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SYNTHESIS OF THE C1-C7 AND C8-C18 SEGMENTS OF *ent*-AMPHIDININ A

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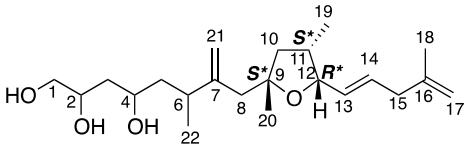
Dedicated to Professor Isao Kuwajima on the occasion of his 77th birthday

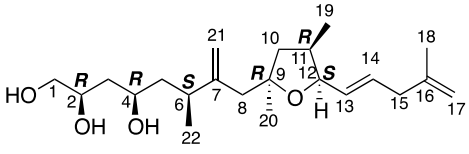
Abstract – A stereoselective synthesis of the C1-C7 and C8-C18 segments of the enantiomer of amphidinin A, a cytotoxic polyketide from the culture cells of a symbiotic marine dinoflagellate *Amphidinium* sp. (strain Y-5), has been achieved, utilizing sulfone-aldehyde coupling, Sharpless asymmetric dihydroxylation, Katsuki-Sharpless asymmetric epoxidation, and Julia-Kocienski olefination.

INTRODUCTION

Amphidinin A is a cytotoxic linear polyketide isolated from the culture cells of a symbiotic marine dinoflagellate *Amphidinium* sp. (strain Y-5) producing a number of macrolides.[1] Amphidinin A exhibits moderate cytotoxicity against murine lymphoma L1210 and human epidermoid carcinoma KB cells in vitro (IC_{50} values, 3.6 and 3.0 μg/mL, respectively). The planar structure and partial relative configuration (THF ring moiety; C9-C12) of amphidinin A were elucidated by 2D NMR in 1994.[2] In order to compare the NMR data and optical rotation of the synthetic amphidinin A with those of natural amphidinin A and to study structure-activity relationship, we started the synthesis of the C8-C18 segment of amphidinin A along with the relative configuration elucidated by NOESY data.[2] More recently, we have proposed the absolute configuration of amphidinin A as **1**[3] on the basis of *J*-based configuration analysis,[4] modified Mosher's method,[5,6] and density functional theory (DFT) calculations.[7]

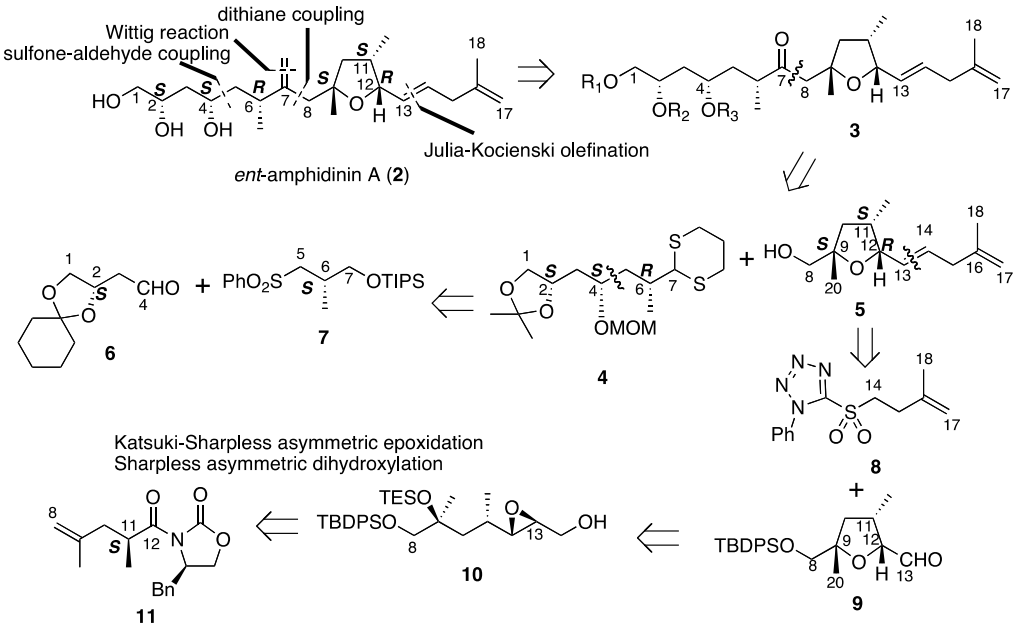


proposed structure of amphidinin A in 1994



proposed structure of amphidinin A (**1**) in 2014

The proposed absolute configuration of the C8-C18 segment in amphidinin A[3] was reverse to the relative configuration proposed in the previous paper,[2] that is, it was the enantiomer of the proposed structure of amphidinin A.[3] Therefore, in order to validate our proposed absolute configuration of amphidinin A (**1**),[3] we decided to perform a stereoselective synthesis of the C1-C7 and C8-C18 fragments of *ent*-amphidinin A (**2**) as follows (Scheme 1), employing sufone-aldehyde coupling, Sharpless asymmetric dihydroxylation,[8] Katsuki-Sharpless asymmetric epoxidation,[9] and Julia-Kocienski olefination.[10]

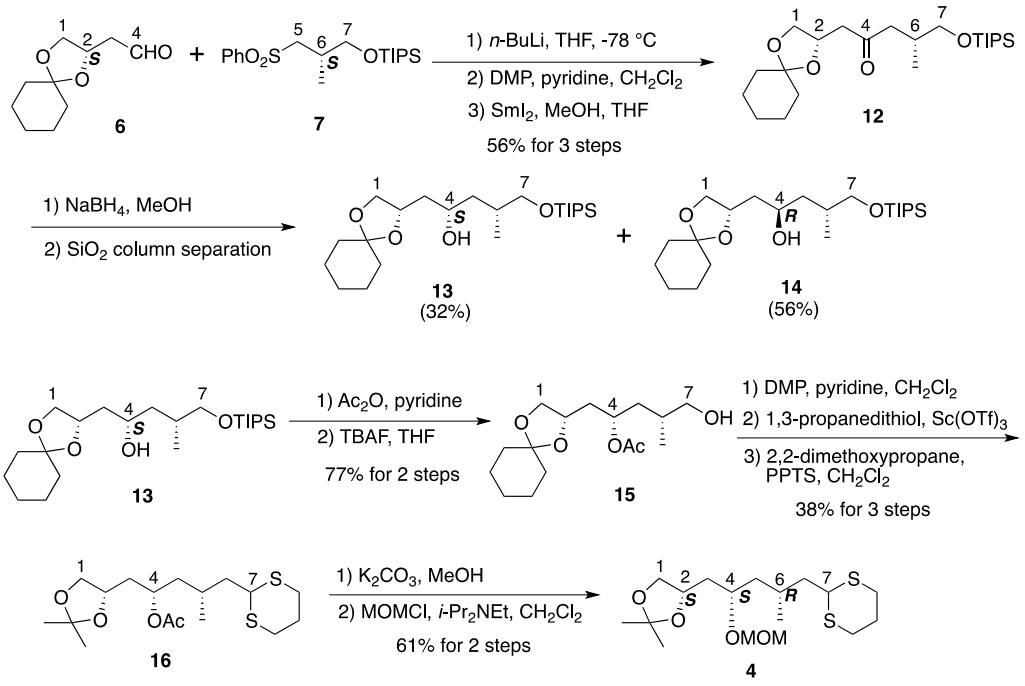


Scheme 1. Retrosynthetic analysis of *ent*-amphidinin A (**2**)

RESULTS AND DISCUSSION

As outlined retrosynthetically in Scheme 1, *ent*-amphidinin A (**2**) could be obtained by olefination of ketone **3**, which could be provided by dithiane coupling of the C1-C7 segment **4** with the C8-C18 segment **5**. The C1-C7 segment **4**, containing three stereogenic centers, could be derived via sulfone-aldehyde coupling reaction of **7**[11] with **6**.[12] The C8-C18 segment **5**, bearing a THF ring, could be synthesized by Julia-Kocienski reaction[10] between sulfone **8** and aldehyde **9**. The aldehyde **9** could be provided through THF ring formation reaction of epoxide **10**, which is conceived to be obtained via Sharpless asymmetric dihydroxyration[8] and Katsuki-Sharpless epoxidation[9] of **11**.[13]

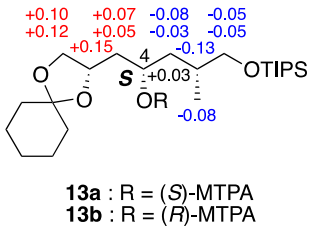
The synthesis of the C1-C7 segment **4** is described in Scheme 2. Known aldehyde **6**,[12] derived from L-malic acid in three steps, was subjected to coupling with sulfone **7**[11] to afford hydroxy sulfone, which was oxidized with Dess-Matin periodinane[14] to give the ketone bearing a sulfone. Selective removal of the sulfone moiety of the ketone was accomplished via samarium(II) iodide-mediated reduction in THF and MeOH to provide **12** in 56% yield for the three steps. Reduction of ketone **12** with $NaBH_4$ in MeOH



Scheme 2.

Synthesis of the C-1-C-7 segment **4** from **6** and **7**

gave diols **13** and **14** (32% and 56%, respectively), which were separated by silica gel column chromatography. Protection of the secondary hydroxy group in **13** with Ac_2O in pyridine provided the acetate, the TIPS group of which was removed by TBAF in THF to yield alcohol **15** in 77% yield for the two steps. Oxidation of **15** with Dess-Martin periodinane[14] was followed by 1,3-dithiane ring formation catalyzed by $Sc(OTf)_2$ to yield dithiane with 1,2-diol moiety, which was treated with 2,2-dimethoxypropane and PPTS to afford dithiane **16**. The acetyl group in **16** was removed with K_2CO_3 in MeOH to provide alcohol, the secondary hydroxy group of which was protected as the MOM ether to furnish the (2*S*,4*S*,6*R*)-C1-C7 segment **4** due to the absolute configuration of the starting materials (**6**, **7)** and a modified Mosher's method as follows (Figure 1).



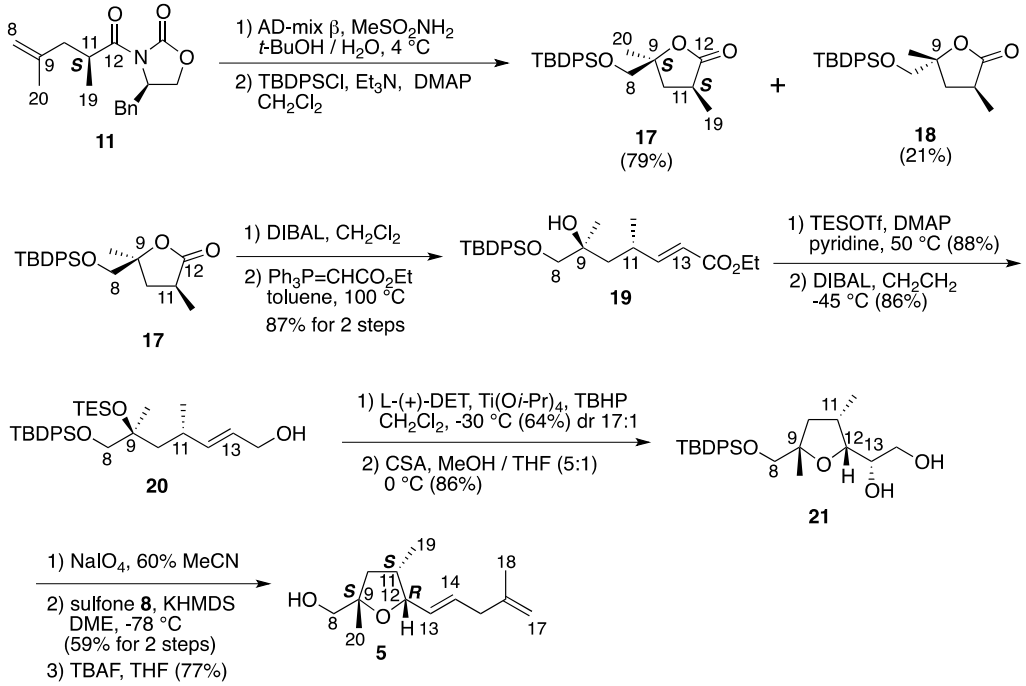
13a : R = (*S*)-MTPA
13b : R = (*R*)-MTPA

Figure 1. Δδ Values [Δδ (in ppm) = δ_S-δ_R] obtained for (*S*)- and (*R*)-MTPA esters at C4 (**13a** and **13b**, respectivly) of alcohol **13**

The absolute configuration at C4 in **13** was elucidated to be *S* by a modified Mosher's method.[5,6] Treatment of **13** with (*R*)- (-)- and (*S*)-(+)-2-methoxy-2-trifluoro-2-phenylacetyl chloride (MTPACl)

provided the (*S*)- and (*R*)-MTPA esters (**13a** and **13b**, respectively) of **13**. Δδ Values ((Δδ) δ_S - δ_R) obtained from ^{1}H NMR data of **13a** and **13b** are shown in Figure 1.

As shown in Scheme 3, the C8-C18 segment **5** was synthesized. Sharpless asymmetric dihydroxylation[8] of terminal olefin **11**[13] with AD-mix β to introduce tertiary hydroxy group at C9 stereoselectively proceeded with concomitant cyclization to give lactones,[15] which were converted into the TBDPS ethers as a separable mixture **17** and **18** (79% and 21%, respectively) by silica gel column chromatography. Treatment of lactone **17** with DIBAL at -78 °C gave lactol, which was subject to Wittig reaction with ethyl (triphenylphosphoranylidene)acetate to afford (*E*)-α,β-unsaturated ester **19** in 87% yield for the two steps with an *E*/*Z* ratio of greater than 20:1. The absolute configuration of (9*S*) for **17** was confirmed by the NOESY data[16] of **17** due to the (*S*) configuration at C11 in **11**. The tertiary hydroxy group in **19** was protected as the TES ether with TESOTf in pyridine at 50 °C and the ester moiety was reduced with DIBAL to yield allylic alcohol **20**. With allylic alcohol **20** in hand, our attention was next focused on Katsuki-Sharpless asymmetric epoxidation.[9] Katsuki-Sharpless asymmetric epoxidation[9] using L-(+)-diethyl tartrate (DET) afforded epoxy alcohol (64%, dr 17:1), which was treated with CSA to provide diol **21** and the minor epimer was separated during these transformation. Treatment of diol **21** with $NaIO_4$ in 60% MeCN was followed by Julia-Kocienski reaction[10] of the corresponding aldehyde with sulfone **8**[17] in DME to provide olefin with an *E*-selectivity (*E*/*Z*, 9:1), the TBDPS group of which was removed by TBAF in THF to furnish the (9*S*,11*S*,12*R*)-C8-C18 segment **5** and the *Z* isomer was separated at this stage. The absolute configuration of (9*S*, 11*S*, 12*R*) for **5** was established through the correlation of the NOESY data[18] of **5** with the (*S*) configuration at C11 in starting material **11**.



Scheme 3. Synthesis of the C8-C18 segment **5** from **11**

The small ^{1}H NMR chemical shift differences between natural amphidinin A (**1**)[2] and the C8-C18 segment **5** indicated that relative configurations at C9, C11, and C12 in **5** corresponded to those of amphidinin A (**1**)[3] (Table 1). The ^{13}C NMR chemical shift differences between amphidinin A (**1**) and **5** also showed small differences due to lack of hydrophilic moiety (C1-C7) exception at C8 and C10 (Table 2).

Table 1. Difference in ^{1}H NMR chemical shifts between amphidinin A (**1**) and synthetic C8-C18 segment **5** (C_6D_6, 600 MHz)

	Natural amphidinin A (**1**)[2]	Synthetic C8-C18 (**5**)	
position	δ_H multiplicity, *J* in Hz	δ_H multiplicity, *J* in Hz	$\Delta\delta$
8a	2.18 d, 13.3	3.48 d, 11.1	+1.30
8b	2.12 d, 13.2	3.39 d, 11.1	+1.27
10a	1.20 dd, 12.3, 9.2	1.45 dd, 12.1, 9.6	+0.25
10b	1.61 dd, 12.3, 7.3	1.61 dd, 12.1, 7.2	-0.00
11	2.09 m	2.26 m	+0.17
12	4.15 dd, 8.4, 7.8	4.37 dd, 7.6, 7.6	+0.22
13	5.36 dd, 15.2, 8.4	5.50 dd, 15.3, 8.0	+0.14
14	5.57 dt, 15.2, 8.4	5.61 dt, 15.3, 6.9	+0.04
15	2.62 d, 6.9	2.65 dd, 6.6, 6.5	+0.03
17a	4.86 s	4.83 s	-0.03
17b	4.85 s	4.83 s	-0.02
18	1.69 s	1.66 s	-0.03
19	0.77 d, 7.0	0.83 d, 7.0	+0.06
20	1.08 s	1.10 s	+0.02

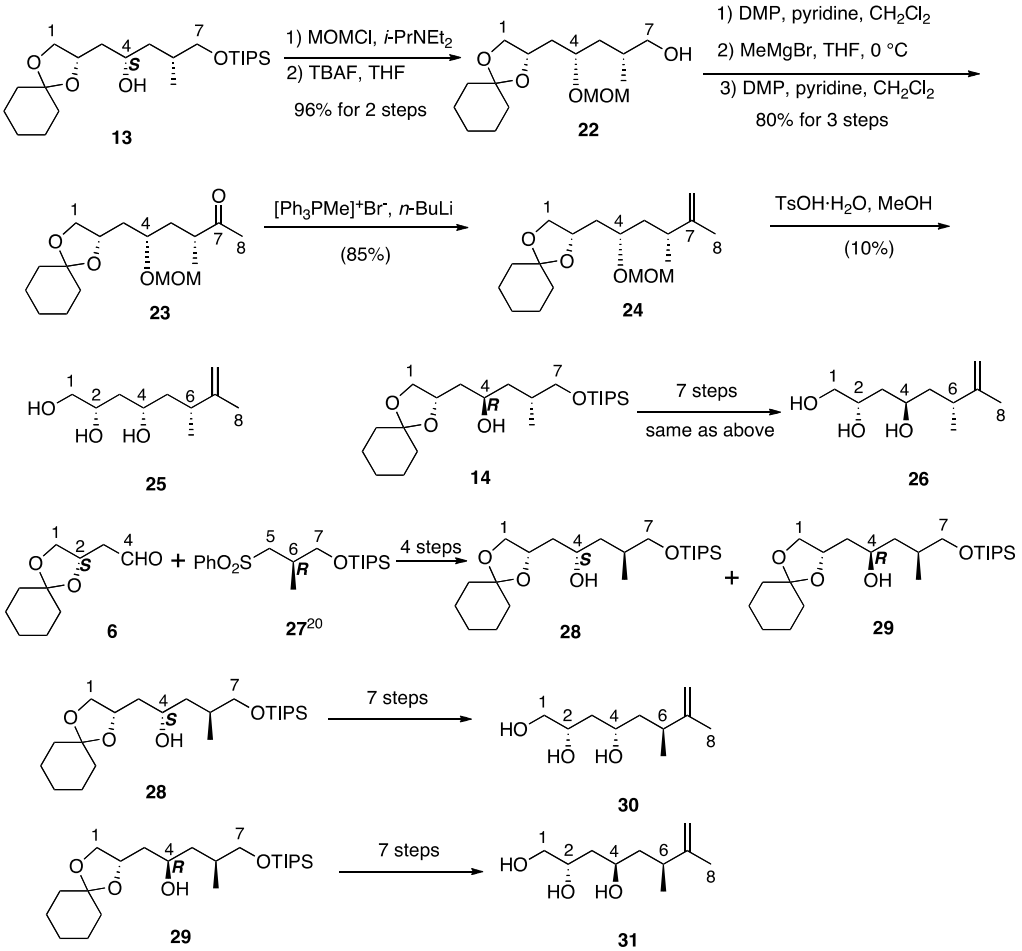
Table 2. Difference in ^{13}C NMR chemical shifts between amphidinin A (**1**) and synthetic C8-C18 segment **5** (C_6D_6, 150 MHz)

	Natural amphidinin A (**1**)[2]	Synthetic C8-C18 (**5**)	
position	δ_C	δ_C	$\Delta\delta$
8	51.0	69.2	+18.2
9	83.0	83.8	-0.8
10	47.7	41.1	-6.6
11	36.7	36.9	-0.2
12	83.7	82.8	-0.9
13	129.4	130.7	+1.3
14	132.7	130.8	-1.9
15	41.7	41.1	-0.6
16	144.2	144.3	+0.1
17	111.2	111.2	0.0
18	22.6	22.4	-0.2
19	15.6	15.3	-0.3
20	26.0	23.9	-2.1

On the other hand, four possible C1-C8 segment diastereomers (**25**, **26**, **30**, and **31**), containing three stereogenic centers, of amphidinin A (**1**) were prepared as shown in Scheme 4.[19] Protection of the

secondary hydroxy group in **13** with MOMCl and *i*-PrNEt$_2$ provided the MOM ether, the TIPS group of which was removed by TBAF in THF to yield alcohol **22** in 96% yield for the two steps. Oxidation of **22** with Dess-Martin periodinane[14] was followed by Grignard reaction with MeMgBr in THF to yield the corresponding alcohol, which was oxidized with Dess-Martin periodinane[14] to afford ketone **23**. Wittig methylenation of **23** with $[Ph_3PCH_3]^+Br^-$ and *n*-BuLi gave olefin **24**, the protecting groups of which were removed by TsOH·H$_2$O to furnish a C1-C8 segment diastereomer **25** of amphidinin A (**1**). The other C1-C8 segment diastereomers (**26**, **30**, and **31**) were prepared by almost the same procedure as described for synthesis of **25**.

Figures 2 and 3 show the difference in ^{1}H and ^{13}C NMR chemical shifts between amphidinin A (**1**) and four synthetic C1-C8 segment diastereomeres (**25**, **26**, **30**, and **31**), respectively. While ^{1}H NMR chemical shifts differences of **1** and **25** or **31** were less than those of **1** and **26** or **30** (Figure 2), ^{13}C NMR chemical shifts differences of **1** and **25** or **30** were less than those of **1** and **26** or **31** (Figure 3). These results indicated that relative configurations at C2, C4, and C6 in **25** corresponded to those of amphidinin A (**1**).[3]



Scheme 4. Synthesis of the C1-C8 segment diastereomers (**25, 26, 30,** and **31**)

In conclusion, the stereocontrolled synthesis of the C1-C7 segment **4** and C8-C18 segment **5** of *ent*-amphidinin A (**2**) has been achieved. As a result, it was indicated that the relative configurations at C2, C4, and C6 in **25** and at C9, C11, and C12 in **5** corresponded to those of amphidinin A (**1**)[3] due to the smaller ^{1}H and ^{13}C NMR chemical shift differences between synthetic compounds (**25** and **5**) and natural amphidinin A (**1**).[2] Progress toward the total synthesis of *ent*-amphidinin A (**2**) will be reported in due course.

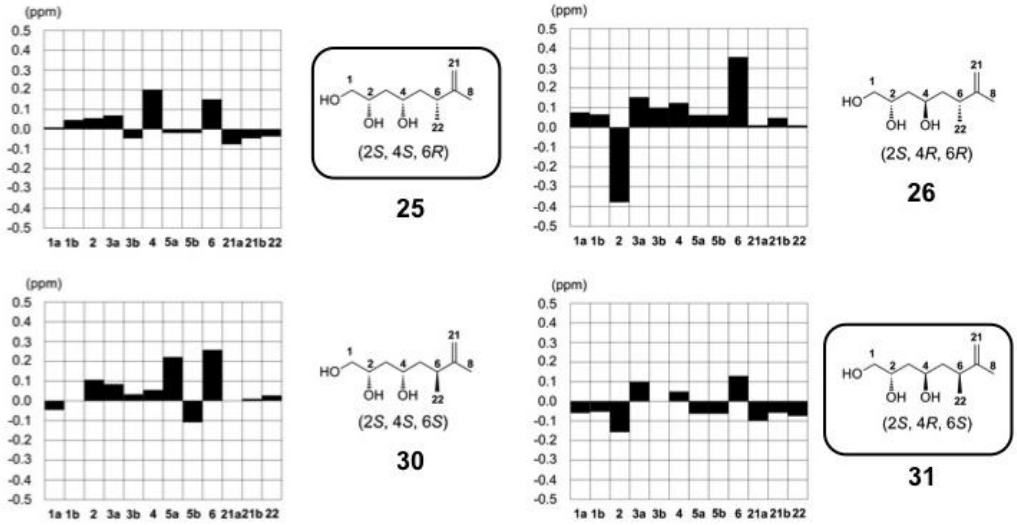


Figure 2. Difference in ^{1}H NMR chemical shifts between amphidinin A (**1**)[2] and synthetic C1-C8 segment diastereomers (**25**, **26**, **30**, and **31**)(C_6D_6, 600 MHz)

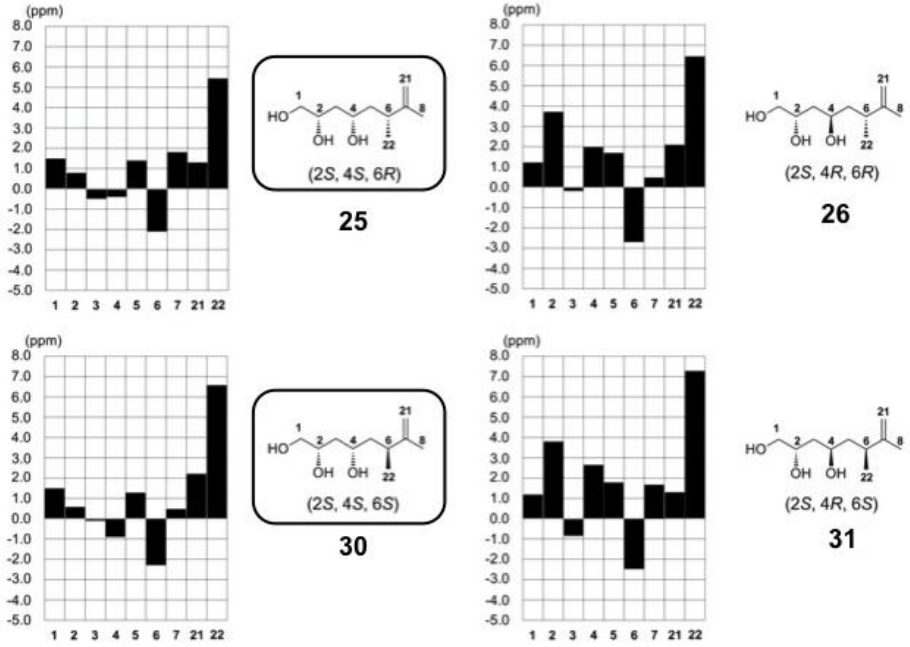


Figure 3. Difference in ^{13}C NMR chemical shifts between amphidinin A (**1**) [2] and synthetic C1-C8 segment diastereomers (**25**, **26**, **30**, and **31**)(C_6D_6, 150 MHz)

EXPERIMENTAL

General Experimental Procedures. Optical rotations were recorded on a JASCO P-1030 polarimeter at the sodium D line (589 nm). The IR spectrum was taken on a JASCO FT/IR-5300 spectrometer and absorbance bands are reported in wavenumber (cm^{-1}). ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX-600 (600 MHz), JEOL ECA500 (500 MHz), or ECX400P (400 MHz) spectrometer. The 7.26 and 77.0 ppm resonances of residual $CDCl_3$ and the 7.20 and 128.0 ppm resonances of residual benzene-d_6 were used as internal references for ^1H and ^{13}C NMR spectra, respectively. The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. ESI mass spectra were recorded on a Thermo Fisher Scientific Exactive or JEOL JMS-T100LP spectrometer. Silica gel column chromatography was carried out on Wakogel C-200 (75~150 μm) or C-300 (45~75 μm). Analytical thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 F_{254} plates with visualization by ultraviolet, anisaldehyde stain solution and/or phosphomolybdic acid stain solution. Reagents and solvents were purified by standard means. All reactions sensitive to oxygen or moisture were conducted under an argon atmosphere.

Kotone 12. To a solution of sulfone **7** (1.37 g, 3.70 mmol) in THF (15 mL) cooled to –78 °C was added *n*-BuLi (2.5 M solution in *n*-hexane, 2.0 mL, 5.0 mmol) dropwise. The mixture was stirred at –78 °C for 30 min, and then a solution of aldehyde **6** (279 mg, 1.52 mmol) in THF (5 mL) was added dropwise, and the resulting mixture was stirred at –78 °C for 25 min. The reaction was quenched by addition of saturated aqueous NH_4Cl (15 mL) and the mixture was warmed to room temperature. The reaction mixture was extracted with EtOAc (3 × 50 mL), washed with brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure to yield crude hydroxy sulfones. The hydroxy sulfones were employed in the next experiment without separation of the diastereomers. To a stirred solution of the diastereomeric mixture of hydroxy sulfones (1.86 g) in pyridine/ CH_2Cl_2 (1:9, v/v, 20 mL) was added Dess-Martin periodinane (2.09 g, 4.94 mmol) and the reaction mixture was stirred for 20 min at room temperature. To the reaction mixture was added saturated aqueous $Na_2S_2O_3$ (60 mL) and extracted with Et_2O (3 × 50 mL). The organic layers were washed with 3 M aqueous HCl (25 mL), saturated aqueous $NaHCO_3$ (25 mL), and brine (25 mL), dried over Na_2SO_4, filtered, and concentrated to afford sulfones. The residual oil was passed through silica gel pad (*n*-hexane/Et_2O 10:1→7:1, *n*-hexane/EtOAc 10:1→7:1) to remove reagents. The sulfones were employed in the next experiment without separation of the diastereomers. To a stirred solution of the sulfones (724 mg) and MeOH (0.27 mL) in THF (20 mL) was added SmI_2 (0.1 M solution in THF, 65.5 mL, 6.55 mmol). After being stirred for 1.5 h, the mixture was diluted with EtOAc (35 mL). The organic layer was washed with saturated aqueous $Na_2S_2O_3$ (30 mL) and brine (30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane/Et_2O 20:1→10:1→7:1→5:1, *n*-hexane/EtOAc

10:1) to yield ketone **12** (350 mg, 0.849 mmol, 56% for the three steps) as a colorless oil; $[\alpha]_D^{25}$ +6.1 (*c* 0.75, $CHCl_3$); IR (neat) ν_{max} 2940, 2866, 1713, 1463, 1365, 1102 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.45 (1H, m), 4.17 (1H, dd, *J* = 8.3, 6.3 Hz), 3.58 (1H, dd, *J* = 9.7, 5.2 Hz), 3.51 (1H, dd, *J* = 8.3, 6.3 Hz), 3.44 (1H, dd, *J* = 9.7, 6.3 Hz), 2.91 (1H, dd, *J* = 16.8, 5.7 Hz), 2.69 (1H, dd, *J* = 16.0, 4.6 Hz), 2.56 (1H, dd, *J* = 16.8, 7.2 Hz), 2.21 (2H, m), 1.58 (8H, m), 1.38 (2H, m), 1.11-1.02 (21H, m), 0.90 (3H, d, *J* = 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.8, 109.4, 71.5, 69.2, 67. 7, 47.7, 47.2, 36.6, 35.0, 32.1, 25.1, 24.0, 23.8, 18.0, 16.7, 11.9; ESIMS (positive) *m/z* 435 $(M+Na)^+$; HRESIMS (positive) *m/z* 435.2893 [$(M+Na)^+$, calcd for $C_{23}H_{44}O_4SiNa$, 435.2901].

Alcohols 13 and 14. To a solution of ketone **12** (373 mg, 0.904 mmol) in MeOH (20 mL) cooled to 0 °C was added $NaBH_4$ (82 mg, 2.2 mmol) and the resulting mixture was stirred at room temperature for 2 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (20 mL) and extracted with EtOAc (3 × 50 mL). Combined extracts were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane/Et_2O 20:1→15:1→10:1→7:1→5:1, *n*-hexane/EtOAc 10:1→5:1) to give alcohols **13** (121 mg, 0.292 mmol, 32%) and **14** (211 mg, 0.509 mmol, 56%).

13: colorless oil; $[\alpha]_D^{23}$ +1.2 (*c* 0.97, $CHCl_3$); IR (neat) ν_{max} 3523, 2940, 2866, 1463, 1101 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.29 (1H, m), 4.09 (1H, dd, *J* = 8.0, 5.7 Hz), 3.95 (1H, m), 3.58 (3H, m), 1.86 (1H, m), 1.66 (2H, m), 1.57 (8H, m), 1.52 (1H, m), 1.45 (1H, *J* = 7.7, 6.0 Hz), 1.40 (2H, m), 1.14-1.04 (21H, m), 0.94 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.8, 75.1, 69.4, 68.5, 68.4, 41.9, 40.7, 36.5, 35.2, 32.5, 25.1, 24.0, 23.9, 18.0, 17.7, 11.9; ESIMS (positive) *m/z* 437 $(M+Na)^+$; HRESIMS (positive) *m/z* 437.3058 [$(M+Na)^+$, calcd for $C_{23}H_{46}O_4SiNa$, 437.3058].

14: colorless oil; $[\alpha]_D^{23}$ +4.0 (*c* 0.88, $CHCl_3$); IR (neat) ν_{max} 3442, 2940, 2866, 1463, 1102 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.31 (1H, m), 4.08 (1H, dd, *J* = 8.0, 6.3 Hz), 3.88 (1H, m), 3.61 (1H, dd, *J* = 9.8, 4.6 Hz), 3.56 (1H, m), 3.50 (1H, dd, *J* = 9.8, 8.0 Hz), 1.86 (1H, m), 1.75 (1H, ddd, *J* = 13.9, 7.3, 3.3 Hz), 1.67 (1H, m), 1.58 (8H, m), 1.44 (2H, m), 1.39 (2H, m), 1.15-1.06 (21H, m), 0.91 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.0, 73.6, 69.6, 69.5, 67.8, 43.8, 41.4, 36.6, 35.3, 34.4, 25.2, 24.1, 23.9, 18.0, 17.8, 11.9; ESIMS (positive) *m/z* 437 $(M+Na)^+$; HRESIMS (positive) *m/z* 437.3052 [$(M+Na)^+$, calcd for $C_{23}H_{46}O_4SiNa$, 437.3058].

Alcohol 15. To a solution of alcohol **13** (78 mg, 0.19 mmol) in pyridine (2 mL) was added Ac_2O (2 mL). After being stirred for 5 h, the mixture was concentrated under reduced pressure. Purification by silica gel column chromatography (*n*-hexane/EtOAc 20:1→15:1→10:1) afforded the acetate (86 mg, 0.19, quantitative) as a colorless oil; $[\alpha]_D^{20}$ -0.52 (*c* 1.01, $CHCl_3$); IR (neat) ν_{max} 2940, 2866, 1463, 1366, 1237, 1101 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.06 (1H, m), 4.13 (1H, m), 4.06 (1H, dd, *J* = 7.8, 6.3 Hz), 3.51 (3H, m), 2.03 (3H, s), 1.94 (1H, ddd, *J* = 14.4, 8.0, 6.2 Hz), 1.73 (2H, m), 1.66 (1H, dd, *J* = 13.3, 6.9 Hz),

1.57 (8H, m), 1.42 (1H, dd, *J* = 8.2, 6.9 Hz), 1.38 (2H, m), 1.06 (21H, m), 0.94 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 109.3, 72.6, 70.3, 69.2, 67.6, 38.3, 37.6, 36.6, 35.1, 32.7, 25.1, 24.0, 23.8, 21.3, 18.0, 17.3, 11.9; ESIMS (positive) *m/z* 479 $(M+Na)^+$; HRESIMS (positive) *m/z* 479.3161 [$(M+Na)^+$, calcd for $C_{21}H_{43}O_4SiNa$, 479.3161]. To a solution of the above acetate protected with TIPS group (443 mg, 0.971 mmol) in THF (15 mL) at 0 °C was added TBAF (1.0 M solution in THF, 1.5 mL, 1.5 mmol). The reaction mixture was stirred at room temperature for 2 h, added saturated aqueous NH_4Cl (15 mL), and extracted with EtOAc (3 × 30 mL). Combined extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1→3:1→1:1→1:3) gave alcohol **15** (223 mg, 0.742 mmol, 77% for the two steps) as a colorless oil; $[\alpha]_D^{19}$ -4.2 (*c* 0.96, $CHCl_3$); IR (neat) ν_{max} 3442, 2935, 2865, 1448, 1366, 1241, 1101, 1035 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.10 (1H, ddd, *J* = 11.9, 7.8, 4.3 Hz), 4.14 (1H, dt, *J* = 13.3, 6.5 Hz), 4.04 (1H, dd, *J* = 8.2, 6.0 Hz), 3.49 (3H, m), 2.03 (3H, s), 1.92 (1H, dt, *J* = 22.0, 7.3 Hz), 1.72 (4H, m), 1.57 (8H, m), 1.47 (1H, dd, *J* = 16.7, 8.5 Hz), 1.38 (2H, m), 0.94 (3H, d, *J* = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 109.5, 72.5, 70.2, 69.1, 67.5, 38.1, 37.7, 36.5, 35.1, 32.3, 25.1, 24.0, 23.8, 21.3, 17.3; ESIMS (positive) *m/z* 323 $(M+Na)^+$; HRESIMS (positive) *m/z* 323.1839 [$(M+Na)^+$, calcd for $C_{16}H_{28}O_5Na$, 323.1834].

Dithiane 16. To a stirred solution of alcohol **15** (46 mg, 0.15 mmol) in pyridine/CH_2Cl_2 (1:9, v/v, 2 mL) was added Dess-Martin periodinane (163 mg, 0.385 mmol). After the solution was stirred at room temperature for 15 min, saturated aqueous $Na_2S_2O_3$ (5 mL) was added, and extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with 3 M aqueous HCl (5 mL), saturated aqueous $NaHCO_3$ (5 mL), and brine (5 mL), dried over Na_2SO_4, filtered, and concentrated. The residual oil was passed through silica gel pad (*n*-hexane/EtOAc 7:1→5:1→3:1) to remove reagents. To a solution of the crude aldehyde (36 mg) in CH_2Cl_2 (3 mL) was added 1,3-propanedithiol (24 μL, 0.24 mmol) and $Sc(OTf)_3$ (18 mg, 36 μmol). After being stirred for 2.5 h, the reaction mixture was concentrated *in vacuo* to yield crude dihiane with dihydroxy group. To a solution of the crude dithiane in CH_2Cl_2 (3 mL) was added 2,2-dimethoxypropane (0.43 mL, 3.5 mmol) and PPTS (6.0 mg, 24 μmol). After being stirred for 10 min, the reaction mixture was concentrated under reduced pressure. Purification by silica gel column chromatography (*n*-hexane/EtOAc 10:1→7:1→5:1→3:1) afforded dithiane **16** protected with acetonide (20 mg, 56 μmol, 38% for the three steps) as a colorless oil: $[\alpha]_D^{20}$ +9.6 (*c* 0.86, $CHCl_3$); IR (neat) ν_{max} 2933, 1735, 1371, 1238, 1063 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.06 (1H, m), 4.19 (1H, d, *J* = 3.2 Hz), 4.14 (1H, m), 4.06 (1H, dd, *J* = 7.7, 6.0 Hz), 3.52 (1H, t, *J* = 7.7 Hz), 2.88 (4H, m), 2.10 (2H, m), 2.04 (3H, s), 1.93 (3H, m), 1.74 (1H, ddd, *J* = 14.5, 6.5, 4.2 Hz), 1.60 (1H, m), 1.39 (3H, s), 1.33 (3H, s), 1.10 (3H, d, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 108.8, 72.9, 69.7, 69.4, 54.5, 38.4, 37.9,

35.1, 31.1, 30.7, 26.9, 26.3, 25.7, 21.3, 17.4; ESIMS (positive) *m/z* 371 $(M+Na)^+$; HRESIMS (positive) *m/z* 371.1321 [$(M+Na)^+$, calcd for $C_{16}H_{28}O_4S_2Na$, 371.1321].

Dithiane 4. To a stirred solution of dithiane **16** protected as the acetate (51 mg, 0.15 mmol) in MeOH (8 mL) was added K_2CO_3 (154 mg, 1.11 mmol). After the solution was stirred for 4 h, reaction mixture was diluted with EtOAc (50 mL), washed with saturated aqueous NH_4Cl (25 mL), and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine (25 mL), dried over Na_2SO_4, filtered, and concentrated. The mixture was passed through a silica gel pad (*n*-hexane/EtOAc 10:1→7:1→5:1→4:1→3:1→1:1) to remove reagents. To a stirred solution of the crude alcohol (31 mg) and *i*-Pr_2NEt (0.27 mL, 1.5 mmol) in CH_2Cl_2 (2 mL) cooled to 0 °C was added MOMCl (77 μL, 1.0 mmol), and the resulting solution was stirred at room temperature for 16 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (2 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (*n*-hexane/Et_2O 12:1→10:1→8:1→6:1→4:1) to furnish dihiane **4** (32 mg, 91 μmol, 61% for the two steps) as a colorless oil; $[\alpha]_D^{20}$ +10.8 (*c* 0.80, $CHCl_3$); IR (neat) ν_{max} 2932, 1379, 1214, 1153, 1098, 1035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.65 (1H, *J* = 7.4 Hz), 4.61 (1H, *J* = 7.4 Hz), 4.24 (1H, d, *J* = 3.7 Hz), 4.23 (1H, m), 4.07 (1H, dd, *J* = 8.0, 5.7 Hz), 3.74 (1H, m), 3.49 (1H, t, *J* = 8.0 Hz), 3.39 (3H, s), 2.89 (4H, m), 2.09 (2H, m), 1.93 (1H, dt, *J* = 14.2, 6.0 Hz), 1.84 (1H, m), 1.70 (1H, m), 1.55 (2H, m), 1.40 (3H, s), 1.35 (3H, s), 1.11 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 108.5, 95.0, 72.9, 69.7, 55.9, 54.8, 38.6, 37.8, 35.0, 31.2, 30.7, 27.0, 26.4, 25.8, 21.0, 17.6; ESIMS (positive) *m/z* 373 $(M+Na)^+$; HRESIMS (positive) *m/z* 373.1489 [$(M+Na)^+$, calcd for $C_{16}H_{30}O_4S_2Na$, 373.1483].

(*S*)-MTPA ester 13a. To a solution of alcohol **13** (1.1 mg, 2.7 μmol) in CH_2Cl_2 (0.2 mL) at room temperature were added Et_3N (3.0 μL, 22 μmol), DMAP (0.30 mg, 2.5 μmol), and (*R*)-MTPACl (3.0 μL, 17 μmol). After 18 h at room temperature, the reaction was quenched with *N*,*N*-dimethyl-1,3-propanediamine (3.0 μL, 23 μmol) and the resultant mixture was stirred for 10 min. The reaction mixture was concentrated and the residue was purified by silica gel column chromatography (*n*-hexane/EtOAc 20:1→15:1→10:1) to yield (*S*)-MTPA ester **13a** (1.6 mg, 2.5 μmol, 96%) as a colorless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 7.53 (2H, m; Ph), 7.39 (3H, m; Ph), 5.26 (1H, m; H-4), 4.10 (1H, m; H-2), 4.01 (1H, dd, *J* = 8.0, 5.7 Hz; H-1a), 3.54 (3H, s; OMe), 3.52 (1H, dd, *J* = 9.9, 5.2 Hz; H-7a), 3.47 (1H, dd, *J* = 8.0, 6.9 Hz; H-1b), 3.45 (1H, dd, *J* = 9.9, 4.9 Hz; H-7b), 2.06 (1H, dt, *J* = 14.3, 6.6 Hz; H-3a), 1.78 (2H, m; H-3b, H-5a), 1.57 (8H, m; cyclohexylidene), 1.53 (1H, m; H-6), 1.44 (1H, m: H-5b). 1.38 (2H, m; cyclohexylidene), 1.08-1.02 (21H, m; TIPS), 0.86 (3H, d, *J* = 6.9 Hz; H-22); ESIMS (positive) *m/z* 653 $(M+Na)^+$; HRESIMS (positive) *m/z* 653.3465 [$(M+Na)^+$, calcd for $C_{33}H_{53}O_6F_3SiNa$, 653.3456].

(*R*)-MTPA ester 13b. To a solution of alcohol **13** (0.65 mg, 1.6 μmol) was treated with (*S*)-MTPACl by the same prodedure as described above to afford (*R*)-MTPA ester **13b** (0.28 mg, 0.45 μmol, 29%) as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (2H, m; Ph), 7.40 (3H, m; Ph), 5.23 (1H, m; H-4), 3.95 (1H, m; H-2), 3.91 (1H, dd, *J* = 7.5, 5.7 Hz; H-1a), 3.55 (3H, s; OMe), 3.57 (1H, dd, *J* = 9.8, 5.2 Hz; H-7a), 3.35 (1H, dd, *J* = 7.5, 6.9 Hz; H-1b), 3.50 (1H, dd, *J* = 9.8, 5.7 Hz; H-7b), 1.99 (1H, dt, *J* = 14.1, 6.4 Hz; H-3a), 1.86 (1H, dt, *J* = 13.5, 6.6 Hz; H-5a), 1.73 (1H, ddd, *J* = 14.1, 6.6, 4.6 Hz; H-3b), 1.66 (1H, m; H-6), 1.53 (8H, m; cyclohexylidene), 1.47 (1H, m; H-5b), 1.37 (2H, m; cyclohexylidene), 1.09-1.01 (21H, m; TIPS), 0.94 (3H, d, *J* = 6.9 Hz; H-22); ESIMS (positive) *m/z* 653 $(M+Na)^+$; HRESIMS (positive) *m/z* 653.3458 [$(M+Na)^+$, calcd for $C_{33}H_{53}O_6F_3SiNa$, 653.3456].

Lactones 17 and 18. AD-mix β (48.7 g) and $MeSO_2NH_2$ were stirred in *t*-BuOH/H_2O (1:1, v/v, 200 mL) at 0 °C for 30 min. To this mixture was added a solution of olefin **11** (9.98 g, 34.7 mmol) in *t*-BuOH/H_2O (1:1, v/v, 100 mL), and the mixture was stirred at 4 °C for 34 h. The reaction was quenched by the addition of saturated aqueous Na_2SO_3 (150 mL), and the whole was stirred at 0 °C for another 30 min then extracted with EtOAc (4 × 40 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, and concentrated *in vacuo* to afford crude lactones. To a stirred solution of the crude lactones (14.47 g), Et_3N (9.0 mL, 64.7 mmol), and DMAP (852 mg, 6.97 mmol) in CH_2Cl_2 (2 mL) cooled to 0 °C was added TBDPSCl (13.5 mL, 51.9 mmol), and the resulting solution was stirred at room temperature for 22 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (100 mL) and extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with H_2O (100 mL) and brine (100 mL), drided with Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (*n*-hexane/Et_2O 15:1 *n*-hexane/EtOAc 15:1→10:1→5:1) to afford lacones **17** (10.5 g, 27.4 mmol, 79% for the two steps) and **18** (2.73 g, 7.15 mmol, 21% for the two steps).

Lactone 17: colorless oil; $[\alpha]_D^{20}$ +7.0 (*c* 1.76, $CHCl_3$); IR (neat) ν_{max} 2931, 2858, 1771, 1113 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.65 (4H, m), 7.43-7.38 (6H, m), 3.68 (1H, d, *J* = 10.9 Hz), 3.54 (1H, d, *J* = 10.9 Hz), 2.83 (1H, m), 2.08 (2H, m), 1.33 (3H, s), 1.29 (3H, d, *J* = 6.8 Hz), 1.06 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.2, 135.7, 135.6, 133.1, 132.6, 129.8, 127.8, 83.7, 68.6, 37.2, 34.8, 26.7, 22.8, 19.3, 15.7; ESIMS (positive) *m/z* 405 $(M+Na)^+$; HRESIMS (positive) *m/z* 405.1861 [$(M+Na)^+$, calcd for $C_{23}H_{30}O_3SiNa$, 405.1856].

Lactone 18: colorless oil; $[\alpha]_D^{18}$ -26 (*c* 1.99, $CHCl_3$); IR (neat) ν_{max} 2933, 2858, 1772, 1113 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.65 (4H, m), 7.46-7.38 (6H, m), 3.66 (1H, d, *J* = 10.9 Hz), 3.50 (1H, d, *J* = 10.9 Hz), 2.95 (1H, m), 2.61 (1H, dd, *J* = 12.7, 9.5 Hz), 1.34 (3H, s), 1.29 (1H, dd, *J* = 12.7, 10.4 Hz), 1.28 (3H, d, *J* = 7.2 Hz), 1.06 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.9, 135.6, 135.5, 134.8, 132.8,

132.3, 129.9, 127.8, 83.6, 77.2, 69.5, 39.6, 36.2, 26.7, 24.3, 19.1, 16.7; ESIMS (positive) *m/z* 405 $(M+Na)^+$; HRESIMS (positive) *m/z* 405.1860 [$(M+Na)^+$, calcd for $C_{23}H_{30}O_3SiNa$, 405.1856].

(*E*)-α,β-Unsaturated ester 19. To a solution of lactone **17** (586 mg, 1.53 mmol) in CH_2Cl_2 (20 mL) cooled to –78 °C was added DIBAL (1.0 M solution in *n*-hexane, 1.6 mL, 1.6 mmol) dropwise. After the solution was stirred for 30 min at -78 °C, the reaction was quenched with MeOH (3 mL) and saturated aqueous Rochelle solution (25 mL) and the resultant mixture was stirred for 30 min at room temperature. The reaction mixture was extracted with EtOAc (3 × 40 mL), washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure to yield crude lactols. The lactols were employed to the next step without further purification. To a solution of crude lactols in toluene (20 mL) was added ethyl (triphenylphosphoranylidene)acetate (801 mg, 2.30 mmol) and the reaction mixture was stirred for 12 h at 100 °C. The reaction mixture was concentrated *in vacuo*, and the residue was purified by silica gel column chromatography (*n*-hexane/EtOAc 10:1→7:1→5:1→3:1) to afford ester **19** (606 mg, 1.33 mmol, 87% for the two steps) as a colorless oil; $[\alpha]_D^{19}$ +18.4 (*c* 0.36, $CHCl_3$); IR (neat) ν_{max} 3479, 2960, 2931, 2858, 1717 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67-7.63 (4H, m), 7.45-7.38 (6H, m), 6.94 (1H, dd, *J* = 15.5, 8.4 Hz), 5.69 (1H, *J* = 15.5, 0.9 Hz), 4.16 (2H, q, *J* = 7.0 Hz), 3.46 (1H, d, *J* = 9.6 Hz), 3.40 (1H, d, *J* = 9.6 Hz), 2.52 (1H, m), 2.33 (1H, brs), 1.68 (1H, dd, *J* = 14.2, 8.6 Hz), 1.51 (1H, dd, *J* = 14.2, 4.3 Hz), 1.28 (3H, t, *J* = 7.0 Hz), 1.14 (3H, s), 1.08 (9H, s), 1.06 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 155.5, 135.6, 132.9, 129.9, 129.8, 127.8, 119.0, 72.7, 70.9, 60.1, 44.7, 32.6, 26.9, 23.9, 21.9, 19.3, 14.2; ESIMS (positive) *m/z* 477 $(M+Na)^+$; HRESIMS (positive) *m/z* 477.2440 [$(M+Na)^+$, calcd for $C_{27}H_{38}O_4SiNa$, 477.2432].

Allylic alcohol 20. To a stirred solution of (*E*)-α,β-unsaturated ester **19** (379 mg, 0.834 mmol) and DMAP (20 mg, 0.16 mmol) in pyridine (2.5 mL) cooled to 0 °C was added TESOTf (145 μL, 0.642 mmol), and the resulting solution was stirred at 50 °C for 4 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with H_2O (20 mL) and brine (3 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (*n*-hexane/Et_2O 150:1→100:1→50:1→10:1) to afford TES ether (419 mg, 0.736 mmol, 88%) as a colorless oil; $[\alpha]_D^{20}$ +39.9 (*c* 2.03, $CHCl_3$); IR (neat) ν_{max} 2956, 2875, 1719, 1110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66-7.63 (4H, m), 7.45-7.36 (6H, m), 6.97 (1H, dd, *J* = 15.8, 8.4 Hz), 5.72 (1H, dd, *J* = 15.8, 0.9 Hz), 4.17 (2H, q, *J* = 7.2 Hz), 3.47 (1H, d, *J* = 9.5 Hz), 3.32 (1H, d, *J* = 9.5 Hz), 2.56 (1H, m), 1.74 (1H, dd, *J* = 14.0, 7.2 Hz), 1.59 (1H, dd, *J* = 14.0, 5.0 Hz), 1.27 (3H, t, *J* = 7.2 Hz), 1.16 (3H, s), 1.07 (9H, s), 1.07 (3H, d, *J* = 6.8 Hz), 0.84 (9H, t, *J* = 7.7 Hz) , 0.47 (6H, q, *J* = 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 156.4, 135.7, 133.4, 129.6, 127.6, 118.6, 76.0, 70.4, 60.0, 45.8, 32.5, 26.9, 26.0, 21.9, 19.2, 14.3, 7.0, 6.7; ESIMS (positive) *m/z* 591 $(M+Na)^+$; HRESIMS (positive) *m/z* 591.3290 [$(M+Na)^+$, calcd for $C_{33}H_{52}O_4Si_2Na$, 591.3296]. The ethyl

ester (419 mg, 0.736 mmol) was dissolved in CH_2Cl_2 (15 mL), and DIBAL (1.0 M solution in *n*-hexane, 2.2 mL, 2.2 mmol) was slowly added to the solution at -45 °C. After the solution was stirred for 30 min at -78 °C, the reaction was quenched with MeOH (2 mL) and saturated aqueous Rochelle solution (20 mL), and the resultant mixture was stirred for 30 min at room temperature. The reaction mixture was extracted with EtOAc (3 × 40 mL), washed with brine (15 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/Et_2O 50:1→30:1→10:1, *n*-hexane/EtOAc 10:1) to yield allylic alcohol **20** (332 mg, 0.631 mmol, 86%) as a colorless oil; $[\alpha]_D^{20}$ +25.5 (*c* 0.87, $CHCl_3$); IR (neat) ν_{max} 3347, 2956, 2875, 1459, 1428, 1113, 1011 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67-7.64 (4H, m), 7.45-7.36 (6H, m), 5.62 (1H, ddt, *J* = 15.8, 8.4, 1.2 Hz), 5.48 (1H, dt, *J* = 15.6, 5.7 Hz), 3.96 (2H, dd, *J* = 5.7, 1.2 Hz), 3.50 (1H, *J* = 9.5 Hz), 3.36 (1H, d, *J* = 9.5 Hz), 2.42 (1H, m), 1.67 (1H, dd, *J* = 14.0, 7.2 Hz), 1.52 (1H, dd, *J* = 14.0, 4.5 Hz), 1.20 (3H, s), 1.07 (9H, s), 1.02 (3H, d, *J* = 6.8 Hz), 0.88 (9H, t, *J* = 8.0 Hz), 0.50 (6H, q, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 135.7, 133.7, 133.6, 129.6, 126.1, 76.2, 70.2, 63.9, 46.3, 32.2, 26.9, 26.6, 22.9, 19.2, 7.1, 6.8; ESIMS (positive) *m/z* 549 $(M+Na)^+$; HRESIMS (positive) *m/z* 549.3191 [$(M+Na)^+$, calcd for $C_{31}H_{50}O_3Si_2Na$, 549.3191].

Diol 21. Titanium (IV) isopropoxide (110 μL, 0.372 mmol) was added to a stirred suspension of crushed molecular sieves 4A (100 mg) in CH_2Cl_2 (3 mL) containing diethyl (+)-tartrate (88 mg, 0.427 mmol) at -30 °C. After 10 min, a solution of allylic alcohol **20** (162 mg, 0.308 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise, and the mixture was stirred for 30 min. Then a 3.8 M toluene solution of *tert*-butyl hydroperoxide (TBHP, 250 μL, 0.950 mmol) was added and the whole was stirred for 4 h at -30 °C. The reaction was quenched by addition of 10% aqueous tartric acid (1.0 mL) and the mixture was filtered with Celite pad. The filtrate was diluted with Et_2O and washed with H_2O, and the organic layer was concentrated. The residue in Et_2O (5 mL) was treated with 1 M aqueous NaOH (2 mL) at 0 °C for 1 h. The reaction mixture was diluted with Et_2O (20 mL), washed with H_2O (3 × 4 mL) and brine (3 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by silica gel column chromatography (*n*-hexane/EtOAc 20:1→15:1→10:1→5:1) afforded epoxide (107 mg, 0.197 mmol, 64%, dr 17:1) as a colorless oil; $[\alpha]_D^{20}$ +4.7 (*c* 2. 71, $CHCl_3$); IR (neat) ν_{max} 3412, 2956, 2875, 1459, 1428, 1112, 1011 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69-7.65 (4H, m), 7.45-7.36 (6H, m), 3.89 (1H, dd, *J* = 12.5, 2.5 Hz), 3.57 (1H, dd, *J* = 12.5, 4.8 Hz), 3.51 (1H, d, *J* = 9.5 Hz), 3.37 (1H, *J* = 9.5 Hz), 2.96 (1H, m), 2.85 (1H, dd, *J* = 5.9, 2.3 Hz), 1.82 (1H, dd, *J* = 13.7, 4.8 Hz), 1.76 (1H, m), 1.48 (1H, dd, *J* = 13.7, 6.3 Hz), 1.25 (3H, s), 1.08 (9H, s), 0.97 (3H, d, *J* = 6.8 Hz), 0.86 (9H, t, *J* = 7.9 Hz), 0.48 (6H, q, 7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 133.5, 129.6, 127.6, 76.1, 70.3, 62.1, 60.7, 56.8, 43.5, 30.5, 26.9, 26.2, 19.2, 17.6, 7.0, 6.8; ESIMS (positive) *m/z* 565 $(M+Na)^+$; HRESIMS (positive) *m/z* 565.3136 [$(M+Na)^+$, calcd for $C_{31}H_{50}O_4Si_2Na$, 565.3140]. A solution of the epoxide (53 mg, 98 μmol) in MeOH/THF (5:1,

v/v, 1.2 mL) was treated with CSA (5.6 mg, 24 μmol) at 0 °C for 2.5 h. After addition of saturated aqueous $NaHCO_3$ (3 mL), the whole was extracted with EtOAc (3 × 25 mL), washed with brine (3 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc 8:1→6:1→4:1→2:1→1:1) to separate the minor isomer and diol **21** (36 mg, 84 μmol, 86%). **21**: colorless oil; $[\alpha]_D^{20}$ -4.6 (*c* 1.55, $CHCl_3$); IR (neat) ν_{max} 3390, 2967, 2930, 2858, 1112 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69-7.67 (4H, m), 7.45-7.36 (6H, m), 3.73 (2H, m), 3.67 (1H, m), 3.53 (1H, d, *J* = 10.4 Hz), 3.48 (1H, d, *J* = 10.4 Hz), 2.55 (1H, m), 2.38 (1H, brs), 1.80 (1H, dd, *J* = 12.7, 7.7 Hz), 1.73 (1H, dd, *J* = 12.7, 6.8 Hz), 1.19 (3H, s), 1.07 (9H, s), 1.03 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 135.6, 133.4, 133.3, 129.7, 127.7, 127.6, 83.0, 81.5, 70.7, 70.3, 65.4, 41.5, 35.1, 26.8, 24.2, 19.3, 15.0; ESIMS (positive) *m/z* 451 $(M+Na)^+$; HRESIMS (positive) *m/z* 451.2283 [$(M+Na)^+$, calcd for $C_{25}H_{36}O_4SiNa$, 451.2275].

Olefin 5. To a solution of diol **21** (21 mg, 49 μmol) in MeCN/H_2O (3:2, v/v, 0.6 mL) cooled to 0 °C was added $NaIO_4$ (21 mg, 98 μmol), and the resulting solution was stirred at 0 °C for 30 min. The reaction was diluted with H_2O (3 mL), extracted with EtOAc (3 × 8 mL), washed with brine (3 mL), dried over Na_2SO_4, filtered, and concentrated to afford crude aldehyde. To a solution of sulfone **8** (20 mg, 72 μmol) in 1,2-demthoxyethane (0.45 mL) was added KHMDS (0.7 M in toluene, 0.1 mL, 70 μmol) dropwise at -78 °C. After the solution was stirred for 15 min at -78 °C, a solution of crude aldehyde (19 mg) in 1,2-demthoxyethane (0.4 mL) was added dropwise, and the mixture was stirred for 30 min at -78 °C. The reaction was quenched by addition of saturated aqueous NH_4Cl (3 mL) and extracted with EtOAc (3 × 8 mL). Combined organic extracts were washed with brine (3 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel column chromatography (*n*-hexane/Et_2O 150:1→100:1→50:1→30:1→20:1) afforded olefin (13 mg, 29 μmol, 59% for the two steps, *E*/*Z* 9:1) as a colorless oil; $[\alpha]_D^{20}$ -4.2 (*c* 0.80, $CHCl_3$); IR (neat) ν_{max} 2963, 2929, 2858, 1459, 1428, 1112 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71-7.69 (4H, m), 7.42-7.38 (6H, m), 5.58 (1H, dt, *J* = 14.9, 6.9 Hz), 5.46 (ddt, *J* = 14.8, 8.0, 1.1 Hz), 4.70 (1H, s), 4.67 (1H, s), 4.43 (1H, dd, *J* = 7.8, 7.4 Hz), 3.56 (2H, s), 2.66 (2H, dd, *J* = 6.6, 6.6 Hz), 2.50 (1H, m), 1.82 (1H, m), 1.77 (1H, m), 1.67 (3H, brs), 1.23 (3H, s), 1.07 (9H, s), 0.89 (3H, d, *J* = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.5, 135.7, 133.7, 133.5, 130.5, 130.2, 129.5, 127.6, 110.7, 82.9, 82.8, 70.9, 41.6, 40.8, 36.6, 26.9, 24.6, 22.4, 19.3, 15.2; ESIMS (positive) *m/z* 471 $(M+Na)^+$; HRESIMS (positive) *m/z* 471.2701 [$(M+Na)^+$, calcd for $C_{29}H_{40}O_2SiNa$, 471.2690]. To a solution of the above olefin with TBDPS group (5.0 mg, 11 μmol) in THF (0.5 mL) at 0 °C was added TBAF (1.0 M solution in THF, 15 μL, 15 μmol). The reaction mixture was stirred at room temperature for 28 h, treated with saturated aqueous NH_4Cl (2 mL), and extracted with EtOAc (3 × 8 mL). Combined organic extracts were washed with brine (3 mL), dried over Na_2SO_4, filtered, and concentrated.

The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc 10:1→8:1→6:1→4:1) to separate *Z* isomer and olefin **5** (2.0 mg, 9.5 μmol, 77%). **5**: colorless oil; $[\alpha]_D^{25}$ –3.6 (c 0.8, MeOH); IR (neat) ν_{max} 3440, 2938, 2868, 1465, 1103 cm^{-1}; ^1H NMR (Table 1); ^{13}C NMR (Table 2); ESIMS (positive) *m/z* 233 $(M+Na)^+$; HRESIMS (positive) *m/z* 233.1519 [$(M+Na)^+$, calcd for $C_{13}H_{22}O_2Na$, 233.1517].

Alcohol 22. To a solution of alcohol **13** (121 mg, 0.292 mmol) and *i*-Pr_2NEt (0.76 mL, 4.4 mmol) in CH_2Cl_2 (5 mL) cooled to 0 °C was added MOMCl (0.22 mL, 2.92 mmol), and the resulting solution was stirred at room temperature for 17 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (8 mL), and the resulting mixture was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (*n*-hexane/Et_2O 15:1→10:1→7:1) to afford MOM ether (129 mg, 0.281 mmol, 96%) as a colorless oil; $[\alpha]_D^{25}$ +7.5 (*c* 1.04, $CHCl_3$) IR (neat) ν_{max} 2939, 2866, 1463, 1099, 1039 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.63 (2H, s), 4.24 (1H, m), 4.07 (1H, dd, *J* = 8.0, 5.8 Hz), 3.73 (1H, m), 3.52 (3H, m), 3.37 (3H, s), 1.93 (1H, ddd, *J* = 13.9, 6.2, 6.2 Hz), 1.72 (4H, m), 1.58 (8H, m), 1.38 (2H, m), 1.10-0.98 (21H, m), 0.93 (3H, d, *J* = 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.0, 95.2, 73.6, 72.5, 69.4, 68.2, 55.6, 38.2, 38.0, 36.7, 35.3, 32.7, 25.2, 24.0, 23.9, 18.0, 17.3, 12.0; ESIMS (positive) *m/z* 481 $(M+Na)^+$; HRESIMS (positive) *m/z* 481.3313 [$(M+Na)^+$, calcd for $C_{25}H_{50}O_5SiNa$, 481.3320]. To a solution of MOM ether with TIPS group (125 mg, 0.274 mmol) in THF (3.5 m) at 0 °C was added TBAF (1.0 M solution in THF, 0.41 mL, 0.41 mmol). The reaction mixture was stirred at room temperature for 3 h, treated with saturated aqueous NH_4Cl (3 mL), and extracted with EtOAc (3 × 15 mL). Combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1→4:1→3:1→2:1→1:1) gave alcohol **22** (86.0 mg, 0.274 mmol, quantitative) as a colorless oil; $[\alpha]_D^{22}$ -2.6 (*c* 0.91, $CHCl_3$) IR (neat) ν_{max} 3445, 2935, 2865, 1448, 1098, 1037 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.65 (2H, s), 4.21 (1H, m), 4.06 (1H, dd, *J* = 7.7, 6.0 Hz), 3.84 (1H, m), 3.51 (2H, m), 3.45 (1H, dd, *J* = 17.2, 6.3 Hz), 3.38 (3H, s), 2.35 (1H, brs), 1.94 (1H, ddd, *J* = 14.3, 7.5, 5.8 Hz), 1.84 (1H, m), 1.73 (1H, dt, *J* = 14.2, 5.9 Hz), 1.67 (1H, ddd, *J* = 14.3, 7.5, 5.7 Hz), 1.58 (8H, m), 1.51 (1H, dt, *J* = 14.2, 5.9 Hz), 1.39 (2H, m), 0.93 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 109.4, 95.4, 73.7, 72.4, 69.3, 68.1, 55.7, 38.3, 37.8, 36.6, 35.3, 32.1, 25.1, 24.0, 23.9, 17.8; ESIMS (positive) *m/z* 325 $(M+Na)^+$; HRESIMS (positive) *m/z* 325.1985 [$(M+Na)^+$, calcd for $C_{16}H_{30}O_5Na$, 325.1986].

Ketone 23. To a solution of alcohol **22** (43.0 mg, 0.141 mmol) in pyridine/CH_2Cl_2 (1:9, v/v, 2 mL) was added Dess-Martin periodinane (150 mg, 0.353 mmol). After being stirred at room temperature for 25 min, the reaction mixture was treated with saturated aqueous $Na_2S_2O_3$ (4 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with 3 M aqueous HCl (10 mL), saturated aqueous $NaHCO_3$ (10 mL), and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated to afford

crude aldehyde. To a stirred solution of the crude aldehyde (51 mg) in THF (1 mL) cooled to 0 °C was added a solution of MeMgBr (3.0 M solution in THF, 0.11 mL, 0.33 mmol). After 1 h at 0 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl (4 mL) and the resulting mixture was extracted with EtOAc (3 × 10 mL). Combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated. The residual oil was passed through silica gel pad (*n*-hexane/EtOAc 5:1→4:1→3:1→2:1→1:1) to remove reagents. To a solution of the diastereomeric mixture of alcohols (40 mg) in pyridine/CH_2Cl_2 (1:9, v/v, 1.8 mL) was added Dess-Martin periodinane (134 mg, 0.316 mmol). After being stirred at room temperature for 30 min, the reaction mixture was treated with saturated aqueous $Na_2S_2O_3$ (4 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with 3 M aqueous HCl (10 mL), saturated aqueous $NaHCO_3$ (10 mL), and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by silica gel column chromatography (*n*-hexane/EtOAc 10:1→7:1→5:1→3:1→1:1) afforded ketone **23** (36.0 mg, 0.113 mmol, 80% for the three steps) as a colorless oil; $[\alpha]_D^{23}$ -1.0 (*c* 0.99, $CHCl_3$) IR (neat) ν_{max} 2936, 2855, 1714, 1448, 1363, 1101, 1036 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.65 (2H, s), 4.21 (1H, m), 4.06 (1H, dd, *J* = 7.8, 5.9 Hz), 3.64 (1H, m), 3.50 (1H, t, *J* = 7.8 Hz), 3.36 (3H, s), 2.77 (1H, m), 2.17 (3H, s), 2.01 (1H, ddd, *J* = 14.3, 8.8, 4.5 Hz), 1.93 (1H, ddd, *J* = 14.3, 7.0, 5.4 Hz), 1.68 (1H, dt, *J* = 14.4, 5.7 Hz), 1.59 (8H, m), 1.52 (1H, dt, *J* = 7.2, 4.7 Hz), 1.39 (2H, m), 1.11 (3H, d, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.3, 109.3, 95.8, 73.7, 72.2, 69.3, 55.8, 43.1, 38.4, 37.4, 36.7, 35.3, 28.4, 27.5, 25.1, 24.0, 17.2; ESIMS (positive) *m/z* 337 $(M+Na)^+$; HRESIMS (positive) *m/z* 337.1984 [$(M+Na)^+$, calcd for $C_{17}H_{30}O_5Na$, 337.1996].

Olefin 24. To a cooled mixture of methyltriphenylphosphonium bromide (297 mg, 0.833 mmol) in THF (3.5 mL) was added *n*-BuLi (2.5 M solution in *n*-hexane, 0.33 mL, 0.83 mmol), and the reaction mixture was stirred at 0 °C for 30 min. To the reaction mixture was added a solution of ketone **23** (36.0 mg, 113 μmol) in THF (3 mL) dropwise at 0 °C. After the reaction mixture was stirred for 3.5 h at room temperature, the reaction was quenched by addition of saturated aqueous NH_4Cl (5 mL) and the resulting mixture was extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by silica gel column chromatography (*n*-hexane/Et_2O 10:1→7:1→5:1, *n*-hexane/EtOAc 7:1→5:1→3:1) afforded olefin **24** (30 mg, 96 μmol, 85%) as a colorless oil; $[\alpha]_D^{23}$ +19 (*c* 0.79, $CHCl_3$) IR (neat) ν_{max} 2935, 2865, 1448, 1365, 1103, 1039 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.73 (2H, m), 4.62 (2H, s), 4.21 (1H, ddd, *J* = 13.3, 7.3, 6.0 Hz), 4.06 (1H, dd, *J* = 7.8, 6.0 Hz), 3.61 (1H, m), 3.49 (1H, t, *J* = 7.8 Hz), 3.37 (3H, s), 2.41 (1H, m), 1.92 (1H, ddd, *J* = 14.2, 7.2, 5.3 Hz), 1.69 (1H, m), 1.66 (3H, s), 1.63 (1H, m), 1.58 (8H, m), 1.49 (1H, ddd, *J* = 14.2, 8.7, 5.3 Hz), 1.38 (2H, m), 1.02 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 110.3, 109.1, 96.2,

74.3, 72.4, 69.5, 55.7, 39.9, 38.8, 37.6, 36.6, 35.3, 25.2, 24.0, 23.9, 20.4, 18.5; ESIMS (positive) *m/z* 335 $(M+Na)^+$; HRESIMS (positive) *m/z* 335.2193 [$(M+Na)^+$, calcd for $C_{18}H_{32}O_4Na$, 335.2193].

Triol 25. To a solution of **24** (10.0 mg, 32.3 μmol) in MeOH (1 mL) was added $TsOH \cdot H_2O$ (32.0 mg, 0.168 mmol) and the mixture was stirred at room temperature for 22 h. The reaction mixture was diluted with $CHCl_3$ (4 mL) and passed through silica gel pad to remove reagents. The resultant mixture was concentrated, and the residue was purified by column chromatography on silica gel (*n*-hexane/acetone 1:1→1:3→1:5, MeOH) to afford **25** (0.58 mg, 3.1 μmol, 10 %) as a colorless oil; $[\alpha]_D^{20}$ -16.8 (*c* 0.11, MeOH) IR (neat) ν_{max} 3334, 2924, 1651, 1467 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 4.96 (1H, s), 4.88 (1H, s), 3.96 (1H, m), 3.90 (1H, m), 3.64 (1H, dd, *J* = 11.3, 3.3 Hz), 3.52 (1H, dd, *J* = 11.3, 6.6 Hz), 2.62 (1H, dt, *J* = 21.6, 6.9 Hz), 1.68 (3H, s), 1.66 (1H, m), 1.51 (2H, m), 1.44 (1H, dt, *J* = 14.4, 3.0 Hz), 1.10 (3H, d, *J* = 7.2 Hz); ^{13}C NMR (150 MHz, C_6D_6) δ 149.5, 110.7, 72.7, 69.9, 67.0, 43.6, 40.3, 37.8, 20.6, 18.8; ESIMS (positive) *m/z* 211 $(M+Na)^+$; HRESIMS (positive) *m/z* 211.1308 [$(M+Na)^+$, calcd for $C_{10}H_{20}O_3Na$, 211.1305].

Triol 26: colorless oil; $[\alpha]_D^{20}$ -25.6 (*c* 0.08, MeOH) IR (neat) ν_{max} 3353, 2923, 1732, 1467 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 4.86 (1H, s), 4.78 (1H, s), 4.40 (1H, m), 3.97 (1H, m), 3.57 (1H, dd, *J* = 10.8, 3.0 Hz), 3.50 (1H, dd, *J* = 10.8, 7.2 Hz), 2.40 (1H, dt, *J* = 21.0, 6.9 Hz), 1.69 (3H, s), 1.57 (1H, ddd, *J* = 14.1, 8.7, 2.7 Hz), 1.42 (2H, ddd, *J* = 14.3, 9.2, 3.2 Hz), 1.29 (1H, ddd, *J* = 14.1, 7.2, 4.8 Hz), 1.04 (3H, d, *J* = 7.2 Hz); ^{13}C NMR (150 MHz, C_6D_6) δ 150.8, 109.9, 69.8, 67.5, 67.2, 43.3, 40.0, 38.4, 19.6, 19.1; ESIMS (positive) *m/z* 211 $(M+Na)^+$; HRESIMS (positive) *m/z* 211.1311 [$(M+Na)^+$, calcd for $C_{10}H_{20}O_3Na$, 211.1305].

Triol 30: colorless oil; $[\alpha]_D^{22}$ -23.4 (*c* 0.11, MeOH); IR (neat) 3396, 2923, 1641, 1445, 1085 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 4.88 (1H, br s), 4.81 (1H, br s), 4.04 (1H, m), 3.91 (1H, m), 3.70 (1H, m), 3.57 (1H, m), 2.50 (1H, m), 1.70 (3H, brs), 1.64 (1H, m), 1.60 (1H, m), 1.35 (1H, m), 1.25 (1H, m), 1.03 (3H m); ^{13}C NMR (150 MHz, C_6D_6) δ 150.8, 109.8, 72.9, 70.4, 67.0, 43.7, 39.9, 38.0, 19.5, 19.1; ESIMS (positive) *m/z* 211 $(M+Na)^+$; HRESIMS (positive) *m/z* 211.1309 [$(M+Na)^+$, calcd for $C_{10}H_{20}O_3Na$, 211.1305].

Triol 31: colorless oil; $[\alpha]_D^{23}$ -99.4 (*c* 0.15, MeOH); IR (neat) 3400, 2925, 1645, 1455, 1085 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 4.98 (1H, br s), 4.90 (1H, br s), 4.17 (1H, m), 4.05 (1H, m), 3.72 (1H, dd, *J* = 11.1, 2.9 Hz), 3.63 (1H, dd, *J* = 11.1, 7.6 Hz), 2.64 (1H, m), 1.71 (3H, brs), 1.63 (1H, m), 1.55 (2H, m), 1.39 (1H, m), 1.14 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (150 MHz, C_6D_6) δ 149.6, 110.7, 69.8, 67.4, 66.9, 43.2, 40.6, 38.2, 20.6, 18.8; ESIMS (positive) *m/z* 211 $(M+Na)^+$; HRESIMS (positive) *m/z* 211.1307 [$(M+Na)^+$, calcd for $C_{10}H_{20}O_3Na$, 211.1305].

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15. For a closely related cyclization, see: P. A. Allen, M. A. Brimble, and H. Prabaharan, *Synlett*, 1999, 295.
16. Compound **17**: NOESY cross peaks ($CDCl_3$, 600 MHz): H_2-8/H_3-19 and H-11/H_3-20.
17. The corresponding sulfide[21] was oxidized with hydrogen peroxide in the presence of $(NH_4)Mo_7O_{24}\cdot 4H_2O$.[22]
18. Compound **5**: NOESY cross peaks (C_6D_6, 600 MHz): H-11/H-12 and H_3-20, H-12/H_3-20, and H-13/H_3-19.
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