemical). A linear gradient of 20–60% aqueous MeCN was applied for 50 min at a flow rate of 5.0 mL/min, with monitoring at 215 nm, to give the C33–C42 fragment **4** (0.2 mg, 31% in two steps). ^{1}H NMR (800 MHz, CD_3OD) δ 5.83 (ddd, *J*=17.0, 10.6, 6.0 Hz, 1H), 5.80–5.75 (m, 1H), 5.23–5.18 (m, 2H), 5.06–5.04 (m, 2H), 5.00 (d, *J*=10.6 Hz, 1H), 4.35 (dt, *J*=8.8, 6.6 Hz, 1H), 4.20–4.18 (m, 1H), 2.30–2.27 (m, 1H), 2.23–2.21 (m, 1H), 2.19–2.15 (m, 2H), 1.70 (d, *J*=0.9 Hz, 3H); HRMS (ESI) calcd for $C_{11}H_{18}O_2Na$ $(M+Na)^+$ 205.1204, found: 205.1206.

4.3. Bis-(*S*)-MTPA ester derived from degraded product 4

To a mixture of degraded product **4** (0.1 mg, 0.55 μmol) and 4-(dimethylamino)pyridine (0.3 mg, 2.43 μmol) in CH_2Cl_2 (20 μL) were added Et_3N (0.8 μL, 5.65 μmol) and (*R*)-MTPACl (1.0 μL, 5.29 μmol) at room temperature. The mixture was stirred at room temperature for 10 h. The reaction mixture was concentrated and purified by column chromatography (hexane/acetone=9:1, 4:1, 1:1). The fraction eluted with hexane/acetone (9:1) was purified by Develosil HG-5 reversed-phase HPLC column (ϕ 10.0×250 mm). A linear gradient of 70–100% aqueous MeCN was applied for 50 min at a flow rate of 4.0 mL/min, with monitoring at 215 nm, to give the corresponding bis-(*S*)-MTPA ester (0.1 mg). ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.50–7.48 (m, 4H), 7.40–7.38 (m, 6H), 5.76 (ddd, *J*=17.0, 10.6, 7.3 Hz, 1H), 5.68 (dt, *J*=8.7, 6.4 Hz, 1H), 5.60–5.50 (m, 2H), 5.33 (d, *J*=17.0 Hz, 1H), 5.24 (d, *J*=10.6 Hz, 1H), 5.24–5.22 (m, 1H), 5.01 (dt, *J*=17.0, 1.4 Hz, 1H), 5.01–5.00 (m, 1H), 3.53 (s, 3H), 3.52 (s, 3H), 2.45 (dd, *J*=13.3, 6.0 Hz, 1H), 2.38–2.34 (m, 1H), 2.31 (dd, *J*=13.3, 7.8 Hz, 1H), 2.28–2.24 (m, 1H), 1.71 (d, *J*=1.4 Hz, 3H); HRMS (ESI) calcd for $C_{31}H_{32}F_6O_6Na$ $(M+Na)^+$ 637.2001, found: 637.1998.

4.4. Bis-(*R*)-MTPA ester derived from degraded product 4

To a mixture of degraded product **4** (0.1 mg, 0.55 μmol) and 4-(dimethylamino)pyridine (0.3 mg, 2.43 μmol) in CH_2Cl_2 (20 μL) were added Et_3N (0.8 μL, 5.65 μmol) and (*S*)-MTPACl (1.0 μL, 5.29 μmol) at room temperature. The mixture was stirred at room temperature for 33 h. The reaction mixture was concentrated and purified by column chromatography (hexane/acetone=15:1). The concentrated residue was purified by Develosil HG-5 reversed-phase HPLC column (ϕ 10.0×250 mm). A linear gradient of 80–100% aqueous MeCN was applied for 50 min at a flow rate of 5.0 mL/min, with monitoring at 215 nm, to give the corresponding bis-(*R*)-MTPA ester (0.1 mg). ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.49–7.47 (m, 4H), 7.40–7.37 (m, 6H), 5.71–5.69 (m, 2H), 5.68–5.62 (m, 1H), 5.53–5.51 (m, 1H), 5.22 (d, *J*=17.0 Hz, 1H), 5.18–5.16 (m, 1H), 5.17 (d, *J*=10.1 Hz, 1H), 5.10 (d, *J*=17.5 Hz, 1H), 5.09 (d, *J*=10.6 Hz, 1H), 3.52 (s, 3H), 3.51

(s, 3H), 2.48 (dd, J=14.7, 6.4 Hz, 1H), 2.45 (dd, J=14.7, 6.9 Hz, 1H), 2.36–2.31 (m, 2H), 1.77 (d, J=1.4 Hz, 3H); HRMS (ESI) calcd for $C_{31}H_{32}F_6O_6Na$ $(M+Na)^+$ 637.2001, found: 637.2001.

4.5. Acetylenic alcohol 6

To a solution of ethyl propiolate (0.35 mL, 3.42 mmol) in THF (10 mL) was added *n*-BuLi (1.58 M solution in hexane, 2.2 mL, 3.42 mmol) at −78 °C, and the mixture was stirred at −78 °C for 20 min. To the resulting solution were added $BF_3\cdot OEt_2$ (0.42 mL, 3.42 mmol) and a solution of epoxide **5** (230 mg, 1.14 mmol) in THF (2.0 mL+1.0 mL) at −78 °C, and the mixture was stirred at 0 °C for 2 h. The reaction was quenched with MeOH, and then the resulting mixture was extracted with Et_2O. The extract was washed successively with water and brine, and dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc=20:1, 10:1, 4:1) gave acetylenic alcohol **6** (329 mg, 96%). Yellow oil; R_f=0.38 (hexane/EtOAc=4:1); $[\alpha]_D^{28}$ +2.4 (*c* 1.00, $CHCl_3$); IR (neat) 3444, 2929, 2236, 1714 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.19 (q, J=7.1 Hz, 2H), 4.05 (br d, J=6.4 Hz, 1H), 3.93–3.88 (m, 1H), 3.82 (ddd, J=10.2, 8.6, 3.6 Hz, 1H), 3.66 (br s, 1H), 2.57 (dd, J=17.1, 5.6 Hz, 1H), 2.49 (dd, J=17.1, 6.8 Hz, 1H), 1.86–1.70 (m, 2H), 1.28 (t, J=7.1 Hz, 3H), 0.88 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 85.7, 74.8, 69.9, 62.2, 61.9, 37.2, 27.3, 25.9, 18.2, 14.1, −5.5, −5.5; HRMS (ESI) calcd for $C_{15}H_{28}O_4SiNa$ $(M+Na)^+$ 323.1655, found: 323.1651.

4.6. Silyl ether 7

To a solution of acetylenic alcohol **6** (310 mg, 1.03 mmol) in CH_2Cl_2 (10 mL) were added 2,6-lutidine (0.18 mL, 1.55 mmol) and TBSOTf (0.29 mL, 1.24 mmol) at 0 °C. After the mixture was stirred at 0 °C for 20 min, the reaction was quenched with MeOH. The mixture was diluted with Et_2O. The organic layer was washed with water and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc=1:0, 40:1, 20:1) gave silyl ether **7** (404 mg, 95%). Yellow oil; R_f=0.68 (hexane/EtOAc=10:1); $[\alpha]_D^{26}$ +14.8 (*c* 1.00, $CHCl_3$); IR (neat) 2955, 2237, 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.19 (q, J=7.1 Hz, 2H), 4.05–3.99 (m, 1H), 3.71–3.62 (m, 2H), 2.51 (dd, J=17.1, 6.1 Hz, 1H), 2.46 (dd, J=17.1, 5.8 Hz, 1H), 1.82–1.66 (m, 2H), 1.27 (t, J=7.1 Hz, 3H), 0.87 (s, 18H), 0.08 (s, 3H), 0.05 (s, 3H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 86.6, 74.6, 67.5, 61.7, 59.2, 40.0, 28.0, 26.0, 25.8, 18.3, 18.1, 14.1, −4.5, −4.7, −5.2; HRMS (ESI) calcd for $C_{21}H_{42}O_4Si_2Na$ $(M+Na)^+$ 437.2519, found: 437.2559.

4.7. Aldehyde 10

To a solution of alkyne **7** (115 mg, 0.277 mmol) in MeOH (1.2 mL) were added PhSH (0.20 mL, 0.305 mmol) and NaOMe (3.0 mg, 55.5 μmol). After being stirred at room temperature for 36 h, the mixture was filtered through a silica gel pad and washed with Et_2O. Concentration and short column chromatography (hexane/EtOAc=100:1, 20:1) gave (*Z*)-thioether **8** (146 mg), which was used in the next reaction without further purification.

To a suspension of CuI (232 mg, 1.22 mmol) in THF (2.5 mL) was added MeMgBr (3.0 M solution in Et_2O, 0.37 mL, 1.11 mmol) dropwise at −78 °C. The reaction mixture was warmed to 0 °C and then cooled back to −78 °C. To the resulting mixture was added (*Z*)-thioether **8** (146 mg) obtained above in THF (1.0 mL+0.5 mL). After the solution was warmed to room temperature and stirred for 1 h, the reaction was quenched with MeOH. The solution was filtered through a silica gel pad and washed with Et_2O. Concentration and short column chromatography (hexane/EtOAc=50:1) gave α,β-unsaturated ester **9** (102 mg), which was used in the next reaction without further purification.

To a solution of α,β-unsaturated ester **9** (102 mg) obtained above in CH_2Cl_2 (2.8 mL) was added DIBALH (1.0 M solution in hexane, 0.65 mL, 0.65 mmol) dropwise at −78 °C. After the mixture was stirred for 1 h, the reaction was quenched with MeOH. The mixture was filtered through a Celite pad and washed with EtOAc. Concentration and column chromatography (hexane/EtOAc=20:1, 10:1) gave the corresponding allylic alcohol (83.1 mg, 77% in three steps). Colorless oil; R_f=0.30 (hexane/EtOAc=4:1); $[\alpha]_D^{29}$ +13.4 (*c* 2.00, $CHCl_3$); IR (neat) 3348, 2929 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.41 (td, J=6.8, 0.5 Hz, 1H), 4.11 (d, J=6.8 Hz, 2H), 3.98–3.91 (m, 1H), 3.65 (t, J=6.5 Hz, 2H), 2.20 (dd, J=13.1, 5.8 Hz, 1H), 2.13 (dd, J=13.1, 6.7 Hz, 1H), 1.68–1.51 (m, 2H), 1.66 (d, J=0.5 Hz, 3H), 0.87 (s, 9H), 0.86 (s, 9H), 0.03 (s, 3H), 0.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.5, 126.3, 67.8, 59.8, 59.3, 48.0, 40.0, 26.0, 25.9, 18.3, 18.1, 16.9, −4.3, −4.6, −5.2; HRMS (ESI) calcd for $C_{20}H_{44}O_3Si_2Na$ $(M+Na)^+$ 411.2727, found: 411.2744.

To a solution of the allylic alcohol (84.1 mg, 0.216 mmol) obtained above in CH_2Cl_2 (2.0 mL) and DMSO (1.0 mL) were added Et_3N (0.20 mL, 1.43 mmol) and $SO_3\cdot$pyr (103 mg, 0.648 mmol) at 0 °C. After being stirred at 0 °C for 2 h, the mixture was diluted with Et_2O. The organic layer was washed with saturated aqueous NH_4Cl, water, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc=20:1, 10:1) gave aldehyde **10** (78.3 mg, 94%). Colorless oil; R_f=0.60 (hexane/EtOAc=4:1); $[\alpha]_D^{25}$ +13.3 (*c* 1.95, $CHCl_3$); IR (neat) 2954, 1678, 1633 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.96 (d, J=8.0 Hz, 1H), 5.86 (d, J=8.0 Hz, 1H), 4.10–4.04 (m, 1H), 3.64 (t, J=6.3 Hz, 2H), 2.35 (d, J=6.1 Hz, 2H), 2.17 (d, J=1.2 Hz, 3H), 1.65–1.59 (m, 2H), 0.87 (s, 9H), 0.85 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.7, 160.8, 129.7, 67.9, 59.3, 48.7, 40.3, 26.0, 25.9, 18.4, 18.3, 18.1, −4.4, −4.5, −5.3; HRMS (ESI) calcd for $C_{20}H_{42}O_3Si_2Na$ $(M+Na)^+$ 409.2570, found: 409.2503.

4.8. Homoallylic alcohol 11

To a mixture of (*S*)-BINOL (94.2 mg, 0.329 mmol) and MS4A (500 mg) in CH_2Cl_2 (2.9 mL) were added TfOH (43 μL, 0.493 mmol) and $Ti(Oi\text{-}Pr)_4$ (98 μL, 0.329 mmol). After being stirred at reflux conditions for 1 h, the mixture was cooled to room temperature. To the mixture was added a solution of aldehyde **10** (318 mg, 0.822 mmol) in CH_2Cl_2 (0.7 mL+0.4 mL). To the resulting mixture was added allyltributylstannane (0.28 mL, 0.904 mmol) at −78 °C. The mixture was gradually warmed up to −20 °C. After the mixture was stirred at −20 °C for 29 h, the reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was filtered through a Celite pad and washed with Et_2O. The organic layer was washed with water and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc=20:1, 10:1) gave homoallylic alcohol **11** (145 mg, 34%, 74% based on recovered starting material) and aldehyde **10** (175 mg, 55% recovery). For homoallylic alcohol **11**. Colorless oil; R_f=0.45 (hexane/EtOAc=4:1); $[\alpha]_D^{24}$+3.2 (*c* 0.50, $CHCl_3$); IR (neat) 3366, 2929, 1641 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.83–5.73 (m, 1H), 5.21 (d, J=8.5 Hz, 1H), 5.11 (d, J=15.3 Hz, 1H), 5.08 (d, J=9.0 Hz, 1H), 4.42–4.36 (m, 1H), 3.98–3.92 (m, 1H), 3.64 (t, J=6.6 Hz, 2H), 2.28–2.09 (m, 4H), 1.67 (s, 3H), 0.87 (s, 18H), 0.04 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 134.3, 129.9, 117.8, 67.7, 67.7, 59.7, 48.3, 42.2, 39.8, 26.0, 26.0, 18.3, 18.1, 17.2, −4.2, −4.5, −5.2; HRMS (ESI) calcd for $C_{23}H_{48}O_3Si_2Na$ $(M+Na)^+$ 451.3040, found: 451.3033.

4.9. Alcohol 12

To a solution of alcohol **11** (179 mg, 0.417 mmol) in CH_2Cl_2 (4.0 mL) were added imidazole (70.8 mg, 1.04 mmol) and TBDPSCl (0.22 mL, 0.833 mmol) at room temperature. After the mixture was stirred at room temperature for 2 h, the reaction was quenched

with saturated aqueous NH_4Cl. The mixture was diluted with Et_2O. The organic layer was washed with water and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc=100:1) gave the corresponding silyl ether (264 mg, 95%). Colorless oil; R_f=0.80 (hexane/EtOAc=10:1); $[\alpha]_D^{28}$ −4.4 (*c* 3.00, $CHCl_3$); IR (neat) 2930, 1641 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68–7.63 (m, 4H), 7.42–7.30 (m, 6H), 5.76–5.65 (m, 1H), 5.19 (d, *J*=9.0 Hz, 1H), 4.94 (d, *J*=14.9 Hz, 1H), 4.94 (d, *J*=11.7 Hz, 1H), 4.41–4.35 (m, 1H), 3.86–3.79 (m, 1H), 3.62–3.55 (m, 2H), 2.32–2.19 (m, 2H), 2.06–1.93 (m, 2H), 1.59 (ddd, *J*=13.9, 7.3, 3.2 Hz, 1H), 1.41–1.33 (m, 1H), 1.14 (s, 3H), 1.04 (s, 9H), 0.88 (s, 9H), 0.86 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 135.8, 134.6, 134.4, 134.4, 132.7, 130.7, 129.4, 129.2, 127.4, 127.2, 116.7, 70.1, 67.8, 59.7, 48.5, 43.1, 39.2, 27.1, 26.0, 19.4, 18.3, 18.1, 17.0, −4.2, −4.7, −5.2, −5.2; HRMS (ESI) calcd for $C_{39}H_{66}O_3Si_3Na$ $(M+Na)^+$ 689.4218, found: 689.4274.

To a solution of the silyl ether (145 mg, 0.214 mmol) obtained above in CH_2Cl_2 (1.4 mL) and MeOH (0.8 mL) was added CSA (10.0 mg, 42.9 μmol) at 0 °C. After the mixture was stirred at 0 °C for 10 min, the reaction was quenched with Et_3N. Concentration and column chromatography (hexane/EtOAc=50:1, 10:1) gave alcohol **12** (42.8 mg, 36%, 82% based on recovered starting material) and silyl ether (80.9 mg, 56% recovery). For alcohol **12**: colorless oil; R_f=0.22 (hexane/EtOAc=10:1); $[\alpha]_D^{26}$ −3.7 (*c* 1.15, $CHCl_3$); IR (neat) 3445, 3072, 2930, 1640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67–7.62 (m, 4H), 7.41–7.30 (m, 6H), 5.73–5.62 (m, 1H), 5.17 (dd, *J*=8.8, 1.2 Hz, 1H), 4.93 (d, *J*=11.2 Hz, 1H), 4.93 (d, *J*=16.1 Hz, 1H), 4.40–4.35 (m, 1H), 3.91–3.85 (m, 1H), 3.74 (br s, 1H), 3.61 (br s, 1H), 2.39 (br s, 1H), 2.32–2.18 (m, 2H), 2.05 (d, *J*=7.1 Hz, 2H), 1.67–1.59 (m, 1H), 1.45–1.37 (m, 1H), 1.11 (d, *J*=1.2 Hz, 3H), 1.02 (s, 9H), 0.87 (s, 9H), 0.06 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 135.8, 134.5, 134.4, 134.3, 132.0, 131.1, 129.4, 129.3, 127.4, 127.2, 116.8, 70.8, 69.9, 60.3, 47.3, 43.1, 36.7, 27.0, 25.9, 19.4, 18.0, 17.0, −4.3, −4.8; HRMS (ESI) calcd for $C_{33}H_{52}O_3Si_2Na$ $(M+Na)^+$ 575.3353, found: 575.3356.

4.10. Diol 14

To a mixture of alcohol **12** (12.2 mg, 22.1 μmol) and *o*-nitrophenyl selenocyanate (10.0 mg, 44.2 μmol) in THF (0.5 mL) were added pyridine (18 μL, 0.221 mmol) and tributylphosphine (11 μL, 44.2 μmol). The mixture was stirred at room temperature for 30 min. To the resulting mixture was added 30% H_2O_2 (50 μL) at room temperature. The stirring was continued at room temperature for 1 h. The mixture was diluted with Et_2O. The organic layer was washed with water, saturated aqueous Na_2SO_3, and brine, and then dried over Na_2SO_4. Concentration and short column chromatography (hexane/EtOAc=100:1) gave alkene **13** (11.8 mg), which was used in the next reaction without further purification.

To a solution of alkene **13** (11.8 mg) obtained above in THF (0.5 mL) was added TBAF (1.0 M solution in THF, 0.44 mL, 0.440 mmol), and the mixture was stirred at 40 °C for 19 h. The mixture was filtered through a silica gel pad and washed with EtOAc. Concentration and column chromatography (hexane/EtOAc=3:1) gave diol **14** (2.6 mg, 65% in two steps). Colorless oil; R_f=0.18 (hexane/EtOAc=1:1); $[\alpha]_D^{24}$ −19.8 (*c* 0.22, $CHCl_3$); IR (neat) 3366, 2929, 1641 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 5.84 (ddd, *J*=16.6, 10.5, 6.1 Hz, 1H), 5.82–5.74 (m, 1H), 5.23–5.18 (m, 1H), 5.21 (dt, *J*=17.1, 1.7 Hz, 1H), 5.09–4.99 (m, 3H), 4.36 (dt, *J*=8.8, 6.6 Hz, 1H), 4.20 (dt, *J*=7.6, 6.4 Hz, 1H), 2.33–2.15 (m, 4H), 1.71 (d, *J*=1.2 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 142.1, 135.8, 135.4, 131.6, 117.2, 114.5, 71.9, 68.8, 43.2, 17.0; HRMS (ESI) calcd for $C_{11}H_{18}O_2Na$ $(M+Na)^+$ 205.1204, found: 205.1228.

4.11. Ketone 15

To a solution of aldehyde **10** (224 mg, 0.580 mmol) in THF (6.0 mL) was added allylmagnesium bromide (1.0 M solution in Et_2O, 0.87 mL, 0.870 mmol) at 0 °C. After the mixture was stirred at 0 °C for 20 min, the reaction was quenched with MeOH. The mixture was filtered through a Celite pad and washed with Et_2O. The organic layer was washed with water and brine, and then dried over Na_2SO_4. Concentration and short column chromatography (hexane/EtOAc=20:1) gave the corresponding alcohol (249 mg) as a diastereomixture, which was used in the next reaction without further purification.

To a solution of the alcohol (249 mg) obtained above in CH_2Cl_2 (6.0 mL) were added pyridine (0.94 mL, 11.6 mmol) and Dess–Martin periodinane (1.20 g, 2.90 mmol) at room temperature. After being stirred at room temperature for 3 h, the mixture was filtered through a silica gel pad and washed with Et_2O. Concentration and column chromatography (hexane/EtOAc=40:1) gave ketone **15** (192 mg, 77% in two steps). Colorless oil; R_f=0.62 (hexane/EtOAc=4:1); $[\alpha]_D^{25}$ −1.7 (*c* 3.28, $CHCl_3$); IR (neat) 2954, 1690, 1618 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.06 (br s, 1H), 5.77 (ddt, *J*=17.2, 10.2, 6.9 Hz, 1H), 5.15–5.07 (m, 2H), 4.05–3.99 (m, 1H), 3.64 (t, *J*=6.4 Hz, 2H), 3.14 (dt, *J*=6.8, 1.2 Hz, 2H), 2.25 (d, *J*=6.4 Hz, 2H), 2.12 (d, *J*=1.2 Hz, 3H), 1.63–1.58 (m, 2H), 0.86 (s, 9H), 0.84 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H), 0.01 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 156.4, 131.2, 124.9, 118.3, 67.7, 59.4, 49.5, 49.2, 40.4, 25.9, 25.9, 20.0, 18.3, 18.1, −4.5, −4.5, −5.3; HRMS (ESI) calcd for $C_{23}H_{46}O_3Si_2Na$ $(M+Na)^+$ 449.2883, found: 449.2933.

4.12. Homoallylic alcohol 16

To a solution of ketone **15** (43.7 mg, 0.102 mmol) and (*S*)-2-methyl-CBS-oxazaborolidine (56.8 mg, 0.205 mmol) in toluene (1.0 mL) was added $BH_3 \cdot SMe_2$ (20 μL, 0.205 mmol) at −78 °C. After the mixture was stirred at −30 °C for 18 h, the reaction was quenched with MeOH. The mixture was filtered through a silica gel pad and washed with Et_2O. Concentration and column chromatography (hexane/EtOAc=30:1, 10:1) gave allylic alcohol **16** (35.0 mg, 80%). Colorless oil; R_f=0.45 (hexane/EtOAc=4:1); $[\alpha]_D^{26}$ +19.5 (*c* 1.46, $CHCl_3$); IR (neat) 3366, 2929, 1641 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.85–5.75 (m, 1H), 5.21 (d, *J*=8.6 Hz, 1H), 5.14–5.08 (m, 2H), 4.41–4.36 (m, 1H), 3.99–3.93 (m, 1H), 3.64 (t, *J*=6.5 Hz, 2H), 2.26 (t, *J*=6.7 Hz, 2H), 2.20 (dd, *J*=13.4, 5.6 Hz, 1H), 2.12 (dd, *J*=13.4, 6.8 Hz, 1H), 1.69 (s, 3H), 1.65–1.50 (m, 2H), 0.87 (s, 9H), 0.86 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0, 134.4, 129.7, 117.9, 67.8, 67.6, 59.8, 47.9, 42.1, 39.9, 26.0, 26.0, 18.3, 18.1, 17.4, −4.3, −4.5, −5.2, −5.2; HRMS (ESI) calcd for $C_{23}H_{48}O_3Si_2Na$ $(M+Na)^+$ 451.3040, found: 451.3057.

4.13. Silyl ether 17

To a solution of alcohol **16** (35.0 mg, 81.6 μmol) in CH_2Cl_2 (1.0 mL) were added imidazole (13.9 mg, 0.204 mmol) and TBDPSCl (43 μL, 0.164 mmol) at room temperature. After the mixture was stirred at room temperature for 2 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with Et_2O. The organic layer was washed with water and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc=100:1) gave silyl ether **17** (53.1 mg, 98%). Colorless oil; R_f=0.80 (hexane/EtOAc=10:1); $[\alpha]_D^{24}$ +25.4 (*c* 0.63, $CHCl_3$); IR (neat) 2929 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67–7.62 (m, 4H), 7.39–7.32 (m, 6H), 5.76–5.66 (m, 1H), 5.21 (d, *J*=8.6 Hz, 1H), 4.93 (d, *J*=11.9 Hz, 1H), 4.92 (d, *J*=15.1 Hz, 1H), 4.37 (dt, *J*=8.8, 6.1 Hz, 1H), 3.89–3.83 (m, 1H), 3.62–3.58 (m, 2H), 2.29–2.16 (m, 2H), 2.09 (dd, *J*=13.5, 4.8 Hz, 1H), 1.94 (dd, *J*=13.5, 7.7 Hz, 1H), 1.59–1.51 (m, 1H), 1.45–1.37 (m, 1H), 1.17 (s, 3H), 1.02 (s, 9H), 0.88 (s, 9H), 0.85 (s, 9H), 0.06 (s, 6H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 135.8, 134.8, 134.5, 134.4, 132.6, 130.5, 129.4, 129.2, 127.3, 127.2, 116.2, 70.1, 67.7, 59.8, 47.8, 43.1, 39.5, 27.1, 26.0, 26.0, 19.4, 18.3, 18.1, 17.0, 1.1,

−4.2, −4.6, −5.2; HRMS (ESI) calcd for $C_{39}H_{66}O_3Si_3Na$ $(M+Na)^+$ 689.4218, found: 689.4218.

4.14. Alcohol 18

To a solution of silyl ether **17** (53.1 mg, 78.4 μmol) in CH_2Cl_2 (0.7 mL) and MeOH (0.4 mL) was added CSA (3.7 mg, 15.7 μmol) at 0 °C. After the mixture was stirred at 0 °C for 20 min, the reaction was quenched with Et_3N. Concentration and column chromatography (hexane/EtOAc=50:1, 10:1) gave alcohol **18** (13.5 mg, 31%, 64% based on recovered starting material) and silyl ether **17** (28.8 mg, 54% recovery). For alcohol **18**: colorless oil; R_f=0.22 (hexane/EtOAc=10:1); $[\alpha]_D^{25}$ +34.4 (*c* 0.18, $CHCl_3$); IR (neat) 3435, 2930 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66–7.62 (m, 4H), 7.41–7.31 (m, 6H), 5.77–5.67 (m, 1H), 5.19 (d, *J*=9.0 Hz, 1H), 4.97–4.93 (m, 2H), 4.39 (dt, *J*=8.9, 6.2 Hz, 1H), 3.89–3.83 (m, 1H), 3.69–3.64 (m, 1H), 3.56–3.50 (m, 1H), 2.32–2.18 (m, 2H), 2.11 (dd, *J*=13.4, 4.2 Hz, 1H), 2.06–1.99 (m, 1H), 1.55–1.50 (m, 1H), 1.36–1.26 (m, 1H), 1.12 (d, *J*=1.0 Hz, 3H), 1.01 (s, 9H), 0.86 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 135.8, 134.7, 134.6, 132.0, 130.9, 129.6, 129.5, 129.3, 127.6, 127.4, 127.3, 116.8, 70.4, 70.1, 60.3, 47.2, 43.0, 37.1, 27.0, 25.9, 19.4, 18.0, 16.8, −4.3, −4.7; HRMS (ESI) calcd for $C_{33}H_{52}O_3Si_2Na$ $(M+Na)^+$ 575.3353, found: 575.3303.

4.15. Diol 19

To a mixture of alcohol **18** (13.3 mg, 24.1 μmol) and *o*-nitrophenyl selenocyanate (11.0 mg, 48.2 μmol) in THF (0.5 mL) were added pyridine (8.0 μL, 96.4 μmol) and tributylphosphine (12 μL, 48.2 μmol). After the mixture was stirred for 30 min at room temperature, the reaction was quenched with water. The mixture was diluted with Et_2O. The organic layer was washed with water and brine, and then dried over Na_2SO_4. Concentration and short column chromatography (hexane/EtOAc=100:1) gave the corresponding selenide (19.8 mg), which was used in the next reaction without further purification.

To a solution of the selenide (19.8 mg) obtained above in THF (0.5 mL) was added 30% H_2O_2 (10 μL) at room temperature. The stirring was continued at room temperature for 1 h. The mixture was diluted with Et_2O. The organic layer was washed with water, saturated aqueous Na_2SO_3, and brine, and then dried over Na_2SO_4. Concentration and short column chromatography (hexane/EtOAc=150:1) gave the corresponding alkene (13.1 mg), which was used in the next reaction without further purification.

To a solution of the alkene (13.1 mg) obtained above in THF (0.5 mL) was added TBAF (1.0 M solution in THF, 0.49 mL, 0.490 mmol), and the mixture was stirred at 40 °C for 6 h. The mixture was filtered through a silica gel pad and washed with EtOAc. Concentration and column chromatography (hexane/EtOAc=1:1) gave diol **19** (3.0 mg, 68% in three steps). Colorless oil; R_f=0.28 (hexane/EtOAc=1:1); $[\alpha]_D^{24}$ +12.9 (*c* 0.08, $CHCl_3$); IR (neat) 3365, 2926, 1641 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 5.88 (ddd, *J*=17.3, 10.2, 5.8 Hz, 1H), 5.86–5.76 (m, 1H), 5.24–5.19 (m, 1H), 5.22 (dt, *J*=17.3, 1.7 Hz, 1H), 5.09–5.00 (m, 3H), 4.37 (dt, *J*=8.5, 6.6 Hz, 1H), 4.20 (dt, *J*=7.3, 6.0 Hz, 1H), 2.34–2.25 (m, 2H), 2.24–2.16 (m, 2H), 1.71 (d, *J*=1.5 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 142.3, 136.0, 135.3, 131.4, 117.1, 114.3, 72.1, 68.9, 43.3, 17.3; HRMS (ESI) calcd for $C_{11}H_{18}O_2Na$ $(M+Na)^+$ 205.1204, found: 205.1231.

4.16. Bis-(*S*)-MTPA ester prepared from synthetic diol 14

To a mixture of diol **14** (2.8 mg, 15.4 μmol) and 4-(dimethylamino)pyridine (3.8 mg, 30.8 μmol) in CH_2Cl_2 (0.3 mL) were added Et_3N (6.0 μL, 42.4 μmol) and (*R*)-MTPACl (7.0 μL, 37.0 μmol) at room temperature. The mixture was stirred at room temperature for 30 min. The mixture was diluted with Et_2O. The organic layer was washed with saturated aqueous NH_4Cl, water, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc=20:1) gave the corresponding bis-(*S*)-MTPA ester (8.1 mg, 86%). Colorless oil; R_f=0.30 (hexane/EtOAc=10:1); $[\alpha]_D^{24}$−42.8 (*c* 0.20, $CHCl_3$); IR (neat) 2952, 1746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50–7.48 (m, 4H), 7.38–7.35 (m, 6H), 5.75 (ddd, *J*=17.1, 10.5, 7.3 Hz, 1H), 5.66 (dt, *J*=9.3, 6.6 Hz, 1H), 5.60–5.50 (m, 2H), 5.31 (dd, *J*=17.1, 1.0 Hz, 1H), 5.22 (dd, *J*=10.5, 0.7 Hz, 1H), 5.22–5.20 (m, 1H), 5.02–4.98 (m, 2H), 3.51 (s, 3H), 3.50 (s, 3H), 2.46–2.21 (m, 4H), 1.70 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 165.6, 136.8, 134.2, 132.2, 129.5, 129.4, 128.3, 128.2, 127.3, 127.2, 125.7, 119.3, 118.5, 77.2, 76.2, 73.0, 55.4, 43.7, 38.8, 17.7; HRMS (ESI) calcd for $C_{31}H_{32}F_6O_6Na$ $(M+Na)^+$ 637.2001, found: 637.1985.

4.17. Bis-(*R*)-MTPA ester prepared from synthetic diol 14

To a mixture of diol **14** (1.5 mg, 8.23 μmol) and 4-(dimethylamino)pyridine (2.0 mg, 16.5 μmol) in CH_2Cl_2 (0.3 mL) were added Et_3N (3.2 μL, 23.0 μmol) and (*S*)-MTPACl (3.7 μL, 19.7 μmol) at room temperature. The mixture was stirred at room temperature for 1 h. The mixture was diluted with Et_2O. The organic layer was washed with saturated aqueous NH_4Cl, water, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc=20:1) gave the corresponding bis-(*R*)-MTPA ester (4.5 mg, 89%). Colorless oil; R_f=0.30 (hexane/EtOAc=10:1); $[\alpha]_D^{24}$+56.5 (*c* 0.18, $CHCl_3$); IR (neat) 2951, 1746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48–7.46 (m, 4H), 7.38–7.34 (m, 6H), 5.72–5.59 (m, 3H), 5.54–5.49 (m, 1H), 5.22–5.06 (m, 5H), 3.51 (s, 3H), 3.50 (s, 3H), 2.49–2.41 (m, 2H), 2.36–2.29 (m, 2H), 1.76 (d, *J*=1.0 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 165.7, 165.5, 136.7, 134.1, 132.4, 129.5, 129.5, 128.3, 128.2, 127.3, 127.3, 125.6, 118.8, 118.6, 77.2, 75.8, 73.2, 55.5, 43.8, 38.9, 17.7; HRMS (ESI) calcd for $C_{31}H_{32}F_6O_6Na$ $(M+Na)^+$ 637.2001, found: 637.2042.

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