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Synthesis and Structural Implication of the JKLMN-Ring Fragment of Caribbean Ciguatoxin C-CTX-1

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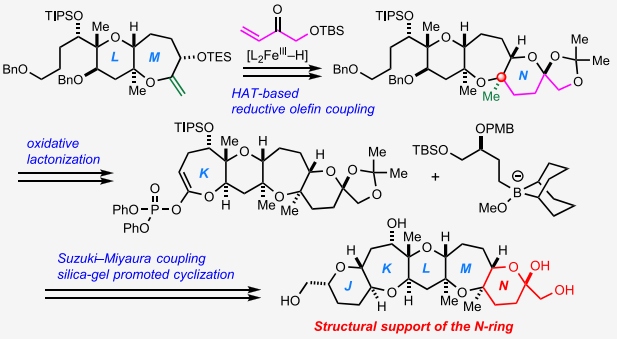
ABSTRACT: Synthesis of the JKLMN-ring fragment of Caribbean ciguatoxin C-CTX-1, the causative toxin of ciguatera fish poisoning in the Caribbean Sea and the Northeast Atlantic areas, is described in detail. Key to the synthesis are a [2,3]-sigmatropic rearrangement to construct a seven-membered α-hydroxy *exo*-enol ether, stereoselective construction of an angular tetrasubstituted stereogenic center on the seven-membered M-ring by a hydrogen atom transfer-based reductive olefin coupling, Suzuki−Miyaura coupling of the KLMN-ring enol phosphate with a highly congested M-ring, and silica gel-mediated epoxide ring opening to form the J-ring. Comparison of the nuclear magnetic resonance spectroscopic data for the synthesized fragment with those for the natural product provided support for the formerly assigned structure of the N-ring in the right-hand terminal of C-CTX-1.



INTRODUCTION

Ciguatera fish poisoning (CFP) is a foodborne disease prevalent in circumtropical areas of the Pacific Ocean, Indian Ocean, and Caribbean Sea with more than 20,000−60,000 patients annually, and continues to be a serious public health problem around the world.[1,2] Because of the globalization of trade, in addition to climate change, the incidence of CFP has recently been spreading in temperate regions,[3] and thus prevention of CFP is a global issue to be urgently addressed. Pacific ciguatoxins, the causative toxins for CFP in the Pacific Ocean, are produced by the epiphytic dinoflagellate *Gambierdiscus toxicus*, enter the food chain, and accumulate in many fish.[4] So far, more than 20 Pacific ciguatoxin congeners, including CTX3C (**1**)[5] (Figure 1), have been identified from toxic fish and/or *G. toxicus*.[6] Hirama and colleagues have reported the total synthesis of four Pacific ciguatoxins, including CTX3C (**1**),[7] and developed a sandwich enzyme-linked immunosorbent assay utilizing monoclonal antibodies for their sensitive and specific detection.[8]

In contrast to the Pacific ciguatoxins, research on Caribbean ciguatoxins has not made much progress because of the extremely limited availability of toxins from natural sources. A major Caribbean ciguatoxin, C-CTX-1, the causative toxin for CFP in the Caribbean Sea and the Northeast Atlantic areas, was first isolated in 1995 by Dickey and co-workers from Caribbean barracuda (*Sphyraena barracuda*) and horse-eye jack (*Caranx latus*).[9] In 1997, Vernoux and Lewis isolated C-CTX-1, along with a minor analogue, C-CTX-2, from horse-eye jack.[10] The structures of C-CTX-1 (**2**) and C-CTX-2 (**3**) were determined from extensive two dimensional nuclear magnetic resonance (2D NMR) experiments (Figure 1).[11] Compared to the typical Pacific ciguatoxins, such as **1**, Caribbean ciguatoxins possess 14 ether rings with a more complicated architecture. In particular, the sterically congested seven-membered M-ring with two pseudoaxially oriented angular methyl groups in a 1,3-relationship represents a formidable synthetic challenge.[12] Very recently, it has been reported on the basis of LC−MS/MS analysis that the N-ring of C-CTX-1 (**2**) is more likely a seven-membered ring as shown in structure **4** rather than a six-membered ring.[13] Hence, the structure of the N-ring should be confirmed using synthetic methods.

As part of our synthetic studies toward C-CTX-1 and its structural fragments as synthetic haptens for the development of antibody-based immunological detection methods, we have already developed a synthetic route to the LMN-ring fragment of C-CTX-1, in which a hydrogen atom transfer (HAT)-based olefin coupling[14] was utilized for an efficient construction of the M-ring.[15] We describe herein in detail an advanced synthetic route to the JKLMN-ring fragment of C-CTX-1 through Suzuki−Miyaura coupling and 6-*exo* epoxide opening, providing support for the originally assigned structure of the right-hand N-ring.

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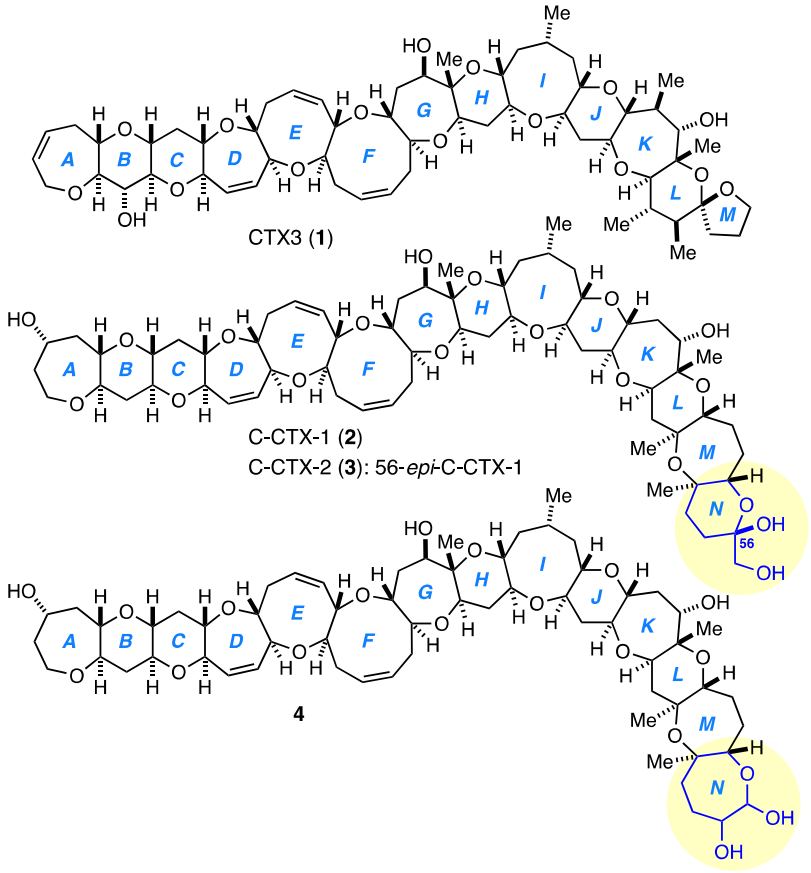

Figure 1. Structures of CTX3C (**1**), C-CTX-1 (**2**), C-CTX-2 (**3**), and newly proposed structure **4** for C-CTX-1.

RESULTS AND DISCUSSION

Synthesis Plan. Retrosynthetic analysis of the JKLMN-ring fragment **5** of C-CTX-1 (**2**) is depicted in Scheme 1. We envisioned that the J-ring of **5** would be constructed by acid- or base-catalyzed 6-*exo* epoxide opening and the precursor epoxide could be derived from enol ether **6**. Compound **6** would be synthesized from enol phosphate **7** and alkylborate **8** through Suzuki−Miyaura coupling,[16,17] and enol phosphate **7** in turn would be accessed from compound **9**. For the construction of the C53 tetrasubstituted stereogenic center as well as installation of a four-carbon unit required for the N-ring, we planned to use a HAT-based reductive olefin coupling[14,18] of *exo*-enol ether **10** with vinyl ketone **11**. The *exo*-enol ether **10** would be derived from allylic selenide **12** through [2,3]-sigmatropic rearrangement.[19] The selenide **12** would be available from the corresponding allylic alcohol, which in turn, would be accessed from enol phosphate **13** through Stille coupling with (tributylstannyl)methanol.

Synthesis of Enol Phosphate 13. The synthesis of enol phosphate **13** was carried out according to the previous method[15] with some modifications (Scheme 2). Benzylation of the known alcohol **14**[12b] (93%) and ozonolysis of the derived benzyl ether **15** provided the corresponding aldehyde, which was subjected to Brown asymmetric allylboration using (−)-*B*-allyldiisopinocamphenylborane.[20] The desired homoallylic alcohol **17** was obtained in 73% yield (two steps) with a diastereomeric ratio of 10:1. However, during scaleup, we could not secure reproducibility of the diastereomer ratio of this allylboration (4.8:1 to 15:1). No conversion of the aldehyde to **17** was observed under Keck allylation.[21] In contrast, allyltitanation with the Hafner−Duthaler reagent[22] provided gram amounts of **17** in high yield (89% in two steps) and with excellent and reproducible diastereoselectivity (dr > 20:1). The configuration of the C44 stereogenic center was confirmed using the NOE data after conversion to bis-acetonide derivative **18** (Figure 2). Protection of alcohol **17** as its TIPS ether and hydroboration of the terminal olefin using dicyclohexylborane followed by benzylation provided bis-benzyl ether **19** in 91% overall yield. Removal of the *p*-methoxybenzylidene acetal under acidic conditions afforded diol **20** in 96% yield. Diol **20** was subjected to one-pot triflation and triethylsilyl (TES) protection[23] provided a triflate, which was then treated with allylmagnesium bromide in the presence of CuBr[24] to afford elongated olefin **21** in 96% yield in two steps. Removal of the TES group of **21** with TsOH (98%), followed by Dess−Martin oxidation[25] of the resulting secondary alcohol **22**, provided ketone **23** in 98% yield. Upon treatment of ketone **23** with excess Me_3Al (CH_2Cl_2, −78 to −15 °C),[26] the requisite tertiary alcohol **24** was obtained in 92% yield along with a small amount of its diastereomer (7%). The configuration of the C48 stereogenic center of **24** was determined by NOE. Hydroboration of **24** provided diol **25**, which was oxidized with 2-hydroxy-2-azaadamantane (AZADOL) and $PhI(OAc)_2$ in CH_2Cl_2/pH 7 buffer (1:1)[27] to afford hydroxy carboxylic acid **26** in 87% yield in two steps. Yamaguchi lactonization[28] of **26** provided seven-membered lactone **27** in 96% yield. Finally, lactone **27** was converted into enol phosphate **13** in 97% yield by treatment with KHMDS and $(PhO)_2P(O)Cl$ [HMPA, tetrahydrofuran (THF), −78 °C].

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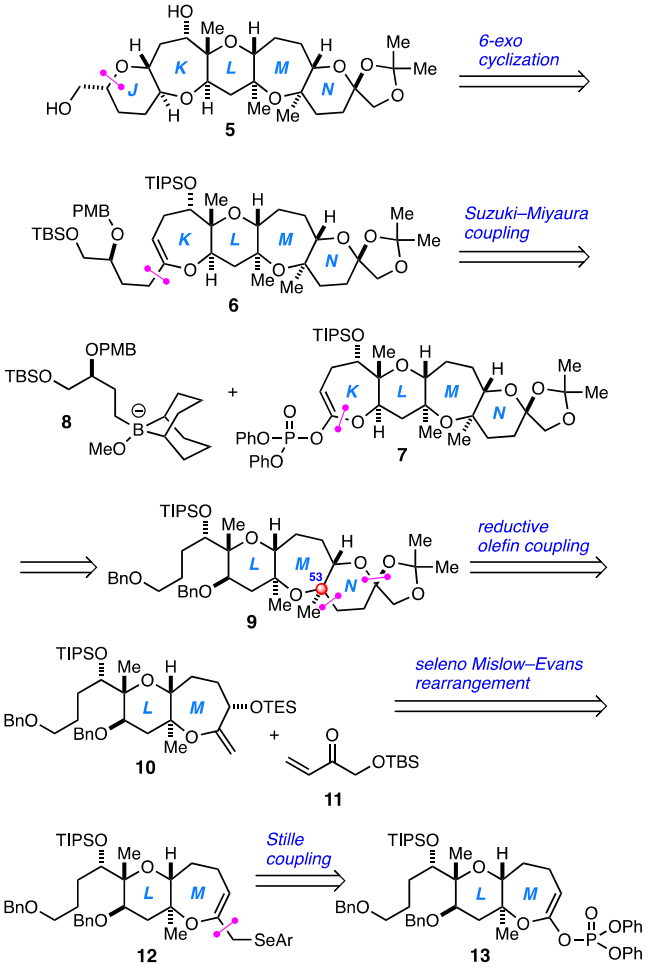
Scheme 1. Retrosynthetic Analysis of JKLMN-Ring Fragment 5 of C-CTX-1



Synthesis of *exo*-Enol Ether 10. With the desired enol phosphate **13** in hand, we next attempted the hydroxymethylation by Stille coupling.[29] Thus, Stille coupling of enol phosphate **13** with (tributylstannyl)methanol[30,31] using Pd(PPh$_3$)$_4$ and LiCl (THF, reflux) gave allylic alcohol **28** in 85% yield (Scheme 3). Alcohol **28** was then converted into 2-nitrophenylselenide **12** in 88% yield according to the Grieco–Nishizawa protocol.[32] The [2,3]-sigmatropic rearrangement[19] of selenide **12** was best achieved by treatment with aqueous H_2O_2 and 4-dimethylaminopyridine (DMAP) in THF at −44 °C to room temperature, giving *α*-hydroxy *exo*-enol ether **29** with the incorrect configuration at C52 in 68% yield. Under these conditions, the desired alcohol **31** was obtained in only small amounts (<2%). The C52 configuration of **29** was confirmed using the NOE data as shown in Figure 3. The observed stereoselectivity in this [2,3]-sigmatropic rearrangement could be explained by the steric hindrance of the C48 angular methyl group. The C52 hydroxy group of **29** was inverted by modified Mitsunobu conditions (4-$NO_2C_6H_4CO_2H$, Ph_3P, DEAD, toluene, 0 °C),[33] and subsequent methanolysis of the resulting 4-nitrobenzoate **30** (K_2CO_3 and MeOH) led to alcohol **31** in 74% yield in two steps. TES protection of **31** completed the synthesis of *exo*-enol ether **10** in 95% yield.

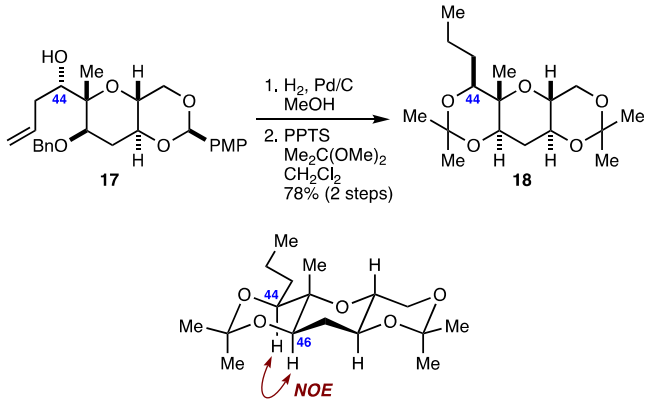
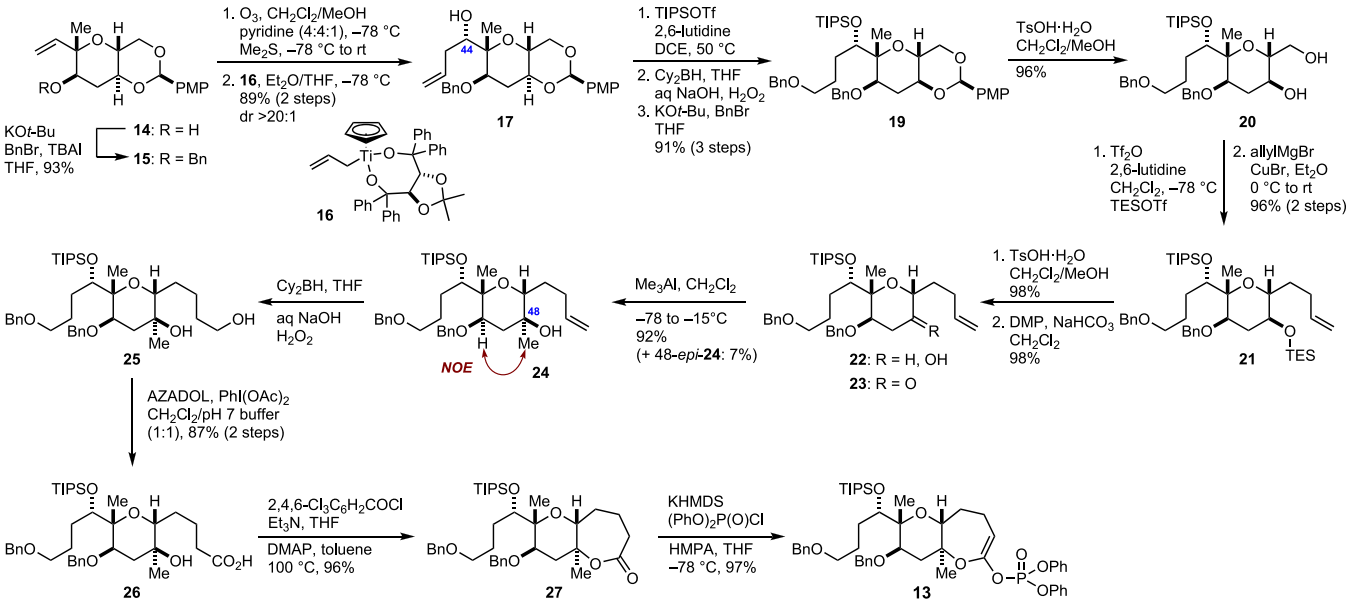


Figure 2. Configurational assignment of homoallylic alcohol **17**.

Scheme 2. Synthesis of Enol Phosphate 13



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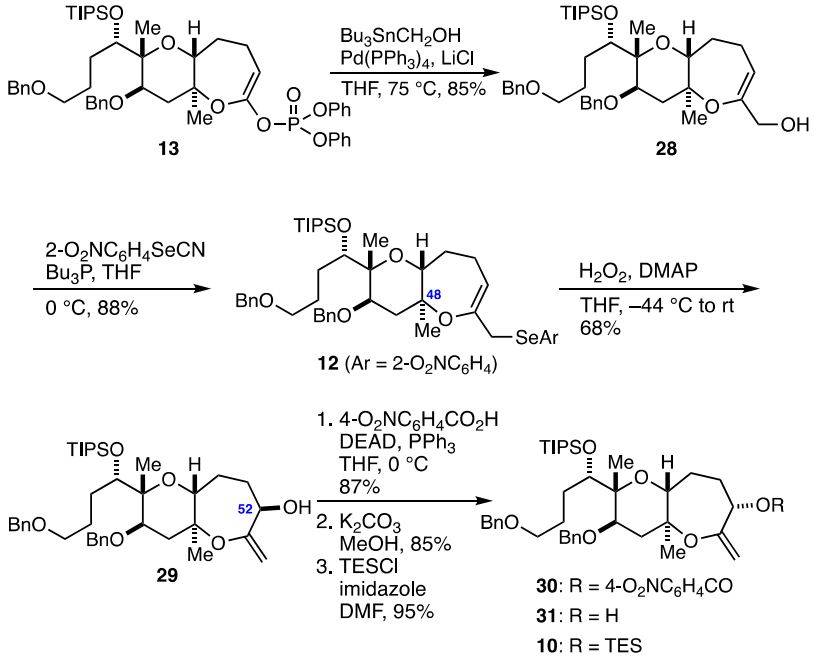
Scheme 3. Synthesis of *exo*-Enol Ether 10



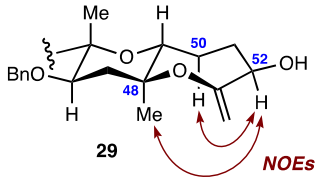
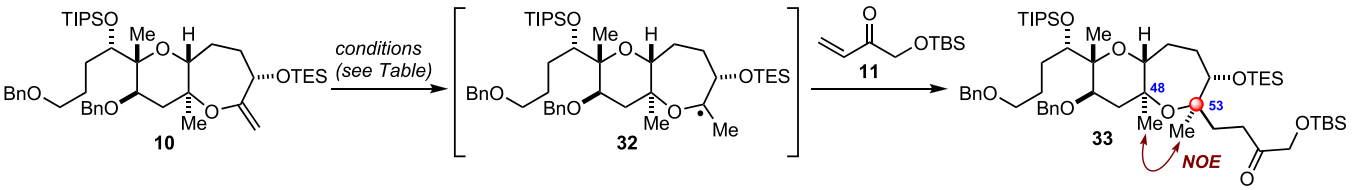


Figure 3. Configurational assignment of alcohol **29**.

Synthesis of LMN-Ring Fragment 9. With the key intermediate **10** in hand, we next investigated the crucial HAT-based reductive olefin coupling[14] with the known vinyl ketone **11**[34] using a combination of (isopropoxy)phenylsilane Ph(*i*-PrO)SiH_2[35] and iron(III) diisobutyrylmethanoate (Fe(dibm)$_3$)[14a,b] (Table 1). Thus, slow addition of Ph(*i*-PrO)SiH_2 (3.5 equiv) to *exo*-enol ether **10** and vinyl ketone **11** (3.5 equiv) in the presence of Fe(dibm)$_3$ (10 mol %) and Na_2HPO_4 (1 equiv) in EtOAc/*i*-PrOH (1:1) at room temperature led to the desired product **33** in moderate yield (44%) as a single stereoisomer (Table 1, entry 1). The yield of **33** was improved by increasing the molar amounts of **11** and Fe(dibm)$_3$ (entry 2). Baran and colleagues reported that olefin cross-coupling of glucal derivatives required the slow addition of a large excess of both methyl vinyl ketone and $PhSiH_3$ to obtain an acceptable yield.[14a,b] Thus, a solution of vinyl ketone **11** (5 equiv) and Ph(*i*-PrO)SiH_2 (5 equiv) in EtOAc was slowly added using a syringe pump to a mixture of **10**, Fe(dibm)$_3$ (30 mol %), and Na_2HPO_4 in *i*-PrOH to provide **33** in 63% yield (entry 3). Finally, running the reaction in the degassed solvents further improved the yield of the desired ketone **33** to 70% (entry 4). The configuration of the newly generated stereogenic center of C53 was confirmed by an NOE observed between two methyl groups. The stereochemical outcome of this radical reaction could be ascribed to the effective shielding of the α-face of the seven-membered ring by the C48 angular methyl and C52 triethysilyloxy substituents of the intermediary radical species **32**.

Selective removal of the *tert*-butyldimethylsilyl (TBS) and TES ethers of **33** under acidic conditions (CSA, CH_2Cl_2/MeOH) gave methyl acetal **34** in 85% yield as a single

Table 1. Optimization of HAT-Based Reductive Olefin Coupling[a]



entry	Fe(dibm)$_3$ (mol %)	Ph(*i*-PrO)SiH_2 (equiv)	enone **11** (equiv)	yield (%)
1[b]	10	3.5	3.5	44
2[b]	15	5	5	57
3[c]	30	5	5	63
4[c,d]	30	5	5	70

[a]The reaction was performed in the presence of Na_2HPO_4 (1 equiv) in EtOAc/*i*-PrOH (1:1). [b]Silane was added to a solution of *exo*-olefin, enone, and Fe(dibm)$_3$ in EtOAc/*i*-PrOH. [c]A solution of enone and silane in EtOAc was slowly added via a syringe pump to a solution of *exo*-olefin and Fe(dibm)$_3$ in *i*-PrOH. [d]The solvents were degassed with argon for 1 h.

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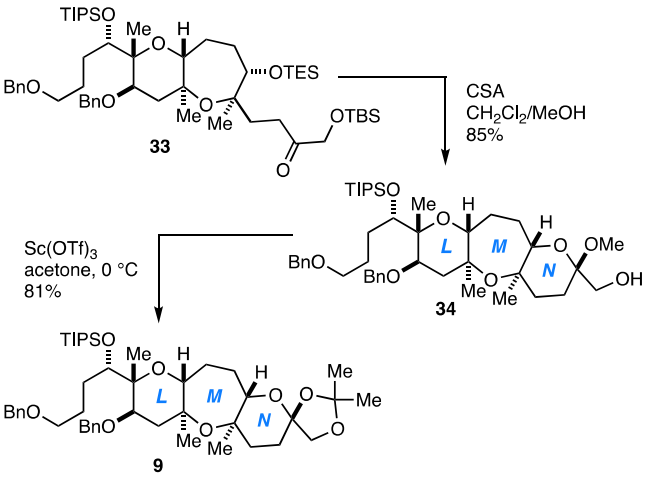
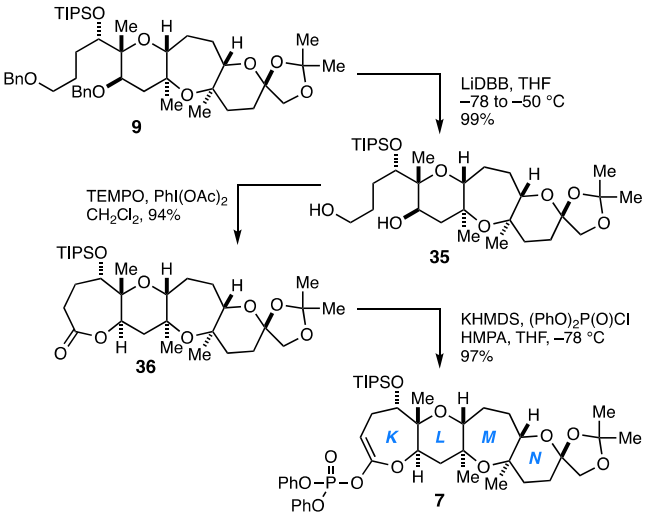
diastereomer (Scheme 4). Subsequent treatment of methyl acetal **34** with scandium(III) triflate[12b,36] in acetone provided the desired LMN-ring fragment **9** of C-CTX-1 in 81% yield.

Scheme 4. Synthesis of LMN-Ring Fragment 9



Synthesis of KLMN-Ring Enol Phosphate 7. Removal of the benzyl ethers of **9** was carried out with lithium 4,4′-di-*tert*-biphenylide (LiDBB)[37] to give diol **35** in 99% yield (Scheme 5). Oxidative lactonization of 1,6-diol **35** using a catalytic

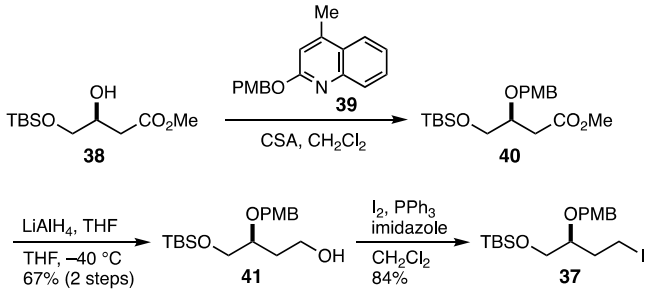
Scheme 5. Synthesis of KLMN-Ring Enol Phosphate 7



amount of TEMPO and $PhI(OAc)_2$ as a stoichiometric oxidant (CH_2Cl_2, 0.1 M, room temperature)[38] proceeded smoothly to provide seven-membered lactone **36** in 94% yield. Lactone **36** was converted to the requisite enol phosphate **7** in 97% yield by the action of KHMDS and $(PhO)_2P(O)Cl$.

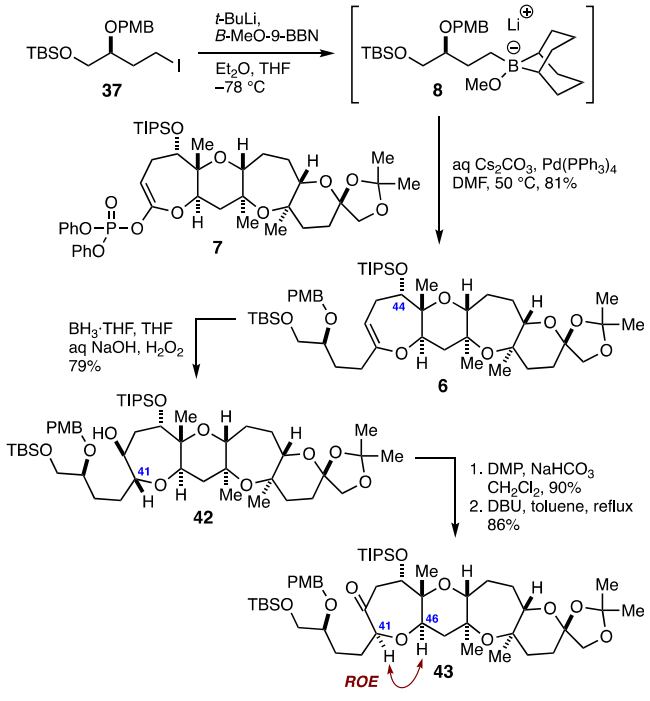
Synthesis of Iodide 37. The synthesis of iodide **37**, the precursor of alkylborate **8**, commenced with the known alcohol **38**,[39] which was readily available from (−)-malic acid in three steps (Scheme 6). Protection of **38** as its PMB ether using 2-(4-methoxybenzyloxy)-4-methylquinoline **39** in the presence of CSA (0.1 equiv) (CH_2Cl_2, room temperature, 4 days)[40] provided **40**,[41] which was reduced with $LiAlH_4$ (THF, −40 °C) to give primary alcohol **41** in 67% yield in two steps. Iodination of alcohol **41** with I_2, PPh_3, and imidazole provided iodide **37** in 84% yield.

Scheme 6. Synthesis of Iodide 37



Synthesis of Ketone 43. Suzuki−Miyaura coupling of enol phosphate **7** with alkylborate **8**, in situ generated from iodide **37** (*t*-BuLi, *B*-MeO-9-BBN, Et_2O/THF, −78 °C to room temperature),[42] was carried out in the presence of $Pd(PPh_3)_4$ as a catalyst and the aqueous Cs_2CO_3 solution as a base in dimethylformamide (DMF) at 50 °C, giving the desired enol ether **6** in 81% yield (Scheme 7). Hydroboration

Scheme 7. Synthesis of Ketone 43



of **6** with BH_3·THF followed by oxidative workup gave alcohol **42** (79%) with the incorrect configuration at C41 because of the sterically encumbered pseudoaxially oriented tri(isopropyl)silyloxy group at the C44 position.[43] Dess−Martin oxidation[25] of alcohol **42** (90%), followed by treatment of the resultant ketone with excess 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene under reflux conditions, provided the desired ketone **43** (86%). The relative configuration at the C41 position of **43** was confirmed using the ROE data.

Synthesis of JKLMN-Ring Fragment 5. With the desired ketone **43** in hand, the next task was the construction of the J-ring. To this end, stereoselective reduction of ketone **43** was next investigated. After some experimentation, it was found that DIBALH reduction of **43** (CH_2Cl_2, −78 °C) gave the desired alcohol **44** albeit in a moderate yield (51%) (Scheme 8). The configuration at the C42 position was confirmed by

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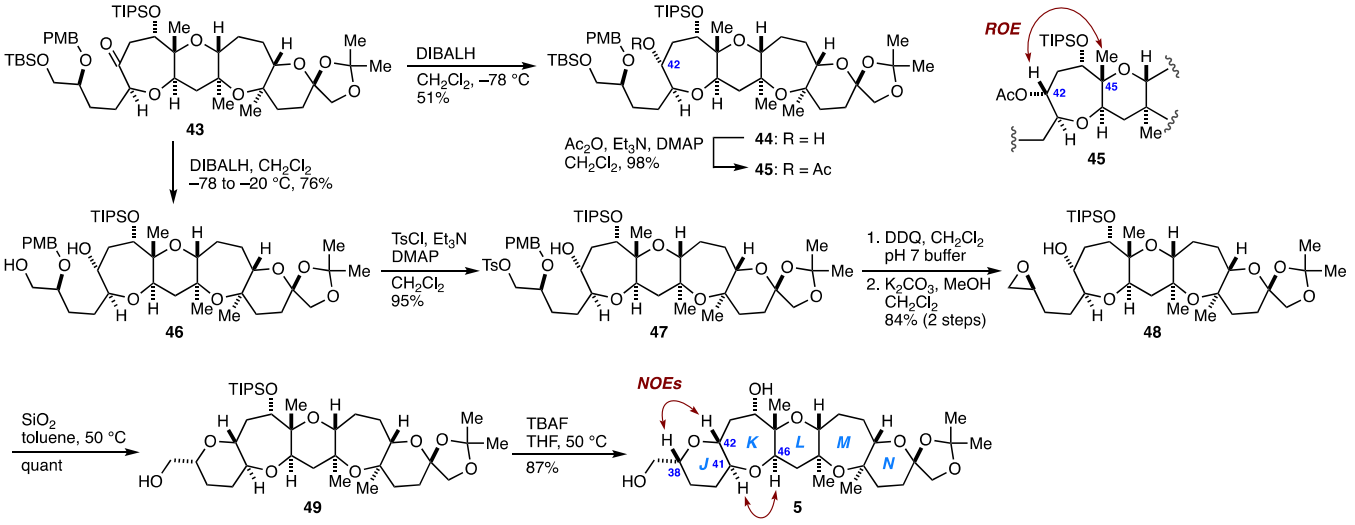
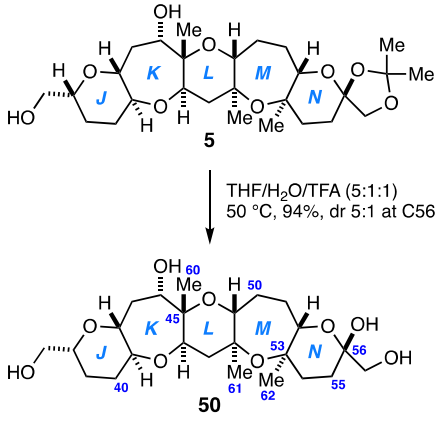
Scheme 8. Synthesis of JKLMN-Ring Fragment 5



derivatization to the corresponding acetate **45** and ROE experiments. After careful examination of the DIBALH reduction of **43**, its low yield was ascribed to the partial deprotection of the primary TBS ether under the current reaction conditions.[44] Thus, ketone **43** was treated with excess DIBALH in CH_2Cl_2 at −78 °C for 1 h, and then allowed to warm to −20 °C and stirred for 3 h to complete the deprotection of the primary hydroxy group by reductive cleavage of the TBS ether. Under these conditions, diol **46** was obtained in 76% yield with a diastereomer ratio of >20:1. Selective tosylation of the primary alcohol within **46** (TsCl, Et_3N, DMAP, CH_2Cl_2) provided tosylate **47** in 95% yield. Oxidative removal of the PMB ether of **47** with DDQ, followed by treatment with K_2CO_3 in CH_2Cl_2/MeOH, afforded epoxide **48** in 84% yield in two steps. The final 6-*exo* cyclization in the epoxide opening of **48** to form the J-ring proved to be unexpectedly difficult. Cyclization of **48** under basic conditions using potassium dimsylate[45] in THF provided the desired **49** in only a low yield (32%). An acidic treatment of epoxide **48** using CSA, PPTS, or $Sc(OTf)_3$ also resulted in a low yield of **49** because of the competitive cleavage of the acetonide group. Upon careful experimentation, it was found that cyclization product **49** was formed in small amounts during the experiment on a thin layer chromatography (TLC) plate for a long time. Accordingly, epoxide **48** was dissolved in a slurry of silica gel in toluene and stirred at 50 °C for 13 h 40 min to effect clean cyclization, giving the desired **49** in quantitative yield.[46] Finally, desilylation of **49** with tetra-*n*-butylammonium fluoride (TBAF) (THF, 50 °C) completed the synthesis of the JKLMN-ring fragment **5** in 87% yield. The relative configuration of the newly generated stereogenic centers within **5** was determined by NOE experiments.

Structural Implication of the N-Ring of Caribbean Ciguatoxin C-CTX-1. In order to confirm the structure of the N-ring of C-CTX-1, we decided to synthesize tetrahydroxy JKLMN-ring fragment **50** and compare its NMR data with those reported for the natural product. Thus, cleavage of the acetonide of compound **5** with THF/H_2O/TFA (5:1:1) at 50 °C gave tetraol **50** in 94% yield as an approximately 5:1 mixture of anomers at the C56 position (Scheme 9). The ^1H and ^{13}C NMR data for **50** thus prepared were carefully compared to those for the corresponding portion of the natural

Scheme 9. Synthesis of Tetrahydroxy JKLMN-Ring Fragment 50



product.[47] As shown in Figure 4, the ^1H NMR chemical shifts in the KLMN-ring region of **50** matched well with those reported for the natural product within 0.06 ppm, while the ^{13}C NMR chemical shifts for **50** also corresponded to those for C-CTX-1 within ±1.0 ppm except that for C62 (C53-Me).[48] Especially, the ^1H and ^{13}C NMR signals of the C57 hydroxymethyl group were clearly observed in compound **50**, and their chemical shifts were virtually identical to those reported for the natural product, but there is no corresponding partial structure in the revised structure **4**. These results demonstrated that the formerly assigned structure of the right-hand terminal of C-CTX-1 by the Lewis group is most likely represented by structure **50**, which contains the six-membered N-ring.

CONCLUSIONS

In conclusion, we have reported an advanced synthetic route to the JKLMN-ring fragment of Caribbean ciguatoxin C-CTX-1. Highlights of the synthesis are a [2,3]-sigmatropic rearrangement of allylic selenoxide to form the α-hydroxy *exo*-enol ether, a HAT-based reductive olefin coupling for the stereoselective construction of an angular tetrasubstituted stereogenic center on the seven-membered M-ring, and silica-gel-promoted 6-*exo* epoxide opening to form the J-ring. Additional salient features

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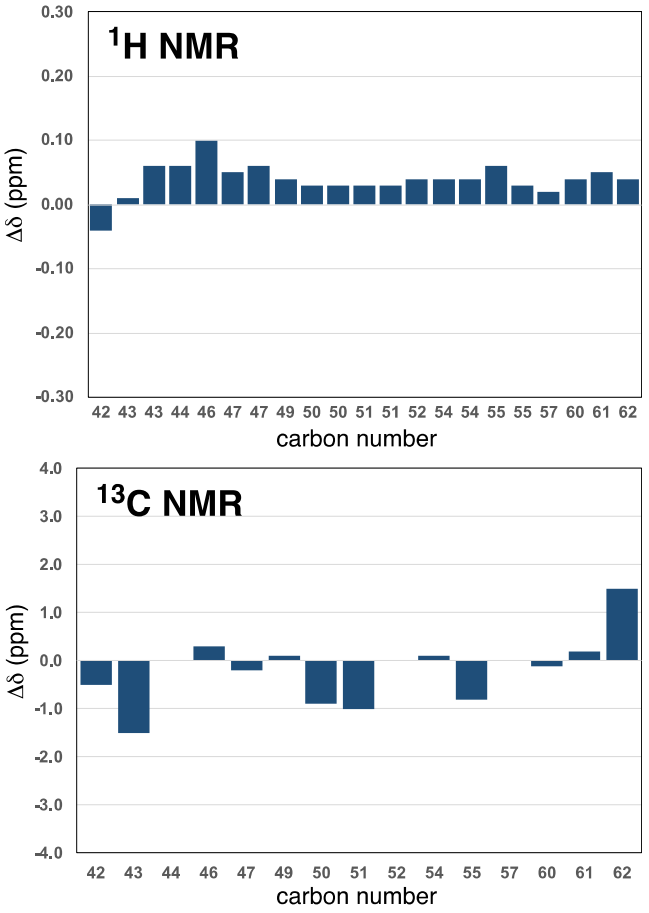

Figure 4. Differences in ^{1}H and ^{13}C NMR chemical shifts between C-CTX-1 and synthetic fragment **50**. $\Delta\delta = \delta$ (natural product) $- \delta$ (synthetic fragment) in ppm (pyridine-d_5).

include a hydroxymethylation by Stille coupling of seven-membered enol phosphate, TEMPO/PhI(OAc)$_2$-mediated oxidative lactonization of a 1,6-diol, and Suzuki–Miyaura coupling of the KLMN-ring enol phosphate containing the sterically congested M-ring. The present synthesis also provided support for the formerly assigned structure of the N-ring of C-CTX-1. The first synthesis of the JKLMN-ring fragment of C-CTX-1 enabled the preparation of a nontoxic hapten to generate monoclonal antibodies that specifically recognize the right-hand structure of C-CTX-1. Further studies along this line and toward the total synthesis of C-CTX-1 are underway and will be reported in due course.

EXPERIMENTAL SECTION

General Methods. All reactions sensitive to moisture and/or air were carried out under an atmosphere of argon in dry, freshly distilled solvents under anhydrous conditions using oven-dried glassware unless otherwise noted. Anhydrous acetone, acetonitrile (MeCN), 1,2-dichloroethane (DCE), dichloromethane (CH_2Cl_2), DMF, ethyl acetate (EtOAc), methanol (MeOH), and 2-propanol (*i*-PrOH) were purchased, and anhydrous diethyl ether (Et_2O), THF, and toluene were purified using a Glass Contour solvent purification system. 2,6-lutidine and triethylamine (Et_3N) were distilled from calcium hydride under an atmosphere of argon. Hexamethylphosphoramide (HMPA) was distilled from calcium hydride under reduced pressure. All other chemicals were purchased at the highest commercial grade and used directly. Analytical TLC was performed using a precoated glass plate (silica gel 60 F_{254}, 0.25 mm thickness). Flash column chromatography was carried out using silica gel (spherical, neutral, and 40–100 mesh). Optical rotations were measured on a digital polarimeter at 589 nm. IR spectra were recorded as a thin film on a KBr disk using an FT-IR spectrometer and reported in wavenumbers (cm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded using 600 and 150 MHz NMR spectrometers, respectively. Chemical shift values are reported in ppm (δ) downfield from tetramethylsilane with reference to internal residual solvents [^{1}H NMR, $CHCl_3$ (7.26), C_6HD_5 (7.16), and C_5HD_4N (7.21); ^{13}C NMR, $CDCl_3$ (77.0), C_6D_6 (128.0), and C_5D_5N (123.5)]. Coupling constants (J) are reported in hertz (Hz). The following abbreviations were used to designate the multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or unresolved; and br = broad. High-resolution mass spectra (HRMS) were measured on an electron spin ionization-time of flight mass spectrometer. The diastereomer ratio (dr) and the E/Z isomer ratio were estimated by ^{1}H NMR spectroscopic analysis, unless otherwise noted.

Benzyl Ether ***15***. To a solution of alcohol **14** (20.40 g, 66.59 mmol) in THF (320 mL) at 0 °C was added *t*-BuOK (17.26 g, 153.8 mmol). The resultant solution was stirred at room temperature for 20 min. To this mixture were added sequentially BnBr (12.0 mL, 101 mmol) and *n*-Bu_4NI (2.47 g, 6.69 mmol), and the resultant solution was stirred at room temperature for 2 h. The reaction was quenched with the saturated aqueous NH_4Cl solution (100 mL) at 0 °C. The mixture was extracted with EtOAc (500 mL), and the organic layer was washed with brine (2 × 100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 5 to 10 to 15 to 20% EtOAc/hexanes) gave benzyl ether **15** (24.68 g, 93%) as a colorless solid: mp 83.0–84.0 °C; $[\alpha]_D^{24.3}$ −35.9 (*c* 1.29, $CHCl_3$); IR (neat): 2984, 2940, 2863, 1615, 1518, 1250, 1092, 1034, 829, 698 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.44–7.40 (m, 2H), 7.36–7.27 (m, 5H), 6.92–6.88 (m, 2H), 6.04 (dd, J = 17.4, 11.0 Hz, 1H), 5.48 (s, 1H), 5.34 (dd, J = 17.4, 1.4 Hz, 1H), 5.13 (dd, J = 11.0, 1.4 Hz, 1H), 4.61 (d, J = 11.9 Hz, 1H), 4.50 (d, J = 11.9 Hz, 1H), 4.27 (m, 1H), 3.80 (s, 3H), 3.70–3.64 (m, 2H), 3.47 (m, 1H), 3.43 (dd, J = 11.5, 4.6 Hz, 1H), 2.41 (ddd, J = 11.9, 4.6, 4.1 Hz, 1H), 1.80 (ddd, J = 11.9, 11.5, 11.5 Hz, 1H), 1.41 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 160.1, 142.6, 138.1, 130.0, 128.3 (2C), 127.7, 127.5 (2C), 127.4 (2C), 113.7 (2C), 113.5, 101.6, 79.0, 77.32, 77.29, 71.6, 70.0, 66.3, 55.3, 30.9, 15.9; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{24}H_{29}O_5$, 397.2010; found, 397.2013.

Aldehyde ***S1***. Ozone gas was bubbled through a solution of benzyl ether **15** (6.12 g, 15.4 mmol) in CH_2Cl_2/MeOH/pyridine (4:4:1, v/v/v, 153 mL) at −78 °C until a blue color persisted for 34 min. After passing O_2 gas to remove excess O_3 for 12 min, Me_2S (7.0 mL, 94.6 mmol) was added to the reaction mixture. The resultant solution was allowed to warm to room temperature and stirred for 3 h. The mixture was concentrated under reduced pressure. The residue was diluted with EtOAc (250 mL), washed with H_2O (80 mL) and brine (80 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude aldehyde **S1** (6.29 g) was used in the next step without further purification.

Preparation of Duthaler–Hafner Reagent ***16***. To a suspension of $CpTiCl_3$ (4.49 g, 20.06 mmol) in anhydrous cyclohexane (400 mL) was added (4*R*,*trans*)-2,2-dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanol (9.37 g, 20.08 mmol). The reaction flask was fitted with a Soxhlet extractor containing 16 g of MgO (activated at 450 °C (heat gun) for 3.5 h under reduced pressure), and the mixture was stirred under reflux (oil bath) for 19 h 20 min. The resultant mixture was cooled to room temperature, and the solvent was evaporated with caution. The residue was twice dissolved in anhydrous Et_2O (200 mL), stirred at room temperature for 10–15 min, and concentrated under reduced pressure. Duthaler–Hafner reagent **16** thus obtained as a pale yellow solid was used in the next step without further purification.

Homoallylic Alcohol ***17***. To a solution of the above Duthaler–Hafner reagent **16** in Et_2O (300 mL) at 0 °C was added allylmagnesium chloride (2.0 M solution in THF, 9.6 mL, and 19.2 mmol) dropwise over 5 min, and the resultant orange-brown suspension was stirred at 0 °C for 1 h 50 min. The resultant

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suspension was cooled to −78 °C, and a solution of the above crude aldehyde **S1** (6.29 g) in THF (25 mL + 2 × 5 mL rinse) was added dropwise over 10 min. The resultant mixture was stirred at −78 °C for 3.5 h. The reaction was quenched with pH 7.0 phosphate buffer (150 mL). The mixture was allowed to warm to room temperature and stirred for 4 days. The mixture was filtered through a pad of Celite, washing with EtOAc (250 mL). The aqueous layer was separated and extracted with EtOAc (120 mL). The combined organic extracts were washed with brine (2 × 100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 10 to 20 to 30 to 35% EtOAc/hexanes) gave homoallylic alcohol **17** (6.05 g, 89% in two steps, dr > 20:1) as a colorless solid and (4*R*,*trans*)-2,2-dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanol (9.09 g, 97%) was recovered: data for **17**: mp 76.0−77.0 °C; $[\alpha]_D^{19.8}$ −61.3 (*c* 1.32, $CHCl_3$); IR (neat): 3501, 2948, 2865, 2360, 2341, 1615, 1518, 1463, 1386, 1367, 1250, 1173, 1094, 1030, 829, 699 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.43−7.40 (m, 2H), 7.37−7.33 (m, 2H), 7.32−7.28 (m, 3H), 6.91−6.88 (m, 2H), 5.88 (dddd, *J* = 17.0, 10.1, 7.3, 6.4 Hz, 1H), 5.48 (s, 1H), 5.12−5.05 (m, 2H), 4.66 (d, *J* = 11.5 Hz, 1H), 4.45 (d, *J* = 11.5 Hz, 1H), 4.21 (m, 1H), 3.80 (s, 3H), 3.79 (dd, *J* = 11.5, 4.6 Hz, 1H), 3.65−3.59 (m, 3H), 3.42 (m, 1H), 3.03 (m, 1H), 2.54 (ddd, *J* = 11.5, 4.6, 4.6 Hz, 1H), 2.38 (m, 1H), 2.14 (m, 1H), 1.79 (ddd, *J* = 11.9, 11.5, 11.5 Hz, 1H), 1.34 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 160.1, 137.3, 136.4, 129.8, 128.5 (2C), 127.9, 127.7 (2C), 127.4 (2C), 116.5, 113.7 (2C), 101.7, 78.5, 77.9, 77.2, 76.9, 70.2, 69.8, 66.2, 55.3, 35.4, 30.0, 12.6; HRMS (FAB) *m*/*z*: $[M + H]^+$ calcd for $C_{26}H_{33}O_6$, 441.2272; found, 441.2274.

Bis-acetonide ***18***. To a solution of homoallylic alcohol **17** (22.1 mg, 0.0502 mmol) in MeOH (1 mL) was added 10% Pd/C (11 mg), and the resultant mixture was stirred at room temperature under an atmosphere of H_2 (balloon) for 22 h. The mixture was filtered through a pad of Celite eluting with EtOAc and MeOH, and the filtrate was concentrated under reduced pressure to give crude tetraol (13.5 mg).

To a solution of the above tetraol in CH_2Cl_2 (1 mL) were added 2,2-dimethoxypropane (0.2 mL, 1.6 mmol) and PPTS (2.8 mg, 0.011 mmol), and the resultant solution was stirred at room temperature for 17 h. The mixture was neutralized with Et_3N (0.1 mL) and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10% EtOAc/hexanes) gave bis-acetonide **18** (12.3 mg, 78% in two steps): $[\alpha]_D^{26.4}$ −6.9 (*c* 1.26, $CHCl_3$); IR (neat): 2991, 2958, 2873, 1466, 1269, 1200, 1120, 1104, 1069, 1041, 931, 903, 863, 755 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 3.79 (dd, *J* = 10.6, 5.0 Hz, 1H), 3.68 (dd, *J* = 11.5, 4.1 Hz, 1H), ca. 3.66 (m, 1H, overlapped), 3.65 (dd, *J* = 10.6, 10.5 Hz, 1H), 3.52 (dd, *J* = 9.6, 2.3 Hz, 1H), 3.48 (ddd, *J* = 10.5, 10.1, 5.0 Hz, 1H), 1.92 (ddd, *J* = 11.5, 4.1, 4.1 Hz, 1H), 1.76 (ddd, *J* = 11.5, 11.5, 11.5 Hz, 1H), 1.56−1.44 (m, 2H, overlapped), 1.49 (s, 3H), 1.47 (s, 3H), 1.41 (s, 3H), 1.40 (s, 3H), 1.32−1.22 (m, 2H, overlapped), 1.24 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 100.2, 99.4, 77.7, 74.0, 73.0, 70.7, 68.1, 63.5, 30.3, 29.9, 29.6, 29.2, 19.6, 19.3, 19.2, 14.0, 10.6; HRMS (FAB) *m*/*z*: $[M + H]^+$ calcd for $C_{17}H_{31}O_5$ 315.2166; found, 315.2166.

Bis-benzyl Ether ***19***. To a solution of alcohol **17** (10.42 g, 23.65 mmol) in DCE (200 mL) were sequentially added 2,6-lutidine (8.4 mL, 72.1 mmol) and TIPSOTf (7.8 mL, 29.0 mmol). The resultant solution was heated to 50 °C (oil bath) for 22.5 h. Additional TIPSOTf (1.9 mL, 7.07 mmol) was added, and the resultant solution was stirred at 50−60 °C (oil bath) for 5.5 h. The reaction was quenched with MeOH (3 mL) at room temperature, and the resultant mixture was stirred at room temperature for 15 min. The mixture was diluted with CH_2Cl_2 (200 mL), washed with the saturated aqueous $NaHCO_3$ solution (150 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5% EtOAc/hexanes) gave TIPS ether **S2** (15.46 g) as a pale yellow oil, which was contaminated with a small amount of TIPSOH. Data for **S2**: $[\alpha]_D^{21.1}$ −37.6 (*c* 1.13, $CHCl_3$); IR (neat): 2943, 2864, 1615, 1463, 1384, 1365, 1250, 1173, 1092, 1034, 883, 827, 678 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.44−7.40 (m, 2H), 7.36−7.26 (m, 5H), 6.91−6.87 (m, 2H), 5.85 (dddd, *J* = 17.0, 10.0, 6.9, 6.9 Hz, 1H), 5.44 (s, 1H), 5.02−4.95 (m, 2H), 4.61 (d, *J* = 11.5 Hz, 1H), 4.51 (d, *J* = 11.5 Hz, 1H), 4.18 (m, 1H), 4.11 (dd, *J* = 11.5, 4.6 Hz, 1H), 3.84 (dd, *J* = 6.9, 4.6 Hz, 1H), 3.80 (s, 3H), 3.65−3.58 (m, 2H), 3.40 (m, 1H), 2.64 (m, 1H), 2.43 (ddd, *J* = 11.5, 4.6, 4.6 Hz, 1H), 2.33 (m, 1H), 1.73 (ddd, *J* = 11.9, 11.9, 11.4 Hz, 1H), 1.28 (s, 3H), 1.15−1.08 (m, 21H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 160.1, 138.2, 137.6, 130.1, 128.3 (2C), 127.7 (2C), 127.6, 127.4 (2C), 115.9, 113.7 (2C), 101.7, 80.8, 79.0, 76.9, 73.0, 70.7, 69.9, 66.3, 55.3, 39.2, 30.8, 18.5 (3C), 18.4 (3C), 14.3, 13.3 (3C); HRMS (FAB) *m*/*z*: $[M + H]^+$ calcd for $C_{35}H_{53}O_6Si$, 597.3608; found, 597.3617.

To a solution of cyclohexene (7.0 mL, 69.1 mmol) in THF (140 mL) at 0 °C was slowly added BH_3·THF (0.9 M solution in THF, 34.0 mL, 30.6 mmol), and the resultant solution was stirred at 0 °C for 1 h. To the resultant white suspension was slowly added a solution of the above TIPS ether **S2** (15.46 g) in THF (25 mL + 2 × 5 mL rinse) over 12 min. The resultant solution was stirred at room temperature for 1 h. To this solution at 0 °C were slowly added 3 M aqueous NaOH solution (34 mL) followed by 30% aqueous H_2O_2 solution (34 mL). The resultant mixture was stirred at room temperature for 1.5 h. The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 60 mL). The combined organic layers were washed with brine (2 × 80 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10 to 20 to 30% EtOAc/hexanes) gave alcohol **S3** (15.03 g) as a colorless oil: $[\alpha]_D^{21.6}$ −36.7 (*c* 1.45, $CHCl_3$); IR (neat): 3433, 2943, 2865, 1615, 1518, 1464, 1384, 1366, 1250, 1173, 1033, 883, 829, 678 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.44−7.39 (m, 2H), 7.35−7.26 (m, 5H), 6.91−6.87 (m, 2H), 5.43 (s, 1H), 4.61 (d, *J* = 11.5 Hz, 1H), 4.46 (d, *J* = 11.5 Hz, 1H), 4.17 (m, 1H), 4.08 (dd, *J* = 11.5, 4.6 Hz, 1H), 3.80 (s, 3H), 3.72 (m, 1H), 3.65−3.58 (m, 2H), 3.58−3.53 (m, 2H), 3.40 (m 1H), 2.44 (ddd, *J* = 11.5, 4.6, 4.6 Hz, 1H), 1.85−1.72 (m, 2H), 1.72 (ddd, *J* = 11.5, 11.5, 11.5 Hz, 1H), 1.60−1.47 (m, 2H), 1.26 (s, 3H), 1.17−1.06 (m, 21H), one proton missing due to H/D exchange; $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 160.1, 138.3, 130.1, 128.3 (2C), 127.8 (2C), 127.6, 127.4 (2C). 113.7 (2C), 101.7, 80.8, 79.6, 76.9, 73.1, 70.8, 69.9, 66.4, 63.3, 55.3, 31.3, 30.8, 30.6, 18.6 (3C), 18.5 (3C), 14.3, 13.5 (3C); HRMS (FAB) *m*/*z*: $[M + Na]^+$ calcd for $C_{35}H_{54}O_7SiNa$, 637.3531; found, 637.3541.

To a solution of the above alcohol **S3** (15.03 g) in THF (180 mL) at 0 °C was added KO*t*-Bu (8.00 g, 71.3 mmol), and the resultant solution was stirred at room temperature for 30 min. To this solution at 0 °C was added benzyl bromide (4.2 mL, 35.1 mmol), and the resultant solution was stirred at room temperature for 1.5 h. Additional benzyl bromide (0.4 mL, 3.3 mmol) was added, and the resultant solution was stirred at room temperature for 40 min. MeOH (3 mL) was added, and the resultant mixture was stirred at room temperature for 1 h. The reaction was quenched with the saturated aqueous NH_4Cl solution (50 mL). The resultant mixture was extracted with EtOAc (200 mL), and the organic layer was washed with H_2O (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5 to 10 to 15% EtOAc/hexanes) gave benzyl ether **19** (15.20 g, 91% in three steps) as a colorless oil: $[\alpha]_D^{25.6}$ −25.7 (*c* 1.69, $CHCl_3$); IR (neat): 2924, 2863, 1615, 1517, 1462, 1364, 1250, 1092, 1034, 883, 828, 734, 698, 678 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.44−7.40 (m, 2H), 7.35−7.23 (m, 10H), 6.91−6.87 (m, 2H), 5.43 (s, 1H), 4.58 (d, *J* = 11.9 Hz, 1H), 4.51−4.44 (m, 2H, overlapped), 4.48 (d, *J* = 11.9 Hz, 1H), 4.17 (m, 1H), 4.08 (dd, *J* = 11.5, 4.6 Hz, 1H), 3.80 (s, 3H), 3.72 (m, 1H), 3.65−3.58 (m, 2H), 3.45−3.36 (m, 3H), 3.42 (m, 1H), 1.93−1.80 (m, 2H), 1.72 (ddd, *J* = 11.5, 11.5, 11.5 Hz, 1H), 1.62−1.53 (m, 2H), 1.26 (s, 3H), 1.16−1.06 (m, 21H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 160.1, 138.7, 138.3, 130.1, 128.30 (2C), 128.28 (2C), 127.7 (2C), 127.5 (3C), 127.4 (3C), 113.7 (2C), 101.7, 80.8, 79.7, 76.9, 73.0, 72.8, 70.78, 70.71, 69.9, 66.3, 55.3, 31.0, 30.9, 28.4, 18.6 (3C), 18.5 (3C), 14.3, 13.4 (3C); HRMS (FAB) *m*/*z*: $[M + Na]^+$ calcd for $C_{42}H_{60}O_7SiNa$, 727.4001; found, 727.4005.

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Diol ***20***. To a solution of *p*-methoxybenzylidene acetal **19** (4.37 g, 6.20 mmol) in CH_2Cl_2/MeOH (1:1, v/v, 120 mL) at room temperature was added $TsOH{\cdot}H_2O$ (356.8 mg, 1.876 mmol), and the resulting solution was stirred at room temperature for 3 h. The reaction was quenched with Et_3N (3 mL). The mixture was concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 20 to 30 to 40 to 50% EtOAc/hexanes) gave diol **20** (3.50 g, 96%) as a colorless oil: $[\alpha]_D^{22.6}$ −13.9 (*c* 1.50, $CHCl_3$); IR (neat): 3398, 2943, 2866, 1463, 1455, 1362, 1207, 1109, 1058, 883, 734, 697, 678 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.35−7.23 (m, 10H), 4.57 (d, *J* = 11.5 Hz, 1H), 4.50−4.44 (m, 3H), 3.92 (dd, *J* = 11.0, 4.6 Hz, 1H), 3.78 (ddd, *J* = 11.0, 6.9, 4.6 Hz, 1H), 3.75 (dd, *J* = 5.9, 3.2 Hz, 1H), 3.67 (m, 1H), 3.53−3.44 (m, 2H), 3.39 (dd, *J* = 6.4, 6.0 Hz, 2H), 2.30 (ddd, *J* = 12.4, 4.6, 4.6 Hz, 1H), 2.26−2.17 (m, 2H), 1.90−1.77 (m, 2H), 1.69−1.54 (m, 3H), 1.23 (s, 3H), 1.12−1.05 (m, 21H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 138.6, 138.3, 128.3 (4C), 127.7 (2C), 127.5 (3C), 127.4, 80.1, 78.7, 74.0, 73.5, 72.8, 71.1, 70.6, 67.8, 64.3, 33.8, 30.8, 28.1, 18.5 (3C), 18.4 (3C), 13.8, 13.4 (3C); HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{34}H_{54}O_6SiNa$, 609.3582; found, 609.3582.

Olefin ***21***. To a solution of diol **20** (3.42 g, 5.83 mmol) and 2,6-lutidine (2.7 mL, 23.2 mmol) in CH_2Cl_2 (100 mL) at −80 °C was slowly added Tf_2O (98%, 1.05 mL, 6.27 mmol), and the resultant solution was stirred at −80 °C for 30 min. To this mixture was slowly added TESOTf (2.6 mL, 11.5 mmol), and the resultant solution was stirred at −80 °C for 40 min. The reaction was quenched with the saturated aqueous $NaHCO_3$ solution (50 mL). The mixture was extracted with CH_2Cl_2 (100 mL), washed with brine (50 mL), washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10% EtOAc/hexanes) gave triflate **S4**, which was unstable and immediately used in the next reaction.

To a suspension of CuBr (838 mg, 5.84 mmol) in Et_2O (20 mL) at 0 °C was slowly added allylmagnesium bromide (1.0 M solution in Et_2O, 30 mL, 30 mmol) over 5 min, and the resultant solution was stirred at 0 °C for 30 min. To the resultant black solution was slowly added a solution of the above triflate **S4** in Et_2O (15 mL + 2 × 5 mL rinse) over 10 min. The resultant solution was stirred at 0 °C for 1 h, then allowed to warm to room temperature, and stirred for 17.5 h. The reaction was quenched with the saturated aqueous NH_4Cl solution (30 mL) at 0 °C with caution. The mixture was stirred at room temperature for 50 min and filtered through a pad of Celite eluting with Et_2O (ca. 100 mL). The organic layer was separated, washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 2 to 4 to 6% EtOAc/hexanes) gave olefin **21** (4.06 g, 96% in two steps) as a colorless oil: $[\alpha]_D^{25.0}$ +14.3 (*c* 1.99, $CHCl_3$); IR (neat): 2946, 2867, 1455, 1361, 1240, 1108, 1014, 884, 733, 697, 677 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.35−7.22 (m, 10H), 5.79 (dddd, *J* = 17.4, 10.1, 6.9, 6.4 Hz, 1H), 4.98 (d, *J* = 17.4 Hz, 1H), 4.93 (dm, *J* = 10.1 Hz, 1H), 4.53 (d, *J* = 11.9 Hz, 1H), 4.48 (d, *J* = 11.9 Hz, 1H), 4.50−4.45 (m, 2H), 3.96 (dd, *J* = 11.9, 4.6 Hz, 1H), 3.71 (br d, *J* = 5.9 Hz, 1H), 3.45−3.36 (m, 2H), 3.25 (dd, *J* = 9.6, 9.2 Hz, 1H), 3.20 (ddd, *J* = 10.5, 9.2, 4.6 Hz, 1H), 2.24 (m, 1H), 2.09 (ddd, *J* = 12.4, 5.0, 4.6 Hz, 1H), 2.02 (m, 1H), 1.90−1.81 (m, 3H), 1.64−1.53 (m, 2H), 1.50 (ddd, *J* = 11.9, 11.5, 11.5 Hz, 1H), 1.25 (m, 1H), 1.14 (s, 3H), 1.18−1.08 (m, 21H), 0.94 (t, *J* = 7.8 Hz, 9H), 0.56 (q, *J* = 7.8 Hz, 6H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 138.9, 138.78, 138.76, 128.3 (2C), 128.2 (2C), 127.8 (2C), 127.5 (2C), 127.39, 127.37, 114.2, 79.9, 79.1, 73.7, 72.9, 72.8, 71.0, 70.8, 70.5, 35.6, 31.00, 30.98, 30.2, 28.4, 18.6 (3C), 18.5 (3C), 14.0, 13.4 (3C), 6.8 (3C), 5.0 (3C); HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{43}H_{72}O_5Si_2Na$, 747.4810; found, 747.4810.

Alcohol ***22***. To a solution of olefin **21** (4.03 g, 5.56 mmol) in CH_2Cl_2/MeOH (1:1, v/v, 70 mL) at room temperature was added $TsOH{\cdot}H_2O$ (317.4 mg, 1.669 mmol), and the resulting solution was stirred at room temperature for 1 h 40 min. The reaction was quenched with Et_3N (2.0 mL). The mixture was concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10 to 20% EtOAc/hexanes) gave alcohol **22** (3.34 g, 98%) as a colorless oil: $[\alpha]_D^{25.4}$ −2.3 (*c* 1.54,00, $CHCl_3$); IR (neat): 3388, 2943, 2865, 1455, 1361, 1102, 1058, 883, 734, 697, 678 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.35−7.23 (m, 10H), 5.80 (dddd, *J* = 17.0, 10.1, 6.9, 6.4 Hz, 1H), 5.00 (dm, *J* = 17.0 Hz, 1H), 4.95 (dm, *J* = 10.1 Hz, 1H), 4.56 (d, *J* = 11.5 Hz, 1H), 4.48 (d, *J* = 11.5 Hz, 1H), 4.50−4.45 (m, 2H, overlapped), 3.99 (dd, *J* = 11.0, 4.6 Hz, 1H), 3.72 (dd, *J* = 6.9, 3.2 Hz, 1H), 3.44−3.36 (m, 2H), 3.30−3.24 (m, 2H), 2.31−2.23 (m, 2H), 2.07 (m, 1H), 1.91−1.79 (m, 3H), 1.66−1.52 (m, 3H), 1.38 (m, 1H), 1.17 (s, 3H), 1.15−1.07 (m, 21H), one proton missing due to H/D exchange; $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 138.8, 138.64, 138.57, 128.3 (4C), 127.7 (2C), 127.50 (2C), 127.46, 127.38, 114.6, 79.5, 79.3, 73.69, 73.66, 72.8, 71.1, 70.8, 70.3, 34.4, 31.4, 31.0, 30.0, 28.3, 18.6 (3C), 18.5 (3C), 13.7, 13.4 (3C); HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{37}H_{58}O_5SiNa$, 633.3946; found, 633.3945.

Ketone ***23***. To a suspension of alcohol **22** (3.46 g, 5.66 mmol) and $NaHCO_3$ (2.41 g, 28.7 mmol) in CH_2Cl_2 (60 mL) at 0 °C was added Dess−Martin periodinane (95%, 5.06 g, 11.3 mmol), and the resultant mixture was stirred at room temperature for 2 h. The reaction was quenched with a 1:1 mixture of the saturated aqueous $NaHCO_3$ solution and the saturated aqueous $Na_2S_2O_3$ solution (70 mL) at 0 °C. The resultant mixture was stirred at room temperature for 20 min. The mixture was extracted with EtOAc (200, 60 mL), and the combined organic layers were washed with the saturated aqueous $NaHCO_3$ solution (60 mL) and brine (60 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5 to 15% EtOAc/hexanes) gave ketone **23** (3.37 g, 98%) as a colorless oil: $[\alpha]_D^{25.7}$ +54.3 (*c* 1.80, $CHCl_3$); IR (neat): 2943, 2866, 1736, 1455, 1097, 1069, 883, 735, 697, 680 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.36−7.24 (m, 10H), 5.77 (dddd, *J* = 17.4, 10.1, 6.9, 6.4 Hz, 1H), 5.01 (dd, *J* = 17.4, 1.9 Hz, 1H), 4.96 (dm, *J* = 10.1 Hz, 1H), 4.54 (d, *J* = 11.5 Hz, 1H), 4.50 (s, 2H), 4.35 (d, *J* = 11.5 Hz, 1H), 4.22 (dd, *J* = 3.7, 2.8 Hz, 1H), 3.97 (dd, *J* = 9.1, 3.2 Hz, 1H), 3.77 (dd, *J* = 5.5, 5.0 Hz, 1H), 3.48−3.41 (m, 2H), 2.83 (dd, *J* = 15.6, 2.7 Hz, 1H), 2.66 (dd, *J* = 15.6, 4.1 Hz, 1H), 2.17 (m, 1H), 2.11 (m, 1H), 1.98−1.90 (m, 2H), 1.84−1.74 (m, 2H), 1.63−1.52 (m, 2H), 1.26 (s, 3H), 1.10−1.05 (m, 21H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 212.2, 138.7, 138.0, 137.9, 128.3 (4C), 127.6, 127.54 (2C), 127.46 (2C), 127.43, 115.2, 82.1, 77.0, 76.5, 75.4, 72.8, 71.4, 70.6, 39.8, 30.7, 29.6, 29.0, 27.8, 18.4 (3C), 18.3 (3C), 13.5, 13.3 (3C); HRMS (FAB) *m*/*z*: $[M + Na]^+$ calcd for $C_{37}H_{56}O_5SiNa$, 631.3789; found, 631.3792.

Alcohols ***24*** *and 47-epi-****24***. To a solution of ketone **23** (3.37 g, 5.53 mmol) in CH_2Cl_2 (55 mL) at −78 °C was slowly added Me_3Al (1.4 M solution in *n*-hexane, 15.0 mL, 21.0 mmol). The resultant solution was stirred at −78 °C for 6 h, then allowed to warm to −15 °C and stirred for 16.5 h. The reaction was quenched with MeOH (2 mL). The mixture was diluted with the saturated aqueous potassium sodium tartrate solution (50 mL) and EtOAc (50 mL), and the resultant mixture was vigorously stirred at room temperature for 50 min. The mixture was extracted with EtOAc (120, 50 mL), and the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10 to 20 to 30% EtOAc/hexanes) gave alcohol **24** (3.19 g, 92%) as a colorless oil, along with its diastereomeric alcohol 47-*epi*-**24** (0.24 g, 7%) as a colorless oil. Data for **24**: $[\alpha]_D^{24.8}$ +0.73 (*c* 1.02, $CHCl_3$); IR (neat): 3421, 2943, 2865, 2360, 1639, 1455, 1378, 1362, 1098, 1072, 883, 733, 697, 679 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.35−7.24 (m, 10H), 5.81 (dddd, *J* = 17.4, 10.1, 7.3, 6.4 Hz, 1H), 5.00 (dd, *J* = 17.4, 1.9 Hz, 1H), 4.94 (dm, *J* = 10.1 Hz, 1H), 4.54 (d, *J* = 11.5 Hz, 1H), 4.50−4.45 (m, 2H), 4.45 (d, *J* = 11.5 Hz, 1H), 3.84 (dd, *J* = 10.1, 4.1 Hz, 1H), 3.72 (dd, *J* = 5.0, 5.0 Hz, 1H), 3.40 (dd, *J* = 6.8, 6.4 Hz, 2H), 3.36 (dd, *J* = 10.6, 1.8 Hz, 1H), 2.26 (m, 1H), 2.03 (m, 1H), 1.97−1.90 (m, 2H), 1.81 (m, 1H), 1.71 (dd, *J* = 12.4, 10.1 Hz, 1H), 1.70−1.51 (m, 3H), 1.33 (m, 1H), 1.21 (s, 3H), 1.12 (s, 3H), 1.14−1.07 (m, 21H, overlapped), one proton missing due to H/D exchange; $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 138.9, 138.8, 138.4, 128.32 (2C), 128.28 (2C), 127.7 (2C), 127.6, 127.5 (2C),

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127.4, 114.5, 80.4, 78.1, 75.8, 74.9, 72.7, 71.36, 71.34, 70.8, 40.5, 30.73, 30.71, 28.2, 28.0, 21.6, 18.5 (3C), 18.4 (3C), 13.6 (3C), 13.5; HRMS (FAB) m/z: $[M + Na]^+$ calcd for $C_{38}H_{60}O_5SiNa$, 647.4102; found, 647.4110. Data for 47-*epi*-**24**: $[\alpha]_D^{24.4}$ −5.38 (c 1.19, $CHCl_3$); IR (neat): 3579, 3480, 2944, 2866, 2360, 1639, 1455, 1362, 1097, 911, 883, 815, 734, 697, 679 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.35−7.21 (m, 10H), 5.79 (dddd, J = 17.0, 10.1, 7.3, 5.9 Hz, 1H), 5.00 (dm, J = 17.0 Hz, 1H), 4.96 (dm, J = 10.1 Hz, 1H), 4.56 (d, J = 11.5 Hz, 1H), 4.49−4.44 (m, 2H), 4.42 (d, J = 11.5 Hz, 1H), 4.09 (dd, J = 11.9, 5.3 Hz, 1H), 3.76 (dd, J = 6.2, 4.4 Hz, 1H), 3.40−3.35 (m, 3H), 2.25 (m, 1H), 2.16 (dd, J = 13.1, 5.3 Hz, 1H), 2.03 (m, 1H), 1.94 (m, 1H), 1.84 (m, 1H), 1.65−1.48 (m, 4H), 1.51 (dd, J = 12.8, 11.9 Hz, 1H, overlapped), 1.16 (s, 3H), 1.14−1.08 (m, 24H), one proton missing due to H/D exchange; $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 138.7, 138.6 (2C), 128.3 (2C), 128.2 (2C), 127.6 (2C), 127.5 (2C), 127.40, 127.38, 114.7, 80.0, 79.6, 74.8, 72.8, 71.4, 71.1, 70.7, 70.5, 39.6, 31.0, 30.2, 28.3, 27.2, 24.2, 18.4 (6C), 13.8 (3C), 13.6; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{38}H_{60}O_5SiNa$, 647.4102; found, 647.4128.

Diol ***25***. To a solution of cyclohexene (4.0 mL, 39.5 mmol) in THF (70 mL) at 0 °C was slowly added BH_3·THF (0.9 M solution in THF, 20.0 mL, 18.0 mmol), and the resultant solution was stirred at 0 °C for 1 h. To the resultant white suspension was slowly added a solution of alcohol **24** (4.46 g, 7.14 mmol) in THF (20 mL + 2 × 5 mL rinse) over 35 min. The resultant solution was stirred at room temperature for 1 h. To this solution at 0 °C were slowly added 3 M aqueous NaOH solution (30 mL) followed by 30% aqueous H_2O_2 solution (30 mL). The resultant mixture was vigorously stirred at room temperature for 90 min. The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 100 mL). The combined organic layers were washed with the saturated aqueous $Na_2S_2O_3$ solution (80 mL) and brine (80 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, first round: 40 to 50 to 60% EtOAc/hexanes, second round: 40 to 70% EtOAc/hexanes) gave diol **25** (4.70 g, quantitative) as a colorless oil: $[\alpha]_D^{24.4}$ +1.49 (c 1.13, $CHCl_3$); IR (neat): 3373, 2943, 2865, 1455, 1378, 1362, 1098, 1072, 883, 734, 697, 679 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.35−7.24 (m, 10H), 4.53 (d, J = 11.5 Hz, 1H), 4.47 (s, 2H), 4.44 (d, J = 11.5 Hz, 1H), 3.81 (dd, J = 9.6, 4.1 Hz, 1H), 3.71 (dd, J = 5.0, 5.0 Hz, 1H), 3.64−3.58 (m, 2H), 3.39 (dd, J = 6.9, 6.4 Hz, 2H), 3.33 (d, J = 9.6 Hz, 1H), 1.94 (dd, J = 12.8, 4.1 Hz, 1H), 1.90 (m, 1H), 1.80 (m, 1H), 1.71 (dd, J = 12.8, 9.6 Hz, 1H), 1.70−1.49 (m, 8H), 1.22 (s, 3H), 1.11 (s, 3H), 1.11−1.06 (m, 21H), two protons missing due to H/D exchange; $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 138.7, 138.4, 128.33 (2C), 128.28 (2C), 127.7 (2C), 127.6, 127.5 (2C), 127.4, 80.4, 77.9, 76.6, 74.9, 72.7, 71.4, 71.3, 70.8, 62.9, 40.4, 32.7, 30.6, 28.2, 28.1, 22.9, 21.6, 18.4 (3C), 18.3 (3C), 13.6 (3C), 13.4; HRMS (FAB) m/z: $[M + Na]^+$ calcd for $C_{38}H_{62}O_6SiNa$, 665.4208; found, 665.4212.

Carboxylic Acid ***26***. To a solution of the above diol **25** (4.70 g, 7.31 mmol) in CH_2Cl_2/pH 7.0 phosphate buffer (1:1, v/v, 48 mL) at 0 °C were sequentially added AZADOL (115.4 mg, 0.7532 mmol) and $PhI(OAc)_2$ (7.07 g, 21.9 mmol). The resultant solution was stirred at room temperature for 3 h 40 min. The reaction was quenched with the saturated aqueous $Na_2S_2O_3$ solution (50 mL) at 0 °C. The mixture was extracted with EtOAc (120 mL, 2 × 60 mL), washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 40 to 50 to 60 to 70% EtOAc/hexanes) gave carboxylic acid **26** (4.11 g, 87% in two steps) as a colorless oil: $[\alpha]_D^{26.5}$ −1.91 (c 1.49, $CHCl_3$); IR (neat): 3409, 2943, 2866, 1710, 1455, 1380, 1363, 1252, 1206, 1097, 883, 735, 697, 679 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.35−7.24 (m, 10H), 4.54 (d, J = 11.5 Hz, 1H), 4.48 (s, 2H), 4.44 (d, J = 11.5 Hz, 1H), 3.81 (dd, J = 10.1, 4.1 Hz, 1H), 3.72 (dd, J = 5.0, 5.0 Hz, 1H), 3.40 (dd, J = 6.4, 6.4 Hz, 2H), 3.35 (d, J = 10.1 Hz, 1H), 2.40−2.30 (m, 2H), 1.98−1.87 (m, 2H), 1.86−1.76 (m, 2H), 1.72 (dd, J = 12.4, 10.1 Hz, 1H), 1.70−1.60 (m, 3H), 1.53 (m, 1H), 1.26 (m, 1H), 1.23 (s, 3H), 1.11 (s, 3H), 1.13−1.05 (m, 21H, overlapped), two protons missing due to H/D exchange; $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 178.6, 138.6, 138.3, 128.32 (2C), 128.27 (2C), 127.7 (2C), 127.6, 127.5 (2C), 127.4, 80.5, 77.9, 76.4, 74.8, 72.7, 71.4, 71.3, 70.8, 40.3, 33.9, 30.5, 28.1, 27.7, 22.1, 21.5, 18.4 (3C), 18.3 (3C), 13.5 (3C), 13.4; HRMS (FAB) m/z: $[M + Na]^+$ calcd for $C_{38}H_{60}O_7SiNa$, 679.4001; found, 679.4012.

Lactone ***27***. To a solution of carboxylic acid **26** (4.11 g, 6.26 mmol) and Et_3N (2.7 mL, 19.4 mmol) in THF (62 mL) at 0 °C was slowly added 2,4,6-trichlorobenzoyl chloride (1.4 mL, 8.95 mmol), and the resultant solution was stirred at room temperature for 50 min. The mixture was filtered through a pad of Celite and washed with benzene (ca. 50 mL). The filtrate was concentrated under reduced pressure to give a crude mixed anhydride. To a solution of DMAP (3.86 g, 31.6 mmol) in toluene (550 mL) at 100 °C (oil bath) was slowly added a solution of the above mixed anhydride in toluene (150 mL + 2 × 20 mL rinse) over 3 h. The resultant mixture was stirred at 100 °C (oil bath) for further 55 min. The mixture was cooled to room temperature and transferred to a separatory funnel with EtOAc (140 mL). The mixture was washed with cold 1 M aqueous HCl solution (100 mL), the saturated aqueous $NaHCO_3$ solution (100 mL), and brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10 to 20 to 30% EtOAc/hexanes) gave lactone **27** (3.83 g, 96%) as a pale yellow oil: $[\alpha]_D^{24.8}$ −37.8 (c 1.40, $CHCl_3$); IR (neat): 2944, 2866, 1728, 1455, 1273, 1201, 1100, 1067, 1052, 884, 734, 697, 679 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.35−7.24 (m, 10H), 4.53 (d, J = 11.5 Hz, 1H), 4.49−4.44 (m, 2H), 4.43 (d, J = 11.5 Hz, 1H), 3.86 (dd, J = 11.9, 4.6 Hz, 1H), 3.73 (dd, J = 5.9, 4.1 Hz, 1H), 3.60 (dd, J = 11.0, 2.8 Hz, 1H), 3.42−3.35 (m, 2H), 2.78 (m, 1H), 2.51 (m, 1H), 2.19 (dd, J = 12.6, 4.8 Hz, 1H), 1.97−1.77 (m, 5H), 1.71−1.49 (m, 4H), 1.44 (s, 3H), 1.21 (s, 3H), 1.12−1.06 (m, 21H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 174.0, 138.7, 138.1, 128.30 (2C), 128.28 (2C), 127.9 (2C), 127.6, 127.46 (2C), 127.41, 80.7, 80.0, 78.9, 73.5, 72.8, 72.1, 70.9, 70.7, 40.4, 36.8, 30.9 (2C), 28.3, 20.6, 19.1, 18.5 (3C), 18.4 (3C), 13.7, 13.6 (3C); HRMS (FAB) m/z: $[M + Na]^+$ calcd for $C_{38}H_{58}O_6SiNa$, 661.3895; found, 661.3903.

Enol Phosphate ***13***. To a solution of lactone **27** (3.83 g, 5.99 mmol) in THF (60 mL) were added HMPA (4.2 mL, 24.1 mmol) and $(PhO)_2P(O)Cl$ (3.8 mL, 18.4 mmol). To this solution at −78 °C was slowly added KHMDS (0.5 M solution in toluene, 36 mL, 18 mmol) dropwise over 15 min, and the resultant solution was stirred at −78 °C for 1 h. The reaction was quenched with 3% NH_4OH (30 mL). The resultant mixture was diluted with Et_2O (30 mL) and vigorously stirred at room temperature for 20 min. The mixture was extracted with EtOAc (160 mL), and the organic layer was washed with H_2O (60 mL) and brine (60 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10 to 15 to 20% EtOAc/hexanes) gave enol phosphate **13** (5.07 g, 97%) as a pale yellow oil, which was unstable and used immediately in the next reaction without further purification: ^1H NMR (600 MHz, $CDCl_3$): δ 7.37−7.17 (m, 20H), 4.86 (m, 1H), 4.49 (d, J = 11.5 Hz, 1H), 4.48−4.42 (m, 1H), 4.36 (d, J = 11.5 Hz, 1H), 3.82 (dd, J = 11.9, 4.6 Hz, 1H), 3.71 (dd, J = 5.9, 4.1 Hz, 1H), 3.51 (dd, J = 11.5, 2.8 Hz, 1H), 3.40−3.32 (m, 2H), 2.09 (m 1H), 2.04−1.97 (m, 2H), 1.90 (m, 1H), 1.79 (m, 1H), 1.76 (dd, J = 11.9, 11.9 Hz, 1H), 1.62−1.53 (m, 2H), 1.52−1.41 (m, 2H), 1.31 (s, 3H), 1.21 (s, 3H), 1.11−1.04 (m, 21H).

Allylic Alcohol ***28***. LiCl (99%, 749.6 mg, 17.5 mmol) was placed in a flask and dried with a heat gun under reduced pressure for 40 min. $Pd(PPh_3)_4$ (1.01 g, 0.874 mmol) and THF (40 mL) were added to the flask, and the resultant mixture was stirred at room temperature for 15 min. To the resultant clear yellow solution were slowly added a solution of the above enol phosphate **13** (5.07 g, 5.82 mmol) in THF (20 mL + 2 × 5 mL rinse) followed by a solution of n-Bu_3SnCH_2OH (3.85 g, 12.0 mmol) in THF (20 + 10 mL rinse). The resultant solution was heated to 75 °C (oil bath) for 3 h. The resultant brown solution was cooled to room temperature and treated with H_2O (60 mL). The mixture was extracted with EtOAc (150, 60 mL), and the combined organic layers were washed with brine (60 mL), dried over

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$MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (10% w/w anhydrous K_2CO_3–silica gel, 10 to 20 to 25% EtOAc/hexanes) gave allylic alcohol **28** (3.22 g, 85%) as a pale yellow oil: $[\alpha]_D^{24.1}$ −9.53 (*c* 1.29, $CHCl_3$); IR (neat): 3420, 2943, 2865, 1717, 1454, 1362, 1097, 735, 697, 679 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.35–7.24 (m, 10H), 5.15 (dd, *J* = 6.9, 5.0 Hz, 1H), 4.57 (d, *J* = 11.5 Hz, 1H), 4.49–4.43 (m, 2H), 4.43 (d, *J* = 11.5 Hz, 1H), 3.91–3.83 (m, 3H), 3.75 (dd, *J* = 6.0, 4.1 Hz, 1H), 3.56 (dd, *J* = 11.5, 3.2 Hz, 1H), 3.41–3.34 (m, 2H), 2.15 (dd, *J* = 11.9, 5.0 Hz, 1H), 2.12–2.03 (m, 2H), 1.94 (m, 1H), 1.86 (dd, *J* = 11.9, 11.9 Hz, 1H), 1.82 (m, 1H), 1.68–1.56 (m, 3H), 1.56–1.43 (m, 2H), 1.24 (s, 3H), 1.20 (s, 3H), 1.12–1.06 (m, 21H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 152.4, 138.7, 138.4, 128.28 (2C), 128.25 (2C), 127.8 (2C), 127.5 (3C), 127.4, 108.2, 79.9, 79.0, 77.9, 76.7, 72.9, 72.7, 70.8, 70.7, 65.2, 40.2, 30.9, 28.3, 27.1, 21.9, 18.5 (3C), 18.4 (3C), 16.4, 13.9, 13.6 (3C); HRMS (FAB) *m*/*z*: $[M + H]^+$ calcd for $C_{39}H_{61}O_6Si$, 653.4232; found, 653.4233.

Selenide ***12***. To a solution of allylic alcohol **28** (3.00 g, 4.59 mmol) and 2-nitrophenyl selenocyanate (98%, 1.33 g, 5.74 mmol) in THF (50 mL) at 0 °C was slowly added *n*-Bu_3P (1.6 mL, 6.48 mmol), and the resultant solution was stirred at 0 °C for 70 min. The mixture was concentrated under reduced pressure, and the residue was directly purified by flash column chromatography (silica gel, 5 to 10 to 15% EtOAc/hexanes) to give selenide **12** (3.38 g, 88%) as a bright yellow oil: $[\alpha]_D^{24.5}$ −3.14 (*c* 1.27, $CHCl_3$); IR (neat): 2942, 2865, 1515, 1454, 1331, 1303, 1098, 1066, 731, 697, 679 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.28 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.66 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.48 (ddd, *J* = 8.3, 8.2, 1.4 Hz, 1H), 7.34–7.22 (m, 11H), 5.24 (dd, *J* = 6.4, 5.5 Hz, 1H), 4.54 (d, *J* = 11.5 Hz, 1H), 4.49–4.43 (m, 2H), 4.40 (d, *J* = 11.5 Hz, 1H), 3.83 (dd, *J* = 11.9, 5.0 Hz, 1H), 3.73 (dd, *J* = 5.9, 4.1 Hz, 1H), 3.56–3.47 (m, 3H), 3.40–3.33 (m, 2H), 2.11–2.05 (m, 3H), 1.91 (m, 1H), 1.82 (dd, *J* = 12.4, 11.9 Hz, 1H), 1.81 (m, 1H), 1.63–1.54 (m, 2H), 1.54–1.42 (m, 2H), 1.22 (s, 3H), 1.21 (s, 3H), 1.11–1.05 (m, 21H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 149.2, 146.7, 138.7, 138.4, 134.5, 133.4, 129.5, 128.27 (2C), 128.24 (2C), 127.7 (2C), 127.5 (3C), 127.4, 126.2, 125.4, 110.5, 79.9, 79.0, 78.4, 76.4, 72.82, 72.76, 70.8, 70.6, 39.9, 32.8, 30.8, 28.3, 27.0, 22.6, 18.5 (3C), 18.4 (3C), 16.4, 13.9, 13.6 (3C); HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{45}H_{63}NO_7SeSiNa$, 860.3431; found, 860.3425.

exo-Olefins ***29***. To a solution of selenide **12** (3.38 g, 4.04 mmol) and DMAP (2.60 g, 21.3 mmol) in THF (65 mL) at −44 °C was slowly added 30% aqueous H_2O_2 solution (5.0 mL, ca. 44 mmol), and the resultant solution was stirred at −44 °C for 1 h. The mixture was allowed to warm to room temperature and stirred for 15 h 20 min. The reaction was quenched with a 1:1 mixture of the saturated aqueous $NaHCO_3$ solution and the saturated aqueous $Na_2S_2O_3$ solution (60 mL) at 0 °C. The mixture was extracted with EtOAc (2 × 80 mL), and the combined organic layers were washed with brine (60 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10 to 15 to 20% EtOAc/hexanes) gave *exo*-olefin **29** (1.79 g, 68%) as a pale yellow oil, along with a small amount of its C52 diastereomeric alcohol **31** (39.4 mg) as a pale yellow oil. Data for **29**: $[\alpha]_D^{26.5}$ −32.6 (*c* 0.86, $CHCl_3$); IR (neat): 3427, 2943, 2866, 1715, 1455, 1361, 1097, 1071, 883, 735, 697, 679 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.34–7.22 (m, 10H), 4.77 (d, *J* = 0.9 Hz, 1H), 4.63 (s, 1H), 4.56 (d, *J* = 11.5 Hz, 1H), 4.49–4.43 (m, 2H), 4.41 (d, *J* = 11.5 Hz, 1H), 4.20 (m, 1H), 3.82 (dd, *J* = 11.5, 5.0 Hz, 1H), 3.72 (dd, *J* = 5.5, 4.6 Hz, 1H), 3.61 (dd, *J* = 10.6, 3.2 Hz, 1H), 3.40–3.33 (m, 2H), 2.13 (dd, *J* = 12.4, 5.0 Hz, 1H), 1.99–1.89 (m, 2H), 1.83 (dd, *J* = 11.9, 11.9 Hz, 1H), 1.81 (m, 1H), 1.74–1.54 (m, 4H), 1.50 (m, 1H), 1.21 (s, 3H), 1.20 (s, 3H), 1.12–1.05 (m, 21H), one proton missing due to H/D exchange; $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 162.8, 138.7, 138.4, 128.27 (2C), 128.25 (2C), 127.7 (2C), 127.48, 127.45 (2C), 127.38, 97.3, 80.0, 78.9, 78.6, 73.4, 73.0, 72.7 (2C), 70.8, 70.7, 40.1, 32.8, 30.8, 28.3, 26.7, 19.0, 18.5 (3C), 18.4 (3C), 14.1, 13.6 (3C); HRMS (FAB) *m*/*z*: $[M + H]^+$ calcd for $C_{39}H_{61}O_6Si$, 653.4232; found, 653.4235.

4-Nitrobenzoate ***30***. To a solution of alcohol **29** (1.79 g, 2.74 mmol) and PPh_3 (2.16 g, 8.24 mmol) in THF (30 mL) at 0 °C were sequentially added 4-nitrobenzoic acid (1.37 g, 8.20 mmol) and DEAD (2.2 M solution in toluene, 3.7 mL, 8.14 mmol). The resultant solution was stirred at room temperature for 1 h. The reaction was quenched with the saturated aqueous $NaHCO_3$ solution (30 mL) at 0 °C. The mixture was extracted with EtOAc (160 mL), and the organic layer was washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5 to 8 to 10% EtOAc/hexanes) gave 4-nitrobenzoate **30** (1.91 g, 87%) as a bright yellow oil: $[\alpha]_D^{25.5}$ −15.8 (*c* 1.09, $CHCl_3$); IR (neat): 2944, 2865, 1725, 1530, 1348, 1270, 1100, 1069, 1014, 883, 719, 697, 679 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.31–8.28 (m, 2H), 8.22–8.18 (m, 2H), 7.35–7.24 (m, 10H), 7.58 (m, 1H), 7.48–7.43 (m, 2H), 7.35–7.23 (m, 10H), 5.93 (br d, *J* = 5.5 Hz, 1H), 4.82 (s, 1H), 4.79 (s, 1H), 4.59 (d, *J* = 11.5 Hz, 1H), 4.50–4.45 (m, 2H), 4.44 (d, *J* = 11.5 Hz, 1H), 3.88 (dd, *J* = 11.5, 5.0 Hz, 1H), 3.77 (dd, *J* = 5.5, 4.6 Hz, 1H), 3.65 (m, 1H), 3.43–3.36 (m, 2H), 2.17 (dd, *J* = 11.9, 5.0 Hz, 1H), 2.09 (m, 1H), 1.96 (m, 1H), 1.92–1.79 (m, 4H), 1.72 (m, 1H), 1.61 (m, 1H), 1.53 (m, 1H), 1.40 (s, 3H), 1.25 (s, 3H), 1.16–1.07 (m, 21H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 163.5, 156.6, 150.5, 138.7, 138.2, 135.7, 130.6 (2C), 128.3 (4C), 127.7 (2C), 127.5, 127.41 (2C), 127.38, 123.6 (2C), 104.6, 80.0, 79.1, 78.9, 74.0, 73.9, 72.9, 72.7, 70.73, 70.66, 40.4, 30.8, 28.3, 27.3, 25.0, 18.5 (3C), 18.4 (3C), 18.0, 14.1, 13.6 (3C); HRMS (FAB) *m*/*z*: $[M + Na]^+$ calcd for $C_{46}H_{63}NO_9SiNa$, 824.4164; found, 824.4173.

Alcohol ***31***. To a solution of 4-nitrobenzoate **30** (1.91 g, 2.38 mmol) in MeOH/THF (1:1, v/v, 40 mL) was added K_2CO_3 (989.4 mg, 7.159 mmol). The resultant solution was stirred at room temperature for 50 min. The reaction was quenched with the saturated aqueous NH_4Cl solution (20 mL) at 0 °C. The mixture was extracted with CH_2Cl_2 (4 × 40 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10 to 20 to 30% EtOAc/hexanes) gave alcohol **31** (1.32 g, 85%) as a pale yellow oil, which was unstable under both neutral and acidic conditions and immediately used in the next reaction without further identification. Data for **31**: $[\alpha]_D^{25.4}$ −11.7 (*c* 0.92, $CHCl_3$); IR (neat): 3444, 2943, 2866, 1715, 1455, 1380, 1362, 1208, 1097, 1070, 883, 734, 697, 679 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.35–7.23 (m, 10H), 4.64 (s, 1H), 4.61 (s, 1H), 4.57 (d, *J* = 11.5 Hz, 1H), 4.49–4.44 (m, 2H), 4.44 (m, 1H), 4.42 (d, *J* = 11.5 Hz, 1H), 3.85 (dd, *J* = 11.5, 5.0 Hz, 1H), 3.74 (dd, *J* = 5.5, 4.6 Hz, 1H), 3.55 (dd, *J* = 11.0, 2.8 Hz, 1H), 3.41–3.34 (m, 2H), 2.15 (dd, *J* = 11.9, 5.0 Hz, 1H), 1.99–1.78 (m, 4H), 1.81 (dd, *J* = 11.9, 11.9 Hz, 1H, overlapped), 1.70–1.47 (m, 4H), 1.35 (s, 3H), 1.20 (s, 3H), 1.12–1.06 (m, 21H), one proton missing due to H/D exchange; $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 161.2, 138.7, 138.4, 128.27 (2C), 128.25 (2C), 127.7 (2C), 127.48, 127.46 (2C), 127.38, 100.9, 79.9, 78.9 (2C), 73.6, 73.1, 72.8, 71.1, 70.8, 70.7, 39.8, 30.83, 30.80, 28.3, 24.5, 18.8, 18.5 (3C), 18.4 (3C), 14.0, 13.6 (3C).

TES Ether ***10***. To a solution of alcohol **31** (1.32 g, 2.02 mmol) and imidazole (692.9 mg, 10.18 mmol) in DMF (20 mL) at 0 °C was slowly added TESCl (1.0 mL, 5.97 mmol), and the resultant solution was stirred at room temperature for 1 h. The reaction was quenched with the saturated aqueous $NaHCO_3$ solution (4 mL) at 0 °C. The mixture was extracted with *t*-BuOMe (100 mL) and washed with H_2O (50 mL). The aqueous layer was extracted with *t*-BuOMe (2 × 50 mL), and the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 3 to 4% EtOAc/hexanes) gave TES ether **10** (1.47 g, 95%) as a colorless oil: $[\alpha]_D^{25.7}$ −13.6 (*c* 1.03, $CHCl_3$); IR (neat): 2946, 2868, 1456, 1379, 1240, 1099, 1069, 1011, 883, 734, 697, 679 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.35–7.22 (m, 10H), 4.56 (d, *J* = 11.5 Hz, 1H), 4.51 (s, 1H), 4.49–4.44 (m, 2H), 4.43 (dd, *J* = 5.9, 2.3 Hz, 1H), 4.411 (s, 1H), 4.406 (d, *J* = 11.5 Hz, 1H), 3.81 (dd, *J* = 11.9, 5.0 Hz, 1H), 3.73 (dd, *J* = 5.9, 4.1 Hz, 1H), 3.50 (dd, *J* = 11.5, 2.8 Hz, 1H), 3.42–3.34 (m, 2H), 2.15 (dd, *J* = 11.9, 5.0 Hz, 1H), 1.98–1.88 (m, 2H), 1.86–1.72 (m, 3H), 1.67–1.55 (m, 2H), 1.54–1.47 (m,

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2H), 1.38 (s, 3H), 1.20 (s, 3H), 1.14−1.06 (m, 21H), 0.96 (t, J = 8.0 Hz, 9H), 0.61 (q, J = 8.0 Hz, 6H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 162.3, 138.7, 138.5, 128.3 (2C), 128.2 (2C), 127.8 (2C), 127.5 (2C), 127.41, 127.36, 98.9, 79.6, 79.0, 78.8, 74.4, 73.0, 72.7, 71.1, 70.8, 70.5, 40.7, 31.7, 30.8, 28.3, 24.7, 18.5 (3C), 18.4 (3C), 18.1, 14.0, 13.6 (3C), 6.8 (3C), 4.8 (3C); HRMS (FAB) m/z: $[M + Na]^+$ calcd for $C_{45}H_{74}O_6Si_2Na$, 789.4916; found, 789.4927.

Ketone ***33***. To a suspension of TES ether **10** (480.3 mg, 0.6260 mmol), Na_2HPO_4 (90.7 mg, 0.639 mmol), and $Fe(dibm)_3$ (99.0 mg, 0.190 mmol) in *i*-PrOH (degassed with argon for 1 h, 6 mL) was added a solution of vinyl ketone **11** (669.7 mg, 3.343 mmol) and Ph(*i*-PrO)SiH_2 (0.60 mL, 3.25 mmol) in EtOAc (degassed with argon for 1 h, 6 + 1 mL rinse) via a syringe pump over 2.5 h. The resultant solution was stirred at room temperature for further 2 h. The reaction was quenched with brine (10 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (4 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 3 to 4 to 5% EtOAc/hexanes) gave ketone **33** (427.3 mg, 70%) as a colorless oil: $[\alpha]_D^{26.3}$ −7.6 (c 1.03, $CHCl_3$); IR (neat): 2952, 2866, 1720, 1463, 1378, 1362, 1254, 1102, 1070, 1005, 839, 735, 697, 678 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.34−7.21 (m, 10H), 4.54 (d, J = 11.5 Hz, 1H), 4.48−4.43 (m, 2H), 4.37 (d, J = 11.5 Hz, 1H), 4.22−4.15 (m, 2H), 3.79 (dd, J = 11.9, 4.6 Hz, 1H), 3.75 (d, J = 5.9 Hz, 1H), 3.70 (dd, J = 6.4, 4.1 Hz, 1H), 3.40−3.33 (m, 2H), 3.20 (dd, J = 11.5, 3.7 Hz, 1H), 2.78 (ddd, J = 17.9, 10.1, 5.5 Hz, 1H), 2.52 (ddd, J = 17.9, 10.1, 5.0 Hz, 1H), 1.93 (dd, J = 12.4, 4.6 Hz, 1H), ca. 1.92 (m, 1H, overlapped), 1.89−1.77 (m, 3H), 1.76 (m, 1H), 1.67 (m, 1H), 1.58 (m, 1H), 1.51 (dd, J = 12.4, 11.9 Hz, 1H), ca. 1.47 (m, 1H, overlapped), 1.41 (s, 3H), 1.42−1.33 (m, 2H), 1.19 (s, 3H), 1.15 (s, 3H), 1.14−1.06 (m, 21H), 0.96 (t, J = 7.8 Hz, 9H), 0.93 (s, 9H), 0.60 (q, J = 7.8 Hz, 6H), 0.093 (s, 3H), 0.090 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 211.8, 138.8 (2C), 128.3 (2C), 128.1 (2C), 127.7 (2C), 127.5 (2C), 127.33, 127.26, 80.6, 79.4, 79.3, 77.2, 76.4, 76.3, 72.8, 72.7, 70.9, 70.3, 69.3, 42.0, 37.1, 33.8, 30.9, 28.4, 27.4, 25.8 (3C), 24.0, 23.5, 18.5 (3C), 18.4 (3C), 18.2, 17.6, 14.2, 13.7 (3C), 6.9 (3C), 4.9 (3C), −5.5 (2C); HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{55}H_{97}O_8Si_3$, 969.6486; found, 969.6493.

Methyl Acetal ***34***. To a solution of ketone **33** (427.3 mg, 0.4407 mmol) in CH_2Cl_2/MeOH (1:1, v/v, 44 mL) was added CSA (53.9 mg, 0.232 mmol), and the resultant solution was stirred at room temperature for 23 h. The reaction was quenched with Et_3N (0.3 mL). The mixture was concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 30 to 40% EtOAc/hexanes) gave methyl acetal **34** (282.7 mg, 85%) as a colorless oil: $[\alpha]_D^{25.7}$ −63.2 (c 0.99, $CHCl_3$); IR (neat): 3464, 2944, 2866, 1456, 1379, 1115, 1071, 883, 735, 697, 679 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.35−7.21 (m, 10H), 4.54 (d, J = 11.5 Hz, 1H), 4.49−4.43 (m, 2H), 4.37 (d, J = 11.5 Hz, 1H), 3.78 (dd, J = 11.9, 5.0 Hz, 1H), 3.71 (dd, J = 6.0, 4.1 Hz, 1H), 3.67−3.62 (m, 2H), 3.51 (dd, J = 11.5, 5.5 Hz, 1H), 3.46 (dd, J = 11.5, 6.4 Hz, 1H), 3.40−3.33 (m, 2H), 3.24 (s, 3H), 2.06 (dd, J = 12.4, 5.0 Hz, 1H), 1.88 (m, 1H), 1.85−1.70 (m, 7H), 1.68−1.55 (m, 5H), 1.50 (m, 1H), 1.29 (s, 3H), 1.25 (s, 3H), 1.19 (s, 3H), 1.12−1.06 (m, 21H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 138.7, 138.6, 128.26 (2C), 128.18 (2C), 127.8 (2C), 127.5 (2C), 127.36, 127.34, 97.7, 79.5, 78.9, 77.9, 76.1, 72.9, 72.8, 72.7, 72.6, 70.9, 70.4, 64.2, 48.3, 41.6, 35.9, 30.8, 28.9, 28.2, 24.7, 24.3, 20.6, 18.50 (3C), 18.48, 18.43 (3C), 13.9, 13.6 (3C); HRMS (FAB) m/z: $[M + Na]^+$ calcd for $C_{44}H_{70}O_8SiNa$, 777.4732; found, 777.4736.

LMN-Ring Fragment ***9***. To a solution of methyl acetal **34** (282.7 mg, 0.3744 mmol) in acetone (38 mL) at 0 °C was added $Sc(OTf)_3$ (56.5 mg, 0.115 mmol), the resultant yellow solution was stirred at 0 °C for 1 h 20 min. The reaction was quenched with Et_3N (0.3 mL). The mixture was concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5 to 10 to 20% EtOAc/hexanes) gave LMN-ring fragment **9** (237.5 mg, 81%) as a colorless oil: $[\alpha]_D^{26.0}$ −60.4 (c 0.74, $CHCl_3$); IR (neat): 2944, 2866, 1455, 1381, 1114, 1067, 1036, 984, 883, 734, 697, 679 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.34−7.21 (m, 10H), 4.54 (d, J = 11.5 Hz, 1H), 4.48−4.43 (m, 2H), 4.37 (d, J = 11.5 Hz, 1H), 3.93 (d, J = 8.3 Hz, 1H), 3.91 (dd, J = 10.6, 5.0 Hz, 1H), 3.78 (dd, J = 11.9, 4.6 Hz, 1H), 3.70 (dd, J = 5.9, 4.1 Hz, 1H), 3.69 (d, J = 8.3 Hz, 1H), 3.67 (dd, J = 11.0, 4.6 Hz, 1H), 3.40−3.33 (m, 2H), 2.06 (dd, J = 12.4, 4.6 Hz, 1H), 1.92−1.85 (m, 2H), 1.84−1.71 (m, 4H), 1.70−1.54 (m, 6H), 1.50 (s, 3H), 1.50 (m, 1H, overlapped), 1.40 (s, 3H), 1.26 (s, 3H), 1.19 (s, 3H), 1.12−1.05 (m, 21H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 138.7, 138.6, 128.3 (2C), 128.2 (2C), 127.8 (2C), 127.5 (2C), 127.36, 127.34, 111.1, 103.0, 79.5, 79.0, 77.9, 76.0, 74.6, 73.5, 72.8, 72.7, 72.6, 70.9, 70.4, 41.6, 37.1, 30.9, 30.4, 28.3, 27.2, 26.8, 24.7, 24.5, 20.6, 18.6, 18.5 (3C), 18.4 (3C), 14.0, 13.6 (3C); HRMS (FAB) m/z: $[M + Na]^+$ calcd for $C_{46}H_{72}O_8SiNa$, 803.4889; found, 803.4893.

Diol ***35***. To a solution of bis-benzyl ether **9** (441.1 mg, 0.5647 mmol) in THF (18 mL) at −78 °C was added LiDBB (ca. 0.4 M solution in THF, 15 mL, 6.0 mmol) dropwise over 5 min. The resultant solution was stirred at −78 °C for 1 h, then allowed to warm to −50 °C and stirred for 45 min. The reaction was quenched with the saturated aqueous NH_4Cl solution (15 mL). The resultant mixture was warmed to room temperature, extracted with EtOAc (150 mL), and the organic layer was washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 30 to 50% EtOAc/hexanes) gave diol **35** (337.3 mg, 99%) as a colorless amorphous powder: $[\alpha]_D^{22.5}$ −5.5 (c 0.55, $CHCl_3$); IR (neat): 3477, 2947, 2869, 1464, 1382, 1209, 1118, 1065, 1036, 985, 756 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 3.92 (d, J = 8.5 Hz, 1H), 3.90−3.85 (m, 2H), 3.74 (dd, J = 11.9, 5.0 Hz, 1H), 3.69 (d, J = 8.5 Hz, 1H), 3.62 (m, 1H), 3.59 (dd, J = 11.5, 4.6 Hz, 1H), 3.41 (s, 1H), 1.96−1.85 (m, 3H), 1.84−1.59 (m, 10H), 1.56 (M, 1H), 1.51 (s, 3H), 1.40 (s, 3H), 1.30 (s, 3H), 1.25 (s, 3H), 1.23 (s, 3H), 1.15−1.08 (m, 21H), one proton missing due to H/D exchange; $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 111.1, 103.0, 82.3, 78.5, 77.3, 76.0, 74.5, 73.5, 73.0, 72.6, 63.2, 43.8, 36.9, 31.1, 30.3, 29.9, 27.3, 26.7, 24.7, 24.3, 20.2, 18.5, 18.2 (3C), 18.1 (3C), 13.5 (3C), 10.1; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{32}H_{60}O_8SiNa$, 623.3950; found, 623.3952.

Lactone ***36***. To a solution of diol **35** (337.3 mg, 0.5613 mmol) in CH_2Cl_2 (18 mL) were added sequentially $PhI(OAc)_2$ (549.2 mg, 1.705 mmol) and TEMPO (9.1 mg, 0.058 mmol), and the resultant solution was stirred at room temperature for 16.5 h. The reaction was quenched with the saturated aqueous $NaHCO_3$ solution/saturated aqueous $Na_2S_2O_3$ solution (1:1, v/v, 20 mL), and the resultant mixture was stirred at room temperature for 30 min. The mixture was extracted with EtOAc (100 mL), and the organic layer was washed with the saturated aqueous $NaHCO_3$ solution (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 10 to 20% EtOAc/hexanes) gave lactone **36** (315.3 mg, 94%) as a colorless amorphous powder: $[\alpha]_D^{23.1}$ +15.1 (c 0.52, $CHCl_3$); IR (neat): 2945, 2868, 1741, 1382, 1262, 1120, 1037, 984, 883, 756 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 4.68 (dd, J = 12.4, 5.9 Hz, 1H), 3.95 (br d, J = 3.7 Hz, 1H), 3.93 (d, J = 8.7 H, 1H), 3.89 (dd, J = 13.3, 3.7 Hz, 1H), 3.69 (d, J = 8.7 Hz, 1H), 3.61 (dd, J = 10.6, 3.7 Hz, 1H), 3.13 (ddd, J = 14.0, 14.0, 2.3 Hz, 1H), 2.32 (dd, J = 14.0, 5.7 Hz, 1H), 2.03 (dd, J = 12.8, 5.9 Hz, 1H), 1.94 (dd, J = 14.0, 14.0 Hz, 1H), 1.92−1.85 (m, 2H), 1.81 (dd, J = 12.8, 12.4 Hz, 1H), 1.80−1.65 (m, 7H), 1.50 (s, 3H), 1.40 (s, 3H), 1.33 (s, 3H), 1.26 (s, 3H), 1.14 (s, 3H), 1.12−1.06 (m, 21H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 174.9, 111.0, 102.9, 77.4, 76.1, 74.5, 73.8, 73.6, 73.0, 70.4, 42.4, 36.8, 30.2, 27.9, 27.2, 26.9, 26.7, 24.6, 24.3, 19.9, 18.5, 18.3 (3C), 18.2 (3C), 14.6, 12.9 (3C), one oxygenated quaternary carbon missing due to overlapping with $CDCl_3$ signals; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{32}H_{56}O_8SiNa$, 619.3637; found, 619.3636.

Enol Phosphate ***7***. To a solution of lactone **36** (171.6 mg, 0.2875 mmol), which was azeotropically dried with toluene (×3), in THF (6 mL) were added HMPA (0.20 mL, 1.15 mmol) and $(PhO)_2P(O)Cl$ (0.18 mL, 0.871 mmol). To this solution at −78 °C was added slowly KHMDS (0.5 M solution in toluene, 1.8 mL, 0.90 mmol), and the resultant solution was stirred at −78 °C for 3 h. The reaction was

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quenched with 3% aqueous NH_4OH solution (8 mL). The mixture was allowed to warm to room temperature and stirred for 20 min. The resultant mixture was extracted with EtOAc (60 mL), and the organic layer was washed with H_2O (8 mL) and brine (8 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 20% EtOAc/hexanes) gave enol phosphate **7** (230.9 mg, 97%) as a colorless amorphous powder, which was unstable and used immediately in the next Suzuki−Miyaura reaction without further purification.

Alcohol ***40***. To a solution of TBS ether **38** (1.57 g, 6.32 mmol) and 2-(4-methoxybenzyloxy)-4-methylquinoline **39** (3.56 g, 12.7 mmol) in CH_2Cl_2 (30 mL) was added CSA (147.4 mg, 0.6346 mmol), and the resultant solution was stirred at room temperature for 91 h. The mixture was poured into the saturated aqueous $NaHCO_3$ solution (40 mL) and extracted with EtOAc (160 mL). The organic layer was washed with 1 M aqueous HCl solution (3 × 30 mL), the saturated aqueous $NaHCO_3$ solution (30 mL), and brine (30 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was roughly purified by column chromatography (silica gel, 5 to 10 to 25% EtOAc/hexanes) gave PMB ether **40** (2.30 g) as a colorless oil, which was contaminated by some impurities and used in the next reaction without further purification: ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.26−7.23 (m, 2H), 6.88−6.85 (m, 2H), 4.58 (d, J = 11.0 Hz, 1H), 4.54 (d, J = 11.0 Hz, 1H), 3.94 (m, 1H), 3.81 (s, 3H), 3.70 (dd, J = 10.6, 5.3 Hz, 1H), 3.67 (s, 3H), 3.56 (dd, J = 10.6, 6.2 Hz, 1H), 2.63 (dd, J = 15.5, 4.8 Hz, 1H), 2.51 (dd, J = 15.5, 7.8 Hz, 1H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 172.2, 159.2, 130.5, 129.4 (2C), 113.8 (2C), 76.4, 72.2, 64.7, 53.3, 51.6, 37.4, 25.9 (3C), 18.3, −5.4, −5.5.

To a solution of the above PMB ether **40** (2.30 g) in THF (40 mL) at −40 °C was added $LiAlH_4$ (281.7 mg, 7.423 mmol), and the resultant solution was stirred at −40 °C for 1 h. The reaction was quenched with the saturated potassium sodium tartrate solution (20 mL). The resultant mixture was diluted with EtOAc (15 mL) and the saturated potassium sodium tartrate solution (10 mL), and vigorously stirred at room temperature for 75 min. The mixture was extracted with EtOAc (100 mL), and the organic layer was washed with brine (40 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 20 to 33% EtOAc/hexanes) gave alcohol **41** (1.44 g, 67% in two steps) as a colorless oil: $[\alpha]_D^{22.5}$ −34.2 (c 1.85, $CHCl_3$); IR (neat): 3419, 2953, 2929, 2857, 1613, 1514, 1464, 1302, 1250, 1173, 1090, 1034, 837, 777, 668 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.28−7.25 (m, 2H), 6.90−6.86 (m, 2H), 4.66 (d, J = 11.0 Hz, 1H), 4.51 (d, J = 11.0 Hz, 1H), 3.80 (s, 3H), 3.77 (dd, J = 10.1, 5.0 Hz, 1H), 3.73 (t, J = 5.5 Hz, 2H), 3.66 (m, 1H), 3.63 (dd, J = 10.1, 5.5 Hz, 1H), 1.91 (br, 1H), 1.85−1.72 (m, 2H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 159.3, 130.5, 129.5 (2C), 113.9 (2C), 78.6, 71.9, 65.4, 60.4, 55.3, 34.3, 25.9 (3C), 18.3, −5.41, −5.44; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{18}H_{32}O_4SiNa$, 363.1962; found, 363.1962.

Iodide ***37***. To a solution of imidazole (126.9 mg, 1.864 mmol) in CH_2Cl_2 (10 mL) were sequentially added PPh_3 (334.2 mg, 1.274 mmol) and I_2 (338.7 mg, 1.335 mmol), and the resultant solution was stirred at room temperature for 20 min. To this solution was added a solution of alcohol **41** (391.1 mg, 1.148 mmol) in CH_2Cl_2 (7 + 3 mL rinse) dropwise over 8 min. The resultant solution was stirred at room temperature for 40 min. The reaction was quenched with the saturated aqueous $Na_2S_2O_3$ solution (20 mL). The mixture was extracted with EtOAc (80 mL), and the organic layer was washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 5 to 10% EtOAc/hexanes) gave iodide **37** (436.0 mg, 84%) as a colorless oil: $[\alpha]_D^{22.4}$ −53.5 (c 1.91, $CHCl_3$); IR (neat): 2953, 2929, 2856, 1613, 1514, 1464, 1302, 1116, 1038, 837, 777 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6): δ 7.25−7.22 (m, 2H), 6.82−6.79 (m, 2H), 4.55 (d, J = 11.5 Hz, 1H), 4.39 (d, J = 11.5 Hz, 1H), 3.55 (dd, J = 9.7, 4.1 Hz, 1H), 3.50−3.43 (m, 2H), 3.31 (s, 3H), 3.09 (ddd, J = 9.5, 8.7, 7.3 Hz, 1H), 3.02 (ddd, J = 9.5, 6.9, 5.0 Hz, 1H), 1.95−1.84 (m, 2H), 0.96 (s, 9H), 0.035 (s, 3H), 0.031 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, C_6D_6): δ 159.8, 131.4, 129.6 (2C), 114.1 (2C), 79.3, 72.3, 65.0, 54.8, 36.5, 26.0 (3C), 18.4, 3.1, −5.3 (2C); HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{18}H_{31}IO_3SiNa$, 473.0979; found, 473.0982.

Enol Ether ***6***. To a solution of iodide **37** (296.5 mg, 0.6583 mmol) and β-methoxy-9-borabicyclo[3.3.1]nonane (β-MeO-9-BBN) (1.0 M solution in n-hexane, 1.3 mL, 1.3 mmol) in Et_2O (6 mL) at −78 °C was added t-BuLi (1.62 M solution in pentane, 0.95 mL, 1.54 mmol) at once. The resultant mixture was stirred at −78 °C for 10 min and then diluted with THF (6 mL). The mixture was allowed to warm to room temperature and stirred for 1 h to generate alkylborate **8**. The resultant solution was treated with 3 M aqueous Cs_2CO_3 solution (0.65 mL, 1.95 mmol) and stirred at room temperature for 20 min. To this mixture were sequentially added a solution of the above enol phosphate **7** (230.9 mg, 0.2785 mmol) in DMF (6 mL + 2 × 1 mL rinse) and a solution of $Pd(PPh_3)_4$ (50.6 mg, 0.0438 mmol) in THF (1 + 1 mL rinse), and the resultant mixture was stirred at 50 °C (oil bath) for 17 h 15 min. The reaction was quenched with H_2O at room temperature. The mixture was extracted with EtOAc (50 mL), and the organic layer was washed with H_2O (10 mL) and brine (2 × 10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, first round: 5 to 10 to 20% EtOAc/hexanes, second round: 5 to 7 to 10% EtOAc/hexanes) gave enol ether **6** (203.2 mg, 81%) as a pale yellow oil: $[\alpha]_D^{25.4}$ +12.6 (c 1.17, $CHCl_3$); IR (neat): 2948, 2865, 1514, 1464, 1381, 1249, 1119, 1063, 1036, 837, 777, 677 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6): δ 7.36−7.31 (m, 2H), 6.85−6.81 (m, 2H), 4.70 (d, J = 11.5 Hz, 1H), 4.58−4.54 (m, 2H), 4.32−4.24 (m, 2H), 3.96 (d, J = 8.3 Hz, 1H), 3.87 (m, 1H), 3.81−3.74 (m, 2H), 3.64 (dd, J = 10.3, 4.3 Hz, 1H), 3.58 (m, 1H), 3.51 (d, J = 8.3 Hz, 1H), 3.32 (s, 3H), 2.40−2.21 (m, 5H), 2.14−2.02 (m, 3H), 1.96−1.77 (m, 5H), 1.75 (m, 1H), 1.55 (s, 3H), 1.46 (s, 3H), 1.37 (s, 3H), 1.23 (s, 3H), 1.23−1.18 (m, 21H), 1.17−1.09 (m, 2H), 1.06 (s, 3H), 1.01 (s, 9H), 0.104 (s, 3H), 0.095 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, C_6D_6): δ 159.6, 159.3, 132.0, 129.2 (2C), 114.0 (2C), 111.1, 103.5, 101.1, 80.2, 79.2, 78.4, 76.2, 74.9, 74.4, 74.3, 73.5, 72.5, 72.1, 66.2, 54.7, 43.9, 37.6, 32.5, 30.9, 30.6, 29.8, 27.4, 27.1, 26.2 (3C), 25.2, 25.1, 20.7, 18.8, 18.7 (3C), 18.6 (3C), 18.5, 13.7, 13.4 (3C), −5.2 (2C); HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{50}H_{86}O_{10}Si_2Na$, 925.5652; found, 925.5652.

Alcohol ***42***. To a solution of enol ether **6** (201.2 mg, 0.2227 mmol) in THF (5 mL) at 0 °C was added BH_3·THF (0.9 M solution in THF, 0.75 mL, 0.675 mmol). The resultant solution was stirred at 0 °C for 15 min, then allowed to warm to room temperature and stirred for 2 h. The mixture was cooled to 0 °C and treated with 3 M aqueous NaOH solution (0.5 mL, 1.5 mmol) followed by 30% aqueous H_2O_2 solution (0.6 mL, 1.5 mmol). The resultant mixture was stirred at room temperature for 1 h. The mixture was diluted with t-BuOMe (40 mL), washed with H_2O (6 mL) and brine (6 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 15 to 20 to 25% EtOAc/hexanes) gave alcohol **42** (162.7 mg, 79%) as a colorless oil, which was used in the next reaction without further purification: ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30−7.26 (m, 2H), 6.88−6.84 (m, 2H), 4.62 (d, J = 11.5 Hz, 1H), 4.52 (d, J = 11.5 Hz, 1H), 4.12 (m, 1H), 3.93 (d, J = 8.8 Hz, 1H), 3.88 (dd, J = 10.1, 3.7 Hz, 1H), 3.84 (d, J = 5.9 Hz, 1H), 3.79 (s, 3H), 3.71 (dd, J = 10.5, 5.5 Hz, 1H), 3.60−3.54 (m, 3H), 3.45 (m, 1H), 3.23 (m, 1H), 2.08 (dd, J = 13.3, 11.0 Hz, 1H), 1.92−1.79 (m, 4H), 1.78−1.62 (m, 8H), 1.62−1.56 (m, 2H), 1.53 (m, 1H), 1.50 (s, 3H), 1.50−1.44 (m, 2H), 1.40 (s, 3H), 1.26 (s, 3H), 1.24 (s, 3H), 1.16 (s, 3H), 1.12−1.06 (m, 21H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 159.1, 131.2, 129.3 (2C), 113.7 (2C), 111.1, 103.0, 82.6, 79.8, 78.4, 77.9, 75.8, 74.6, 73.7, 73.4, 72.9, 71.7, 69.4, 65.5, 64.6, 55.3, 44.5, 39.7, 37.0, 30.3, 28.5, 28.3, 27.2, 26.7, 26.0 (3C), 24.7, 24.6, 120.3, 18.5, 18.4 (6C), 18.3, 15.7, 12.8 (3C), −5.30, −5.34.

Ketone ***43***. To a suspension of alcohol **42** (162.7 mg, 0.176 mmol) and $NaHCO_3$ (80.2 mg, 0.955 mmol) in CH_2Cl_2 (9 mL) at 0 °C was added Dess−Martin periodinane (95%, 199.9 mg, 0.4477 mmol), and the resultant mixture was stirred at room temperature for 1 h. The

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reaction was quenched with the saturated aqueous $NaHCO_3$ solution/saturated aqueous $Na_2S_2O_3$ solution (1:1, v/v, 10 mL). The mixture was stirred at room temperature for 10 min. The mixture was extracted with EtOAc (40 mL), and the organic layer was washed with saturated aqueous $NaHCO_3$ (6 mL) and brine (6 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 15% EtOAc/hexanes) gave ketone **S5** (146.7 mg, 90%) as a colorless oil, which was used in the next reaction without further purification: ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.28−7.24 (m, 2H), 6.87−6.84 (m, 2H), 4.60 (d, J = 11.0 Hz, 1H), 4.51 (d, J = 11.0 Hz, 1H), 3.93 (d, J = 8.7 Hz, 1H), 3.93−3.89 (m, 3H), 3.82 (dd, J = 12.8, 5.0 Hz, 1H), 3.79 (s, 3H), 3.72−3.66 (m, 3H), 3.56 (dd, J = 10.6, 5.5 Hz, 1H), 3.43 (m, 1H), 3.04 (d, J = 12.8 Hz, 1H), 2.66 (dd, J = 12.8, 6.9 Hz, 1H), 2.15 (m, 1H), 1.93−1.61 (m, 12H), 1.55 (m, 1H), 1.50 (s, 3H), 1.40 (s, 3H), 1.32 (s, 3H), 1.29 (s, 3H), 1.24 (s, 3H), 1.11−1.05 (m, 21H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 211.5, 159.1, 131.0, 129.3 (2C), 113.7 (2C), 111.1, 103.1, 84.8, 79.7, 78.8, 78.1, 76.0, 74.6, 74.4, 73.5, 73.4, 71.9, 66.0, 65.5, 55.3, 46.5, 43.9, 37.0, 30.3, 28.4, 27.2, 26.7, 26.0 (3C), 24.5, 24.4, 24.3, 20.4, 18.5, 18.3, 18.2 (6C), 14.4, 12.8 (3C), −5.34, −5.30.

To a solution of the above ketone **S5** (146.7 mg, 0.1596 mmol) in toluene (8 mL) was added DBU (0.95 mL, 6.36 mmol), and the resultant solution was stirred under reflux (oil bath) for 48 h. The mixture was cooled to room temperature and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 5 to 10 to 20 to 30% EtOAc/hexanes) gave ketone **43** (126.2 mg, 86%) as a colorless oil: $[\alpha]_D^{23.4}$ −64.7 (c 1.10, $CHCl_3$); IR (neat): 2948, 2866, 1715, 1514, 1464, 1381, 1249, 1116, 1066, 1036, 837, 756 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27−7.23 (m, 2H), 6.87−6.84 (m, 2H), 4.59 (d, J = 11.0 Hz, 1H), 4.46 (d, J = 11.0 Hz, 1H), 3.94 (br d, J = 6.9 Hz, 1H), 3.93 (d, J = 8.7 Hz, 1H), 3.91 (m, 1H), 3.79 (s, 3H), 3.72−3.67 (m 3H), 3.652 (dd, J = 10.6, 5.7 Hz, 1H), 3.647 (dd, J = 12.8, 4.6 Hz, 1H), 3.53 (dd, J = 10.6, 5.4 Hz, 1H), 3.42 (m, 1H), 2.97 (d, J = 13.1 Hz, 1H), 2.60 (dd, J = 13.1, 7.1 Hz, 1H), 1.93−1.85 (m, 2H), 1.83−1.54 (m, 12H), 1.50 (s, 3H), 1.40 (s, 3H), 1.31 (s, 3H), 1.29 (s, 3H), 1.25 (s, 3H), 1.10−1.04 (m, 21H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 213.6, 131.1, 129.3 (3C), 113.7 (2C), 111.1, 103.1, 101.1, 87.0, 79.0, 78.7, 78.1, 76.0, 74.6, 74.3, 73.5 (2C), 71.8, 65.7, 55.3, 45.7, 43.0, 37.1, 30.3, 29.0, 27.4, 27.2, 26.8, 26.0 (3C), 24.5, 24.4, 20.5, 18.5, 18.3, 18.2 (6C), 14.6, 12.8 (3C), −5.4, −5.3; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{50}H_{86}O_{11}Si_2Na$, 941.5601; found, 941.5601.

Alcohol ***44***. To a solution of ketone **43** (17.4 mg, 0.0189 mmol) in CH_2Cl_2 (2 mL) at −78 °C was added DIBALH (1.0 M solution in n-hexane, 0.06 mL, 0.06 mmol), and the resultant solution was stirred at −78 °C for 50 min. The reaction was quenched with the saturated aqueous potassium sodium tartrate solution (1 mL). The mixture was diluted with EtOAc (2 mL) and vigorously stirred at room temperature for 45 min. The mixture was extracted with EtOAc (15 mL), and the organic layer was washed with brine (4 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (20% EtOAc/hexanes) gave alcohol **44** (8.8 mg, 51%) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27−7.24 (m, 2H), 6.87−6.84 (m, 2H), 4.61 (br d, J = 7.3 Hz, 1H), 4.60 (d, J = 11.2 Hz, 1H), 4.48 (d, J = 11.2 Hz, 1H), 4.10 (br d, J = 5.0 Hz, 1H), 3.93 (d, J = 8.5 Hz, 1H), 3.89 (m, 1H), 3.86 (dd, J = 12.4, 5.0 Hz, 1H), 3.81−3.77 (m, 4H), 3.69 (d, J = 8.5 Hz, 1H), 3.68−3.62 (m, 3H), 3.55 (dd, J = 10.3, 4.8 Hz, 1H), 3.44 (m, 1H), 2.21 (ddd, J = 15.5, 5.5, 5.5 Hz, 1H), 1.92−1.84 (m, 3H), 1.82−1.52 (m, 11H), 1.50 (s, 3H), 1.45 (m, 1H), 1.40 (s, 3H), 1.32 (s, 3H), 1.25 (s, 3H), 1.20−1.09 (m, 24H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 159.0, 131.2, 129.3 (2C), 113.7 (2C), 111.0, 103.1, 86.2, 79.3, 78.6, 78.4, 77.8, 76.5, 75.9, 74.6, 73.5, 73.3, 71.8, 71.6, 65.9, 55.3, 43.6, 37.1, 32.0, 30.7, 30.4, 27.7, 27.2, 26.8, 26.0 (3C), 24.5, 24.4, 20.6, 18.5, 18.4 (4C), 18.3 (3C), 15.4, 12.8 (3C), −5.4, −5.3.

Acetate ***45***. To a solution of alcohol **44** (8.8 mg, 0.0095 mmol), Et_3N (20 μL, 0.144 mmol), and a catalytic amount of DMAP in CH_2Cl_2 (1 mL) was added Ac_2O (10 μL, 0.106 mmol), and the resultant solution was stirred at room temperature for 1.5 h. The mixture was diluted with EtOAc (12 mL), washed with the saturated aqueous $NaHCO_3$ solution (4 mL) and brine (4 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 10 to 20% EtOAc/hexanes) gave acetate **45** (9.0 mg, 98%) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27−7.24 (m, 2H), 6.87−6.83 (m, 2H), 4.77 (ddd, J = 9.2, 9.2, 3.2 Hz, 1H), 4.62 (d, J = 11.3 Hz, 1H), 4.47 (d, J = 11.3 Hz, 1H), 3.94 (dd, J = 4.6, 2.8 Hz, 1H), 3.93 (d, J = 8.8 Hz, 1H), 3.90 (dd, J = 11.0, 3.7 Hz, 1H), 3.87 (dd, J = 13.3, 4.1 Hz, 1H), 3.84 (m, 1H), 3.79 (s, 3H), 3.68 (d, J = 8.8 Hz, 1H), 3.673 (dd, J = 10.6, 6.0 Hz, 1H), 3.669 (dd, J = 11.0, 4.6 Hz, 1H), 3.57 (dd, J = 10.6, 4.8 Hz, 1H), 3.42 (m, 1H), 2.51 (ddd, J = 16.0, 9.2, 2.8 Hz, 1H), 1.96 (s, 3H), 1.91−1.84 (m, 2H), 1.84−1.56 (m, 12H), 1.49 (s, 3H), 1.40 (s, 3H), 1.34 (s, 3H), 1.28 (m, 1H), 1.25 (s, 3H), 1.11 (s, 3H), 1.11−1.07 (m, 21H), 0.91 (s, 9H), 0.061 (s, 3H), 0.058 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 170.2, 159.0, 131.3, 129.2, (2C), 113.7 (2C), 111.1, 103.1, 81.0, 79.3, 79.2, 78.3, 76.3, 76.0, 74.6, 74.5 (2C), 73.36, 73.34, 71.8, 65.9, 55.3, 42.6, 37.3, 37.1, 30.4, 29.2, 27.7, 27.2, 26.8, 26.0 (3C), 24.5, 24.3, 21.1, 20.8, 18.5, 18.4 (3C), 18.3 (4C), 13.6, 12.8 (3C), −5.3, −5.4; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{52}H_{90}O_{12}Si_2Na$, 985.5863; found, 985.5861.

Diol ***46***. To a solution of ketone **43** (59.7 mg, 0.0649 mmol) in CH_2Cl_2 (3 mL) at −78 °C was added DIBALH (1.0 M solution in n-hexane, 0.4 mL, 0.4 mmol). The resultant solution was stirred at −78 °C for 1 h, and then allowed to warm to −20 °C and stirred for 3 h. The reaction was quenched with the saturated aqueous potassium sodium tartrate solution (5 mL). The resultant mixture was diluted with EtOAc (5 mL) and vigorously stirred at room temperature for 1 h. The mixture was extracted with EtOAc (10 mL, 6 mL), and the combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (1 to 2 to 4% MeOH/$CHCl_3$) gave diol **46** (39.8 mg, 76%) as a colorless oil: $[\alpha]_D^{22.6}$ −18.1 (c 0.39, $CHCl_3$); IR (neat): 3449, 2944, 2867, 1514, 1464, 1381, 1248, 1092, 1035, 985, 755, 678 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.28−7.24 (m, 2H), 6.90−6.86 (m, 2H), 4.54 (d, J = 11.5 Hz, 1H), 4.45 (d, J = 11.5 Hz, 1H), 4.11 (br d, J = 5.0 Hz, 1H), 3.93 (d, J = 8.7 Hz, 1H), 3.92−3.86 (m, 2H), 3.2−3.78 (m, 4H), 3.69 (d, J = 8.7 Hz, 1H), 3.68−3.62 (m, 3H), 3.55−3.48 (m, 2H), 2.22 (ddd, J = 15.4, 5.5, 5.5 Hz, 1H), 1.92−1.85 (m, 3H), 1.82−1.62 (m, 10H), 1.55 (m, 1H), 1.50 (s, 3H), 1.49 (m, 1H), 1.39 (s, 3H), 1.33 (s, 3H), 1.25 (s, 3H), 1.14 (s, 3H), 1.13−1.09 (m, 21H), two protons missing due to H/D exchange; ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 159.3, 130.6, 129.4 (2C), 113.9 (2C), 111.1, 103.1, 86.4, 79.0, 78.5, 78.4, 77.8, 76.5, 76.0, 74.6, 73.5, 73.3, 71.8, 71.1, 64.1, 55.3, 43.5, 37.1, 31.9, 30.6, 30.4, 27.2, 27.0, 26.7, 24.5, 24.4, 20.6, 18.5, 18.4 (3C), 18.3 (3C), 15.4, 12.8 (3C); HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{44}H_{74}O_{11}SiNa$, 829.4893; found, 829.4893.

Tosylate ***47***. To a solution of diol **46** (38.3 mg, 0.0475 mmol), Et_3N (0.07 mL, 0.50 mmol), and DMAP (6.5 mg, 0.053 mmol) in CH_2Cl_2 (2 mL) was added TsCl (27.2 mg, 0.143 mmol), and the resultant solution was stirred at room temperature for 19.5 h. The reaction was quenched with the saturated aqueous $NaHCO_3$ solution (5 mL). The mixture was extracted with EtOAc (15 and 5 mL), and the combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (25 to 30 to 40% EtOAc/hexanes) gave tosylate **47** (43.3 mg, 95%) as a colorless oil: $[\alpha]_D^{22.1}$ −24.0 (c 0.85, $CHCl_3$); IR (neat): 3444, 2945, 2868, 1514, 1464, 1368, 1248, 1177, 1095, 1035, 983, 756, 667 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.80−7.76 (m, 2H), 7.34−7.30 (m, 2H), 7.19−7.15 (m, 2H), 6.86−6.82 (m, 2H), 4.47 (d, J = 11.5 Hz, 1H), 4.39 (d, J = 11.5 Hz, 1H), 4.09 (br d, J = 4.6 Hz, 1H), 4.03−3.97 (m, 2H), 3.93 (d, J = 8.7 Hz, 1H), 3.90 (dd, J = 8.3, 6.8 Hz, 1H), 3.84 (dd, J = 12.4, 5.0 Hz, 1H), 3.81−3.79 (m, 4H), 3.73 (m, 1H), 3.69 (d, J = 8.7 Hz, 1H), 3.65 (dd, J = 11.0, 4.1 Hz, 1H), 3.63−3.56 (m, 2H), 2.44 (s, 3H), 2.19 (ddd, J = 15.1, 5.5, 5.5 Hz, 1H), 1.93−1.57 (m, 12H), 1.50 (s, 3H), 1.48 (m, 1H), 1.43−1.32 (m, 2H, overlapped),

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1.40 (s, 3H), 1.32 (s, 3H), 1.26 (s, 3H), 1.20−1.08 (m, 24H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 159.2, 144.7, 133.0, 130.2, 129.8 (2C), 129.4 (2C), 128.0 (2C), 113.8 (2C), 111.1, 103.1, 85.8, 78.5, 78.4, 77.8, 76.4, 76.0, 75.7, 74.6, 73.5, 73.2, 71.8, 71.7, 71.6, 55.3, 43.6, 37.1, 31.8, 30.40, 30.37, 27.7, 27.2, 26.8, 24.5, 24.4, 21.6, 20.6, 18.5, 18.4 (3C), 18.3 (3C), 15.4, 12.8 (3C); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{51}H_{80}SO_{13}SiNa$, 983.4981; found, 983.4984.

Epoxide **48**. To a solution of tosylate **47** (41.8 mg, 0.0435 mmol) in CH_2Cl_2 (2.5 mL)/pH 7.0 phosphate buffer (5:1, v/v, 3 mL) was added DDQ (29.6 mg, 0.130 mmol), and the mixture was stirred at room temperature for 2 h. The reaction was quenched with the saturated aqueous $NaHCO_3$ solution/saturated aqueous $Na_2S_2O_3$ solution (1:1, v/v, 10 mL). The mixture was extracted with EtOAc (20 mL, 10 mL), and the combined organic layers were washed with the saturated aqueous $NaHCO_3$ solution (6 mL) and brine (6 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (10 to 30 to 40% EtOAc/hexanes) gave diol **S6** (38.1 mg): $[\alpha]_D^{23.3}$ −15.9 (*c* 1.50, $CHCl_3$); IR (neat): 3442, 2945, 1463, 1368, 1177, 1118, 1096, 1035, 983, 756, 667 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.82−7.99 (m, 2H), 7.38−7.34 (m, 2H), 4.11 (br d, *J* = 5.5 Hz, 1H), 3.97−3.87 (m, 4H, overlapped), 3.93 (d, *J* = 8.7 Hz, 1H), 3.81−3.76 (m, 2H), 3.69 (d, *J* = 8.7 Hz, 1H), 3.67 (m, 1H), 3.64 (dd, *J* = 10.5, 4.1 Hz, 1H), 2.45 (s, 3H), 2.23 (ddd, *J* = 15.6, 5.5, 5.5 Hz, 1H), 1.92−1.83 (m, 3H), 1.80−1.58 (m, 11H), 1.49 (s, 3H), 1.48 (m, 1H), 1.39 (s, 3H), 1.39 (m, 1H, overlapped), 1.32 (s, 3H), 1.25 (s, 3H), 1.19−1.08 (m, 25H), one proton missing due to H/D exchange; $^{13}C\{^1H\}$ NMR (150 MHz, C_6D_6): δ 144.9, 132.8, 129.9 (2C), 128.0 (2C), 111.0, 103.0, 86.2, 78.4, 78.2, 77.7, 76.3, 76.0, 74.6, 73.7, 73.5, 73.3, 71.7, 69.4, 43.3, 37.0, 31.5, 31.2, 30.4, 29.7, 27.2, 26.7, 24.5, 24.3, 21.6, 20.5, 18.5, 18.34 (3C), 18.28 (3C), 15.4, 12.7 (3C); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{43}H_{72}SO_{12}SiNa$, 863.4406; found, 863.4406.

To a solution of the above diol **S6** (38.1 mg) in CH_2Cl_2/MeOH (2:1, v/v, 3 mL) was added K_2CO_3 (30.2 mg, 0.219 mmol), and the resultant solution was stirred at room temperature for 45 min. To this mixture was added MeOH (1 mL), and the mixture was stirred for further 45 min. The reaction was quenched with the saturated aqueous NH_4Cl solution (3 mL). The mixture was extracted with CH_2Cl_2 (3 × 6 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (30 to 40% EtOAc/hexanes) gave epoxide **48** (24.5 mg, 84% in two steps) as a colorless oil: $[\alpha]_D^{21.4}$ −31.2 (*c* 0.98, $CHCl_3$); IR (neat): 3456, 2945, 2868, 1464, 1382, 1247, 1209, 1098, 1065, 1035, 985, 882, 755, 679 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 4.60 (d, *J* = 7.8 Hz, 1H), 4.11 (br d, *J* = 5.5 Hz, 1H), 3.93 (d, *J* = 8.2 Hz, 1H), 3.91−3.86 (m, 2H), 3.80 (m, 1H), 3.70 (ddd, *J* = 9.7, 3.7, 3.2 Hz, 1H), 3.69 (d, *J* = 8.2 Hz, 1H), 3.66 (dd, *J* = 11.0, 4.6 Hz, 1H), 2.92 (m, 1H), 2.74 (dd, *J* = 5.0, 4.1 Hz, 1H), 2.47 (dd, *J* = 5.0, 2.7 Hz, 1H), 2.22 (ddd, *J* = 15.6, 5.5, 5.5 Hz, 1H), 1.94−1.84 (m, 3H), 1.82−1.62 (m, 8H), 1.62−1.53 (m, 3H), 1.50 (s, 3H), 1.47 (m, 1H), 1.39 (s, 3H), 1.33 (s, 3H), 1.25 (s, 3H), 1.21−1.09 (m, 21H, overlapped), 1.14 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 111.1, 103.1, 85.5, 78.6, 78.4, 77.8, 76.5, 76.0, 74.6, 73.5, 73.3, 71.7, 51.9, 47.2, 43.5, 37.1, 32.0, 31.3, 30.4, 28.8, 27.2, 26.7, 24.5, 24.4, 20.6, 18.5, 18.4 (3C), 18.3 (3C), 15.3, 12.8 (3C); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{36}H_{64}O_9SiNa$, 691.4212; found, 691.4212.

Alcohol **49**. To a solution of epoxide **48** (16.1 mg, 0.0241 mmol) in toluene (2 mL) was added silica gel (100 mg), and the resultant mixture was stirred at 50 °C (oil bath) for 13 h 40 min. The mixture was filtered through a cotton plug, and the filter cake was washed with EtOAc. The filtrate was concentrated under reduce pressure to give alcohol **49** (16.3 mg, quantitative) as a colorless oil: $[\alpha]_D^{28.1}$ −39.1 (*c* 0.32, $CHCl_3$); IR (neat): 3465, 2944, 2867, 1464, 1381, 1259, 1209, 1092, 1036, 754 cm^{-1}; ^1H NMR (600 MHz, C_6D_6): δ 4.26 (dd, *J* = 9.9, 4.8 Hz, 1H), 4.22 (dd, *J* = 12.8, 4.6 Hz, 1H), 4.00 (dd, *J* = 3.7, 3.2 Hz, 1H), 3.96 (d, *J* = 8.5 Hz, 1H), 3.83 (dd, *J* = 11.0, 4.6 Hz, 1H), 3.77 (ddd, *J* = 10.1, 9.6, 4.6 Hz, 1H), 3.50 (d, *J* = 8.5 Hz, 1H), 3.44 (br dd, *J* = 11.0, 2.7 Hz, 1H), 3.36 (dd, *J* = 11.0, 6.4 Hz, 1H), 3.29 (ddd, *J* = 9.6, 9.2, 4.1 Hz, 1H), 3.05 (m, 1H), 2.32 (ddd, *J* = 16.1, 9.2, 4.1 Hz, 1H), 2.24 (dd, *J* = 12.8, 4.1 Hz, 1H), 2.20 (ddd, *J* = 12.4, 11.9, 7.4 Hz, 1H), 2.05 (dd, *J* = 12.8, 12.8 Hz, 1H), 1.97−1.90 (m, 2H), 1.90−1.70 (m, 5H), 1.55 (s, 3H), 1.52−1.42 (m, 3H), 1.49−1.39 (m, 2H, overlapped), 1.45 (s, 3H), 1.31 (m, 1H), 1.27−1.10 (m, 26H), 0.96 (s, 3H), one proton missing due to H/D exchange; $^{13}C\{^1H\}$ NMR (150 MHz, C_6D_6): δ 111.2, 103.5, 80.1, 80.0, 78.7, 77.6, 77.3, 76.9, 76.4, 74.9, 74.0, 73.8, 73.2, 65.8, 43.8, 38.7, 37.7, 31.8, 30.8, 27.4, 27.1, 27.0, 25.1, 24.9, 21.2, 18.8, 18.6 (3C), 18.5 (3C), 13.4, 13.2 (3C); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{36}H_{64}O_9SiNa$, 691.4212; found, 691.4213.

JKLMN-Ring Fragment 5. To a solution of alcohol **49** (17.3 mg, 0.0259 mmol) in THF (2 mL) was added TBAF (1.0 M solution in THF, 0.26 mL, 0.26 mmol), and the resultant solution was stirred at 50 °C (oil bath) for 3.5 h. The reaction was quenched with the saturated aqueous NH_4Cl solution (3 mL) at room temperature. The mixture was extracted with EtOAc (8 mL, 2 × 4 m L), and the combined organic layers were washed with brine (4 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, first round: 2 to 4% MeOH/$CHCl_3$, second round: 15 to 20 to 25 to 30% acetone/benzene) gave JKLMN-ring fragment **5** (11.6 mg, 87%) as a colorless oil: $[\alpha]_D^{22.0}$ −44.0 (*c* 1.13, $CHCl_3$); IR (neat): 3466, 2986, 2948, 2873, 1458, 1382, 1209, 1090, 1036, 984, 909, 865, 756, 666 cm^{-1}; ^1H NMR (600 MHz, C_6D_6): δ 4.20 (dd, *J* = 11.0, 3.7 Hz, 1H), 3.96 (d, *J* = 8.5 Hz, 1H), 3.93 (dd, *J* = 12.8, 1.6 Hz, 1H), 3.75−3.69 (m, 2H), 3.51 (d, *J* = 8.5 Hz, 1H), 3.39 (br dd, *J* = 11.2, 3.2 Hz, 1H), 3.34 (dd, *J* = 11.2, 6.4 Hz, 1H), 3.28 (ddd, *J* = 10.6, 9.7, 4.6 Hz, 1H), 3.15 (ddd, *J* = 9.7, 8.3, 6.9 Hz, 1H), 3.05 (m, 1H), 2.79 (m, 1H), 2.38 (ddd, *J* = 15.5, 6.9, 6.4 Hz, 1H), 2.18 (ddd, *J* = 13.7, 13.3, 5.9 Hz, 1H), 2.15 (dd, *J* = 12.8, 4.6 Hz, 1H), 2.03 (ddd, *J* = 15.5, 8.3, 4.1 Hz, 1H), 1.96 (dd, *J* = 12.8, 12.8 Hz, 1H), 1.90−1.75 (m, 4H), 1.71 (ddd, *J* = 13.3, 4.6, 2.7 Hz, 1H), 1.55 (s, 3H), 1.52−1.42 (m, 3H), 1.36 (s, 3H), 1.27 (m, 1H), 1.25 (s, 3H), 1.21 (s, 3H), 1.17−1.06 (m, 2H), 0.93 (s, 3H), one proton missing due to H/D exchange; $^{13}C\{^1H\}$ NMR (150 MHz, C_6D_6): δ 111.2, 103.5, 79.3, 79.0, 78.8, 78.1, 77.6, 76.4, 74.9, 74.4, 74.0, 73.5, 72.6, 65.7, 44.0, 37.9, 37.7, 31.2, 30.8, 27.4, 27.0, 26.8, 25.1, 24.8, 20.5, 18.8, 15.2; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{27}H_{44}O_9Na$, 535.2878; found, 535.2881.

Tetrahydroxy JKLMN-Ring Fragment 50. A solution of **5** (3.1 mg, 0.00605 mmol) in THF/H_2O/TFA (5:1:1, v/v, 0.8 mL) was stirred at 50 °C (oil bath) for 15 h 20 min. The reaction was quenched with 3% aqueous NH_4OH solution (1 mL) at 0 °C. The mixture was extracted with CH_2Cl_2 (5 × 2 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 5 to 10% MeOH/$CHCl_3$) gave tetrahydroxy JKLMN-ring fragment **50** (2.7 mg, 94%) as a colorless amorphous powder: $[\alpha]_D^{22.1}$ −23.6 (*c* 0.59, $CHCl_3$); IR (neat): 3418, 2950, 2874, 1716, 1456, 1382, 1260, 1217, 1086, 1038, 752, 666 cm^{-1}; ^1H NMR (600 MHz, pyridine-d_5): δ 6.99 (s, 1H), 6.44 (m, 1H), 6.20 (m, 1H), 5.95 (d, *J* = 2.5 Hz, 1H), 4.58 (dd, *J* = 11.5, 2.8 Hz, 1H), 4.44 (dd, *J* = 13.0, 4.7 Hz, 1H), 4.08 (m, 1H), 3.97−3.88 (m, 4H), 3.88 (m, 1H), 3.81 (m, 1H), 3.63−3.54 (m, 2H), 2.65 (ddd, *J* = 15.5, 8.1, 5.3 Hz, 1H), 2.47 (ddd, *J* = 13.5, 13.3, 4.6 Hz, 1H), 2.29−2.21 (m, 2H), 2.16−2.08 (m, 2H), 2.07 (dd, *J* = 12.6, 12.4 Hz, 1H), 2.04−1.94 (m, 2H), 1.94−1.85 (m, 3 H), 1.80−1.70 (m, 2H), 1.59−1.48 (m, 2H, overlapped), 1.50 (s, 3H), 1.43 (s, 3H), 1.20 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, pyridine-d_5): δ 96.3, 80.1, 79.8, 78.9, 78.6, 78.3, 77.4, 74.8, 73.7, 72.9, 72.5, 69.6, 65.7, 44.2, 38.5, 37.1, 32.0, 29.8, 28.0, 25.5, 25.2, 20.8, 18.9, 14.1; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{24}H_{40}O_9Na$, 495.2565; found, 495.2565.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c03031.

Comparison of NMR chemical shifts for compound **50** with the data for Caribbean ciguatoxin C-CTX-1 and copies of ^1H and ^{13}C NMR spectra of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(47) The comparison table for the ^{1}H and ^{13}C NMR chemical shifts for compound **50** and the natural product is furnished in the Supporting Information.
(48) Although observed ^{13}C NMR chemical shift for C43 significantly deviated from that for the natural product, we inferred that this difference may be influenced by the presence or absence of the left-hand I-ring structure. The reason for the significant discrepancy of the ^{13}C NMR chemical shift observed for C62 is not clear, but upon careful examination of the HMQC spectra of C-CTX-1 in refs 9b and 11, the originally assigned ^{13}C NMR chemical shift for C62 might be incorrect.

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