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Progress toward the Total Synthesis of Goniodomin A: Stereocontrolled, Convergent Synthesis of the C12−C36 Fragment

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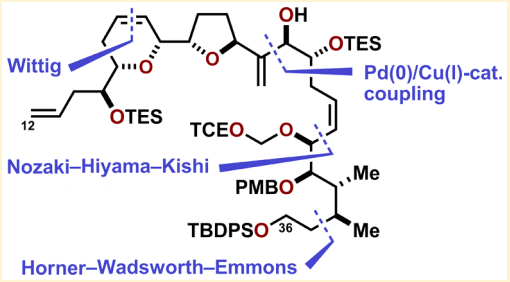
Supporting Information

ABSTRACT: Goniodomin A is a marine polyether macrolide natural product isolated from the dinoflagellate *Alexandrium hiranoi*. In this paper, we report stereocontrolled, convergent synthesis of a fully functionalized C12−C36 fragment of goniodomin A. The synthesis of the C12−C25 vinylstannane involved a Wittig reaction and a reductive cycloetherification for the construction of the dihydropyran ring. The C26−C36 thioester was synthesized via a Nozaki−Hiyama−Kishi reaction of an aldehyde and an iodoalkyne, the former of which was easily prepared from (*R*)-malic acid as a chiral source by taking advantage of substrate-controlled diastereoselective reactions. Finally, a palladium-catalyzed coupling of the C12−C25 vinylstannane and the C26−C36 thioester completed the synthesis of the target compound.



INTRODUCTION

Goniodomin A (**1**, Figure 1) is a marine polyether macrolide originally isolated from the dinoflagellate *Alexandrium hiranoi*

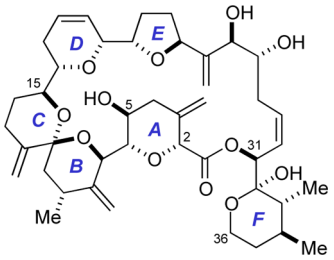


Figure 1. Structure of goniodomin A (**1**).

as an antifungal substance by Murakami and colleagues.[1] A subsequent report by Moeller et al. described the isolation of **1** from the dinoflagellate *Alexandrium monilatium* as a cytotoxic agent.[2] On the basis of NMR analyses, Murakami et al. have determined the gross structure of **1**, characterized by a 32-membered macrolactone containing an array of five- and six-membered cyclic ethers.[1] More recently, we have assigned the absolute configuration of **1** through detailed conformational analyses based on ROESY correlations, degradation/derivatization experiments, and syntheses and NMR analyses of model compounds.[3] Goniodomin A (**1**) is known to target the actin cytoskeleton of eukaryotic cells. Previous work has demonstrated that **1** upregulates actomyosin ATPase activity by altering the conformation of actin,[4−6] increases filamentous actin content of human astrocytoma cells,[7] and inhibits angiogenesis partly through inhibition of actin reorganization of endothelial cells.[8]

As part of our studies toward the total synthesis of **1**, we have reported the synthesis of the C1−C15[9] and C15−C36[10] fragments.[11] Our previous synthesis of the C15−C36 fragment **2** featured palladium-catalyzed coupling[12,13] of the C15−C25 vinylstannane **3** and the C26−C36 thioester **4** (Scheme 1). The C15−C25 vinylstannane **3** was synthesized in 24 linear steps including a 2-fold application of domino Sharpless asymmetric epoxidation/*exo* cyclization (i.e., **5** to **6** and **7** to **8**). The C26−C36 thioester **4** was prepared in 23 steps, in which Carreira asymmetric alkynylation[14] of the aldehyde **9** with the terminal alkyne **10** was utilized as the key transformation. However, we were unable to produce sufficient quantities of the key intermediates **3** and **4** mainly because of the lack of synthetic efficiency and low material throughput. To address this problem, we now report stereocontrolled, convergent synthesis of the fully elaborated C12−C36 fragment **12** (Figure 2).

RESULTS AND DISCUSSION

Synthesis Plan. We planned to synthesize the target compound **12** from the C12−C25 vinylstannane **13** and the C26−C36 thioester **14** via a Pd(0)/Cu(I)-catalyzed coupling[12,13] (Scheme 2). It was envisioned that the 2,6-*cis*-substituted dihydropyran ring of **13** would be rapidly constructed via a Wittig reaction of the phosphonium salt **15** and the aldehyde **16**, followed by a reductive cycloetherification. The 2,5-*trans*-substituted tetrahydrofuran ring of **16** would be accessible from the allylic alcohol **17** by exploiting a domino Sharpless asymmetric epoxidation/5-*exo* cyclization reaction. Meanwhile, it was envisaged that **14** would be available via a Nozaki−Hiyama−Kishi (NHK) reaction[15] of the

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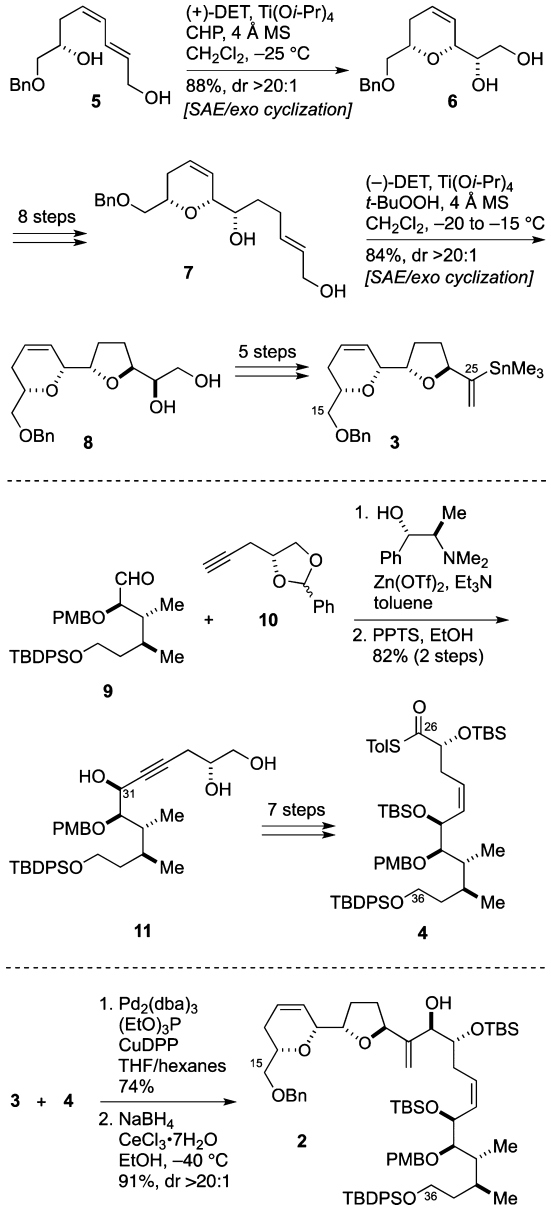
Scheme 1. Previous Synthesis of the C15−C36 Fragment 2[a]



[a]Abbreviations: CHP = cumene hydroperoxide, dba = dibenzylideneacetone, DPP = diphenylphosphinate, MS = molecular sieves, PPTS = pyridinium *p*-toluenesulfonate, TBDPS = *tert*-butyldiphenylsilyl, Tol = *p*-tolyl.

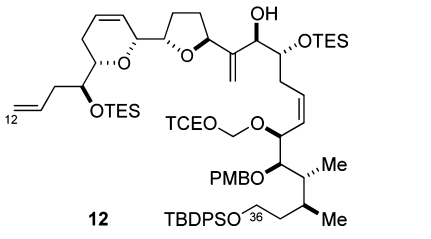
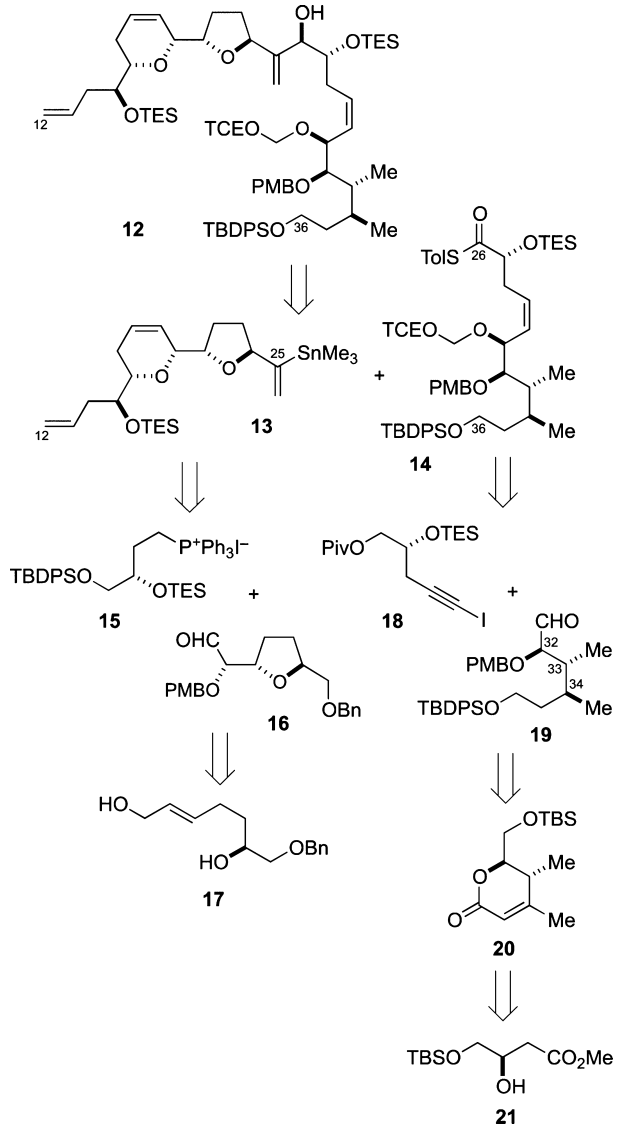


Figure 2. Structure of the C12−C36 fragment **12**. TCE = 2,2,2-trichloroethyl, TES = triethylsilyl.

iodoalkyne **18** and the aldehyde **19**.[16] We planned to utilize commercially available (*R*)-malic acid as the source of the C32 stereogenic center and to introduce the C33 and C34 stereogenic centers by taking advantage of substrate-controlled

Scheme 2. Synthesis Plan toward 12



stereoselective reactions. Thus, the aldehyde **19** was traced back to the α,β-unsaturated lactone **20** via a stereoselective hydrogenation. The latter would be obtainable from the alcohol **21** by considering a Fráter−Seebach alkylation[17] and an intramolecular Horner−Wadsworth−Emmons (HWE) reaction.

Synthesis of the C12−C25 Vinylstannane 13. The synthesis of **13** commenced with known alcohol **22**,[18] prepared in one step from commercially available benzyl (*S*)-glycidyl ether (Scheme 3). Olefin cross-metathesis[19] of **22** with methyl acrylate under the influence of the second-generation Grubbs catalyst (**G-II**)[20] delivered the α,β-unsaturated ester **23** (68%, *E*/*Z* 17:1). DIBALH reduction of **23** led to the allylic alcohol **17** in 89% yield. Sharpless asymmetric epoxidation of **17** using (−)-DET as a chiral ligand and spontaneous 5-*exo* cyclization of the derived epoxy diol provided the 2,5-*trans*-substituted tetrahydrofuran **24** in 82% yield as a single stereoisomer (dr >20:1) after purification by flash column chromatography using silica gel. In the present case, cumene hydroperoxide was found to be superior oxidant to *tert*-butyl hydroperoxide. The relative configuration of **24** was established on the basis of NOE experiments, as shown. Next, a three-step protecting group

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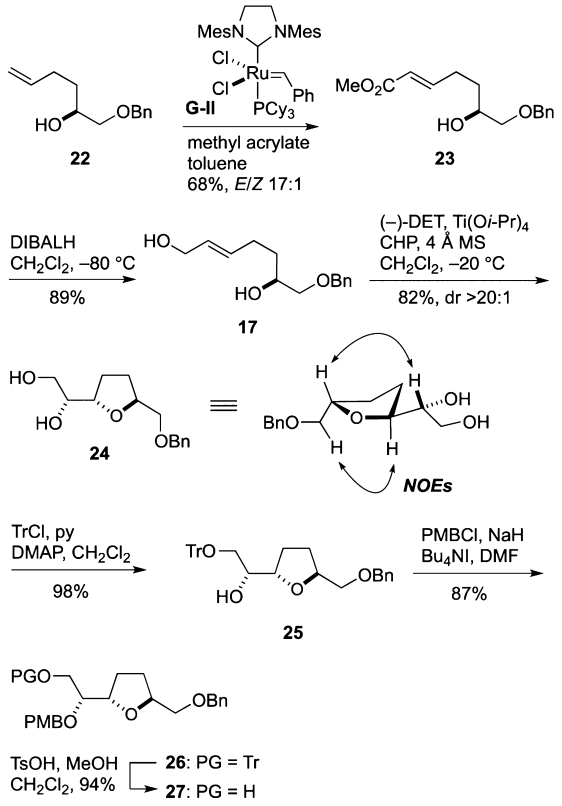
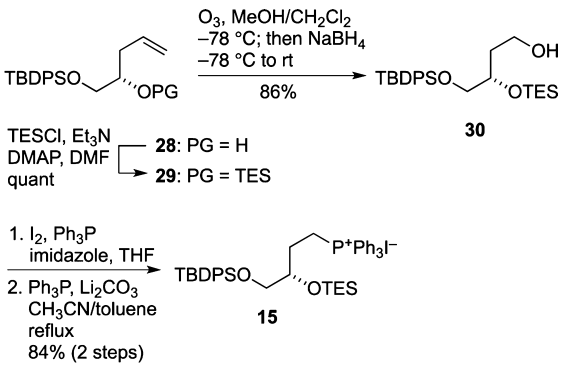
Scheme 3. Synthesis of Alcohol 27



manipulation was applied to the alcohol **24**, leading to the desired alcohol **27** without incident.

The phosphonium salt **15** was synthesized in four steps from known homoallylic alcohol **28**,[21] available in two steps from (*R*)-glycidol (Scheme 4). Silylation of **28** with TESCl/Et_3N/DMAP gave the TES ether **29** (quant). Ozonolysis of the double bond of **29** and reductive workup delivered the alcohol **30** (86%). Iodination of **30** under standard conditions provided the corresponding iodide, which was reacted with Ph_3P to afford the phosphonium salt **15** (84%, two steps).

Scheme 4. Synthesis of Phosphonium Salt 15



Wittig reaction of the phosphonium salt **15** with the aldehyde **16**, prepared from the alcohol **27** (TEMPO/aq NaOCl[22]), was best achieved by deprotonation of **15** (1.15 equiv) with NaHMDS (1.1 equiv) followed by addition of **16** (THF, −78 to 0 °C) to give (*Z*)-olefin **31** in 84% yield (two steps from **27**) as a single stereoisomer (*Z*/*E* > 20:1) (Scheme 5). Other bases, including *n*-BuLi, LiHMDS, and KHMDS, were less effective for this reaction. Oxidative removal of the PMB group of **31** with DDQ (86%) and the ensuing oxidation of the resultant allylic alcohol **32** with Dess−Martin periodinane[23] led to the α,β-unsaturated ketone **33** (96%). Reductive cycloetherification of **33** required optimization experiments. It was eventually found that treatment of **33** with Et_3SiH/TMSOTf[24] *in the presence of THF* in CH_2Cl_2 at −78 °C successfully delivered the 2,6-*cis*-substituted dihydropyran **34** in 93% yield (dr >20:1). The addition of THF was found to be essential for suppressing undesired side reaction, i.e., loss of the TBDPS group, which might occur via an intramolecular attack of the TBDPS ether to an oxocarbenium ion generated in situ from **33**. In the absence of THF, exposure of **33** to Et_3SiH and TMSOTf (CH_2Cl_2, −78 °C) gave **34** in 64% yield (dr >20:1). It was also found that the low reaction temperature was mandatory for achieving the high diastereoselectivity; running the reaction at higher temperature resulted in erosion of diastereoselectivity. The relative configuration between the C16 and C20 stereogenic centers was established on the basis of NOE correlations, as shown. Debenzylation of **34** with lithium naphthalenide gave the corresponding alcohol **35** (85%), which was oxidized under Swern conditions[25] and then alkynylated with Ohira−Bestmann reagent[26] to afford the alkyne **36** (84%, two steps). Removal of the silyl group from **36** (97%), Parikh−Doering oxidation,[27] and allylation under chelate-controlled conditions (allylSiMe_3, $MgBr_2$·OEt_2, CH_2Cl_2, 0 °C)[28] furnished the homoallylic alcohol **38** (68%, two steps, dr >20:1). The absolute configuration of the C15 stereogenic center was established on the basis of a modified Mosher analysis (Figure 3).[29] After the terminal alkyne was hydrated via oxymercuration, the free hydroxy group was silylated with TESCl/imidazole to give the ketone **39** (92%, two steps). Treatment of **39** with KHMDS/$PhNTf_2$ generated an enol triflate, which was immediately reacted with hexamethylditin in the presence of $Pd(PPh_3)_4$ (LiCl, THF, 70 °C)[30] to afford the C12−C25 vinylstanne **13** (73%, two steps).

Synthesis of the C26−C36 Thioester 14. The synthesis of **14** started with known alcohol **21**,[31] derived from (*R*)-malic acid in three steps (Scheme 6). Stereoselective alkylation[17] of **21** (LDA, THF, −78 to −20 °C; then MeI, −20 °C to room temperature) provided the alkylated product **40** in 91% yield with good diastereoselectivity (dr 8:1). The minor diastereomer was removed at a later stage (vide infra). Amidation of **40** with an aluminum amide prepared in situ from MeONHMe·HCl/Me_3Al[32] gave the Weinreb amide **41**. Treatment of **41** with methylmagnesium bromide[33] led to the methyl ketone **42**. Esterification[34] of **42** with diethylphosphonoacetic acid cleanly provided the ester **43** in 82−93% yield. Intramolecular HWE reaction of **43** was best achieved by its exposure to DBU in the presence of LiCl in acetonitrile at room temperature,[35] giving the α,β-unsaturated lactone **20** in 72−83% yield. At this stage, the minor C33 epimer was removed by flash column chromatography using silica gel. Hydrogenation of **20** afforded the lactone **44** in 99% yield with greater than 20:1 diastereoselectivity. Thus, we successfully constructed the C32−C34 stereotriad in a fully stereocontrolled manner. Reduction of **44** to the corresponding diol **45** with $LiAlH_4$ was rather problematic due to partial migration of the silyl group. This problem was addressed by using $LiBH_4$. Under these conditions, the diol **45** could be obtained in 99% yield and with good reproducibility. Selective silylation of the primary alcohol of **45** as its TBDPS ether and cleavage of the TBS ether under mild acidic conditions gave the 1,2-diol **46**.[3,10]

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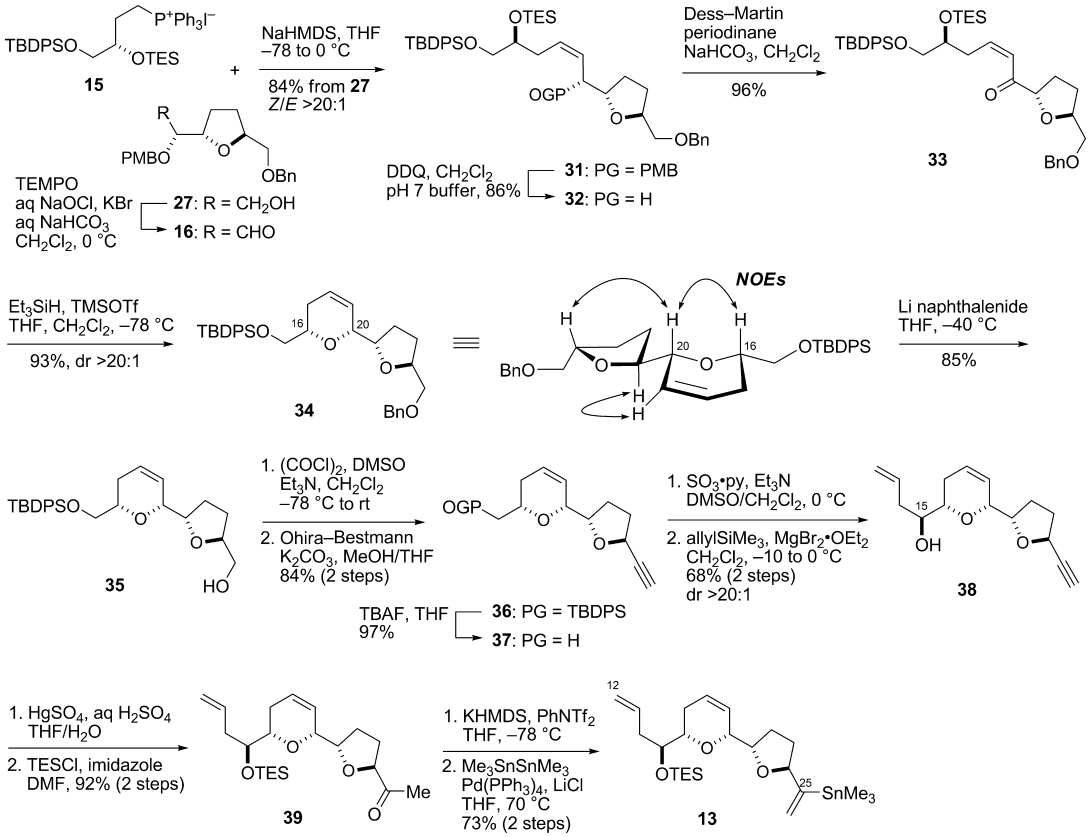
Scheme 5. Synthesis of the C12−C25 Vinylstannane 13



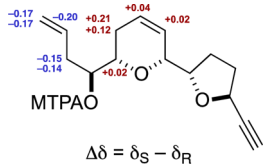


Figure 3. Modified Mosher analysis of **38**.

Acetalization of **46** with *p*-methoxybenzaldehyde dimethyl acetal, followed by regioselective reduction of the resultant acetal with DIBALH, provided the alcohol **47**[3,10] in 94% yield (two steps). Parikh−Doering oxidation[27] of **47** gave the aldehyde **19** in 98% yield.

The iodoalkyne **18** was synthesized in two steps from known alcohol **48**[36] (Scheme 7). Silylation of **48** as its TES ether (90%), followed by iodination of the terminal alkyne **49** (NIS, $AgNO_3$, acetone or I_2, morpholine, benzene, 60 °C), led to the iodoalkyne **18** quantitatively. Diimide reduction of **18** with *o*-nitrobenzenesulfonyl hydrazide (NBSH) in the presence of Et_3N (*i*-PrOH/THF, room temperature)[37] gave the (*Z*)-vinyl iodide **50** (42%).[38]

Initially, NHK reaction[15] of the aldehyde **19** and the (*Z*)-vinyl iodide **50** (2 equiv) was examined (Scheme 8). However, the allylic alcohol **51** was isolated in only 19% yield (dr 3:1), and deiodination and homocoupling of **50** were observed as serious side reactions. In contrast, NHK reaction[15] of **19** with the iodoalkyne **18** (1 wt % $NiCl_2/CrCl_2$ (10 equiv), THF, room temperature) afforded a 2:1 mixture of propargylic alcohols **52a,b** in 86−99% yield (Scheme 8). Excess amounts (3.5 equiv) of **18** were required for complete consumption of **19**. However, the corresponding deiodinated product **49** could be recovered after workup and reused. The NHK reaction could be performed on multigram quantities with good reproducibility. The major diastereomer **52a** had the desired C31 configuration, and the minor diastereomer **52b** could be separated by carefully performing flash column chromatography using silica gel. In practice, however, **52a,b** were not separated and used directly in the next reaction. Thus, **52a,b** were oxidized with Dess−Martin periodinane[23] to give the alkynyl ketone **53** (96%), which was reduced with $Zn(BH_4)_2$ (Et_2O, −78 to −40 °C)[39] in a stereocontrolled manner by taking advantage of the C32 alkoxy group (66−76% yield, dr >20:1 after purification by flash column chromatography), and then hydrogenated over Lindlar's catalyst to afford the allylic alcohol **51** (99%). The absolute configuration of the C31 stereogenic center was established on the basis of a modified Mosher analysis (Figure 4).[29] Protection of **51** with 2,2,2-trichloroethoxymethyl chloride ($TCEOCH_2Cl$)/*i*-Pr_2NEt and removal of the pivaloyl group with DIBALH gave the alcohol **54** (91%, two steps). Parikh−Doering oxidation[27] and subsequent Pinnick oxidation[40] led to the corresponding carboxylic acid. During the latter process, cleavage of the TES ether was observed spontaneously. Subsequent esterification with TolSH by the action of PyBOP[41] afforded the alcohol **55** (85% for the three steps). Reprotection of the C27 hydroxy group furnished the C26−C36 thioester **14** (97%).

Completion of the C12−C36 Fragment 12. The C12−C25 vinylstannane **13** (1.1 equiv) and the C26−C36 thioester **14** were coupled by the action of the $Pd_2(dba)_3/(EtO)_3P$[10,12] catalyst system and CuDPP in THF/hexanes at room temperature to furnish the α,β-unsaturated ketone **56** in 93% yield (Scheme 9). Finally, stereoselective reduction of **56** under Luche conditions[42] provided the C12−C36 fragment **12** in 86%

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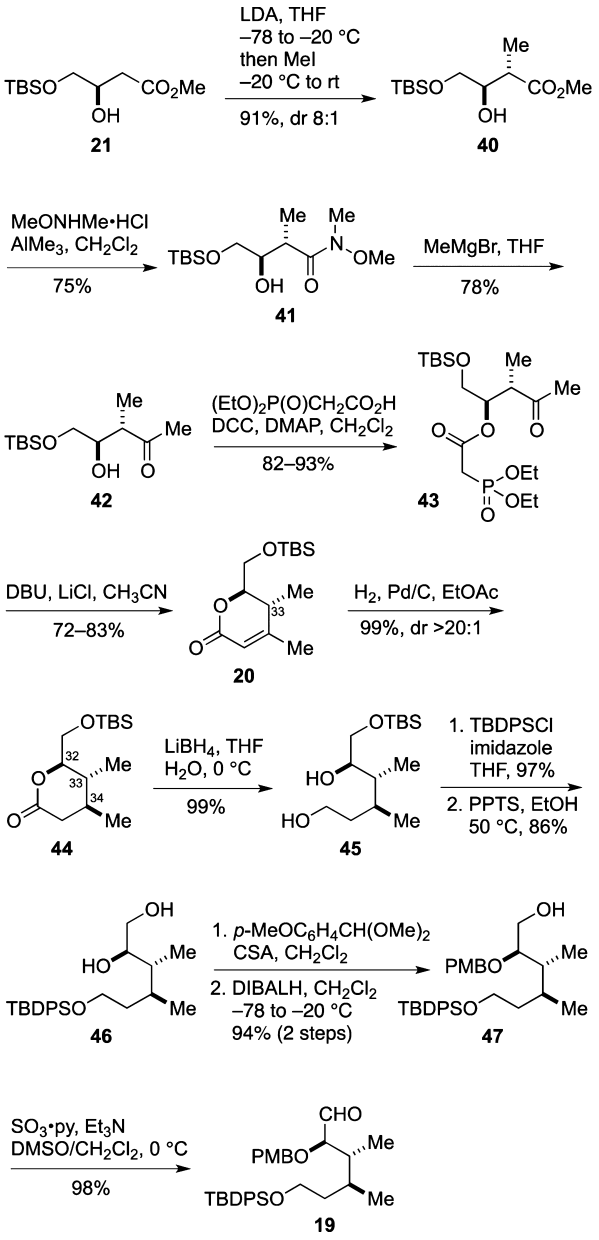
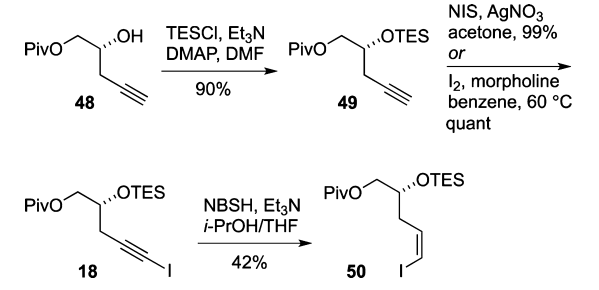
Scheme 6. Synthesis of Aldehyde 19



Scheme 7. Synthesis of Iodoalkyne 18 and (*Z*)-Vinyl Iodide 50



yield with greater than 20:1 diastereoselectivity. The configuration of the C26 stereogenic center of **12** was determined by derivatization to the acetonide **57**, as shown. The stereoselectivity can be explained by considering a polar Felkin–Anh model,[43] as described previously.[10]

CONCLUSION

In this paper, we describe our approach toward the C12–C36 fragment **12** of goniodomin A. The highly stereocontrolled synthesis of the C12–C25 vinylstannane **13** proceeded in 21 linear steps from commercially available benzyl (*S*)-glycidyl ether and involved a domino Sharpless asymmetric epoxidation/5-*exo* cyclization for the construction of the 2,5-*trans*-substituted tetrahydrofuran ring and a Wittig reaction and a reductive cycloetherification for the formation of the 2,6-*cis*-substituted dihydropyran ring. Meanwhile, the synthesis of the C26–C36 thioester **14** (25 steps from (*R*)-malic acid) featured a substrate-controlled stereoselective construction of the C33 and C34 stereogenic centers and an NHK reaction to assemble the requisite carbon backbone. The key intermediates **13** and **14** were efficiently coupled via a palladium-catalyzed reaction. The fully functionalized and appropriately protected C12–C36 fragment **12** should be amenable to further elaboration. Work toward the total synthesis of goniodomin A (**1**) is currently in progress and will be reported in due course.

EXPERIMENTAL SECTION

General Remarks. All reactions sensitive to moisture and/or air were carried out under an atmosphere of argon in dry, freshly distilled solvents under anhydrous conditions using oven-dried glassware unless otherwise noted. Anhydrous THF, Et_2O, and toluene were purified by a Glass Contour solvent purification system under an atmosphere of argon immediately prior to use. DCE, *i*-Pr_2NH, *i*-Pr_2NEt, 2,6-lutidine, MeOH, pyridine, and Et_3N were distilled from CaH_2 under an atmosphere of argon. Acetone was distilled from P_2O_5 under an atmosphere of argon. DMF and DMSO were distilled from magnesium sulfate under reduced pressure. Degassed solvents were obtained by repeating the freeze–thaw cycle three times immediately prior to use. All other chemicals were purchased at the highest commercial grade and used directly. Analytical TLC was performed using E. Merck silica gel 60 F_{254} plates (0.25 mm thickness). Flash column chromatography was carried out using Kanto Chemical silica gel 60N (40–100 mesh, spherical, neutral) or Fuji Silysia silica gel BW-300 (200–400 mesh). ^1H and ^{13}C NMR chemical shift values are reported in ppm (δ) downfield from tetramethylsilane with reference to internal residual solvent [^1H NMR, $CHCl_3$ (7.24), C_6HD_5 (7.15), CHD_2OD (3.31); ^{13}C NMR, $CDCl_3$ (77.0), C_6D_6 (128.0), CD_3OD (49.8)]. 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; br = broad. Diastereomer ratio (dr) and *E*/*Z* isomer ratio were estimated by ^1H NMR spectroscopic analysis (600 MHz), unless otherwise noted. High-resolution mass spectra (HRMS) were measured on a mass spectrometer equipped with a Q-TOF system and an electrospray ionization (ESI) ion source.

***α,β*-Unsaturated Ester 23.** To a solution of alcohol **22** (11.15 g, 54.05 mmol) in toluene (400 mL) was added a solution of the second-generation Grubbs catalyst (264.0 mg, 0.311 mmol) in toluene (10 mL), and the resultant solution was stirred at room temperature for 3 h. To this solution was added a solution of the second-generation Grubbs catalyst (157.4 mg, 0.185 mmol) in toluene (5 mL), and the resultant solution was stirred at room temperature for 2.5 h. After complete consumption of the starting material, the reaction mixture was then stirred at room temperature for 10.5 h under air, and then concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 20–30% EtOAc/hexanes) gave α,β-unsaturated ester **23** (9.69 g, 68%) as a 17:1 mixture of *E*/*Z* isomers: $[\alpha]_D^{24}$ +1.2 (*c* 1.00, $CHCl_3$); IR (film) 3447, 1655, 1436, 1073, 1202, 1095 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 7.20–7.16 (m, 4H), 7.10 (m, 1H), 7.01 (ddd, J = 15.6, 7.3, 7.3 Hz, 1H), 5.85 (ddd, J = 15.6, 1.4, 1.4 Hz, 1H), 4.20 (s, 2H), 3.51 (m, 1H), 3.42 (s, 3H), 3.04 (dd, J = 9.2, 3.7 Hz, 1H), 2.97 (dd, J = 9.2, 6.4 Hz, 1H), 2.08 (m, 1H), 2.04 (d, J = 4.1 Hz, 1H), 1.96 (m, 1H), 1.29 (m, 1H), 1.13 (m, 1H);

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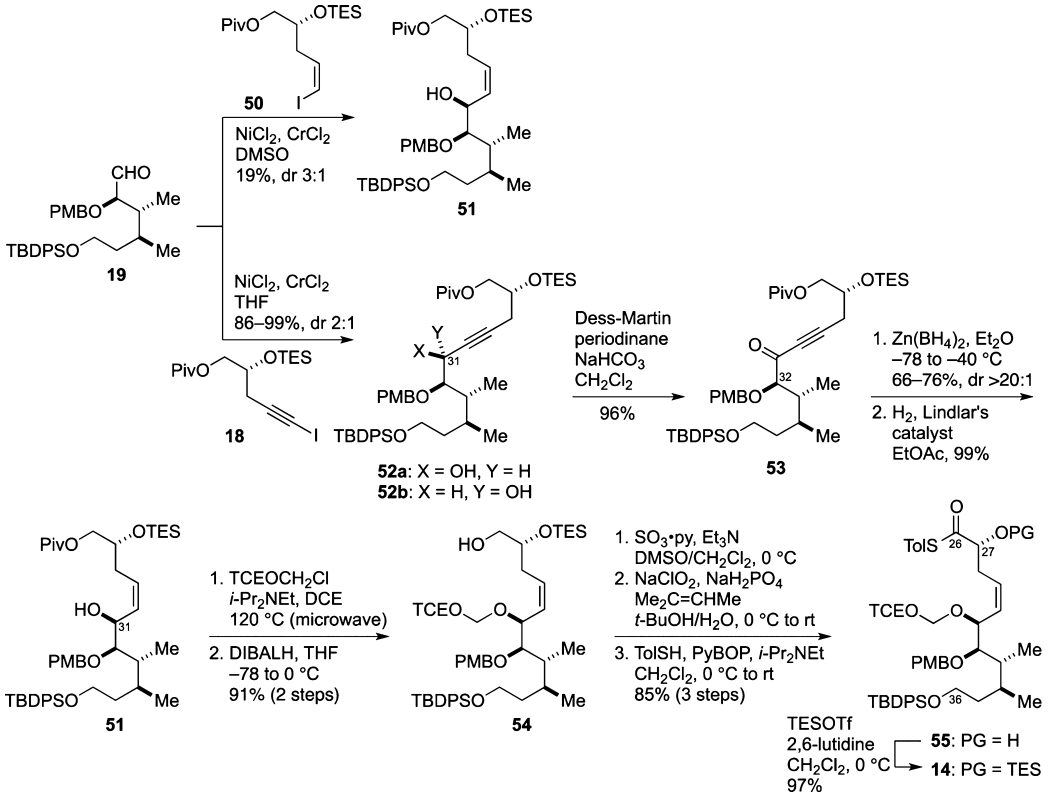
Scheme 8. Synthesis of the C26−C36 Thioester 14



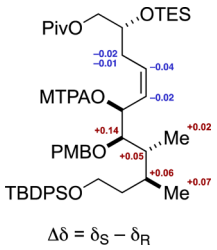


Figure 4. Modified Mosher analysis of propargylic alcohol **51**.

^{13}C NMR (150 MHz, C_6D_6) δ 166.6, 149.0 (2C), 138.6, 128.6, 128.3, 127.8, 121.6 (2C), 74.6, 73.3, 69.4, 50.9, 31.6, 28.3; HRMS (ESI) calcd for $C_{15}H_{20}O_4Na$ [(M + Na)$^+$] 287.1254, found 287.1252.

Allylic Alcohol 17. To a solution of α,β-unsaturated ester **23** (5.08 g, 19.2 mmol) in CH_2Cl_2 (150 mL) at −80 °C was added dropwise DIBALH (1.02 M solution in *n*-hexane, 80.0 mL, 81.6 mmol), and the resultant mixture was stirred at −80 °C for 65 min. The reaction was quenched with MeOH. The resultant mixture was diluted with EtOAc and saturated aqueous potassium sodium tartrate solution and stirred vigorously until the layers became clear. The organic layer was separated, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 50−80% EtOAc/hexanes) gave allylic alcohol **17** (4.02 g, 89%) as a colorless oil: $[\alpha]_D^{24}$ +4.8 (*c* 1.00, $CHCl_3$); IR (film) 3375, 2918, 2859, 1454, 1091, 972 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 7.22−7.20 (m, 2H), 7.18−7.15 (m, 2H), 7.09 (m, 1H), 5.54−5.53 (m, 2H), 4.23 (s, 2H), 3.88 (br s, 2H), 4.71 (dddd, *J* = 7.8, 7.8, 3.7, 3.7 Hz, 1H), 3.19 (dd, *J* = 9.1, 3.7 Hz, 1H), 3.13 (dd, *J* = 9.1, 7.8 Hz, 1H), 2.50 (br s, 1H), 2.16 (m, 1H), 2.08 (m, 1H), 1.53−1.42 (m, 2H), 1.35 (m, 1H); ^{13}C NMR (150 MHz, C_6D_6) δ 138.7, 131.5, 130.4, 128.6 (2C), 128.3, 127.9, 127.8, 75.0, 73.3, 69.8, 63.4, 33.0, 28.6; HRMS (ESI) calcd for $C_{14}H_{20}O_3Na$ [(M + Na)$^+$] 259.1305, found 259.1308.

Diol 24. To a suspension of allylic alcohol **17** (5.89 g, 24.9 mmol), (−)-DET (7.72 g, 37.4 mmol), and 4 Å molecular sieves (6.02 g) in CH_2Cl_2 (200 mL) at −20 °C was added dropwise Ti(O-*i*-Pr)$_4$ (9.50 mL, 32.4 mmol), and the resultant mixture was stirred at that temperature for 30 min. To this mixture was added dropwise cumene hydroperoxide (80 wt %, 9.50 mL, 51.4 mmol), and the resultant mixture was stirred at that temperature for 11.5 h. The reaction was diluted with Et_2O, then quenched with 1 M aqueous NaOH solution, and the resultant mixture was stirred at room temperature for 8 h 40 min. The mixture was filtered through a pad of Celite, diluted with EtOAc, washed with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 60% EtOAc/hexanes then EtOAc) gave diol **24** (5.17 g, 82%, dr >20:1) as a colorless oil: $[\alpha]_D^{24}$ −9.7 (*c* 1.00, $CHCl_3$); IR (film) 3393, 2871, 1069, 1027, 738 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34−7.30 (m, 4H), 7.26 (m, 1H), 4.57 (d, *J* = 11.9 Hz, 1H), 4.52 (d, *J* = 11.9 Hz, 1H), 4.18 (m, 1H), 3.94 (m, 1H), 3.75 (m, 1H), 3.66 (dd, *J* = 11.5, 3.7 Hz, 1H), 3.57 (dd, *J* = 11.5, 6.8 Hz, 1H), 3.45−3.40 (m, 2H), 2.51 (br, 2H), 2.00 (m, 1H), 1.92 (m, 1H), 1.83 (m, 1H), 1.65 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.1, 128.4 (2C), 127.7 (2C), 127.6, 80.1, 78.4, 73.3, 73.0, 72.7, 63.8, 28.4, 26.8; HRMS (ESI) calcd for $C_{14}H_{20}O_4Na$ [(M + Na)$^+$] 275.1254, found 275.1241.

Trityl Ether 25. To a solution of diol **24** (6.33 g, 25.1 mmol) in CH_2Cl_2 (120 mL) were added pyridine (6.0 mL, 74 mmol), TrCl (7.70 g, 27.8 mmol), and DMAP (0.64 g, 5.2 mmol), and the resultant solution was stirred at room temperature for 16 h. The reaction mixture was diluted with EtOAc and washed with H_2O and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10−40% EtOAc/hexanes) gave trityl ether **25** (12.18 g, 98%) as a colorless oil: $[\alpha]_D^{24}$ −9.5 (*c* 1.00, $CHCl_3$); IR (film) 3446, 2934, 2875, 1448, 1073, 747 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43−7.41 (m, 6H), 7.32−7.25 (m, 11H), 7.23−7.19 (m, 3H), 4.56 (d, *J* = 12.4 Hz, 1H), 4.52 (d, *J* = 12.4 Hz, 1H), 4.14 (m, 1H), 4.02 (ddd, *J* = 7.3, 5.0, 5.0 Hz, 1H), 3.89 (m, 1H), 3.41 (d, *J* = 5.0 Hz, 2H), 3.25 (dd, *J* = 9.7, 6.4 Hz, 1H), 3.16 (dd, *J* = 9.7, 4.6 Hz, 1H), 2.31 (d, *J* = 3.2 Hz, 1H), 1.94 (m, 1H), 1.81−1.77 (m, 2H), 1.62 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.8 (2C),

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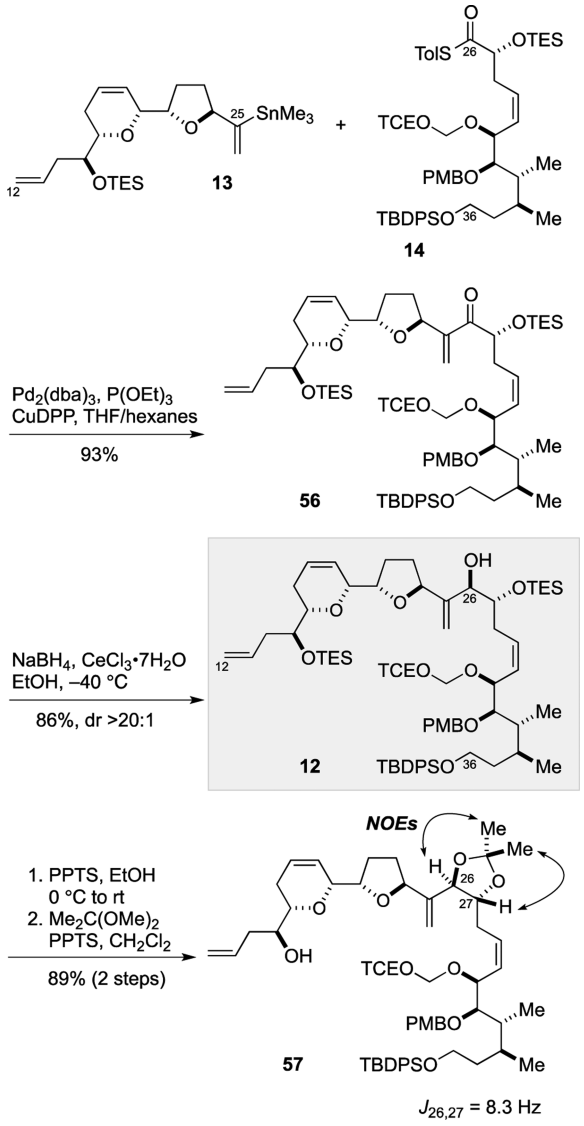
Scheme 9. Completion of the Synthesis of the C12−C36 Fragment 12



138.2, 128.6 (6C), 128.3 (3C), 127.8 (6C), 127.7 (2C), 127.6, 127.0 (3C), 86.7, 79.9, 78.5, 73.3, 72.9, 71.7, 64.9, 28.4, 26.2; HRMS (ESI) calcd for $C_{33}H_{34}O_4Na$ [(M + Na)$^+$] 517.2349, found 517.2362.

PMB Ether 26. To a solution of trityl ether **25** (5.03 g, 10.2 mmol) in DMF (50 mL) at 0 °C was added NaH (60 wt % in mineral oil, 0.63 g, 16 mmol), and the resultant mixture was stirred at 0 °C for 30 min. To this solution at 0 °C were added PMBCl (1.70 mL, 12.5 mmol) and Bu_4NI (384.3 mg, 1.04 mmol), and the resultant solution was stirred at room temperature for 6 h. The reaction was quenched with saturated aqueous NH_4Cl solution at 0 °C. The resultant mixture was extracted with *t*-BuOMe. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5−10% EtOAc/hexanes) gave PMB ether **26** (5.48 g, 87%) as a colorless oil: $[\alpha]_D^{24}$ −25.2 (*c* 1.00, $CHCl_3$); IR (film) 2930, 2872, 1513, 1248, 1079 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45−7.43 (m, 6H), 7.33−7.31 (m, 4H), 7.29−7.24 (m, 9H), 7.22−7.19 (m, 3H), 6.85−6.83 (m, 2H), 4.66 (d, *J* = 11.5 Hz, 1H), 4.57 (d, *J* = 11.9 Hz, 1H), 4.57 (d, *J* = 11.5 Hz, 1H), 4.53 (d, *J* = 11.9 Hz, 1H), 4.17−4.12 (m, 2H), 3.79 (s, 3H), 3.72 (ddd, *J* = 5.0, 5.0, 5.0 Hz, 1H), 3.43 (d, *J* = 5.5 Hz, 2H), 3.24 (dd, *J* = 10.0, 5.9 Hz, 1H), 3.14 (dd, *J* = 10.0, 5.0 Hz, 1H), 1.93 (m, 1H), 1.85−1.79 (m, 2H), 1.60 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.0, 144.1 (2C), 138.4, 131.1, 129.4 (2C), 128.7 (6C), 128.3 (2C), 127.9, 127.7 (6C), 127.6 (2C), 127.5, 127.2, 126.9 (2C), 113.6 (2C), 86.7, 79.9, 79.7, 78.3, 73.3, 72.9, 72.8, 64.2, 55.2, 28.7, 26.5; HRMS (ESI) calcd for $C_{41}H_{42}O_5Na$ [(M + Na)$^+$] 637.2924, found 637.2901.

Alcohol 27. To a solution of PMB ether **26** (10.95 g, 17.81 mmol) in MeOH/CH_2Cl_2 (1:1, v/v, 180 mL) at 0 °C was added *p*-toluenesulfonic acid monohydrate (3.72 g, 19.6 mmol), and the resultant mixture was stirred at room temperature for 50 min. The reaction mixture was neutralized with Et_3N at 0 °C and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 20−60% EtOAc/hexanes) gave alcohol **27** (6.22 g, 94%) as a colorless oil: $[\alpha]_D^{24}$ −17.4 (*c* 1.00, $CHCl_3$); IR (film) 3446, 2871, 1513, 1247, 1075, 1033 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34−7.31 (m, 4H), 7.29−7.23 (m, 3H), 6.87−6.84 (m, 2H), 4.58 (s, 2H), 4.56 (d, *J* = 12.4 Hz, 1H), 4.53 (d, *J* = 12.4 Hz, 1H), 4.18 (m, 1H), 4.05 (m, 1H), 3.71 (dd, *J* = 11.5, 5.0 Hz, 1H), 3.78 (s, 3H), 3.65 (dd, *J* = 11.5, 5.5 Hz, 1H), 3.48 (ddd, *J* = 5.3, 5.3, 5.3 Hz, 1H), 3.46−3.42 (m, 2H), 2.04−1.95 (m, 3H), 1.79 (m, 1H), 1.67 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.3, 138.2, 130.4, 129.5 (2C), 128.3 (2C), 127.60 (2C), 127.55, 113.8 (2C), 80.31, 80.26, 78.2, 73.3, 72.6, 72.5, 62.6, 55.2, 28.3, 28.2; HRMS (ESI) calcd for $C_{22}H_{28}O_5Na$ [(M + Na)$^+$] 395.1829, found 395.1825.

TES Ether 29. To a solution of homoallylic alcohol **28** (14.54 g, 42.70 mmol) in DMF (150 mL) were added TESCl (7.90 mL, 47.2 mmol), Et_3N (19.0 mL, 136 mmol), and DMAP (379.5 mg, 3.10 mmol), and the resultant solution was stirred at room temperature for 30 min. The reaction mixture was diluted with *t*-BuOMe and washed with saturated aqueous NH_4Cl solution, H_2O, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5% EtOAc/hexanes) gave TES ether **29** (19.40 g, quant) as a pale yellow oil: $[\alpha]_D^{24}$ −5.1 (*c* 1.00, $CHCl_3$); IR (film) 2955, 2932, 2876, 1428, 1112, 701 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67−7.64 (m, 4H), 7.41−7.39 (m, 2H), 7.37−7.34 (m, 4H), 5.82 (dddd, *J* = 17.0, 10.1, 7.3, 7.3 Hz, 1H), 5.06 (ddd, *J* = 17.0, 3.7, 1.4 Hz, 1H), 5.01 (ddd, *J* = 10.1, 1.4, 1.4 Hz, 1H), 3.74 (m, 1H), 3.54 (dd, *J* = 10.1, 5.0 Hz, 1H), 3.48 (dd, *J* = 10.1, 6.4 Hz, 1H), 2.45 (m, 1H), 2.23 (m, 1H), 1.03 (s, 9H), 0.87 (t, *J* = 7.8 Hz, 9H), 0.50 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.61, 135.58, 135.1 (2C), 133.7, 133.6, 129.6 (2C), 127.6 (4C), 116.9 (2C), 72.5, 67.2, 39.0, 26.8 (3C), 19.2, 6.8 (3C), 4.9 (3C); HRMS (ESI) calcd for $C_{27}H_{42}O_2Si_2Na$ [(M + Na)$^+$] 477.2616, found 477.2605.

Alcohol 30. Ozone was bubbled through a solution of TES ether **29** (19.40 g, 42.66 mmol) in CH_2Cl_2/MeOH (1:1, v/v, 160 mL) at −78 °C until a pale blue color was persisted. After oxygen was bubbled through the solution to remove excess ozone, $NaBH_4$ (6.51 g, 172 mmol) was added to the solution at −78 °C. The resultant solution was gradually warmed to room temperature and stirred at room temperature for 11 h. The reaction was quenched with saturated aqueous NH_4Cl solution at 0 °C. The resultant mixture was extracted with EtOAc, and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5−30% EtOAc/hexanes) gave alcohol **30** (16.9 g, 86%) as a colorless oil: $[\alpha]_D^{24}$ −15.7 (*c* 1.00, $CHCl_3$); IR (film) 3421, 2955, 2932, 2876, 1428, 1112, 1083, 1007 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67−7.63 (m, 4H), 7.44−7.40 (m, 2H), 7.39−7.35 (m, 4H), 3.91 (m, 1H), 3.81 (m, 1H), 3.74 (m, 1H), 3.59 (dd, *J* = 10.1, 4.6 Hz, 1H), 3.55 (dd, *J* = 10.1, 7.8 Hz, 1H), 2.61 (br s, 1H), 1.97 (m, 1H), 1.80 (m, 1H), 1.03 (s, 9H), 0.85 (t, *J* = 7.8 Hz, 9H), 0.47 (dq, *J* = 1.8, 7.8 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.6 (4C), 133.3, 133.2, 129.8, 129.7, 127.7 (4C), 72.1, 67.0, 60.1, 36.2, 26.8 (3C), 19.2, 6.7 (3C), 4.7 (3C); HRMS (ESI) calcd for $C_{26}H_{42}O_3Si_2Na$ [(M + Na)$^+$] 481.2565, found 481.2575.

Phosphonium Salt 15. To a solution of alcohol **30** (16.9 g, 36.8 mmol) in THF (150 mL) at 0 °C were added imidazole (5.16 g, 75.8 mmol), PPh_3 (17.4 g, 66.3 mmol), and I_2 (8.46 g, 66.7 mmol), and the resultant solution was stirred at room temperature for 25 min. The reaction was quenched with saturated aqueous Na_2SO_3 solution at 0 °C. The resultant mixture was extracted with EtOAc, and the organic

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layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5% EtOAc/hexanes) gave an alkyl iodide (25.85 g), which was contaminated with some impurities and used in the next step without further purification.

To a solution of the above alkyl iodide (25.85 g) in MeCN/toluene (4:1, v/v, 100 mL) were added PPh_3 (28.9 g, 110 mmol) and Li_2CO_3 (27.0 g, 365 mmol), and the resultant mixture was refluxed for 10 h. After being cooled to room temperature, the reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, benzene then 10% MeOH/benzene) gave phosphonium salt **15** (25.61 g, 84% for the two steps) as a white foam: $[\alpha]_D^{24}$ −6.2 (*c* 1.00, $CHCl_3$); IR (film) 2953, 2930, 2873, 1438, 1112, 741 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.83−7.79 (m, 3H), 7.72−7.68 (m, 12H), 7.55−7.50 (m, 4H), 7.40−7.36 (m, 2H), 7.33−7.28 (m, 4H), 4.00 (m, 1H), 3.68 (dd, *J* = 10.6, 4.1 Hz, 1H), 3.58−3.50 (m, 2H), 3.27 (m, 1H), 1.93−1.84 (m, 2H), 0.92 (s, 9H), 0.81 (t, *J* = 7.8 Hz, 9H), 0.47 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.5 (d, *J* = 4.3 Hz, 3C), 135.32 (2C), 135.30 (2C), 133.5 (d, *J* = 10.1 Hz, 6C), 132.97, 132.95, 130.7 (d, *J* = 11.5 Hz, 6C), 129.9, 129.8, 128.3, 127.8 (4C), 118.0, 117.5, 70.7 (d, *J* = 15.8 Hz), 66.3, 26.9 (3C), 26.8, 19.2, 18.2 (d, *J* = 54.6 Hz), 6.8 (3C), 4.8 (3C); HRMS (ESI) calcd for $C_{44}H_{56}O_2PSi_2$ [(M − I) $^-$] 703.3556, found 703.3579.

Olefin 31. To a solution of alcohol **26** (5.77 g, 15.5 mmol) in CH_2Cl_2 (30 mL) at 0 °C were added aqueous KBr solution (0.5 M, 3.0 mL, 1.5 mmol), 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) (128.3 mg, 0.821 mmol), and a 1:1 mixture of sodium hypochlorite solution (1.43 M, 14.0 mL, 20.0 mmol) and saturated aqueous $NaHCO_3$ solution (14 mL), and the resultant mixture was stirred at 0 °C for 30 min. The reaction was quenched with saturated aqueous Na_2SO_3 solution. The resultant mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude aldehyde (6.11 g) was azeotropically dried with toluene and used in the next step without further purification.

To a solution of phosphonium salt **15** (15.45 g, 18.60 mmol) in THF (120 mL) at −50 °C was added NaHMDS (1.0 M solution in THF, 17.0 mL, 17 mmol), and the resultant mixture was stirred at 0 °C for 30 min. To this solution at −78 °C was added dropwise a solution of above aldehyde **16** (6.11 g) in THF (10 mL + 5 mL rinse). The resultant mixture was stirred at −78 °C for 20 min and then at 0 °C for 1 h 10 min. The reaction was quenched with saturated aqueous NH_4Cl solution. The resultant mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5−10% EtOAc/hexanes) gave olefin **31** (10.30 g, 84% for the two steps, *Z*/*E* >20:1) as a pale red oil: $[\alpha]_D^{24}$ −20.8 (*c* 1.00, $CHCl_3$); IR (film) 2954, 2932, 2874, 2859, 1513, 1248, 1112, 1081 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.65−7.63 (m, 4H), 7.40−7.37 (m, 2H), 7.35−7.33 (m, 4H), 7.32−7.29 (m, 4H), 7.25 (m, 1H), 7.18−7.16 (m, 2H), 6.81−6.78 (m, 2H), 5.76 (ddd, *J* = 11.0, 7.3, 7.3 Hz, 1H), 5.41 (dd, *J* = 11.0, 9.2 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.47 (d, *J* = 11.5 Hz, 1H), 4.25 (d, *J* = 11.5 Hz, 1H), 4.19−4.15 (m, 2H), 4.05 (ddd, *J* = 6.9, 6.9, 4.0 Hz, 1H), 3.75 (s, 3H), 3.73 (m, 1H), 3.54 (dd, *J* = 10.1, 5.0 Hz, 1H), 3.48 (dd, *J* = 10.1, 6.0 Hz, 1H), 3.46 (dd, *J* = 10.1, 5.5 Hz, 1H), 3.41 (dd, *J* = 10.1, 5.0 Hz, 1H), 2.47 (dddd, *J* = 14.0, 7.3, 7.3, 1.8 Hz, 1H), 2.18 (dddd, *J* = 14.0, 7.3, 7.3, 1.8 Hz, 1H), 1.95 (m, 1H), 1.92−1.81 (m, 2H), 1.63 (dddd, *J* = 11.9, 8.2, 8.2, 8.2 Hz, 1H), 1.03 (s, 9H), 0.87 (t, *J* = 7.9 Hz, 9H), 0.49 (q, *J* = 7.9 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.9, 138.5, 135.6 (3C), 133.54, 133.45, 131.1, 131.0, 129.6, 129.0 (3C), 128.3 (3C), 127.64 (4C), 127.60 (3C), 127.4, 113.6 (2C), 81.5, 78.6, 76.5, 73.3, 72.9, 72.7, 70.0, 67.6, 55.2, 33.1, 28.7, 26.84 (3C), 26.78, 19.2, 6.8 (3C), 4.9 (3C); HRMS (ESI) calcd for $C_{48}H_{66}O_6Si_2Na$ [(M + Na)$^+$] 817.4290, found 817.4306.

Allylic Alcohol 32. To a solution of olefin **31** (13.14 g, 16.52 mmol) in CH_2Cl_2/pH 7 buffer (10:1, v/v, 110 mL) at 0 °C was added DDQ (4.53 g, 20.0 mmol), and the resultant solution was stirred at room temperature for 1 h. The reaction was quenched with saturated aqueous Na_2SO_3 solution at 0 °C. The whole mixture was filtered through a pad of Celite to remove insoluble materials, and the filtrate was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10−30% EtOAc/hexanes) gave allylic alcohol **32** (9.57 g, 86%) as a pale yellow oil: $[\alpha]_D^{24}$ 22.3 (*c* 1.00, $CHCl_3$); IR (film) 3449, 2954, 2875, 1428, 1113, 1081 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.65−7.63 (m, 4H), 7.42−7.39 (m, 2H), 7.38−7.34 (m, 4H), 7.32−7.31 (m, 4H), 7.26 (m, 1H), 5.65 (dddd, *J* = 11.5, 7.8, 7.8, 1.0 Hz, 1H), 5.47 (dd, *J* = 11.5, 8.2 Hz, 1H), 4.59 (d, *J* = 12.4 Hz, 1H), 4.57 (m, 1H), 4.52 (d, *J* = 12.4 Hz, 1H), 4.21 (dddd, *J* = 8.3, 5.5, 5.5, 5.5 Hz, 1H), 3.99 (ddd, *J* = 8.7, 6.4, 3.7 Hz, 1H), 3.74 (dddd, *J* = 7.3, 7.3, 4.6, 4.6 Hz, 1H), 3.53 (dd, *J* = 10.1, 4.6 Hz, 1H), 3.46 (dd, *J* = 10.1, 7.3 Hz, 1H), 3.43−3.42 (m, 2H), 2.52 (m, 1H), 2.36 (br s, 1H), 2.31 (m, 1H), 1.99 (m, 1H), 1.91−1.82 (m, 2H), 1.61 (m, 1H), 1.03 (s, 9H), 0.85 (t, *J* = 7.8 Hz, 9H), 0.47 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.3, 135.6 (4C), 133.52, 133.45, 130.1, 129.7, 129.63, 129.61, 128.3 (2C), 127.7 (2C), 127.7 (4C), 127.6, 81.8, 78.8, 73.4, 73.0, 72.1, 68.6, 67.1, 32.9, 28.7, 26.8 (3C), 25.5, 19.2, 6.8 (3C), 4.7 (3C); HRMS (ESI) calcd for $C_{40}H_{58}O_5Si_2Na$ [(M + Na)$^+$] 697.3715, found 697.3701.

***α,β*-Unsaturated Ketone 33.** To a solution of allylic alcohol **32** (9.57 g, 14.2 mmol) in CH_2Cl_2 (100 mL) at 0 °C were added $NaHCO_3$ (5.99 g, 71.3 mmol) and Dess−Martin periodinane (7.23 g, 17.0 mmol), and the resultant solution was stirred at room temperature for 1 h. The reaction was quenched with a 1:1 mixture of saturated aqueous $NaHCO_3$ solution and saturated aqueous Na_2SO_3 solution at 0 °C. The resultant mixture was extracted with *t*-BuOMe, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10% EtOAc/hexanes) gave *α,β*-unsaturated ketone **33** (9.11 g, 96%) as a pale yellow oil: $[\alpha]_D^{24}$ −24.4 (*c* 1.00, $CHCl_3$); IR (film) 3070, 2954, 2875, 1427, 1112, 1083, 702 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.65−7.63 (m, 4H), 7.41−7.32 (m, 10H), 7.27 (m, 1H), 6.49 (ddd, *J* = 11.5, 1.8, 1.8 Hz, 1H), 6.39 (ddd, *J* = 11.5, 6.8, 6.8 Hz, 1H), 4.59 (d, *J* = 12.4 Hz, 1H), 4.56 (d, *J* = 12.4 Hz, 1H), 4.45 (dd, *J* = 6.8, 6.8 Hz, 1H), 4.30 (m, 1H), 3.85 (dddd, *J* = 5.5, 5.5, 5.5, 5.5 Hz, 1H), 3.55 (dd, *J* = 10.1, 5.0 Hz, 1H), 3.53−3.49 (m, 2H), 3.48 (dd, *J* = 10.1, 6.4 Hz, 1H), 2.99−2.91 (m, 2H), 2.20 (m, 1H), 1.96−1.86 (m, 2H), 1.73 (m, 1H), 1.02 (s, 9H), 0.86 (t, *J* = 7.8 Hz, 9H), 0.50 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 201.8, 147.3, 138.2, 135.6 (2C), 133.5, 133.4, 129.6 (2C), 128.3 (2C), 127.63 (3C), 127.61 (4C), 127.58 (2C), 123.3, 84.1, 79.4, 73.4, 72.3, 71.9, 67.5, 34.8, 29.1, 27.9, 26.8 (3C), 19.1, 6.8 (3C), 4.8 (3C); HRMS (ESI) calcd for $C_{40}H_{56}O_5Si_2Na$ [(M + Na)$^+$] 695.3558, found 695.3549.

D/E-Ring Fragment 34. To a solution of *α,β*-unsaturated ketone **33** (9.11 g, 13.6 mmol) in CH_2Cl_2 (140 mL) at −78 °C were added Et_3SiH (20.0 mL, 126 mmol) and TMSOTf (5.00 mL, 27.7 mmol), and the resultant solution was stirred for 5 min at −78 °C. To the reaction mixture was added THF (7.0 mL), and the resultant solution was stirred at −78 °C for 20 min. The reaction was quenched with saturated aqueous $NaHCO_3$ solution. The resultant mixture was extracted with EtOAc, and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5−10% EtOAc/hexanes) gave the D/E-ring fragment **34** (6.85 g, 93%, dr >20:1) as a pale yellow oil: $[\alpha]_D^{24}$ −9.8 (*c* 1.00, $CHCl_3$); IR (film) 2929, 2857, 1428, 1113, 1083 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.68−7.66 (m, 4H), 7.41−7.30 (m, 10H), 7.26 (m, 1H), 5.87 (m, 1H), 5.77 (ddd, *J* = 10.6, 1.4, 1.4 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.53 (d, *J* = 12.0 Hz, 1H), 4.22 (m, 1H), 4.12 (m, 1H), 3.91 (ddd, *J* = 6.4, 6.4, 6.4 Hz, 1H), 3.76 (dd, *J* = 10.1, 5.5 Hz, 1H), 3.72 (m, 1H), 3.63 (dd, *J* = 10.1, 5.0 Hz, 1H), 3.47−3.42 (m, 2H), 2.07 (m, 1H), 2.02−1.88 (m, 4H), 1.64 (dddd, *J* = 11.9, 8.2, 8.2, 8.2 Hz, 1H), 1.03 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.4, 135.6 (4C), 133.74, 133.71, 129.5 (2C), 128.3 (2C), 127.6 (3C), 127.6 (4C), 127.5, 125.3, 81.5, 78.5, 76.9, 74.0, 73.3, 72.8, 66.8, 28.4, 27.7, 27.0, 26.8 (3C), 19.3; HRMS (ESI) calcd for $C_{34}H_{42}O_4SiNa$ [(M + Na)$^+$] 565.2745, found 565.2754.

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Alcohol 35. To a suspension of lithium wire (328.1 mg, 47.3 mmol) in THF (120 mL) was added naphthalene (7.40 g, 57.7 mmol), and the resultant suspension was sonicated until a deep-green color was persisted, then stirred at room temperature for 1 h 40 min. To this solution at −40 °C was added a solution of the D/E-ring fragment **34** (6.26 g, 11.5 mmol) in THF (15 mL + 5 mL rinse) via cannula, and the resultant solution was stirred at −40 °C for 10 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 brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10−30% EtOAc/hexanes) gave alcohol **35** (4.42 g, 85%) as a colorless oil: $[\alpha]_D^{24}$ −3.4 (*c* 1.00, $CHCl_3$); IR (film) 3435, 2929, 2858, 1428, 1113, 1074 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.68−7.66 (m, 4H), 7.42−7.39 (m, 2H), 7.37−7.35 (m, 4H), 5.89 (m, 1H), 5.74 (ddd, *J* = 10.6, 1.4, 1.4 Hz, 1H), 4.15−4.11 (m, 2H), 3.91 (ddd, *J* = 6.1, 6.1, 6.1 Hz, 1H), 3.77 (dd, *J* = 10.1, 5.5 Hz, 1H), 3.73 (m, 1H), 3.64 (dd, *J* = 10.1, 4.6 Hz, 1H), 3.63 (dd, *J* = 11.9, 3.2 Hz, 1H), 3.45 (dd, *J* = 11.9, 6.0 Hz, 1H), 2.09 (m, 1H), 2.00 (m, 1H), 1.96−1.89 (m, 4H), 1.65 (m, 1H), 1.04 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.6 (4C), 133.7, 129.5 (2C), 127.6 (5C), 127.2, 125.6, 81.4, 80.0, 76.8, 74.1, 66.8, 64.8, 27.7, 27.4, 27.2, 26.8 (3C), 19.3; HRMS (ESI) calcd for $C_{27}H_{36}O_4SiNa$ [(M + Na)$^+$] 475.2275, found 475.2290.

Alkyne 36. To a solution of DMSO (1.30 mL 18.3 mmol) in CH_2Cl_2 (60 mL) at −78 °C was added oxalyl chloride (1.20 mL, 14.0 mmol), and the resultant mixture was stirred at that temperature for 20 min. To the solution at −78 °C was added alcohol **35** (4.07 g, 8.99 mmol) in CH_2Cl_2 (10 mL + 5 mL rinse). After 30 min, Et_3N (3.80 mL, 27.3 mmol) was added at −78 °C, and the solution was stirred at room temperature for 40 min. The reaction 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. The crude aldehyde (6.13 g) was azeotropically dried with toluene and used in the next step without further purification.

To a solution of the above aldehyde (6.13 g) in MeOH/THF (4:1, v/v, 41 mL) at 0 °C were added Ohira−Bestmann reagent (2.32 g, 12.1 mmol) in MeOH (5 mL + 2 mL rinse) and K_2CO_3 (3.11 g, 22.5 mmol). The resultant mixture was stirred at room temperature for 5 h. The reaction mixture was diluted with EtOAc, and the organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5% EtOAc/hexanes) gave alkyne **36** (3.37 g, 84% for the two steps) as a pale yellow oil: $[\alpha]_D^{24}$ −8.6 (*c* 1.00, $CHCl_3$); IR (film) 3291, 2929, 2857, 1113, 1063 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.68−7.65 (m, 4H), 7.42−7.39 (m, 2H), 7.38−7.35 (m, 4H), 5.89 (m, 1H), 5.71 (dddd, *J* = 10.1, 2.8, 1.4, 1.4 Hz, 1H), 4.69 (ddd, *J* = 7.3, 3.2, 1.9 Hz, 1H), 4.15 (m, 1H), 4.04 (ddd, *J* = 7.7, 5.4, 5.4 Hz, 1H), 3.76 (dd, *J* = 10.1, 5.1 Hz, 1H), 3.72 (m, 1H), 3.64 (dd, *J* = 10.1, 4.6 Hz, 1H), 2.40 (d, *J* = 1.9 Hz, 1H), 2.19−1.97 (m, 4H), 1.96−1.91 (m, 2H), 1.04 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.6 (4C), 133.70, 133.68, 129.6 (2C), 127.6 (4C), 127.1, 125.7, 83.8, 81.1, 76.5, 74.0, 72.4, 68.5, 66.7, 33.2, 27.7, 26.8 (3C), 26.3, 19.3; HRMS (ESI) calcd for $C_{28}H_{34}O_3SiNa$ [(M + Na)$^+$] 469.2169, found 469.2165.

Alcohol 37. To a solution of alkyne **36** (4.20 g, 9.40 mmol) in THF (60 mL) at 0 °C was added TBAF (1.0 M solution in THF, 11.3 mL, 11 mmol), and the resultant solution was stirred at room temperature for 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution at 0 °C, and the resultant mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10−40% EtOAc/hexanes) gave alcohol **37** (1.89 g, 97%) as a pale yellow oil: $[\alpha]_D^{24}$ −2.3 (*c* 1.00, $CHCl_3$); IR (film) 3443, 3291, 2916, 2884, 1083, 1059 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.87 (m, 1H), 5.70 (dddd, *J* = 10.1, 2.7, 1.4, 1.4 Hz, 1H), 4.69 (ddd, *J* = 6.8, 5.5, 2.3 Hz, 1H), 4.18 (m, 1H), 4.06 (ddd, *J* = 7.3, 5.9, 5.9 Hz, 1H), 3.69 (ddd, *J* = 10.1, 6.4, 3.2 Hz, 1H), 3.63 (m, 1H), 3.53 (ddd, *J* = 10.1, 6.8, 3.7 Hz, 1H), 2.41 (d, *J* = 2.3 Hz, 1H), 2.23 (br s, 1H), 2.16 (m, 1H), 2.10−2.01 (m, 2H), 1.97 (m, 1H), 1.92−1.83 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 126.8, 125.4, 83.6, 80.8, 76.3, 73.9, 72.7, 68.6, 65.6, 33.2, 26.6, 26.3; HRMS (ESI) calcd for $C_{12}H_{16}O_3Na$ [(M + Na)$^+$] 231.0992, found 231.1001.

Homoallylic Alcohol 38. To a solution of alcohol **37** (1.61 g, 7.73 mmol) and Et_3N (4.30 mL, 30.9 mmol) in CH_2Cl_2/DMSO (1:1, v/v, 40 mL) at 0 °C was added SO_3·pyridine complex (3.73 g, 23.4 mmol), and the resultant mixture was stirred at 0 °C for 30 min. The reaction mixture was diluted with Et_2O, 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. The crude aldehyde (1.79 g) was a used in the next step without further purification.

To the above aldehyde (1.79 g) in CH_2Cl_2 (50 mL) at 0 °C was added $MgBr_2$·OEt_2 (4.85g, 18.8 mmol), and the resultant mixture was stirred at room temperature for 20 min. The solution was cooled to −10 °C and treated with allyltrimethylsilane (1.80 mL, 11.3 mmol), and the resultant mixture was stirred at 0 °C for 200 min. To the reaction mixture at −10 °C was added allyltrimethylsilane (0.60 mL, 3.8 mmol), and the resultant mixture was stirred at 0 °C for 3 h 40 min. The reaction was quenched with H_2O. The resultant mixture was extracted with EtOAc, and the organic layer was washed with 1 M aqueous HCl solution, saturated aqueous $NaHCO_3$ solution, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10% EtOAc/hexanes) gave homoallylic alcohol **38** (1.31 g, 68% for the two steps, dr >20:1) as a pale yellow oil: $[\alpha]_D^{25}$ +2.6 (*c* 1.00, $CHCl_3$); IR (film) 3445, 3297, 2979, 2906, 1061 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.88 (dddd, *J* = 16.9, 10.1, 6.8, 6.8 Hz, 1H), 5.86 (m, 1H), 5.72 (dddd, *J* = 10.6, 2.8, 1.4, 1.4 Hz, 1H), 5.11−5.05 (m, 2H), 4.67 (ddd, *J* = 7.8, 5.5, 2.3 Hz, 1H), 4.12 (m, 1H), 4.05 (ddd, *J* = 7.3, 6.0, 6.0 Hz, 1H), 3.55 (m, 1H), 3.44 (ddd, *J* = 10.1, 6.4, 3.2 Hz, 1H), 2.60 (br d, *J* = 2.7 Hz, 1H), 2.41 (d, *J* = 2.3 Hz, 1H), 2.32 (m, 1H), 2.22−2.14 (m, 2H), 2.11−2.04 (m, 2H), 2.00−1.84 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 134.4, 126.8, 125.4, 117.3, 83.5, 80.8, 76.6, 75.9, 73.2, 72.7, 68.6, 36.9, 33.2, 26.9, 26.6; HRMS (ESI) calcd for $C_{15}H_{20}O_3Na$ [(M + Na)$^+$] 271.1305, found 271.1318.

TES Ether 39. To a solution of homoallylic alcohol **38** (61.9 mg, 0.25 mmol) in THF/H_2O (3:1, v/v, 2.4 mL) at 0 °C was added saturated $HgSO_4$ solution in 1% aqueous H_2SO_4 (1.1 mL), and the resultant solution was stirred at room temperature for 2.4 h. The reaction mixture was diluted with brine and extracted with EtOAc. The organic layer was washed with a 5:1 mixture of brine and saturated aqueous $NaHCO_3$ solution, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude methyl ketone (67.9 mg) was azeotropically dried with benzene and used in the next step without further purification.

To a solution of the above methyl ketone (67.9 mg) and imidazole (44.1 mg, 0.65 mmol) in DMF (2.5 mL) at 0 °C was added TESCl (0.054 mL, 0.32 mmol), and the resultant solution was stirred at room temperature for 40 min. The reaction was quenched with saturated aqueous NH_4Cl solution at 0 °C. The resultant mixture was extracted with EtOAc, and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5−10% EtOAc/hexanes) gave TES ether **39** (87.7 mg, 92% for the two steps) as a colorless oil: $[\alpha]_D^{23}$ −23.1 (*c* 1.0, $CHCl_3$); IR (film) 2953, 2911, 2875, 1718, 1459, 1354, 1078, 1005, 741 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.90 (dddd, *J* = 10.3, 5.8, 2.1, 2.0 Hz, 1H), 5.83 (dddd, *J* = 17.2, 10.0, 7.3, 6.8 Hz, 1H), 5.66 (dddd, *J* = 10.3, 2.8, 1.4, 1.4 Hz, 1H), 5.06−4.99 (m, 2H), 4.41 (dd, *J* = 8.2, 6.7 Hz, 1H), 4.20 (m, 1H), 4.08 (ddd, *J* = 6.5, 6.2, 5.2 Hz, 1H), 3.74 (ddd, *J* = 7.3, 5.2, 4.8 Hz, 1H), 3.52 (ddd, *J* = 11.0, 5.2, 3.4 Hz, 1H), 2.35 (ddddd, *J* = 14.1, 6.2, 4.8, 1.4, 1.4 Hz, 1H), 2.22 (m, 1H), 2.16 (s, 3H), 2.15−2.05 (m, 2H), 1.95−1.82 (m, 4H), 0.92 (t, *J* = 7.9 Hz, 9H), 0.58 (q, *J* = 7.9 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 210.9, 135.5, 126.7, 126.3, 116.7, 84.4, 82.6, 76.9, 76.0, 73.8, 37.2, 29.1, 26.4, 25.78, 25.73, 6.9

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(3C), 5.0 (3C); HRMS (ESI) calcd for $C_{21}H_{36}O_4SiNa$ [(M + Na)$^+$] 403.2275, found 403.2269.

Vinylstannane 13. To a solution of KHMDS (0.5 M solution in toluene, 0.49 mL, 0.25 mmol) in THF (1 mL) at −78 °C was added dropwise a solution of TES ether **39** (85.4 mg, 0.224 mmol) in THF (0.5 mL + 0.5 mL rinse), and the resultant mixture was stirred at −78 °C for 1 h. To this solution was added a solution of $PhNTf_2$ (96.2 mg, 0.269 mmol) in THF (0.5 mL + 0.5 mL rinse), and the resultant mixture was stirred at −78 °C for 3.5 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution. The resultant mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude enol triflate (170.8 mg) was azeotropically dried with benzene and used in the next step without further purification.

To a solution of the above enol triflate (170.8 mg) in THF (2.2 mL) were successively added LiCl (95.1 mg, 2.24 mmol), $Pd(PPh_3)_4$ (25.9 mg, 0.0224 mol), and $(Me_3Sn)_2$ (0.116 mL, 0.560 mmol), and the resultant mixture was stirred at 70 °C for 4.2 h. After being cooled to room temperature, the reaction mixture was diluted with Et_2O and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure. The residue was passed through a pad of silica gel (1% Et_3N/hexanes) to remove polar impurities, and the filtrate was concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10% EtOAc/hexanes) gave vinylstannane **13** (85.9 mg, 73% for the two steps) as a colorless oil: $[\alpha]_D^{22}$ −3.6 (*c* 1.0, benzene); IR (film) 2952, 2911, 2875, 1094, 1060, 1005, 913, 767, 741 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 5.98 (dddd, *J* = 16.8, 10.0, 7.2, 6.9 Hz, 1H), 5.88 (m, 1H), 5.78 (dd, *J* = 1.7, 1.7 Hz, 1H), 5.74 (dddd, *J* = 10.0, 5.8, 2.1, 2.0 Hz, 1H), 5.29 (dd, *J* = 1.7, 1.7 Hz, 1H), 5.12 (ddd, *J* = 16.8, 3.4, 1.4 Hz, 1H), 5.07 (m, 1H), 4.61 (m, 1H), 4.12 (m, 1H), 3.97 (dd, *J* = 13.7, 6.8 Hz, 1H), 3.78 (ddd, *J* = 6.8, 5.2, 5.2 Hz, 1H), 3.59 (ddd, *J* = 10.7, 5.5, 3.1 Hz, 1H), 2.47 (ddddd, *J* = 14.0, 6.5, 4.8, 1.4, 1.4 Hz, 1H), 2.20 (ddd, *J* = 14.0, 6.9, 6.8 Hz, 1H), 2.03 (m, 1H), 1.99−1.84 (m, 3H), 1.75 (m, 1H), 1.51 (m, 1H), 1.03 (t, *J* = 7.9 Hz, 9H), 0.67 (q, *J* = 7.9 Hz, 6H), 0.24 (s, 9H); ^{13}C NMR (150 MHz, C_6D_6) δ 159.1, 135.9, 127.9, 125.5, 122.4, 116.9, 86.0, 81.7, 78.4, 76.6, 74.5, 37.9, 34.1, 29.0, 26.4, 7.3 (3C), 5.5 (3C), 8.7 (3C); HRMS (ESI) calcd for $C_{24}H_{44}O_3SiSnNa$ [(M + Na)$^+$] 551.1974, found 551.1991.

***β*-Hydroxy Ester 40.** To a solution of *i*-Pr_2NH (24.2 mL, 173 mmol) in THF (360 mL) at 0 °C was added *n*-BuLi (2.65 M solution in *n*-hexane, 62.1 mL, 165 mmol), and the resultant solution was stirred at 0 °C for 20 min. To this solution at −78 °C was added *β*-hydroxy ester **21** (19.22 g, 77.38 mmol) in THF (20 mL + 5 × 2 mL rinse) via cannula. The resultant solution was allowed to warm to −20 °C and stirred at that temperature for 35 min. To this mixture was added MeI (6.00 mL, 96.4 mmol), and the resultant mixture was allowed to warm to room temperature over a period of 25 min. The reaction was quenched with saturated aqueous NH_4Cl solution. The reaction mixture was extracted with 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 flash column chromatography (silica gel, 10% EtOAc/hexanes) gave *β*-hydroxy ester **40** (18.45 g, 91%) as an inseparable 8:1 mixture of diastereomers: $[\alpha]_D^{24}$ +12.3 (*c* 1.00, $CHCl_3$); IR (film) 3480, 2953, 2930, 2884, 2858, 1740, 1463, 1254, 1119, 838, 778 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.71 (m, 1H), 3.68 (s, 3H), 3.66 (dd, *J* = 10.1, 3.6 Hz, 1H), 3.58 (dd, *J* = 10.1, 5.5 Hz, 1H), 2.84 (d, *J* = 6.9 Hz, 1H), 2.67 (dq, *J* = 7.3, 6.9 Hz, 1H), 1.16 (d, *J* = 7.3 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.9, 73.5, 64.5, 51.7, 42.0, 25.8 (3C), 18.2, 13.9, 5.46, 5.51; HRMS (ESI) calcd for $C_{12}H_{26}O_4SiNa$ [(M + Na)$^+$] 285.1493, found 285.1475.

Amide 41. To a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (16.9 g, 173 mmol) in CH_2Cl_2 (270 mL) at 0 °C was added Me_3Al (1.4 M solution in hexanes, 100 mL, 140 mmol and 2.0 M solution in hexanes, 17.5 mL, 35.0 mmol), and the resultant mixture was stirred at 0 °C for 30 min. To this solution was added *β*-hydroxy ester **40** (15.16 g, 57.76 mmol) in CH_2Cl_2 (15 mL + 5 × 2 mL rinse) via cannula, and the resultant solution was stirred at room temperature for 6.5 h. The reaction was quenched with saturated aqueous potassium sodium tartrate solution. The resultant mixture was diluted with EtOAc and stirred vigorously for 13 h, at which point the layers became clear. The reaction mixture was extracted with 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 flash column chromatography (silica gel, 10−30% EtOAc/hexanes) gave amide **41** (12.66 g, 75%) as a pale yellow oil: $[\alpha]_D^{24}$ +29.4 (*c* 1.00 $CHCl_3$); IR (film) 3420, 2954, 2930, 2857, 1636, 1471, 1387, 1253, 993, 837, 777 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 4.29 (d, *J* = 8.2 Hz, 1H), 3.83 (m, 1H), 3.71 (dd, *J* = 10.5, 4.6 Hz, 1H), 3.67 (dd, *J* = 10.5, 6.4 Hz, 1H), 3.26 (br s, 1H), 3.18 (s, 3H), 2.82 (s, 3H), 1.27 (d, *J* = 6.4 Hz, 3H), 0.91 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.1, 74.4, 65.2, 61.5, 35.9, 31.8, 25.8 (3C), 18.2, 14.6, 5.41, 5.44; HRMS (ESI) calcd for $C_{13}H_{29}NO_4SiNa$ [(M + Na)$^+$] 314.1758, found 314.1775.

Ketone 42. To a solution of amide **41** (12.48 g, 42.82 mmol) in THF (210 mL) at 0 °C was added MeMgBr (3.0 M solution in Et_2O, 71.3 mL, 214 mmol). The resultant solution was stirred at room temperature for 13.5 h. The reaction was quenched with saturated aqueous NH_4Cl solution at 0 °C. The reaction mixture was extracted with 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 flash column chromatography (silica gel, 20% EtOAc/hexanes) gave ketone **42** (8.21 g, 78%) as a pale yellow oil: $[\alpha]_D^{25}$ +3.7 (*c* 1.00, $CHCl_3$); IR (film) 3465, 2954, 2929, 2858, 1712, 1463, 1361, 1254, 1119, 1093, 838, 778 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.70 (m, 1H), 3.65 (dd, *J* = 10.5, 4.1 Hz, 1H), 3.54 (dd, *J* = 10.5, 5.9 Hz, 1H), 2.89 (d, *J* = 5.9 Hz, 1H), 2.73 (dq, *J* = 7.3, 6.8 Hz, 1H), 2.19 (s, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 212.9, 73.8, 64.9, 48.5, 29.8, 25.8 (3C), 18.2, 13.4, 5.4, 5.5 HRMS (ESI) calcd for $C_{12}H_{26}O_3SiNa$ [(M + Na)$^+$] 269.1543, found 269.1567.

Ester 43. To a solution of ketone **42** (8.11 g, 32.9 mmol) and $(EtO)_2P(O)CH_2CO_2H$ (9.42 g, 48.0 mmol) in CH_2Cl_2 (325 mL) were added DMAP (815 mg, 6.67 mmol) and DCC (10.2 g, 49.4 mmol), and the resultant mixture was stirred at room temperature for 10.5 h. The reaction mixture was filtered through a cotton plug and the filtrate concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 12−50% EtOAc/benzene) gave ester **43** (11.38 g, 82%) as a colorless oil: $[\alpha]_D^{24}$ +27.8 (*c* 1.00, $CHCl_3$); IR (film) 3466, 2954, 2930, 2857, 1739, 1261, 1116, 1026, 971, 838, 779 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.15 (m, 1H), 4.15−4.10 (m, 4H), 3.72 (dd, *J* = 11.0, 4.3 Hz, 1H), 3.67 (dd, *J* = 11.0, 4.6 Hz, 1H), 2.96 (m, 1H), 2.92 (d, *J* = 9.6 Hz, 1H), 2.88 (d, *J* = 9.6 Hz, 1H), 2.17 (s, 3H), 1.31 (dd, *J* = 7.3, 6.4 Hz, 6H), 1.09 (d, *J* = 7.3 Hz, 3H), 0.84 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (150 MHz, C_6D_6) δ 207.2, 165.3 (d, *J* = 5.7 Hz), 76.3, 62.4 (d, *J* = 5.7 Hz), 62.2 (d, *J* = 5.7 Hz), 62.1, 47.5, 35.3 (d, *J* = 7.2 Hz), 34.4 (d, *J* = 7.2 Hz), 28.6, 26.0 (3C), 18.4, 16.3 (t, *J* = 5.7 Hz), 12.0, 5.4, 5.6; HRMS (ESI) calcd for $C_{18}H_{37}O_7PSiNa$ [(M + Na)$^+$] 447.1938, found 447.1919.

***α,β*-Unsaturated Lactone 20.** To a suspension of LiCl (2.97 g, 70.1 mmol) in CH_3CN (320 mL) were added DBU (10.5 mL, 70.2 mmol) and a solution of ester **43** (14.88 g, 35.05 mmol) in CH_3CN (20 mL + 10 mL rinse), and the resultant mixture was stirred at room temperature for 1.5 h. The reaction was quenched with saturated aqueous NH_4Cl solution. The resultant mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 8−50% EtOAc/hexanes) gave *α,β*-unsaturated lactone **20** (7.62 g, 81%) as a colorless oil: $[\alpha]_D^{25}$ −61.9 (*c* 1.00, $CHCl_3$); IR (film) 2953, 2930, 2884, 2856, 1723, 1471, 1461, 1382, 1255, 1126, 1101, 837, 778 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.69 (s, 1H), 4.14 (ddd, *J* = 8.7, 6.4, 4.1 Hz, 1H), 3.75 (dd, *J* = 10.6, 4.1 Hz, 1H), 3.69 (dd, *J* = 10.6, 6.4 Hz, 1H), 2.55 (m, 1H), 1.92 (s, 3H), 1.18 (d, *J* = 7.3 Hz, 3H), 0.83 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.6, 160.7, 115.5, 82.5, 62.6, 33.1, 25.7 (3C), 21.4, 18.2, 16.3, 5.51, 5.53; HRMS (ESI) calcd for $C_{14}H_{26}O_3SiNa$ [(M + Na)$^+$] 293.1543, found 293.1526.

Lactone 44. To a solution of *α,β*-unsaturated lactone **20** (6.95 g, 25.7 mmol) in EtOAc (130 mL) was added 10% Pd/C (699 mg), and

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the resultant suspension was stirred vigorously at room temperature for 20 h under an atmosphere of H_2 (ballon). The mixture was filtered through a plug of Celite, and the filtrate was concentrated under reduced pressure to give lactone **44** (6.96 g, 99%, dr >20:1) as a colorless oil: $[\alpha]_D^{25}$ +10.3 (*c* 1.00, $CHCl_3$); IR (film) 2955, 2929, 2883, 2857, 1741, 1472, 1463, 1252, 1128, 1094, 837, 778 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.91 (ddd, *J* = 9.6, 2.8, 2.3 Hz, 1H), 3.82 (dd, *J* = 11.5, 2.3 Hz, 1H), 3.75 (dd, *J* = 11.5, 2.8 Hz, 1H), 2.58 (dd, *J* = 17.0, 5.0 Hz, 1H), 2.06 (dd, *J* = 17.0, 10.0 Hz, 1H) 1.70−1.61 (m, 2H), 0.99 (d, *J* = 6.4 Hz, 6H), 0.86 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.6, 85.8, 63.1, 38.0, 35.3, 32.4, 25.8 (3C), 19.4, 18.2, 14.9, 5.3, 5.5; HRMS (ESI) calcd for $C_{14}H_{28}O_3SiNa$ [(M + Na)$^+$] 295.1700, found 295.1715.

Diol 45. To a solution of lactone **44** (6.92 g, 25.4 mmol) in THF/H_2O (130 mL) at 0 °C was added dropwise $LiBH_4$ (2.0 M solution in THF, 34.0 mL, 68.0 mmol), and the resultant solution was stirred at 0 °C for 11.5 h. The reaction was quenched with saturated aqueous potassium sodium tartrate solution at 0 °C. The resultant mixture was stirred at room temperature for 7 h. The resultant mixture was extracted with 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 flash column chromatography (silica gel, 20−40% EtOAc/hexanes) gave diol **45** (6.93 g, 99%) as a colorless oil: $[\alpha]_D^{26}$ −7.9 (*c* 1.00, $CHCl_3$); IR (film) 3357, 2956, 2929, 2883, 2858, 1471, 1462, 1253, 1099, 1058, 837, 777 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.73−3.60 (m, 3H), 3.44−3.38 (m, 2H), 2.68 (br s, 1H), 2.14 (m, 1H), 1.91 (br s, 1H), 1.55−1.46 (m, 3H), 0.88 (s, 9H), 0.80 (d, *J* = 6.8 Hz, 3H), 0.67 (d, *J* = 6.8 Hz, 3H), 0.05 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 73.2, 65.9, 61.1, 38.7, 38.2, 28.1, 25.9 (3C), 18.2, 13.6, 9.4, −5.3, −5.4; HRMS (ESI) calcd for $C_{14}H_{32}O_3SiNa$ [(M + Na)$^+$] 299.2013, found 299.2012.

Diol 46. To a solution of diol **45** (6.87 g, 24.8 mmol) in THF (125 mL) were added imidazole (4.08 g, 59.9 mmol) and TBDPSCl (7.74 mL, 29.8 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 brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (3% EtOAc/hexanes) gave a TBDPS ether (12.36 g, 97%) as a colorless oil: $[\alpha]_D^{26}$ −6.4 (*c* 1.00, $CHCl_3$); IR (film) 3582, 2956, 2929, 2857, 1471, 1462, 1427, 1254, 1095, 836, 778, 738 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.67−7.65 (m, 4H), 7.42−7.35 (m, 6H), 3.72−3.64 (m, 3H), 3.43−3.37 (m, 2H), 2.46 (d, *J* = 2.8 Hz, 1H), 2.10 (m, 1H), 1.57−1.44 (m, 3H), 1.03 (s, 9H), 0.88 (s, 9H), 0.74 (d, *J* = 6.9 Hz, 3H), 0.64 (d, *J* = 6.9 Hz, 3H), 0.05 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.6 (4C), 134.1 (2C), 129.5 (2C), 127.6 (4C), 73.2, 65.8, 62.8, 39.1, 38.1, 28.6, 26.9 (3C), 25.9 (3C), 19.2, 18.3, 13.7, 9.6, −5.3, −5.4; HRMS (ESI) calcd for $C_{30}H_{50}O_3Si_2Na$ [(M + Na)$^+$] 537.3191, found 537.3187.

To the above alcohol (11.7 g, 22.7 mmol) in EtOH (113 mL) was added PPTS (1.14 g, 4.54 mmol), and the resultant solution was heated at 50 °C for 12.5 h. The reaction mixture was neutralized with Et_3N and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (10−60% EtOAc/hexanes) gave diol **46** (7.86 g, 86%) as a colorless oil: $[\alpha]_D^{26}$ −3.4 (*c* 1.00 $CHCl_3$); IR (film) 3376, 2959, 2930, 2857, 1471, 1461, 1427, 1388, 1110, 1086, 998, 822, 739 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.67−7.63 (m, 4H), 7.42−7.34 (m, 6H), 3.74−3.64 (m, 3H), 3.50−3.40 (m, 2H), 2.05 (m, 1H), 2.00 (br s, 1H), 1.95 (br s, 1H), 1.57−1.43 (m, 3H), 1.03 (s, 9H), 0.74 (d, *J* = 6.9 Hz, 3H), 0.67 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.6 (4C), 134.0 (2C), 129.5 (2C), 127.6 (4C), 73.9, 65.3, 62.4, 39.2, 38.0, 28.5, 26.9 (3C), 19.2, 13.7, 9.7; HRMS (ESI) calcd for $C_{24}H_{36}O_3SiNa$ [(M + Na)$^+$] 423.2326, found 423.2336.

Alcohol 47. To a solution of diol **46** (7.86 g, 19.6 mmol) in CH_2Cl_2 (100 mL) at 0 °C were added *p*-$MeOC_6H_4CH(OMe)_2$ (6.70 mL, 39.3 mmol) and CSA (455 mg, 1.96 mmol), and the resultant solution was stirred at room temperature for 2.5 h. The reaction mixture was neutralized with Et_3N and concentrated under reduced pressure. The residue was roughly purified by flash column chromatography (silica gel, 3% EtOAc/hexanes) to give an acetal (13.29 g), which was used directly without further purification.

To a solution of the above acetal (13.29 g) in CH_2Cl_2 (100 mL) at −78 °C was added DIBALH (1.02 M solution in *n*-hexane, 77.0 mL, 78.5 mmol), and the resultant solution was allowed to warm to −20 °C over a period of 2.5 h. The reaction was quenched with MeOH. The resultant mixture was diluted with EtOAc and saturated aqueous potassium sodium tartrate solution and stirred vigorously at room temperature for 3.5 h, at which point the layers became clear. The resultant mixture was extracted with 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 flash column chromatography (silica gel, 10−50% EtOAc/hexanes) gave alcohol **47** (9.58 g, 94% for the two steps) as a colorless oil: $[\alpha]_D^{24}$ −7.1 (*c* 1.00, $CHCl_3$); IR (film) 3443, 2957, 2930, 2857, 1612, 1513, 1427, 1247, 1111, 1089, 1037, 822, 738 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.67−7.64 (m, 4H), 7.42−7.33 (m, 6H), 7.22 (d, *J* = 8.8 Hz, 2H), 6.84−6.81 (m, 2H), 4.46 (s, 2H), 3.79−3.75 (m, 4H), 3.72−3.64 (m, 2H), 3.54 (ddd, *J* = 11.5, 6.4, 5.0 Hz, 1H), 3.31 (ddd, *J* = 8.7, 5.5, 3.2 Hz, 1H), 2.03 (m, 1H), 1.82 (dd, *J* = 6.4, 6.0 Hz, 1H), 1.76 (m, 1H), 1.58 (m, 1H), 1.42 (m, 1H), 1.02 (s, 9H), 0.71 (d, *J* = 7.3 Hz, 3H), 0.70 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.2, 135.6 (4C), 134.0 (2C), 130.5, 129.5 (2C), 129.4 (2C), 127.6 (4C), 113.9 (2C), 81.3, 71.6, 62.4, 61.4, 55.2, 38.1, 37.5, 28.7, 26.8 (3C), 19.2, 14.3, 10.1; HRMS (ESI) calcd for $C_{32}H_{44}O_4SiNa$ [(M + Na)$^+$] 543.2901, found 543.2885.

Aldehyde 19. To a solution of alcohol **47** (1.27 g, 2.44 mmol) in CH_2Cl_2/DMSO (1:1, v/v, 12 mL) at 0 °C were added Et_3N (1.35 mL, 9.69 mmol) and SO_3·pyridine (1.17 g, 7.35 mmol), and the resultant mixture was stirred at 0 °C for 40 min. The reaction was quenched with 1 M aqueous HCl solution at 0 °C. The resultant mixture was extracted with *t*-BuOMe, and the organic layer was washed with saturated aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5% EtOAc/hexanes) gave aldehyde **19** (1.24 g, 98%) as a pale yellow oil: $[\alpha]_D^{26}$ −49.0 (*c* 1.00, $CHCl_3$); IR (film) 2958, 2931, 2857, 1730, 1612, 1513, 1427, 1249, 1111, 1089, 1036, 822, 740, 703 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.52 (d, *J* = 3.7 Hz, 1H), 7.67−7.63 (m, 4H), 7.42−7.33 (m, 6H), 7.23−7.20 (m, 2H), 6.85−6.81 (m, 2H), 4.52 (d, *J* = 11.5 Hz, 1H), 4.33 (d, *J* = 11.5 Hz, 1H), 3.77 (s, 3H), 3.70−3.62 (m, 2H), 3.40 (dd, *J* = 9.2, 3.7 Hz, 1H), 2.15 (m, 1H), 1.86 (m, 1H), 1.54 (m, 1H), 1.42 (m, 1H), 1.02 (s, 9H), 0.68 (d, *J* = 7.3 Hz, 3H), 0.64 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 203.9, 159.4, 135.6 (4C), 134.0 (2C), 129.7 (2C), 129.5 (2C), 129.4, 127.6 (4C), 113.8 (2C), 85.4, 72.3, 62.2, 55.2, 37.7, 37.0, 28.2, 26.8 (3C), 19.1, 13.6, 9.3; HRMS (ESI) calcd for $C_{32}H_{42}O_4SiNa$ [(M + Na)$^+$] 541.2745, found 541.2724.

TES Ether 49. To a solution of propargylic alcohol **48** (5.38 g, 29.2 mmol) in DMF (60 mL) were added TESCl (6.40 mL, 38.2 mmol), Et_3N (12.1 mL, 87.3 mmol), and DMAP (367 mg, 3.00 mmol), and the resultant solution was stirred at room temperature for 90 min. The reaction mixture was diluted with *t*-BuOMe, washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 1% EtOAc/hexanes) gave TES ether **49** (7.83 g, 90%) as a colorless oil: $[\alpha]_D^{24}$ −9.4 (*c* 1.00, $CHCl_3$); IR (film) 3314, 2957, 2913, 2877, 1734, 1480, 1282, 1157, 1122, 1038, 1003 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.12−3.98 (m, 3H), 2.42 (ddd, *J* = 16.8, 6.6, 2.4 Hz, 1H), 2.35 (ddd, *J* = 16.8, 6.0, 2.4 Hz, 1H), 1.97 (t, *J* = 2.4 Hz, 1H), 1.19 (s, 9H), 0.94 (t, *J* = 8.3 Hz, 9H), 0.61 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.3, 80.4, 70.3, 68.8, 67.0, 38.8, 27.2 (3C), 24.7, 6.7 (3C), 4.8 (3C); HRMS (ESI) calcd for $C_{16}H_{30}O_3SiNa$ [(M + Na)$^+$] 321.1856, found 321.1835.

Iodoalkyne 18. To a solution of TES ether **49** (6.95 g, 23.3 mmol) and morpholine (26.3 mL, 302 mmol) in benzene (120 mL) was added I_2 (11.8 g, 46.5 mmol). The resultant mixture was heated at 60 °C for 5.5 h. After cooling to room temperature, the reaction mixture was diluted with Et_2O, and washed with saturated aqueous Na_2SO_3 solution, H_2O, and saturated aqueous NH_4Cl solution. The organic

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layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 4% EtOAc/hexanes) gave iodoalkyne **18** (9.87 g, quant) as a pale yellow oil: $[\alpha]_D^{25}$ −3.7 (*c* 1.00, $CHCl_3$); IR (film) 2956, 2911, 2876, 1732, 1479, 1457, 1282, 1238, 1157, 1122, 1002 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.05−3.96 (m, 3H), 2.58 (dd, *J* = 16.8, 6.0 Hz, 1H), 2.51 (dd, *J* = 16.8, 6.0 Hz, 1H), 1.19 (s, 9H), 0.94 (t, *J* = 8.2 Hz, 9H), 0.60 (q, *J* = 7.7 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.2, 90.7, 77.2, 68.9, 67.1, 38.8, 27.2 (3C), 27.1, 6.8 (3C), 4.8 (3C); HRMS (ESI) calcd for $C_{16}H_{29}IO_3SiNa$ [(M + Na)$^+$] 447.0823, found 447.0821.

(*Z*)-Vinyl Iodide 50. To a solution of iodoalkyne **18** (214 mg, 0.505 mmol) in THF/*i*-PrOH (1:1, v/v, 5 mL) at 0 °C were added NBSH (273.8 mg, 1.262 mmol) and Et_3N (0.175 mL, 1.26 mmol). The resultant mixture was stirred at room temperature for 41 h. The reaction mixture was diluted with EtOAc, washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 1−5% acetone/hexanes) gave (*Z*)-vinyl iodide **50**, which was contaminated with some impurities. Further purification by preparative HPLC gave (*Z*)-vinyl iodide **50** (90.9 mg, 42%) as a colorless oil: $[\alpha]_D^{23}$ −1.1 (*c* 1.00, $CHCl_3$); IR (film) 2956, 2910, 2876, 1731, 1480, 1458, 1397, 1364, 1281, 1238, 1152, 1117, 1003 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.32−6.26 (m, 2H), 4.00−3.89 (m, 3H), 2.37−2.35 (m, 2H), 1.20 (s, 9H), 0.94 (t, *J* = 7.8 Hz, 9H), 0.60 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.4, 137.0, 84.7, 68.7, 67.4, 40.1, 38.9, 27.3 (3C), 6.9 (3C), 5.0 (3C); HRMS (ESI) calcd for $C_{16}H_{31}IO_3SiNa$ [(M + Na)$^+$] 449.0979, found 449.0982.

Allylic Alcohol 51 via NHK Coupling of 19 and 50. To a solution of $CrCl_2$ (95%, 100 mg, 0.773 mmol) and $NiCl_2$ (1.0 mg, 7.7 mmol) in degassed DMSO (1 mL) was added a solution of aldehyde **19** (42.4 mg, 81.7 mmol) and (*Z*)-vinyl iodide **50** (69.7 mg, 163 mmol) in degassed DMSO (1.05 mL + 2 × 0.2 mL rinse) via cannula. The resultant solution was stirred at room temperature for 62.5 h. The reaction was quenched with 1 M DL-serine solution in saturated aqueous $NaHCO_3$ solution at 0 °C, and the resultant solution was stirred vigorously at room temperature for 10 min. The mixture was filtered through a pad of Celite, and the filtrate was extracted with Et_2O, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5−20% EtOAc/hexanes) gave allylic alcohol **51** (12.6 mg, 19%) as an inseparatable 3:1 mixture of diastereomers, and recovered aldehyde **19** (28.0 mg, 34%), respectively. The spectroscopic data of **51** are described below.

Propargylic Alcohols 52a,b. To a solution of $CrCl_2$ (95%, 7.65 g, 62.3 mmol) and $NiCl_2$ (76.5 mg, 0.59 mmol) in degassed THF (30 mL) was added a solution of aldehyde **19** (3.23 g, 6.23 mmol) and iodoalkyne **18** (9.25 g, 21.8 mmol) in degassed THF (26 mL + 6 mL rinse). The resultant solution was stirred at room temperature for 61 h. The reaction was quenched with 1 M DL-serine solution in saturated aqueous $NaHCO_3$ solution at 0 °C, and the resultant solution was stirred vigorously for 10 min. The mixture was filtered through a pad of Celite, and the filtrate was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5−15% EtOAc/hexanes) gave propargylic alcohols **52a,b** (5.07 g, 99%) as a 2:1 mixture of diastereomers. A portion of the mixture of **52a,b** could be separated by careful flash column chromatography (silica gel, 5−15% EtOAc/hexanes) to give analytically pure **52a** and **52b**. Data for major isomer **52a**: $[\alpha]_D^{21}$ +11.5 (*c* 1.00, $CHCl_3$); IR (film) 3502, 2957, 2933, 2876, 1731, 1613, 1513, 1460, 1427, 1388, 1361, 1283, 1247, 1156, 1111, 1036, 999, 822, 741, 702 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.66−7.65 (m, 4H), 7.41−7.33 (m, 6H), 7.24−7.23 (m, 2H), 6.82−6.80 (m, 2H), 4.66 (d, *J* = 11.5 Hz, 1H), 4.56 (d, *J* = 11.0 Hz, 1H), 4.45 (br s, 1H), 4.12 (dd, *J* = 11.0, 4.1 Hz, 1H), 4.03 (dd, *J* = 11.0, 5.0 Hz, 1H), 3.96 (m, 1H), 3.76 (s, 3H), 3.72−3.62 (m, 2H), 3.38 (dd, *J* = 9.7, 3.7 Hz, 1H), 2.45−2.36 (m, 2H), 2.14 (m, 1H), 1.81 (m, 1H), 1.55−1.54 (m, 2H), 1.45 (m, 1H), 1.18 (s, 9H), 1.01 (s, 9H), 0.93 (t, *J* = 7.8 Hz, 9H), 0.72 (d, *J* = 7.3 Hz, 3H), 0.71 (d, *J* = 6.9 Hz, 3H), 0.58 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.4, 159.3, 135.7 (4C), 134.2, 130.8, 129.57, 129.56 (4C), 127.7 (4C), 114.0 (2C), 84.1, 82.7, 80.4, 74.6, 69.0, 67.2, 64.7, 62.7, 55.3, 39.6, 38.9, 38.5, 28.3, 27.3 (3C), 27.0 (3C), 25.2, 19.3, 13.8, 10.1, 6.9 (3C), 4.9 (3C); HRMS (ESI) calcd for $C_{48}H_{72}O_7Si_2Na$ [(M + Na)$^+$] 839.4709, found 839.4716. Data for minor isomer **52b**: $[\alpha]_D^{22}$ −18.1 (*c* 1.00, $CHCl_3$); IR (film) 3503, 2957, 2932, 2876, 1730, 1613, 1513, 1461, 1427, 1388, 1362, 1282, 1247, 1155, 1111, 1037, 999, 822, 739, 702 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.66−7.63 (m, 4H), 7.41−7.32 (m, 6H), 7.26−7.24 (m, 2H), 6.81−6.79 (m, 2H), 4.90 (d, *J* = 10.5 Hz, 1H), 4.59 (d, *J* = 10.1 Hz, 1H), 4.38 (br s, 1H), 4.13 (dd, *J* = 11.0, 5.0 Hz, 1H), 4.03 (dd, *J* = 11.0, 5.0 Hz, 1H), 3.99 (m, 1H), 3.76 (s, 3H), 3.72−3.63 (m, 2H), 3.38 (d, *J* = 1.4 Hz, 1H), 2.48 (ddd, *J* = 16.9, 6.8, 2.3 Hz, 1H), 2.40 (ddd, *J* = 16.5, 5.5, 2.3 Hz, 1H), 2.10 (m, 1H), 1.76 (m, 1H), 1.60−1.53 (m, 2H), 1.45 (m, 1H), 1.18 (s, 9H), 1.01 (s, 9H), 0.94 (t, *J* = 8.3 Hz, 9H), 0.72 (d, *J* = 7.4 Hz, 3H), 0.71 (d, *J* = 6.8 Hz, 3H), 0.60 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.2, 159.2, 135.5 (4C), 134.0, 130.4, 129.6 (2C), 129.5 (2C), 127.6 (4C), 113.8, 113.7 (2C), 83.8, 83.2, 81.4, 74.7, 68.9, 67.1, 62.4, 62.0, 55.2, 38.8, 38.5, 38.2, 28.1, 27.2 (3C), 26.8 (3C), 25.1, 19.1, 13.7, 10.3, 6.8 (3C), 4.8 (3C); HRMS (ESI) calcd for $C_{48}H_{72}O_7Si_2Na$ [(M + Na)$^+$] 839.4709, found 839.4713.

Alkynyl Ketone 53. To a solution of propargylic alcohols **52a,b** (3.82 g, 4.67 mmol) in CH_2Cl_2 (47 mL) were added $NaHCO_3$ (1.96 g, 23.3 mmol) and Dess−Martin periodinane (2.97 g, 7.00 mmol), and the resultant mixture was stirred at room temperature for 1.5 h. The reaction was quenched with a 1:1 mixture of saturated aqueous $NaHCO_3$ solution and saturated aqueous Na_2SO_3 solution at 0 °C. The resultant mixture was diluted with Et_2O, washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 20% EtOAc/hexanes) gave alkynyl ketone **53** (3.65 g, 96%) as a yellow oil: $[\alpha]_D^{25}$ +57.0 (*c* 1.00 $CHCl_3$); IR (film) 2957, 2934, 2876, 2361, 2341, 2210, 1733, 1672, 1613, 1514, 1247, 1154, 1112, 740, 703 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 7.80−7.76 (m, 4H), 7.26−7.22 (m, 8H), 6.80−6.76 (m, 2H), 4.68 (m, 1H), 4.23 (m, 1H), 4.14−4.08 (m, 2H), 3.92 (m, 1H), 3.74−3.67 (m, 3H), 3.33 (s, 3H), 2.45 (m, 1H), 2.40−2.32 (m, 2H), 2.27 (m, 1H), 1.61 (m, 1H), 1.39 (m, 1H), 1.19−1.16 (m, 9H), 1.15−1.13 (m, 9H), 0.98−0.93 (m, 9H), 0.79−0.75 (m, 3H), 0.64−0.61 (m, 3H), 0.59−0.54 (m, 6H); ^{13}C NMR (150 MHz, C_6D_6) δ 189.7, 177.4, 159.9, 136.0 (4C), 134.4, 130.0 (2C), 129.8 (2C), 128.5 (4C), 128.3, 128.0 (2C), 114.0 (2C), 91.5, 87.7, 72.2, 68.8, 67.0, 62.6, 54.7, 39.1, 38.8, 38.4, 28.6, 27.2 (3C), 27.1 (3C), 25.6, 19.4, 13.5, 9.7, 7.0 (3C), 5.1 (3C); HRMS (ESI) calcd for $C_{48}H_{70}O_7Si_2Na$ [(M + Na)$^+$] 837.4552, found 837.4576.

Propargylic Alcohol 52a via $Zn(BH_4)_2$ Reduction of Alkynyl Ketone 53. To a solution of alkynyl ketone **53** (1.87 g, 2.29 mmol) in Et_2O (23 mL) at −78 °C was added $Zn(BH_4)_2$ (0.5 M solution in Et_2O, 19.3 mL, 9.65 mmol), and the resultant mixture was stirred at −40 °C for 46 h. The reaction was quenched with 20% aqueous AcOH at −40 °C. The resultant mixture was extracted with Et_2O, and the organic layer was washed with saturated aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 8−15% EtOAc/hexanes) gave propargylic alcohol **52a** (1.24 g, 66%, dr >20:1) as a yellow oil. Data for **52a** are reported above.

Allylic Alcohol 51. To a solution of propargylic alcohol **52a** (1.23 g, 1.51 mmol) in EtOAc (20 mL) was added Lindlar's catalyst (0.26 g), and the resultant mixture was stirred at room temperature under an atmosphere of H_2 (balloon) for 8 h. At this point, additional Lindlar's catalyst (0.13 g) was added to the reaction mixture. The resultant mixture was further stirred at room temperature under an atmosphere of H_2 (balloon) for 2 h. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure to give allylic alcohol **51** (1.23 g, 99%) as a yellow oil: $[\alpha]_D^{26}$ +6.4 (*c* 1.00, $CHCl_3$); IR (film) 3522, 2957, 2876, 1731, 1514, 1248, 1156, 1111, 740 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.67−7.64 (m, 4H), 7.41−7.33 (m, 6H), 7.24 (d, *J* = 8.7 Hz, 2H), 6.82−6.79 (m, 2H), 5.83 (dd, *J* = 11.0, 9.1 Hz, 1H), 5.62 (ddd, *J* = 11.0, 7.8, 7.3 Hz, 1H), 4.69 (d, *J* = 11.0 Hz, 1H), 4.59 (d, *J* = 11.5 Hz, 1H), 4.47 (m, 1H), 4.02−

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3.91 (m, 3H), 3.76 (s, 3H), 3.70−3.62 (m, 2H), 3.45 (dd, J = 9.2, 2.8 Hz, 1H), 2.43 (m, 1H), 2.30 (m, 1H), 2.20−2.14 (m, 2H), 1.56−1.41 (m, 3H), 1.20 (s, 9H), 1.01 (s, 9H), 0.94 (t, J = 7.8 Hz, 9H), 0.74 (d, J = 6.8 Hz, 3H), 0.67 (d, J = 6.8 Hz, 3H), 0.61 (q, J = 7.8 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.4, 159.0, 135.6 (4C), 134.1 (2C), 131.3, 130.7, 129.4 (2C), 129.2 (2C), 128.6, 127.6 (4C), 113.7 (2C), 84.4, 74.7, 69.6, 68.9, 67.1, 62.6, 55.2, 38.83, 38.77, 38.4, 33.1, 28.3, 27.2 (3C), 26.8 (3C), 19.1, 13.8, 10.3, 6.8 (3C), 4.8 (3C); HRMS (ESI) calcd for $C_{48}H_{74}O_7Si_2Na$ [(M + Na)$^+$] 841.4865, found 841.4869.

Alcohol 54. To a mixture of $TCEOCH_2Cl$ (13.0 g, 65.4 mmol), Bu_4NI (0.64 g, 1.7 mmol), and i-Pr_2NEt (22.8 mL, 131 mmol) in DCE (22 mL) was added a solution of allylic alcohol **51** (3.58 g, 4.37 mmol) in DCE (20 mL + 2 mL rinse) via cannula. The resultant mixture was stirred at 120 °C for 2 h under microwave irradiation. The reaction mixture was cooled to room temperature and filtered through a plug of silica gel. The filtrate was concentrated under reduced pressure. The residue was roughly purified by flash column chromatography (silica gel, 10% EtOAc/hexanes) to give a trichloroethoxymethyl ether (8.04 g), which was contaminated with some impurities. This material was used in the next step without further purification.

To a solution of the above trichloroethoxymethyl ether (8.04 g) in THF (44 mL) at −78 °C was added dropwise DIBALH (1.02 M solution in n-hexane, 17.1 mL, 17.5 mmol). The resultant mixture was allowed to warm to 0 °C over a period of 0.5 h. The reaction was quenched with MeOH at −78 °C. The reaction mixture was diluted with EtOAc and saturated aqueous potassium sodium tartrate solution, and the resultant mixture was stirred vigorously at room temperature until the layers became clear. The organic layer was separated, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10% EtOAc/hexanes) gave alcohol **54** (3.55 g, 91% for the two steps) as a pale orange oil: $[\alpha]_D^{23}$ +49.9 (c 1.00, $CHCl_3$); IR (film) 3466, 2956, 2933, 2875, 1513, 1248, 1111, 1084, 1019, 723, 703 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66−7.63 (m, 4H), 7.40−7.38 (m, 2H), 7.36−7.33 (m, 4H), 7.24−7.21 (m, 2H), 6.81−6.78 (m, 2H), 5.81 (ddd, J = 11.3, 8.2, 6.2 Hz, 1H), 5.61 (m, 1H), 4.89 (d, J = 7.2 Hz, 1H), 4.81 (d, J = 7.2 Hz, 1H), 4.78 (d, J = 11.0 Hz, 1H), 4.67 (dd, J = 10.0, 2.4 Hz, 1H), 4.46 (d, J = 11.0 Hz, 1H), 4.21 (d, J = 11.3 Hz, 1H), 4.08 (d, J = 11.3 Hz, 1H), 3.77 (m, 1H), 3.75 (s, 3H), 3.68−3.59 (m, 2H), 3.51 (ddd, J = 11.3, 5.8, 4.1 Hz, 1H), 3.48−3.42 (m, 2H), 2.46 (m, 1H), 2.29 (dddd, J = 14.8, 6.2, 6.2, 2.0 Hz, 1H), 2.14 (m, 1H), 2.00 (dd, J = 6.5, 6.1 Hz, 1H), 1.53−1.46 (m, 2H), 1.43 (m, 1H), 1.00 (s, 9H), 0.95 (t, J = 7.9 Hz, 9H), 0.69 (d, J = 7.3 Hz, 3H), 0.68 (d, J = 7.2 Hz, 3H), 0.60 (q, J = 7.9 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.0, 135.5 (4C), 134.09, 134.07, 132.1, 131.2, 129.45, 129.44, 129.3 (2C), 127.5 (4C), 126.3, 113.6 (2C), 96.8, 92.4, 83.3, 79.8, 74.2, 73.7, 72.4, 65.9, 62.7, 55.2, 38.7, 38.4, 32.7, 28.2, 26.8 (3C), 19.1, 13.6, 10.7, 6.8 (3C), 4.9 (3C); HRMS (ESI) calcd for $C_{46}H_{69}Cl_3O_7Si_2Na$ [(M + Na)$^+$] 917.3540, found 917.3542.

Alcohol 55. To a solution of alcohol **54** (1.134 g, 1.265 mmol) and Et_3N (0.880 mL, 6.32 mmol) in CH_2Cl_2/DMSO (1:1, v/v, 12.6 mL) at 0 °C was added SO_3·pyridine complex (604 mg, 3.79 mmol), and the resultant solution was stirred at 0 °C for 3.5 h. The reaction was quenched with a 1:1 mixture of saturated aqueous $NaHCO_3$ solution and saturated aqueous Na_2SO_3 solution. The reaction mixture was extracted with Et_2O, and the organic layer was washed with brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was roughly purified by flash column chromatography (7−15% EtOAc/hexanes) to give crude aldehyde (1.081 g), which was immediately used in the next reaction.

To a solution of the above aldehyde (1.081 g), 2-methyl-2-butene (1.28 mL, 12.1 mmol), and NaH_2PO_4 (434 mg, 3.62 mmol) in t-BuOH/H_2O (5:1, v/v, 12 mL) at 0 °C was added $NaClO_2$ (79% purity, 415 mg, 3.63 mmol). The resultant mixture was then allowed to warm to room temperature over a period of 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution at 0 °C. The reaction mixture was extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude carboxylic acid (1.186 g) was azeotropically dried with benzene and used in the next step without further purification.

To a solution of the above carboxylic acid (1.186 g) in CH_2Cl_2 (12 mL) at 0 °C were added p-toluenethiol (165 mg, 1.33 mmol), i-Pr_2NEt (0.274 mL, 1.57 mmol), and PyBOP (692 mg, 1.33 mmol). The resultant mixture was stirred at room temperature for 1.5 h before it was concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 1−3% EtOAc/hexanes, gradient elution) gave alcohol **55** (966.7 mg, 85% for the three steps) as a colorless oil: $[\alpha]_D^{24}$ +109.1 (c 1.0, $CHCl_3$); IR (film) 3481, 2958, 2931, 2895, 2858, 1698, 1514, 1247, 1111, 1084, 1019, 808, 704 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67−7.62 (m, 4H), 7.41−7.32 (m, 6H), 7.28−7.20 (m, 6H), 6.83−6.79 (m, 2H), 5.81 (ddd, J = 11.0, 8.9, 6.5 Hz, 1H), 5.70 (m, 1H), 4.99 (d, J = 6.9 Hz, 1H), 4.84 (d, J = 6.9 Hz, 1H), 4.72 (d, J = 11.0 Hz, 1H), 4.67 (dd, J = 10.0, 3.5 Hz, 1H), 4.49 (d, J = 11.0 Hz, 1H), 4.35 (ddd, J = 6.5, 4.4, 4.1 Hz, 1H), 4.22 (d, J = 11.3 Hz, 1H), 4.11 (d, J = 11.3 Hz, 1H), 3.76 (s, 3H), 3.69−3.60 (m, 2H), 3.54 (d, J = 4.8 Hz, 1H), 3.48 (dd, J = 8.6, 3.8 Hz, 1H), 2.79 (dddd, J = 14.5, 8.9, 4.1, 1.1 Hz, 1H), 2.60 (dddd, J = 14.5, 6.8, 6.5, 1.4 Hz, 1H), 2.36 (s, 3H), 2.12 (m, 1H), 1.60−1.50 (m, 2H), 1.43 (m, 1H), 1.01 (s, 9H), 0.75 (d, J = 6.9 Hz, 3H), 0.72 (d, J = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.1, 159.1, 139.7, 135.5 (4C), 134.6 (2C), 134.0 (2C), 130.7, 130.1 (2C), 129.9, 129.6 (2C), 129.5 (2C), 127.6 (5C), 123.6, 113.6 (2C), 96.6, 92.8, 83.1, 79.8, 76.7, 74.2, 73.8, 62.6, 55.2, 38.6, 38.4, 33.7, 28.4, 26.9 (3C), 21.3, 19.1, 14.1, 10.9; HRMS (ESI) calcd for $C_{47}H_{59}Cl_3O_7SSiNa$ [(M + Na)$^+$] 923.2709, found 923.2704.

Thioester 14. To a solution of alcohol **55** (886.4 mg, 0.9822 mmol) in CH_2Cl_2 (9.8 mL) at 0 °C were added 2,6-lutidine (0.27 mL, 2.4 mmol) and TESOTf (0.27 mL, 1.2 mmol), and the resultant solution was stirred at 0 °C for 30 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 brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 7−10% EtOAc/hexanes) gave thioester **14** (965.5 mg, 97%) as a colorless oil: $[\alpha]_D^{24}$ +88.0 (c 1.0, $CHCl_3$); IR (film) 2956, 2933, 1878, 1699, 1514, 1248, 1112, 1089, 1019, 807, 724, 703 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66−7.62 (m, 4H), 7.41−7.37 (m, 2H), 7.37−7.32 (m, 4H), 7.24−7.20 (m, 4H), 7.19−7.16 (m, 2H), 6.80−6.77 (m, 2H), 5.89 (ddd, J = 11.3, 6.9, 6.8 Hz, 1H), 5.68 (dddd, J = 11.3, 10.0, 1.7, 1.4 Hz, 1H), 4.87 (d, J = 6.9 Hz, 1H), 4.81 (d, J = 6.9 Hz, 1H), 4.80 (d, J = 11.3 Hz, 1H), 4.65 (dd, J = 10.0, 1.4 Hz, 1H), 4.45 (d, J = 11.3 Hz, 1H), 4.38 (dd, J = 5.8, 5.5 Hz, 1H), 4.22 (d, J = 11.3 Hz, 1H), 4.07 (d, J = 11.3 Hz, 1H), 3.75 (s, 3H), 3.68−3.59 (m, 2H), 3.43 (dd, J = 10.0, 1.7 Hz, 1H), 2.67−2.59 (m, 2H), 2.33 (s, 3H), 2.15 (m, 1H), 1.52−1.39 (m, 3H), 1.01 (t, J = 7.9 Hz, 9H), 1.01 (s, 9H), 0.73−0.68 (m, 6H), 0.67 (d, J = 6.9 Hz, 3H), 0.66 (d, J = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.9, 158.9, 139.3, 135.5 (4C), 134.6 (2C), 134.11, 134.08, 131.3, 130.4, 129.9 (2C), 129.4 (2C), 129.3 (2C), 127.6 (4C), 127.0, 124.4, 113.6 (2C), 96.9, 92.3, 83.3, 79.7, 77.9, 74.1, 73.6, 62.7, 55.2, 38.8, 38.5, 34.5, 28.1, 26.8 (3C), 21.3, 19.1, 13.3, 10.6, 6.8 (3C), 4.7 (3C); HRMS (ESI) calcd for $C_{53}H_{73}Cl_3O_7SSi_2Na$ [(M + Na)$^+$] 1037.3573, found 1037.3587.

α,β-Unsaturated Ketone 56. To a suspension of thioester **14** (120 mg, 0.118 mmol), CuDPP (66.4 mg, 0.236 mmol), and $Pd_2(dba)_3$ (10.8 mg, 0.0118 mmol) in degassed hexanes (0.5 mL) was added a portion (0.25 mL, 0.047 mmol) of a stock solution of triethylphosphite (0.032 mL, 0.19 mmol) in degassed THF (0.97 mL). After the mixture was stirred at room temperature for 30 min, a solution of vinylstannane **13** (68.0 mg, 0.130 mmol) in degassed THF/hexanes (1:2, v/v, 1 mL + 0.5 mL rinse) was added. The resultant mixture was stirred at room temperature for 5 h. The reaction mixture was diluted with hexanes and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (2−10% EtOAc/hexanes) gave α,β-unsaturated ketone **56** (138.5 mg, 93%) as a pale yellow oil: $[\alpha]_D^{23}$ +39.5 (c 1.0, $CHCl_3$); IR (film) 2955, 2911, 2875, 1684, 1514, 1248, 1111, 1087, 1019, 725, 703 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67−7.62 (m, 4H), 7.41−7.37 (m, 2H), 7.37−7.32

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(m, 4H), 7.24−7.20 (m, 2H), 6.81−6.77 (m, 2H), 6.27 (s, 1H), 6.15 (s, 1H), 5.92−5.77 (m, 3H), 5.75 (m, 1H), 5.65 (br dd, J = 11.3, 10.0 Hz, 1H), 5.05 (br d, J = 16.8 Hz, 1H), 5.02 (ddd, J = 10.3, 1.0, 1.0 Hz, 1H), 4.88 (d, J = 6.9 Hz, 1H), 4.82 (d, J = 6.9 Hz, 1H), 4.80 (d, J = 10.7 Hz, 1H), 4.79 (br d, J = 13.7 Hz, 1H), 4.69 (dd, J = 8.6, 4.4 Hz, 1H), 4.62 (br d, J = 9.6 Hz, 1H), 4.46 (d, J = 10.7 Hz, 1H), 4.21 (d, J = 11.3 Hz, 1H), 4.11 (m, 1H), 4.08 (d, J = 11.3 Hz, 1H), 3.99 (dd, J = 12.7, 6.2 Hz, 1H), 3.76 (m, 1H), 3.75 (s, 3H), 3.67−3.58 (m, 2H), 3.53 (ddd, J = 10.3, 5.2, 3.1 Hz, 1H), 3.44 (dd, J = 10.0, 1.7 Hz, 1H), 2.62 (dddd, J = 15.1, 8.2, 4.4, 1.7 Hz, 1H), 2.44−2.34 (m, 3H), 2.20−2.05 (m, 3H), 1.98−1.86 (m, 3H), 1.53−1.38 (m, 4H), 1.00 (s, 9H), 0.94 (t, J = 7.9 Hz, 9H), 0.91 (t, J = 7.9 Hz, 9H), 0.66 (d, J = 6.9 Hz, 3H), 0.65 (d, J = 6.8 Hz, 3H), 0.60 (q, J = 7.9 Hz, 6H), 0.56 (q, J = 7.9 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.6, 158.9, 147.3, 135.5 (5C), 134.08, 134.07, 131.6, 131.3, 129.4 (2C), 129.3 (2C), 127.5 (4C), 127.3, 126.3, 125.8, 124.1, 116.7, 113.6 (2C), 96.9, 92.2, 83.3, 81.5, 79.7, 77.5, 77.1, 76.2, 75.3, 74.2, 73.84, 73.76, 62.7, 55.2, 38.7, 38.4, 37.2, 34.4, 32.8, 28.1, 27.2, 26.8 (3C), 25.8, 19.1, 13.3, 10.6, 6.9 (3C), 6.8 (3C), 5.1 (3C), 4.7 (3C); HRMS (ESI) calcd for $C_{67}H_{101}O_{10}Cl_3Si_3Na$ [(M + Na)$^+$] 1277.5660, found 1277.5686.

C12−C36 Fragment 12. To a solution of α,β-unsaturated ketone **56** (106.6 mg, 0.0848 mmol) and $CeCl_3\bullet 7H_2O$ (47.4 mg, 0.127 mmol) in EtOH (4.3 mL) at −40 °C was added $NaBH_4$ (4.2 mg, 0.110 mmol), and the resultant mixture was stirred at −40 °C for 2.5 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 brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5−10% EtOAc/hexanes) gave the C12−C36 fragment **12** (91.4 mg, 86%, dr >20:1) as a colorless oil: $[\alpha]_D^{24}$ +35.8 (c 1.0, $CHCl_3$); IR (film) 3482, 2955, 2875, 1514, 1462, 1427, 1247, 1111, 1085, 1019, 739, 724, 703 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67−7.62 (m, 4H), 7.41−7.37 (m, 2H), 7.37−7.32 (m, 4H), 7.24−7.22 (m, 2H), 6.81−6.77 (m, 2H), 5.87 (m, 1H), 5.84 (dddd, J = 16.8, 10.0, 7.2, 6.8 Hz, 1H), 5.78 (ddd, J = 11.3, 8.6, 5.2 Hz, 1H), 5.75 (m, 1H), 5.67 (m, 1H), 5.20 (s, 1H), 5.10 (s, 1H), 5.05 (br d, J = 16.8 Hz, 1H), 5.02 (m, 1H), 4.90 (d, J = 6.9 Hz, 1H), 4.85 (d, J = 6.9 Hz, 1H), 4.82 (d, J = 11.0 Hz, 1H), 4.67 (dd, J = 10.0, 1.4 Hz, 1H), 4.49 (br d, J = 13.4 Hz, 1H), 4.47 (d, J = 11.0 Hz, 1H), 4.22 (d, J = 11.3 Hz, 1H), 4.10 (d, J = 11.3 Hz, 1H), 4.07 (br s, 1H), 3.96−3.92 (m, 2H), 3.87 (ddd, J = 6.4, 6.2, 3.8 Hz, 1H), 3.74 (m, 1H), 3.75 (s, 3H), 3.69−3.60 (m, 2H), 3.52 (ddd, J = 10.6, 5.2, 3.1 Hz, 1H), 3.45 (br dd, J = 10.0, 2.0 Hz, 1H), 2.85 (br d, J = 6.5 Hz, 1H), 2.58 (m, 1H), 2.37 (m, 1H), 2.20−2.03 (m, 5H), 1.99 (m, 1H), 1.95−1.85 (m, 2H), 1.75 (dddd, J = 12.0, 8.2, 7.9, 7.6 Hz, 1H), 1.53−1.38 (m, 3H), 1.01 (s, 9H), 0.94 (t, J = 7.9 Hz, 18H), 0.68 (d, J = 6.8 Hz, 3H), 0.67 (d, J = 6.9 Hz, 3H), 0.60 (q, J = 7.9 Hz, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.9, 149.3, 135.5 (5C), 134.09, 134.07, 131.6, 131.3, 129.4 (2C), 129.3 (2C), 127.5 (5C), 126.7, 125.6, 116.7, 113.6 (2C), 110.6, 96.9, 92.8, 83.4, 81.2, 79.8, 79.7, 77.3, 76.0, 74.3, 74.1 (2C), 73.8, 73.6, 62.7, 55.2, 38.7, 38.4, 37.2, 33.1, 31.6, 28.1, 27.4, 26.8 (3C), 25.8, 19.1, 13.3, 10.6, 6.93 (3C), 6.91 (3C), 5.14 (3C), 5.06 (3C); HRMS (ESI) calcd for $C_{67}H_{103}Cl_3O_{10}Si_3Na$ [(M + Na)$^+$] 1279.5817, found 1279.5820.

Acetonide 57. To a solution of the C12−C36 fragment **12** (6.4 mg, 0.0051 mmol) in EtOH (0.26 mL) at 0 °C was added PPTS (0.3 mg, 0.001 mmol), and the resultant solution was stirred at 0 °C for 30 min and then at room temperature for 3 h. The reaction mixture was neutralized with Et_3N and concentrated under reduced pressure. The residue was passed through a short silica gel column (eluted with 50% EtOAc/hexanes) to give crude triol (5.3 mg), which was used directly in the next reaction.

To a solution of the above triol (5.3 mg) in CH_2Cl_2 (0.51 mL) were added 2,2-dimethoxypropane (0.013 mL, 0.10 mmol) and PPTS (0.3 mg, 0.001 mmol), and the resultant solution was stirred at room temperature for 6 h. The reaction mixture was neutralized with Et_3N and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 20% EtOAc/hexanes) gave acetonide **57** (4.9 mg, 89% for the two steps) as a colorless oil: $[\alpha]_D^{23}$ +45.0 (c 1.0, $CHCl_3$); IR (film) 3438, 2955, 2930, 2861, 1513, 1427, 1379, 1247, 1084, 1022, 703 cm^{-1}; H NMR (600 MHz, C_6D_6) δ 7.81−7.77 (m, 4H), 7.41−7.38 (m, 2H), 7.26−7.22 (m, 6H), 6.86−6.83 (m, 2H), 6.02 (dddd, J = 17.2, 10.3, 7.2, 6.9 Hz, 1H), 5.95 (ddd, J = 11.3, 7.2, 6.9 Hz, 1H), 5.88 (m, 1H), 5.83 (m, 1H), 5.63 (dddd, J = 10.0, 5.5, 2.1, 2.0 Hz, 1H), 5.46 (s, 1H), 5.28 (s, 1H), 5.10−5.05 (m, 2H), 5.04 (d, J = 11.0 Hz, 1H), 4.89 (dd, J = 10.0, 2.1 Hz, 1H), 4.85 (d, J = 6.8 Hz, 1H), 4.62 (d, J = 11.0 Hz, 1H), 4.60 (br d, J = 7.2 Hz, 1H), 4.57 (d, J = 6.9 Hz, 1H), 4.21 (d, J = 8.3 Hz, 1H), 4.16 (d, J = 11.0 Hz, 1H), 4.07 (ddd, J = 8.3, 8.2, 3.4 Hz, 1H), 4.02 (m, 1H), 3.98 (dd, J = 13.4, 6.5 Hz, 1H), 3.87 (d, J = 11.0 Hz, 1H), 3.80−3.71 (m, 2H), 3.60 (dd, J = 9.6, 2.1 Hz, 1H), 3.50 (ddd, J = 6.8, 6.5, 4.4, Hz, 1H), 3.33 (m, 1H), 3.31 (s, 3H), 2.66 (m, 1H), 2.58 (br s, 1H), 2.56−2.47 (m, 2H), 2.25 (m, 1H), 2,16 (m, 1H), 2.21 (m, 1H), 1.95−1.80 (m, 3H), 1.78−1.71 (m, 2H), 1.64−1.46 (m, 3H), 1.43 (s, 3H), 1.42 (s, 3H), 1.17 (s, 9H), 0.80 (d, J = 6.9 Hz, 3H), 0.78 (d, J = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 159.6, 147.1, 136.0 (4C), 135.3, 134.5 (2C), 132.7, 131.9, 129.8 (2C), 129.5 (2C), 127.8 (4C), 127.7, 126.6, 125.2, 116.9, 114.0 (2C), 112.3, 108.6, 97.5, 92.3, 84.0, 82.3, 81.2, 80.1, 79.92, 79.89, 77.8, 76.3, 74.6, 73.9, 73.5, 62.8, 54.8, 38.8 (2C), 37.5, 32.8, 31.5, 28.4, 28.2, 27.5, 27.2, 27.1 (4C), 19.4, 13.9, 11.1; HRMS (ESI) calcd for $C_{58}H_{79}O_{10}Cl_3SiNa$ [(M + Na)$^+$] 1091.4400, found 1091.4392.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02650.

^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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