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Stereocontrolled synthesis and structural confirmation of the C14–C24 degraded fragment of symbiodinolide

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ABSTRACT

The C14–C24 fragment of symbiodinolide possessing the 17*R*/18*R*/21*R* absolute configuration, which was obtained as one of the degraded products of symbiodinolide, and its diastereomer possessing the 17*R*/18*S*/21*R* absolute stereochemistry were synthesized stereoselectively from *cis*-2-butene-1,4-diol, respectively. The detailed comparison of the synthetic products with the degraded product in the spectroscopic data confirmed unambiguously that the stereostructure of the C14–C24 fragment was 17*R*, 18*R*, and 21*R*.

1. Introduction

A variety of biologically and physiologically active secondary metabolites have been isolated from marine origin.[1] In particular, polyether and polyol compounds with a large molecular weight, such as brevetoxins, maitotoxin, and palytoxins are some of the most attractive molecules due to their extraordinary structures and significant biological activities.[2]

Symbiodinolide (**1**) is a polyol macrolide which was isolated from the symbiotic marine dinoflagellate *Symbiodinium* sp. (Fig. 1).[3] Symbiodinolide (**1**) exhibits a voltage-dependant N-type Ca^{2+} channel-opening activity at 7 nM and COX-1 inhibition effect at 2 μM. The planar structure and partial stereochemistry of **1** were determined by spectroscopic analysis[3] and chemical synthesis.[4] Previously, we carried out the degradation of **1** via the cross-metathesis with ethylene using Hoveyda–Grubbs second generation catalyst[5] to give the C14–C24 fragment **2** (Scheme 1).[6] The absolute configurations at C17 and C21 positions were elucidated to be 17*R* and 21*R* by applying the modified Mosher method[7] to bis-(*S*) and (*R*)-MTPA esters **3** and **4** derived from the degraded product **2**. The absolute stereochemistry at C18 position was assigned to be 18*R* on the basis of *J*-based configuration analysis[8] and NOE correlations in **1**. Herein, we report the stereocontrolled synthesis of (17*R*,18*R*,21*R*)-diol possessing the proposed stereostructure of **2** and its C18 epimer, and comparison of these synthetic products with the degraded product **2** in the spectroscopic data, which has resulted in the unambiguous confirmation of the absolute configuration of the C14–C24 fragment.[9]

2. Results and discussion

2.1. Synthesis of (17*R*,18*R*,21*R*)-diol 15

First, we investigated the stereoselective synthesis of (17*R*,18*R*,21*R*)-diol **15** (Scheme 2). The coupling reaction of known aldehyde **5**, which was prepared from *cis*-2-butene-1,4-diol,[10] with propionyl oxazolidinethione **6** (1.5 equiv) was performed in the presence of $TiCl_4$ (1.6 equiv)/(−)-sparteine (3.8 equiv) to give Evans type *syn* aldol adduct **7** as a single stereoisomer.[11] The absolute configuration at the C17 position was determined by the modified Mosher method.[7] The alcohol **7** was transformed to lactone **9** for the stereochemical elucidation at the C18 position. Thus, removal of the oxazolidinethione chiral auxiliary with DIBALH and subsequent Wittig reaction of the resulting aldehyde with $Ph_3P{=}CHCO_2Me$ provided α,β-unsaturated ester **8**. Hydrogenation of **8** was carried out with H_2 and Pd/C in EtOAc, and the ester moiety was reduced with DIBALH to afford the corresponding diol. Treatment of the diol with TEMPO/NaClO gave the lactone **9**.[12] The NOEs H-17/H-20α and CH_3-18/H-20β were observed as shown with the arrows, which confirmed the absolute configuration at C18 position of **9** to be *R*. Therefore, the absolute configuration of **7** was elucidated to be 17*R* and 18*S*.

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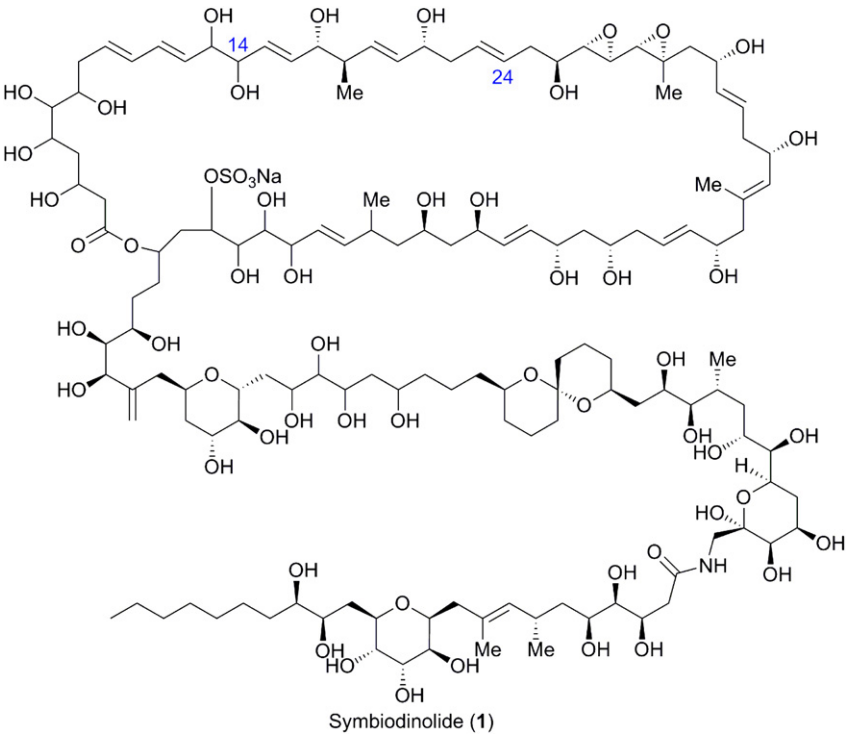
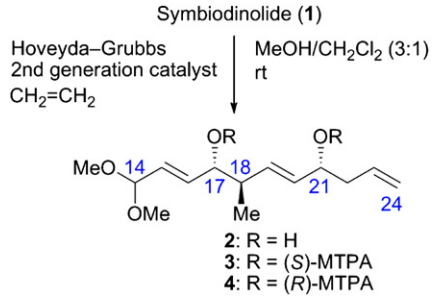
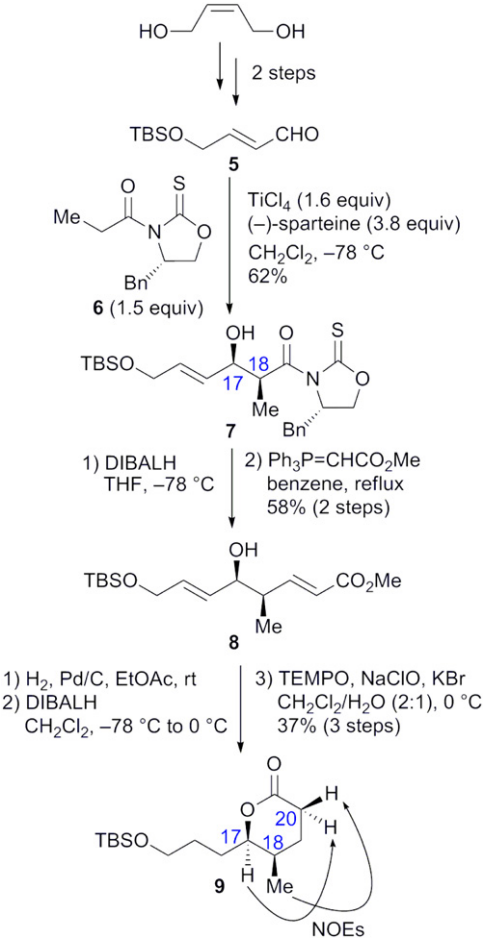


Figure 1. Structure of symbiodinolide (**1**).



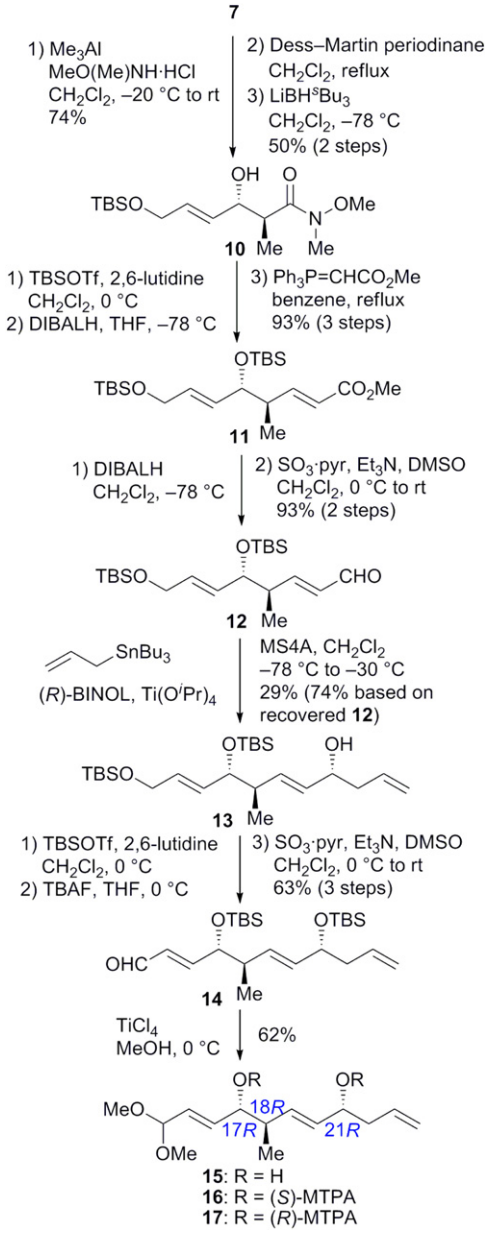
Scheme 1. Degradation of symbiodinolide (**1**) via the cross-metathesis with ethylene.

Further transformation of **7** to the (17*R*,18*R*,21*R*)-diol **15** was described in Scheme 3. The oxazolidinethione chiral auxiliary was removed by transamination with Me_3Al/MeO(Me)NH·HCl to give the corresponding Weinreb amide.[13] Dess–Martin periodinane oxidation[14] and subsequent diastereoselective reduction[15] yielded alcohol **10** as a sole product.[16,17] Protection of the resulting hydroxy group of **10** with TBSOTf/2,6-lutidine afforded the corresponding TBS ether. Reduction of the amide moiety with DIBALH and Wittig homologation with $Ph_3P{=}CHCO_2Me$ provided α,β-unsaturated ester **11**. DIBALH reduction of **11** followed by Parikh–Doering oxidation[18] gave aldehyde **12** in 93% yield by two steps. Treatment of **12** with allyltributylstannane/(*R*)-BINOL/Ti(O^{i}Pr)$_4$/MS4A provided allylated product **13** as a sole product.[16,19] The resulting hydroxy moiety of **13** was protected with TBSOTf/2,6-lutidine to give the corresponding TBS ether. Selective removal of the primary TBS group with TBAF and subsequent Parikh–Doering oxidation[18] gave aldehyde **14** in 63% yield by three steps. Methyl acetalization and deprotection of the silyl groups in one-pot were performed with $TiCl_4$ in MeOH to provide the (17*R*,18*R*,21*R*)-diol **15**.[20] The ^{1}H NMR data of the synthetic **15** were identical to those of the degraded **2**.[6b] However, this result did not completely exclude the possibility of other stereoisomers, especially the 18-epimer, because the stereochemistries at the C17 and C21 positions of the degraded **2** were



Scheme 2. Synthesis and structural elucidation of **7**.

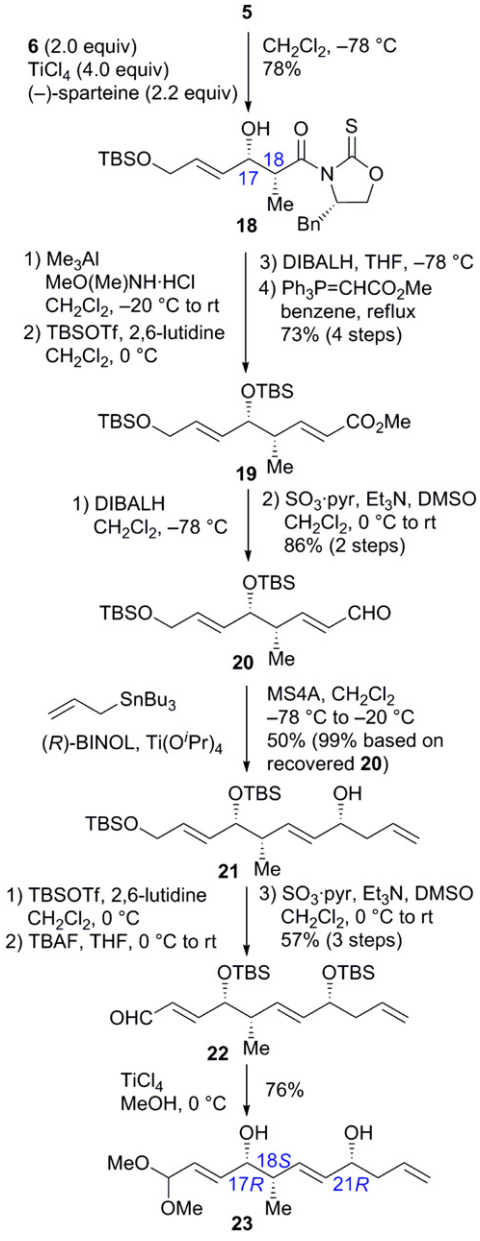
unambiguously determined by the modified Mosher method. Therefore, we next tried to synthesize (17*R*,18*S*,21*R*)-diol.



Scheme 3. Synthesis of **15**.

2.2. Synthesis of (17*R*,18*S*,21*R*)-diol 23

The stereoselective synthesis of the (17*R*,18*S*,21*R*)-diol **23** was examined through the sequence similar to that described in Scheme 2 and 3. Treatment of the aldehyde **5** with the propionyl oxazolidinethione **6** (2.0 equiv)/$TiCl_4$ (4.0 equiv)/(−)-sparteine (2.2 equiv) gave non-Evans type *syn* aldol product **18** in 78% yield as a single stereoisomer (Scheme 4).[11,21] The aldol adduct **18** was converted to α,β-unsaturated ester **19** by four-step sequence: (1) transamination with Me_3Al/MeO(Me)NH·HCl,[13] (2) silylation of the hydroxy moiety at the C17 position with TBSOTf/2,6-lutidine, (3) reduction of the amide group with DIBALH, and (4) Wittig reaction with $Ph_3P{=}CHCO_2Me$. Reduction of **19** with DIBALH and subsequent Parikh–Doering oxidation[18] gave aldehyde **20** in 86% yield by two steps. The asymmetric allylation of **20** was carried out by the Keck's procedure[19] to provide homoallylic alcohol **21** as a sole product.[16] Resulting hydroxy moiety of **21** was protected as the TBS ether, followed by selective desilylation and Parikh–Doering oxidation[18] afforded aldehyde **22** in 57% yield by three steps. Final transformation including acetalization and desilylation was carried out with $TiCl_4$/MeOH to give the (17*R*,18*S*,21*R*)-diol **23**.[20]



Scheme 4. Synthesis of **23**.

2.3. Confirmation of the absolute configuration

The synthetic diols **15** and **23** were submitted to the extensive 2D NMR analysis. The ^1H NMR data of the synthetic product **15** were identical to those of the degraded product **2** obtained from **1**.[6b] On the other hand, the ^1H NMR data of the synthetic adduct **23** were different from those of the degraded product **2**. The characteristic differences are the chemical shifts of H-17 and H-18 (Fig. 2). Furthermore, we synthesized bis-(*S*) and (*R*)-MTPA esters **16** and **17** from the synthetic product **15**, and compared the spectroscopic data of these synthetic bis-MTPA esters with those of the bis-MTPA esters **3** and **4** derived from **2**.[6b] The ^1H NMR data of the synthetic products **16** and **17** matched with those of **3** and **4**, respectively.

Therefore, the absolute configuration of the C14–C24 fragment of **1** was confirmed unambiguously to be 17*R*, 18*R*, and 21*R*.

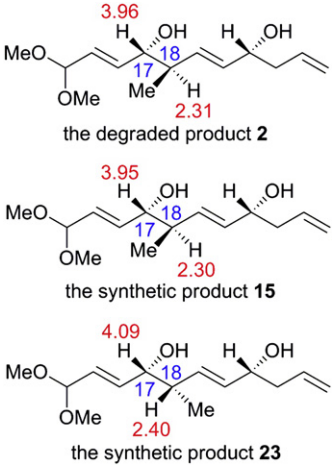


Figure 2. Chemical shifts in ppm of H-17 and H-18 of compounds **2**, **15**, and **23** referred to $CDCl_3$ (δ 7.26).

3. Conclusion

We synthesized the (17*R*,18*R*,21*R*)-diol **15** in 16 steps and the (17*R*,18*S*,21*R*)-diol **23** in 14 steps from commercially available *cis*-2-butene-1,4-diol, respectively. The spectroscopic data of the synthetic product **15** matched with those of the degraded product **2**. The bis-(*S*) and (*R*)-MTPA esters **16** and **17** prepared from **15** were identical to the bis-(*S*) and (*R*)-MTPA esters **3** and **4** derived from **2** in the spectroscopic data, which confirmed that the absolute stereochemistry of the C14–C24 fragment was 17*R*, 18*R*, and 21*R*. Further structural and synthetic studies on **1** are underway in our laboratories.

4. Experimental section

4.1. General

Reagents were used as received from commercial suppliers unless otherwise indicated. All reactions were carried out under an atmosphere of N_2 or Ar. Reaction solvents were purchased as dehydrated solvents and stored with active molecular sieves 4 Å under Ar prior to use for reactions. All solvents for work-up procedure were used as received. All inorganic salt solutions are aqueous unless otherwise stated. 'Brine' refers to saturated aqueous NaCl solution. 'Concentration' refers to removal of solvent under reduced pressure (10–100 mmHg) with a rotary evaporator, followed by a period under high vacuum (<0.1 mmHg) unless otherwise indicated. Column chromatography was performed with Fuji Silysia silica gel BW-300 or Kanto Chemical silica gel 60 N. Analytical thin-layer chromatography (TLC) was performed with glass TLC plates (Merck 0.25 mm coated silica gel 60 F_{254} plates). Data for ^{1}H NMR spectra are reported in the following format: chemical shift (multiplicity, coupling constant, number of atoms). Chemical shifts are reported in parts per million (ppm) relative to the internal residual solvent (^{1}H NMR, $CDCl_3$ 7.26 ppm or C_6D_6 7.16 ppm; ^{13}C NMR, $CDCl_3$ 77.0 ppm). 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.

4.1.1. Alcohol **7**. To a solution of propionyl oxazolidinethione **6** (5.00 g, 20.1 mmol) in CH_2Cl_2 (40 mL) were added $TiCl_4$ (2.3 mL, 21.1 mmol) and (−)-sparteine (11.7 mL, 51.0 mmol) at 0 °C. The mixture was stirred for 20 min at 0 °C. To the mixture was added aldehyde **5** (2.68 g, 13.4 mmol) in CH_2Cl_2 (3.0+2.0 mL rinse) at −78 °C. After the mixture was stirred for 40 min at the same temperature, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc, 10:1, 5:1, 1:1) gave alcohol **7** (3.70 g, 62%): colorless solid; R_f=0.20 (hexane/EtOAc, 4:1); mp 73 °C; $[\alpha]_D^{28}$ +58.6 (*c* 0.50, $CHCl_3$); IR (neat) 3532, 2949, 1673 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.19 (m, 5H), 5.85 (dt, *J*=15.5, 4.4 Hz, 1H), 5.71 (dd, *J*=15.5, 5.6 Hz, 1H), 4.93–4.88 (m, 1H), 4.80–4.73 (m, 1H), 4.55 (t, *J*=4.4 Hz, 1H), 4.33–4.25 (m, 2H), 4.18 (d, *J*=4.4 Hz, 2H), 3.24 (dd, *J*=13.4, 3.4 Hz, 1H), 2.76 (dd, *J*=13.4, 10.1 Hz, 1H), 1.28 (d, *J*=7.0 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.0, 177.3, 135.0, 131.7, 129.3, 129.0, 128.8, 127.4, 72.3, 70.3, 63.1, 60.2, 42.9, 37.6, 26.0, 18.5, 11.1, −5.1; HRMS (ESI-TOF) calcd for $C_{23}H_{35}NO_4SSiNa$ $(M+Na)^+$ 472.1954, found 472.1964.

4.1.2. Ester **8**. To a solution of oxazolidinethione **7** (31.0 mg, 69.0 μmol) in THF (1.0 mL) was added DIBALH (1.04 M in hexane, 0.41 mL, 0.414 mmol) at −78 °C. After the mixture was stirred for 10 min at the same temperature, the reaction was quenched with MeOH. The mixture was filtered through a Celite pad and washed with EtOAc. Concentration and short column chromatography (hexane/EtOAc, 10:1) gave the corresponding aldehyde (12.0 mg), which was used for the next reaction without further purification.

To a solution of the aldehyde obtained above (12.0 mg) in benzene (1.0 mL) was added $Ph_3P{=}CHCO_2Me$ (62.0 mg, 0.186 mmol) at room temperature. The mixture was stirred for 4 h at reflux conditions. Concentration and column chromatography (hexane/EtOAc, 10:1) gave ester **8** (12.6 mg, 58% in two steps): colorless oil; R_f=0.29 (hexane/EtOAc, 4:1); $[\alpha]_D^{26}$ +4.8 (*c* 0.63, $CHCl_3$); IR (neat) 3446, 2929, 1726, 1656 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (dd, *J*=15.8, 7.7 Hz, 1H), 5.84 (dd, *J*=15.8, 1.3 Hz, 1H), 5.78 (dt, *J*=15.4, 4.3 Hz, 1H), 5.68 (ddt, *J*=15.4, 6.3, 1.5 Hz, 1H), 4.16 (br d, *J*=4.3 Hz, 2H), 4.11–4.10 (m, 1H), 3.71 (s, 3H), 2.56–2.47 (m, 1H), 1.06 (d, *J*=6.8 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 150.3, 132.2, 129.4, 121.5, 75.1, 62.9, 51.5, 42.5, 26.0, 18.4, 14.5, −5.2; HRMS (ESI-TOF) calcd for $C_{16}H_{30}O_4SiNa$ $(M+Na)^+$ 337.1811, found 337.1844.

4.1.3. Lactone **9**. The mixture of ester **8** (9.0 mg, 28.6 μmol) and Pd/C (1.0 mg) was stirred under H_2 atmosphere for 10 min at room temperature. The catalyst was filtered off. Concentration and short column chromatography (hexane/EtOAc, 10:1) gave the corresponding alkane (6.4 mg), which was used for the next reaction without further purification.

To a solution of the ester obtained above (6.4 mg) in CH_2Cl_2 (1.0 mL) was added DIBALH (1.02 M in hexane, 91.0 μL, 94.2 μmol) at −78 °C. The mixture was warmed to 0 °C and stirred for 20 min at the same temperature. The reaction was quenched with MeOH. The mixture was filtered through a Celite pad and washed with EtOAc. Concentration and short column chromatography (hexane/EtOAc, 3:1) gave the corresponding diol (3.5 mg), which was used for the next reaction without further purification.

To a solution of the diol obtained above (3.5 mg) in CH_2Cl_2 (0.6 mL) and H_2O (0.3 mL) were added aqueous KBr (1.0 M, 94.0 μL), TEMPO (catalytic amount), and NaClO (1:1 mixture of commercially available bleach solution and saturated aqueous $NaHCO_3$, a few drops) at 0 °C. After the mixture was stirred for 10 min at the same temperature, the reaction was quenched with saturated aqueous Na_2SO_3. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc, 6:1) gave lactone **9** (3.0 mg, 37% in three steps): colorless oil; R_f=0.71 (hexane/EtOAc, 1:1); $[\alpha]_D^{28}$ +40.8

(c 0.13, $CHCl_3$); IR (neat) 2927, 1739 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 3.76–3.72 (m, 1H, H17), 3.54–3.49 (m, 1H, H14a), 3.45–3.40 (m, 1H, H14b), 2.17–2.09 (m, 1H, H20β), 2.05–1.97 (m, 1H, H20α), 1.67–1.18 (m, 7H, H15a,b, H16a,b, H18, and H19a,b), 0.97 (s, 9H, TBS), 0.53 (d, J=7.1 Hz, 3H, CH_3-18), 0.05 (s, 3H, TBS), 0.05 (s, 3H, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.8, 62.6, 29.4, 28.7, 28.6, 26.9, 26.2, 26.0, 12.6, −5.2; HRMS (ESI-TOF) calcd for $C_{15}H_{30}O_3SiNa$ $(M+Na)^+$ 309.1862, found 309.1870.

4.1.4. Alcohol ***10***. To a solution of MeO(Me)NH·HCl (2.18 g, 22.4 mmol) in CH_2Cl_2 (35 mL) was added Me_3Al (1.08 M in hexane, 21.0 mL, 22.4 mmol) at 0 °C. The mixture was stirred for 30 min at room temperature. To the mixture was added oxazolidinethione **7** (3.35 g, 7.45 mmol) in CH_2Cl_2 (7.0+3.0 mL rinse) at −20 °C. The mixture was warmed to room temperature and stirred for 1 h at the same temperature. The reaction was quenched with MeOH. The mixture was filtered through a Celite pad and washed with EtOAc. Concentration and column chromatography (hexane/EtOAc, 6:1, 2:1) gave the corresponding amide (1.76 g, 74%): yellow oil; R_f=0.43 (hexane/EtOAc, 1:1); $[\alpha]_D^{25}$ +13.5 (c 0.15, $CHCl_3$); IR (neat) 3436, 2927, 1639 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.85 (dt, J=15.6, 4.5 Hz, 1H), 5.66 (dd, J=15.6, 5.5 Hz, 1H), 4.44 (br s, 1H), 4.18 (d, J=4.5 Hz, 2H), 3.72 (br s, 1H), 3.68 (s, 3H), 3.18 (s, 3H), 2.93 (br s, 1H), 1.15 (d, J=7.1 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.1, 129.1, 71.9, 63.2, 61.6, 39.6, 26.0, 18.5, 10.7, −5.1, −5.1; HRMS (ESI-TOF) calcd for $C_{15}H_{31}NO_4SiNa$ $(M+Na)^+$ 340.1920, found 340.1908.

To a solution of the alcohol obtained above (207 mg, 0.652 mmol) in CH_2Cl_2 (3.3 mL) was added Dess–Martin periodinane (1.10 g, 2.60 mmol) at room temperature. The mixture was stirred for 2 h at reflux conditions. Short column chromatography (hexane/EtOAc, 4:1) gave the corresponding ketone (197 mg), which was used for the next reaction without further purification.

To a solution of the ketone obtained above (197 mg) in CH_2Cl_2 (3.1 mL) was added $LiBH^sBu_3$ (1.00 M in THF, 0.75 mL, 0.75 mmol) at −78 °C. After the mixture was stirred for 20 min at the same temperature, the reaction was quenched with MeOH. Concentration and column chromatography (hexane/EtOAc, 4:1, 2:1) gave alcohol **10** (104 mg, 50% in two steps): colorless oil; R_f=0.30 (hexane/EtOAc, 1:1); $[\alpha]_D^{26}$ +18.8 (c 0.78, $CHCl_3$); IR (neat) 3434, 2930, 1642 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.82 (dtd, J=15.3, 4.3, 0.9 Hz, 1H), 5.71 (ddt, J=15.3, 6.1, 1.4 Hz, 1H), 4.21–4.18 (m, 1H), 4.17 (dt, J=4.3, 1.4 Hz, 2H), 3.68 (s, 3H), 3.17 (s, 3H), 2.97 (br s, 1H), 1.18 (d, J=7.1 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.5, 130.3, 74.5, 63.0, 61.5, 40.6, 40.6, 26.0, 18.4, 14.9, −5.1; HRMS (ESI-TOF) calcd for $C_{15}H_{31}NO_4SiNa$ $(M+Na)^+$ 340.1920, found 340.1927.

4.1.5. Ester ***11***. To a solution of alcohol **10** (162 mg, 0.509 mmol) in CH_2Cl_2 (5.0 mL) were added 2,6-lutidine (0.28 mL, 2.44 mmol) and TBSOTf (0.42 mL, 1.83 mmol) at 0 °C. The mixture was stirred for 40 min at the same temperature. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and short column chromatography (hexane/EtOAc, 9:1) gave the corresponding silyl ether (225 mg), which was used for the next reaction without further purification.

To a solution of the amide obtained above (225 mg) in THF (5.0 mL) was added DIBALH (1.04 M in hexane, 0.98 mL, 1.01 mmol) at −78 °C. After the mixture was stirred for 1 h at the same temperature, the reaction was quenched with MeOH and H_2O. The mixture was filtered through a Celite pad and washed with EtOAc. Concentration and short column chromatography (hexane/EtOAc, 10:1) gave the corresponding aldehyde (180 mg), which was used for the next reaction without further purification.

To a solution of the aldehyde obtained above (180 mg) in benzene (2.5 mL) was added $Ph_3P{=}CHCO_2Me$ (565 mg, 1.69 mmol) at room temperature. The mixture was stirred for 4 h at reflux conditions. Concentration and column chromatography (hexane/EtOAc, 10:1) gave ester **11** (203 mg, 93% in three steps): colorless oil; R_f=0.46 (hexane/EtOAc, 10:1); $[\alpha]_D^{26}$ +12.6 (c 0.90, $CHCl_3$); IR (neat) 2929, 1730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.94 (dd, J=15.7, 7.8 Hz, 1H), 5.77 (d, J=15.7 Hz, 1H), 5.65 (dt, J=15.4, 4.4 Hz, 1H), 5.56 (dd, J=15.4, 6.2 Hz, 1H), 4.14 (d, J=4.4 Hz, 2H), 4.01 (t, J=6.2 Hz, 1H), 3.70 (s, 3H), 2.43–2.35 (m, 1H), 1.00 (d, J=6.8 Hz, 3H), 0.88 (s, 9H), 0.86 (s, 9H), 0.04 (s, 6H), 0.01 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 151.4, 130.9, 130.6, 120.9, 76.2, 63.0, 51.4, 43.7, 26.0, 25.9, 18.4, 18.2, 15.2, −4.1, −4.8, −5.1; HRMS (ESI-TOF) calcd for $C_{22}H_{44}O_4Si_2Na$ $(M+Na)^+$ 451.2676, found 451.2688.

4.1.6. Aldehyde ***12***. To a solution of ester **11** (16.0 mg, 37.3 μmol) in CH_2Cl_2 (1.0 mL) was added DIBALH (1.04 M in hexane, 87.0 μL, 90.0 μmol) at −78 °C. After the mixture was stirred for 10 min at the same temperature, the reaction was quenched with MeOH. The mixture was filtered through a Celite pad and washed with EtOAc. Concentration and short column chromatography (hexane/EtOAc, 10:1) gave the corresponding alcohol (14.2 mg), which was used for the next reaction without further purification.

To a solution of the alcohol obtained above (14.2 mg) in CH_2Cl_2 (0.3 mL) and DMSO (0.2 mL) were added Et_3N (0.14 mL, 0.984 mmol) and SO_3·pyr (71.2 mg, 0.448 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 2 h at the same temperature. The mixture was diluted with Et_2O, washed with saturated aqueous NH_4Cl, H_2O, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc, 50:1) gave aldehyde **12** (13.9 mg, 93% in two steps): colorless oil; R_f=0.70 (hexane/EtOAc, 4:1); $[\alpha]_D^{25}$ +9.8 (c 0.23, $CHCl_3$); IR (neat) 2929, 1697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.48 (d, J=7.8 Hz, 1H), 6.85 (dd, J=15.8, 7.8 Hz, 1H), 6.07 (dd, J=15.8, 7.8 Hz, 1H), 5.68 (dt, J=15.3, 4.2 Hz, 1H), 5.58 (dd, J=15.3, 6.0 Hz, 1H), 4.14 (d, J=4.2 Hz, 2H), 4.06 (t, J=6.0 Hz, 1H), 2.57–2.49 (m, 1H), 1.07 (d, J=6.8 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.04 (s, 6H), 0.03 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.9, 160.5, 132.8, 131.2, 130.5, 76.3, 62.9, 44.1, 25.9, 25.9, 18.4, 18.3, 15.6, −3.9, −4.8, −5.1; HRMS (ESI-TOF) calcd for $C_{21}H_{42}O_3Si_2Na$ $(M+Na)^+$ 421.2570, found 421.2579.

4.1.7. Homoallylic alcohol ***13***. To a mixture of (*R*)-BINOL (55.5 mg, 0.194 mmol) and MS 4 Å (20 mg) in CH_2Cl_2 (0.5 mL) was added Ti(O^iPr)$_4$ (57.0 μL, 0.194 mmol) at room temperature. After being stirred for 1 h at reflux conditions, the mixture was cooled to room temperature. To the mixture was added a solution of aldehyde **12** (75.6 mg, 0.194 mmol) in CH_2Cl_2 (0.4+0.4 mL rinse). To the resulting mixture was added allyltributylstannane (66.0 μL, 0.213 mmol) at −78 °C. The mixture was gradually warmed to −30 °C. After the mixture was stirred for 63 h at the same temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ and MeOH. The mixture was filtered through a Celite pad and washed with EtOAc. The filtrate was dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc, 40:1, 20:1) gave homoallylic alcohol **13** (24.4 mg, 29%, 74% based on recovered starting material) and aldehyde **12** (45.6 mg, 60% recovery). For homoallylic alcohol **13**: colorless oil; R_f=0.58 (hexane/EtOAc, 4:1); $[\alpha]_D^{25}$ +5.2 (c 0.38, $CHCl_3$); IR (neat) 3433, 2929 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.79 (ddt, J=17.2, 10.2, 7.0 Hz, 1H), 5.67–5.55 (m, 3H), 5.46 (ddd, J=15.6, 6.6, 0.9 Hz, 1H), 5.13–5.08 (m, 2H), 4.14 (d, J=4.1 Hz, 2H), 4.13–4.08 (m, 1H), 3.98 (t, J=5.3 Hz, 1H), 2.32–2.22 (m, 3H), 0.94 (d, J=6.8 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.05 (s, 6H), 0.02 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.4, 134.0, 132.1, 131.1, 130.2, 117.8, 76.6, 72.0, 63.3, 43.2, 42.0, 26.0, 26.0, 18.5, 18.3, 15.6, −4.1, −4.7, −5.1; HRMS (ESI-TOF) calcd for $C_{24}H_{48}O_3Si_2Na$ $(M+Na)^+$ 463.3040, found 463.3042.

4.1.8. Aldehyde ***14***. To a solution of alcohol **13** (14.3 mg, 32.4 μmol) in CH_2Cl_2 (1.0 mL) were added 2,6-lutidine (9.0 μL, 77.8 μmol) and

TBSOTf (13.0 μL, 58.3 μmol) at 0 °C. The mixture was stirred for 20 min at the same temperature. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and short column chromatography (hexane/EtOAc, 20:1) gave the corresponding silyl ether (17.8 mg), which was used for the next reaction without further purification.

To a solution of the silyl ether obtained above (17.8 mg) in THF (1.0 mL) was added TBAF (1.0 M in THF, 0.16 mL, 0.160 mmol) at 0 °C. After being stirred for 2 h at the same temperature, the mixture was filtered through a silica gel pad and washed with Et_2O. Concentration and column chromatography (hexane/EtOAc, 40:1, 20:1) gave the corresponding alcohol (8.6 mg), which was used for the next reaction without further purification.

To a solution of the alcohol obtained above (8.6 mg) in CH_2Cl_2 (0.4 mL) and DMSO (0.2 mL) were added Et_3N (72.0 μL, 0.516 mmol) and SO_3·pyr (36.8 mg, 0.234 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 3 h at the same temperature. The mixture was diluted with Et_2O, washed with saturated aqueous NH_4Cl, H_2O, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc, 50:1) gave aldehyde **14** (9.0 mg, 63% in three steps): colorless oil; R_f=0.47 (hexane/EtOAc, 10:1); $[\alpha]_D^{25}$ −30.0 (*c* 0.15, $CHCl_3$); IR (neat) 2928, 1697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.51 (d, *J*=8.0 Hz, 1H), 6.73 (dd, *J*=15.5, 4.5 Hz, 1H), 6.23 (ddd, *J*=15.5, 8.0, 1.7 Hz, 1H), 5.80–5.69 (m, 1H), 5.54 (dd, *J*=15.6, 6.8 Hz, 1H), 5.45 (dd, *J*=15.6, 6.0 Hz, 1H), 5.03–4.99 (m, 2H), 4.34 (td, *J*=4.5, 1.7 Hz, 1H), 4.10 (q, *J*=6.0 Hz, 1H), 2.47–2.39 (m, 1H), 2.28–2.15 (m, 2H), 0.99 (d, *J*=7.1 Hz, 3H), 0.91 (s, 9H), 0.87 (s, 9H), 0.06 (s, 3H), 0.06 (s, 3H), 0.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.1, 158.1, 134.9, 134.4, 131.9, 130.2, 116.8, 75.3, 73.0, 43.2, 42.7, 25.9, 25.8, 18.3, 18.2, 15.4, −4.2, −4.5, −4.6, −4.9; HRMS (ESI-TOF) calcd for $C_{24}H_{46}O_3Si_2Na$ $(M+Na)^+$ 461.2883, found 461.2886.

*4.1.9. Diol **15**.* To a solution of aldehyde **14** (23.7 mg, 54.0 μmol) in MeOH (2.5 mL) was added $TiCl_4$ (1.00 M in CH_2Cl_2, 0.54 mL, 0.540 mmol) at 0 °C. After the mixture was stirred for 20 min at the same temperature, the reaction was quenched with Et_3N. The mixture was filtered through a silica gel pad and washed with EtOAc. Concentration and column chromatography (hexane/EtOAc, 1:1, 1:3) gave diol **15** (8.6 mg, 62%): colorless oil; R_f=0.30 (hexane/EtOAc, 1:3); $[\alpha]_D^{23}$ −27.4 (*c* 0.13, CH_3OH); IR (neat) 3399, 2925 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.86 (dd, *J*=15.6, 6.0 Hz, 1H), 5.83–5.76 (m, 1H), 5.68 (dd, *J*=15.6, 4.8 Hz, 1H), 5.61–5.59 (m, 2H), 5.16–5.12 (m, 2H), 4.81 (d, *J*=4.8 Hz, 1H), 4.19–4.16 (m, 1H), 3.95 (t, *J*=6.6 Hz, 1H), 3.32 (s, 3H), 3.32 (s, 3H), 2.36–2.27 (m, 3H), 1.02 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.3, 134.3, 134.1, 132.4, 128.3, 118.2, 102.4, 75.2, 71.5, 52.8, 52.7, 42.7, 42.0, 16.4; HRMS (ESI-TOF) calcd for $C_{14}H_{24}O_4Na$ $(M+Na)^+$ 279.1572, found 279.1591.

*4.1.10. Bis-(S)-MTPA ester **16**.* To a solution of diol **15** (0.9 mg, 3.5 μmol) in CH_2Cl_2 (0.2 mL) were added DMAP (1.7 mg, 14.0 μmol), Et_3N (1.4 μL, 9.8 μmol), and (*R*)-MTPACl (1.6 μL, 8.4 μmol) at 0 °C. After the mixture was stirred for 10 min at the same temperature, the reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc, 20:1) gave bis-(*S*)-MTPA ester **16** (1.8 mg, 74%): colorless oil; R_f=0.33 (hexane/EtOAc, 4:1); $[\alpha]_D^{24}$ −45.4 (*c* 0.06, $CHCl_3$); IR (neat) 2924, 1748 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.50–7.47 (m, 4H, Ph), 7.42–7.36 (m, 6H, Ph), 5.73–5.60 (m, 3H, H15, H19, and H23), 5.68 (dd, *J*=16.2, 6.0 Hz, 1H, H16), 5.48–5.44 (m, 2H, H20 and H21), 5.34 (t, *J*=6.0 Hz, 1H, H17), 5.11–5.09 (m, 2H, H24a,b), 4.74 (d, *J*=4.2 Hz, 1H, H14), 3.53 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 3.24 (s, 3H, OCH_3), 3.24 (s, 3H, OCH_3), 2.57–2.51 (m, 1H, H18), 2.46–2.34 (m, 2H, H22a,b), 0.97 (d, *J*=6.6 Hz, 3H, CH_3-18); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 165.6, 134.4, 132.5, 132.2, 132.0, 131.8, 129.5, 129.5, 128.8, 128.5, 128.3, 128.2, 127.4, 127.3, 118.6, 101.3, 79.1, 76.0, 55.6, 55.5, 52.5, 52.4, 40.1, 38.7, 15.7; HRMS (ESI-TOF) calcd for $C_{34}H_{38}F_6O_8Na$ $(M+Na)^+$ 711.2369, found 711.2394.

*4.1.11. Bis-(R)-MTPA ester **17**.* To a solution of diol **15** (3.9 mg, 15.2 μmol) in CH_2Cl_2 (0.2 mL) were added DMAP (3.7 mg, 30.4 μmol), Et_3N (5.6 μL, 42.6 μmol), and (*S*)-MTPACl (6.8 μL, 36.5 μmol) at 0 °C. After the mixture was stirred for 10 min at the same temperature, the reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc, 15:1) gave bis-(*R*)-MTPA ester **17** (8.6 mg, 82%): colorless oil; R_f=0.33 (hexane/EtOAc, 4:1); $[\alpha]_D^{25}$ +39.1 (*c* 0.07, $CHCl_3$); IR (neat) 2925, 1748 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.51–7.49 (m, 4H, Ph), 7.40–7.39 (m, 6H, Ph), 5.79 (dd, *J*=15.6, 7.2 Hz, 1H, H16), 5.72 (dd, *J*=15.6, 4.0 Hz, 1H, H15), 5.70 (dd, *J*=15.6, 7.8 Hz, 1H, H19), 5.64–5.62 (m, 1H, H23), 5.53 (dd, *J*=15.6, 7.0 Hz, 1H, H20), 5.44 (q, *J*=7.0 Hz, 1H, H21), 5.41–5.39 (m, 1H, H17), 5.02–5.00 (m, 2H, H24a,b), 4.78 (d, *J*=4.0 Hz, 1H, H14), 3.51 (s, 3H, OCH_3), 3.51 (s, 3H, OCH_3), 3.25 (s, 3H, OCH_3), 3.25 (s, 3H, OCH_3), 2.58–2.53 (m, 1H, H18), 2.40–2.30 (m, 2H, H22a,b), 0.95 (d, *J*=7.2 Hz, 3H, CH_3-18); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 165.6, 134.8, 132.4, 132.2, 129.6, 129.5, 128.8, 128.6, 128.3, 128.2, 127.3, 118.5, 101.1, 79.1, 76.1, 55.4, 52.4, 52.4, 40.1, 38.6, 15.5; HRMS (ESI-TOF) calcd for $C_{34}H_{38}F_6O_8Na$ $(M+Na)^+$ 711.2369, found 711.2395.

*4.1.12. Alcohol **18**.* To a solution of propionyl oxazolidinethione **6** (957 mg, 3.84 mmol) in CH_2Cl_2 (13 mL) were added $TiCl_4$ (0.84 mL, 7.68 mmol) and (−)-sparteine (0.97 mL, 4.22 mmol) at 0 °C. The mixture was stirred for 20 min at 0 °C. To the mixture was added aldehyde **5** (385 mg, 1.92 mmol) in CH_2Cl_2 (1.0+1.0 mL rinse) at −78 °C. After the mixture was stirred for 1 h at the same temperature, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc, 12:1, 6:1) gave alcohol **18** (674 mg, 78%): colorless solid; R_f=0.29 (hexane/EtOAc, 4:1); mp 78 °C; $[\alpha]_D^{26}$ +78.8 (*c* 0.85, $CHCl_3$); IR (neat) 3507, 2929, 1688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.20 (m, 5H), 5.89 (dt, *J*=15.4, 4.4 Hz, 1H), 5.78 (dd, *J*=15.4, 5.3 Hz, 1H), 4.98–4.88 (m, 2H), 4.67 (br s, 1H), 4.33–4.25 (m, 2H), 4.21 (br d, *J*=4.4 Hz, 2H), 3.27 (dd, *J*=13.3, 3.4 Hz, 1H), 2.74 (dd, *J*=13.3, 10.1 Hz, 1H), 2.63 (d, *J*=3.2 Hz, 1H), 1.20 (d, *J*=6.8 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.2, 177.0, 135.1, 131.8, 129.3, 129.0, 128.6, 127.4, 72.2, 70.2, 63.1, 60.1, 42.5, 37.9, 26.0, 18.5, 11.0, −5.1; HRMS (ESI-TOF) calcd for $C_{23}H_{35}NO_4SSiNa$ $(M+Na)^+$ 472.1954, found 472.1956.

*4.1.13. Ester **19**.* To a solution of MeO(Me)NH·HCl (195 mg, 2.00 mmol) in CH_2Cl_2 (4.0 mL) was added Me_3Al (1.08 M in hexane, 1.9 mL, 2.00 mmol) at 0 °C. The mixture was stirred for 30 min at room temperature. To the mixture was added oxazolidinethione **18** (300 mg, 0.667 mmol) in CH_2Cl_2 (0.7+0.3 mL rinse) at −20 °C. The mixture was warmed to room temperature and stirred for 1 h at the same temperature. The reaction was quenched with MeOH. The mixture was filtered through a Celite pad and washed with EtOAc. Concentration and short column chromatography (hexane/EtOAc, 4:1) gave the corresponding amide (211 mg), which was used for the next reaction without further purification: ^1H NMR (400 MHz, $CDCl_3$) δ 5.85 (dt, *J*=15.6, 4.5 Hz, 1H), 5.66 (dd, *J*=15.6, 5.5 Hz, 1H), 4.44 (br s, 1H), 4.18 (d, *J*=4.5 Hz, 2H), 3.68 (s, 3H), 3.18 (s, 3H), 2.93 (br s, 1H), 1.15 (d, *J*=7.1 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H).

To a solution of alcohol obtained above (211 mg) in CH_2Cl_2 (3.3 mL) were added 2,6-lutidine (0.37 mL, 3.20 mmol) and TBSOTf (0.55 mL, 2.40 mmol) at 0 °C. The mixture was stirred for 20 min at the same temperature. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and short column chromatography (hexane/EtOAc, 9:1) gave the

corresponding silyl ether (276 mg), which was used for the next reaction without further purification.

To a solution of the amide obtained above (276 mg) in THF (5.0 mL) was added DIBALH (1.04 M in hexane, 1.30 mL, 1.30 mmol) at −78 °C. After the mixture was stirred for 1 h at the same temperature, the reaction was quenched with MeOH and H_2O. The mixture was filtered through a Celite pad and washed with EtOAc. Concentration and short column chromatography (hexane/EtOAc, 40:1) gave the corresponding aldehyde (184 mg), which was used for the next reaction without further purification.

To a solution of the aldehyde obtained above (184 mg) in benzene (5.0 mL) was added $Ph_3P{=}CHCO_2Me$ (769 mg, 2.30 mmol) at room temperature. The mixture was stirred for 4 h at reflux conditions. Concentration and column chromatography (hexane/EtOAc, 10:1) gave ester **19** (209 mg, 73% in four steps): colorless oil; R_f=0.46 (hexane/EtOAc, 10:1); $[\alpha]_D^{26}$ −6.3 (*c* 0.15, $CHCl_3$); IR (neat) 2929, 1729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.00 (dd, *J*=15.8, 7.6 Hz, 1H), 5.77 (d, *J*=15.8 Hz, 1H), 5.65 (dt, *J*=15.5, 4.0 Hz, 1H), 5.57 (dd, *J*=15.5, 5.8 Hz, 1H), 4.14 (d, *J*=4.0 Hz, 2H), 4.05 (t, *J*=5.8 Hz, 1H), 3.70 (s, 3H), 2.46–2.38 (m, 1H), 1.01 (d, *J*=6.8 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.04 (s, 6H), 0.02 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 151.6, 130.8, 130.3, 120.6, 75.9, 63.1, 51.4, 43.5, 26.0, 25.9, 18.4, 18.3, 14.3, −4.1, −4.8, −5.1; HRMS (ESI-TOF) calcd for $C_{22}H_{44}O_4Si_2Na$ $(M+Na)^+$ 451.2676, found 451.2690.

*4.1.14. Aldehyde **20**.* To a solution of ester **19** (90.4 mg, 0.211 mmol) in CH_2Cl_2 (2.0 mL) was added DIBALH (1.04 M in hexane, 0.49 mL, 0.506 mmol) at −78 °C. After the mixture was stirred for 10 min at the same temperature, the reaction was quenched with MeOH. The mixture was filtered through a Celite pad and washed with EtOAc. Concentration and short column chromatography (hexane/EtOAc, 10:1) gave the corresponding alcohol (79.3 mg), which was used for the next reaction without further purification.

To a solution of the alcohol obtained above (79.3 mg) in CH_2Cl_2 (1.4 mL) and DMSO (0.7 mL) were added Et_3N (0.19 mL, 1.40 mmol) and $SO_3{\cdot}$pyr (101 mg, 0.632 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 2 h at the same temperature. The mixture was diluted with Et_2O, washed with saturated aqueous NH_4Cl, H_2O, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc, 50:1) gave aldehyde **20** (72.6 mg, 86% in two steps): colorless oil; R_f=0.70 (hexane/EtOAc, 4:1); $[\alpha]_D^{26}$ −14.3 (*c* 0.35, $CHCl_3$); IR (neat) 2929, 1696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.48 (d, *J*=7.8 Hz, 1H), 6.87 (dd, *J*=15.9, 6.8 Hz, 1H), 6.07 (ddd, *J*=15.9, 7.8, 1.3 Hz, 1H), 5.69 (dt, *J*=15.4, 4.4 Hz, 1H), 5.58 (dd, *J*=15.4, 6.3 Hz, 1H), 4.15–4.11 (m, 3H), 2.62–2.54 (m, 1H), 1.06 (d, *J*=6.8 Hz, 3H), 0.88 (s, 9H), 0.88 (s, 9H), 0.04 (s, 6H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.9, 160.6, 132.5, 131.4, 129.6, 75.8, 62.9, 43.8, 25.9, 25.9, 18.4, 18.3, 14.2, −4.1, −4.8, −5.1; HRMS (ESI-TOF) calcd for $C_{21}H_{42}O_3Si_2Na$ $(M+Na)^+$ 421.2570, found 421.2574.

*4.1.15. Homoallylic alcohol **21**.* To a mixture of (*R*)-BINOL (56.1 mg, 0.196 mmol) and MS4A (20 mg) in CH_2Cl_2 (0.5 mL) was added $Ti(O^iPr)_4$ (58.0 μL, 0.196 mmol) at room temperature. After being stirred for 1 h at reflux conditions, the mixture was cooled to room temperature. To the mixture was added a solution of aldehyde **20** (78.1 mg, 0.196 mmol) in CH_2Cl_2 (0.4+0.2 mL rinse). To the resulting mixture was added allyltributylstannane (67.0 μL, 0.216 mmol) at −78 °C. The mixture was gradually warmed to −20 °C. After the mixture was stirred for 42 h at the same temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ and MeOH. The mixture was filtered through a Celite pad and washed with EtOAc. The filtrate was dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc, 30:1, 10:1) gave homoallylic alcohol **21** (42.9 mg, 50%, 99% based on recovered starting material) and aldehyde **20** (39.2 mg, 50% recovery). For homoallylic alcohol **21**: colorless oil; R_f=0.58 (hexane/EtOAc, 4:1); $[\alpha]_D^{26}$ +0.3 (*c* 1.36, $CHCl_3$); IR (neat) 3390, 2929 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.79 (ddt, *J*=17.2, 10.2, 7.0 Hz, 1H), 5.65–5.59 (m, 3H), 5.44 (dd, *J*=15.6, 6.6 Hz, 1H), 5.13–5.08 (m, 2H), 4.13 (br d, *J*=3.2 Hz, 2H), 4.09 (q, *J*=6.6 Hz, 1H), 3.95 (t, *J*=4.9 Hz, 1H), 2.33–2.19 (m, 3H), 0.96 (d, *J*=6.8 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.05 (s, 6H), 0.01 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.4, 132.0, 131.2, 130.1, 117.8, 76.6, 72.1, 63.2, 43.3, 42.1, 26.0, 26.0, 18.5, 18.3, 15.4, −4.0, −4.7, −5.1; HRMS (ESI-TOF) calcd for $C_{24}H_{48}O_3Si_2Na$ $(M+Na)^+$ 463.3040, found 463.3054.

*4.1.16. Aldehyde **22**.* To a solution of alcohol **21** (5.6 mg, 12.7 μmol) in CH_2Cl_2 (0.5 mL) were added 2,6-lutidine (3.6 μL, 30.5 μmol) and TBSOTf (5.3 μL, 22.9 μmol) at 0 °C. The mixture was stirred for 10 min at the same temperature. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and short column chromatography (hexane/EtOAc, 80:1) gave the corresponding silyl ether (5.9 mg), which was used for the next reaction without further purification.

To a solution of the silyl ether obtained above (5.9 mg) in THF (0.5 mL) was added TBAF (1.0 M in THF, 0.11 mL, 0.110 mmol) at 0 °C. After being stirred for 20 min at room temperature, the mixture was filtered through a silica gel pad and washed with Et_2O. Concentration and column chromatography (hexane/EtOAc, 60:1) gave the corresponding alcohol (5.5 mg), which was used for the next reaction without further purification.

To a solution of the alcohol obtained above (5.5 mg) in CH_2Cl_2 (0.2 mL) and DMSO (0.1 mL) were added Et_3N (10.0 μL, 70.0 μmol) and $SO_3{\cdot}$pyr (5.1 mg, 31.8 μmol) at 0 °C. The mixture was warmed to room temperature and stirred for 1 h at the same temperature. The mixture was diluted with Et_2O, washed with saturated aqueous NH_4Cl, H_2O, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc, 80:1) gave aldehyde **22** (3.2 mg, 57% in three steps): colorless oil; R_f=0.47 (hexane/EtOAc, 10:1); $[\alpha]_D^{26}$ −24.8 (*c* 0.60, $CHCl_3$); IR (neat) 2929, 1697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.53 (d, *J*=7.9 Hz, 1H), 6.76 (dd, *J*=15.5, 4.7 Hz, 1H), 6.21 (ddd, *J*=15.5, 7.9, 1.5 Hz, 1H), 5.79–5.68 (m, 1H), 5.46–5.43 (m, 2H), 5.02–4.98 (m, 2H), 4.20 (td, *J*=4.7, 1.5 Hz, 1H), 4.07 (q, *J*=5.9 Hz, 1H), 2.41–2.33 (m, 1H), 2.27–2.13 (m, 2H), 1.02 (d, *J*=6.8 Hz, 3H), 0.90 (s, 9H), 0.86 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H), −0.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.2, 158.1, 134.9, 134.4, 131.9, 130.7, 116.7, 75.6, 73.3, 43.2, 43.1, 25.9, 25.8, 18.3, 18.2, 16.1, −4.1, −4.4, −4.6, −4.8; HRMS (ESI-TOF) calcd for $C_{24}H_{46}O_3Si_2Na$ $(M+Na)^+$ 461.2883, found 461.2895.

*4.1.17. Diol **23**.* To a solution of aldehyde **22** (1.8 mg, 4.10 μmol) in MeOH (0.2 mL) was added $TiCl_4$ (1.00 M in CH_2Cl_2, 4.5 μL, 41.0 μmol) at 0 °C. After the mixture was stirred for 20 min at the same temperature, the reaction was quenched with Et_3N. The mixture was filtered through a silica gel pad and washed with EtOAc including 1% Et_3N. Concentration and column chromatography (hexane/EtOAc including 1% Et_3N, 4:1, 1:1) gave diol **23** (0.8 mg, 76%): colorless oil; R_f=0.35 (hexane/EtOAc, 1:3); $[\alpha]_D^{23}$ −13.2 (*c* 0.08, CH_3OH); IR (neat) 3398, 2925 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.87 (dd, *J*=15.6, 6.0 Hz, 1H), 5.83–5.76 (m, 1H), 5.66 (dd, *J*=15.6, 4.8 Hz, 1H), 5.64–5.55 (m, 2H), 5.16–5.12 (m, 2H), 4.81 (d, *J*=4.8 Hz, 1H), 4.18–4.15 (m, 1H), 4.09 (br d, *J*=3.6 Hz, 1H), 3.32 (s, 3H), 3.32 (s, 3H), 2.43–2.37 (m, 1H), 2.35–2.27 (m, 2H), 1.04 (d, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.9, 134.2, 133.8, 132.5, 127.9, 118.2, 102.3, 74.9, 71.6, 52.7, 42.3, 42.1, 15.3; HRMS (ESI-TOF) calcd for $C_{14}H_{24}O_4Na$ $(M+Na)^+$ 279.1572, found 279.1599.

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