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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.6b01700 • Publication Date (Web): 26 Aug 2016

Just Accepted

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Stereodivergent Synthesis and Configurational Assignment of the C1–C15 Segment of Amphirionin-5

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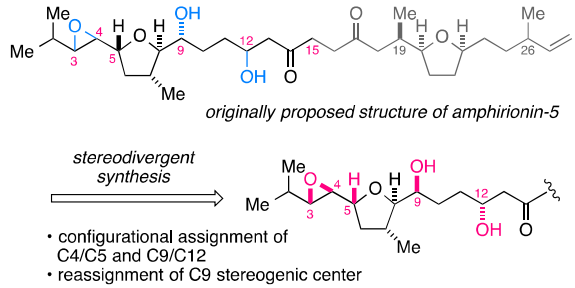
TOC graphic


originally proposed structure of amphirionin-5
stereodivergent synthesis
• configurational assignment of C4/C5 and C9/C12
• reassignment of C9 stereogenic center

ABSTRACT: The relative configuration of the C3–C12 portion of amphirionin-5, a novel marine polyketide with potent cell proliferation-promoting activity, was established by the stereodivergent synthesis of six diastereomeric model compounds and comparison of their NMR spectroscopic data with those reported for the natural product. This study led to the elucidation of the relative configuration between C4/C5 and C9/C12 and to the reassignment of the proposed configuration of the C9 position of amphirionin-5.

INTRODUCTION

Dinoflagellates of the genus *Amphidinium* are an enormously rich source of structurally diverse secondary metabolites with complex molecular structures and potent biological activities. In particular, more than 45 cytotoxic macrolides, amphidinolides and iriomoteolides, have been isolated from *Amphidinium* sp. to date.[1] Recently, the novel complex tetrahydrofuran ring-containing linear polyketides, amphirionins-5 (**1**),[2] -4 (**2**),[3,4] and -2 (**3**),[5] which exhibit intriguing biological activities, were identified from *Amphidinium* sp. by Tsuda and co-workers (Figure 1). Of these, amphirionin-5 (**1**) was isolated, along with cytotoxic macrolides iriomoteolides-1a[6] and -3a,[7] from cultivated algal cells of the benthic dinoflagellate *Amphidinium* sp. strain KCA09053 collected off the coast of Iriomote Island, Okinawa Prefecture, Japan.[2] The gross structure and partial relative configuration of amphirionin-5 were assigned through extensive 2D-NMR studies and *J*-based configurational analyses.[8] Structurally, amphirionin-5 consists of a linear polyketide skeleton containing two tetrahydrofuran rings, a *trans*-epoxide, and eleven stereogenic centers. However, despite detailed NMR analysis, the relative configurations of the C4/C5 stereogenic centers and the stereochemistry of the two isolated C12 and C26 stereogenic centers could not be resolved, and the absolute configuration also remained unknown. In particular, the remote stereogenic centers at C12 and C19 could not be correlated with each other.

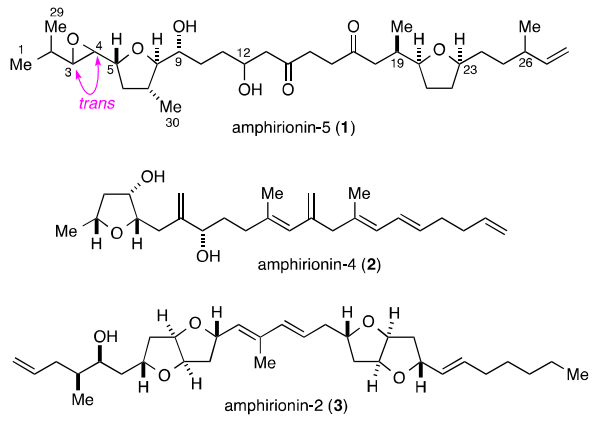


Figure 1. Structures of amphirionins-5 (**1**), -4 (**2**), and -2 (**3**).

Most importantly, this linear polyketide natural product exhibited potent cell proliferation-promoting activity on murine bone marrow stromal ST-2 cells (282%) and murine osteoblastic MC3T3-E1 cells (320%) at a dose of 10 ng/mL, and it did not induce cellular differentiation or morphological changes in the dose range of 0.001–1000 ng/mL or exhibit cytotoxicity at higher doses (1–10 μg/mL).[2] This intriguing biological profile of amphirionin-5 suggests that it may be a promising candidate for the regenerative treatment of bone and joint disease and for the prevention or treatment of osteoporosis. However, further studies on the mechanism of action of amphirionin-5 have been hampered not only by its limited availability from the natural source, but also by the incomplete stereochemical assignment of its structure. A synthetic approach is therefore required to address these issues.

The promising biological properties of amphirionin-5, as well as its complex molecular structure

and undefined stereochemistry, prompted our current efforts toward the total synthesis and complete configurational assignment of the compound. We describe herein the assignment of the relative configuration of the C3–C12 portion of amphirionin-5 through stereodivergent synthesis of six diastereomeric model compounds and comparison of their NMR spectroscopic data with those reported for the natural product. Portions of this work have previously been published in a preliminary form.[9]

RESULTS AND DISCUSSION

Stereochemical-Determination Strategy. Based on our previous work on the stereochemical assignment of acyclic portions of the large polycyclic ether natural products maitotoxin and prymnesins,[10,11] we predicted that the relative configurations of C4/C5 and C9/C12 of amphirionin-5 could be assigned by the synthesis of appropriate designed model compounds and subsequent comparison of their NMR data with those reported for the natural product (Figure 2).[12] The first phase of the stereochemical-determination of the C1–C15 segment of amphirionin-5 was the assignment of the unresolved relative configuration between C4 and C5 (Step 1). We therefore decided to prepare two possible diastereomeric model compounds, (3*S*,4*S*,5*R*)-**4** and (3*R*,4*R*,5*R*)-**5**, of the C1–C12 segment of amphirionin-5 using a stereodivergent approach and to compare their NMR data with those reported for the natural product. Once we assigned the relative configuration

of C4 and C5, the next phase of our studies relied on the synthesis of two possible diastereomers, (9*R*,12*R*)-**6** and (9*R*,12*S*)-**7**, of the C1–C15 segment with the assigned configuration at C3–C5 for comparison of their NMR characteristics with that of the natural product (Step 2). Although the two stereogenic centers at C9 and C12 are separated by two methylene units, differences in their relative configurations should be detected as small but distinct variations in their NMR characteristics, allowing the two possible diastereomers to be distinguished by currently available NMR spectroscopic techniques.[10c,e,13]

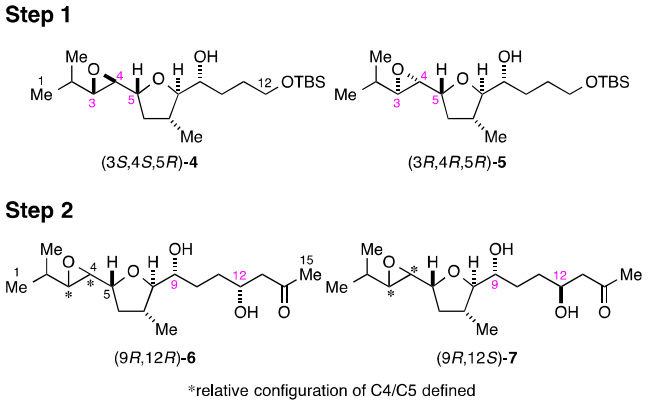
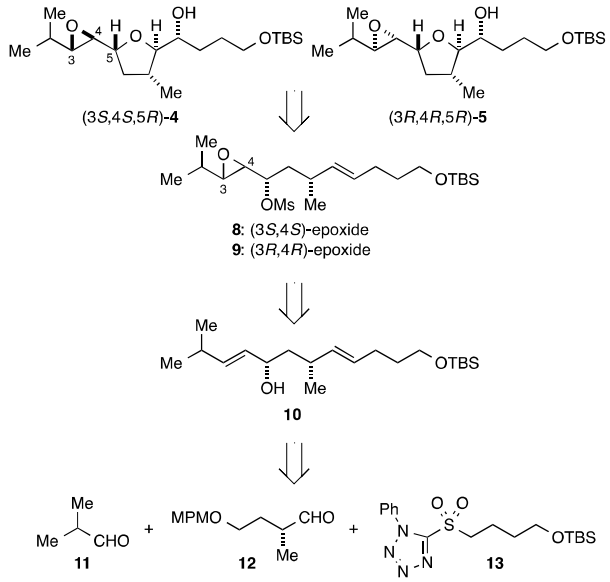


Figure 2. Stereochemical-determination strategy for the C1–C15 portion.

Synthetic Plan for the C1–C12 Segment. Our retrosynthetic analysis of the two possible diastereomeric model compounds (3*S*,4*S*,5*R*)-**4** and (3*R*,4*R*,5*R*)-**5** for the C1–C12 segment of amphirionin-5 is depicted in Scheme 1. We envisioned that the 2,5-*trans*-substituted

tetrahydrofuran ring of **4** and **5** could be constructed through a domino Sharpless asymmetric dihydroxylation[14]/stereospecific 5-*exo* cyclization of mesylates (3*S*,4*S*)-**8** and (3*R*,4*R*)-**9**, respectively.[15] The two diastereomeric epoxides **8** and **9** would be accessed by branching from a common intermediate, allylic alcohol **10**, by Katsuki–Sharpless asymmetric epoxidation[16] using (+)- or (–)-tartrate ester as a chiral ligand. Allylic alcohol **10** would be obtained by means of Corey–Bakshi–Shibata reduction[17] of the precursor α,β-unsaturated ketone, which in turn would be assembled from the three fragments isobutyraldehyde (**11**), aldehyde **12**, and sulfone **13** through Julia–Kocienski olefination[18] and Horner–Wadsworth–Emmons reaction in a convergent fashion.

Scheme 1. Retrosynthetic Analysis of the C1–C12 Segments 4 and 5

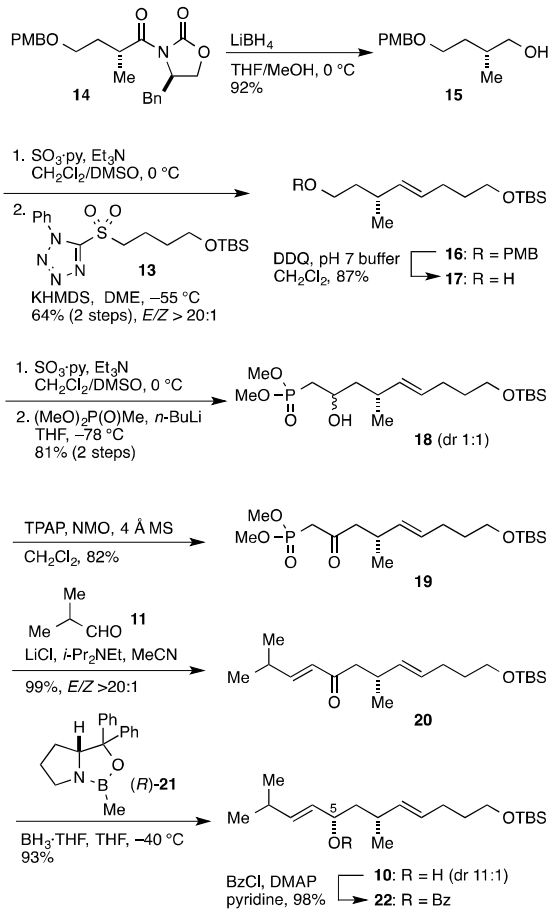


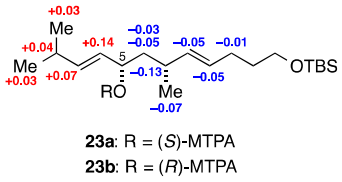
Synthesis of Allylic Alcohol 10. The synthesis of allylic alcohol **10** started with the known imide

14.[19] The chiral auxiliary of **14** was reductively removed with $LiBH_4$ in THF/MeOH[20] to provide primary alcohol **15**[21] in 92% yield (Scheme 2). Parikh–Doering oxidation[22] of **15** afforded the corresponding aldehyde **12**, which was subjected to Julia–Kocienski olefination[18] using the known phenyltetrazolyl sulfone **13**[23] and KHMDS in DME at –55 °C to produce (*E*)-alkene **16** in 64% yield for the two steps as a single stereoisomer (*E*/*Z* >20:1). Oxidative removal of the *p*-methoxybenzyl (PMB) group of **16** with DDQ provided primary alcohol **17** in 87% yield. Parikh–Doering oxidation[22] of **17** gave the corresponding aldehyde, which was reacted with the lithium anion generated from dimethyl methylphosphonate using *n*-BuLi to provide β-hydroxy phosphonate **18** in 81% yield (two steps) as a 1:1 diastereomeric mixture of alcohols. Subsequent oxidation of **18** with tetra-*n*-propylammonium perruthenate (TPAP)/*N*-methylmorpholine *N*-oxide (NMO)[24] delivered β-keto phosphonate **19** in 82% yield. Horner–Wadsworth–Emmons reaction of **19** with isobutyraldehyde (**11**) under Masamune–Roush conditions (LiCl, *i*-Pr_2NEt, MeCN)[25] provided (*E*)-α,β-unsaturated ketone **20** in nearly quantitative yield as a single stereoisomer (*E*/*Z* >20:1). Finally, Corey–Bakshi–Shibata reduction[17] of **20** using (*R*)-2-methyl-CBS-oxazaborolidine **21** (1.0 equiv) and BH_3·THF (2.0 equiv) in THF at –40 °C furnished the desired allylic alcohol **10** in 93% yield.[26] The diastereomer ratio (dr) of **10** was determined to be 11:1 by HPLC analysis of the corresponding benzoate derivative **22**. The absolute configuration of the newly generated stereogenic center at C5[27] was unambiguously established by a modified Mosher analysis[28] after

derivatizing **10** to the corresponding (*S*)- and (*R*)-MTPA esters **23a** and **23b**, respectively (Figure 3).

Scheme 2. Synthesis of Allylic Alcohol 10.





23a: R = (*S*)-MTPA
23b: R = (*R*)-MTPA

Figure 3. Determination of the absolute configuration at C5 of alcohol **10**. The numbers in red and blue are the difference (Δδ) in the ^{1}H NMR chemical shifts between **23a** and **23b** (Δδ = δ (**23a**) – δ

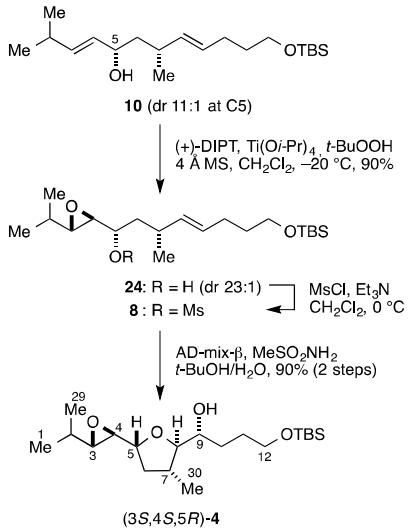
(**23b**) in $CDCl_3$).

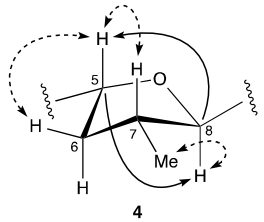
Stereodivergent Synthesis of the C1–C12 Segments 4 and 5. With the requisite allylic alcohol **10** in hand, we proceeded to the stereodivergent synthesis of the diastereomeric C1–C12 segments **4** and **5**. Katsuki–Sharpless asymmetric epoxidation[16] of allylic alcohol **10** using (+)-diisopropyl tartrate (DIPT) as a chiral ligand provided a "matched" case, and allylic alcohol **10** (dr 11:1) smoothly underwent epoxidation to afford the desired epoxy alcohol **24** in 90% yield with high diastereoselectivity (dr ca. 23:1) after 2.5 h (Scheme 3). Alcohol **24** was then converted to the corresponding mesylate **8** (MsCl, Et_3N), which was subjected to Sharpless asymmetric dihydroxylation[14] using AD-mix-β□ Diastereoselective dihydroxylation with concomitant stereospecific 5-*exo* cyclization took place to form a tetrahydrofuran ring, and the desired C1–C12 segment (3*S*,4*S*,5*R*)-**4** was obtained in 90% yield for the two steps. The relative configuration of the 2,5-*trans*-substituted tetrahydrofuran ring in **4** was confirmed by means of HMBC correlations and NOE data, and the absolute configuration of the C9 stereogenic center was unambiguously established by derivatization of **4** to the corresponding (*S*)- and (*R*)-MTPA esters **25a** and **25b**, respectively, and a modified Mosher analysis[28] (Figure 4).

Although the Katsuki–Sharpless asymmetric epoxidation[16] is well recognized as a reliable asymmetric reaction, the relative configurations of the C3–C5 positions of epoxy alcohol **24** were

further confirmed by NMR analysis of a suitable tetrahydropyran derivative. Thus, Sharpless asymmetric dihydroxylation[14] of **24** using AD-mix-β provided triol **26** (87%), which upon treatment with PPTS (0.1 equiv) in $(CH_2Cl)_2$ at 40 °C induced a 6-*exo* epoxide ring-opening cyclization to form tetrahydropyran **27** in 57% yield (Scheme 4). The relative configuration of **27** was unambiguously established by means of HMBC spectra, NOE analysis, and $^3J_{H,H}$ data, as shown in Figure 5.

Scheme 3. Synthesis of the C1–C12 Segment (3*S*,4*S*,5*R*)-4





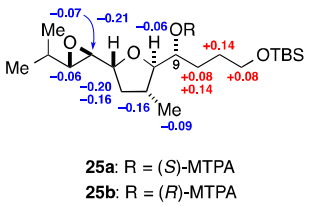
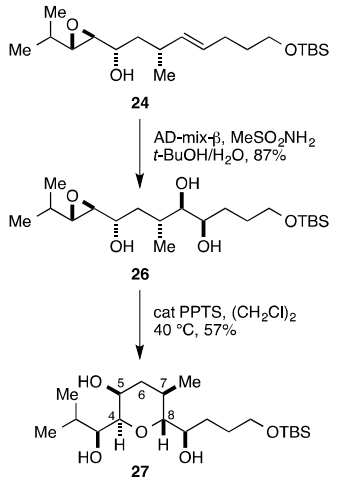


Figure 4. Stereochemical assignment of alcohol **4**. Single-headed arrows indicate HMBC correlations and double-headed dashed arrows denote key NOEs. The numbers in red and blue are the difference ($\Delta\delta$) in the ^{1}H NMR chemical shifts between **25a** and **25b** ($\Delta\delta$ = δ (**25a**) – δ (**25b**) in $CDCl_3$).

Scheme 4. Synthesis of Tetrahydropyran Derivative 27



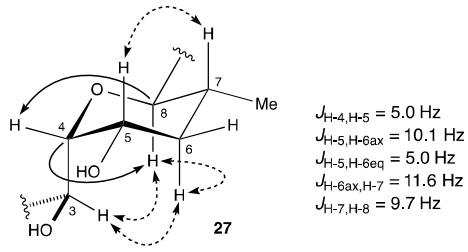


Figure 5. Stereochemical assignment of tetrahydropyran **27**. Single-headed arrows indicate HMBC correlations and double-headed dashed arrows denote key NOEs.

The diastereomeric C1–C12 segment (3*R*,4*R*,5*R*)-**5** was prepared using the same sequence of reactions from allylic alcohol **10** via epoxy alcohol **28** (Scheme 5). In this case, Katsuki–Sharpless asymmetric epoxidation of **10** using (–)-DIPT provided a typical "mismatched" pair,[16b,c] and thus the starting allylic alcohol **10** in a diastereomerically enriched form (dr 22:1 at C5) obtained by kinetic resolution was used for asymmetric epoxidation. In the presence of (–)-DIPT, the epoxidation of allylic alcohol **10** was much slower than that using (+)-DIPT (2.5 h) and required a prolonged reaction time (15.5 h) for consumption of the starting material, and a 1.4:1 mixture of diastereomeric epoxides **28** and **24** was obtained. This mixture of epoxides was readily separable by flash column chromatography on silica gel to afford the desired epoxide **28** in 55% yield with a diastereomer ratio of 22:1, along with **24** (40%, dr 27:1). Mesylation of **28**, followed by one-pot Sharpless asymmetric dihydroxylation[14]/5-*exo* cyclization of the resultant mesylate **9**, furnished the desired (3*R*,4*R*,5*R*)-**5** in 86% yield for the two steps. The relative configuration of the tetrahydrofuran ring moiety of **5** was confirmed by NMR analysis (HMBC and NOEs), and the absolute configuration of the C9 stereogenic center was established by the modified Mosher method[28] using the corresponding (*S*)- and (*R*)-MTPA esters **29a** and **29b**, as shown in Figure 6.

Scheme 5. Synthesis of the Diastereomeric C1–C12 Segment (3*R*,4*R*,5*R*)-5

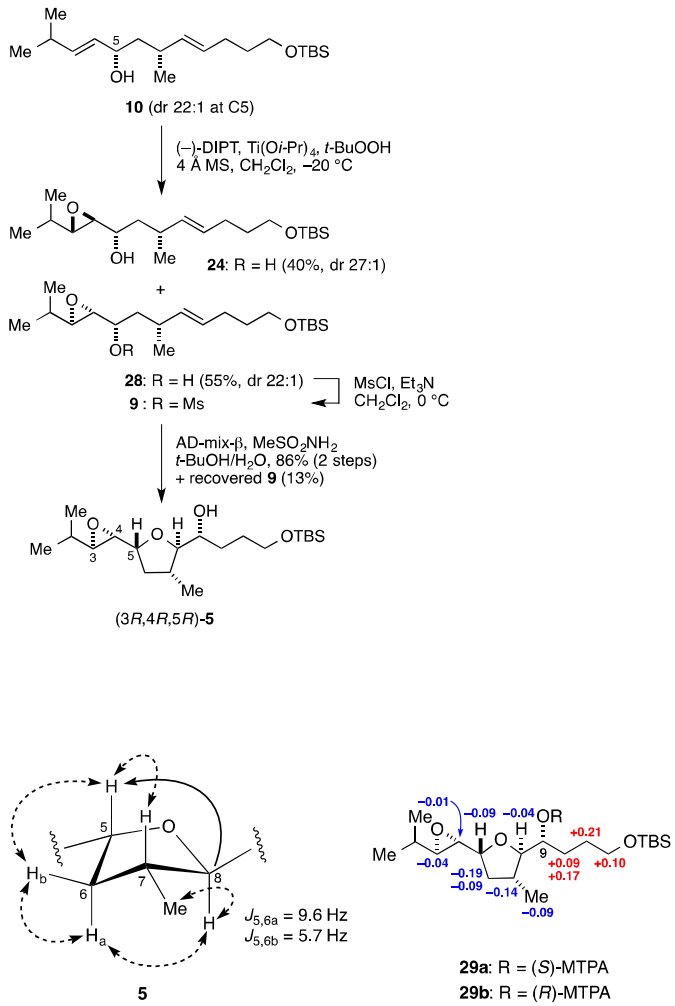


Figure 6. Stereochemical assignment of alcohol **5**. Single-headed arrow indicates HMBC correlation and double-headed dashed arrows denote key NOEs. The numbers in red and blue are the difference (Δδ) in the ^{1}H NMR chemical shifts between **29a** and **29b** (Δδ = δ (**29a**) – δ (**29b**) in $CDCl_3$).

NMR Comparison of Compounds 4 and 5 with the Natural Product. The ^{1}H and ^{13}C NMR chemical shifts in the C1–C9 region of the two diastereomeric model compounds **4** and **5** thus obtained were compared with those of the corresponding moiety of the natural product.[29] As shown

in Figure 7A, the ^{1}H NMR chemical shifts in the C1–C6 region of **4** were virtually identical with those reported for the natural product ($|\Delta\delta| < 0.02$ ppm), whereas significant deviations of chemical shifts ($|\Delta\delta| > 0.06$ ppm) were observed for diastereomer **5** in the C3–C5 region.[30] Similarly, the ^{13}C NMR chemical shifts in the C1–C6 region of **4** were in good agreement with those of the natural product ($|\Delta\delta| < 0.7$ ppm), whereas compound **5** displayed obviously different chemical shifts; in particular, the observed ^{13}C NMR chemical shifts for C5 and C6 of **3** significantly deviated from those of the natural product by over 1.0 ppm (Figure 7B).[30] These results strongly suggested that the relative configuration of the C3–C5 portion of amphirionin-5 is represented by structure **4**. However, we were surprised to find that there were significant and similar discrepancies in the ^{1}H and ^{13}C NMR chemical shifts in the right-hand C7–C9 region for both compounds **4** and **5**. In particular, the largest deviations in the ^{1}H and ^{13}C NMR chemical shifts were observed for H-9 ($\Delta\delta$ = 0.27 ppm), C9 ($\Delta\delta$ = 1.9 ppm), and the attached C30 methyl group ($\Delta\delta > 1.3$ ppm). From these large deviations in the NMR chemical shifts between compounds **4**/**5** and the natural product, we inferred that the C9 stereogenic center of amphirionin-5 might have been incorrectly assigned and that the most likely configuration of the C9 stereogenic center of amphirionin-5 is inverted, as represented by the revised structure **30** (Scheme 6).

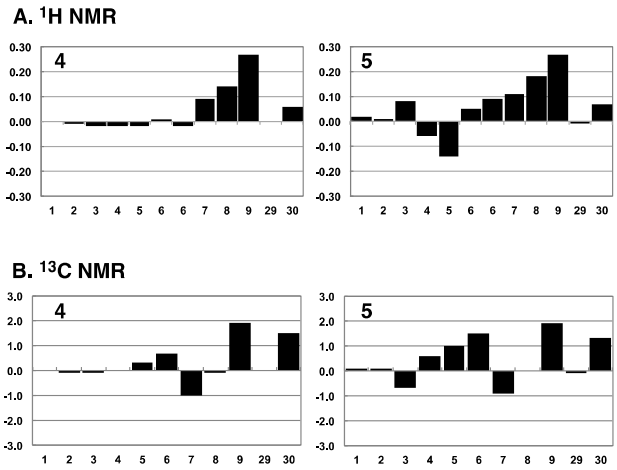


Figure 7. Differences in ^{1}H and ^{13}C NMR chemical shifts between amphirionin-5 (500 and 125 MHz, respectively) and model compounds **4** and **5** (600 and 150 MHz, respectively). The *x*- and *y*-axes represent the carbon number and $\Delta\delta = \delta$ (natural product) – δ (model compound) in ppm ($CDCl_3$), respectively.

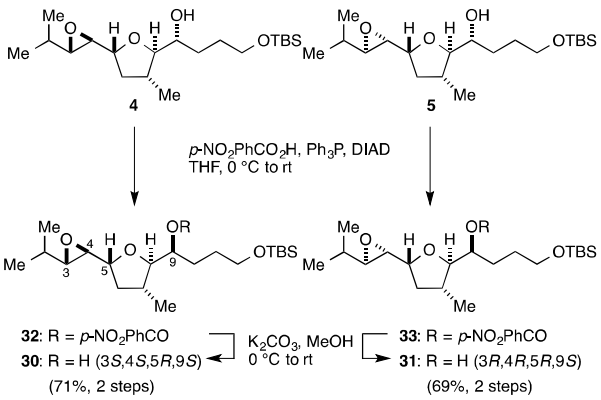
Synthesis of the Diastereomers 30 and 31 and their NMR Comparison with the Natural Product. Thus, the C9 hydroxy group of **4** and **5** was inverted using modified Mitsunobu conditions (*p*-$NO_2C_6H_4CO_2H$, Ph_3P, diisopropyl azodicarboxylate (DIAD), THF) (Scheme 6).[31] Methanolysis of the resultant *p*-nitrobenzoates **32** and **33** (K_2CO_3, MeOH) led to alcohols (3*S*,4*S*,5*R*,9*S*)-**30** and (3*R*,4*R*,5*R*,9*S*)-**31**, respectively.

The ^{1}H and ^{13}C NMR spectroscopic data of **30** and **31** were once again compared with those reported for the natural product. As expected, the ^{1}H and ^{13}C NMR chemical shifts in the C1–C9 region for diastereomer **30** were virtually identical to those reported for the natural product (Figure

8).[30] In contrast, significant differences in the ^{1}H and ^{13}C NMR chemical shifts were observed for other diastereomer **31** in the C3–C6 region, as was the case for compound **5** (Figure 7). In addition, $^{3}J_{H,H}$ data of the C1–C9 portion of **30** corresponded well with the data of amphirionin-5.[30] These results convincingly defined the relative configuration of the C1–C9 portion of amphirionin-5 as that represented by structure **30** with the (3*S**,4*S**,5*R**,7*R**,8*R**,9*S**)-stereochemistry.

The relative configuration of the C8/C9 stereogenic centers of the natural amphirionin-5 had been elucidated to be 8*R**,9*R** applying *J*-based configuration analysis[8] mainly based on coupling constants ($^{3}J_{H\text{-}8,H\text{-}9}$ = 4.1 Hz, $^{2}J_{C\text{-}8,H\text{-}9}$ = –7 Hz, and $^{2}J_{C\text{-}9,H\text{-}8}$ = –6 Hz).[2] Because both of the $^{3}J_{H\text{-}8,H\text{-}9}$ values (3.2 and 4.6 Hz) for (8*R*,9*R*)-**4** and (8*R*,9*S*)-**30**, respectively, were not completely different from that for the natural amphirionin-5 (4.1 Hz), elucidation of one of the other, or both of $^{2}J_{C\text{-}8,H\text{-}9}$ and $^{2}J_{C\text{-}9,H\text{-}8}$ values from the HETLOC spectrum of the natural amphirionin-5 might be wrong. Nevertheless, the remeasurement of the HETLOC spectrum of amphirionin-5 was not possible because of a lack of the natural sample.

Scheme 6. Synthesis of the Diastereomers 30 and 31



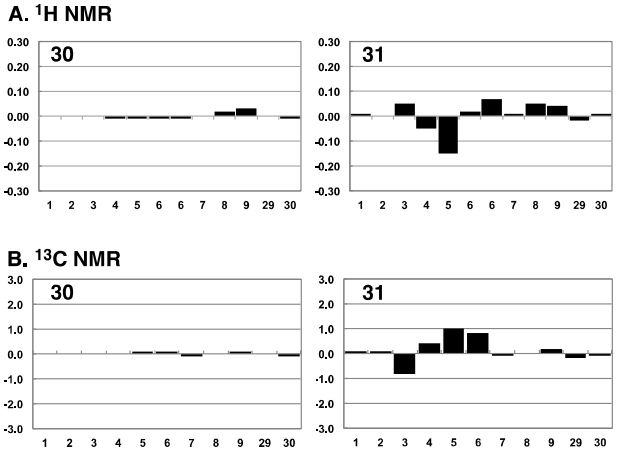
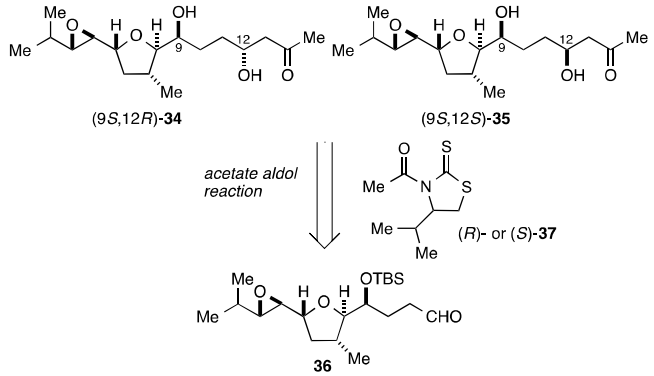


Figure 8. Differences in ^{1}H and ^{13}C NMR chemical shifts between amphirionin-5 (500 and 125 MHz, respectively) and model compounds **30** and **31** (600 and 150 MHz, respectively). The *x*- and *y*-axes represent the carbon number and $\Delta\delta = \delta$ (natural product) – δ (model compound) in ppm ($CDCl_3$), respectively.

Synthesis of the Diastereomeric C1–C15 Segments 34 and 35. Having established the relative configuration of the C3–C9 portion of amphirionin-5, we next sought to determine the unexplored

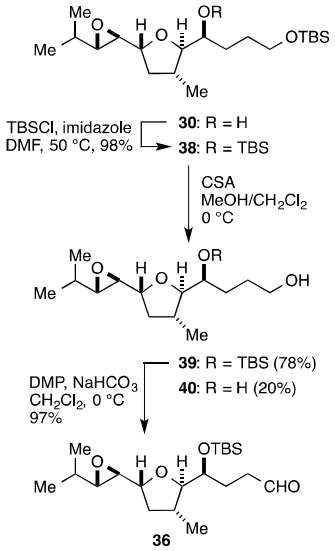
configuration of the remote C12 stereogenic center. For this purpose, we proceeded with the synthesis of two possible diastereomeric model compounds, (9*S*,12*R*)-**34** and (9*S*,12*S*)-**35**, for the C1–C15 segments (Scheme 7). We originally planned to synthesize these two compounds by means of an acetate aldol reaction[32] of aldehyde **36** with a metal enolate derived from either the (*R*)- or (*S*)-enantiomer of *N*-acetyl-4-isopropyl-1,3-thiazolidine-2-thione (**37**) developed by Nagao and co-workers.[33]

Scheme 7. Initial Synthesis Plan for the C1–C15 Segments 34 and 35



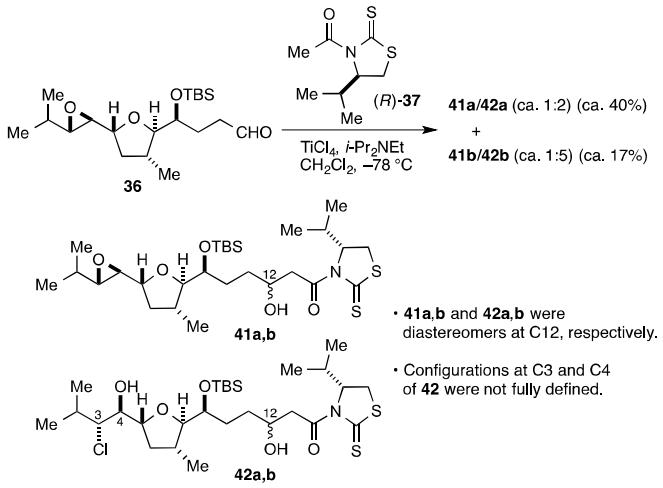
The synthesis of aldehyde **36** commenced with alcohol **30**, which was protected as its TBS ether with TBSCl/imidazole in DMF at 50 °C to give bis-TBS ether **38** in 98% yield (Scheme 8). Selective cleavage of the primary TBS ether of **38** under acidic conditions (CSA (0.1 equiv), MeOH/CH_2Cl_2 (1:1), 0 °C) led to primary alcohol **39** in 78% yield, along with diol **40** (20%). Dess–Martin oxidation[34] of **39** provided aldehyde **36** in 97% yield.

Scheme 8. Synthesis of Aldehyde 36



We initially attempted an aldol reaction of **36** with (*R*)-*N*-acetyl-4-isopropyl-1,3-thiazolidine-2-thione ((*R*)-**37**)[33] under Vilarrasa's conditions ($TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2, –78 °C).[35] However, the epoxide ring of **36** was extremely labile under Lewis acidic conditions, resulting in a moderate yield of the desired aldol products **41a**,**b** with low diastereoselectivity, and formation of the epoxide ring-opening products **42a**,**b** as the major components (Scheme 9).

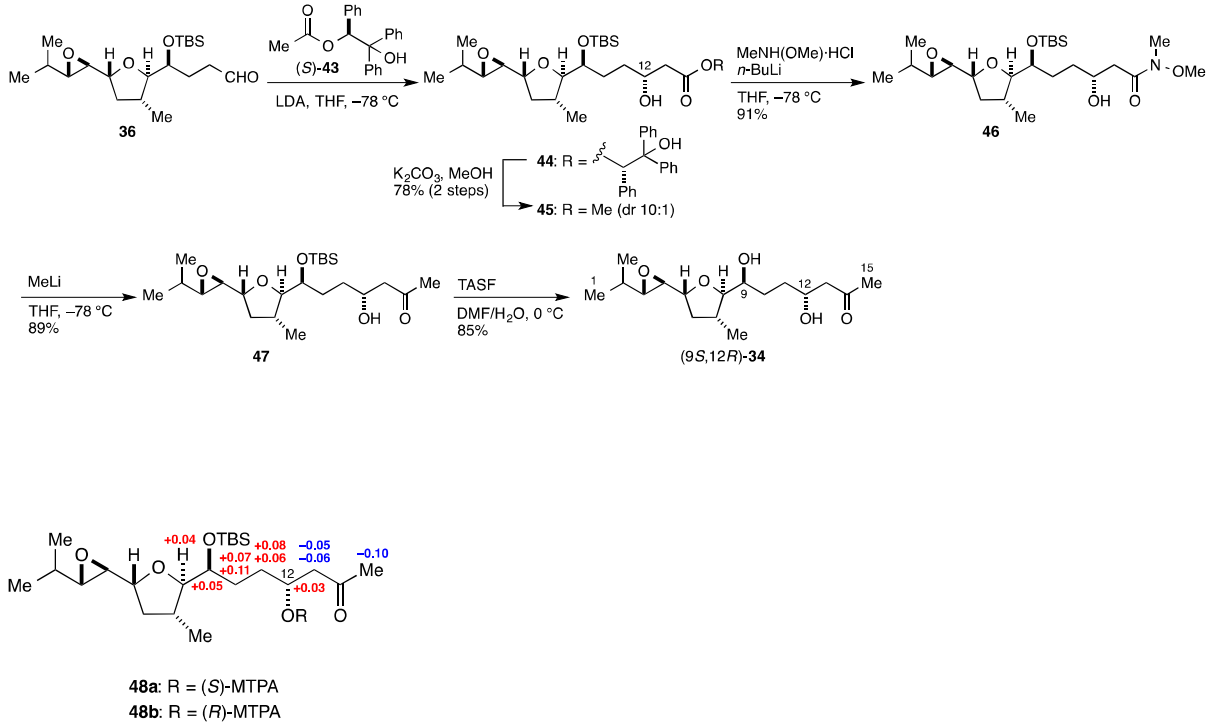
Scheme 9. Unsuccessful Acetate Aldol Reaction of 36



In order to suppress the lability of the epoxide ring in **36**, we next selected a diastereoselective aldol reaction using 2-acetoxy-1,1,2-triphenylethanol **43** developed by Braun et al.[36] under basic conditions. Thus, diastereoselective aldol reaction of **36** with the lithium enolate derived from (*S*)-**43** using 2 equiv of LDA in THF at –78 °C gave the desired β-hydroxy ester **44** (Scheme 10). As the diastereomer ratio could not be determined at this point, ester **44** thus obtained was further transesterified to the corresponding methyl ester **45** with K_2CO_3/MeOH in 78% yield for the two steps. At this stage, the diastereomer ratio of the aldol reaction was estimated to be 10:1 by integration of the SiMe signal in the ^{1}H NMR spectrum. Methyl ester **45** was converted to the corresponding Weinreb amide **46** in 91% yield by reaction with *N,O*-dimethylhydroxylamine hydrochloride and *n*-BuLi (THF, –78 °C).[37] Direct conversion of **44** to the corresponding Weinreb amide **46** was also achieved in good yield (71%), but large excess amounts of MeNH(OMe)·HCl (10 equiv) and *n*-BuLi (20 equiv) were required for complete consumption of **44**. Therefore, ester

44 was converted to amide **46** by a two-step sequence of reactions. Subsequent treatment of **46** with methyllithium (THF, –78 °C) provided methyl ketone **47** in 89% yield.[38] The absolute configuration of the C12 stereogenic center, which was newly generated in the aldol reaction, was unambiguously established by derivatization of **47** to the corresponding (*S*)- and (*R*)-MTPA esters **48a** and **48b**, respectively, and a modified Mosher analysis[28] (Figure 9). Finally, cleavage of the TBS ether of **47** using tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF)[39] (DMF/H_2O, 0 °C) furnished the desired C1–C15 segment (9*S*,12*R*)-**34** in 85% yield after HPLC purification.

Scheme 10. Synthesis of the C1–C15 Segment 34 through Braun Acetate Aldol Reaction



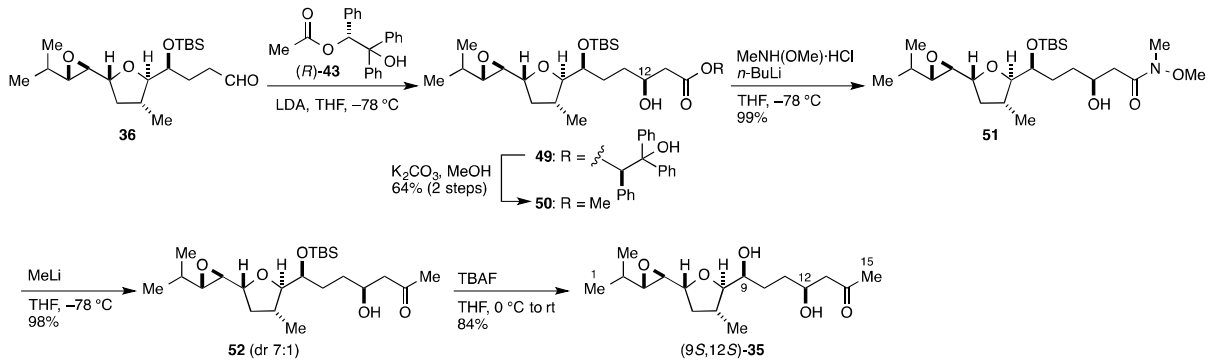
48a: R = (*S*)-MTPA
48b: R = (*R*)-MTPA

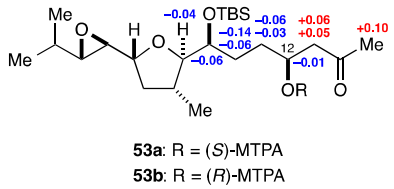
Figure 9. Determination of the absolute configuration at C12 of alcohol **47**. The numbers in red and

blue are the difference (Δδ) in the ^{1}H NMR chemical shifts between **48a** and **48b** (Δδ = δ (**48a**) – δ (**48b**) in $CDCl_3$).

The other diastereomeric C1–C15 segment, (9*S*,12*S*)-**35**, was prepared in a similar manner from aldehyde **36**, as summarized in Scheme 11. Aldol reaction of **36** with the lithium enolate derived from (*R*)-**43** (LDA (2 equiv), THF, –78 °C) followed by methanolysis (K_2CO_3, MeOH) provided β-hydroxy ester **50** (64%, two steps), which was converted to methyl ketone **52** via Weinreb amide **51** in 97% yield for the two steps with a 7:1 diastereomer ratio at C12. The absolute configuration of the C12 stereogenic center of **52** was established by the modified Mosher method[28] using the corresponding (*S*)- and (*R*)-MTPA esters **53a** and **53b**, as shown in Figure 10. Removal of the TBS group of **52** with TBAF[40] gave rise to the requisite C1–C15 segment (9*S*,12*S*)-**35** in 84% yield after HPLC purification.

Scheme 11. Synthesis of the Diastereomeric C1–C15 Segment 35





53a: R = (*S*)-MTPA
53b: R = (*R*)-MTPA

Figure 10. Determination of the absolute configuration at C12 of alcohol **52**. The numbers in red and blue are the difference (Δδ) in the ^{1}H NMR chemical shifts between **53a** and **53b** (Δδ = δ (**53a**) – δ (**53b**) in $CDCl_3$).

Assignment of the Relative Configuration of the C1–C15 Segment of Amphirionin-5. The ^{1}H and ^{13}C NMR chemical shifts in the region of C1–C12 for the two diastereomeric model compounds **34** and **35** were compared with the data reported for the natural product. As shown in Figure 11, diastereomer **34** displayed NMR chemical shifts, and particularly ^{1}H NMR shifts, that were virtually identical to those reported for the natural product. In contrast, upon careful examination of the NMR data of diastereomer **35**, small but distinct differences in the chemical shifts were detected between **35** and the natural product. Remarkably, distinct deviations in the ^{1}H and ^{13}C NMR chemical shifts were observed for H-11 (Δδ = 0.09 and –0.04 ppm) and C10 (Δδ = –0.6 ppm) that are deemed sufficiently so as to be distinguishable. It is critical that these protons and carbon are located in the region bridging by the two stereogenic centers at C9 and C12.[10e] These results conclusively demonstrated that compound **34** represents the relative configuration of

the corresponding portion of the natural product amphirionin-5.[41] Consequently, we assigned the relative configuration of the C3–C12 portion of amphirionin-5 as 3*S**,4*S**,5*R**,7*R**,8*R**, 9*S**,12*R** (Figure 12).

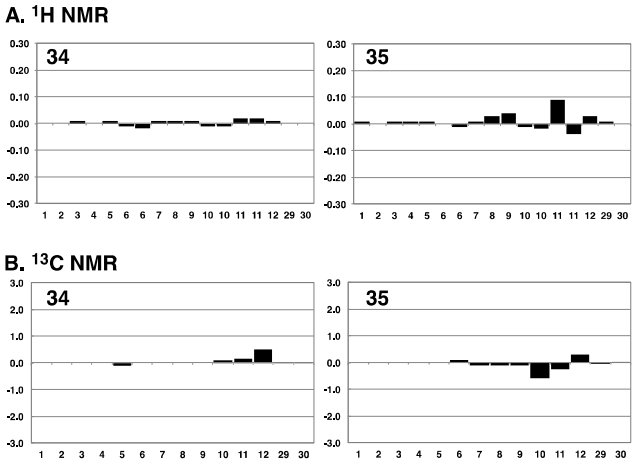


Figure 11. Differences in ^{1}H and ^{13}C NMR chemical shifts between amphirionin-5 (500 and 125 MHz, respectively) and model compounds **34** and **35** (600 and 150 MHz, respectively). The *x*- and *y*-axes represent the carbon number and $\Delta\delta = \delta$ (natural product) – δ (model compound) in ppm ($CDCl_3$), respectively.

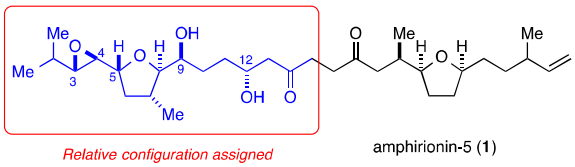


Figure 12. Assigned relative configuration of the C3–C12 portion of amphirionin-5 (**1**).

CONCLUSIONS

In summary, we assigned the relative configuration of the C3–C12 portion of amphirionin-5 as 3*S**,4*S**,5*R**,7*R**,8*R**,9*S**,12*R** by stereodivergent synthesis of six diastereomeric model compounds and by carefully comparing their NMR data with those reported for the natural product. Four diastereomeric model compounds for the C1–C12 segment of amphirionin-5 were synthesized in a stereodivergent fashion. The key features of the synthesis route included (1) convergent synthesis of the common intermediary allylic alcohol by exploiting Julia–Kocienski olefination, Horner–Wadsworth–Emmons reaction, and Corey–Bakshi–Shibata reduction, (2) efficient construction of the 2,5-*trans*-substituted tetrahydrofuran ring by a domino Sharpless asymmetric dihydroxylation/stereospecific 5-*exo* cyclization, and (3) Mitsunobu inversion reaction. Comparison of the NMR data of the four diastereomeric model compounds with those reported for the natural product enabled not only assignment of the relative configuration of the C4/C5 stereogenic centers, but also reassignment of the originally proposed configuration at C9 of amphirionin-5. Furthermore, synthesis of two possible diastereomeric model compounds for the C1–C15 segment through an acetate aldol reaction and comparison of their NMR data with those of the natural product defined the relative configuration of the remote stereogenic centers at C9 and C12 bridged by two methylene units. Further studies aimed at the complete stereochemical assignment and total synthesis of amphirionin-5 are underway and will be reported in due course.

EXPERIMENTAL SECTION

General Methods. 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 CH_2Cl_2 was purchased and anhydrous THF was purified by a Glass Contour solvent purification system. Acetonitrile (MeCN), 1,2-dichloroethane (DCE), diisopropylamine, diisopropylethylamine, 1,2-dimethoxyethane (DME), pyridine, and triethylamine (Et_3N) were distilled from calcium hydride under an atmosphere of argon. DMF and DMSO were distilled from magnesium sulfate under reduced pressure. All other chemicals were purchased at highest commercial grade and used directly. Analytical thin-layer chromatography (TLC) was performed using pre-coated glass plate (silica gel 60 F_{254}, 0.25-mm thickness). Flash column chromatography was carried out using silica gel (spherical, neutral, 40–100 mesh; granular, 200–400 mesh). Reverse-phase HPLC was performed using an UV/Visible detector. Optical rotations were measured on a digital polarimeter at 589 nm. IR spectra were recorded as a thin film on a KBr disk using an FT-IR spectrometer and reported in wavenumbers (cm^{-1}). ^1H and ^{13}C NMR spectra were recorded at 600 and 150 MHz NMR spectrometers, respectively. Chemical shift values are reported in ppm (δ) downfield from tetramethylsilane with reference to internal residual solvent [^1H NMR, C*H*Cl_3 (7.26), C_6HD_5 (7.16); ^{13}C NMR, $CDCl_3$ (77.0), C_6D_6 (128.0)]. Coupling

constants (*J*) are reported in hertz (Hz). The following abbreviations were used to designate the multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or unresolved; br = broad. High-resolution mass spectra (HRMS) were measured on an ESI-TOF mass spectrometer. Diastereomer ratio (dr) and *E*/*Z* isomer ratio were estimated by ^{1}H NMR spectroscopic analysis, unless otherwise noted.

*(R)-4-((4-Methoxybenzyl)oxy)-2-methylbutan-1-ol (**15**).* To a solution of imide **14**[19] (8.68 g, 21.9 mmol) and MeOH (2.70 mL, 66.7 mmol) in THF (200 mL) at 0 °C was added $LiBH_4$ (3 M solution in THF, 22 mL, 66 mmol). The resultant solution was stirred at 0 °C for 1 h. The reaction was carefully quenched with saturated potassium sodium tartrate solution and Et_2O at 0 °C. The resultant mixture was diluted with Et_2O and saturated aqueous potassium sodium tartrate solution and vigorously stirred at room temperature. The reaction mixture was extracted with EtOAc, and the organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 20 to 40 to 50% EtOAc/hexanes) gave alcohol **15** (4.50 g, 92%) as a colorless oil. The spectroscopic data of **15** were compared with those the earlier known compound[21] and found to be identical.

*(R,E)-tert-Butyl((8-((4-methoxybenzyl)oxy)-6-methyloct-4-en-1-yl)oxy)dimethylsilane (**16**).*

To a solution of alcohol **15** (2.10 g, 9.36 mmol) and Et_3N (5.20 mL, 37.3 mmol) in CH_2Cl_2/DMSO (1:1, v/v, 90 mL) at 0 °C was added SO_3·pyridine (4.38 g, 27.5 mmol), and the resultant mixture was stirred at 0 °C for 1 h. The mixture was diluted with *t*-BuOMe, washed with 1 M aqueous HCl solution, saturated aqueous $NaHCO_3$ solution, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give crude aldehyde **12** (2.25 g), which was used in the next reaction without further purification.

To a solution of phenyltetrazolyl sulfone **13**[23] (5.48 g, 13.8 mmol) in DME (75 mL) at −55 °C was added KHMDS (0.5 M solution in toluene, 28 mL, 14 mmol), and the resultant solution was stirred at −55 °C for 2 h. To this solution was added a solution of the above aldehyde in DME (2 mL + 2 mL rinse), and the resultant solution was stirred at −55 °C for 3 h. The reaction was quenched with saturated aqueous NH_4Cl solution. The reaction 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, 0 to 1.5 to 2.5 to 5% EtOAc/hexanes) gave olefin **16** (2.30 g, 64% for the two steps, *E*/*Z* >20:1) as a pale yellow oil: $[\alpha]_D^{23}$ −22.2 (*c* 1.00, $CHCl_3$); IR (neat) 2953, 2928, 2856, 2360, 2341, 1513, 1249, 1100, 836 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.27–7.24 (m, 2H), 6.89–6.86 (m, 2H), 5.35 (ddd, *J* = 15.1, 7.3, 6.4 Hz, 1H), 5.25 (dddd, *J* = 15.1, 7.8, 1.4, 1.4 Hz, 1H), 4.42 (d, *J* = 11.5 Hz, 1H), 4.40 (d, *J* = 11.5 Hz, 1H), 3.80 (s, 3H), 3.59 (dd, *J* = 6.4, 6.4 Hz, 2H), 3.46–3.39 (m, 2H),

2.24 (m, 1H), 2.03–1.99 (m, 2H), 1.62–1.49 (m, 4H), 0.96 (d, J = 6.9 Hz, 3H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.1, 136.0, 130.8, 129.2 (2C), 128.4, 113.7 (2C), 72.5, 68.3, 62.6, 55.2, 36.8, 33.6, 32.7, 28.7, 26.0 (3C), 21.0, 18.4, −5.3 (2C); HRMS (ESI) calcd for $C_{23}H_{40}O_3SiNa$ [$(M + Na)^+$] 415.2639; found 415.2637.

*(R,E)-8-((tert-Butyldimethylsilyl)oxy)-3-methyloct-4-en-1-ol (**17**).* To a solution of PMB ether **16** (3.49 g, 8.89 mmol) in CH_2Cl_2/pH 7 buffer (10:1, v/v, 99 mL) at 0 °C was added DDQ (2.44 g, 10.7 mmol), and the resultant mixture was stirred at room temperature for 2 h 40 min. The reaction was quenched with saturated aqueous $NaHCO_3$ solution. The mixture was extracted with EtOAc, and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 2.5 to 6% EtOAc/benzene) gave alcohol **17** (2.11 g, 87%) as a pale yellow oil: $[\alpha]_D^{23}$ –17.5 (*c* 1.00, $CHCl_3$); IR (neat) 3334, 2929, 2858, 1471, 1388, 1255, 1103, 969, 837, 775 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 5.42 (ddd, J = 15.1, 6.9, 5.9 Hz, 1H), 5.29 (dddd, J = 15.1, 8.3, 1.4, 1.4 Hz, 1H), 3.67–3.62 (m, 2H), 3.60 (dd, J = 6.7, 6.7 Hz, 2H), 2.24 (m, 1H), 2.06–2.00 (m, 2H), 1.60–1.47 (m, 4H), 1.31 (br, 1H), 0.99 (d, J = 6.9 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.0, 128.8, 62.5, 61.4, 39.8, 33.9, 32.6, 28.7, 25.9 (3C), 21.2, 18.3, −5.3 (2C); HRMS (ESI) calcd for $C_{15}H_{32}O_2SiNa$ [$(M + Na)^+$] 295.2064; found

295.2064.

*Dimethyl ((4R,E)-9-((tert-Butyldimethylsilyl)oxy)-2-hydroxy-4-methylnon-5-en-1-yl) phosphonate (**18**).* To a solution of alcohol **17** (2.072 g, 7.604 mmol) in CH_2Cl_2/DMSO (1:1, v/v, 70 mL) at 0 °C were added Et_3N (4.20 mL, 30.1 mmol) and SO_3·pyridine (3.63 g, 22.8 mmol), and the resultant mixture was stirred at 0 °C for 1 h. The mixture was extracted with *t*-BuOMe, and the organic layer was washed with 1 M aqueous HCl solution, saturated aqueous $NaHCO_3$ solution, and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was roughly purified by column chromatography (silica gel, 2 to 5% EtOAc/hexanes) to give aldehyde (2.036 g), which was used in the next reaction without further purification.

To a solution of dimethyl methylphosphonate (3.30 mL, 30.5 mmol) in THF (70 mL) at −78 °C was added *n*-BuLi (2.6 M solution in hexanes, 11.5 mL, 29.9 mmol), and the resultant solution was stirred at −78 °C for 40 min. To this solution was added a solution of the above aldehyde (2.036 g) in THF (2 mL + 2 mL rinse), and the resultant solution was stirred at −78 °C for 1.5 h. The reaction was quenched with saturated aqueous NH_4Cl solution. The 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, 50 to 100% EtOAc/hexanes) gave β-hydroxy phosphonate **18** (2.443 g,

81% for the two steps, dr 1:1) as a colorless oil: $[\alpha]_D^{24}$ –15.9 (*c* 1.00, $CHCl_3$); IR (neat) 3389, 2954, 2929, 2856, 1462, 1253, 1100, 1061, 1036, 970, 836, 775 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 5.44 (ddd, *J* = 15.1, 6.9, 6.9 Hz, 0.5H), 5.40 (ddd, *J* = 15.6, 6.9, 6.9 Hz, 0.5H), 5.30 (dd, *J* = 15.6, 8.3 Hz, 0.5H), 5.22 (dd, *J* = 15.1, 8.2 Hz, 0.5H), 4.07–3.96 (m, 1H), 3.77–3.73 (m, 6H), 3.61–3.57 (m, 2H), 3.28 (m, 0.5H), 3.17 (m, 0.5H), 2.36 (m, 0.5H), 2.25 (m, 0.5H), 2.05–1.98 (m, 2H), 1.98–1.82 (m, 2H), 1.75 (m, 0.5H), 1.64–1.52 (m, 1.5H), 1.37 (dd, *J* = 12.8, 6.4, 6.4 Hz, 0.5H), 1.31 (ddd, *J* = 13.3, 10.1, 3.7 Hz, 0.5H), 0.99 (d, *J* = 7.3 Hz, 1.5H), 0.98 (d, *J* = 7.3 Hz, 1.5H), 0.885 (s, 4.5H), 0.882 (s, 4.5H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.0 (0.5C), 135.3 (0.5C), 129.4 (0.5C), 128.7 (0.5C), 65.0 (0.5C, d, $J_{C,P}$ = 5.7 Hz), 64.6 (0.5C, d, $J_{C,P}$ = 5.7 Hz), 62.6 (0.5C), 62.5 (0.5C), 52.4–52.3 (2C), 45.6 (0.5C, d, $J_{C,P}$ = 15.8 Hz), 45.3 (0.5C, d, $J_{C,P}$ = 15.8 Hz), 33.8 (0.5C), 33.4 (0.5C), 33.1 (0.5C, d, $J_{C,P}$ = 136.4 Hz), 32.7 (0.5C), 32.6 (0.5C), 32.4 (0.5C, d, $J_{C,P}$ = 136.4 Hz), 28.72 (0.5C), 28.70 (0.5C), 25.9 (3C), 21.6 (0.5C), 20.8 (0.5C), 18.3 (1C), –5.3 (2C); HRMS (ESI) calcd for $C_{18}H_{39}O_5PSiNa$ $[(M + Na)^+]$ 417.2197; found 417.2197.

Dimethyl (R,E)-(9-((tert-Butyldimethylsilyl)oxy)-4-methyl-2-oxonon-5-en-1-yl)phosphonate ***(19).*** To a suspension of β-hydroxy phosphonate **18** (2.346 g, 5.946 mmol) and 4 Å molecular sieves (3.07 g) in CH_2Cl_2 (50 mL) at 0 °C were added NMO (1.012 g, 8.641 mmol) and TPAP (216.4 mg, 0.6158 mmol), and the resultant mixture was stirred at room temperature for 2 h. The

reaction mixture was concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 40 to 60% EtOAc/hexanes) gave β-keto phosphonate **19** (1.905 g, 82%) as a pale brown oil: $[\alpha]_D^{25}$ −11.5 (*c* 1.00, $CHCl_3$); IR (neat) 2955, 2929, 2856, 1715, 1255, 1099, 1032, 836, 775 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 5.41 (ddd, *J* = 15.1, 6.9, 6.9 Hz, 1H), 5.32 (dd, *J* = 15.1, 6.9 Hz, 1H), 3.78 (d, $J_{H,P}$ = 11.0 Hz, 3H), 3.77 (d, $J_{H,P}$ = 11.0 Hz, 3H), 3.57 (dd, *J* = 6.6, 6.6 Hz, 2H), 3.05 (d, $J_{H,P}$ = 22.6 Hz, 2H) 2.67 (m, 1H), 2.60 (dd, *J* = 16.5, 6.8 Hz, 1H), 2.54 (dd, *J* = 16.5, 7.3 Hz, 1H), 2.03–1.97 (m, 2H), 1.57–1.51 (m, 2H), 0.99 (d, *J* = 6.4 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 201.0 (d, $J_{C,P}$ = 5.8 Hz), 134.3, 129.0, 62.5, 53.0 (d, $J_{C,P}$ = 7.2 Hz, 2C), 51.2, 41.7 (d, $J_{C,P}$ = 128.6 Hz), 32.5, 32.3, 28.7, 25.9 (3C), 20.3, 18.3, −5.3 (2C); HRMS (ESI) calcd for $C_{18}H_{37}O_5PSiNa$ $[(M + Na)^+]$ 415.2040; found 415.2043.

(R,3E,8E)-12-((tert-Butyldimethylsilyl)oxy)-2,7-dimethyldodeca-3,8-dien-5-one (20). To a solution of β-keto phosphonate **19** (1.855 g, 4.725 mmol) in MeCN (45 mL) were added LiCl (400.6 mg, 9.450 mmol), *i*-Pr_2NEt (1.60 mL, 9.19 mmol), and isobutyraldehyde (**11**) (0.90 mL, 9.9 mmol), and the resultant mixture was stirred at room for 15 h. The reaction was quenched with saturated aqueous NH_4Cl solution. The 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, 2 to 10%

EtOAc/hexanes) gave α,β-unsaturated ketone **20** (1.590 g, 99%, *E*/*Z* >20:1) as a colorless oil: $[\alpha]_D^{26}$ −8.9 (*c* 1.00, $CHCl_3$); IR (neat) 2957, 2928, 2857, 1254, 1100, 836, 775, 667 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 6.76 (dd, *J* = 16.1, 6.4 Hz, 1H), 6.01 (dd, *J* = 16.1, 1.8 Hz, 1H), 5.43–5.32 (m, 2H), 3.58 (dd, *J* = 6.6, 6.6 Hz, 2H), 2.68 (m, 1H), 2.55 (dd, *J* = 15.1, 6.5 Hz, 1H), 2.45 (m, 1H), 2.44 (dd, *J* = 15.1, 7.3 Hz, 1H), 2.03–1.98 (m, 2H), 1.58–1.52 (m, 2H), 1.06 (d, *J* = 6.9 Hz, 6H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.3, 153.5, 135.0, 128.5, 127.9, 62.5, 47.4, 32.9, 32.6, 31.1, 28.7, 26.0 (3C), 21.3 (2C), 20.4, 18.3, −5.3 (2C); HRMS (ESI) calcd for $C_{20}H_{38}O_2SiNa$ [$(M + Na)^+$] 361.2533; found 361.2554.

*(3E,5S,7R,8E)-12-((tert-Butyldimethylsilyl)oxy)-2,7-dimethyldodeca-3,8-dien-5-ol (**10**).* To a solution of α,β-unsaturated ketone **20** (1.5721 g, 4.643 mmol) and (*R*)-2-methyl-CBS-oxazaborolidine **21** (1.0 M solution in toluene, 4.6 mL, 4.6 mmol) in THF (12 mL) at −40 °C was added BH_3·THF (0.90 M solution in THF, 10.5 mL, 9.45 mmol), and the resultant solution was stirred at −40 °C for 1 h. The reaction was quenched with MeOH. 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, first round: 3 to 3.5 to 10% EtOAc/hexanes; second round: 2 to 3.5 to 50% EtOAc/hexanes) gave a□□□□□□□□□□□□□□□ **10** (1.4701 g, 93%) as a colorless oil,

along with the corresponding (8*Z*)-isomer (60.7 mg, 4%), which was produced in the Julia–Kocienski olefination, as a colorless oil. The diastereomer ratio of **10** was determined to be 11:1 by HPLC analysis of the corresponding benzoate **22**. Data for **10**: $[\alpha]_D^{25}$ –7.8 (*c* 1.00, $CHCl_3$); IR (neat) 3348, 2956, 2928, 2858, 1462, 1386, 1362, 1254, 1102, 969, 836, 774 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz, major diastereomer) δ 5.59 (ddd, *J* = 15.6, 6.4, 0.9 Hz, 1H), 5.43 (ddd, *J* = 15.2, 6.9, 6.9 Hz, 1H), 5.41 (ddd, *J* = 15.6, 6.9, 1.4 Hz, 1H), 5.28 (dddd, *J* = 15.2, 8.3, 1.4, 1.4 Hz, 1H), 4.07 (m, 1H), 3.60 (dd, *J* = 6.4, 6.4 Hz, 2H), 2.34–2.24 (m, 2H), 2.07–2.01 (m, 2H), 1.61–1.55 (m, 2H), 1.49 (ddd, *J* = 13.7, 8.7, 5.5 Hz, 1H), 1.44 (br s, 1H), 1.38 (ddd, *J* = 13.7, 9.2, 4.6 Hz, 1H), 0.983 (d, *J* = 6.9 Hz, 3H), 0.980 (d, *J* = 6.9 Hz, 3H), 0.976 (d, *J* = 6.4 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.4, 136.0, 130.2, 128.9, 71.0, 62.6, 44.7, 33.4, 32.7, 30.6, 28.7, 26.0 (3C), 22.34, 22.29, 21.4, 18.3, –5.3 (2C); HRMS (ESI) calcd for $C_{20}H_{40}O_2SiNa$ [$(M + Na)^+$] 363.2690; found 363.2689. Data for (8*Z*)-isomer: $[\alpha]_D^{25}$ +20.5 (*c* 1.00, $CHCl_3$); IR (neat) 3418, 2956, 2928, 2858, 1463, 1386, 1362, 1255, 1100, 970, 836, 775 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 5.58 (ddd, *J* = 15.6, 6.4, 1.0 Hz, 1H), 5.41 (ddd, *J* = 15.6, 6.4, 1.4 Hz, 1H), 5.34 (ddd, *J* = 11.0, 7.4, 7.4 Hz, 1H), 5.13 (dddd, *J* = 10.3, 10.3, 1.3, 1.3 Hz, 1H), 4.01 (m, 1H), 3.64–3.61 (m, 2H), 2.72 (m, 1H), 2.26 (m, 1H), 2.20–2.08 (m, 2H), 1.74 (m, 1H), 1.62–1.54 (m, 2H), 1.51 (ddd, *J* = 13.8, 9.2, 4.6 Hz, 1H), 1.31 (ddd, *J* = 13.8, 9.6, 3.7 Hz, 1H), 0.977 (d, *J* = 6.4 Hz, 3H), 0.975 (d, *J* = 6.4 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$)

δ 138.0, 136.0, 130.4, 128.7, 70.9, 62.7, 45.1, 33.0, 30.6, 28.2, 26.0 (3C), 23.7, 22.34, 22.31, 21.7, 18.4, –5.23, –5.26; HRMS (ESI) calcd for $C_{20}H_{40}O_2SiNa$ [$(M + Na)^+$] 363.2690; found 363.2689.

(3E,5S,7R,8E)-12-((tert-Butyldimethylsilyl)oxy)-2,7-dimethyldodeca-3,8-dien-5-yl Benzoate ***(22).*** To a solution of allylic alcohol **10** (2.9 mg, 8.5 μmol) in pyridine (0.3 mL) were added benzoyl chloride (0.010 mL, 87 μmol) and a crystal of DMAP (ca. 1 mg), and the resultant solution was stirred at room temperature for 22.5 h. The reaction was quenched with MeOH. The resultant mixture was stirred at room temperature for 30 min. The 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, 0 to 4% EtOAc/hexanes) gave benzoate **22** (3.7 mg, 98%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.06–8.03 (m, 2H), 7.56–7.53 (m, 1H), 7.46–7.42 (m, 2H), 5.74 (dd, *J* = 14.6, 6.5 Hz, 1H), 5.48–5.40 (m, 2H), 5.34–5.25 (m, 2H), 3.58 (dd, *J* = 6.4, 6.4 Hz, 2H), 2.31–2.21 (m, 2H), 2.03–1.98 (m, 2H), 1.80 (ddd, *J* = 14.2, 8.7, 5.5 Hz, 1H), 1.59–1.50 (m, 3H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 6H), 0.88 (s, 9H), 0.034 (s, 3H), 0.031 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.7, 140.8, 135.2, 132.6, 131.0, 129.5 (2C), 129.2, 128.3 (2C), 125.6, 73.9, 62.6, 42.2, 33.4, 32.6, 30.7, 28.8, 26.0 (3C), 22.14, 22.07, 21.1, 18.4, –5.3 (2C); HRMS (ESI) calcd for $C_{27}H_{44}O_3SiNa$ [$(M + Na)^+$] 467.2952; found 467.2958. The diastereomer ratio (dr) of this

benzoate was determined to be 11:1 by reverse-phase HPLC analysis [Develosil C30-HG-5 column (4.6 mm I.D. × 150 mm), solvent: 87.5% MeCN/H_2O, flow rate: 1.0 mL/min, UV detection: 254 nm, major peak: t_R = 146.5 min; minor peak: t_R = 155.1 min].

(S)-MTPA ester ***23a.*** To a solution of alcohol **10** (3.2 mg, 9.3 μmol) in DCE (0.5 mL) were added (*S*)-MTPA acid (13 mg, 56 μmol), DCC (10 mg, 48 μmol), and DMAP (1.5 mg, 12 μmol), and the resultant mixture was stirred at room temperature for 11 h 5 min. To the mixture was added (*S*)-MTPA acid (10 mg, 43 μmol), and the resultant mixture was stirred for further 7 h 10 min. The mixture was diluted with *t*-BuOMe, and insoluble material was filtered. The filtrate was concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, first round: hexanes then 3% EtOAc/hexanes) gave (*S*)-MTPA ester **23a** (2.9 mg, 56%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.54–7.51 (m, 2H), 7.41–7.35 (m, 3H), 5.82 (dd, *J* = 15.1, 6.6 Hz, 1H), 5.44 (ddd, *J* = 9.1, 8.2, 4.1 Hz, 1H), 5.39 (ddd, *J* = 15.1, 8.2, 1.4 Hz, 1H), 5.31 (ddd, *J* = 15.1, 6.6, 6.6 Hz, 1H), 5.19 (dd, *J* = 15.1, 8.2 Hz, 1H), 3.61 (t, *J* = 6.4 Hz, 2H), 3.54 (d, *J* = 1.0 Hz, 3H), 2.29 (m, 1H), 2.06–2.00 (m, 3H), 1.70 (ddd, *J* = 14.2, 9.1, 5.0 Hz, 1H), 1.60–1.55 (m, 2H), 1.43 (ddd, *J* = 14.2, 9.6, 4.1 Hz, 1H), 0.977 (d, *J* = 6.9 Hz, 3H), 0.975 (d, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 6.4 Hz, 3H), 0.90 (s, 9H), 0.05 (s, 6H); HRMS (ESI) calcd for $C_{30}H_{47}O_4F_3SiNa$ [$(M + Na)^+$] 579.3088; found 579.3098.

*(R)-MTPA ester **23b.*** To a solution of alcohol **10** (2.8 mg, 8.1 μmol) in DCE (0.5 mL) were added (R)-MTPA acid (11 mg, 47 μmol), DCC (11 mg, 53 μmol), and DMAP (1.2 mg, 9.8 μmol), and the resultant mixture was stirred at room temperature for 11.5 h. The mixture was diluted with *t*-BuOMe, and insoluble material was filtered. The filtrate was concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, first round: hexanes then 3% EtOAc/hexanes; second round: hexanes then 3% EtOAc/hexanes) gave (*R*)-MTPA ester **23b** (3.1 mg, 70%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.51–7.49 (m, 2H), 7.40–7.35 (m, 3H), 5.75 (dd, *J* = 15.6, 5.9 Hz, 1H), 5.42 (ddd, *J* = 9.0, 7.8, 4.6 Hz, 1H), 5.36 (ddd, *J* = 15.2, 6.8, 6.8 Hz, 1H), 5.28–5.21 (m, 2H), 3.61 (t, *J* = 6.4 Hz, 2H), 3.56 (d, *J* = 0.9 Hz, 3H), 2.25 (m, 1H), 2.16 (m, 1H), 2.07–2.02 (m, 2H), 1.73 (ddd, *J* = 14.2, 9.1, 5.5 Hz, 1H), 1.60–1.55 (m, 2H), 1.48 (ddd, *J* = 14.2, 9.2, 5.0 Hz, 1H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.952 (d, *J* = 6.9 Hz, 3H), 0.950 (d, *J* = 6.9 Hz, 3H), 0.90 (s, 9H), 0.05 (s, 6H); HRMS (ESI) calcd for $C_{30}H_{47}O_4F_3SiNa$ [$(M + Na)^+$] 579.3088; found 579.3077.

*(1S,3R,E)-8-((tert-Butyldimethylsilyl)oxy)-1-((2S,3S)-3-isopropyloxiran-2-yl)-3-methyloct-4-en-1-ol (**24**).* To a suspension of allylic alcohol **10** (1.4572 g, 4.278 mmol, dr 11:1) and 4 Å molecular sieves (1.4856 g) in CH_2Cl_2 (35 mL) at −20 °C were added a solution of (+)-DIPT

(345.8 mg, 1.4762 mmol) in CH_2Cl_2 (4 mL + 2 mL rinse) and Ti(O*i*-Pr)$_4$ (0.35 mL, 1.2 mmol), and the resultant mixture was stirred at −20 °C for 1 h. To this mixture was added *t*-BuOOH (4.3 M in isooctane solution, 2.0 mL, 8.6 mmol), and the resultant mixture was stirred at −20 °C for 2.5 h. The reaction was quenched with 1 M aqueous NaOH solution (20 mL). The resultant biphasic mixture was stirred at room temperature for 30 min. The mixture was filtered through a pad of Celite. The filtrate was extracted with *t*-BuOMe, and the organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, first round: 4 to 5 to 6% EtOAc/hexanes; second round: 4 to 5 to 6% EtOAc/hexanes) gave epoxy □□□□□□□ **24** (1.3654 g, 90%, dr 23:1) as a colorless oil: $[\alpha]_D^{25}$ −20.2 (*c* 1.00, $CHCl_3$); IR (neat) 3465, 2956, 2928, 2857, 2359, 2340, 1471, 1462, 1254, 1102, 970, 835, 775 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 5.45 (ddd, *J* = 15.1, 6.9, 6.9 Hz, 1H), 5.23 (dddd, *J* = 15.1, 8.2, 1.4, 1.4 Hz, 1H), 3.80 (m, 1H), 3.59 (dd, *J* = 6.5, 6.5 Hz, 2H), 2.79–2.76 (m, 2H), 2.41 (m, 1H), 2.06–2.01 (m, 2H), 1.80 (br s, 1H), 1.60–1.50 (m, 3H), 1.44 (ddd, *J* = 14.2, 9.6, 4.6 Hz, 1H), 1.38 (ddd, *J* = 13.8, 10.1, 3.2 Hz, 1H), 1.02 (d, *J* = 6.9 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.3, 129.6, 66.5, 62.6, 60.2, 60.1, 40.7, 33.5, 32.6, 30.1, 28.7, 26.0 (3C), 21.9, 19.1, 18.3 (2C), –5.3 (2C); HRMS (ESI) calcd for $C_{20}H_{40}O_3SiNa$ [$(M + Na)^+$] 379.2639; found 379.2634.

*C1–C12 Segment (3S,4S,5R)-**4**.* To a solution of epoxy alcohol **24** (1.3521 g, 3.791 mmol) in CH_2Cl_2 (40 mL) at 0 °C were added Et_3N (1.60 mL, 11.5 mmol) and MsCl (0.60 mL, 7.8 mmol), and the resultant solution was stirred at 0 °C for 45 min. The reaction mixture was extracted with EtOAc, and the organic layer was washed sequentially 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 **8** (1.6977 g), which was used in the next reaction without further purification.

To a solution of the above mesylate **8** in *t*-BuOH/H_2O (1:1, v/v, 40 mL) were added $MeSO_2NH_2$ (362.8 mg, 3.814 mmol) and AD-mix-β (5.3168 g), and the resultant mixture was stirred at room temperature for 16.5 h. The reaction was quenched with saturated aqueous Na_2SO_3 solution, and the resultant mixture was stirred at room temperature for 30 min. The mixture was extracted with EtOAc, and the organic layer was washed with 1 M aqueous NaOH solution and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 7 to 8 to 20% EtOAc/hexanes) gave tetrahydrofuran **4** (1.2653 g, 90% for the two steps) as a colorless oil: $[\alpha]_D^{25}$ –11.6 (*c* 1.00, $CHCl_3$); IR (neat) 3446, 2956, 2929, 2857, 2367, 2321, 1472, 1458, 1387, 1254, 1098, 835, 775 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 3.82 (ddd, *J* = 9.4, 5.5, 5.1 Hz, 1H), 3.68–3.61 (m, 2H), 3.46 (m, 1H), 3.37 (dd, *J* = 8.3, 3.2 Hz, 1H), 2.79 (dd, *J* = 5.1, 2.3 Hz, 1H), 2.68 (dd, *J* = 6.8, 2.3 Hz, 1H), 2.34 (d, *J* = 6.9 Hz,

1H), 2.25–2.16 (m, 2H), 1.71 (m, 1H), 1.67–1.48 (m, 5H), 1.06 (d, J = 6.0 Hz, 3H), 1.01 (d, J = 6.9 Hz, 3H), 0.94 (d, J = 6.9 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 88.6, 78.4, 71.1, 63.1, 61.2, 59.3, 38.2, 35.2, 31.1, 30.2, 29.1, 25.9 (3C), 19.0, 18.3 (2C), 16.8, –5.3 (2C); HRMS (ESI) calcd for $C_{20}H_{40}O_4SiNa$ [$(M + Na)^+$] 395.2588; found 395.2588.

*(S)-MTPA ester **25a.*** To a solution of alcohol **4** (3.8 mg, 10 μmol) in DCE (0.5 mL) at 0 °C were added Et_3N (20 μL, 0.14 mmol), a crystal of DMAP (ca. 1 mg), and one drop of (*R*)-MTPACl, and the resultant solution was stirred at room temperature for 12 h. The mixture was extracted with EtOAc, washed with saturated aqueous NH_4Cl solution and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 0 to 3 to 4% EtOAc/hexanes) gave (*S*)-MTPA ester **25a** (5.4 mg, 90%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.60–7.57 (m, 2H), 7.41–7.38 (m, 3H), 5.11 (ddd, J = 9.1, 5.0, 4.1 Hz, 1H), 3.68 (ddd, J = 10.1, 6.0, 4.6 Hz, 1H), 3.61 (ddd, J = 6.4, 6.4, 0.9 Hz, 2H), 3.55 (s, 3H), 3.54 (dd, J = 7.8, 4.1 Hz, 1H), 2.70 (dd, J = 4.6, 2.3 Hz, 1H), 2.62 (dd, J = 6.8, 2.3 Hz, 1H), 1.98 (ddd, J = 11.9, 7.4, 6.4 Hz, 1H), 1.89–1.73 (m, 3H), 1.60–1.48 (m, 3H), 1.41 (ddd, J = 11.9, 9.6, 9.6 Hz, 1H), 1.01 (d, J = 6.9 Hz, 3H), 0.98 (d, J = 6.9 Hz, 3H), 0.91 (d, J = 6.9 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); HRMS (ESI) calcd for $C_{30}H_{47}O_6F_3SiNa$ [$(M + Na)^+$] 611.2986; found 611.2991.

*(R)-MTPA ester **25b.*** To a solution of alcohol **4** (3.0 mg, 9.1 μmol) in DCE (0.5 mL) at 0 °C were added Et_3N (20 μL, 0.14 mmol), a crystal of DMAP (ca. 1 mg), and one drop of (*S*)-MTPACl, and the resultant solution was stirred at room temperature for 12 h. The reaction was quenched with saturated aqueous NH_4Cl solution. The 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, 0 to 2 to 3% EtOAc/hexanes) gave (*R*)-MTPA ester **25b** (2.9 mg, 54%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.64–7.60 (m, 2H), 7.43–7.37 (m, 3H), 5.13 (ddd, *J* = 9.2, 6.0, 4.1 Hz, 1H), 3.89 (ddd, *J* = 10.0, 5.9, 4.1 Hz, 1H), 3.61–3.57 (m, 4H), 3.57–3.49 (m, 2H), 2.77 (dd, *J* = 4.1, 2.3 Hz, 1H), 2.68 (dd, *J* = 7.0, 2.3 Hz, 1H), 2.18 (ddd, *J* = 12.4, 7.3, 5.9 Hz, 1H), 2.01 (m, 1H), 1.73 (m, 1H), 1.64 (m, 1H), 1.57–1.49 (m, 2H), 1.47–1.36 (m, 2H), 1.10 (d, *J* = 6.4 Hz, 3H), 1.00 (d, *J* = 6.4 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.87 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); HRMS (ESI) calcd for $C_{30}H_{47}O_6F_3SiNa$ $[(M + Na)^+]$ 611.2986; found 611.2968.

*(1S,3R,4R,5R)-8-((tert-butyldimethylsilyl)oxy)-1-((2S,3S)-3-isopropyloxiran-2-yl)-3-methyloctane-1,4,5-triol (**26**).* To a solution of epoxy alcohol **24** (27.6 mg, 0.0787 mmol) in *t*-BuOH/H_2O (1:1, v/v, 1 mL) were added $MeSO_2NH_2$ (7.5 mg, 0.079 mmol) and AD-mix-β (0.11 g), and the resultant mixture was stirred at room temperature for 9 h 10 min. The reaction was

quenched with Na_2SO_3, and the resultant mixture was stirred at room temperature for 1 h. The mixture was extracted with EtOAc, and the organic layer was washed with 3 M aqueous NaOH 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 50% EtOAc/hexanes) gave triol **26** (26.2 mg, 87%) as a colorless oil: $[\alpha]_D^{25}$ –5.9 (*c* 1.00, $CHCl_3$); IR (neat) 3398, 2956, 2929, 2858, 1471, 1387, 1327, 1255, 1097, 836, 776 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 3.82 (ddd, *J* = 8.7, 3.2, 3.2 Hz, 1H), 3.70–3.61 (m, 3H), ca. 3.51 (br, 1H), 3.41 (m, 1H), 3.22 (dd, *J* = 6.4, 4.1 Hz, 1H), 2.80–2.75 (m, 2H), 2.04 (m, 1H), 1.88 (br, 1H), 1.74 (ddd, *J* = 14.7, 5.5, 3.2 Hz, 1H), 1.71–1.61 (m, 4H), 1.58 (m, 1H), 1.54 (m, 1H), 1.03 (d, *J* = 7.3 Hz, 3H), 1.01 (d, *J* = 6.4 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 78.0, 71.6, 66.3, 63.5, 61.1, 60.1, 35.9, 32.4, 31.5, 30.1, 29.1, 25.9 (3C), 19.0, 18.34, 18.28, 17.4, –5.41, –5.43; HRMS (ESI) calcd for $C_{20}H_{42}O_5SiNa$ [$(M + Na)^+$] 413.2694; found 413.2683.

(2R,3S,5R,6R)-6-((R)-4-((tert-Butyldimethylsilyl)oxy)-1-hydroxybutyl)-2-((S)-1-hydroxy-2-methylpropyl)-5-methyltetrahydro-2H-pyran-3-ol (27). To a solution of triol **26** (22.1 mg, 56.3 μmol) in DCE (1 mL) was added PPTS (1.5 mg, 6.0 μmol), and the resultant solution was stirred at 40 °C for 2 h 50 min. The reaction mixture was neutralized with Et_3N and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 7 to 10%

EtOAc/hexanes) gave tetrahydrofuran **27** (12.5 mg, 57%) as a colorless oil: $[\alpha]_D^{23}$ –13.5 (*c* 1.00, $CHCl_3$); IR (neat) 3345, 2954, 2929, 2857, 1463, 1254, 1093, 834, 776 cm^{-1}; ^1H NMR (C_6D_6, 600 MHz) δ 4.05 (dd, *J* = 9.2, 2.8 Hz, 1H), 3.87 (ddd, *J* = 10.1, 5.0, 5.0 Hz, 1H), 3.82 (dd, *J* = 9.2, 5.0 Hz, 1H), 3.61 (m, 1H), 3.58–3.51 (m, 2H), 3.26 (br, 1H), 2.84 (br, 1H), 2.79 (dd, *J* = 9.7, 1.4 Hz, 1H), 2.08–1.98 (m, 2H), 1.88 (m, 1H), 1.82–1.70 (m, 2H), 1.66–1.59 (m, 2H), 1.52 (m, 1H), 1.37 (apparent, q, *J* = ca. 11.6 Hz, 1H), 1.17 (d, *J* = 6.9 Hz, 3H), 1.16 (d, *J* = 6.9 Hz, 3H), 0.99 (s, 9H), 0.76 (d, *J* = 6.9 Hz, 3H), 0.070 (s, 3H), 0.066 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 79.2, 73.4, 71.9, 69.9, 69.6, 63.4, 36.6, 32.0, 30.3, 30.0, 28.7, 26.1 (3C), 20.1, 18.5, 17.8, 14.7, –5.3 (2C); HRMS (ESI) calcd for $C_{20}H_{42}O_5SiNa$ [$(M + Na)^+$] 413.2694; found 413.2689.

*Kinetic resolution of allylic alcohol **10**.* To a suspension of allylic alcohol **10** (190.4 mg, 0.5590 mmol, dr 9.5:1 determined by HPLC analysis of the corresponding benzoate) and 4 Å molecular sieves (205 mg) in CH_2Cl_2 (4 mL) at −20 °C were added a solution of (−)-DIPT (39.6 mg, 0.169 mmol) in CH_2Cl_2 (1 mL + 0.5 mL rinse) and Ti(O*i*-Pr)$_4$ (0.040 mL, 0.14 mmol), and the resultant mixture was stirred at −20 °C for 1 h. To this mixture was added *t*-BuOOH (4.3 M in isooctane solution, 0.26 mL, 1.1 mmol), and the resultant mixture was stirred at −20 °C for 1 h 50 min. The reaction mixture was diluted with *t*-BuOMe and 1 M aqueous NaOH solution at 0 °C. The resultant biphasic mixture was stirred at 0 °C for 3 h. The mixture was filtered through a pad of Celite. The

filtrate was extracted with *t*-BuOMe, and the organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 5 to 15% EtOAc/hexanes) gave recovered allylic alcohol **10** (144.7 mg, 76%, dr 22:1 determined by HPLC analysis of the corresponding benzoate) as a colorless oil, along with epoxy alcohol **28** (21.6 mg, 11%, dr 15:1) and an inseparable mixture of epoxy □□□□□□□s **24** and 3,4,5-*epi*-**24** (20.1 mg, 10%, dr ca. 1:1) as colorless oils. Data for **10**: $[\alpha]_D^{26}$ –7.6 (*c* 1.00, $CHCl_3$); HRMS (ESI) calcd for $C_{20}H_{40}O_2SiNa$ [$(M + Na)^+$] 363.2690; found 363.2685. The other spectroscopic data of **10** were identical to those described above. Data for **28**: $[\alpha]_D^{24}$ –1.3 (*c* 1.00, $CHCl_3$); HRMS (ESI) calcd for $C_{20}H_{40}O_3SiNa$ [$(M + Na)^+$] 379.2639; found 379.2629. The other spectroscopic data of **28** were identical to those described below. Data for **24** and 3,4,5-*epi*-**24** (ca. 1:1 mixture): $[\alpha]_D^{26}$ –15.4 (*c* 1.00, $CHCl_3$); IR (neat) 3454, 2957, 2929, 2858, 1463, 1386, 1362, 1254, 1102, 969, 836, 775 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 5.45 (ddd, *J* = 15.3, 6.9, 6.9 Hz, 0.5H), 5.44 (ddd, *J* = 15.4, 6.4, 6.4 Hz, 0.5H), 5.36 (dd, *J* = 15.3, 7.5 Hz, 0.5H), 5.23 (dd, *J* = 15.4, 8.5 Hz, 0.5H), 3.83 (m, 0.5H), 3.80 (m, 0.5H), 3.59 (dd, *J* = 6.4, 6.4 Hz, 2H), 2.81–2.75 (m, 2H), 2.41 (m, 0.5H), 2.35 (m, 0.5H), 2.06–2.01 (m, 2H), 1.93 (br, 0.5H), 1.81 (br, 0.5H), 1.60–1.47 (m, 3.5H), 1.47–1.35 (m, 1.5H), 1.025 (d, *J* = 6.9 Hz, 1.5H), 1.022 (d, *J* = 6.4 Hz, 1.5H), 1.014 (d, *J* = 6.9 Hz, 1.5H), 1.010 (d, *J* = 6.9 Hz, 1.5H), 0.952 (d, *J* = 6.9 Hz, 1.5H), 0.947 (d, *J* = 6.9 Hz, 1.5H), 0.89 (s, 9H), 0.041 (s, 3H), 0.038 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ

136.3 (0.5C), 135.3 (0.5C), 129.6 (0.5C), 128.6 (0.5C), 66.9 (0.5C), 66.5 (0.5C), 62.55 (0.5C), 62.52 (0.5C), 60.20 (0.5C), 60.16 (0.5C), 60.11 (0.5C), 60.0 (0.5C), 40.9 (0.5C), 40.7 (0.5C), 33.51 (0.5C), 33.46 (0.5C), 32.65 (0.5C), 32.59 (0.5C), 30.1 (1C), 28.74 (0.5C), 28.71 (0.5C), 26.0 (3C), 21.9 (0.5C), 20.5 (0.5C), 19.1 (1C), 18.3 (2C), –5.3 (2C); HRMS (ESI) calcd for $C_{20}H_{40}O_3SiNa$ $[(M + Na)^+]$ 379.2639; found 379.2636.

*(1S,3R,E)-8-((tert-Butyldimethylsilyl)oxy)-1-((2R,3R)-3-isopropyloxiran-2-yl)-3-methyloct-4-en-1-ol (**28**).* To a suspension of allylic alcohol **10** (139.8 mg, 0.4104 mmol, dr 22:1) and 4 Å molecular sieves (142 mg) in CH_2Cl_2 (3 mL) at −20 °C were added a solution of (−)-DIPT (31.3 mg, 0.134 □mol) in CH_2Cl_2 (0.5 mL + 0.5 mL rinse) and Ti(O*i*-Pr)$_4$ (0.030 mL, 0.11 mmol), and the resultant mixture was stirred at −20 °C for 1 h. To this mixture was added *t*-BuOOH (4.3 M in isooctane solution, 0.20 mL, 0.86 mmol), and the resultant mixture was stirred at −20 °C for 15.5 h. The reaction mixture was diluted with *t*-BuOMe and 1 M aqueous NaOH solution (1 mL) at 0 °C, and the resultant biphasic mixture was stirred at 0 °C for 4 h. The mixture was filtered through a pad of Celite. The filtrate was extracted with EtOAc, and the organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (5 to 15% EtOAc/hexanes) gave epoxy □□□□□□□ **28** (80.6 mg, 55%, dr 22:1) as a colorless oil, along with diastereomeric epoxy alcohol **24** (58.2 mg, 40%, dr

27:1) as a colorless oil. Data for **28**: $[\alpha]_D^{25}$ –5.4 (*c* 1.00, $CHCl_3$); IR (neat) 3444, 2956, 2928, 2857, 2359, 1472, 1254, 1101, 836, 775 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 5.45 (ddd, *J* = 15.1, 6.9, 6.9 Hz, 1H), 5.22 (br dd, *J* = 15.1, 8.2 Hz, 1H), 3.59 (dd, *J* = 6.4, 6.4 Hz, 2H), 3.47 (m, 1H), 2.75 (dd, *J* = 5.0, 2.3 Hz, 1H), 2.67 (dd, *J* = 7.3, 2.3 Hz, 1H), 2.39 (m, 1H), 2.06–2.01 (m, 2H), 1.77 (br d, *J* = 5.5 Hz, 1H), 1.61–1.51 (m, 4H), 1.37 (ddd, *J* = 14.2, 9.6, 3.2 Hz, 1H), 1.01 (d, *J* = 6.4 Hz, 3H), 1.00 (d, *J* = 6.4 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.3, 129.6, 69.5, 62.6, 62.0, 61.0, 41.6, 33.2, 32.7, 30.1, 28.7, 26.0 (3C), 21.8, 19.0, 18.34, 18.29, –5.3 (2C); HRMS (ESI) calcd for $C_{20}H_{40}O_3SiNa$ [$(M + Na)^+$] 379.2639; found 379.2622. Dada for **24**: $[\alpha]_D^{24}$ –21.3 (*c* 1.00, $CHCl_3$). The other spectroscopic data of **24** were identical to those described above.

*C1–C12 Segment (3R,4R,5R)-**5**.* To a solution of epoxy alcohol **28** (75.6 mg, 0.212 mmol) in CH_2Cl_2 (2 mL) at 0 °C were added Et_3N (0.090 mL, 0.65 mmol) and MsCl (0.030 mL, 0.39 mmol), and the resultant solution was stirred at 0 °C for 1 h. The reaction mixture was extracted with EtOAc, and the organic layer was washed sequentially 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 **9** (165.7 mg), which was used in the next reaction without further purification.

To a solution of the above mesylate **9** in *t*-BuOH/H_2O (1:1, v/v, 2 mL) were added $MeSO_2NH_2$ (21.6 mg, 0.227 mmol) and AD-mix-β (301.2 mg), and the resultant mixture was stirred at room temperature for 13 h. The reaction was quenched with saturated aqueous Na_2SO_3 solution, and the resultant mixture was stirred at room temperature for 1 h. The mixture was extracted with EtOAc, and the organic layer was washed with 1 M aqueous NaOH solution and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 6 to 20% EtOAc/hexanes) gave tetrahydrofuran **5** (67.9 mg, 86% for the two steps) as a colorless oil, along with recovered mesylate **9** (11.8 mg, 13% for the two steps) as a colorless oil. Data for **5**: $[\alpha]_D^{24}$ +9.5 (*c* 1.00, $CHCl_3$); IR (neat) 2956, 2929, 2857, 1463, 1384, 1254, 1098, 835, 774 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 3.93 (ddd, *J* = 9.7, 6.0, 4.2 Hz, 1H), 3.67–3.60 (m, 2H), 3.46 (m, 1H), 3.33 (dd, *J* = 8.3, 3.7 Hz, 1H), 2.83 (dd, *J* = 4.2, 2.3 Hz, 1H), 2.59 (dd, *J* = 6.8, 2.3 Hz, 1H), 2.41 (br d, *J* = 5.1 Hz, 1H), 2.20 (m, 1H), 2.15 (ddd, *J* = 11.5, 6.0, 5.4 Hz, 1H), 1.70 (m, 1H), 1.66–1.49 (m, 4H), 1.41 (ddd, *J* = 11.5, 10.0, 10.0, 1H), 1.05 (d, *J* = 6.4 Hz, 3H), 0.99 (d, *J* = 6.4 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 88.5, 77.7, 71.1, 63.1, 61.8, 58.7, 37.4, 35.1, 31.0, 30.0, 29.1, 25.9 (3C), 18.9, 18.4, 18.3, 17.0, −5.4 (2C); HRMS (ESI) calcd for $C_{20}H_{40}O_4SiNa$ $[(M + Na)^+]$ 395.2588; found 395.2581. Data for **9**: $[\alpha]_D^{24}$ −5.4 (*c* 1.00, $CHCl_3$); IR (neat) 2956, 2929, 2856, 1464, 1358, 1254, 1175, 1100, 977, 929, 836, 776 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 5.52 (ddd,

J = 15.6, 6.6, 6.6 Hz, 1H), 5.17 (dd, *J* = 15.6, 8.7 Hz, 1H), 4.28 (ddd, *J* = 9.4, 8.0, 3.4 Hz, 1H), 3.59 (dd, *J* = 6.4, 6.4 Hz, 2H), 3.14 (s, 3H), 2.93 (dd, *J* = 7.8, 1.9 Hz, 1H), 2.64 (dd, *J* = 7.0, 1.9 Hz, 1H), 2.36 (m, 1H), 2.07–2.00 (m, 2H), 1.80 (ddd, *J* = 14.2, 9.6, 4.5 Hz, 1H), 1.61–1.51 (m, 2H), 1.44 (ddd, *J* = 14.2, 10.1, 3.2 Hz, 1H), 1.02 (d, *J* = 6.4 Hz, 3H), 1.01 (d, *J* = 6.4 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 133.7, 131.1, 83.8, 62.5 (2C), 58.4, 39.4, 38.9, 32.7, 32.5, 30.2, 28.8, 26.0 (3C), 21.4, 18.9, 18.3, 18.2, −5.3 (2C); HRMS (ESI) calcd for $C_{21}H_{42}O_5SSiNa$ $[(M + Na)^+]$ 457.2414; found 457.2402.

*(S)-MTPA ester **29a**.* To a solution of alcohol **5** (3.8 mg, 10 μmol) in DCE (0.5 mL) at 0 °C were added Et_3N (20 μL, 0.14 mmol), a crystal of DMAP (ca. 1 mg), and one drop of (*R*)-MTPACl, and the resultant solution was stirred at room temperature for 12.5 h. The mixture was extracted with EtOAc, washed with saturated aqueous NH_4Cl solution and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 0 to 5% EtOAc/hexanes) gave (*S*)-MTPA ester **29a** (4.0 mg, 67%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.61–7.58 (m, 2H), 7.40–7.37 (m, 3H), 5.12 (ddd, *J* = 8.2, 4.6, 4.6 Hz, 1H), 3.72 (ddd, *J* = 9.6, 5.5, 4.5 Hz, 1H), 3.61 (ddd, *J* = 6.4, 6.4, 2.3 Hz, 2H), 3.55 (s, 3H), 3.54 (dd, *J* = 7.8, 4.6 Hz, 1H), 2.78 (dd, *J* = 4.5, 2.3 Hz, 1H), 2.49 (dd, *J* = 6.9, 2.3 Hz, 1H), 1.95 (ddd, *J* = 11.5, 6.0, 5.5 Hz, 1H), 1.88 (m, 1H), 1.81 (m, 1H), 1.76 (m, 1H), 1.61–1.49 (m, 3H), 1.34 (ddd, *J* = 11.5,

9.6, 9.6 Hz, 1H), 1.01 (d, *J* = 6.4 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); HRMS (ESI) calcd for $C_{30}H_{47}O_6F_3SiNa$ [(M + Na)$^+$] 611.2986; found 611.3006.

*(R)-MTPA ester **29b**.* To a solution of alcohol **5** (4.0 mg, 11 μmol) in DCE (0.5 mL) at 0 °C were added Et_3N (20 μL, 0.14 mmol), a crystal of DMAP (ca. 1 mg), and one drop of (*S*)-MTPACl, and the resultant solution was stirred at room temperature for 12 h. The mixture was extracted with EtOAc, washed with saturated aqueous NH_4Cl and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 0 to 5% EtOAc/hexanes) gave (*R*)-MTPA ester **29b** (3.9 mg, 62%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.63–7.60 (m, 2H), 7.40–7.36 (m, 3H), 5.12 (ddd, *J* = 9.2, 6.4, 3.7 Hz, 1H), 3.81 (ddd, *J* = 9.6, 5.9, 4.6 Hz, 1H), 3.50 (s, 3H), 3.58 (dd, *J* = 6.9, 6.4 Hz, 1H), 3.56–3.47 (m, 2H), 2.79 (dd, *J* = 4.6, 2.3 Hz, 1H), 2.53 (dd, *J* = 6.9, 2.3 Hz, 1H), 2.14 (ddd, *J* = 12.4, 7.8, 5.9 Hz, 1H), 2.02 (m, 1H), 1.72 (m, 1H), 1.59 (m, 1H), 1.52 (m, 1H), 1.43 (ddd, *J* = 12.4, 9.6, 9.6 Hz, 1H), 1.42–1.33 (m, 2H), 1.10 (d, *J* = 6.9 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H), 0.87 (s, 9H), 0.015 (s, 3H), 0.009 (s, 3H); HRMS (ESI) calcd for $C_{30}H_{47}O_6F_3SiNa$ [(M + Na)$^+$] 611.2986; found 611.2980.

*(S)-4-((tert-Butyldimethylsilyl)oxy)-1-((2R,3R,5R)-5-((2S,3S)-3-isopropyloxiran-2-yl)-3-methyltetrahydrofuran-2-yl)butyl 4-Nitrobenzoate (**32**).* To a solution of alcohol **4** (285.3 mg, 0.766 mmol) in THF (8 mL) at 0 °C were added PPh_3 (0.99 g, 3.8 mmol), *p*-nitrobenzoic acid (637.5 mg, 3.815 mmol), and DIAD (1.9 M solution in toluene, 2.0 mL, 3.8 mmol). The resultant solution was stirred at room temperature for 2 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, 3 to 4% EtOAc/hexanes) gave *p*-nitrobenzoate **32** (295.4 mg, 74%, dr >20:1) as a pale yellow oil: $[\alpha]_D^{25}$ –14.3 (*c* 1.00, $CHCl_3$); IR (neat) 2957, 2929, 2857, 2377, 2309, 1724, 1607, 1529, 1463, 1346, 1273, 1101, 1014, 835, 781, 774, 720 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 8.31–8.27 (m, 2H), 8.23–8.20 (m, 2H), 5.23 (ddd, *J* = 8.7, 5.0, 3.7 Hz, 1H), 3.86 (ddd, *J* = 10.5, 5.9, 4.6 Hz, 1H), 3.73 (dd, *J* = 7.8, 5.1 Hz, 1H), 3.66–3.58 (m, 2H), 2.77 (dd, *J* = 4.6, 2.3 Hz, 1H), 2.69 (dd, *J* = 6.9, 2.3 Hz, 1H), 2.28–2.19 (m, 2H), 1.92–1.79 (m, 2H), 1.66–1.51 (m, 4H), 1.12 (d, *J* = 6.4 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.87 (s, 9H), 0.024 (s, 3H), 0.020 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.3, 150.5, 135.7, 130.7 (2C), 123.6 (2C), 86.4, 78.4, 77.1, 62.5, 61.1, 59.0, 38.3, 36.6, 30.1, 28.6, 26.7, 25.9 (3C), 19.0, 18.33, 18.29, 17.9, –5.3 (2C); HRMS (ESI) calcd for $C_{27}H_{43}NO_7SiNa$ [$(M + Na)^+$] 544.2701; found 544.2704.

*C1–C12 Segment (3S,4S,5R,9S)-**30**.* To a solution of *p*-nitrobenzoate **32** (1.1311 g, 2.1680 mmol) in MeOH (20 mL) at 0 °C was added K_2CO_3 (453.5 mg, 3.281 mmol), and the resultant solution was stirred at room temperature for 1 h. The mixture was extracted with EtOAc, washed with saturated aqueous NH_4Cl solution and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 6 to 20% EtOAc/hexanes) gave alcohol **30** (0.7725 g, 96%, dr >20:1) as a colorless oil: $[\alpha]_D^{24}$ –17.2 (*c* 1.00, $CHCl_3$); IR (neat) 2956, 2928, 2857, 2367, 2324, 1716, 1698, 1541, 1507, 1457, 1257, 1097, 1034, 836, 768 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 3.81 (ddd, *J* = 9.6, 6.4, 5.0 Hz, 1H), 3.70 (m, 1H), 3.68–3.63 (m, 2H), 3.49 (dd, *J* = 8.2, 4.6 Hz, 1H), 2.77 (dd, *J* = 5.1, 2.3 Hz, 1H), 2.73 (d, *J* = 3.6 Hz, 1H), 2.66 (dd, *J* = 6.9, 2.3 Hz, 1H), 2.31 (m, 1H), 2.21 (ddd, *J* = 12.4, 7.3, 6.4 Hz, 1H), 1.74–1.59 (m, 3H), 1.55 (m, 1H), 1.51 (ddd, *J* = 12.4, 10.1, 9.6 Hz, 1H), 1.46 (m, 1H), 1.13 (d, *J* = 6.4 Hz, 3H), 1.01 (d, *J* = 6.4 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 88.5, 78.6, 72.9, 63.3, 61.1, 59.3, 38.8, 34.3, 30.1, 29.7, 29.4, 25.9 (3C), 19.0, 18.4, 18.3 (2C), –5.4 (2C); HRMS (ESI) calcd for $C_{20}H_{40}O_4SiNa$ [$(M + Na)^+$] 395.2588; found 395.2578.

(S)-4-((tert-Butyldimethylsilyl)oxy)-1-((2R,3R,5R)-5-((2R,3R)-3-isopropyloxiran-2-yl)-3-

*methyltetrahydrofuran-2-yl)butyl 4-Nitrobenzoate (**33**).* To a solution of alcohol **5** (46.7 mg, 0.125 mmol) in THF (1 mL) at 0 °C were added PPh_3 (162.3 mg, 0.6188 mmol), *p*-nitrobenzoic acid (102.6 mg, 0.6139 mmol), and DIAD (1.9 M solution in toluene, 0.30 mL, 0.57 mmol). The resultant solution was stirred at room temperature for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution. The resultant mixture was extracted EtOAc, and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 3 to 4% EtOAc/hexanes) gave *p*-nitrobenzoate **33** (48.6 mg, 75%, dr >20:1) as a colorless oil: $[\alpha]_D^{23}$ +3.7 (*c* 1.00, $CHCl_3$); IR (neat) 2958, 2929, 2857, 1724, 1530, 1471, 1463, 1346, 1273, 1101, 1013, 835, 776, 719 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 8.30–8.27 (m, 2H), 8.23–8.20 (m, 2H), 5.25 (ddd, *J* = 8.7, 4.6, 4.6 Hz, 1H), 3.91 (ddd, *J* = 9.2, 6.0, 4.1 Hz, 1H), 3.73 (dd, *J* = 8.3, 4.6 Hz, 1H), 3.66–3.58 (m, 2H), 2.84 (dd, *J* = 4.6, 2.3 Hz, 1H), 2.53 (dd, *J* = 6.4, 2.3 Hz, 1H), 2.25 (m, 1H), 2.16 (ddd, *J* = 11.9, 6.4, 6.0 Hz, 1H), 1.92–1.80 (m, 2H), 1.65–1.51 (m, 3H), 1.45 (ddd, *J* = 11.9, 9.6, 9.6 Hz, 1H), 1.12 (d, *J* = 6.4 Hz, 3H), 0.98 (d, *J* = 6.4 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.86 (s, 9H), 0.020 (s, 3H), 0.016 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.3, 150.6, 135.7, 130.7 (2C), 123.6 (2C), 86.2, 78.5, 77.0, 62.5, 61.9, 58.4, 37.1, 36.5, 30.0, 28.6, 26.6, 25.9 (3C), 18.8, 18.4, 18.3, 18.1, −5.3 (2C); HRMS (ESI) calcd for $C_{27}H_{43}NO_7SiNa$ [$(M + Na)^+$] 544.2701; found 544.2703.

*C1–C12 Segment (3R,4R,5R,9S)-**31.*** To a solution of *p*-nitrobenzoate **33** (41.0 mg, 0.0786 mmol) in MeOH (1 mL) at 0 °C was added K_2CO_3 (31.2 mg, 0.226 mmol), and the resultant solution was stirred at room temperature for 1 h. The mixture was extracted with EtOAc, and the organic layer was washed with saturated aqueous NH_4Cl solution and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 6 to 20% EtOAc/hexanes) gave alcohol **31** (27.1 mg, 92%, dr >20:1) as a colorless oil: $[\alpha]_D^{23}$ −1.0 (*c* 1.00, $CHCl_3$); IR (neat) 3464, 2957, 2929, 2857, 1471, 1462, 1386, 1254, 1097, 835, 776 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 3.95 (ddd, *J* = 9.2, 6.4, 4.1 Hz, 1H), 3.69 (m, 1H), 3.65 (dd, *J* = 5.7, 5.7 Hz, 2H), 3.46 (dd, *J* = 8.0, 4.4 Hz, 1H), 2.82 (dd, *J* = 4.1, 2.3 Hz, 1H), 2.76 (br s, 1H), 2.60 (dd, *J* = 6.8, 2.3 Hz, 1H), 2.30 (m, 1H), 2.18 (ddd, *J* = 11.9, 6.8, 6.4 Hz, 1H), 1.73–1.60 (m, 3H), 1.55 (m, 1H), 1.50–1.40 (m, 2H), 1.11 (d, *J* = 6.4 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 88.5, 77.7, 72.8, 63.3, 61.8, 58.9, 38.1, 34.3, 30.0, 29.7, 29.4, 25.9 (3C), 18.9, 18.46, 18.42, 18.3, −5.4 (2C); HRMS (ESI) calcd for $C_{20}H_{40}O_4SiNa$ [$(M + Na)^+$] 395.2588; found 395.2589.

*(S)-5-((2R,3R,5R)-5-((2S,3S)-3-Isopropyloxiran-2-yl)-3-methyltetrahydrofuran-2-yl)-2,2,3, 3,10,10,11,11-octamethyl-4,9-dioxa-3,10-disiladodecane (**38**).* To a solution of alcohol **30** (752.5 mg, 2.020 mmol) in DMF (20 mL) at 0 °C were added imidazole (693.5 mg, 10.19 mmol)

and TBSCl (768.2 mg, 5.097 mmol), and the resultant solution was stirred at 50 °C for 16.5 h. The reaction was quenched with saturated aqueous NH_4Cl solution. The mixture was extracted with *t*-BuOMe, and the organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 0 to 10% EtOAc/hexanes) gave bis-TBS ether **38** (960.3 mg, 98%) as a pale yellow oil: $[\alpha]_D^{23}$ −9.2 (*c* 1.00, $CHCl_3$); IR (neat) 2956, 2930, 2857, 2359, 2330, 2089, 1645, 1636, 1254, 1096, 835, 774 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 3.82 (ddd, *J* = 9.2, 6.0, 4.6 Hz, 1H), 3.76 (m, 1H), 3.62–3.55 (m, 2H), 3.52 (dd, *J* = 7.8, 3.6 Hz, 1H), 2.75 (dd, *J* = 4.6, 2.3 Hz, 1H), 2.67 (dd, *J* = 6.9, 2.3 Hz, 1H), 2.32 (m, 1H) 2.16 (ddd, *J* = 12.4, 7.3, 6.0 Hz, 1H), 1.61 (m, 1H), 1.57–1.43 (m, 5H), 1.10 (d, *J* = 6.4 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 18H), 0.05 (s, 6H), 0.03 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 88.0, 77.9, 73.9, 63.3, 61.0, 59.3, 38.8, 34.1, 30.3, 30.2, 28.8, 26.0 (3C), 25.9 (3C), 19.04, 18.96, 18.3 (2C), 18.1, –4.3, –4.5, –5.3 (2C); HRMS (ESI) calcd for $C_{26}H_{54}O_4Si_2Na$ [$(M + Na)^+$] 509.3453; found 509.3449.

*(S)-4-((tert-Butyldimethylsilyl)oxy)-4-((2R,3R,5R)-5-((2S,3S)-3-isopropyloxiran-2-yl)-3-methyltetrahydrofuran-2-yl)butan-1-ol (**39**).* To a solution of bis-TBS ether **38** (954.5 mg, 1.960 mmol) in CH_2Cl_2/MeOH (1:1, v/v, 20 mL) at 0 °C was added CSA (45.2 mg, 0.195 mmol), and the resultant solution was stirred at 0 °C for 55 min. The reaction was quenched with saturated aqueous

$NaHCO_3$ solution. The 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, 10 to 20% EtOAc/hexanes then EtOAc) gave alcohol **39** (569.6 mg, 78%) as a colorless oil, along with diol **40** (98.8 mg, 20%) as a colorless oil. Data for **39**: $[\alpha]_D^{23}$ –14.1 (*c* 1.00, $CHCl_3$); IR (neat) 3444, 2956, 2929, 2857, 2360, 2341, 1471, 1463, 1387, 1253, 1096, 1038, 836, 774 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 3.79 (ddd, *J* = 9.1, 6.0, 5.1 Hz, 1H), 3.75 (m, 1H), 3.67–3.59 (m, 2H), 3.54 (dd, *J* = 7.3, 4.6 Hz, 1H), 2.76 (dd, *J* = 5.1, 2.3 Hz, 1H), 2.66 (dd, *J* = 6.9, 2.3 Hz, 1H), 2.27 (m, 1H), 2.17 (ddd, *J* = 12.4, 7.8, 6.0 Hz, 1H), 1.73–1.48 (m, 6H), 1.47 (ddd, *J* = 12.4, 9.6, 9.6 Hz, 1H), 1.11 (d, *J* = 6.9 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 87.8, 78.1, 73.9, 63.1, 61.0, 59.3, 38.6, 34.9, 30.3, 30.2, 28.5, 25.9 (3C), 19.0, 18.9, 18.3, 18.1, –4.37, –4.43; HRMS (ESI) calcd for $C_{20}H_{40}O_4SiNa$ $[(M + Na)^+]$ 395.2588; found 395.2597. Data for **40**: $[\alpha]_D^{23}$ –23.1 (*c* 1.00, $CHCl_3$); IR (neat) 3397, 2957, 2929, 2871, 2360, 2341, 2328, 1716, 1646, 1541, 1507, 1457, 1040, 1015, 897 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 3.82 (ddd, *J* = 9.6, 6.0, 5.5 Hz, 1H), 3.78 (ddd, *J* = 10.1, 3.7, 2.7 Hz, 1H), 3.71 (m, 1H), 3.67 (m, 1H), 3.52 (dd, *J* = 8.2, 3.7 Hz, 1H), 2.78 (dd, *J* = 5.5, 2.3 Hz, 1H), 2.67 (dd, *J* = 6.9, 2.3 Hz, 1H), 2.59 (br, 1H), 2.37–2.25 (m, 2H), 2.23 (ddd, *J* = 11.9, 7.3, 6.0 Hz, 1H), 1.77–1.65 (m, 3H), 1.59–1.44 (m, 3H), 1.12 (d, *J* = 6.4 Hz, 3H), 1.01 (d, *J* = 6.4 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 88.6,

78.7, 72.9, 62.8, 61.2, 59.3, 38.9, 33.8, 30.1, 29.9, 29.4, 19.0, 18.31, 18.26; HRMS (ESI) calcd for $C_{14}H_{26}O_4Na$ [$(M + Na)^+$] 281.1723; found 281.1725.

*(S)-4-((tert-Butyldimethylsilyl)oxy)-4-((2R,3R,5R)-5-((2S,3S)-3-isopropyloxiran-2-yl)-3-methyltetrahydrofuran-2-yl)butanal (**36**).* To a solution of □□□□□□□ **39** (55.2 mg, 0.148 mmol) in CH_2Cl_2 (3 mL) at 0 °C were added $NaHCO_3$ (62.7 mg, 0.746 mmol) and Dess–Martin periodinane (94.6 mg, 0.223 mmol), and the resultant mixture was stirred at 0 °C for 70 min. The reaction was quenched with a 1:1 mixture of saturated aqueous $NaHCO_3$ solution and saturated aqueous Na_2SO_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. The residue was roughly purified by column chromatography (silica gel, 5 to 10% EtOAc/hexanes) to give □□□□□□□□ **36** (53.3 mg, 97%) as a colorless oil, which was used in the next reaction without further purification: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 9.77 (t, *J* = 1.4 Hz, 1H), 3.80 (ddd, *J* = 9.6, 6.0, 4.5 Hz, 1H), 3.74 (ddd, *J* = 6.4, 4.6, 4.6 Hz, 1H), 3.46 (dd, *J* = 7.4, 4.6 Hz, 1H), 2.76 (dd, *J* = 4.5, 2.3 Hz, 1H), 2.67 (dd, *J* = 6.9, 2.3 Hz, 1H), 2.59 (dddd, *J* = 17.4, 9.2, 6.0, 1.4 Hz, 1H), 2.51 (dddd, *J* = 17.4, 9.2, 6.0, 1.4 Hz, 1H), 2.25–2.15 (m, 2H), 1.89 (m, 1H), 1.78 (m, 1H), 1.54 (m, 1H), 1.48 (ddd, *J* = 11.5, 9.6, 9.2 Hz, 1H), 1.11 (d, *J* = 6.4 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.062 (s, 3H), 0.057 (s, 3H).

Methyl (3R,6S)-6-((tert-Butyldimethylsilyl)oxy)-3-hydroxy-6-((2R,3R,5R)-5-((2S,3S)-3-isopropyloxiran-2-yl)-3-methyltetrahydrofuran-2-yl)hexanoate ***(45).*** To a solution of diisopropylamine (0.16 mL, 1.1 mmol) in THF (2 mL) at –78 °C was added *n*-BuLi (2.66 M solution in hexane, 0.40 mL, 1.1 mmol), and the resultant solution was stirred at 0 °C for 30 min. To a suspension of (*S*)-(–)-2-hydroxy-1,2,2-triphenylethyl acetate ((*S*)-**43**) (101.7 mg, 0.306 mmol) in THF (1.5 mL) at –78 °C was added the above LDA solution (1.6 mL, 0.66 mmol). The resultant mixture was stirred at 0 °C for 30 min. The resultant clear pale yellow solution was cooled to –78 °C, and to this solution was added a solution of the above aldehyde **36** (53.3 mg, 0.144 mmol) in THF (1.2 mL + 0.6 mL and 0.3 mL rinse) dropwise. The resultant solution was stirred at –78 °C for 70 min. The reaction was quenched with saturated aqueous NH_4Cl solution, and the resultant mixture was stirred at room temperature for 10 min. The 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, 0 to 10 to 15 to 20% EtOAc/hexanes) gave β-hydroxy ester **44** (93.0 mg) as a colorless amorphous solid, which was contaminated with some impurities and used in the next reaction without further purification. The diastereomer ratio was determined at a later stage of the synthesis. Data for **44**: ^{1}H NMR ($CDCl_3$, 600 MHz, major diastereomer) δ 7.59–7.56 (m, 2H), 7.39–7.35 (m, 2H), 7.31–7.27

(m, 1H), 7.20–7.10 (m, 8H), 7.08–7.04 (m, 2H), 6.72 (s, 1H), 3.78 (m, 1H), 3.74 (ddd, *J* = 9.6, 6.4, 5.0 Hz, 1H), 3.67 (m, 1H), 3.47 (dd, *J* = 7.8, 4.6 Hz, 1H), 2.94 (s, 1H), 2.76 (dd, *J* = 5.0, 2.3 Hz, 1H), 2.66 (dd, *J* = 6.8, 2.3 Hz, 1H), 2.55 (br d, *J* = 3.2 Hz, 1H), 2.39 (dd, *J* = 16.0, 3.7 Hz, 1H), 2.34 (dd, *J* = 16.0, 9.2 Hz, 1H), 2.23 (m, 1H), 2.15 (ddd, *J* = 12.0, 7.4, 6.4 Hz, 1H), 1.58–1.42 (m, 5H), 1.37 (m, 1H), 1.09 (d, *J* = 6.4 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); HRMS (ESI) calcd for $C_{42}H_{58}O_7SiNa$ [$(M + Na)^+$] 725.3844; found 725.3845.

To a solution of the above ester **44** (93.0 mg, 0.132 mmol) in MeOH (2 mL) was added K_2CO_3 (9.1 mg, 0.066 mmol), and the resultant solution was stirred at room temperature for 2 h. The reaction was quenched with saturated aqueous NH_4Cl solution. The 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, 10 to 15 to 30% EtOAc/hexanes) gave m□□□□□□ester **45** (50.1 mg, 78% for the two steps, dr ca. 10:1) as a colorless oil: $[\alpha]_D^{24}$ –21.6 (*c* 1.00, $CHCl_3$); IR (neat) 3461, 2956, 2930, 2857, 2359, 2328, 1739, 1462, 1438, 1362, 1253, 1200, 1163, 1095, 1038, 1004, 900, 836, 775 cm^{-1}; ^1H NMR (C_6D_6, 600 MHz, major diastereomer) δ 3.85 (m, 1H), 3.82–3.77 (m, 2H), 3.59 (dd, *J* = 7.7, 4.1 Hz, 1H), 3.26 (s, 3H), 2.87 (br, 1H), 2.66–2.62 (m, 2H), 2.22 (dd, *J* = 16.0, 8.7 Hz, 1H), ca. 2.22 (m, 1H overlapped), 2.17 (dd, *J* = 16.0, 3.7 Hz, 1H), 1.87 (ddd, *J* = 11.9, 7.7, 6.4 Hz, 1H),

1.77–1.66 (m, 2H), 1.57–1.45 (m, 2H), 1.39 (m, 1H), 1.36 (ddd, J = 11.9, 9.2, 9.2 Hz, 1H), 1.05 (d, J = 6.4 Hz, 3H), 1.02 (s, 9H), 0.93 (d, J = 6.9 Hz, 3H), 0.79 (d, J = 6.9 Hz, 3H), 0.18 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.0, 88.1, 78.4, 74.6, 68.3, 60.6, 59.3, 51.0, 41.6, 39.0, 35.1, 32.7, 30.54, 30.50, 26.3 (3C), 19.2, 19.0, 18.4 (2C), –4.1, –4.2; HRMS (ESI) calcd for $C_{23}H_{44}O_6SiNa$ [$(M + Na)^+$] 467.2799; found 467.2794.

*(3R,6S)-6-((tert-Butyldimethylsilyl)oxy)-3-hydroxy-6-((2R,3R,5R)-5-((2S,3S)-3-isopropyloxiran-2-yl)-3-methyltetrahydrofuran-2-yl)-N-methoxy-N-methylhexanamide (**46**).*

To a suspension of MeNH(OMe)·HCl (39.2 mg, 0.402 mmol, azeotropically dried with toluene three times) in THF (2 mL) at –78 °C was added *n*-BuLi (2.66 M solution in hexane, 0.30 mL, 0.80 mmol), and the resultant solution was stirred at 0 °C for 20 min. To this solution at –78 °C was added a solution of methyl ester **45** (46.8 mg, 0.105 mmol) in THF (1 mL + 0.6 mL and 0.4 mL rinse). The resultant solution was stirred at –78 °C for 30 min. The reaction was quenched with saturated aqueous NH_4Cl solution. The mixture was extracted with EtOAc, and the organic layer was washed with 1 M aqueous HCl solution, 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, 20 to 50% EtOAc/hexanes) gave □□□□□□□□□□□□□ **46** (47.0 mg, 91%) as a colorless oil: $[\alpha]_D^{26}$ –29.3 (*c* 1.00, $CHCl_3$); IR (neat) 3464, 2957, 2930, 2857,

1646, 1463, 1387, 1254, 1178, 1096, 1038, 1000, 902, 836, 775 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz, major diastereomer) δ 3.96 (m, 1H), 3.83 (m, 1H), 3.80 (ddd, *J* = 9.6, 6.5, 4.6 Hz, 1H), 3.75 (m, 1H), 3.68 (s, 3H), 3.53 (dd, *J* = 7.6, 3.9 Hz, 1H), 3.18 (s, 3H), 2.75 (dd, *J* = 4.6, 2.3 Hz, 1H), 2.66 (dd, *J* = 6.9, 2.3 Hz, 1H), 2.65 (br d, *J* = 16.8 Hz, 1H), 2.45 (br dd, *J* = 16.8, 9.4 Hz, 1H), 2.28 (m, 1H), 2.16 (ddd, *J* = 11.9, 7.3, 6.5 Hz, 1H), 1.65 (m, 1H), 1.61–1.48 (m, 4H), 1.46 (ddd, *J* = 11.9, 9.6, 9.6 Hz, 1H), 1.10 (d, *J* = 6.9 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.8, 88.0, 78.0, 74.0, 68.3, 61.2, 61.0, 59.3, 38.6, 38.2, 34.5, 32.4, 31.8, 30.2, 29.8, 26.0 (3C), 19.0, 18.8, 18.3, 18.1, –4.37, –4.44; HRMS (ESI) calcd for $C_{24}H_{47}NO_6SiNa$ [$(M + Na)^+$] 496.3065; found 496.3060.

(4R,7S)-7-((tert-Butyldimethylsilyl)oxy)-4-hydroxy-7-((2R,3R,5R)-5-((2S,3S)-3-isopropyloxiran-2-yl)-3-methyltetrahydrofuran-2-yl)heptan-2-one ***(47).*** To a solution of Weinreb amide **46** (44.0 mg, 0.0891 mmol) in THF (3 mL) at –78 °C was added MeLi (1.08 M solution in Et_2O, 0.25 mL, 0.27 mmol). The resultant solution was stirred at –78 °C for 1.5 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 to 20 to 30% EtOAc/hexanes) gave methyl ketone **47** (33.8 mg, 89%, dr ca. 10:1) as

a colorless oil: $[\alpha]_D^{25}$ –27.0 (*c* 1.00, $CHCl_3$); IR (neat) 3470, 2957, 2930 , 2857, 1712, 1463, 1361, 1253, 1094, 1040, 902, 836, 775 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz, major diastereomer) δ 3.98 (m, 1H), 3.78 (ddd, *J* = 9.1, 5.9, 5.0 Hz, 1H), 3.73 (m, 1H), 3.51 (dd, *J* = 7.8, 4.3 Hz, 1H), 3.11 (br d, *J* = 3.2 Hz, 1H), 2.75 (dd, *J* = 5.1, 2.3 Hz, 1H), 2.65 (dd, *J* = 7.3, 2.3 Hz, 1H), 2.61 (dd, *J* = 17.4, 2.8 Hz, 1H), 2.53 (dd, *J* = 17.4, 9.2 Hz, 1H), 2.25 (m, 1H), 2.17 (s, 3H), 2.16 (m, 1H), 1.66–1.43 (m, 6H), 1.10 (d, *J* = 6.9 Hz, 3H), 1.00 (d, *J* = 6.4 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.9, 87.8, 78.1, 74.0, 67.9, 61.0, 59.3, 50.1, 38.6, 34.9, 32.2, 30.7, 30.2, 29.8, 25.9 (3C), 19.0, 18.8, 18.3, 18.1, –4.37, –4.41; HRMS (ESI) calcd for $C_{23}H_{44}O_5SiNa$ [$(M + Na)^+$] 451.2850; found 451.2831.

*(S)-MTPA ester **48a**.* To a solution of alcohol **47** (1.9 mg, 4.4 μmol) in DCE (0.5 mL) at 0 °C were added Et_3N (0.020 mL, 0.14 mmol), a crystal of DMAP (ca. 1 mg), and one drop of (*R*)-MTPACl, and the resultant solution was stirred at room temperature for 13.5 h. The reaction was quenched with saturated aqueous NH_4Cl solution. The mixture was extracted with EtOAc, and the organic layer was washed with saturated aqueous NH_4Cl solution and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, first round: 0 to 5 to 15% EtOAc/hexanes; second round: 0 to 10 to 15% EtOAc/hexanes) gave (*S*)-MTPA ester **48a** (2.7 mg, 94%) as a colorless oil: ^1H NMR ($CDCl_3$,

600 MHz) δ 7.51–7.48 (m, 2H), 7.40–7.37 (m, 3H), 5.48 (m, 1H), 3.78 (m, 1H), 3.69 (m, 1H), 3.52 (br s, 3H), 3.44 (dd, *J* = 7.3, 4.1 Hz, 1H), 2.80 (dd, *J* = 16.9, 8.2 Hz, 1H), 2.75 (dd, *J* = 5.1, 2.3 Hz, 1H), 2.66 (dd, *J* = 6.9, 2.3 Hz, 1H), 2.59 (dd, *J* = 16.9, 4.5 Hz, 1H), 2.22–2.13 (m, 2H), 2.04 (s, 3H), 1.84 (m, 1H), 1.70 (m, 1H), 1.60–1.43 (m, 4H), 1.07 (d, *J* = 6.4 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); HRMS (ESI) calcd for $C_{33}H_{51}O_7F_3SiNa$ [$(M + Na)^+$] 667.3248; found 667.3248.

*(R)-MTPA ester **48b**.* To a solution of alcohol **47** (2.0 mg, 4.7 μmol) in DCE (0.5 mL) at 0 °C were added Et_3N (0.020 mL, 0.14 mmol), a crystal of DMAP (ca. 1 mg), and one drop of (*S*)-MTPACl, and the resultant solution was stirred at room temperature for 13 h. The reaction was quenched with saturated aqueous NH_4Cl solution. The 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, 0 to 5 to 15% EtOAc/hexanes) gave (*R*)-MTPA ester **48b** (2.8 mg, 93%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.50–7.47 (m, 2H), 7.40–7.37 (m, 3H), 5.45 (m, 1H), 3.78 (m, 1H), 3.64 (ddd, *J* = 6.8, 4.6, 4.6 Hz, 1H), 3.50 (s, 3H), 3.40 (dd, *J* = 7.3, 4.6 Hz, 1H), 2.85 (dd, *J* = 17.0, 8.3 Hz, 1H), 2.73 (dd, *J* = 4.6, 2.3 Hz, 1H), 2.66 (dd, *J* = 6.9, 2.3 Hz, 1H), 2.65 (dd, *J* = 17.0, 4.1 Hz, 1H), 2.19–2.11 (m, 5H), 1.76 (m, 1H), 1.64 (m, 1H), 1.54 (m, 1H), 1.50–1.42 (m, 2H), 1.36 (m, 1H), 1.04 (d, *J* = 6.0

Hz, 3H), 1.00 (d, J = 6.4 Hz, 3H), 0.94 (d, J = 6.9 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 3H), –0.001 (s, 3H); HRMS (ESI) calcd for $C_{33}H_{51}O_7F_3SiNa$ [$(M + Na)^+$] 667.3248; found 667.3247.

*C1–C15 Segment (9S,12R)-**34.*** To a solution of methyl ketone **47** (30.7 mg, 71.6 μmol) in DMF (3 mL) and H_2O (12 μL) at 0 °C was added TASF (59.4 mg, 0.216 mmol), and the resultant solution was stirred at 0 °C for 15 h 45 min. The reaction was quenched with saturated aqueous $NaHCO_3$ solution. The 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, 40 to 80% EtOAc/hexanes) gave diol **34** (21.8 mg), which was contaminated with some impurities. Further purification by reverse-phase HPLC (COSMOSIL 5C_{18}-AR-II, 20 mm I.D. × 250 mm; UV detection: 210 nm, eluent: 65% MeCN/H_2O; flow rate: 8.0 mL/min; t_R = 19.0 min) gave **34** (19.2 mg, 85%) as a colorless amorphous solid: $[\alpha]_D^{23}$ –43.4 (*c* 1.00, $CHCl_3$); IR (neat) 3328, 3238, 2961, 2905, 1707, 1453, 1358, 1254, 1171, 1041, 984, 901 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 4.09 (m, 1H), 3.79 (ddd, J = 9.7, 6.2, 5.5 Hz, 1H), 3.72 (m, 1H), 3.50 (dd, J = 8.3, 4.1 Hz, 1H), 3.39 (br, 1H), 2.77 (dd, J = 4.8, 2.8 Hz, 1H), 2.66 (br, 1H), 2.65 (dd, J = 6.8, 2.8 Hz, 1H), 2.64–2.56 (m, 2H), 2.30 (m, 1H), 2.21 (ddd, J = 12.4, 6.2, 6.2 Hz, 1H), 2.18 (s, 3H), 1.75–1.64 (m, 2H), 1.58–1.45 (m, 4H), 1.12 (d, J = 6.9 Hz, 3H), 1.01 (d, J = 6.9 Hz, 3H), 0.94 (d, J = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ

209.9, 88.5, 78.8, 73.0, 67.5, 61.1, 59.3, 49.9, 38.9, 34.2, 33.2, 30.7, 30.1, 28.4, 19.0, 18.3 (2C); HRMS (ESI) calcd for $C_{17}H_{30}O_5Na$ [$(M + Na)^+$] 337.1985; found 337.1985.

*Methyl (3S,6S)-6-((tert-Butyldimethylsilyl)oxy)-3-hydroxy-6-((2R,3R,5R)-5-((2S,3S)-3-isopropyloxiran-2-yl)-3-methyltetrahydrofuran-2-yl)hexanoate (**50**).* To a solution of diisopropylamine (0.16 mL, 1.1 mmol) in THF (2 mL) at –78 °C was added *n*-BuLi (2.66 M solution in hexane, 0.40 mL, 1.1 mmol), and the resultant solution was stirred at 0 °C for 30 min. To a suspension of (*R*)-(+)-2-hydroxy-1,2,2-triphenylethyl acetate ((*R*)-**43**) (106.5 mg, 0.3204 mmol) in THF (1.5 mL) at –78 °C was added the above LDA solution (1.7 mL, 0.71 mmol). The resultant mixture was stirred at 0 °C for 30 min. The resultant clear solution was cooled to –78 °C, and to this solution was added a solution of aldehyde **36** (59.4 mg, 0.159 mmol) in THF (1.2 mL + 0.5 mL and 0.3 mL rinse) dropwise. The resultant solution was stirred at –78 °C for 3 h 25 min. The reaction was quenched with saturated aqueous NH_4Cl solution. The 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, 0 to 15 to 20% EtOAc/hexanes) gave β-hydroxy ester **49** (87.4 mg) as a colorless amorphous solid, which was contaminated with some impurities and used in the next reaction without further purification: ^{1}H NMR ($CDCl_3$, 600 MHz, major diastereomer) δ 7.59–7.56 (m, 2H),

7.39–7.35 (m, 2H), 7.30–7.27 (m, 1H), 7.20–7.10 (m, 8H), 7.08–7.04 (m, 2H), 6.72 (s, 1H), 3.82 (m, 1H), 3.79 (ddd, *J* = 9.2, 6.0, 5.0 Hz, 1H), 3.68 (m, 1H), 3.46 (dd, *J* = 7.8, 4.1 Hz, 1H), 2.94 (m, 1H), 2.76 (dd, *J* = 4.6, 2.3 Hz, 1H), 2.66 (dd, *J* = 6.8, 2.3 Hz, 1H), 2.46 (br, 1H), 2.43–2.31 (m, 2H), 2.25 (m, 1H), 2.16 (ddd, *J* = 11.9, 7.3, 5.9 Hz, 1H), 1.63–1.34 (m, 6H), 1.09 (d, *J* = 6.4 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.006 (s, 3H); HRMS (ESI) calcd for $C_{42}H_{58}O_7SiNa$ [$(M + Na)^+$] 725.3844; found 725.3844.

To a solution of the above ester **49** (87.4 mg, 0.124 mmol) in MeOH (4 mL) was added K_2CO_3 (8.9 mg, 0.064 mmol), and the resultant solution was stirred at room temperature for 1.5 h. The reaction was quenched with saturated aqueous NH_4Cl solution. The 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, first round: 10 to 15 to 20% EtOAc/hexanes; second round: 5 to 10 to 15% Et_2O/benzene) gave m□□□□□□ester **50** (45.0 mg, 64% for the two steps) as a colorless oil. The diastereomer ratio was determined at a later stage of the synthesis. Data for **50**: $[\alpha]_D^{26}$ –5.8 (*c* 1.00, $CHCl_3$); IR (neat) 3478, 2956, 2930, 2857, 2343, 1739, 1458, 1362, 1252, 1163, 1096, 1038, 1006, 901, 836, 775 cm^{-1}; ^1H NMR (C_6D_6, 600 MHz, major diastereomer) δ 3.92 (m, 1H), 3.83–3.78 (m, 2H), 3.57 (dd, *J* = 7.8, 4.2 Hz, 1H), 3.26 (s, 3H), 2.81 (br, 1H), 2.67 (dd, *J* = 6.9, 2.3 Hz, 1H), 2.63 (dd, *J* = 4.6, 2.3 Hz, 1H), 2.26 (dd, *J* = 16.1, 8.7 Hz, 1H), 2.23 (m, 1H), 2.20 (dd, *J* = 16.1, 3.7 Hz, 1H),

1.91–1.82 (m, 2H), 1.63 (m, 1H), 1.50 (m, 1H), 1.47–1.34 (m, 3H), 1.03 (d, J = 6.9 Hz, 3H), 1.01 (s, 9H), 0.94 (d, J = 6.9 Hz, 3H), 0.79 (d, J = 6.9 Hz, 3H), 0.17 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.3, 88.0, 78.0, 73.8, 68.0, 61.1, 59.3, 51.7, 41.1, 38.6, 34.7, 32.0, 30.2, 29.6, 26.0 (3C), 19.0, 18.9, 18.3, 18.1, –4.3, –4.4; HRMS (ESI) calcd for $C_{23}H_{44}O_6SiNa$ [(M + Na)$^+$] 467.2799; found 467.2797.

*(3S,6S)-6-((tert-Butyldimethylsilyl)oxy)-3-hydroxy-6-((2R,3R,5R)-5-((2S,3S)-3-isopropyloxiran-2-yl)-3-methyltetrahydrofuran-2-yl)-N-methoxy-N-methylhexanamide (**51**).*

To a suspension of MeNH(OMe)·HCl (32.5 mg, 0.333 mmol, azeotropically dried with toluene three times) in THF (2 mL) at –78 °C was added *n*-BuLi (2.66 M solution in hexane, 0.25 mL, 0.66 mmol), and the resultant solution was stirred at 0 °C for 20 min. To this solution at –78 °C was added a solution of methyl ester **50** (42.7 mg, 0.0960 mmol) in THF (1 mL + 0.6 mL and 0.4 mL rinse). The resultant solution was stirred at –78 °C for 1.5 h. The reaction was quenched with saturated aqueous NH_4Cl solution. The mixture was extracted with EtOAc, and the organic layer was washed with 1 M aqueous HCl solution, 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 50% EtOAc/hexanes) gave □□□□□□□□□□□□□ **51** (46.9 mg, 99%) as a colorless oil: $[\alpha]_D^{26}$ +1.3 (*c* 1.00, $CHCl_3$); IR (neat) 3466, 2956, 2929, 2856,

1643, 1463, 1387, 1253, 1178, 1096, 1038, 1000, 937, 902, 836, 774 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz, major diastereomer) δ 4.00 (m, 1H), 3.81 (ddd, *J* = 9.2, 5.9, 5.1 Hz, 1H), 3.79–3.74 (m, 2H), 3.68 (s, 3H), 3.52 (dd, *J* = 7.8, 4.1 Hz, 1H), 3.19 (s, 3H), 2.75 (dd, *J* = 4.6, 2.3 Hz, 1H), 2.67 (dd, *J* = 6.9, 2.3 Hz, 1H), 2.64 (br d, *J* = 16.5 Hz, 1H), 2.46 (br dd, *J* = 16.5, 9.6 Hz, 1H), 2.29 (m, 1H), 2.16 (ddd, *J* = 12.4, 7.3, 5.9 Hz, 1H), 1.74–1.62 (m, 2H), 1.57–1.43 (m, 4H), 1.10 (d, *J* = 6.4 Hz, 3H), 1.00 (d, *J* = 6.4 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.8, 88.2, 77.9, 73.8, 67.8, 61.2, 61.0, 59.3, 38.6, 38.0, 34.4, 32.1, 31.8, 30.2, 29.5, 26.0 (3C), 19.0, 18.8, 18.3, 18.1, –4.3, –4.4; HRMS (ESI) calcd for $C_{24}H_{47}NO_6SiNa$ [$(M + Na)^+$] 496.3065; found 496.3067.

(4S,7S)-7-((tert-Butyldimethylsilyl)oxy)-4-hydroxy-7-((2R,3R,5R)-5-((2S,3S)-3-isopropyloxiran-2-yl)-3-methyltetrahydrofuran-2-yl)heptan-2-one (***52***)**.** To a solution of Weinreb amide **51** (44.3 mg, 89.7 μmol) in THF (3 mL) at –78 °C was added MeLi (1.08 M solution in Et_2O, 0.25 mL, 0.27 mmol). The resultant solution was stirred at –78 °C for 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution. The 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, 20 to 30% EtOAc/hexanes) gave methyl ketone **52** (37.6 mg, 98%, dr ca. 7:1) as a colorless

oil: $[\alpha]_D^{25}$ –1.8 (*c* 1.00, $CHCl_3$); IR (neat) 3476, 2957, 2929, 2857, 2361, 2336, 1712, 1463, 1361, 1253, 1094, 1038, 902, 836, 775 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz, major diastereomer) δ 4.02 (m, 1H), 3.79 (ddd, *J* = 9.2, 6.0, 5.0 Hz, 1H), 3.73 (ddd, *J* = 6.4, 4.6, 4.2 Hz, 1H), 3.49 (dd, *J* = 7.8, 4.2 Hz, 1H), 2.99 (br d, *J* = 2.7 Hz, 1H), 2.75 (dd, *J* = 5.0, 2.3 Hz, 1H), 2.66 (dd, *J* = 7.3, 2.3 Hz, 1H), 2.59 (dd, *J* = 17.4, 2.7 Hz, 1H), 2.54 (dd, *J* = 17.4, 9.2 Hz, 1H), 2.26 (m, 1H), 2.17 (s, 3H), 2.16 (m, 1H), 1.70–1.55 (m, 2H), 1.53 (m, 1H), 1.50–1.41 (m, 3H), 1.10 (d, *J* = 6.9 Hz, 3H), 0.99 (d, *J* = 6.4 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 9H), 0.044 (s, 3H), 0.039 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.8, 88.0, 78.0, 73.8, 67.5, 61.0, 59.3, 49.9, 38.6, 34.7, 31.9, 30.7, 30.2, 29.5, 25.9 (3C), 19.0, 18.9, 18.3, 18.1, –4.3, –4.4; HRMS (ESI) calcd for $C_{23}H_{44}O_5SiNa$ $[(M + Na)^+]$ 451.2850; found 451.2843.

(S)-MTPA ester ***53a.*** To a solution of alcohol **52** (2.0 mg, 4.7 μmol) in DCE (0.5 mL) at 0 °C were added Et_3N (0.020 □L, 0.14 mmol), a crystal of DMAP (ca. 1 mg), and one drop of (*R*)-MTPACl, and the resultant solution was stirred at room temperature for 40 min. 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, 10% EtOAc/hexanes) gave (*S*)-MTPA ester **53a** (3.0 mg, quantitative) as a colorless oil: ^1H

NMR ($CDCl_3$, 600 MHz) δ 7.51–7.48 (m, 2H), 7.41–7.37 (m, 3H), 5.51 (m, 1H), 3.78 (m, 1H), 3.65 (m, 1H), 3.49 (s, 3H), 3.40 (dd, *J* = 7.4, 4.1 Hz, 1H), 2.86 (dd, *J* = 17.4, 8.3 Hz, 1H), 2.74 (dd, *J* = 4.6, 2.3 Hz, 1H), 2.67 (dd, *J* = 6.9, 2.3 Hz, 1H), 2.63 (dd, *J* = 17.4, 4.6 Hz, 1H), 2.14 (m, 1H), 2.13 (s, 3H), 1.80 (m, 1H), 1.68–1.42 (m, 5H), 1.30 (m, 1H), 1.05 (d, *J* = 5.9 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.4 Hz, 3H), 0.86 (s, 9H), 0.04 (s, 3H), 0.01 (s, 3H); HRMS (ESI) calcd for $C_{33}H_{51}O_7F_3SiNa$ [$(M + Na)^+$] 667.3248; found 667.3248.

*(R)-MTPA ester **53b**.* To a solution of alcohol **52** (1.9 mg, 4.4 μmol) in DCE (0.5 mL) at 0 °C were added Et_3N (0.020 □L, 0.14 mmol), a crystal of DMAP (ca. 1 mg), and one drop of (*S*)-MTPACl, and the resultant solution was stirred at room temperature for 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, first round: 10% EtOAc/hexanes; second round: 8% to 10% EtOAc/hexanes) gave (*R*)-MTPA ester **53b** (2.0 mg, 70%) as a colorless oil: ^1H NMR ($CDCl_3$, 600 MHz) δ 7.53–7.50 (m, 2H), 7.40–7.37 (m, 3H), 5.52 (m, 1H), 3.79 (m, 1H), 3.71 (ddd, *J* = 6.9, 4.2, 4.1 Hz, 1H), 3.54 (s, 3H), 3.44 (dd, *J* = 7.3, 4.1 Hz, 1H), 2.80 (dd, *J* = 16.9, 7.8 Hz, 1H), 2.74 (dd, *J* = 4.6, 2.3 Hz, 1H), 2.66 (dd, *J* = 6.8, 2.3 Hz, 1H), 2.58 (dd, *J* = 16.9, 5.1 Hz, 1H), 2.21–2.14 (m, 2H), 2.03 (s, 3H), 1.86 (m,

1H), 1.68 (m, 1H), 1.65–1.40 (m, 4H), 1.06 (d, J = 6.0 Hz, 3H), 1.00 (d, J = 6.9 Hz, 3H), 0.93 (d, J = 6.9 Hz, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); HRMS (ESI) calcd for $C_{33}H_{51}O_7F_3SiNa$ [(M + Na)$^+$] 667.3248; found 667.3248.

*C1–C15 Segment (9S,12S)-**35.*** To a solution of methyl ketone **52** (17.6 mg, 41.1 μmol) in THF (2 mL) at 0 °C was added TBAF (1.0 M solution in THF, 0.10 mL, 0.10 mmol), and the resultant solution was stirred at room temperature for 25 min. The reaction was quenched with saturated aqueous $NaHCO_3$ solution. The 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, 50 to 80% EtOAc/hexanes) gave diol **35** (14.0 mg), which was contaminated with some impurities. Further purification by reverse-phase HPLC (COSMOSIL 5C_{18}-AR-II, 20 mm I.D. × 250 mm; UV detection: 210 nm, eluent: 75% MeCN/H_2O; flow rate: 8.0 mL/min; t_R = 11.0 min) gave **35** (10.9 mg, 84%) as a colorless amorphous solid: $[\alpha]_D^{23}$ –6.3 (*c* 1.00, $CHCl_3$); IR (neat) 3257, 2960, 2939, 2871, 1710, 1458, 1364, 1094, 1034, 976, 901 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 4.07 (m, 1H), 3.79 (ddd, J = 9.3, 6.0, 5.3 Hz, 1H), 3.69 (ddd, J = 9.8, 4.2, 2.6 Hz, 1H), ca. 3.69 (m, 1H overlapped), 3.48 (dd, J = 8.1, 4.2 Hz, 1H), 2.99 (br, 1H), 2.76 (dd, J = 5.3, 2.3 Hz, 1H), 2.65 (dd, J = 6.9, 2.3 Hz, 1H), 2.63–2.55 (m, 2H), 2.30 (m, 1H), 2.20 (ddd, J = 12.1, 7.5, 6.0 Hz, 1H), 2.17 (s, 3H), 1.72 (m, 1H),

1.61 (m, 2H), 1.58–1.46 (m, 3H), 1.12 (d, J = 6.4 Hz, 3H), 1.00 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.8, 88.6, 78.7, 73.1, 67.7, 61.1, 59.3, 50.1, 38.8, 34.3, 33.6, 30.7, 30.1, 29.1, 19.0, 18.34, 18.30; HRMS (ESI) calcd for $C_{17}H_{30}O_5Na$ $[(M + Na)^+]$ 337.1985; found 337.1985.

ACCOSIATED CONTENTS

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.XXXX.

Comparison of the NMR data of model compounds **4**, **5**, **30**, **31**, **34**, **35**, and amphirionin-5, and ^{1}H and ^{13}C NMR spectra for all new compounds (PDF).

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We thank Professor Hiroyuki Isobe (The University of Tokyo, Tohoku University, ERATO JST) and Dr. Midori Oinuma (Tohoku University, ERATO JST) for NMR measurements, Professor Haruhiko Fuwa (Tohoku University) and Dr. Kotaro Iwasaki (Tohoku University) for helpful discussions. This work was financially supported in part by JSPS KAKENHI Grant Numbers JP16K13082, JP16H01126 in Middle Molecular Strategy, JP23102016,[42] and JP25282228.

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