HETEROCYCLES, Vol. 90, No. 1, 2015, pp. 579 - 599. © 2015 The Japan Institute of Heterocyclic Chemistry
Received, 30th June, 2014, Accepted, 18th July, 2014, Published online, 24th July, 2014
DOI: 10.3987/COM-14-S(K)66

STUDIES TOWARD THE TOTAL SYNTHESIS OF AMPHIDINOLIDE N: STEREOCONTROLLED SYNTHESIS OF THE C13–C29 SEGMENT

Makoto Sasaki,* Yuki Kawashima, and Haruhiko Fuwa

Graduate School of Life Sciences, Tohoku University, 2-1-1 Katahira, Aoba-ku, Sendai 980-8577, Japan; e-mail: masasaki@m.tohoku.ac.jp

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

Abstract – A stereocontrolled synthesis of the C13–C29 segment of amphidinolide N, a marine macrolide natural product that is extremely potent cytotoxic, is described.

INTRODUCTION

Amphidinolides are a large family of cytotoxic macrolide natural products that are produced by the symbiotic marine dinoflagellate, *Amphidinium* sp., which has been isolated from the Okinawan flatworm, *Amphiscolops* sp. More than 30 macrolides with diverse structures have so far been isolated from a variety of strains of *Amphidinium* sp. by Kobayashi and co-workers.[1] Amphidinolide N (**1**, Figure 1), which was isolated from the cultured *Amphidinium* sp. (Y-5 strain) by the Kobayashi group in 1994, is the most potent cytotoxic member of the amphidinolide family discovered so far and its IC_{50} values against murine lymphoma L1210 and human epidermoid carcinoma KB cells are 0.05 and 0.06 ng/mL, respectively.[2] The gross structure of **1**, including its partial stereochemical assignment, was proposed on the basis of 2D NMR spectroscopic studies. The structure has recently been revised, and the relative configuration has been reported.[3] Amphidinolide N consists of a 26-membered macrolide skeleton containing a six-membered hemiacetal, 2,5-*trans*-disubstituted tetrahydrofuran, allylic epoxide, and 13 stereogenic centers. Soon after amphidinolide N had been isolated, Shimizu and co-workers isolated a closely related macrolide, caribenolide I (**2**, Figure 1), from the cultured free-swimming Caribbean dinoflagellate, *Amphidinium* sp. S1-36-5.[4] Compound **2** has the same gross structure as **1**, and it was found to exhibit in vivo antitumor activity.

The potent cytotoxicity of amphidinolides and their diverse and complex molecular architectures make them important targets for total synthesis. Total syntheses of this family of macrolides have been documented by many research groups,[5] but total synthesis of amphidinolide N has not yet been reported

in the literature.[6,7] Here, we describe a stereocontrolled synthesis of the C13–C29 segment **3** (Figure 1) of amphidinolide N.

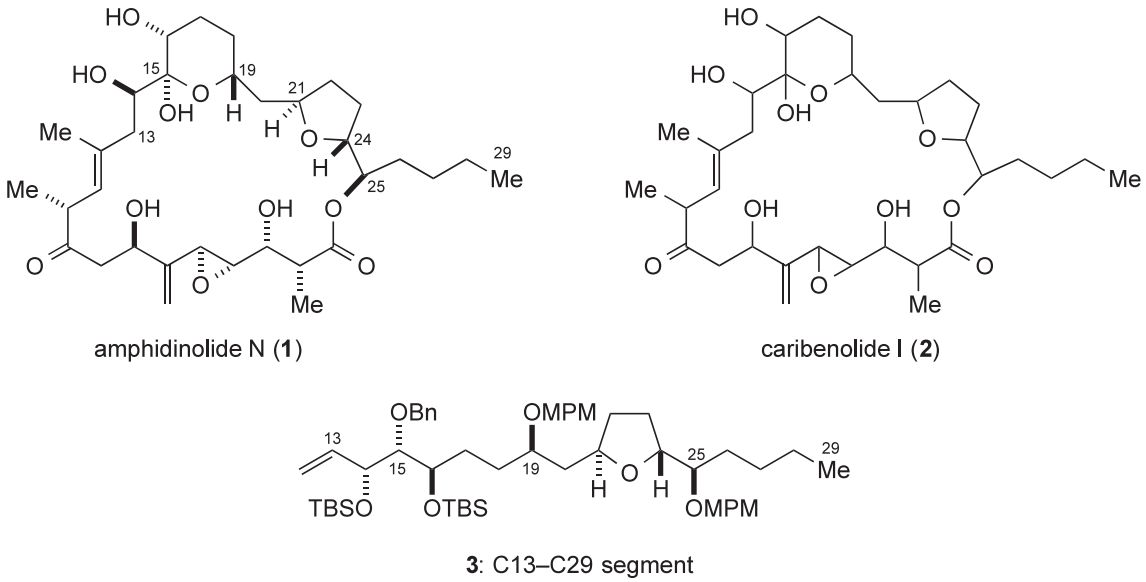
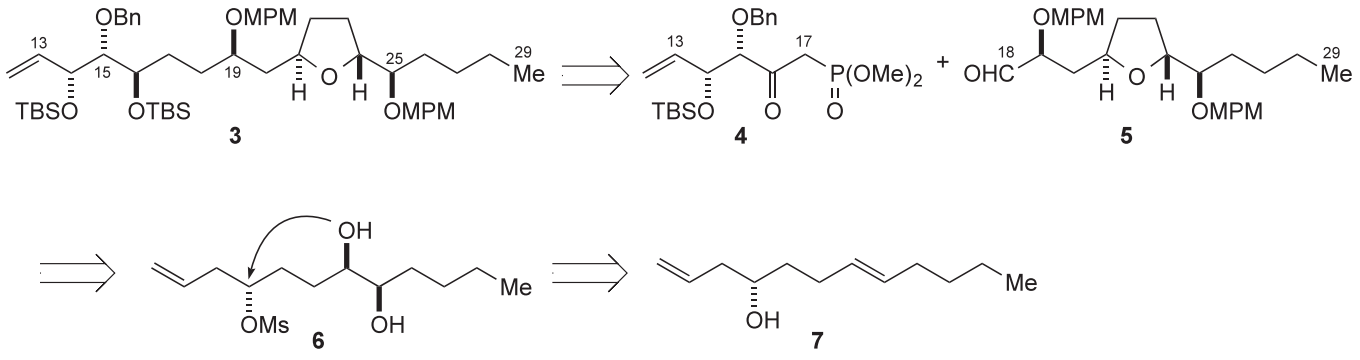


Figure 1. Structures of amphidinolide N, caribenolide I, and the C13–C29 segment

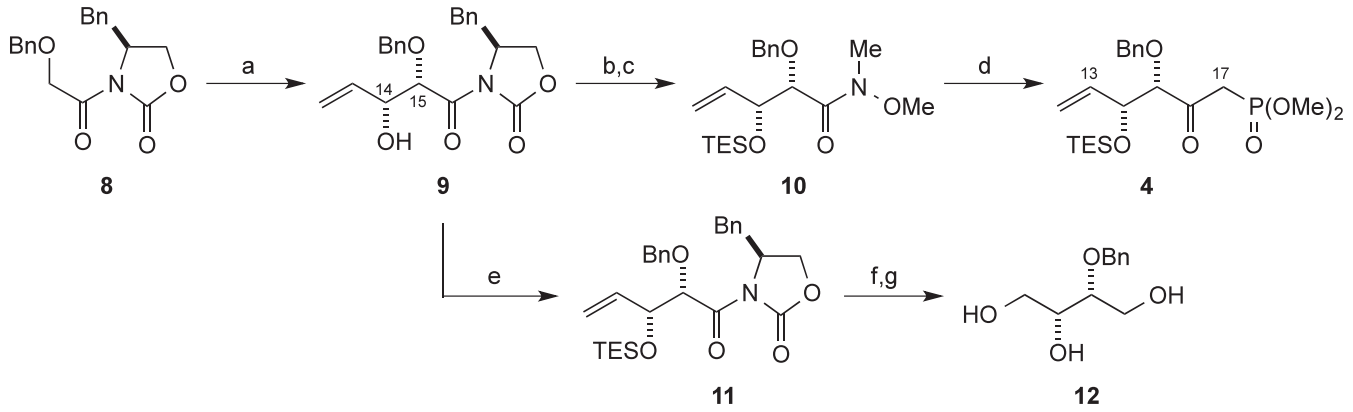
RESULTS and DISCUSSION

Our retrosynthetic plan for the C13–C29 segment **3** is outlined in Scheme 1. We envisaged that **3** would be obtained from two fragments, **4** and **5**, via a Horner–Wadsworth–Emmons (HWE) reaction followed by a 1,4-reduction and chelation-controlled reduction of the product. We expected the 2,5-*trans*-disubstituted tetrahydrofuran of **5** to be constructed via an intramolecular cyclization of diol mesylate **6**, which in turn would be derived through a chemoselective asymmetric dihydroxylation of the precursor diene **7**.



Scheme 1. Retrosynthetic plan for the C13–C29 segment **3**

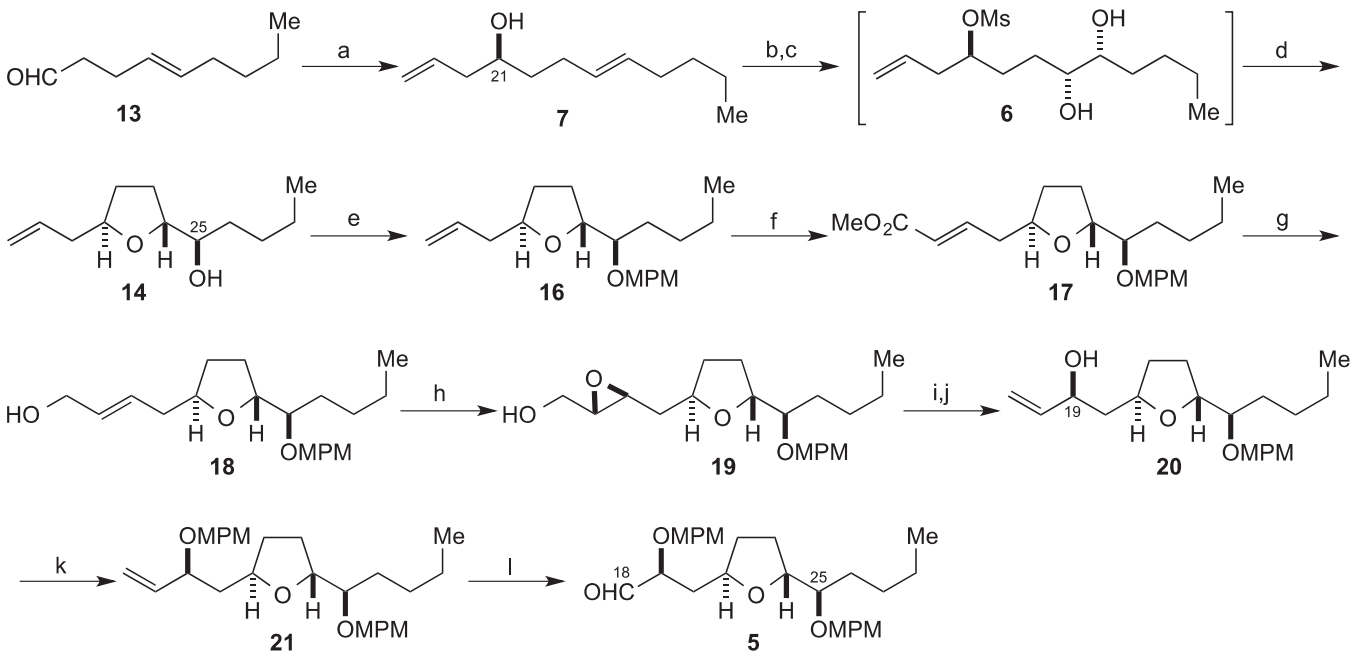
The synthesis of β-keto phosphonate **4** started with (*S*)-4-benzyl-3-((2-benzyloxy)acetyl)oxazolidin-2-one (**8**)[8] (Scheme 2). Evans aldol reaction[9] of the boron enolate derived from **8** with acrolein afforded alcohol **9** in 90% yield as a single stereoisomer. The chiral auxiliary was removed by converting **9** into the corresponding Weinreb amide,[10] and the secondary hydroxy group was protected as its triethylsilyl (TES) ether to give **10** in 79% yield for the two steps. Treating amide **10** with lithiated dimethyl methylphosphonate afforded β-keto phosphonate **4** in 94% yield. The absolute configurations at the C14[11] and C15 positions, which were generated in the Evans aldol reaction, were unambiguously established by converting alcohol **9** into the known triol **12**[12] in a three-step sequence including TES-protection, ozonolysis followed by reduction using $NaBH_4$, and deprotection of the TES ether.



Scheme 2. Reagents and conditions: (a) *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, –78 °C; then acrolein, –78 to 0 °C, 90%, diastereomer ratio (dr) >20:1; (b) MeNH(OMe)·HCl, Me_3Al, THF, 0 °C to room temperature; (c) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 79% (two steps); (d) *n*-BuLi, $(MeO)_2P(O)Me$, THF, –78 °C, 94%; (e) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 73%; (f) O_3, CH_2Cl_2/MeOH, –78 °C, then $NaBH_4$, –78 °C to room temperature; (g) PPTS, CH_2Cl_2/MeOH, room temperature, 47% (two steps).

The synthesis of aldehyde **5** commenced with the known aldehyde **13**.[13] Keck asymmetric allylation[14] of **13** afforded homoallylic alcohol **7** in 87% yield (Scheme 3). The absolute configuration of the C21 stereogenic center was established by a modified Mosher analysis,[15] as shown in Figure 2. The enantiomer ratio (er) of alcohol **7** was found to be 99.2:0.8 from HPLC analysis of the corresponding *p*-methoxybenzoate derivative. Alcohol **7** was then converted into the corresponding mesylate, which was subjected to Sharpless asymmetric dihydroxylation (SAD) using AD-mix-β.[16] Chemoselective dihydroxylation of the disubstituted internal olefin proceeded with concomitant partial cyclization[17] to give a mixture of the corresponding diol **6** and tetrahydrofuran **14**. The obtained unpurified mixture was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene at 100 °C to complete the cyclization, and the desired **14**[18] was produced in 73% yield over the three steps as a single stereoisomer. The absolute configuration of the C25 stereogenic center, which was generated in the SAD, was unambiguously

established using a modified Mosher analysis (Figure 3A).[15] The 2,5-*trans* configuration of the tetrahydrofuran ring of **14** was surmised by the presumed reaction mechanism and established by NOE experiments (Figure 3B).[19] Furthermore, the relative configuration of **14** was unambiguously confirmed by X-ray crystallographic analysis of its triol derivative **15**[20] as shown in Figure 4.[21]



Scheme 3. Reagents and conditions: (a) allyltributylstannane, (*R*)-BINOL, Ti(O*i*-Pr)$_4$, 4 Å molecular sieves, CH_2Cl_2, –78 to –20 °C, 87%, er 99.2:0.8; (b) MsCl, Et_3N, CH_2Cl_2, 0 °C; (c) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH/H_2O (1:1), 0 ºC; (d) DBU, toluene, 100 ºC, 73% (three steps), dr >20:1; (e) NaH, MPMCl, *n*-Bu_4NI, DMF, 0 to 35 ºC, 98%; (f) methyl acrylate, **G-II** (1 mol%), CH_2Cl_2, room temperature, 83%, *E*/*Z* >20:1; (g) DIBALH, CH_2Cl_2, –78 °C, 98%; (h) (+)-diethyl tartrate, Ti(O*i*-Pr)$_4$, *t*-BuOOH, 4 Å molecular sieves, CH_2Cl_2, –20 ºC, 93%, dr >20:1; (i) I_2, PPh_3, imidazole, THF, room temperature; (j) Zn, AcOH, EtOH, room temperature, 95% (two steps); (k) NaH, MPMCl, *n*-Bu_4NI, DMF, 0 ºC to room temperature, 93%; (l) OsO_4, NMO, THF/H_2O (1:1), then $NaIO_4$, room temperature, 90%.

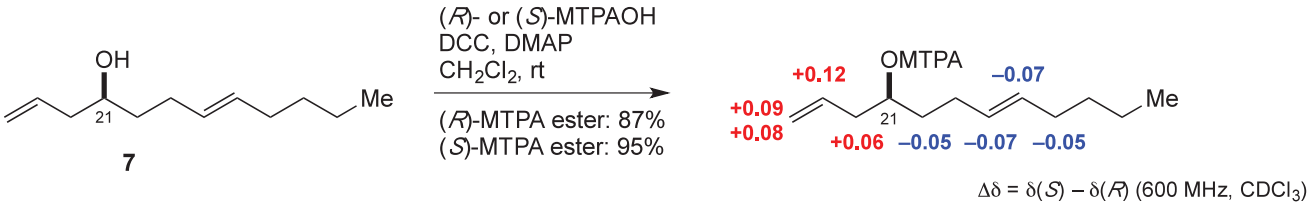


Figure 2. Stereochemical assignment of alcohol **7**

Alcohol **14** was protected as its *p*-methoxybenzyl (MPM) ether, then olefin cross-metathesis[22] of the resultant **16**[18] with methyl acrylate using the Grubbs second-generation catalyst (**G-II**)[23] afforded α,β-unsaturated ester **17** in 83% yield with an *E*/*Z* ratio of greater than 20:1 (Scheme 3). Subsequent

diisobutylaluminum hydride (DIBALH) reduction of **17**, followed by Sharpless asymmetric epoxidation[24] of the resultant allylic alcohol **18** using (+)-diethyl tartrate (DET) as a chiral ligand, produced epoxy alcohol **19** in high overall yield and as a single stereoisomer. Iodination of the primary alcohol of **19** followed by reduction of the product with zinc afforded secondary allylic alcohol **20** in 95% yield for the two steps. The absolute configuration at C19 in **20** was established using a modified Mosher analysis,[15] as shown in Figure 5. Alcohol **20** was protected as its MPM ether (93%), and oxidative cleavage of the terminal double bond of the resulting **21** (OsO_4, *N*-methylmorpholine *N*-oxide (NMO), then $NaIO_4$) gave aldehyde **5** in 90% yield.

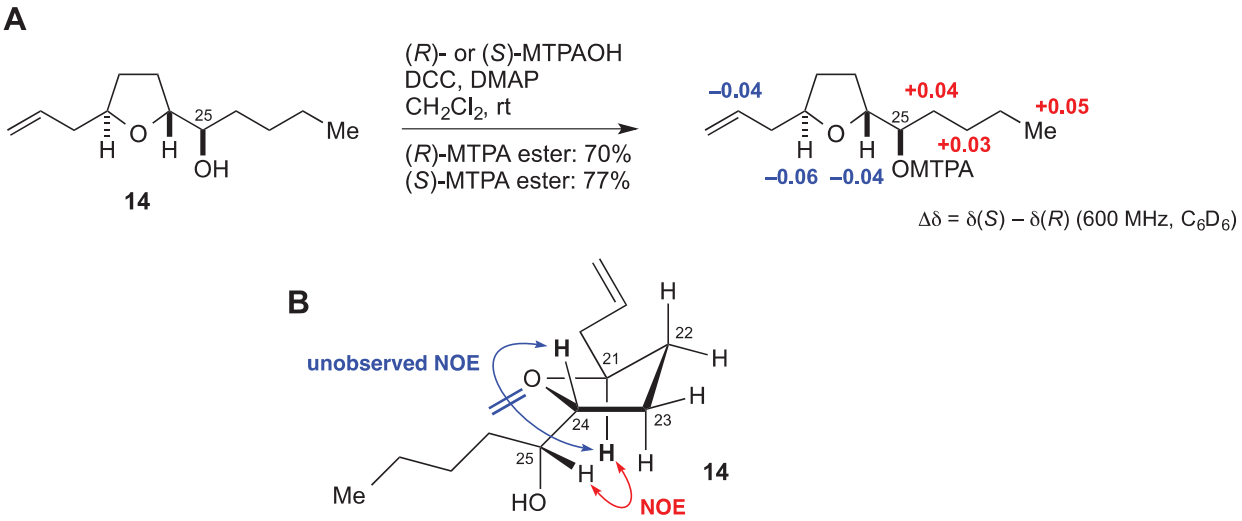


Figure 3. Stereochemical assignment of alcohol **14**

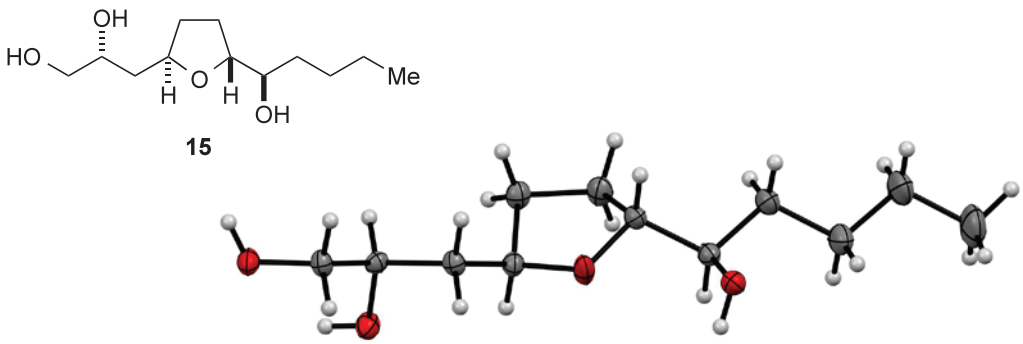


Figure 4. X-Ray crystal structure of triol **15**

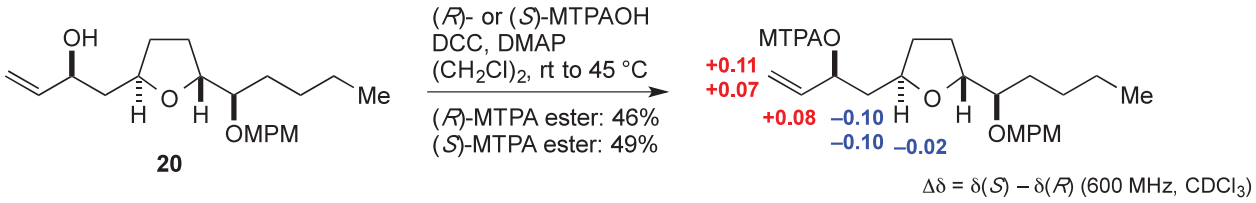
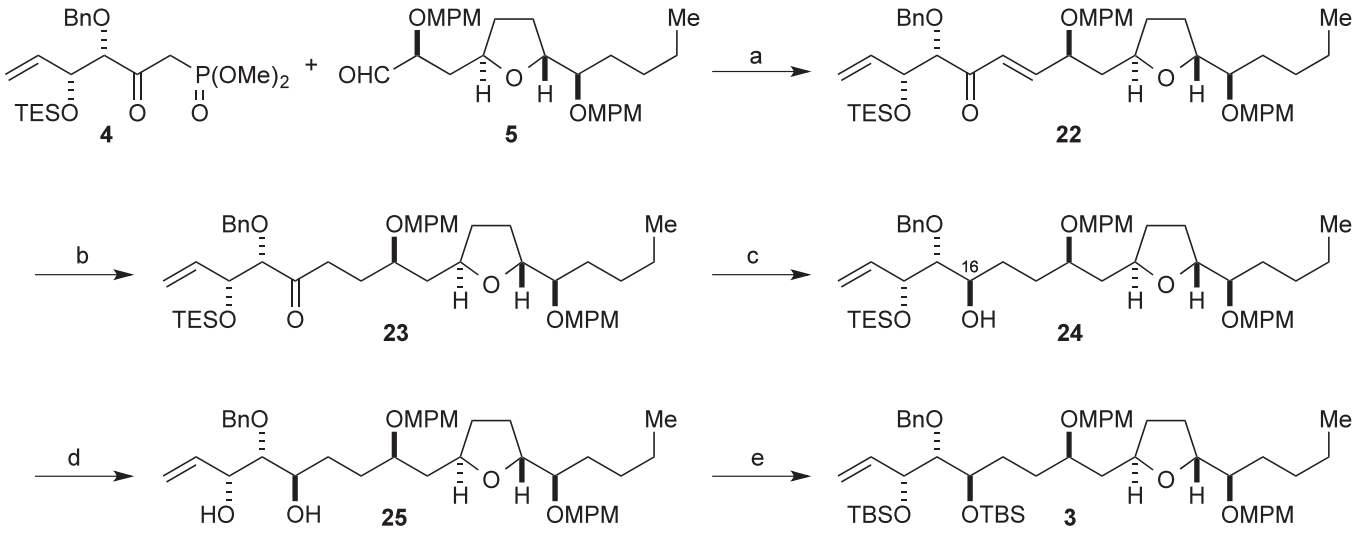


Figure 5. Stereochemical assignment of alcohol **20**

With the requisite fragments in hand, we proceeded to their coupling reaction. HWE reaction of **4** and **5** under Masamune–Roush conditions (LiCl, *i*-Pr_2NEt, MeCN)[25] proceeded smoothly to exclusively give (*E*)-enone **22** in 94% yield (Scheme 4). 1,4-Reduction of **22** using the Stryker reagent[26] gave ketone **23** (95%), which was subjected to chelation-controlled reduction using $Zn(BH_4)_2$[27,28] to give alcohol **24** in 80% yield as a single stereoisomer. Finally, acidic cleavage of the TES ether and protection of the resultant diol **25** as its *tert*-butyldimethylsilyl (TBS) ether afforded bis-TBS ether **3**. The absolute configuration of the newly generated stereogenic center at C16 was established using NOE experiments on the acetonide derivative **26** and from the ^{13}C NMR chemical shifts[29,30] for **26**, as shown in Figure 6.



Scheme 4. Reagents and conditions: (a) LiCl, *i*-Pr_2NEt, MeCN, room temperature, 94%, *E*/*Z* >20:1; (b) $[CuH(PPh_3)]_6$, toluene/H_2O (200:1), room temperature, 95%; (c) $Zn(BH_4)_2$, Et_2O, –78 to –40 °C, 80%, dr >20:1; (d) CSA, MeOH/CH_2Cl_2 (1:1), room temperature, quant; (e) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 90%.

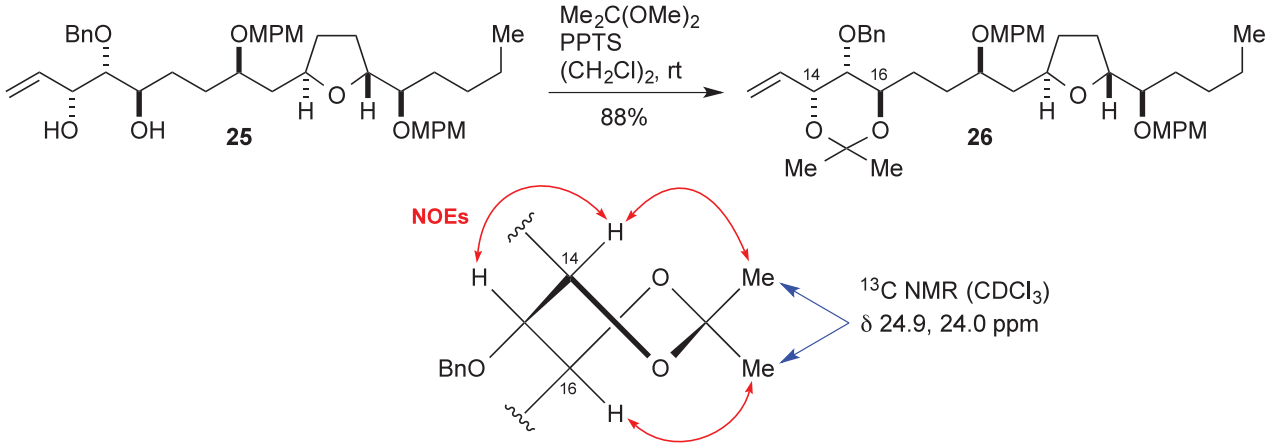


Figure 6. Stereochemical assignment of diol **25**

In conclusion, we have achieved a stereocontrolled synthesis of the C13–C29 segment **3** of amphidinolide N, an exceedingly cytotoxic marine macrolide. The synthesis involves the efficient construction of a 2,5-*trans*-disubstituted tetrahydrofuran via a chemoselective Sharpless asymmetric dihydroxylation–intramolecular cyclization sequence, Horner–Wadsworth–Emmons reaction of the fragments, and chelation-controlled reduction using $Zn(BH_4)_2$ to set the C16 stereogenic center. Further studies aimed at achieving the total synthesis of amphidinolide N are currently being conducted and will be reported in due course.

EXPERIMENTAL

General remarks. All reactions sensitive to moisture and/or air were carried out under an atmosphere of argon in dry, freshly distilled solvents under anhydrous conditions using oven-dried glassware unless otherwise noted. Anhydrous tetrahydrofuran (THF), diethyl ether (Et_2O), and toluene were purified by a Glass Contour solvent purification system under an atmosphere of argon immediately prior to use. Anhydrous dichloromethane (CH_2Cl_2) was purchased from Kanto Chemical Co., Inc. and used as received. *N*,*N*-Dimethylformamide (DMF) was distilled from magnesium sulfate under reduced pressure. Acetonitrile (MeCN), diisopropylethylamine (*i*-Pr_2NEt), 2,6-lutidine, and triethylamine (Et_3N) were distilled from calcium hydride under an atmosphere of argon. All other chemicals were purchased at highest commercial grade and used as received. Analytical thin-layer chromatography was performed using E. Merck silica gel 60 F_{254} plates (0.25-mm thickness). Flash column chromatography was carried out using Kanto Chemical silica gel 60N (40–100 mesh, spherical, neutral) or Fuji Silysia silica gel BW-300 (200–400 mesh). Melting points were measured on a Yanagimoto melting points apparatus and are uncorrected. Optical rotations were recorded on a JASCO P-1020 digital polarimeter. IR spectra were

recorded on a JASCO FT/IR-4100 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM ECA-600 spectrometer. Chemical shift values were reported in δ (ppm) downfield from tetramethylsilane with reference to internal residual solvent [^{1}H NMR, C*H*Cl$_3$ (7.24), C$_6$*H*D$_5$ (7.15); ^{13}C NMR, CDCl$_3$ (77.0), C$_6$D$_6$ (128.0)]. Coupling constants (*J*) were reported in hertz (Hz). The following abbreviations were used to designate the multiplicities: s = singlet; d = doublet; t = triplet; m = multiplet; q = quartet; br = broad. ESI-TOF mass spectra were measured on a Bruker microTOFfocus spectrometer. Diastereomer ratio (dr) was estimated by ^{1}H NMR spectroscopic analysis (600 MHz), unless otherwise noted.

Alcohol 9. To a solution of (*S*)-4-benzyl-3-((2-benzyloxy)acetyl)oxazolidin-2-one (**8**) (100.3 mg, 308.3 μmol) in CH_2Cl_2 (3.0 mL) at 0 ºC were added *n*-Bu_2BOTf (90 μL, 0.36 mmol) and Et_3N (60 μL, 0.43 mmol), and the resultant solution was stirred at 0 ºC for 1 h. To this mixture at –78 ºC was added a solution of acrolein (40 μL, 0.60 mmol). The resultant solution was stirred at –78 ºC for 1 h and allowed to warm to 0 ºC over a period of 1 h. To the solution were added a mixture of MeOH/pH 7 phosphate buffer (7:3, v/v, 3 mL) and a mixture of MeOH/30% aqueous H_2O_2 solution (2:1, v/v, 2 mL), and the resultant mixture was stirred at 0 °C for 1 h. The resultant mixture was extracted with EtOAc, and the organic layer was washed with saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 25 to 40% EtOAc/hexanes) gave alcohol **9** (105.1 mg, 90%) as a colorless oil: $[\alpha]_D^{24}$ +23.5 (*c* 1.00, $CHCl_3$); IR (film) 3480, 3062, 3030, 2924, 2869, 1777, 1705, 1391, 1212, 1112, 700 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 7.38–7.36 (m, 2H), 7.16–7.13 (m, 2H), 7.08–6.98 (m, 4H), 6.84–6.82 (m, 2H), 6.12 (ddd, *J* = 17.0, 10.6, 5.0 Hz, 1H), 5.47 (d, *J* = 3.2 Hz, 1H), 5.42 (ddd, *J* = 17.0, 1.4, 1.4 Hz, 1H), 5.10 (ddd, *J* = 10.6, 1.3, 1.3 Hz, 1H), 4.71 (m, 1H), 4.66 (d, *J* = 11.5 Hz, 1H), 4.37 (d, *J* = 11.5 Hz, 1H), 4.11–4.08 (m, 1H), 3.39 (dd, *J* = 8.3, 1.9 Hz, 1H), 3.09 (dd, *J* = 8.3, 8.3 Hz, 1H), 2.92 (dd, *J* = 13.8, 3.2 Hz, 1H), 2.70 (br s, 1H), 2.28 (dd, *J* = 13.8, 9.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.2, 153.4, 136.9, 136.4, 135.0, 129.4 (2C), 129.0 (2C), 128.5 (2C), 128.4 (2C), 128.2, 127.5, 117.1, 79.6, 73.6, 73.3, 67.0, 55.5, 37.7; HRMS (ESI) calcd for $C_{22}H_{23}NO_5Na$ [$(M + Na)^+$] 404.1468, found 404.1487.

TES ether 10. To a solution of MeNH(OMe)·HCl (108.9 mg, 1.116 mmol) in THF (1.5 mL) at 0 ºC was added Me_3Al (1.09 M solution in *n*-hexane, 1.0 mL, 1.1 mmol), and the resultant solution was stirred at room temperature for 35 min. To this mixture at 0 ºC was added a solution of alcohol **9** (136.7 mg, 358.4 μmol) in THF (0.5 mL + 0.5 mL rinse), and the resultant solution was stirred at room temperature for 3.3 h. The mixture was diluted with saturated aqueous potassium sodium tartrate solution, and the resultant biphasic mixture was vigorously stirred at room temperature until the layers became clear. The resultant mixture was diluted with EtOAc, washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give crude Weinreb amide (168.2 mg), which was contaminated with some impurities and used in the next reaction without further purification.

To a solution of the above Weinreb amide (168.2 mg) in CH_2Cl_2 (3 mL) at 0 ºC were added 2,6-lutidine (200 μL, 1.73 mmol) and TESOTf (240 μL, 1.06 mmol), and the resultant solution was stirred at 0 ºC for 1 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ solution and EtOAc. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 5 to 10% EtOAc/hexanes) gave TES ether **10** (107.8 mg, 79% for the two steps) as a pale yellow oil: $[\alpha]_D^{24}$ –9.4 (*c* 1.00, $CHCl_3$); IR (film) 2954, 2911, 2876, 1671, 1457, 1089, 1005, 739 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.41–7.22 (m, 5H), 5.81 (ddd, *J* = 17.0, 10.6, 6.8 Hz, 1H), 5.23 (d, *J* = 17.0 Hz, 1H), 5.09 (d, *J* = 10.5 Hz, 1H), 4.67 (d, *J* = 12.4 Hz, 1H), 4.55 (d, *J* = 12.4 Hz, 1H), 4.46 (dd, *J* = 6.8, 6.8 Hz, 1H), 4.30 (d, *J* = 6.8 Hz, 1H), 3.43 (s, 3H), 3.10 (s, 3H), 0.92 (t, *J* = 7.8 Hz, 9H), 0.60 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.3, 138.0, 137.0, 128.2 (2C), 127.9 (2C), 127.5, 116.7, 79.4, 75.6, 72.4, 61.2, 32.3, 6.8 (3C), 4.9 (3C); HRMS (ESI) calcd for $C_{20}H_{33}NO_4SiNa$ [$(M + Na)^+$] 402.2071, found 402.2080.

β-Keto phosphonate 4. To a solution of dimethyl methylphosphonate (50 μL, 0.47 mmol) in THF (1.0 mL) at –78 ºC was added *n*-BuLi (1.60 M solution in *n*-hexane, 0.40 mL, 0.64 mmol), and the resultant solution was stirred at –78 ºC for 45 min. To this solution at –78 ºC was added a solution of TES ether **10** (60.1 mg, 0.158 mmol) in THF (0.2 mL + 0.2 mL rinse), and the resultant solution was stirred at –78 °C for 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution. The resultant mixture was diluted with EtOAc, washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 40% EtOAc/hexanes) gave β-keto phosphonate **4** (65.8 mg, 94%) as a colorless oil: $[\alpha]_D^{24}$ +28.9 (*c* 1.00, $CHCl_3$); IR (film) 2955, 2877, 1722, 1258, 1032, 742 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.36–7.26 (m, 5H), 5.86 (ddd, *J* = 17.0, 10.5, 4.1 Hz, 1H), 5.25 (ddd, *J* = 17.0, 1.4, 1.4 Hz, 1H), 5.13 (ddd, *J* = 10.5, 1.4, 1.4 Hz, 1H), 4.74 (d, *J* = 12.0 Hz, 1H), 4.43 (d, *J* = 12.0 Hz, 1H), 4.40 (dddd, *J* = 4.1, 4.1, 1.4, 1.4 Hz, 1H), 4.12 (d, *J* = 4.1 Hz, 1H), 3.75 (d, *J* = 11.0 Hz, 3H), 3.71 (d, *J* = 11.0 Hz, 3H), 3.34 (dd, *J* = 22.4, 14.7 Hz, 1H), 3.23 (dd, *J* = 22.4, 14.7 Hz, 1H), 0.89 (t, *J* = 7.8 Hz, 9H), 0.54 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 201.9 (d, *J* = 7.2 Hz), 137.5, 136.4, 128.4 (2C), 128.2 (2C), 128.0, 116.4, 87.1, 74.4, 73.0, 53.0 (d, *J* = 5.7 Hz), 52.9 (d, *J* = 5.7 Hz), 39.0 (d, *J* = 129.0 Hz), 6.8 (3C), 4.8 (3C); HRMS (ESI) calcd for $C_{21}H_{35}O_6PSiNa$ [$(M + Na)^+$] 465.1833, found 465.1847.

TES ether 11. To a solution of alcohol **9** (233.0 mg, 0.6109 mmol) in CH_2Cl_2 (6 mL) at 0 ºC were added 2,6-lutidine (0.14 mL, 1.2 mmol) and TESOTf (0.17 mL, 0.75 mmol), and the resultant solution was stirred at 0 ºC for 2 h 10 min. The reaction was quenched with saturated aqueous $NaHCO_3$ solution. The resultant mixture was extracted with EtOAc, and the organic layer was washed with saturated aqueous $CuSO_4$ solution and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 2 to 40% EtOAc/hexanes) gave TES

ether **11** (22.7 mg, 73%) as a colorless oil: $[\alpha]_D^{24}$ +58.7 (*c* 1.00, $CHCl_3$); IR (film) 2954, 2912, 2876, 1783, 1706, 1210, 1108, 735 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.39–7.37 (m, 2H), 7.33–7.23 (m, 6H), 7.17–7.16 (m, 2H), 5.94 (ddd, *J* = 17.0, 10.1, 6.0 Hz, 1H), 5.42 (d, *J* = 6.0 Hz, 1H), 5.21 (ddd, *J* = 17.0, 1.4, 1.4 Hz, 1H), 5.14 (ddd, *J* = 10.1, 1.4, 1.4 Hz, 1H), 4.68–4.64 (m, 2H), 4.49 (m, 1H), 4.45 (dd, *J* = 6.0, 6.0 Hz, 1H), 4.10 (dd, *J* = 8.7, 2.3 Hz, 1H), 4.06 (dd, *J* = 8.7, 8.7 Hz, 1H), 3.13 (dd, *J* = 13.8, 3.2 Hz, 1H), 2.57 (dd, *J* = 13.8, 9.7 Hz, 1H), 0.89 (t, *J* = 7.8 Hz, 9H), 0.56 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 153.1, 137.6, 136.8, 135.3, 129.4 (2C), 128.9 (2C), 128.4 (2C), 128.3 (2C), 127.9, 127.3, 116.7, 79.7, 74.9, 73.5, 66.4, 55.7, 37.8, 6.7 (3C), 4.7 (3C); HRMS (ESI) calcd for $C_{28}H_{37}NO_5SiNa$ [$(M + Na)^+$] 518.2333, found 518.2326.

Triol 12. Ozone was bubbled through a solution of TES ether **11** (51.2 mg, 0.103 mmol) in CH_2Cl_2/MeOH (1:1, v/v, 2 mL) at –78 °C until a pale blue color persisted (ca. 25 min). Oxygen was bubbled through the reaction mixture to remove excess ozone, and then $NaBH_4$ (25.3 mg, 0.669 mmol) was added at –78 °C. The resultant mixture was allowed to warm to room temperature over 8 h 20 min. The reaction was quenched with saturated aqueous NH_4Cl solution. The resultant mixture was diluted with EtOAc, washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was roughly purified by column chromatography (silica gel, 30% EtOAc/hexanes) to give crude diol (17.3 mg), which was used in the next reaction without further purification.

To a solution of the above diol (17.3 mg) in MeOH/CH_2Cl_2 (1:1, v/v, 0.6 mL) was added PPTS (2.1 mg, 8.4 μmol), and the resultant solution was stirred at room temperature for 1 h 35 min. The reaction mixture was neutralized with Et_3N and concentrated under reduce pressure. Purification of the residue by column chromatography (silica gel, 50% EtOAc/hexanes to EtOAc) gave triol **12** (10.3 mg, 47% for the two steps) as a white solid, which was recrystallized from $CHCl_3$/hexanes: mp 73.8–76.1 ºC [lit.[12] mp 75.3–76.6 °C]; $[\alpha]_D^{24}$ –15.6 (*c* 0.50, MeOH) [lit.[12] $[\alpha]_D^{25}$ –16.5 (*c* 1.08, EtOH)]; ^1H NMR (600 MHz, $CDCl_3$) δ 7.39–7.18 (m, 5H), 4.71 (d, *J* = 11.5 Hz, 1H), 4.58 (d, *J* = 11.5 Hz, 1H), 3.88 (dd, *J* = 11.8, 4.6 Hz, 1H), 3.83 (dd, *J* = 9.2, 4.6 Hz, 1H), 3.76–3.72 (m, 2H), 3.68 (dd, *J* = 11.8, 4.1 Hz, 1H), 3.57 (dd, *J* = 9.2, 3.9 Hz, 1H), (three protons missing due to H/D exchange); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.6, 128.7 (2C), 128.2, 128.0 (2C), 79.2, 72.5, 71.6, 63.0, 61.0. The spectroscopic data of triol **12** were consistent with those reported in the literature.[12]

Homoallylic alcohol 7. To a mixture of (*R*)-BINOL (407.3 mg, 1.422 mmol), freshly activated 4 Å molecular sieves (2.94 g) in CH_2Cl_2 (16 mL) was added Ti(O*i*-Pr)$_4$ (400 μL, 1.35 mmol), and the resultant mixture was heated under reflux for 1 h. To the reaction mixture at room temperature was added aldehyde **13** (1.91 g, 13.7 mmol) in CH_2Cl_2 (2 mL + 2 × 1 mL rinse), and the resultant mixture was stirred for 10 min. The reaction mixture was cooled to –78 °C and treated with allyltributylstannane (6.40 mL, 20.6 mmol). The resultant mixture was stirred at –20 ºC for 3 days. The reaction was quenched with saturated

aqueous $NaHCO_3$ solution at –78 °C. The resultant mixture was diluted with CH_2Cl_2 (15 mL), allowed to warm to room temperature over 1.5 h, and filtered through a pad of Celite. The filtrate was extracted with Et_2O, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 2 to 10% EtOAc/hexanes) gave homoallylic alcohol **7**, which was contaminated with the starting aldehyde **13**. This material was further purified twice by column chromatography (silica gel, 10% EtOAc/hexanes to EtOAc) to give homoallylic alcohol **7** (2.17 g, 87%) as a pale yellow oil: $[\alpha]_D^{26}$ –5.6 (*c* 1.00, $CHCl_3$); IR (film) 3356, 2956, 2926, 2872, 2854, 2360, 1641, 1437, 993, 967, 913 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.81 (m, 1H), 5.46–5.37 (m, 2H), 5.13 (m, 1H), 5.11 (m, 1H), 3.64 (m, 1H), 2.27 (m, 1H), 2.16–2.04 (m, 3H), 1.96 (ddd, *J* = 6.6, 6.6, 6.6 Hz, 2H), 1.52–1.49 (m, 2H), 1.32–1.25 (m, 4H), 0.86 (t, *J* = 7.4 Hz, 3H), (one proton missing due to H/D exchange); ^{13}C NMR (150 MHz, $CDCl_3$) δ 134.5, 130.8, 129.2, 117.7, 70.0, 41.6, 36.2, 31.9, 31.4, 28.6, 21.9, 13.6.

***p*-Methoxybenzoylation of alcohol 7.** To a solution of homoallylic alcohol **7** (12.7 mg, 69.7 μmol) in pyridine (0.5 mL) were added DMAP (11.9 mg, 97.4 μmol) and *p*-methoxybenzoyl chloride (71.6 mg, 420 μmol). The resultant solution was stirred at room temperature for 15 h. The reaction was quenched with H_2O. The resultant mixture was extracted with EtOAc, and the organic layer was washed four times with 1 M aqueous HCl solution, saturated aqueous $NaHCO_3$ solution, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 2% EtOAc/hexanes) gave the corresponding *p*-methoxybenzoate (18.5 mg, 84%) as a colorless oil: $[\alpha]_D^{24}$ –27.1 (*c* 1.00, $CHCl_3$); IR (film) 2956, 2928, 2853, 1711, 1606, 1510, 1274, 1256, 1168, 1101, 1033, 769 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.99–7.96 (m, 2H), 6.91–6.88 (m, 2H), 5.82 (dddd, *J* = 17.0, 10.1, 6.9, 6.9 Hz, 1H), 5.41–5.34 (m, 2H), 5.12 (dddd, *J* = 11.0, 11.0, 5.9, 5.9 Hz, 1H), 5.08 (ddd, *J* = 17.0, 3.2, 1.0 Hz, 1H), 5.03 (ddd, *J* = 10.1, 1.0, 1.0 Hz, 1H), 3.84 (s, 3H), 2.41 (dd, *J* = 7.3, 7.3 Hz, 2H), 2.10–2.01 (m, 2H), 1.94 (ddd, *J* = 6.4, 6.4, 6.4 Hz, 2H), 1.78–1.65 (m, 2H), 1.30–1.25 (m, 4H), 0.85 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.9, 163.2, 133.7, 131.5 (2C), 131.2, 128.9, 123.1, 117.7, 113.5 (2C), 73.1, 55.4, 38.7, 33.6, 32.2, 31.6, 28.5, 22.2, 13.9; HRMS (ESI) calcd for $C_{20}H_{28}O_3Na$ [$(M + Na)^+$] 339.1931, found 339.1926. The enantiomer ratio of this benzoate was determined to be 99.2:0.8 by chiral HPLC analysis in comparison with authentic racemic material (CHIRALCEL OJ-H, 4.6 mm I.D. × 250 mm, flow rate: 1.0 mL/min, UV detection: 254 nm, eluent: hexanes, major peak: *t* = 16.8 min; minor peak: *t* = 14.1 min).

Tetrahydrofuran 14. To a solution of homoallylic alcohol **7** (2.12 g, 11.6 mmol) in CH_2Cl_2 (100 mL) at 0 ºC were added Et_3N (2.10 mL, 15.1 mmol) and MsCl (1.00 mL, 12.9 mmol). The resultant solution was stirred at 0 ºC for 30 min. The reaction mixture was diluted with EtOAc and washed successively with 1 M aqueous HCl solution, saturated aqueous $NaHCO_3$ solution, and brine. The organic layer was dried

over Na_2SO_4, filtered, and concentrated under reduced pressure to give crude mesylate (3.23 g), which was used in the next reaction without further purification.

To a solution of the above mesylate (3.23 g) in *t*-BuOH/H_2O (1:1, v/v, 100 mL) at 0 ºC were added $MeSO_2NH_2$ (1.11 g, 11.7 mmol) and AD-mix-β (16.3 g). The resultant mixture was vigorously stirred at 0 ºC for 5 h 20 min. The reaction was quenched with solid Na_2SO_3. The resultant mixture was stirred at room temperature for 1 h and then extracted with EtOAc. The organic layer was washed with 3 M aqueous NaOH solution and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give crude product (3.56 g), which was used in the next reaction without further purification.

To a solution of the above material (3.56 g) in toluene (50 mL) was added DBU (2.00 mL, 13.4 mmol), and the resultant solution was stirred at 100 ºC for 1.5 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 0 to 1% EtOAc/benzene) gave tetrahydrofuran **14** (1.68 g, 73% for the three steps, dr >20:1 estimated by 600 MHz ^{1}H NMR spectroscopy) as a pale yellow oil: $[\alpha]_D^{26}$ +13.8 (*c* 1.00, $CHCl_3$); IR (film) 3464, 3077, 2957, 2931, 2871, 2861, 2360, 2340, 1642, 1065, 914 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.78 (dddd, *J* = 17.0, 10.1, 6.9, 6.9 Hz, 1H), 5.07 (ddd, *J* = 17.0, 3.2, 1.4 Hz, 1H), 5.03 (dddd, *J* = 10.1, 3.2, 1.4, 1.4 Hz, 1H), 3.95 (dddd, *J* = 7.8, 6.9, 6.9, 6.9 Hz, 1H), 3.79 (ddd, *J* = 6.9, 6.9, 6.9 Hz, 1H), 3.35 (ddd, *J* = 6.9, 6.9, 5.0 Hz, 1H), 2.35 (ddddd, *J* = 13.8, 6.9, 6.9, 1.4, 1.4 Hz, 1H), 2.21 (ddddd, *J* = 13.8, 6.9, 6.9, 1.4, 1.4 Hz, 1H), 2.02–1.93 (m, 2H), 1.63–1.54 (m, 2H), 1.47 (m, 1H), 1.41–1.28 (m, 5H), 0.88 (t, *J* = 7.3 Hz, 3H), (one proton missing due to H/D exchange); ^{13}C NMR (150 MHz, $CDCl_3$) δ 134.8, 116.9, 82.2, 78.5, 74.1, 39.9, 33.0, 31.8, 28.3, 27.8, 22.8, 14.0; HRMS (ESI) calcd for $C_{12}H_{22}O_2Na$ [$(M + Na)^+$] 221.1512, found 221.1538.

MPM ether 16. To a solution of alcohol **14** (1.68 g, 8.47 mmol) in DMF (40 mL) at 0 ºC was added NaH (60% in mineral oil, 0.53 g, 13 mmol), and the resultant mixture was stirred at room temperature for 35 min. To the resultant mixture at 0 ºC were added *n*-Bu_4NI (319.5 mg, 0.8650 mmol) and MPMCl (1.50 mL, 11.0 mmol), and the resultant mixture was stirred at 35 ºC for 17 h 20 min. The reaction was quenched with saturated aqueous NH_4Cl solution at 0 °C. The resultant mixture was diluted with Et_2O, washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduce pressure. Purification of the residue by column chromatography (silica gel, 5% EtOAc/hexanes) gave MPM ether **16** (2.64 g, 98%) as a colorless oil: $[\alpha]_D^{24}$ +21.9 (*c* 1.00, $CHCl_3$); IR (film) 3074, 2955, 2932, 2861, 1613, 1514, 1248, 1088, 1038, 821 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28–7.26 (m, 2H), 6.86–6.82 (m, 2H), 5.81 (dddd, *J* = 17.0, 10.1, 6.9, 6.9 Hz, 1H), 5.07 (ddd, *J* = 17.0, 3.7, 1.8 Hz, 1H), 5.02 (ddd, *J* = 10.1, 3.7, 1.8 Hz, 1H), 4.64 (d, *J* = 11.0 Hz, 1H), 4.51 (d, *J* = 11.0 Hz, 1H), 4.04 (ddd, *J* = 8.2, 6.9, 6.9 Hz, 1H), 3.98 (dddd, *J* = 8.2, 6.9, 6.9, 6.9 Hz, 1H), 3.78 (s, 3H), 3.28 (m, 1H), 2.36 (ddd, *J* = 13.7, 6.9, 6.9 Hz, 1H), 2.21 (ddd, *J* = 13.7, 6.9, 6.9 Hz, 1H), 1.97 (m, 1H), 1.90 (m, 1H), 1.63 (m, 1H), 1.51 (m, 1H), 1.44–1.42

(m, 3H), 1.32–1.23 (m, 3H), 0.85 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.0, 135.2, 131.4, 129.5 (2C), 116.6, 113.6 (2C), 81.2, 81.1, 78.6, 72.4, 55.3, 40.2, 31.6, 30.5, 28.3, 28.0, 22.8, 14.1; HRMS (ESI) calcd for $C_{20}H_{30}O_3Na$ [$(M + Na)^+$] 341.2087, found 341.2095.

α,β-Unsaturated ester 17. To a solution of MPM ether **16** (914.1 mg, 2.870 mmol) in degassed CH_2Cl_2 (28 mL) were added methyl acrylate (2.60 mL, 29.0 mmol) and a solution of the Grubbs second-generation catalyst (26.4 mg, 31.1 μmol) in degassed CH_2Cl_2 (1 mL + 1 mL rinse), and the resultant solution was stirred at room temperature for 14 h 50 min. The mixture was concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 5 to 10% EtOAc/hexanes) gave α,β-unsaturated ester **17** (901.4 mg, 83%) as a colorless oil: $[\alpha]_D^{24}$ +13.0 (*c* 1.00, $CHCl_3$); IR (film) 2952, 2870, 1725, 1514, 1248, 1037, 822 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26–7.24 (m, 2H), 6.96 (ddd, *J* = 15.5, 7.3, 7.3 Hz, 1H) 6.86–6.83 (m, 2H), 5.89 (ddd, *J* = 15.5, 1.4, 1.4 Hz, 1H), 4.61 (d, *J* = 11.0 Hz, 1H), 4.51 (d, *J* = 11.0 Hz, 1H), 4.08–4.02 (m, 2H), 3.78 (s, 3H), 3.70 (s, 3H), 3.26 (m, 1H), 2.47 (dddd, *J* = 14.0, 6.7, 6.7, 1.4 Hz, 1H), 2.37 (dddd, *J* = 14.0, 6.9, 6.9, 1.4 Hz, 1H), 2.01 (m, 1H), 1.91 (m, 1H), 1.64 (m, 1H), 1.50 (m, 1H), 1.46–1.41 (m, 3H), 1.32–1.23 (m, 3H), 0.86 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.9, 159.0, 145.7, 131.3, 129.5 (2C), 122.8, 113.6 (2C), 81.4, 81.0, 77.5, 72.4, 55.3, 51.4, 38.5, 31.8, 30.5, 28.3, 27.9, 22.8, 14.1; HRMS (ESI) calcd for $C_{22}H_{32}O_5Na$ [$(M + Na)^+$] 399.2142, found 399.2126.

Allylic alcohol 18. To a solution of α,β-unsaturated ester **17** (809.0 mg, 2.149 mmol) in CH_2Cl_2 (20 mL) at –78 ºC was added DIBALH (1.02 M in *n*-hexane, 6.30 mL, 6.43 mmol), and the resultant solution was stirred at –78 ºC for 35 min. The reaction was quenched with MeOH. The mixture was diluted with EtOAc and saturated aqueous potassium sodium tartrate solution, and the resultant biphasic mixture was vigorously stirred at room temperature until the layers became clear. The resultant mixture was diluted with EtOAc, and the organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 10 to 30% EtOAc/hexanes) gave allylic alcohol **18** (734.2 mg, 98%) as a colorless oil: $[\alpha]_D^{24}$ +17.4 (*c* 1.00, $CHCl_3$); IR (film) 3420, 2954, 2932, 2861, 1612, 1513, 1247, 1085, 1036, 821 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26–7.24 (m, 2H), 6.86–6.83 (m, 2H), 5.73–5.66 (m, 2H), 4.64 (d, *J* = 11.0 Hz, 1H), 4.52 (d, *J* = 11.0 Hz, 1H), 4.08–4.06 (m, 2H), 4.04 (ddd, *J* = 8.3, 6.0, 6.0 Hz, 1H), 3.97 (dddd, *J* = 8.7, 6.4, 6.4, 6.4 Hz, 1H), 3.78 (s, 3H), 3.27 (m, 1H), 2.34 (m, 1H), 2.20 (m, 1H), 1.97 (m, 1H), 1.90 (m, 1H), 1.63 (m, 1H), 1.50 (m, 1H), 1.46–1.41 (m, 3H), 1.32–1.23 (m, 3H), 0.86 (t, *J* = 7.3 Hz, 3H), (one proton missing due to H/D exchange); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.0, 131.3, 131.2, 129.5 (2C), 129.2, 113.6 (2C), 81.13, 81.07, 78.6, 72.4, 63.7, 55.2, 38.5, 31.6, 30.4, 28.3, 27.9, 22.8, 14.1; HRMS (ESI) calcd for $C_{21}H_{32}O_4Na$ [$(M + Na)^+$] 371.2193, found 371.2182.

Epoxy alcohol 19. To a mixture of allylic alcohol **18** (592.9 mg, 1.701 mmol), freshly activated 4 Å

molecular sieves (1.06 g), and (+)-diethyl tartrate (113.4 mg, 0.550 mmol) in CH_2Cl_2 (20 mL) at –20 ºC was added Ti(O*i*-Pr)$_4$ (100 μL, 0.338 mmol), and the resultant mixture was stirred at –20 ºC for 30 min. To this mixture was added *t*-BuOOH (4.43 M solution in isooctane, 800 μL, 3.54 mmol), and the resultant mixture was stirred at –20 ºC for 4 h 20 min. The reaction mixture was diluted with *tert*-butyl methyl ether (TBME, 10 mL) and treated with 1 M aqueous NaOH solution (30 mL) at 0 ºC. The resultant biphasic mixture was vigorously stirred at 0 ºC for 1 h. The resultant mixture was filtered through a pad of Celite. The filtrate was diluted with TBME, washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 30 to 40% EtOAc/hexanes) gave epoxy alcohol **19** (576.0 mg, 93%, dr >20:1 as judged by 600 MHz ^{1}H NMR) as a colorless oil: $[\alpha]_D^{24}$ –6.9 (*c* 1.00, $CHCl_3$); IR (film) 3434, 2954, 2934, 2869, 1612, 1512, 1465, 1248, 1086, 1035, 822 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28–7.26 (m, 2H), 6.86–6.83 (m, 2H), 4.64 (d, *J* = 11.0 Hz, 1H), 4.53 (d, *J* = 11.0 Hz, 1H), 4.12 (dddd, *J* = 8.7, 8.7, 6.0, 5.0 Hz, 1H), 4.01 (ddd, *J* = 8.7, 6.4, 6.4 Hz, 1H), 3.86 (m, 1H), 3.78 (s, 3H), 3.60 (m, 1H), 3.27 (m, 1H), 3.08 (ddd, *J* = 7.3, 5.0, 2.3 Hz, 1H), 2.94 (ddd, *J* = 5.0, 2.3, 2.3 Hz, 1H), 2.06 (m, 1H), 1.92 (m, 1H), 1.81 (ddd, *J* = 13.7, 8.7, 5.0 Hz, 1H), 1.67–1.61 (m, 3H), 1.52 (m, 1H), 1.45–1.38 (m, 3H), 1.32–1.23 (m, 3H), 0.86 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.0, 131.3, 129.4 (2C), 113.6 (2C), 81.3, 81.1, 76.4, 72.5, 61.7, 58.6, 55.2, 53.8, 38.2, 32.3, 30.6, 28.5, 27.8, 22.8, 14.0; HRMS (ESI) calcd for $C_{21}H_{32}O_5Na$ [$(M + Na)^+$] 387.2142, found 387.2161.

Secondary allylic alcohol 20. To a solution of epoxy alcohol **19** (557.6 mg, 1.530 mmol) in THF (15 mL) were added imidazole (0.21 g, 3.1 mmol), PPh_3 (0.72 g, 2.8 mmol), and I_2 (0.71 g, 2.8 mmol), and the resultant solution was stirred at room temperature for 30 min. The reaction was quenched with saturated aqueous Na_2SO_3 solution at 0 ºC. The resultant mixture was extracted with EtOAc, and the organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give crude iodide, which was used in the next reaction without further purification.

To a solution of the above iodide in EtOH (15 mL) were added zinc powder (1.01 g, 15.4 mmol) and AcOH (0.18 mL, 3.1 mmol), and the resultant mixture was stirred at room temperature for 30 min. The reaction was quenched with saturated aqueous $NaHCO_3$ solution at 0 ºC. The resultant mixture was filtered through a pad of Celite, and the filtrate was diluted with EtOAc. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 5 to 15% EtOAc/hexanes) gave secondary allylic alcohol **20** (508.3 mg, 95% for the two steps) as a colorless oil: $[\alpha]_D^{24}$ +18.7 (*c* 1.00, $CHCl_3$); IR (film) 3439, 2955, 2934, 2870, 1613, 1514, 1248, 1085, 1037, 821 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27–7.24 (m, 2H), 6.86–6.84 (m, 2H), 5.91 (ddd, *J* = 17.0, 10.6, 5.0 Hz, 1H), 5.29 (ddd, *J* = 17.0, 1.3, 1.3 Hz, 1H), 5.11 (ddd, *J* = 10.6, 1.3, 1.3 Hz, 1H), 4.62 (d, *J* = 11.0 Hz, 1H), 4.50 (d, *J* = 11.0 Hz, 1H), 4.37

(m, 1H), 4.22 (dddd, *J* = 8.7, 5.5, 3.7, 3.7 Hz, 1H), 4.06 (ddd, *J* = 8.2, 6.0, 6.0 Hz, 1H), 3.77 (s, 3H), 3.26 (m, 1H), 2.00 (m, 1H), 1.91 (m, 1H), 1.83–1.72 (m, 2H), 1.66–1.53 (m, 2H), 1.44–1.38 (m, 3H), 1.32–1.22 (m, 3H), 0.86 (t, *J* = 7.3 Hz, 3H), (one proton missing due to H/D exchange); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.0, 140.7, 131.1, 129.5 (2C), 114.0, 113.7 (2C), 81.7, 81.1, 76.6, 72.6, 70.7, 55.2, 40.8, 32.3, 30.6, 28.3, 27.8, 22.8, 14.0; HRMS (ESI) calcd for $C_{21}H_{32}O_4Na$ [(M + Na)$^+$] 371.2193, found 371.2215.

Bis-MPM ether 21. To a solution of allylic alcohol **20** (467.1 mg, 1.340 mmol) in DMF (15 mL) at 0 ºC was added NaH (60% in mineral oil, 101.3 mg, 2.533 mmol), and the resultant mixture was stirred at room temperature for 30 min. To the resultant mixture at 0 ºC were added *n*-Bu_4NI (49.4 mg, 134 μmol) and MPMCl (270 μL, 1.98 mmol), and the resultant mixture was stirred at room temperature for 9 h 15 min. The reaction was quenched with saturated aqueous NH_4Cl solution at 0 °C. The resultant mixture was extracted with TBME, and the organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduce pressure. Purification of the residue by column chromatography (silica gel, 5 to 10% EtOAc/hexanes) gave bis-MPM ether **21** (585.6 mg, 93%) as a colorless oil: $[\alpha]_D^{24}$ –15.9 (*c* 1.00, $CHCl_3$); IR (film) 2954, 2934, 2862, 1613, 1512, 1247, 1037, 821 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27–7.21 (m, 4H), 6.84–6.80 (m, 4H), 5.75 (ddd, *J* = 17.4, 10.6, 7.8 Hz, 1H), 5.22 (ddd, *J* = 17.4, 1.8, 0.9 Hz, 1H), 5.18 (ddd, *J* = 10.6, 1.8, 0.9 Hz, 1H), 4.66 (d, *J* = 11.0 Hz, 1H), 4.50 (d, *J* = 11.0 Hz, 1H), 4.49 (d, *J* = 11.0 Hz, 1H), 4.27 (d, *J* = 11.0 Hz, 1H), 4.17 (dddd, *J* = 8.2, 5.5, 4.1, 4.1 Hz, 1H), 4.02–3.96 (m, 2H), 3.77 (s, 3H), 3.74 (s, 3H), 3.26 (m, 1H), 2.00 (m, 1H), 1.90 (m, 1H), 1.74 (m, 1H), 1.67 (m, 1H), 1.63–1.56 (m, 2H), 1.48–1.38 (m, 3H), 1.32–1.22 (m, 3H), 0.86 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.0, 139.2, 131.5, 130.8, 129.5 (2C), 129.3 (2C), 116.5, 113.7 (2C), 113.6 (2C), 81.4, 81.3, 78.1, 75.5, 72.6, 71.4, 70.2, 55.25, 55.20, 42.2, 32.5, 30.7, 28.7, 27.9, 22.8, 14.1; HRMS (ESI) calcd for $C_{29}H_{40}O_5Na$ [(M + Na)$^+$] 491.2768, found 491.2787.

Aldehyde 5. To a solution of olefin **21** (17.3 mg, 37.0 μmol) in THF/H_2O (1:1, v/v, 0.8 mL) were added OsO_4 (10 mg/mL solution in *t*-BuOH, 45 μL, 1.8 μmol) and NMO (4.8 M solution in H_2O, 25 μL, 0.12 mmol), and the resultant mixture was stirred at room temperature for 15.5 h. To the reaction mixture was added $NaIO_4$ (22.3 mg, 104 μmol), and the resultant mixture was stirred at room temperature for 50 min. The resultant mixture was treated with saturated aqueous Na_2SO_3 solution and stirred at room temperature for 40 min. The reaction mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 10 to 20% EtOAc/hexanes) gave aldehyde **5** (15.7 mg, 90%) as a colorless oil: $[\alpha]_D^{24}$ –19.8 (*c* 1.00, $CHCl_3$); IR (film) 2954, 2868, 1732, 1613, 1513, 1249, 1088, 1035, 821 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.61 (d, *J* = 1.8 Hz, 1H), 7.26–7.24 (m, 4H), 6.86–6.82 (m, 4H), 4.63 (d, *J* = 11.0 Hz, 1H), 4.59 (d, *J* = 11.0 Hz, 1H), 4.49 (d, *J* = 11.0 Hz, 1H), 4.49 (d, *J* = 11.0 Hz,

1H), 4.20 (dddd, *J* = 9.2, 6.0, 3.7, 3.7 Hz, 1H), 4.04 (ddd, *J* = 9.7, 3.7, 1.8 Hz, 1H), 4.00 (ddd, *J* = 8.2, 5.9, 5.9 Hz, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 3.26 (ddd, *J* = 5.9, 5.9, 5.9 Hz, 1H), 2.04 (m, 1H), 1.92 (m, 1H), 1.83 (ddd, *J* = 13.7, 9.2, 3.7 Hz, 1H), 1.73 (ddd, *J* = 13.7, 9.7, 3.7 Hz, 1H), 1.64 (m, 1H), 1.53 (m, 1H), 1.46–1.40 (m, 3H), 1.32–1.22 (m, 3H), 0.87 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 203.1, 159.4, 159.0, 131.3, 129.7 (2C), 129.5, 129.4 (2C), 113.9 (2C), 113.6 (2C), 81.6, 81.34, 81.30, 74.8, 72.8, 72.5, 55.2, 55.2, 36.4, 32.3, 30.7, 28.7, 27.8, 22.8, 14.1; HRMS (ESI) calcd for $C_{28}H_{38}O_6Na$ [$(M + Na)^+$] 493.2561, found 493.2544.

Enone 22. To a solution of β-keto phosphonate **4** (90.0 mg, 0.203 mmol) in MeCN (1.0 mL) were added flame dried LiCl (15.3 mg, 0.361 mmol) and *i*-Pr_2NEt (60 μL, 0.34 mmol), and the resultant solution was stirred at room temperature for 15 min. To the mixture was added a solution of aldehyde **5** (77.9 mg, 0.166 mmol) in MeCN (0.5 mL + 0.5 mL rinse), and the resultant solution was stirred at room temperature for 13.5 h. The reaction was quenched with saturated aqueous NH_4Cl solution at 0 °C. The resultant mixture was extracted with EtOAc, and the organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 10% EtOAc/hexanes) to give enone **22** (123.1 mg, 94%, *E*/*Z* >20:1 as judged by 600 MHz ^{1}H NMR) as a colorless oil: $[\alpha]_D^{24}$ –21.5 (*c* 1.00, $CHCl_3$); IR (film) 2953, 2935, 2873, 1514, 1248, 1084, 1036, 742 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30–7.23 (m, 7H), 7.19–7.17 (m, 2H), 6.85–6.81 (m, 3H), 6.79–6.77 (m, 2H), 6.72 (dd, *J* = 15.6, 0.9 Hz, 1H), 5.86 (ddd, *J* = 17.0, 10.1, 6.4 Hz, 1H), 5.21 (ddd, *J* = 17.0, 1.4, 1.4 Hz, 1H), 5.10 (ddd, *J* = 10.1, 1.4, 1.4 Hz, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 4.64 (d, *J* = 11.0 Hz, 1H), 4.48 (d, *J* = 11.0 Hz, 1H), 4.45 (d, *J* = 11.0 Hz, 1H), 4.42 (d, *J* = 12.0 Hz, 1H), 4.41 (m, 1H), 4.26 (d, *J* = 11.0 Hz, 1H), 4.24–4.18 (m, 2H), 3.99 (ddd, *J* = 8.7, 6.4, 6.4 Hz, 1H), 3.87 (d, *J* = 4.6 Hz, 1H), 3.76 (s, 3H), 3.73 (s, 3H), 3.25 (ddd, *J* = 6.4, 6.4, 6.4 Hz, 1H), 2.00 (m, 1H), 1.89 (m, 1H), 1.71–1.40 (m, 6H), 1.30–1.23 (m, 4H), 0.90–0.85 (m, 12H), 0.53 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 199.8, 159.2, 159.0, 147.3, 137.3, 137.2, 131.4, 130.2, 129.5 (2C), 129.3 (2C), 128.3 (2C), 128.0 (2C), 127.8, 126.2, 116.4, 113.8 (2C), 113.6 (2C), 87.7, 81.3, 76.8, 76.2, 75.3, 75.1, 72.9, 72.6, 71.3, 55.24, 55.19, 41.6, 32.5, 30.7, 28.7, 27.9, 22.8, 14.1, 6.8 (3C), 4.8 (3C); HRMS (ESI) calcd for $C_{47}H_{66}O_8SiNa$ [$(M + Na)^+$] 809.4419, found 809.4434.

Ketone 23. To a solution of $[CuH(PPh_3)]_6$ (68.3 mg, 34.8 μmol) in toluene (1.0 mL) was added a solution of enone **22** (69.1 mg, 87.7 μmol) in toluene (0.4 mL + 0.4 mL rinse), and the resultant solution was stirred at room temperature for 5 min. To this solution was added H_2O (deoxygenated by bubbling N_2 gas, 5 μL), and the resultant mixture was stirred at room temperature for 14 h 40 min. After being stirred for 1 h under air, the reaction mixture was diluted with EtOAc and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 5 to 10% EtOAc/hexanes) gave ketone **23** (65.7 mg, 95%) as a colorless oil: $[\alpha]_D^{24}$ –20.0 (*c* 1.00,

$CHCl_3$); IR (film) 2954, 2935, 2874, 1716, 1613, 1514, 1248, 1085, 1036, 822, 744 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.31–7.24 (m, 7H), 7.20–7.19 (m, 2H), 6.83–6.81 (m, 2H), 6.80–6.77 (m, 2H), 5.85 (ddd, *J* = 17.0, 10.6, 6.4 Hz, 1H), 5.21 (ddd, *J* = 17.0, 1.4, 1.4 Hz, 1H), 5.09 (ddd, *J* = 10.6, 1.4, 1.4 Hz, 1H), 4.65 (d, *J* = 11.0 Hz, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 11.0 Hz, 1H), 4.44 (d, *J* = 11.0 Hz, 1H), 4.41 (d, *J* = 12.0 Hz, 1H), 4.41 (d, *J* = 11.0 Hz, 1H), 4.38 (ddd, *J* = 6.4, 4.6, 1.4 Hz, 1H), 4.13 (m, 1H), 4.00 (ddd, *J* = 8.7, 6.4, 6.4 Hz, 1H), 3.78 (d, *J* = 4.6 Hz, 1H), 3.76 (s, 3H), 3.73 (s, 3H), 3.62 (dddd, *J* = 9.4, 5.5, 5.5, 5.5 Hz, 1H), 3.25 (ddd, *J* = 6.4, 6.4, 6.4 Hz, 1H), 2.68 (ddd, *J* = 18.3, 10.0, 5.5 Hz, 1H), 2.49 (ddd, *J* = 18.3, 10.0, 5.5 Hz, 1H), 2.00 (m, 1H), 1.90 (m, 1H), 1.81 (m, 1H), 1.72 (m, 1H), 1.66–1.53 (m, 4H), 1.45–1.40 (m, 3H), 1.31–1.23 (m, 3H), 0.88 (t, *J* = 7.8 Hz, 9H), 0.86 (t, *J* = 7.3 Hz, 3H), 0.54 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 210.9, 159.00, 158.97, 137.4, 137.1, 131.4, 131.0, 129.4 (2C), 129.3 (2C), 128.3 (2C), 128.0 (2C), 127.9, 116.2, 113.7 (2C), 113.6 (2C), 87.9, 81.5, 81.2, 75.9, 75.7, 75.0, 73.3, 72.6, 71.1, 55.23, 55.21, 41.1, 36.2, 32.7, 30.7, 28.6, 27.9, 27.3, 22.8, 14.1, 6.8 (3C), 4.8 (3C); HRMS (ESI) calcd for $C_{47}H_{68}O_8SiNa$ [$(M + Na)^+$] 811.4576, found 811.4586.

Alcohol 24. To a solution of ketone **23** (27.2 mg, 34.5 μmol) in Et_2O (0.3 mL) at –78 °C was added $Zn(BH_4)_2$ (0.5 M solution in Et_2O, 0.28 mL, 0.14 mmol). The resultant solution was stirred at –78 °C and allowed to warm to –40 ºC over a period of 2 h. The reaction was quenched with saturated aqueous NH_4Cl solution. The resultant mixture was extracted with EtOAc, and the organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 15% EtOAc/hexanes) gave alcohol **24** (21.8 mg, 80%, dr >20:1 as judged by 600 MHz ^1H NMR) as a colorless oil: $[\alpha]_D^{23}$ +15.1 (*c* 1.00, $CHCl_3$); IR (film) 3502, 2954, 2935, 2874, 1514, 1247, 1076, 1036, 821, 743 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.32–7.20 (m, 9H), 6.84–6.81 (m, 2H), 6.77–6.75 (m, 2H), 6.03 (ddd, *J* = 17.4, 10.6, 5.5 Hz, 1H), 5.31 (ddd, *J* = 17.4, 1.4, 1.4 Hz, 1H), 5.23 (ddd, *J* = 10.6, 1.4, 1.4 Hz, 1H), 4.68 (d, *J* = 11.0 Hz, 1H), 4.61 (d, *J* = 11.9 Hz, 1H), 4.59 (d, *J* = 11.9 Hz, 1H), 4.51 (d, *J* = 11.0 Hz, 1H), 4.48 (d, *J* = 11.0 Hz, 1H), 4.40 (d, *J* = 11.0 Hz, 1H), 4.39 (m, 1H), 4.17 (dddd, *J* = 13.8, 8.9, 5.0, 5.0 Hz, 1H), 4.01 (ddd, *J* = 8.7, 6.4, 6.4 Hz, 1H), 3.76 (s, 3H), 3.73 (s, 3H), 3.72 (m, 1H), 3.66 (m, 1H), 3.26 (ddd, *J* = 6.4, 6.4, 6.4 Hz, 1H), 3.24 (dd, *J* = 7.8, 4.1 Hz, 1H), 1.99 (m, 1H), 1.89 (m, 1H), 1.82–1.76 (m, 2H), 1.74–1.58 (m, 4H), 1.48–1.39 (m, 3H), 1.34–1.23 (m, 6H), 0.92 (t, *J* = 7.8 Hz, 9H), 0.86 (t, *J* = 7.3 Hz, 3H), 0.55 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.0, 158.9, 138.1, 136.2, 131.5, 131.2, 129.4 (2C), 129.3 (2C), 128.4 (2C), 128.0 (2C), 127.8, 116.3, 113.6 (2C), 113.6 (2C), 82.3, 81.4, 81.1, 76.5, 76.1, 74.2, 73.6, 72.6, 71.6, 71.0, 55.22, 55.19, 41.1, 32.7, 30.7, 29.9, 28.6, 28.5, 27.9, 22.8, 14.1, 6.7 (3C), 4.6 (3C); HRMS (ESI) calcd for $C_{47}H_{70}O_8SiNa$ [$(M + Na)^+$] 813.4732, found 813.4738.

Diol 25. To a solution of alcohol **24** (10.1 mg, 12.8 μmol) in MeOH/CH_2Cl_2 (1:1, v/v, 0.5 mL) was added CSA (1.18 mg, 5.07 μmol), and the resultant solution was stirred at room temperature for 2 h 50 min. The

reaction was quenched with Et_3N, and the resultant mixture was concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 20 to 40% EtOAc/hexanes) gave diol **25** (8.67 mg, quant) as a colorless oil: $[\alpha]_D^{24}$ +22.2 (*c* 1.00, $CHCl_3$); IR (film) 3421, 2953, 2933, 2869, 1612, 1514, 1248, 1072, 1036 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.32–7.20 (m, 9H), 6.83–6.82 (m, 2H), 6.80–6.79 (m, 2H), 5.99 (ddd, *J* = 17.0, 10.6, 5.0 Hz, 1H), 5.35 (ddd, *J* = 17.0, 1.4, 1.4 Hz, 1H), 5.20 (ddd, *J* = 10.6, 1.4, 1.4 Hz, 1H), 4.64–4.56 (m, 3H), 4.51 (d, *J* = 11.0 Hz, 1H), 4.49 (d, *J* = 11.0 Hz, 1H), 4.42 (d, *J* = 11.0 Hz, 1H), 4.37 (m, 1H), 4.12 (m, 1H), 4.01 (ddd, *J* = 8.3, 6.4, 6.4 Hz, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.73 (m, 1H), 3.64 (m, 1H), 3.29–3.25 (m, 2H), 2.02 (m, 1H), 1.91 (m, 1H), 1.82–1.60 (m, 9H), 1.50–1.39 (m, 4H), 1.34–1.24 (m, 3H), 0.86 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.2, 159.0, 137.9 (2C), 131.3, 130.4, 129.6 (2C), 129.4 (2C), 128.4 (2C), 128.0 (2C), 127.9, 115.8, 113.8 (2C), 113.6 (2C), 82.8, 81.4, 81.1, 76.8, 76.2, 73.4, 72.5, 72.19, 72.16, 71.3, 55.2 (2C), 40.8, 32.8, 30.65, 30.59, 28.9, 28.6, 27.8, 22.8, 14.1; HRMS (ESI) calcd for $C_{41}H_{56}O_8Na$ [(M + Na)$^+$] 699.3867, found 699.3882.

Bis-TBS ether 3. To a solution of diol **25** (39.3 mg, 57.9 μmol) in CH_2Cl_2 (0.8 mL) at 0 °C were added 2,6-lutidine (30 μL, 0.26 mmol) and TBSOTf (40 μL, 0.17 mmol), and the resultant solution was stirred at 0 °C for 65 min. The reaction was quenched with saturated aqueous $NaHCO_3$ solution at 0 °C. The resultant mixture was extracted with EtOAc, and the organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 5% EtOAc/hexanes) gave bis-TBS ether **3** (47.1 mg, 90%) as a colorless oil: $[\alpha]_D^{24}$ –2.4 (*c* 1.00, $CHCl_3$); IR (film) 2954, 2930, 2856, 1514, 1249, 1069, 1038, 835, 776 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.36–7.35 (m, 2H), 7.30–7.19 (m, 7H), 6.83–6.81 (m, 2H), 6.80–6.77 (m, 2H), 5.88 (ddd, *J* = 17.0, 10.6, 6.9 Hz, 1H), 5.21 (ddd, *J* = 17.0, 1.4, 1.4 Hz, 1H), 5.09 (ddd, *J* = 10.6, 1.4, 1.4 Hz, 1H), 4.83 (d, *J* = 11.0 Hz, 1H), 4.68 (d, *J* = 11.0 Hz, 1H), 4.65 (d, *J* = 11.0 Hz, 1H), 4.51 (d, *J* = 11.0 Hz, 1H), 4.45 (d, *J* = 11.0 Hz, 1H), 4.37 (d, *J* = 11.0 Hz, 1H), 4.17 (m, 1H), 4.12 (dd, *J* = 6.9, 6.9 Hz, 1H), 4.03 (ddd, *J* = 8.2, 6.4, 6.4 Hz, 1H), 3.77 (m, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.64 (m, 1H), 3.41 (dd, *J* = 6.9, 1.4 Hz, 1H), 3.28 (ddd, *J* = 6.4, 6.4, 6.4 Hz, 1H), 1.99 (m, 1H), 1.89 (m, 1H), 1.82–1.56 (m, 6H), 1.52–1.38 (m, 4H), 1.30–1.24 (m, 4H), 0.89 (s, 9H), 0.86 (m, 12H), 0.05 (s, 3H), 0.03 (s, 3H), –0.02 (s, 3H), –0.03 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.0 (2C), 139.5, 138.4, 131.4, 131.2, 129.4 (2C), 129.2 (2C), 128.1 (2C), 127.5 (2C), 127.1, 115.5, 113.7 (2C), 113.6 (2C), 87.5, 81.4, 81.1, 76.6, 76.1, 74.8, 74.3, 73.7, 72.6, 71.0, 55.23, 55.21, 41.1, 32.8, 31.2, 30.6, 28.6, 27.9, 27.4, 25.9 (6C), 22.8, 18.2, 18.0, 14.1, –3.9, –4.6, –4.7 (2C); HRMS (ESI) calcd for $C_{53}H_{84}O_8NaSi_2$ [(M + Na)$^+$] 927.5597, found 927.5595.

Acetonide 26. To a solution of diol **25** (8.7 mg, 13 μmol) in $(CH_2Cl)_2$ (0.5 mL) at 0 °C were added PPTS (3.2 mg, 13 μmol) and 2,2-dimethoxypropane (50 μL, 0.41 mmol), and the resultant solution was stirred at room temperature for 11 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution. The

resultant mixture was extracted with EtOAc, and the organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 5 to 10% EtOAc/hexanes) gave acetonide **26** (8.1 mg, 88%) as a colorless oil: $[\alpha]_D^{23}$ +5.2 (*c* 1.00, $CHCl_3$); IR (film) 2933, 2868, 1612, 1513, 1247, 1083, 1036, 821 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.26–7.16 (m, 9H), 6.80–6.78 (m, 2H), 6.75–6.74 (m, 2H), 6.02 (ddd, *J* = 17.4, 10.6, 7.3 Hz, 1H), 5.36 (d, *J* = 17.4 Hz, 1H), 5.24 (d, *J* = 10.6 Hz, 1H), 4.63 (d, *J* = 11.0 Hz, 1H), 4.56 (d, *J* = 11.5 Hz, 1H), 4.48 (d, *J* = 11.0 Hz, 1H), 4.41 (d, *J* = 11.0 Hz, 1H), 4.37 (d, *J* = 11.0 Hz, 1H), 4.34 (d, *J* = 11.5 Hz, 1H), 4.31 (dd, *J* = 7.3, 4.1 Hz, 1H), 4.12 (m, 1H), 3.97 (ddd, *J* = 6.4, 6.4, 6.4 Hz, 1H), 3.73 (s, 3H), 3.70 (s, 3H), 3.61–3.57 (m, 2H), 3.34 (dd, *J* = 7.3, 4.1 Hz, 1H), 3.23 (ddd, *J* = 6.4, 6.4, 6.4 Hz, 1H), 1.96 (m, 1H), 1.87 (m, 1H), 1.82–1.38 (m, 11H), 1.34 (s, 3H), 1.28 (s, 3H), 1.28–1.20 (m, 3H), 0.83 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.0 (2C), 138.1, 134.3, 131.4, 131.1, 129.4 (2C), 129.3 (2C), 128.3 (2C), 127.9 (2C), 127.7, 117.8, 113.7 (2C), 113.6 (2C), 100.8, 82.7, 81.5, 81.2, 76.2, 76.0, 73.6, 73.3, 72.6, 72.0, 71.2, 55.24, 55.22, 41.2, 32.7, 30.7, 30.5, 28.7, 28.6, 27.9, 24.9, 24.0, 22.8, 14.1; HRMS (ESI) calcd for $C_{44}H_{60}O_8Na$ [$(M + Na)^+$] 739.4180, found 739.4164.

ACKNOWLEDGEMENTS

This study was financially supported by JSPS KAKENHI Grant Number 25282228. We are grateful to Dr. Eunsang Kwon (Tohoku University) for X-ray crystallographic analysis.

SUPPORTING INFORMATION

Proofs for the stereochemical assignment of compound **14**, experimental procedure for compound **15**, and ^1H and ^{13}C NMR spectra for all new compounds are available.

REFERENCES AND NOTES

1. For a recent review, see: J. Kobayashi, *J. Antibiot*., 2008, **61**, 271 and references cited therein.
2. M. Ishibashi, N. Yamaguchi, T. Sasaki, and J. Kobayashi, *J. Chem. Soc., Chem. Commun*., 1994, 1455.
3. Y. Takahashi, T. Kubota, M. Imachi, M. R. Wälchli, and J. Kobayashi, *J. Antibiot*., 2013, **66**, 277.
4. I. Bauer, L. Maranda, K. A. Young, and Y. Shimizu, *J. Am. Chem. Soc*., 1995, **60**, 1084.
5. For recent total synthesis of amphidinolides, see: G. Valot, C. S. Regens, D. P. O'Malley, E. Godineau, H. Takikawa, and A. Fürstner, *Angew. Chem. Int. Ed*., 2013, **52**, 9534; S. Mahapatra and R. G. Carter, *J. Am. Chem. Soc*., 2013, **135**, 10792; M.-H. Hwang, S.-J. Han, and D.-H. Lee, *Org. Lett*., 2013, **15**, 3381; I. Volchkov and D. Lee, *J. Am. Chem. Soc*., 2013, **135**, 5324; L. Lu, W. Zhang, S. Nam, D. A. Horne, R. Jove, and R. G. Carter, *J. Org. Chem*., 2013, **78**, 2213; A. Hara, R.

Morimoto, Y. Iwasaki, T. Saitoh, Y. Ishikawa, and S. Nishiyama, *Angew. Chem. Int. Ed.*, 2012, **51**, 9877; S. Mahapatra and R. G. Carter, *Angew. Chem. Int. Ed.*, 2012, **51**, 7948; A. Fürstner, *Isr. J. Chem.*, 2011, **51**, 329 and references cited therein.

6. K. C. Nicolaou, W. E. Brenzovich, P. G. Bulger, and T. M. Francis, *Org. Biomol. Chem.*, 2006, **4**, 2119; K. C. Nicolaou, P. G. Bulger, and W. E. Brenzovich, *Org. Biomol. Chem.*, 2006, **4**, 2158.
7. B. M. Trost and J. Ley, *Org. Lett.*, 2012, **14**, 5632.
8. G. Scheid, E. Ruijter, M. Konarzycka-Bessler, U. T. Bornscheuer, and L. A. Wessjohann, *Tetrahedron: Asymmetry*, 2004, **15**, 2861.
9. D. A. Evans, J. Bartroli, and T. L. Shih, *J. Am. Chem. Soc.,* 1981, **103**, 2127.
10. A. Basha, M. Lipton, and S. M. Weinreb, *Tetrahedron Lett.*, 1977, **18**, 4171.
11. The carbon numbering of compounds in this paper corresponds to that of amphidinolide N.
12. X. Lu, H. S. Byun, and R. Bittman, *J. Org. Chem.*, 2004, **69**, 5433.
13. V. N. Odinokov, R. R. Vakhidov, R. N. Shakhmaev, and V. V. Zorin, *Chem. Nat. Compd.*, 1998, **34**, 186.
14. G. E. Keck, K. H. Tarbet, and L. S. Geraci, *J. Am. Chem. Soc.,* 1993, **115**, 8467.
15. I. Ohtani, T. Kusumi, Y. Kashman, and H. Kakisawa, *J. Am. Chem. Soc.*, 1991, **113**, 4092.
16. H. C. Kolb, M. S. VanNieuwenhze, and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483.
17. For closely related cyclizations, see: J. A. Marshall and J. J. Sabatini, *Org. Lett.*, 2005, **7**, 4819; D. K. Mohapatra, P. Dasari, H. Rahaman, and R. Pal, *Tetrahedron Lett.*, 2009, **50**, 6276; J. S. Yadav, K. Ramesh, U. V. S. Reddy, B. V. S. Reddy, and A. A. K. A. Ghamdi, *Tetrahedron Lett.*, 2011, **52**, 2943.
18. The synthesis of the enantiomers of compounds **14** and **16** has previously been reported in the literature.[6]
19. An added proof for the stereochemical assignment of compound **14** is provided in the Supporting Information.
20. Crystalline triol **15** was obtained as a minor byproduct under unoptimized conditions. For experimental procedure for compound **15**, see the Supporting Information.
21. CCDC 1012729 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via: www.ccdc.cam.ac.uk/data_request/cif.
22. S. J. Connon and S. Blechert, *Angew. Chem. Int. Ed.,* 2003, **42**, 1900.
23. M. Scholl, S. Ding, C. W. Lee, and R. H. Grubbs, *Org. Lett.,* 1999, **1**, 953.
24. T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.,* 1980, **102**, 5974; R. M. Hanson and K. B. Sharpless, *J. Org. Chem.*, 1986, **51**, 1922.
25. M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masamune, W. R. Roush, and T. Sakai,

Tetrahedron Lett., 1984, **25**, 2183.

26. W. S. Mahoney, D. M. Brestensky, and J. M. Stryker, *J. Am. Chem. Soc*., 1988, **110**, 291; B. H. Lipshutz, J. Keith, P. Papa, and R. Vivian, *Tetrahedron Lett*., 1998, **39**, 4627.
27. T. Takahashi, M. Miyazawa, and J. Tsuji, *Tetrahedron Lett*., 1985, **26**, 5139.
28. T. Oishi and T. Nakata, *Acc. Chem. Res.,* 1984, **17**, 338.
29. S. D. Rychnovsky and D. J. Skalitzky, *Tetrahedron Lett*., 1990, **31**, 945.
30. D. A. Evans, D. L. Rieger, and J. R. Gage, *Tetrahedron Lett*., 1990, **31**, 7099.