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Total Synthesis of Polycavernosides A and B, Two Lethal Toxins from Red Alga

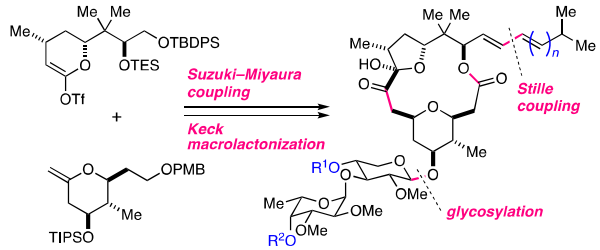
Kotaro Iwasaki,[†] Satori Sasaki,[†] Yusuke Kasai,[†] Yuki Kawashima,[†] Shohei Sasaki,[†] Takanori Ito,[†] Mari Yotsu-Yamashita,[‡] and Makoto Sasaki[*,†]

[†]*Graduate School of Life Sciences, Tohoku University, 2-1-1 Katahira, Aoba-ku, Sendai 980-8577, Japan*

[‡]*Graduate School of Agricultural Science, Tohoku University, 468-1 Aramaki-Aza-Aoba, Aoba-ku, Sendai 980-0845, Japan*

E-mail: masasaki@m.tohoku.ac.jp

TOC graphic



polycavernoside A: R^1 = Me, R^2 = H, n = 2
polycavernoside B: R^1 = Ac, R^2 = Me, n = 1

ABSTRACT: Polycavernosides A and B are glycosidic macrolide natural products isolated as the toxins causing fatal human poisoning by the edible red alga *Gracilaria edulis* (*Polycavernosa tsudai*). Total synthesis of polycavernosides A and B has been achieved via a convergent approach. The synthesis of the macrolactone core structure is highlighted by the catalytic asymmetric syntheses of the two key fragments using hetero-Diels–Alder reaction and Kiyooka aldol reaction as the key steps, their union through Suzuki–Miyaura coupling, and Keck macrolactonization. Finally, glycosylation with the L-fucosyl-D-xylose unit and construction of the polyene side chain through Stille coupling completed the total synthesis of polycavernosides A and B.

INTRODUCTION

Polycavernosides A (**1**) and B (**2**) (Figure 1) were originally isolated in 1993 by Yasumoto and co-workers as the causative toxins for the fatal human poisoning in Guam in 1991 caused by ingestion of the edible red alga *Gracilaria edulis* (*Polycavernosa tsudai*).[1,2] Thirteen people took ill, of which three died. The same alga poisoned 36 people in the Philippines in 2002–2003, killing eight, and again polycavernoside A was identified as the causative agent.[3] The LD_{99} values of polycavernosides A and B in mice by intraperitoneal (ip) injection were estimated to be 200–400 μg/kg, and the symptoms observed in mice were similar to those observed in human patients.[2] The gross structure of polycavernoside A (**1**) was shown through extensive 2D NMR studies to be a novel glycosidic macrolide.[2] The structures of polycavernoside B (**2**) and three minor analogues, polycavernosides A2, A3, and B2, were deduced in 1995 by comparison of their ^{1}H-^{1}H COSY, FABMS, FABMS/MS, and UV spectra with those of polycavernoside A, but further confirmation by HMBC and NOE experiments of these analogues was prevented by the extremely small quantities of sample available.[4] Thereafter, the complete configurational assignment of polycavernoside A was established by the Murai/Fujiwara group through their first total synthesis in 1998.[5] All these polycavernosides consist of the same 16-membered macrolide backbone incorporating a tetrasubstituted tetrahydropyran ring and a five-membered hemiacetal. Structural variations among these analogues are found in a conjugated triene or diene side chain appended at

C15 and a highly methylated L-fucosyl-D-xylose residue attached at C5. Subsequently, Yamashita and co-workers isolated and structurally determined two minor analogues, polycavernosides C and C2, from *G. edulis* collected in Guam in 1992–1994, which have a different aglycon structure from that of **1** and **2**.[6]

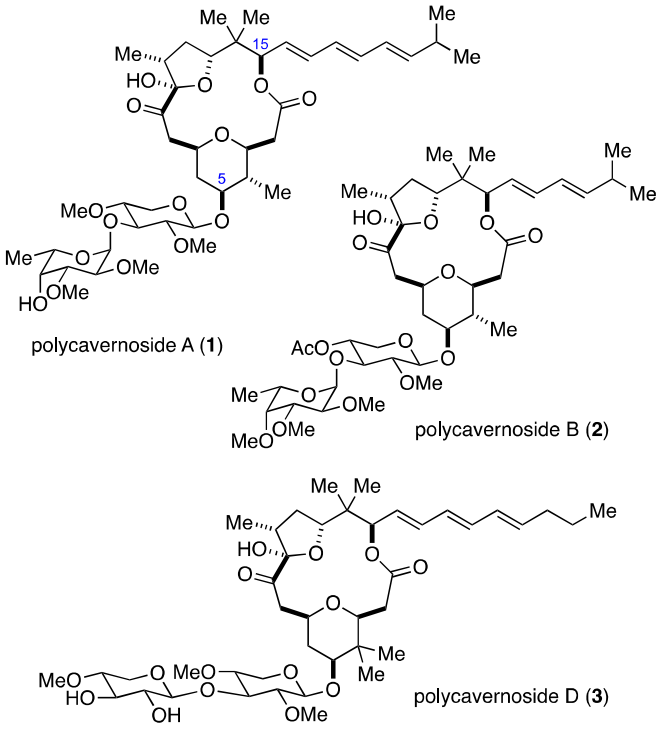


Figure 1. Structures of polycavernosides A (**1**), B (**2**), and D (**3**).

The macrolide skeleton with an embedded tetrahydropyran ring, the polyene side chain, and the distinctive *O*-methylated sugar unit of polycavernosides, highly resemble the structural features of other marine cyanobacterial metabolites, such as lyngbouilloside,[7] lyngbyaloside B,[8] and cyanolide

A.[9] It has therefore been speculated that polycavernosides are also secondary metabolites of cyanobacteria.[3] Gerwick and co-workers recently reported the isolation of a closely related analogue of polycavernosides, polycavernoside D (**3**, Figure 1), from an environmental sample of the marine cyanobacterium *Okeania* sp., thus providing the first experimental evidence that these lethal toxins represent new additions to the family of glycosidic macrolides from cyanobacteria.[10]

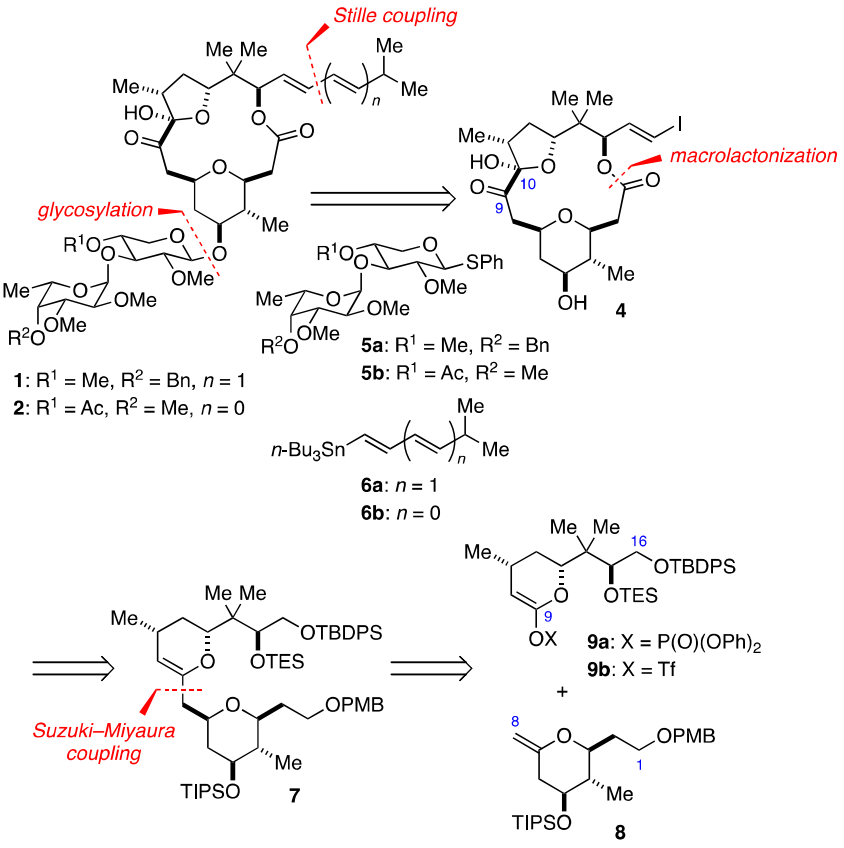
The unique structural features of polycavernoside A, the major polycavernoside, coupled with its lethal toxicity and very limited availability from natural sources, has attracted considerable interest from the synthetic community. Six total and formal total syntheses,[5,11] including ours,[12] and several synthetic approaches,[13] have been disclosed to date, but synthetic studies toward other congeners, including polycavernoside B, have not yet been reported in the literature. In addition, although structure-activity relationship studies and the pharmacological actions of polycavernosides were investigated using synthetic polycavernoside A analogues,[14] their detailed mechanism of action and the molecular targets of these lethal toxins, remain unknown mainly due to the very limited amounts of these natural compounds.

As part of our studies toward the total synthesis of polycavernosides for detailed biological studies, we reported a preliminary total synthesis of polycavernoside A.[12] We describe herein in detail the total synthesis of polycavernosides A and B, allowing elucidation of the complete stereostructure of the latter glycosidic macrolide natural product.

RESULTS AND DISCUSSION

Synthesis Plan. Our retrosynthetic analysis of polycavernosides A (**1**) and B (**2**) is depicted in Scheme 1. We planned to synthesize **1** and **2** from the known compound **4**[5,11a–e,12] as a common intermediate through glycosylation with disaccharide unit **5a** or **5b**, and introduction of the conjugated polyene side chain by Stille coupling with vinylstannane **6a** or **6b**. The compound **4** was envisioned to be derived from bis-pyran **7** through oxidation of the enol ether moiety to the 1,2-dicarbonyl functionality at C9–C10, followed by macrolactone formation. The cyclic enol ether **7**, in turn, could be synthesized from the C1–C8 *exo*-olefin **8** and the C9–C16 enol phosphate **9a** or triflate **9b** via Suzuki–Miyaura coupling.[15,16] These two fragments, **8** and **9**, of comparable complexity would be constructed through catalytic asymmetric reactions.

Scheme 1. Retrosynthetic Analysis of Polycavernosides A (1) and B (2)



Synthesis of the C1–C8 Fragment. The synthesis of the C1–C8 *exo*-olefin **8** started with the known enone **10**,[17] which is readily available in three steps from 1,3-propanediol (Scheme 2). Asymmetric hetero-Diels–Alder reaction between 2-silyloxy diene **11**, derived from **10** with TMSOTf/Et_3N, with aldehyde **12**[18] was carried out with the Jacobsen chiral tridentate chromium(III) catalyst **13** (3 mol%),[19] giving the desired cycloadduct **14**. Subsequent treatment with K_2CO_3 in MeOH delivered an approximately 6:1 mixture of 2,6-*cis*-substituted tetrahydropyran-4-one **15a** with the desired configuration of the methyl group at the C4 stereogenic center and its diastereomer **15b**. The major diastereomer **15a** could be separated from isomer **15b**

by flash column chromatography on silica gel. Isomerization of the minor diastereomer **15b** was realized by treatment with DBU (toluene, room temperature) to avoid loss of material. After two cycles of isomerization, the desired **15a** was obtained in 60% total yield from **10**. Reduction of **15a** under Luche conditions ($NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, –20 °C)[20] provided alcohol **16** in 94% yield as a single stereoisomer at C5 (dr >20:1). At this stage, the enantiomer ratio (er 98:2) of the hetero-Diels–Alder reaction and the relative and absolute configuration of the C5 stereogenic center of **16** were established by the coupling constants and a modified Mosher analysis[21] (Figure 2). After protection of alcohol **16** as its TIPS ether with TIPSOTf/2,6-lutidine (94%), the primary TBS ether of the resultant **18** was selectively removed under acidic conditions (CSA, $MeOH/CH_2Cl_2$, 0 °C) to deliver alcohol **19** in quantitative yield. Iodination of alcohol **19** (I_2, Ph_3P, imidazole, THF) provided iodide **20** in 99% yield. Finally, treatment of **20** with *t*-BuOK in THF at 0 °C effected β-elimination to furnish *exo*-olefin **8**, which was directly used in the next coupling reaction without purification.

Scheme 2. Synthesis of the C1–C8 *exo*-Olefin 8

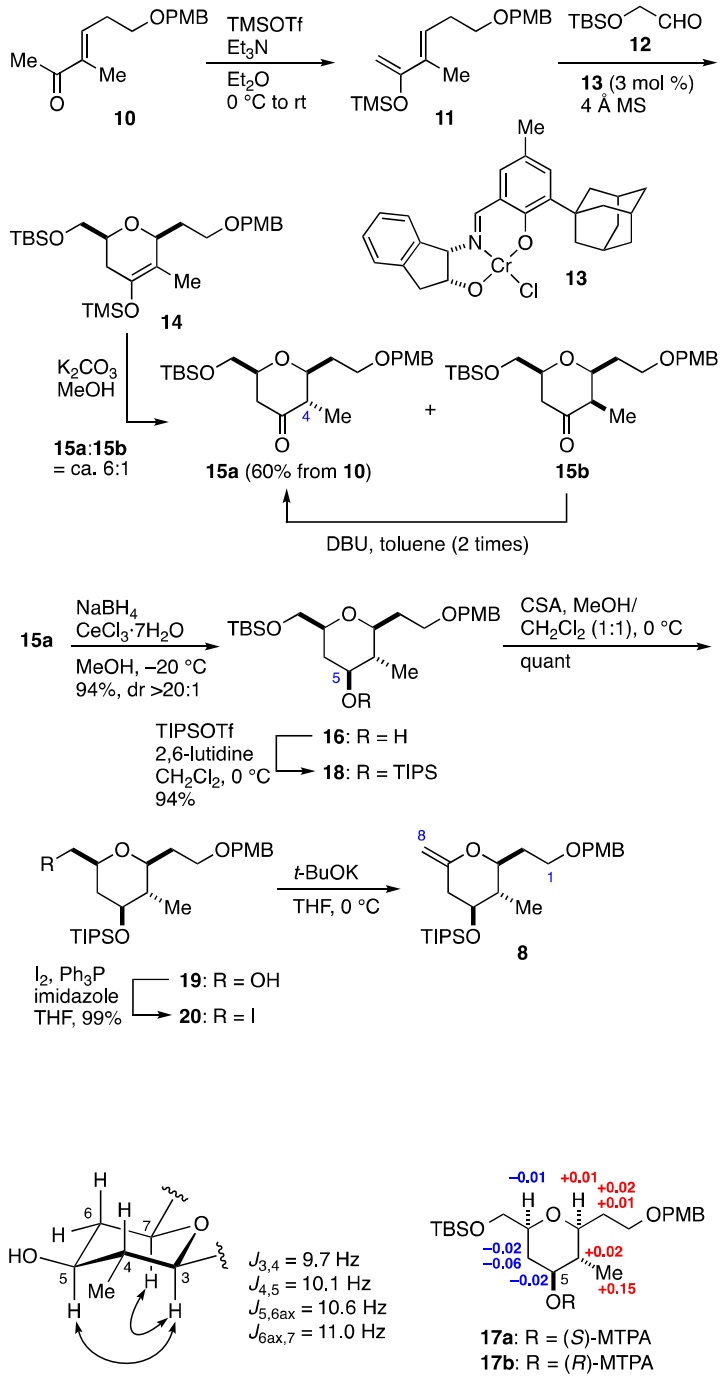
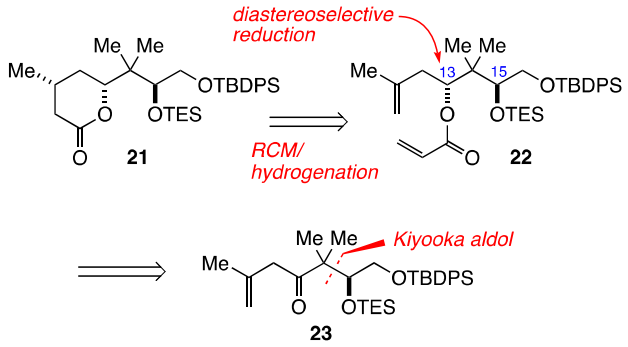


Figure 2. Stereochemical assignment of alcohol **16**. Double-headed arrows denote key NOEs. The numbers in red and blue are the difference (Δδ) in the ^{1}H NMR chemical shifts between **17a** and **17b** (Δδ = δ(**17a**) – δ (**17b**) in $CDCl_3$).

Improved Synthesis of the C9–C16 Fragment. The previous synthesis of lactone **21**, the precursor of the C9–C16 fragment **9** and containing only three stereogenic centers on the 11-carbon skeleton, required a lengthy 14-step sequence from (*R*)-(+)-citronellal.[12] Consequently, we developed the more efficient alternative route to lactone **21** depicted in Scheme 3. Lactone **21** would be derived from diene **22** through ring-closing metathesis (RCM)[22] followed by stereoselective hydrogenation. The stereogenic center at C13 of **22** would be generated by an appropriate diastereoselective reduction of ketone **23**, which in turn would be derived through a Kiyooka asymmetric aldol reaction.[23]

Scheme 3. Retrosynthetic Analysis of Lactone 21

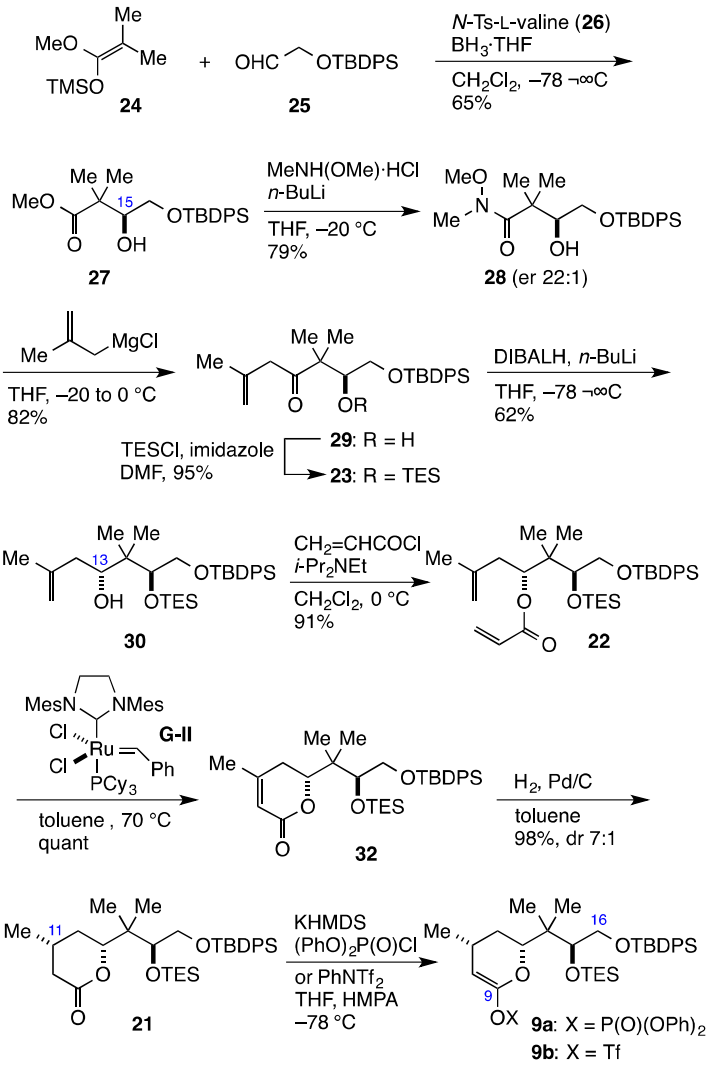


An improved synthesis of the C9–C16 fragment **9** commenced with the Kiyooka aldol reaction[23] of methyl trimethylsilyl dimethylketene acetal **24**[24] with the known aldehyde **25**.[25] The aldol reaction of **25** with **24** in the presence of the chiral oxazaborolidinone, derived from

N-tosyl-L-valine (**26**) and $BH_3 \cdot THF$, in CH_2Cl_2 at –78 °C proceeded enantioselectively to provide the corresponding (*S*)-β-hydroxy ester **27** in 65% yield (Scheme 4). Methyl ester **27** was then converted to the corresponding Weinreb amide **28** in 79% yield by reaction with *N,O*-dimethylhydroxylamine hydrochloride and *n*-BuLi (THF, −20 °C).[26] At this stage, the enantiomer ratio of the Kiyooka aldol reaction was determined to be 22:1 by chiral HPLC analysis. Subsequent treatment of **28** with 2-methylallylmagnesium chloride (THF, –20 to 0 °C) provided ketone **29** (82%),[27] which was protected with TESCl/imidazole to give TES ether **23** in 95% yield. We next investigated the diastereoselective reduction of ketone **23** to the corresponding monoprotected 1,3-*anti*-diol **30**, but this turned out to be more problematic than expected.[28] Although we examined several reducing reagents, including $NaBH_4/CeCl_3 \cdot 7H_2O$, $LiBH_4$, L-Selectride, and K-Selectride, in appropriate solvents, either no diastereoselectivity or no reaction was observed. After extensive experimentation, we found that DIBALH reduction of ketone **23** (CH_2Cl_2, –78 °C) gave the desired alcohol **30** with moderate diastereoselectivity (dr 7:3) in high yield. Finally, the best result was obtained using the ate complex generated from DIBALH and *n*-BuLi in THF at –78 °C,[29] giving a 7:1 mixture of alcohol **30** and its diastereomer at C13. The minor diastereomer was removed by flash column chromatography on silica gel, and the desired alcohol **30** was obtained in pure form in 62% yield. The relative configuration of the 1,3-*anti*-diol

moiety of **30** was established by ^{13}C NMR analysis[30] of the acetonide derivative **31**, as shown in Figure 3.

Scheme 4. Improved Synthesis of the C9–C16 Fragment 9



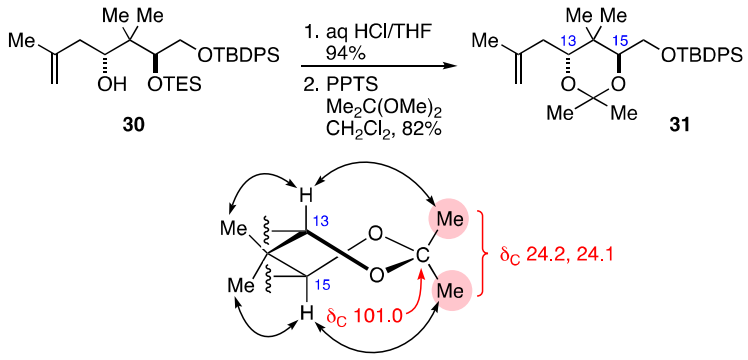


Figure 3. Assignment of the relative configuration between C13 and C15 of alcohol **30**. The numbers in red are the ^{13}C NMR chemical shifts (C_6D_6, 150 MHz). Double-headed arrows denote key NOEs.

Acylation of alcohol **30** with acryloyl chloride/*i*-Pr_2NEt (CH_2Cl_2, 0 °C) gave diene **22** (91%), which was subjected to RCM[22] using the Grubbs second-generation catalyst (**G-II**)[31] in toluene at 70 °C to deliver unsaturated lactone **32** in quantitative yield (Scheme 4). Hydrogenation of **32** (H_2, Pd/C, toluene) provided the requisite lactone **21**[12] in 98% yield with 7:1 diastereoselectivity.[32,33] Thus, lactone **21**, the precursor of the C9–C16 fragment **9**, was available in only eight steps with an overall yield of 22% from readily available starting material. Finally, lactone **21** was converted to the corresponding enol phosphate **9a** and enol triflate **9b** (KHMDS, THF, HMPA, $(PhO)_2P(O)Cl$ or $PhNTf_2$, –78 °C), setting the stage for the crucial Suzuki–Miyaura coupling.

Synthesis of the Macrolactone Core through Suzuki–Miyaura Coupling and Keck Macrolactonization. With the requisite two fragments in hand, we set out to couple them through the Suzuki–Miyaura reaction[15,16] (Scheme 5). We first attempted the Suzuki–Miyaura reaction using enol phosphate **9a**. However, all attempts to effect coupling of the alkylborane, derived from hydroboration of *exo*-olefin **8** with 9-BBN-H, with enol phosphate **9a** in the presence of aqueous Cs_2CO_3 solution and various palladium catalysts, such as $Pd(PPh_3)_4$, $PdCl_2(dppf)\cdot CH_2Cl_2$, or $PdCl_2(dppf)\cdot CH_2Cl_2$ (dppf = 1,1'-bis(diphenylphosphino)ferrocene)/Ph_3As, in DMF at 50 °C provided disappointingly low yields (5–35%) of the desired coupling product **7** (Table 1, entries 1–3). Prolonged reaction times proved ineffective, and a significant amount of the starting lactone with loss of the TES group was recovered (22–87%). These results could be attributable to the low reactivity of enol phosphate **9a** in this Suzuki–Miyaura reaction. Therefore, we decided to exploit the triflate counterpart **9b** as a more reactive substrate for the Suzuki–Miyaura reaction (entry 4). As expected, reaction of the alkylborane generated from *exo*-olefin **8** (9-BBN-H, THF, 0 °C to room temperature) with enol triflate **9b** proceeded smoothly under the influence of aqueous Cs_2CO_3 solution and the $PdCl_2(dppf)\cdot CH_2Cl_2/Ph_3As$ catalysis system in THF/DMF at room temperature,[34,35] giving the desired product **7** in high yield (86–90%). The enol ether **7** thus obtained was unstable and was immediately subjected to epoxidation followed by in situ epoxide ring opening with MeOH (*m*-CPBA, CH_2Cl_2/MeOH, 0 °C) to afford an inconsequential epimeric

mixture of alcohols **33a** and **33b** in 58% and 24% overall yield from iodide **20**, respectively (Scheme 5). At this stage, the minor diastereomer at C11 resulting from hydrogenation of **32** was removed by flash column chromatography on silica gel. The configuration of the hydroxy group of **33a** and **33b** was established by its $^{3}J_{H,H}$ value, as shown in Figure 4. Each alcohol was individually oxidized with tetra-*n*-propylammonium perruthenate (TPAP)/NMO[36] to the same ketone **34** in high yield. It is interesting to note that the reactivity of alcohol **33b** with the axial hydroxy group at C10 was low and that the use of MeCN as a co-solvent was essential to attain a higher yield of ketone **34**. Selective cleavage of the TES ether of **34** under acidic conditions (CSA, CH_2Cl_2/MeOH, 0 °C), followed by oxidative removal of the PMB group with DDQ, provided diol **35** in 84% yield for the two steps. Chemoselective oxidation of the primary alcohol of **35** was realized with TEMPO/$PhI(OAc)_2$ in CH_2Cl_2/H_2O (10:1)[37] to deliver the corresponding carboxylic acid **36** in 97% yield. Subsequent macrolactonization of **36** proved to be unexpectedly difficult. Macrolactonization under Yamaguchi[38] or Shiina[39] conditions resulted in only a low yield (14–34%) or no trace of the desired macrolactone **37**.[40] After extensive experimentation, we found that the best result was obtained by using the Keck protocol[41] with a combination of DCC, pyridine, and PPTS[42] in DCE under reflux conditions to afford macrolactone **37** in 89% yield. Selective cleavage of the primary TBDPS ether of **37** was performed with buffered HF·pyridine to afford primary alcohol **38** in 85% yield. Dess–Martin oxidation[43] of **38** provided aldehyde **39**

(88%), which was subjected to Takai–Utimoto olefination (CHI_3, $CrCl_2$)[44] to afford (*E*)-vinyliodide **40** in 81% yield as a single stereoisomer (*E*/*Z* >20:1). Ensuing treatment of **40** with aqueous TFA in THF[5] effected hydrolysis of the TIPS ether and methyl acetal with concomitant construction of the five-membered hemiacetal to furnish alcohol **4** in 98% yield. The specific rotation value of **4**, $[\alpha]_D^{25}$ –49.1 (*c* 1.00, $CHCl_3$), matched those reported in the literature.[5,11a–e]

Scheme 5. Synthesis of Macrolactone 4.

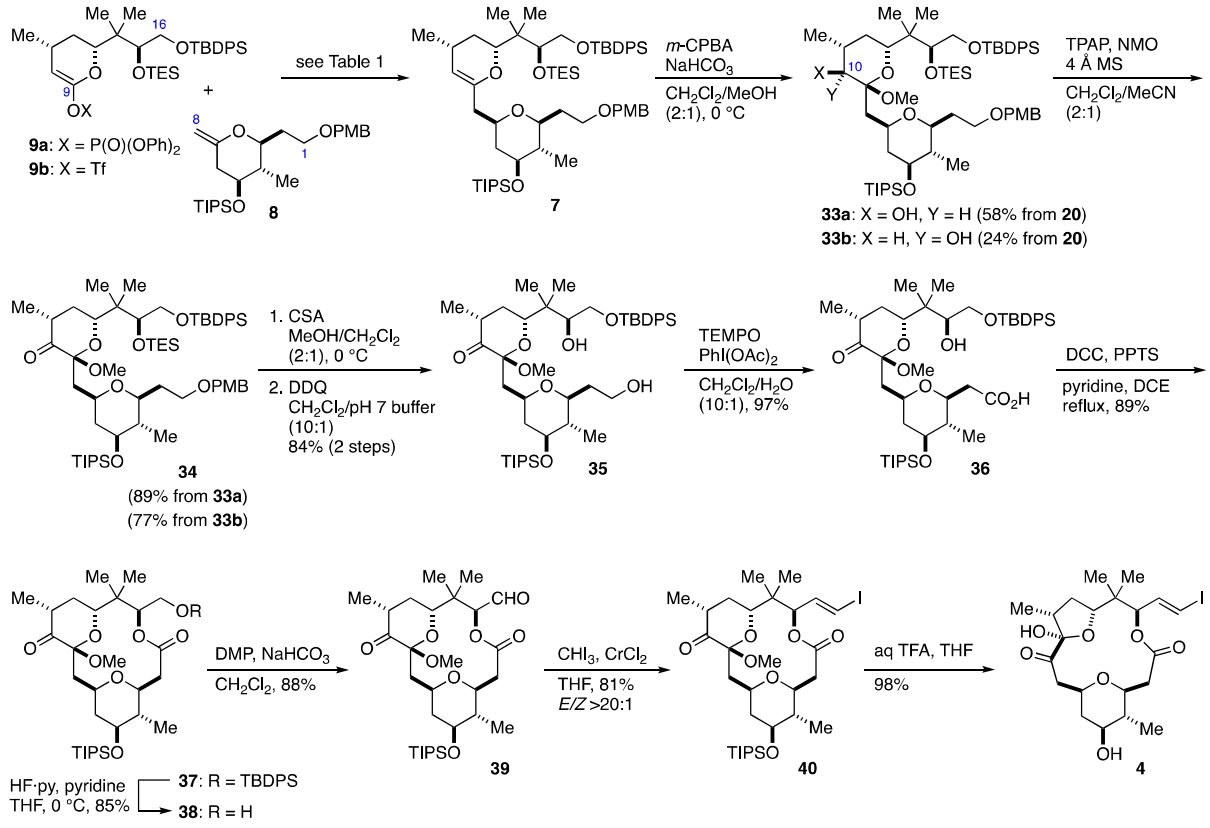


Table 1. Optimization of the Suzuki–Miyaura coupling of 8 and 9

entry	substrate	Pd catalyst (equiv)	ligand (equiv)	temp (°C)	yield (%)
1	**9a**	$Pd(PPh_3)_4$ (0.2)	—	50	35[a]
2	**9a**	$PdCl_2(dppf)\cdot CH_2Cl_2$ (0.1)	—	50	5[a]
3	**9a**	$PdCl_2(dppf)\cdot CH_2Cl_2$ (0.1)	Ph_3As (0.2)	50	19[a]
4	**9b**	$PdCl_2(dppf)\cdot CH_2Cl_2$ (0.1)	Ph_3As (0.4)	rt	86–90

[a] The starting lactone with loss of the TES ether was recovered in 22–87% yields.

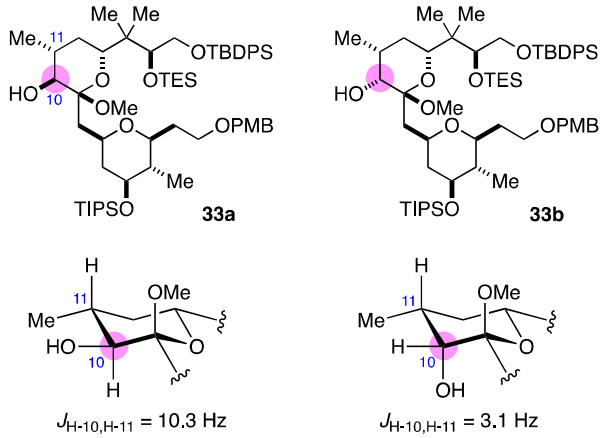
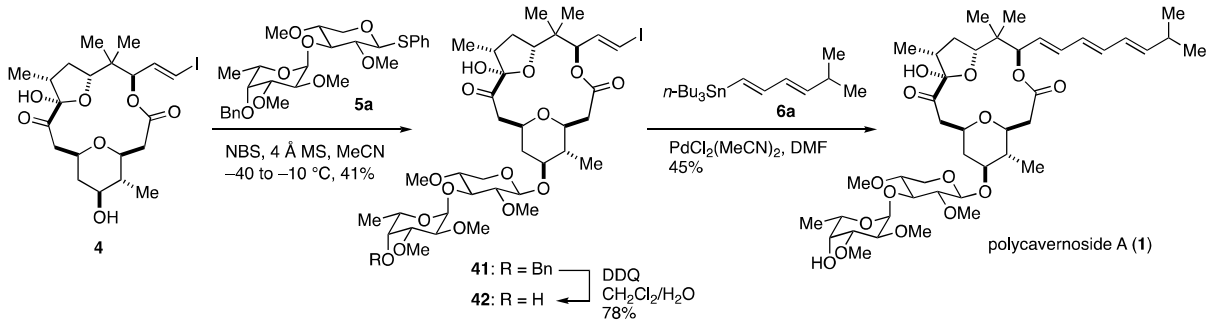


Figure 4. Assignment of the relative configuration of the C10 stereogenic center of **33a** and **33b**.

Total Synthesis of Polycavernoside A. Total synthesis of polycavernoside A was carried out by adapting a literature route.[5,11a–e] Glycosylation of alcohol **4** with the known thioglycoside **5a**[11c,d] was performed under the influence of NBS[50] in the presence of 4 Å molecular sieves in MeCN at –40 to –10 °C to provide the desired glycoside **41**, albeit in moderate yield (41%) (Scheme 6). Oxidative cleavage of the benzyl ether within the sugar part of **41** with DDQ provided alcohol **42** in 78% yield. Construction of the conjugated triene side chain by Stille coupling with the known dienylstannane

6a[11a,b] ($PdCl_2(MeCN)_2$, DMF, 45%) completed the total synthesis of (–)-polycavernoside A (**1**). The spectroscopic data of the synthetic **1** matched with those reported for the natural material.[2] Mouse lethality of the synthetic polycavernoside A was comparable to that of the natural product.

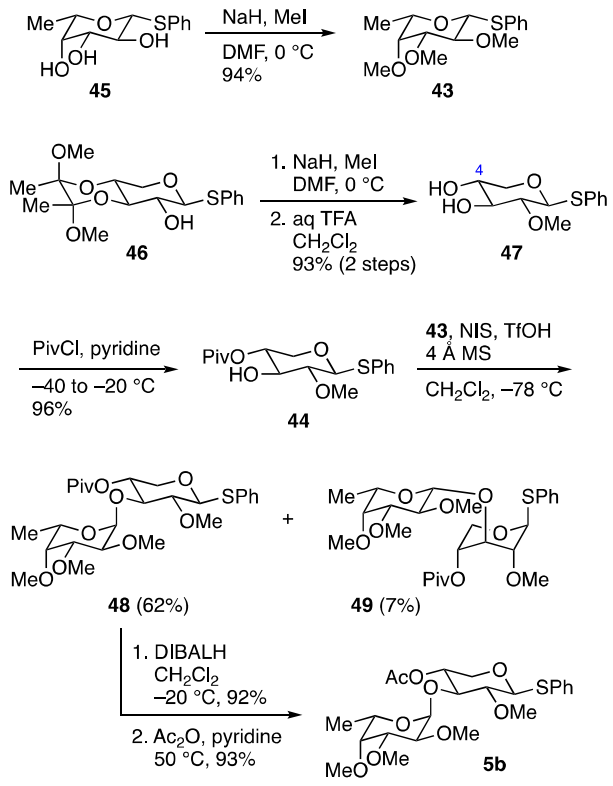
Scheme 6. Total Synthesis of Polycavernoside A



Synthesis of the Polycavernoside B Disaccharide Unit. The L-fucosyl-D-xylose disaccharide unit **5b**, required for the synthesis of polycavernoside B, was prepared from fucosyl thioglycoside **43** and xylosyl thioglycoside **44** based on the armed-disarmed concept (Scheme 7).[45] Armed fucosyl donor **43** was prepared by *O*-methylation of the known thioglycoside **45**[11b,48] in 94% yield. The synthesis of xylosyl thioglycoside **44** started with the known alcohol **46**.[46] *O*-Methylation followed by acidic hydrolysis of the butane-2,3-diacetal[47] provided diol **47** in 93% yield for the two steps. Regioselective acylation of the less hindered alcohol at the C4 position of **47** was realized with pivaloyl chloride in pyridine at low temperature to afford disarmed xylosyl acceptor **44** in 96% yield. Glycosylation of **44** with **43** was carried out under NIS/TfOH conditions[49] (4 Å molecular

sieves, CH_2Cl_2, –78 °C) to afford the desired α-linked disaccharide **48** in 62% yield. Under these conditions, β-linked disaccharide **49**, in which the xylose unit was restricted in the $^1C_4$ conformation, was obtained in 7% yield. The relative configurations of **48** and **49** were assigned on the basis of the $^3J_{H,H}$ values in the ^{1}H NMR spectrum, as shown in Figure 5. Reductive removal of the pivaloyl ester of **48** with DIBALH (92%), followed by acetylation of the resultant hydroxy group, provided the desired disaccharide unit **5b** in 93% yield.

Scheme 7. Synthesis of L-Fucosyl-D-Xylose Disaccharide Unit 5b



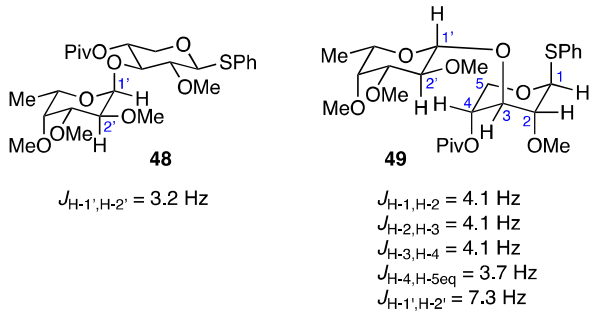
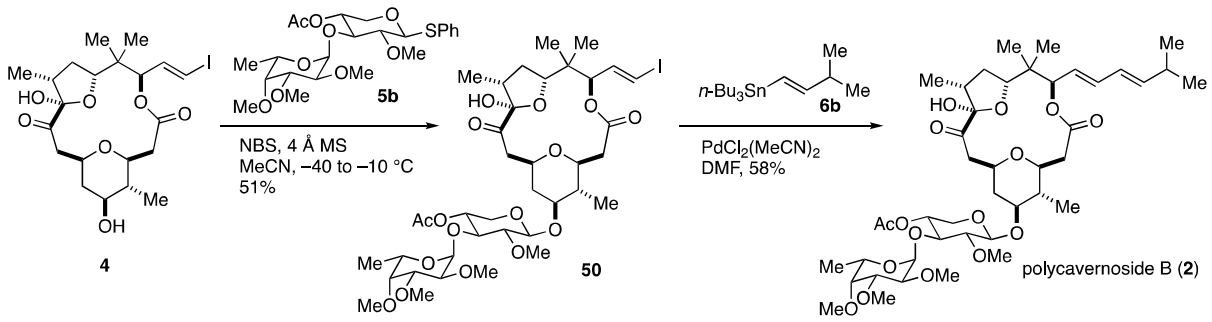


Figure 5. Stereochemical assignment of disaccharides **48** and **49**.

Total Synthesis of Polycavernoside B. Glycosylation of alcohol **4** with thioglycoside **5b** was again performed with NBS in the presence of 4 Å molecular sieves (MeCN, –40 to –10 °C) to afford the requisite β-glycoside **50** in 51% yield (Scheme 8). Finally, Stille coupling of **50** with the known vinylstannane **6b**[54] using $PdCl_2(MeCN)_2$ in DMF furnished (–)-polycavernoside B (**2**) in 58% yield. The ^{1}H NMR spectrum of the synthetic **2** was identical with that reported for the natural polycavernoside B.[4] In addition, mouse lethality of the synthetic polycavernoside B was comparable to that of the natural sample, and observed symptoms in mice elicited upon intraperitoneal administration resembled those caused by the natural sample. Thus, the complete stereostructure of polycavernoside B was unambiguously established by our total synthesis.

Scheme 8. Total Synthesis of Polycavernoside B



CONCLUSION

In conclusion, we have achieved the total synthesis of polycavernosides A and B in 23 and 22 steps (longest linear sequence) and with 0.96% and 2.0% overall yield, respectively. The synthesis of the C1–C8 fragment involved asymmetric hetero-Diels–Alder reaction using Jacobsen catalysis for the construction of the tetrasubstituted tetrahydropyran unit. The C9–C16 fragment was efficiently constructed by exploiting the Kiyooka aldol reaction and diastereoselective reduction to establish the two stereogenic centers at C15 and C17, and a ring-closing metathesis/hydrogenation sequence to form a six-membered lactone unit. Convergent union of the two fragments was achieved through Suzuki–Miyaura coupling, and the macrolactone core was formed through a modified Keck protocol. Late–stage introduction of the L-fucosyl-D-xylosyl disaccharide unit and polyene side chain completed the total synthesis of polycavernosides A and B, establishing for the first time the complete stereostructure of the latter glycosidic macrolide natural product. Our convergent synthetic route allows for the synthesis of sufficient amounts of polycavernosides and their unnatural analogues for detailed biological studies. Further studies along this line are underway

and will be reported in due course.

EXPERIMENTAL SECTION

General Methods. All reactions sensitive to moisture and/or air were carried out under an atmosphere of argon in dry, freshly distilled solvents under anhydrous conditions using oven-dried glassware unless otherwise noted. Anhydrous CH_2Cl_2 was purchased and anhydrous diethyl ether (Et_2O), THF, and toluene were purified by a Glass Contour solvent purification system. Acetonitrile (MeCN), 1,2-dichloroethane (DCE), diisopropylethylamine, pyridine, 2,6-lutidine, methanol (MeOH), and triethylamine (Et_3N) were distilled from calcium hydride under an atmosphere of argon. DMF was distilled from magnesium sulfate under reduced pressure. HMPA was distilled from calcium hydride under reduced pressure. All other chemicals were purchased at highest commercial grade and used directly. Analytical TLC was performed using pre-coated glass plate (silica gel 60 F_{254}, 0.25-mm thickness). Flash column chromatography was carried out using silica gel (spherical, neutral, 40–100 mesh; granular, 200–400 mesh). HPLC was performed using an UV/Visible detector. Optical rotations were measured on a digital polarimeter at 589 nm. IR spectra were recorded as a thin film on a KBr disk using an FT-IR spectrometer and reported in wavenumbers (cm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded at 600 MHz and 150 MHz NMR spectrometers, respectively. Chemical shift values are reported in ppm (δ) downfield from

tetramethylsilane with reference to internal residual solvent [^{1}H NMR, $CHCl_3$ (7.26), C_6HD_5 (7.16), CHD_2CN (1.90); ^{13}C NMR, $CDCl_3$ (77.0), C_6D_6 (128.0), CD_3CN (118.2)]. Coupling constants (*J*) are reported in hertz (Hz). The following abbreviations were used to designate the multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or unresolved; br = broad. High-resolution mass spectra (HRMS) were measured on an ESI-TOF mass spectrometer. Diastereomer ratio (dr) and *E*/*Z* isomer ratio were estimated by ^{1}H NMR spectroscopic analysis, unless otherwise noted.

*(2S,3S,6S)-6-(((tert-Butyldimethylsilyl)oxy)methyl)-2-(2-((4-methoxybenzyl)oxy)ethyl)-3-methyltetrahydro-4H-pyran-4-one (**15a**).* To a solution of enone **10** (2.085 g, 8.400 mmol) and Et_3N (2.34 mL, 16.8 mmol) in Et_2O (16.8 mL) at 0 °C was added TMSOTf (1.60 mL, 8.82 mmol). The resultant solution was stirred at 0 °C for 30 min and then at room temperature for 1 h. The mixture was diluted with hexanes, washed with saturated aqueous $NaHCO_3$ solution, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude 2-silyloxy diene **11** (2.638 g) as a yellow oil. This material was immediately used in the next reaction without further purification.

To a mixture of the above 2-silyloxy diene **11** (2.638 g), activated 4 Å molecular sieves (823.2 mg), and Jacobsen's chiral chromium(III) catalyst **13** (120.3 mg, 0.247 mmol) was added aldehyde **12** (1.73 mL, 9.06 mmol). The resultant mixture was stirred at room temperature for 20.5 h. The

mixture was diluted with hexanes, filtered through a pad of Celite (eluted with hexanes), and the filtrate was concentrated under reduced pressure to give the crude cycloadduct **14** (4.025 g) as a dark green oil. This material was immediately used in the next reaction without further purification.

To a solution of the above cycloadduct **14** (4.025 g) in MeOH (16.7 mL) at room temperature was added K_2CO_3 (116.1 mg, 0.8401 mmol), and the resultant solution was stirred at room temperature for 30 min. The mixture was concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 0% to 20% EtOAc/hexanes) gave ketone **15a** (1.771 g) and a mixture of **10**, **15a**, and **15b** (1.078 g). To a solution of the mixture of **10**, **15a**, and **15b** (1.078 g) in toluene (10 mL) was added DBU (0.5 mL), and the resultant solution was stirred at room temperature for 18.5 h. The mixture was concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 0% to 30% EtOAc/hexanes) gave an additional ketone **15a** (298.5 mg), along with a mixture of **10**, **15a**, and **15b** (674.1 mg). Second treatment of this mixture (674.1 mg) with DBU (0.3 mL) in toluene (5 mL) gave ketone **15a** (73.9 mg) and **10** (541.0 mg, 26%). Totally, 2.143 g (60% from **10**) of ketone **15a** was obtained as a pale yellow oil: $[\alpha]_D^{29}$ −39.4 (*c* 1.12, $CHCl_3$); IR (film) 2954, 2929, 2857, 1716, 1615, 1513, 1457, 1362, 1249, 1097, 1037, 837, 778 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.26–7.22 (m, 2H), 6.89–6.85 (m, 2H), 4.44 (d, *J* = 11.5 Hz, 1H), 4.41 (d, *J* = 11.5 Hz, 1H), 3.80 (s, 3H), 3.70–3.60 (m,

5H), 3.39 (ddd, *J* = 9.7, 9.2, 2.3 Hz, 1H), 2.46–2.38 (m, 2H), 2.29 (m, 1H), 2.05 (dddd, *J* = 14.2, 7.3, 7.3, 2.3 Hz, 1H), 1.78 (dddd, *J* = 14.2, 9.2, 5.5, 5.5 Hz, 1H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.053 (s, 3H), 0.051 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.9, 159.1, 130.5, 129.2 (2C), 113.7 (2C), 79.5, 77.6, 72.6, 66.2, 65.8, 55.2, 50.1, 44.2, 34.3, 25.8 (3C), 18.3, 9.2, –5.3 (2C); HRMS (ESI) calcd for $C_{23}H_{38}O_5SiNa$ [$(M + Na)^+$] 445.2381; found 445.2396.

*(2S,3R,4S,6S)-6-(((tert-Butyldimethylsilyl)oxy)methyl)-2-(2-((4-methoxybenzyl)oxy)ethyl)-3-methyltetrahydro-2H-pyran-4-ol (**16**).* To a solution of ketone **15a** (1.444 g, 3.416 mmol) and $CeCl_3 \cdot 7H_2O$ (1.336 g, 3.586 mmol) in MeOH (68 mL) at −20 °C was added $NaBH_4$ (135.7 mg, 3.586 mmol), and the resultant solution was stirred at –20 °C for 40 min. The reaction was quenched with saturated aqueous NH_4Cl solution. The resultant mixture was allowed to warm to room temperature and extracted with EtOAc/hexanes. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 8% to 20% EtOAc/hexanes) gave alcohol **16** (1.368 g, 94%, dr >20:1) as a colorless oil. The enantiomer ratio (er 98:2) and the absolute configuration of **16** were determined by ^{1}H NMR analysis of the corresponding Mosher esters. Data for **16**: $[\alpha]_D^{22}$ –56.1 (*c* 0.92, $CHCl_3$); IR (film) 3445, 2954, 2928, 2856, 1614, 1513, 1464, 1362, 1302, 1249, 1107, 1037, 836, 778 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27–7.23 (m, 2H), 6.89−6.85 (m, 2H), 4.44 (d, *J* = 11.9 Hz, 1H), 4.41 (d, *J* = 11.9 Hz, 1H), 3.80 (s, 3H), 3.65 (dd, *J* = 10.5, 5.5 Hz, 1H),

3.59 (dd, *J* = 7.7, 5.9 Hz, 2H), 3.50 (dd, *J* = 10.5, 5.5 Hz, 1H), 3.40 (dddd, *J* = 11.0, 5.5, 5.5, 1.8 Hz, 1H), 3.34 (ddd, *J* = 10.6, 10.1, 4.6 Hz, 1H), 3.11 (ddd, *J* = 9.6, 9.6, 2.8 Hz, 1H), 2.03–1.97 (m, 2H), 1.67–1.60 (m, 2H), 1.27–1.18 (m, 2H), 0.97 (d, *J* = 6.4 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.1, 130.7, 129.2 (2C), 113.7 (2C), 77.9, 75.9, 73.5, 72.6, 66.8, 66.3, 55.2, 44.1, 37.7, 33.2, 25.9 (3C), 18.3, 12.8, −5.3, −5.3; HRMS (ESI) calcd for $C_{23}H_{40}O_5SiNa$ [(M + Na)$^+$] 447.2537; found 447.2535.

*tert-Butyl(((2S,4S,5S,6S)-6-(2-((4-methoxybenzyl)oxy)ethyl)-5-methyl-4-((triisopropylsilyl)-oxy)tetrahydro-2H-pyran-2-yl)methoxy)dimethylsilane (**18**).* To a solution of alcohol **16** (1.976 g, 4.653 mmol) in CH_2Cl_2 (23 mL) at 0 °C were added 2,6-lutidine (1.10 mL, 9.30 mmol) and TIPSOTf (1.20 mL, 4.65 mmol), and the resultant solution was stirred at 0 °C for 65 min. The reaction was quenched with saturated aqueous NH_4Cl solution. The resultant mixture was extracted with hexanes, and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 3% to 20% to 30% EtOAc/hexanes) gave TIPS ether **18** (2.545 g, 94%) as a colorless oil: $[\alpha]_D^{21}$ –2.4 (*c* 1.41, $CHCl_3$); IR (film) 2946, 2865, 1613, 1514, 1464, 1361, 1302, 1249, 1090, 1038, 837, 777 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27–7.24 (m, 2H), 6.89–6.85 (m, 2H), 4.44 (d, *J* = 11.5 Hz, 1H), 4.41 (d, *J* = 11.5 Hz, 1H), 3.80 (s, 3H), 3.66 (dd, *J* = 10.1, 5.5 Hz, 1H), 3.58 (dd, *J* = 7.8, 5.9 Hz, 2H), 3.50 (ddd, *J* = 10.5, 9.6, 4.6 Hz, 1H), 3.46 (dd, *J* = 10.1, 5.9 Hz, 1H), 3.36 (dddd, *J* = 11.4,

5.9, 5.5, 1.8 Hz, 1H), 3.11 (ddd, *J* = 9.6, 9.6, 2.3 Hz, 1H), 2.04–1.96 (m, 2H), 1.64 (m, 1H), 1.32–1.23 (m, 2H), 1.09–1.05 (m, 21H), 0.96 (d, *J* = 6.4 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.1, 130.8, 129.2 (2C), 113.7 (2C), 78.1, 75.8, 74.6, 72.6, 66.9, 66.3, 55.3, 44.7, 38.7, 33.3, 25.8 (3C), 18.3 (4C), 18.2 (3C), 13.3, 12.8 (3C), −5.3, −5.4; HRMS (ESI) calcd for $C_{32}H_{60}O_5Si_2Na$ [$(M + Na)^+$] 603.3871; found 603.3886.

*((2S,4S,5S,6S)-6-(2-((4-Methoxybenzyl)oxy)ethyl)-5-methyl-4-((triisopropylsilyl)oxy)-tetrahydro-2H-pyran-2-yl)methanol (**19**).* To a solution of TIPS ether **18** (2.528 g, 4.351 mmol) in MeOH/CH_2Cl_2 (1:1, v/v, 44 mL) at 0 °C was added CSA (204.1 mg, 10.88 mmol), and the resultant solution was stirred at 0 °C for 2 h 25 min. The reaction mixture was neutralized with Et_3N, stirred at room temperature for 25 min, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10% to 20% EtOAc/hexanes) gave primary alcohol **19** (2.040 g, quantitative) as a colorless oil: $[\alpha]_D^{21}$ +5.2 (*c* 1.22, $CHCl_3$); IR (film) 3446, 2943, 2866, 1613, 1514, 1464, 1372, 1302, 1248, 1092, 883, 810 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27–7.24 (m, 2H), 6.89–6.86 (m, 2H), 4.46 (d, *J* = 11.5 Hz, 1H), 4.41 (d, *J* = 11.5 Hz, 1H), 3.80 (s, 3H), 3.61–3.48 (m, 5H), 3.43 (m, 1H), 3.17 (ddd, *J* = 9.6, 9.6, 1.9 Hz, 1H), 2.03 (m, 1H), 1.91 (dd, *J* = 8.3, 4.2 Hz, 1H), 1.79 (ddd, *J* = 12.4, 4.6, 1.9 Hz, 1H), 1.65 (m, 1H), 1.37 (ddd, *J* = 12.4, 11.9, 9.6 Hz, 1H), 1.30 (m, 1H), 1.08–1.05 (m, 21H), 0.98 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.1, 130.6, 129.2 (2C), 113.7 (2C), 78.1, 75.5,

74.3, 72.7, 66.6, 66.1, 55.2, 44.5, 37.5, 33.3, 18.24 (3C), 18.17 (3C), 13.3, 12.8 (3C); HRMS (ESI) calcd for $C_{26}H_{46}O_5SiNa$ [$(M + Na)^+$] 489.3007; found 489.3007.

*(((2S,3S,4S,6S)-6-(Iodomethyl)-2-(2-((4-methoxybenzyl)oxy)ethyl)-3-methyltetrahydro-2H-pyran-4-yl)oxy)triisopropylsilane (**20**).* To a solution of alcohol **19** (510.2 mg, 1.093 mmol) in THF (7.4 mL) at room temperature were added imidazole (50.1 mg, 2.20 mmol), Ph_3P (431.3 mg, 1.644 mmol), and iodine (388.7 mg, 1.531 mmol), and the resultant solution was stirred at room temperature for 3 h 45 min. The reaction was quenched with saturated aqueous Na_2SO_3 solution. The resultant mixture was extracted with EtOAc, and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 0% to 1% EtOAc/hexanes) gave iodide **20** (620.3 mg, 99%) as a pale yellow oil: $[\alpha]_D^{22}$ +17.0 (*c* 1.24, $CHCl_3$); IR (film) 2943, 2865, 1513, 1464, 1247, 1092, 1038, 882, 809 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 7.32–7.29 (m, 2H), 6.85–6.81 (m, 2H), 4.47 (s, 2H), 3.84 (ddd, *J* = 9.2, 9.2, 5.5 Hz, 1H), 3.65 (ddd, *J* = 9.2, 6.4, 4.1 Hz, 1H), 3.34 (ddd, *J* = 10.5, 9.6, 4.6 Hz, 1H), 3.31 (s, 3H), 3.09 (ddd, *J* = 9.6, 9.6, 2.3 Hz, 1H), 3.05 (m, 1H), 2.83 (dd, *J* = 10.1, 7.3 Hz, 1H), 2.72 (dd, *J* = 10.1, 4.6 Hz, 1H), 2.03 (m, 1H), 1.93 (ddd, *J* = 12.0, 4.6, 1.9 Hz, 1H), 1.62 (m, 1H), 1.31 (m, 1H), 1.23 (ddd, *J* = 12.0, 11.5, 10.5 Hz, 1H), 1.13–0.99 (m, 21H), 0.92 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 159.7, 131.6, 129.5 (2C), 114.0 (2C), 78.1, 74.65, 74.61, 73.0, 66.8, 54.7, 44.6, 41.8, 33.9, 18.5 (3C), 18.4 (3C), 13.3, 13.1 (3C), 9.3; HRMS

(ESI) calcd for $C_{26}H_{45}O_4SiINa$ [$(M + Na)^+$] 599.2024; found 599.2042.

*Methyl (S)-4-((tert-butyldiphenylsilyl)oxy)-3-hydroxy-2,2-dimethylbutanoate (**27**).* To a solution of *N*-tosyl-L-valine (**26**) (11.50 g, 42.38 mmol) in CH_2Cl_2 (60 mL) at 0 °C was added $BH_3 \cdot THF$ (0.9 M solution in THF, 47.0 mL, 42.3 mmol), and the resultant solution was stirred at 0 °C for 30 min and then at room temperature for 30 min. To this solution at –78 °C were sequentially added a solution of aldehyde **25** (11.49 g, 38.50 mmol) in CH_2Cl_2 (10 mL + 5 mL and 5 mL rinse) and a solution of methyl trimethylsilyl dimethylketene acetal **24** (8.6 mL, 42 mmol) in CH_2Cl_2 (5 mL + 3 mL and 2 mL rinse), and the resultant solution was stirred at –78 °C for 6 h 35 min. The reaction was quenched with 1 M aqueous HCl solution/THF (1:1, v/v). The resultant mixture was vigorously stirred at room temperature for 14 h 15 min. The mixture was extracted with EtOAc, and the organic layer was washed with saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5% EtOAc/hexanes) gave ester **27** (10.09 g, 65%) as a colorless oil: $[\alpha]_D^{27}$ +4.5 (*c* 1.00, CH_2Cl_2); IR (film) 3565, 2932, 2857, 1732, 1472, 1428, 1112, 822, 740, 702 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.68–7.65 (m, 4H), 7.46–7.38 (m, 6H), 3.84 (ddd, *J* = 7.3, 4.6, 3.7 Hz, 1H), 3.71 (dd, *J* = 10.6, 3.2 Hz, 1H), 3.64 (dd, *J* = 10.6, 7.3 Hz, 1H), 3.61 (s, 3H), 3.01 (d, *J* = 4.6 Hz, 1H), 1.17 (s, 3H), 1.14 (s, 3H) 1.06 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.0, 135.6 (2C), 135.5 (2C), 133.0, 132.9, 129.8 (2C), 127.8 (4C), 76.5, 64.6, 51.9, 45.1, 26.8

(3C), 21.8, 21.2, 19.2; HRMS (ESI) calcd for $C_{23}H_{32}O_4SiNa$ [$(M + Na)^+$] 423.1962; found 423.1966.

(S)-4-((tert-Butyldiphenylsilyl)oxy)-3-hydroxy-N-methoxy-N,2,2-trimethylbutanamide (***28***). To a suspension of MeNH(OMe)·HCl (11.82 g, 121.2 mmol) in THF (220 mL) at –78 °C was added dropwise *n*-BuLi (2.6 M solution in *n*-hexane, 93.0 mL, 242 mmol) over a period of 30 min, and the resultant solution was stirred at –78 °C for 35 min and then at room temperature for 30 min. To this solution at –20 °C was added a solution of ester **27** (9.70 g, 24.2 mmol) in THF (10 mL + 5 mL and 5 mL rinse), and the resultant solution was stirred at –20 °C for 2.5 h. The reaction was quenched with saturated aqueous NH_4Cl solution. The resultant mixture was warmed to room temperature and extracted with EtOAc, and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10% to 20% EtOAc/hexanes) gave Weinreb amide **28** (8.26 g, 79%) as a pale yellow oil: $[\alpha]_D^{26}$ +11.2 (*c* 1.00, $CHCl_3$); IR (film) 3480, 2932, 2857, 1646, 1472, 1427, 1112, 997, 822, 741, 703 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.69–7.66 (m, 4H), 7.45–7.36 (m, 6H), 4.04 (ddd, *J* = 7.3, 5.1, 3.2 Hz, 1H), 3.73 (dd, *J* = 10.5, 3.2 Hz, 1H), 3.67 (dd, *J* = 10.5, 7.3 Hz, 1H), 3.63 (s, 3H), 3.10 (s, 3H), 3.09 (br d, *J* = 5.1 Hz, 1H), 1.24 (s, 3H), 1.17 (s, 3H), 1.06 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.4, 135.621 (2C), 135.59 (2C), 133.3, 133.2, 129.7 (2C), 127.72 (2C), 127.70 (2C), 76.4, 65.1, 60.5, 46.2, 33.7, 26.8 (3C), 21.3, 20.9, 19.2; HRMS (ESI)

calcd for $C_{24}H_{35}NO_4SiNa$ [$(M + Na)^+$] 452.2228; found 452.2222. The enantiomer ratio of **28** was determined to be 22:1 by chiral HPLC analysis [CHIRACEL OD-H (4.6 mm ID × 250 mm); solvent, 1% *i*-PrOH/*n*-hexane; flow rate, 1.0 mL/min; UV detection, 215 nm; major peak, t_R = 17.3 min; minor peak, t_R = 13.8 min].

*(S)-7-((tert-Butyldiphenylsilyl)oxy)-6-hydroxy-2,5,5-trimethylhept-1-en-4-one (**29**).* To a solution of Weinreb amide **28** (8.20 g, 19.1 mmol) in THF (300 mL) at –20 °C was added dropwise 2-methylallylmagnesium chloride (0.80 M solution in Et_2O, 112 mL, 89.6 mmol) over a period of 1 h, and the resultant solution was stirred at 0 °C for 2 h. The reaction was quenched with saturated aqueous NH_4Cl solution. The resultant mixture was extracted with EtOAc, and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 2% to 3% EtOAc/hexanes) gave hydroxy ketone **29** (6.63 g, 82%) as a colorless oil: $[\alpha]_D^{28}$ +10.4 (*c* 1.00, $CHCl_3$); IR (film) 3524, 2932, 2858, 1704, 1471, 1428, 1112, 1053, 893, 822, 741, 703 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.67–7.64 (m, 4H), 7.46–7.38 (m, 6H), 4.90 (m, 1H), 4.69 (m, 1H), 3.88 (ddd, *J* = 8.3, 3.2, 2.8 Hz, 1H), 3.70 (dd, *J* = 10.5, 3.2 Hz, 1H), 3.56 (dd, *J* = 10.5, 8.3 Hz, 1H), 3.26 (dd, *J* = 16.5, 0.9 Hz, 1H), 3.20 (dd, *J* = 16.5, 0.9 Hz, 1H), 2.87 (d, *J* = 2.8 Hz, 1H), 1.69 (m, 3H), 1.10 (s, 3H), 1.06 (s, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 212.3, 139.7, 135.53 (2C), 135.50 (2C), 132.9 (2C),

129.92, 129.88, 127.8 (4C), 114.7, 76.3, 64.5, 50.3, 47.1, 26.8 (3C), 22.6, 21.3, 19.8, 19.2; HRMS (ESI) calcd for $C_{26}H_{36}O_3SiNa$ [$(M + Na)^+$] 447.2326; found 447.2321.

*(S)-7-((tert-Butyldiphenylsilyl)oxy)-2,5,5-trimethyl-6-((triethylsilyl)oxy)hept-1-en-4-one (**23**).* To a solution of hydroxy ketone **29** (6.56 g, 15.4 mmol) in DMF (154 mL) at 0 °C were added imidazole (3.16 g, 46.4 mmol) and TESCl (3.90 mL, 23.1 mmol), and the resultant solution was stirred at room temperature for 2 h 35 min. The reaction was quenched with saturated aqueous NH_4Cl solution. The resultant mixture was extracted with *t*-BuOMe, and the organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 2% EtOAc/hexanes) gave TES ether **23** (7.89 g, 95%) as a colorless oil: $[\alpha]_D^{28}$ –2.5 (*c* 1.00, $CHCl_3$); IR (film) 2956, 2876, 1706, 1471, 1428, 1006, 739, 702 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.67–7.63 (m, 4H), 7.45–7.36 (m, 6H), 4.88 (br s, 1H), 4.65 (br s, 1H), 4.04 (dd, *J* = 6.0, 5.5 Hz, 1H), 3.55 (dd, *J* = 11.0, 5.5 Hz, 1H), 3.46 (dd, *J* = 11.0, 6.0 Hz, 1H), 3.26 (d, *J* = 16.5 Hz, 1H), 3.16 (d, *J* = 16.5 Hz, 1H), 1.68 (br s, 3H), 1.08 (s, 3H), 1.07 (s, 3H), 1.04 (s, 9H), 0.90 (t, *J* = 7.8 Hz, 9H), 0.56 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 211.6, 140.0, 135.7 (2C), 135.6 (2C), 133.1, 133.0, 129.70, 139.66, 127.7 (4C), 114.5, 77.8, 66.2, 51.9, 47.5, 26.8 (3C), 22.7, 21.5, 20.3, 19.1, 6.9 (3C), 5.1 (3C); HRMS (ESI) calcd for $C_{32}H_{50}O_3Si_2Na$ [$(M + Na)^+$] 561.3191; found 561.3209.

(4R,6S)-7-((tert-butyldiphenylsilyl)oxy)-2,5,5-trimethyl-6-((triethylsilyl)oxy)hept-1-en-4-ol ***(30)***. To a solution of DIBALH (1.02 M solution in *n*-hexanes, 21.5 mL, 21.9 mmol) in THF (150 mL) at –78 °C was added *n*-BuLi (1.6 M solution in *n*-hexane, 13.7 mL, 21.9 mmol). To this solution was added a solution of ketone **23** (7.89 g, 14.6 mmol) in THF (5 mL + 5 mL and 3 mL rinse), and the resultant solution was stirred at –78 °C for 1 h 45 min. The reaction was quenched with MeOH. The resultant mixture was diluted with EtOAc and saturated potassium sodium tartrate solution and stirred at room temperature until the layers became clear. The resultant mixture was extracted with EtOAc, and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The diastereomer ratio was estimated to be ca. 7:1 by 600 MHz ^{1}H NMR analysis of the crude product. Purification of the crude material by flash column chromatography (silica gel, first round, 25% to 30% CH_2Cl_2/hexanes; second round, 25% to 30% CH_2Cl_2/hexanes) gave alcohol **30** (4.88 g, 62%) in pure form and as a colorless oil: $[\alpha]_D^{28}$ –3.3 (*c* 1.00, $CHCl_3$); IR (film) 3484, 2955, 1646, 1472, 1427, 1112, 1059, 1006, 739, 702 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69–7.66 (m, 4H), 7.46–7.36 (m, 6H), 4.81 (br s, 1H), 4.78 (br s, 1H), 3.88 (br, 1H), 3.84 (m, 1H), 3.73 (br dd, *J* =8.3, 4.2 Hz, 1H), 3.70–3.63 (m, 2H), 2.07–2.00 (m, 2H), 1.74 (br s, 3H), 1.06 (s, 9H), 0.93 (s, 3H), 0.92 (t, *J* = 7.8 Hz, 9H), 0.72 (s, 3H), 0.66–0.60 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.8, 135.74 (2C), 135.67 (2C), 133.2, 133.1, 129.75, 129.72, 127.72 (2C), 127.67 (2C), 112.2, 83.3, 73.6, 66.2, 40.3, 40.1, 26.9 (3C), 22.45,

22.36, 19.9, 19.1, 6.9 (3C), 5.0 (3C); HRMS (ESI) calcd for $C_{32}H_{52}O_3Si_2Na$ [$(M + Na)^+$] 563.3347; found 563.3353.

*tert-Butyldiphenyl(((4S,6R)-2,2,5,5-tetramethyl-6-(2-methylallyl)-1,3-dioxan-4-yl)methoxy)-silane (**31**).* To a solution of alcohol **30** (18.6 mg, 34.4 mmol) in THF (0.6 mL) at 0 °C was added 1 M aqueous HCl solution (0.12 mL), and the resultant solution was stirred at room temperature for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution at 0 °C. The resultant mixture was extracted with EtOAc, and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was roughly purified by flash column chromatography (silica gel, 5% EtOAc/hexanes) to give diol (14.4 mg, 94%), which was used immediately in the next reaction.

To a solution of the above diol (14.4 mg) in CH_2Cl_2 (1 mL) at 0 °C were added 2,2-dimethoxypropane (6 μL, 0.05 mmol) and PPTS (4 mg, 7 mmol), and the resultant solution was stirred at room temperature for 3.5 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution. The resultant mixture was extracted with EtOAc, and the organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 2% EtOAc/hexanes) gave acetonide **31** (13 mg, 82%): $[\alpha]_D^{25}$ –6.2 (*c* 0.66, $CHCl_3$); IR (film) 2961, 2932, 2857, 1428, 1259, 1200, 1172, 1112, 740, 702 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 7.89–7.83 (m, 4H), 7.26–7.22 (m, 6H), 4.90 (br

s, 1H), 4.89 (br s, 1H), 3.90 (dd, *J* = 10.8, 7.8 Hz, 1H), 3.81 (dd, *J* = 10.8, 3.6 Hz, 1H), 3.75 (dd, *J* = 7.8, 3.6 Hz, 1H), 3.53 (dd, *J* = 10.8, 2.4 Hz, 1H), 2.09 (br dd, *J* = 14.4, 10.8 Hz, 1H), 1.88 (br d, *J* = 14.4 Hz, 1H), 1.75 (s, 3H), 1.46 (s, 3H), 1.37 (s, 3H), 1.21 (s, 9H), 0.72 (s, 3H), 0.56 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 143.8, 136.2 (2C), 136.1 (2C), 134.3, 134.0, 130.0, 129.9, 128.3 (2C), 128.1 (2C), 112.3, 101.0, 77.2, 75.3, 63.7, 38.6, 37.2, 27.0 (3C), 24.2, 24.1, 23.0, 19.7, 19.4, 18.7; HRMS (ESI) calcd for $C_{29}H_{42}O_3SiNa$ [(M + Na)+] 489.2795; found 489.2803.

*(4R,6S)-7-((tert-Butyldiphenylsilyl)oxy)-2,5,5-trimethyl-6-((triethylsilyl)oxy)hept-1-en-4-yl acrylate (**22**).* To a solution of alcohol **30** (4.76 g, 8.80 mmol) in CH_2Cl_2 (88 mL) at 0 °C were added *i*-Pr_2NEt (15.3 mL, 87.8 mmol) and acryloyl chloride (4.80 mL, 59.3 mmol), and the resultant solution was stirred at 0 °C for 3 h 40 min. The reaction was quenched with saturated aqueous $NaHCO_3$ solution. The resultant mixture was extracted with EtOAc, and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10% to 20% CH_2Cl_2/hexanes) gave diene **22** (4.79 g, 91%) as a pale yellow oil: $[\alpha]_D^{28}$ +1.2 (*c* 0.87, $CHCl_3$); IR (film) 2954, 2876, 1726, 1404, 1268, 1188, 1113, 1046, 738, 702 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69–7.65 (m, 4H), 7.45–7.35 (m, 6H), 6.22 (dd, *J* =17.4, 1.4 Hz, 1H), 5.96 (dd, *J* = 17.4, 10.5, 1H), 5.68 (dd, *J* = 10.5, 1.4, 1H), 5.15 (dd, *J* =10.6, 2.7 Hz, 1H), 4.65 (br s, 1H), 4.60 (br s, 1H), 3.78 (m, 1H), 3.63–3.59 (m, 2H), 2.26 (dd, *J* = 13.8, 10.6 Hz, 1H), 2.19 (br d, *J* = 13.8 Hz, 1H),

1.65 (br s, 3H), 1.06 (s, 9H), 0.92 (t, *J* = 7.8 Hz, 9H), 0.89 (s, 3H), 0.80 (s, 3H), 0.64–0.59 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.4, 142.5, 135.8 (2C), 135.7 (2C), 133.4 (2C), 129.8, 129.7, 129.6, 128.9, 127.6 (4C), 113.1, 79.2, 75.4, 66.7, 41.9, 38.9, 26.9 (3C), 22.0, 20.9, 20.7, 19.1, 7.1 (3C), 5.2 (3C); HRMS (ESI) calcd for $C_{35}H_{54}O_4Si_2Na$ [$(M + Na)^+$] 617.3453; found 617.3460.

*(R)-6-((S)-4-((tert-Butyldiphenylsilyl)oxy)-2-methyl-3-((triethylsilyl)oxy)butan-2-yl)-4-methyl-5,6-dihydro-2H-pyran-2-one (**32**).* To a solution of diene **22** (2.07 g, 3.48 mmol) in toluene (340 mL) was added a solution of the Grubbs second-generation catalyst (**G-II**) (298.4 mg, 0.3515 mmol) in toluene (5 mL + 3 mL rinse), and the resultant solution was stirred at 70 °C for 13 h 25 min. The reaction mixture was cooled to room temperature, treated with Et_3N (15 mL), and stirred at room temperature for 3 h 55 min under air to quench the catalyst. The resultant mixture was concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 1% to 4% to 10% EtOAc/hexanes) gave unsaturated lactone **32** (2.04 g, quantitative) as a colorless solid: mp 89–93 °C; $[\alpha]_D^{27}$ +22.8 (*c* 0.82, $CHCl_3$); IR (film) 2953, 2875, 1725, 1254, 1112, 1053, 1010, 739, 703 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68–7.65 (m, 4H), 7.45–7.37 (m, 6H), 5.79 (br s, 1H), 4.56 (dd, *J* = 13.3, 3.2 Hz, 1H), 3.95 (dd, *J* = 5.0, 5.0 Hz, 1H), 3.73 (dd, *J* =11.0, 5.0 Hz, 1H), 3.53 (dd, *J* = 11.0, 5.0 Hz, 1H), 2.35 (m, 1H), 2.06 (dd, *J* = 17.9, 3.2 Hz, 1H), 1.93 (br s, 3H), 1.05 (s, 9H), 0.92 (s, 3H), 0.88 (t, *J* = 7.8 Hz, 9H), 0.81 (s, 3H), 0.59–0.54 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.5, 157.6, 135.7 (2C), 135.6 (2C), 133.2, 133.1, 129.73, 129.69,

127.70 (2C), 127.68 (2C), 116.4, 80.1, 75.5, 66.4, 41.1, 29.5, 26.9 (3C), 23.1, 19.1, 18.1, 17.9, 7.0 (3C), 5.0 (3C); HRMS (ESI) calcd for $C_{33}H_{50}O_4Si_2Na$ [$(M + Na)^+$] 589.3140; found 589.3137.

*(4R,6R)-6-((S)-4-((tert-Butyldiphenylsilyl)oxy)-2-methyl-3-((triethylsilyl)oxy)butan-2-yl)-4-methyltetrahydro-2H-pyran-2-one (**21**).* To a solution of unsaturated lactone **32** (1.91 g, 3.37 mmol) in toluene (112 mL) was added 10% Pd/C (575 mg), and the resultant mixture was stirred at room temperature under an atmosphere of H_2 (balloon) for 11 h. Since the starting material was not consumed at this stage, the resultant mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. To a solution of the residue in toluene (113 mL) was added 30% Pd/C (581 mg), and the resultant mixture was stirred at room temperature under an atmosphere of H_2 (balloon) for 15 h 10 min. The mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10% to 30% EtOAc/hexanes) gave lactone **21** (1.87 g, 98%, dr ca. 7:1) as a pale yellow solid: $[\alpha]_D^{27}$ –4.1 (*c* 1.00, $CHCl_3$); IR (film) 2955, 2876, 1738, 1471, 1428, 1248, 1112, 1004, 740, 704 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, major diastereomer) δ 7.69–7.65 (m, 4H), 7.45–7.37 (m, 6H), 4.45 (dd, *J* = 11.9, 2.7 Hz, 1H), 3.92 (dd, *J* = 5.5, 4.6 Hz, 1H), 3.70 (dd, *J* =11.0, 4.6 Hz, 1H), 3.52 (dd, *J* = 11.0, 5.5 Hz, 1H), 2.64 (ddd, *J* = 17.0, 5.5, 1.8 Hz, 1H), 2.00 (dd, *J* = 17.0, 10.6 Hz, 1H), 1.94 (m, 1H), 1.80 (m, 1H), 1.16 (ddd, *J* = 13.3, 13.3, 11.9 Hz, 1H), 1.05 (s, 9H), 1.01 (d, *J* = 6.4 Hz, 3H), 0.90 (t, *J* = 7.8 Hz, 9H), 0.84 (s, 3H), 0.77 (s, 3H), 0.62–0.56 (m,

6H); ^{13}C NMR (150 MHz, $CDCl_3$, major diastereomer) δ 171.5, 135.72 (2C), 135.67 (2C), 133.2, 133.1, 129.69, 129.66, 127.7 (4C), 83.3, 75.8, 66.5, 41.5, 38.1, 31.0, 26.8 (3C), 26.6, 21.9, 19.1, 17.74, 17.68, 7.0 (3C), 5.1 (3C); HRMS (ESI) calcd for $C_{33}H_{52}O_4Si_2Na$ [$(M + Na)^+$] 591.3296; found 591.3293.

*Triisopropyl(((2S,3S,4S)-2-(2-((4-methoxybenzyl)oxy)ethyl)-3-methyl-6-methylene-tetrahydro-2H-pyran-4-yl)oxy)silane (**8**).* To a solution of iodide **20** (516.8 mg, 0.8962 mmol) in THF (9 mL) at 0 °C was added *t*-BuOK (403.7 mg, 3.598 mmol), and the resultant solution was stirred at 0 °C for 75 min. The solution was diluted with hexanes, and the reaction was quenched with H_2O. The resultant mixture was extracted with hexanes, and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give crude exo-olefin **8**, which was immediately used in the next coupling reaction without purification: ^{1}H NMR (600 MHz, C_6D_6) δ 7.28–7.24 (m, 2H), 6.83–6.80 (m, 2H), 4.66 (d, *J* = 1.7 Hz, 1H), 4.41 (d, *J* = 11.6 Hz, 1H), 4.37 (d, *J* = 11.6 Hz, 1H), 4.20 (d, *J* = 1.7 Hz, 1H), 3.78 (ddd, *J* = 9.3, 8.9, 5.8 Hz, 1H), 3.65 (ddd, *J* = 9.3, 6.9, 4.8 Hz, 1H), 3.54 (ddd, *J* = 10.3, 9.0, 4.8 Hz, 1H), 3.43 (ddd, *J* = 9.3, 9.3, 2.4 Hz, 1H), 3.30 (s, 3H), 2.61 (dd, *J* = 13.1, 4.8 Hz, 1H), 2.30 (dddd, *J* = 13.1, 10.3, 1.7, 1.7 Hz, 1H), 2.05 (m, 1H), 1.77 (m, 1H), 1.56 (m, 1H), 1.10–0.98 (m, 21H), 0.92 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 159.6, 158.1, 131.4, 129.4 (2C), 114.0 (2C), 92.9, 79.4, 74.0, 72.9, 66.6, 54.7, 44.1, 40.1, 34.1, 18.4 (3C), 18.3 (3C), 13.7, 13.0 (3C).

*(2R,4R)-2-((S)-4-((tert-Butyldiphenylsilyl)oxy)-2-methyl-3-((triethylsilyl)oxy)butan-2-yl)-4-methyl-3,4-dihydro-2H-pyran-6-yl trifluoromethanesulfonate (**9b**).* To a solution of lactone **21** (717.5 mg, 1.261 mmol) and HMPA (0.66 mL, 3.8 mmol) in THF (7 mL) at –78 °C was added KHMDS (0.5 M solution in toluene, 3.0 mL, 1.5 mmol), and the resultant solution was stirred at –78 °C for 30 min. To this solution was added a solution of $PhNTf_2$ (540.8 mg, 1.514 mmol) in THF (3 mL + 2 mL and 0.6 mL rinse). The resultant solution was stirred at –78 °C for 1 h 35 min. The reaction was quenched with pH 7 buffer. The resultant mixture was warmed to room temperature and extracted with hexanes, and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was roughly purified by flash column chromatography (silica gel, 2% EtOAc/hexanes) gave enol triflate **9b**, which was immediately used in the next reaction without further purifications.

*(2R,3S,4R,6R)-6-((S)-4-((tert-Butyldiphenylsilyl)oxy)-2-methyl-3-((triethylsilyl)oxy)butan-2-yl)-2-methoxy-2-(((2S,4S,5S,6S)-6-(2-((4-methoxybenzyl)oxy)ethyl)-5-methyl-4-((tri-isopropylsilyl)oxy)tetrahydro-2H-pyran-2-yl)methyl)-4-methyltetrahydro-2H-pyran-3-ol (**33a**) and (2R,3R,4R,6R)-6-((S)-4-((tert-Butyldiphenylsilyl)oxy)-2-methyl-3-((triethylsilyl)oxy)butan-2-yl)-2-methoxy-2-(((2S,4S,5S,6S)-6-(2-((4-methoxybenzyl)oxy)ethyl)-5-methyl-4-((tri-isopropylsilyl)oxy)tetrahydro-2H-pyran-2-yl)methyl)-4-methyltetrahydro-2H-pyran-3-ol (**33b**).* To a solution of the above exo-olefin **8** in THF (4 mL) at 0 °C was added a solution of

9-BBN-H dimer (286.2 mg, 1.173 mmol) in THF (3 mL + 1.5 mL and 0.5 mL rinse). The resultant solution was stirred at room temperature for 65 min. To this solution was added 3 M aqueous Cs_2CO_3 solution (0.90 mL, 2.7 mmol), and the resultant solution was vigorously stirred at room temperature for 35 min. To this mixture were added a solution of the above enol triflate **9b** in DMF (3 mL + 3 mL and 3 mL rinse), Ph_3As (110.8 mg, 0.362 mmol), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (74.1 mg, 0.0907 mmol), and the resultant mixture was stirred at room temperature for 9 h 5 min. The reaction mixture was treated with H_2O and extracted with EtOAc/hexanes (1:1, v/v). The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 1% to 2% EtOAc/hexanes) gave enol ether **7** (930.3 mg) as a pale yellow oil, which was contaminated with some impurities and used in the next step without further purification: IR (film) 2954, 2867, 1677, 1513, 1462, 1247, 1091, 738, 702 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 7.85–7.80 (m, 4H), 7.30–7.24 (m, 8H), 6.83–6.80 (m, 2H), 4.43 (d, *J* = 11.5 Hz, 1H), 4.40 (d, *J* = 11.5 Hz, 1H), 4.37 (br s, 1H), 4.20 (dd, *J* = 5.0, 5.0 Hz, 1H), 4.01–3.96 (m, 2H), 3.85–3.72 (m, 4H), 3.60 (ddd, *J* = 10.1, 10.1, 4.1 Hz, 1H), 3.31 (s, 3H), 3.25 (ddd, *J* = 9.6, 9.6, 2.3 Hz, 1H), 2.83 (m, 1H), 2.28–2.21 (m, 2H), 2.18–2.10 (m, 2H), 1.83 (m, 1H), 1.68 (br dd, *J* = 12.8, 5.5 Hz, 1H), 1.52 (m, 1H), 1.41 (ddd, *J* = 11.5, 11.5, 11.5 Hz, 1H), 1.22–1.12 (m, 22H), 1.20 (s, 9H overlapped), 1.07 (t, *J* = 7.8 Hz, 9H), 1.06 (d, *J* = 6.4 Hz, 3H), 0.99 (s, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 3H), 0.78–0.73 (m, 6H); ^{13}C NMR (150 MHz,

C_6D_6) δ 159.6, 150.2, 136.2 (2C), 136.1 (2C), 133.8 (2C), 131.6, 130.08, 130.06, 129.3 (2C), 128.12 (2C), 128.09 (2C), 114.0 (2C), 104.7, 78.9, 78.7, 76.8, 75.5, 72.9, 72.8, 67.4, 67.2, 54.7, 45.0, 41.6, 41.4, 41.3, 34.1, 31.6, 28.0, 27.2 (3C), 22.1, 19.4, 18.64 (3C), 18.57 (3C), 18.50, 18.4, 13.7, 13.3 (3C), 7.4 (3C), 5.6 (3C); HRMS (ESI) calcd for $C_{59}H_{96}O_7Si_3Na$ [$(M + Na)^+$] 1023.6356; found 1023.6371.

To a solution of the above enol ether **7** (930.3 mg) in CH_2Cl_2/MeOH (2:1, v/v, 9 mL) at 0 °C were added $NaHCO_3$ (303.0 mg, 3.607 mmol) and *m*-CPBA (232.5 mg, 1.347 mmol), and the resultant mixture was stirred at 0 °C for 1.5 h. The resultant mixture was treated with Et_3N (0.3 mL) and warmed to room temperature. The mixture was diluted with Et_2O, and filtered through a pad of Celite (eluted with Et_2O). The filtrate was concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 2% to 4% to 5% to 6% to 7% EtOAc/hexanes) gave alcohols **33a** (541.6 mg, 58% from **20**), which was contaminated with minor impurities, and **33b** (226.2 mg, 24% from **20**) as a pale yellow oil, respectively. Analytical sample of **33a** was purified by flash column chromatography (silica gel, 2% EtOAc/benzene). Data for **33a**: $[\alpha]_D^{27}$ −13.3 (*c* 1.00, C_6H_6); IR (film) 3524, 2952, 2868, 1614, 1513, 1462, 1246, 1087, 739, 703 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 7.83–7.80 (m, 4H), 7.39–7.35 (m, 2H), 7.30–7.23 (m, 6H), 6.84–6.81 (m, 2H), 4.58 (d, *J* = 11.5 Hz, 1H), 4.43 (d, *J* = 11.5 Hz, 1H), 4.03 (dd, *J* = 11.0, 4.6 Hz, 1H), 3.90 (dd, *J* = 5.0, 5.0 Hz, 1H), 3.81–3.75 (m, 4H), 3.70 (m, 1H), 3.65 (m, 1H), 3.43 (ddd, *J* =

10.1, 10.1, 4.1 Hz, 1H), 3.30 (s, 3H), 3.24 (br d, J = 10.1 Hz, 1H), 3.21 (ddd, J = 9.4, 9.4, 2.3 Hz, 1H), 3.11 (s, 3H), 2.17 (m, 1H), 2.09–2.00 (m, 3H), 1.94 (dd, J = 15.6, 7.4 Hz, 1H), 1.83 (m, 1H), 1.69 (m, 1H), 1.60 (ddd, J = 11.9, 11.9, 11.9 Hz, 1H), 1.44–1.38 (m, 2H), 1.26 (d, J = 6.4 Hz, 3H), 1.21 (s, 9H), 1.19 (s, 3H), 1.16–1.11 (m, 21H), 1.04 (t, J = 7.8 Hz, 9H), 0.94 (d, J = 6.4 Hz, 3H), 0.74–0.69 (m, 6H); ^{13}C NMR (150 MHz, C_6D_6) δ 159.6, 136.11 (2C), 136.09 (2C), 133.7 (2C), 131.5, 130.15, 130.11, 129.7 (2C), 128.3 (2C), 128.1 (2C), 114.0 (2C), 99.7, 79.1, 78.5, 78.2, 74.9, 74.0, 73.0, 71.4, 67.3, 66.6, 54.7, 47.5, 44.4, 43.5, 42.9, 42.2, 34.3, 33.9, 32.2, 27.2 (3C), 21.0, 20.4, 19.31, 19.27, 18.49 (3C), 18.46 (3C), 13.6, 13.2 (3C), 7.4 (3C), 5.7 (3C); HRMS (ESI) calcd for $C_{60}H_{100}O_9Si_3Na$ [$(M + Na)^+$] 1071.6567; found 1071.6590. Data for **33b**: $[\alpha]_D^{25}$ −2.4 (*c* 1.00, C_6H_6); IR (film) 3524, 2951, 2868, 1514, 1463, 1247, 1088, 739, 703 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 7.88–7.84 (m, 4H), 7.32–7.24 (m, 8H), 6.84–6.81 (m, 2H), 4.51 (d, J = 11.4 Hz, 1H), 4.48 (d, J = 11.4 Hz, 1H), 4.10 (dd, J = 11.0, 4.1 Hz, 1H), 3.98 (dd, J = 5.5, 4.1 Hz, 1H), 3.94 (dd, J = 11.0, 5.5, Hz, 1H), 3.73 (dd, J = 11.5, 1.9 Hz, 1H), 3.64 (ddd, J = 9.2, 9.2, 5.5 Hz, 1H), 3.61 (dd, J = 3.2, 3.2 Hz, 1H), 3.56 (m, 1H), 3.45 (br dd, J = 11.0, 11.0 Hz, 1H), 3.42–3.37 (m, 2H), 3.30 (s, 3H), 3.05 (ddd, J = 9.6, 9.6, 1.9 Hz, 1H), 3.00 (s, 3H), 2.33 (m, 1H), 2.08 (ddd, J = 12.4, 12.4, 12.4 Hz, 1H), 2.03 (dd, J = 16.1, 9.6 Hz, 1H), 1.95 (m, 1H), 1.79 (ddd, J = 12.4, 4.6, 1.8 Hz, 1H), 1.71 (d, J = 15.6 Hz, 1H), 1.55–1.46 (m, 3H), 1.36 (d, J = 6.9 Hz, 3H), 1.29 (m, 1H), 1.24 (s, 12H), 1.21 (s, 3H), 1.16–1.10 (m, 21H), 1.07 (t, J = 7.8 Hz, 9H), 0.92 (d, J = 6.4 Hz, 3H), 0.79–0.73 (m, 6H);

^{13}C NMR (150 MHz, C_6D_6) δ 159.7, 136.18 (2C), 136.16 (2C), 134.0, 133.9, 131.3, 130.1, 130.0, 129.5 (2C), 128.3 (2C), 128.1 (2C), 114.1 (2C), 101.7, 79.7, 78.8, 75.9, 74.9, 73.0, 71.2, 70.0, 67.6, 66.8, 54.7, 47.2, 44.3, 43.0, 42.4, 38.0, 33.8, 29.6, 27.8, 27.2 (3C), 21.7, 21.0, 19.3, 18.8, 18.46 (3C), 18.43 (3C), 13.6, 13.2 (3C), 7.4 (3C), 5.7 (3C); HRMS (ESI) calcd for $C_{60}H_{100}O_9Si_3Na$ [(M + Na)$^+$] 1071.6567; found 1071.6561.

*(2R,4R,6R)-6-((S)-4-((tert-Butyldiphenylsilyl)oxy)-2-methyl-3-((triethylsilyl)oxy)butan-2-yl)-2-methoxy-2-(((2S,4S,5S,6S)-6-(2-((4-methoxybenzyl)oxy)ethyl)-5-methyl-4-((triisopropylsilyl)oxy)tetrahydro-2H-pyran-2-yl)methyl)-4-methyldihydro-2H-pyran-3(4H)-one (**34**) from alcohol **33a**.* To a suspension of alcohol **33a** (402.8 mg, 0.3837 mmol) and activated 4 Å molecular sieves (401.2 mg) in CH_2Cl_2/MeCN (2:1, v/v, 3.9 mL) were added NMO (93.2 mg, 0.796 mmol) and TPAP (14.3 mg, 0.0407 mmol), and the resultant mixture was stirred at room temperature for 5 h 50 min. To this mixture were added NMO (48.0 mg, 0.410 mmol) and TPAP (6.8 mg, 0.019 mmol), and the resultant mixture was stirred at room temperature for another 2 h. The reaction mixture was filtered through a pad of Celite (eluted with 10% EtOAc/hexanes), and the filtrate was concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 3% to 4% EtOAc/hexanes) gave ketone **34** (358.7 mg, 89%) as a colorless oil: $[\alpha]_D^{28}$ −11.3 (*c* 1.00, $CHCl_3$); IR (film) 2956, 2867, 1735, 1614, 1513, 1464, 1247, 1113, 1090, 1059, 822, 740, 702 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69–7.65 (m, 4H),

7.46–7.42 (m, 2H), 7.41–7.37 (m, 4H), 7.26–7.23 (m, 2H), 6.87–6.84 (m, 2H), 4.42 (d, *J* = 11.5 Hz, 1H), 4.41 (d, *J* = 11.5 Hz, 1H), 4.25 (d, *J* = 11.5 Hz, 1H), 3.39 (s, 3H), 3.73 (dd, *J* = 11.0, 5.9 Hz, 1H), 3.62 (ddd, *J* = 4.6, 4.6, 4.6 Hz, 1H), 3.58 (m, 1H), 3.48 (dd, *J* = 11.0, 4.6 Hz, 1H), 3.46 (m, 1H), 3.41 (ddd, *J* = 10.1, 10.1, 4.6 Hz, 1H), 3.18 (s, 3H), 3.15 (ddd, *J* = 9.2, 9.2, 2.3 Hz, 1H), 2.75 (m, 1H), 2.07–1.95 (m, 4H), 1.84 (m, 1H), 1.66 (m, 1H), 1.52 (ddd, *J* = 12.4, 12.4, 12.4 Hz, 1H), 1.34 (ddd, *J* = 11.6, 11.6, 11.6 Hz, 1H), 1.26 (m, 1H), 1.08 (s, 9H), 1.07–1.03 (m, 21H), 0.98–0.95 (m, 6H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.88 (t, *J* = 7.8 Hz, 9H), 0.85 (s, 3H), 0.53 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.2, 159.0, 135.7 (4C), 133.14, 133.08, 130.8, 129.8 (2C), 129.1 (2C), 127.7 (4C), 113.7 (2C), 100.1, 78.1, 77.0, 74.8, 72.9, 72.6, 71.2, 67.3, 66.4, 55.2, 49.0, 44.2, 42.6, 41.9, 38.0, 36.7, 36.2, 33.4, 26.9 (3C), 19.5, 19.04, 18.99, 18.3 (3C), 18.2 (3C), 14.2, 13.4, 12.8 (3C), 6.9 (3C), 5.1 (3C); HRMS (ESI) calcd for $C_{60}H_{98}O_9Si_3Na$ [$(M + Na)^+$] 1069.6411; found 1069.6400.

*Ketone **34** from alcohol **33b**.* To a suspension of alcohol **33b** (110.8 mg, 0.1056 mmol) and activated 4 Å molecular sieves (110.2 mg) in CH_2Cl_2/MeCN (2:1, v/v, 1.05 mL) were added NMO (52.2 mg, 0.446 mmol) and TPAP (9.6 mg, 0.027 mmol), and the resultant mixture was stirred at room temperature for 14 h 35 min. The reaction mixture was filtered through a pad of Celite (eluted with 10% EtOAc/hexanes), and the filtrate was concentrated under reduced pressure. Purification of

the residue by flash column chromatography (silica gel, 3% to 4% EtOAc/hexanes) gave ketone **34** (85.6 mg, 77%) as a colorless oil.

*(2R,4R,6R)-6-((S)-4-((tert-Butyldiphenylsilyl)oxy)-3-hydroxy-2-methylbutan-2-yl)-2-(((2S, 4S,5S,6S)-6-(2-hydroxyethyl)-5-methyl-4-((triisopropylsilyl)oxy)tetrahydro-2H-pyran-2-yl)-methyl)-2-methoxy-4-methyldihydro-2H-pyran-3(4H)-one (**35**).* To a solution of TES ether **34** (355.4 mg, 0.3392 mmol) in CH_2Cl_2/MeOH (2:1, v/v, 3.6 mL) at 0 °C was added CSA (8.3 mg, 0.036 mmol), and the resultant solution was stirred at room temperature for 3 h 35 min. The reaction was quenched with saturated aqueous $NaHCO_3$ solution at 0 °C. The resultant mixture was extracted with EtOAc, washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude alcohol as a colorless amorphous solid. This material was used in the next reaction without purification.

To a solution of the above alcohol in CH_2Cl_2/pH 7 buffer (10:1, v/v, 3.41 mL) at 0 °C was added DDQ (93.2 mg, 0.411 mmol), and the resultant solution was stirred at room temperature for 2 h 10 min. The reaction was quenched with saturated aqueous Na_2SO_3 solution. The resultant mixture was extracted with EtOAc, and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10% to 15% EtOAc/hexanes) gave diol **35** (231.5 mg, 84% for the two steps) as a colorless amorphous solid: $[\alpha]_D^{26}$ +17.2 (*c* 1.00, $CHCl_3$); IR (film) 3448, 2943, 2866,

1731, 1464, 1428, 1390, 1232, 1112, 1069, 882, 822, 757, 703 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.74–7.71 (m, 2H), 7.71–7.68 (m, 2H), 7.45–7.35 (m, 6H), 4.47 (dd, *J* = 11.9, 1.4 Hz, 1H), 3.85–3.80 (m, 2H), 3.79–3.74 (m, 2H), 3.69 (dd, *J* = 10.5, 7.8 Hz, 1H), 3.63 (m, 1H), 3.47 (ddd, *J* = 10.3, 10.3, 4.4 Hz, 1H), 3.17 (s, 3H), 3.17 (m, 1H, overlapped), 2.89 (m, 1H), 2.10 (dd, *J* = 15.2, 8.8 Hz, 1H), 1.97 (ddd, *J* = 12.8, 5.5, 1.8 Hz, 1H), 1.92 (ddd, *J* = 12.8, 4.6, 1.9 Hz, 1H), 1.81 (m, 1H), 1.78 (dd, *J* = 15.6, 3.2 Hz, 1H), 1.62 (m, 1H), 1.58 (ddd, *J* = 12.8, 12.8, 12.8 Hz, 1H), 1.42 (ddd, *J* = 11.5, 11.5, 11.5 Hz, 1H), 1.30 (m, 1H), 1.08–1.05 (m, 21H), 1.05 (s, 9H), 1.04 (d, *J* = 6.4 Hz, 3H), 0.88 (d, *J* = 6.4 Hz, 3H), 0.82 (s, 3H), 0.75 (s, 3H), two proton missing due to H/D exchange; ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.2, 135.66 (2C), 135.58 (2C), 133.6, 133.4, 129.7 (2C), 127.7 (2C), 127.6 (2C), 100.0, 82.2, 74.9, 74.0, 73.6, 70.9, 65.4, 61.8, 50.1, 44.1, 42.5, 39.6, 38.5, 36.2, 35.2, 34.4, 26.9 (3C), 19.2, 19.1, 18.6, 18.3 (3C), 18.2 (3C), 14.3, 13.3, 12.8 (3C); HRMS (ESI) calcd for $C_{46}H_{76}O_8Si_2Na$ $[(M + Na)^+]$ 835.4971; found 835.5000.

*2-((2S,3S,4S,6S)-6-(((2R,4R,6R)-6-((S)-4-((tert-Butyldiphenylsilyl)oxy)-3-hydroxy-2-methylbutan-2-yl)-2-methoxy-4-methyl-3-oxotetrahydro-2H-pyran-2-yl)methyl)-3-methyl-4-((triisopropylsilyl)oxy)tetrahydro-2H-pyran-2-yl)acetic acid (**36**).* To a solution of diol **35** (227.5 mg, 0.2797 mmol) in CH_2Cl_2/H_2O (10:1, v/v, 2.86 mL) at 0 °C were added $PhI(OAc)_2$ (452.1 mg, 1.404 mmol) and TEMPO (9.0 mg, 0.058 mmol), and the resultant solution was stirred at room temperature for 6.5 h. The reaction was quenched with saturated aqueous Na_2SO_3 solution.

The resultant mixture was extracted with EtOAc, and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10% to 20% to 30% EtOAc/hexanes) gave carboxylic acid **36** (224.6 mg, 97%) as a colorless amorphous solid: $[\alpha]_D^{25}$ −1.5 (*c* 1.00, $CHCl_3$); IR (film) 2941, 2865, 1734, 1464, 1428, 1112, 1066, 882, 824, 703 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.71–7.67 (m, 4H), 7.46–7.37 (m, 6H), 4.20 (dd, *J* = 11.9, 1.8 Hz, 1H), 3.79 (dd, *J* = 10.1, 3.6 Hz, 1H), 3.76 (dd, *J* = 7.4, 3.6 Hz, 1H), 3.68 (dd, *J* = 10.1, 7.4 Hz, 1H), 3.55 (m, 1H), 3.48 (ddd, *J* = 10.5, 10.5, 4.6 Hz, 1H), 3.32 (m, 1H), 3.17 (s, 3H), 2.92 (m, 1H), 2.77 (dd, *J* = 14.7, 3.7 Hz, 1H), 2.50 (dd, *J* = 14.7, 6.9 Hz, 1H), 2.01 (dd, *J* = 15.1, 7.8 Hz, 1H), 1.97 (ddd, *J* = 13.3, 5.5, 1.8 Hz, 1H), 1.95–1.90 (m, 2H), 1.63 (ddd, *J* = 12.7, 12.7, 12.7 Hz, 1H), 1.48–1.38 (m, 2H), 1.08–1.04 (m, 30H), 1.05 (d, *J* = 6.9 Hz, 3H overlapped), 0.99 (d, *J* = 6.4 Hz, 3H), 0.90 (s, 3H), 0.80 (s, 3H), two protons missing due to H/D exchange; ^{13}C NMR (150 MHz, $CDCl_3$) δ□205.9, 172.0, 135.65 (2C), 135.58 (2C), 133.3, 133.0, 129.8 (2C), 127.75 (2C), 127.73 (2C), 100.2, 78.0, 76.4, 75.3, 73.7, 71.8, 65.0, 49.5, 43.6, 42.3, 39.1, 39.0, 38.3, 36.4, 36.3, 26.8 (3C), 20.3, 19.9, 19.1, 18.22 (3C), 18.16 (3C), 14.1, 13.3, 12.8 (3C); HRMS (ESI) calcd for $C_{46}H_{74}O_9Si_2Na$ [$(M + Na)^+$] 849.4764; found 849.4742.

(1S,3R,5R,7R,9S,13S,14S,15S)-9-(((tert-Butyldiphenylsilyl)oxy)methyl)-3-methoxy-5,8,8,14-tetramethyl-15-((triisopropylsilyl)oxy)-10,17,18-trioxatricyclo[11.3.1.1^{3,7}]octadecane-4,

*11-dione (**37**)*. To a solution of DCC (552.8 mg, 2.679 mmol) and PPTS (672.3 mg, 2.675 mmol) in DCE (165 mL) at 100 °C were added pyridine (2.20 mL, 27.3 mmol) followed by a solution of seco acid **36** (219.2 mg, 0.2650 mmol) in DCE (80 mL + 10 mL and 10 mL rinse) over a period of 3 h. The resultant solution was stirred at 100 °C for another 2 h. The solution was cooled to room temperature, diluted with CH_2Cl_2, and concentrated under reduced pressure. The residue was roughly purified by column chromatography (silica gel, EtOAc) to give a crude material. Purification of this material by flash column chromatography (silica gel, 2% to 3% to 4% EtOAc/hexanes) gave macrolide **37** (191.1 mg, 89%) as a colorless amorphous solid: $[\alpha]_D^{23}$ −10.8 (*c* 1.00, $CHCl_3$); IR (film) 2941, 2866, 1731, 1463, 1365, 1309, 1249, 1166, 1113, 1093, 1021, 825, 703 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.71–7.68 (m, 2H), 7.67–7.64 (m, 2H), 7.45–7.36 (m, 6H), 5.27 (dd, *J* = 5.5, 5.5 Hz, 1H), 3.75–3.72 (m, 2H), 3.64 (m, 1H), 3.53 (ddd, *J* = 10.5, 10.5, 4.6 Hz, 1H), 3.45 (dd, *J* = 10.6, 10.5 Hz, 1H), 3.26 (s, 3H), 3.25 (ddd, *J* = 11.5, 11.5, 2.3 Hz, 1H), 2.80 (m, 1H), 2.44 (dd, *J* = 11.5, 2.3 Hz, 1H), 2.32 (dd, *J* = 11.5, 11.5 Hz, 1H), 1.94–1.81 (m, 5H), 1.41–1.33 (m, 2H), 1.20 (s, 3H), 1.07 (d, *J* = 6.9 Hz, 3H), 1.08–1.05 (m, 21H), 1.01 (s, 9H), 0.95 (d, *J* = 6.4 Hz, 3H), 0.81 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ□205.7, 172.8, 135.8 (2C), 135.6 (2C), 133.3 (2C), 129.7, 129.6, 127.67 (2C), 127.65 (2C), 100.6, 79.6, 78.8 (br), 74.7 (br), 74.5, 70.9, 63.6, 47.8, 44.0, 42.3, 40.2, 39.4, 39.2, 36.9 (br), 35.0 (br), 26.7 (3C), 25.1 (br), 20.5 (br), 19.0, 18.3 (3C), 18.2 (3C), 14.2, 13.1, 12.8 (3C); HRMS (ESI) calcd for $C_{46}H_{72}O_8Si_2Na$ [(M +

Na)$^{+}$] 831.4658; found 831.4680.

*(1S,3R,5R,7R,9S,13S,14S,15S)-9-(Hydroxymethyl)-3-methoxy-5,8,8,14-tetramethyl-15-((triisopropylsilyl)oxy)-10,17,18-trioxatricyclo[11.3.1.1^{3,7}]octadecane-4,11-dione (**38**).* To a solution of macrolide **37** (183.7 mg, 0.2270 mmol) in THF (3 mL) at 0 °C were added pyridine (0.9 mL) and HF·pyridine (0.3 mL), and the resultant solution was stirred at 0 °C for 1.5 h and then at room temperature for 4 h 55 min. The solution was poured into saturated aqueous $NaHCO_3$ solution, and the resultant mixture was stirred at room temperature for 1 h 25 min. The resultant mixture was extracted with EtOAc, and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 3% to 30% to 40% EtOAc/hexanes) gave primary alcohol **38** (108.3 mg, 85%) as a colorless amorphous solid, along with the starting **37** (21.3 mg, 12%). Data for **38**: $[\alpha]_D^{26}$ −9.2 (*c* 1.00, $CHCl_3$); IR (film) 3451, 2942, 2868, 1730, 1463, 1373, 1313, 1248, 1165, 1092, 1022, 882, 826, 755, 679 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.20 (br d, *J* = 5.1 Hz, 1H), 3.81 (br d, *J* = 12.0 Hz, 1H), 3.71 (br d, *J* = 11.5, 1H), 3.65 (m, 1H), 3.50 (ddd, *J* = 10.1, 10.1, 4.6 Hz, 1H), 3.42 (dd, *J* = 11.0, 10.1 Hz, 1H), 3.27 (s, 3H), 3.22 (ddd, *J* = 11.5, 10.8, 1.9 Hz, 1H), 2.84 (m, 1H), 2.53 (dd, *J* = 11.5, 1.9 Hz, 1H), 2.32 (dd, *J* = 11.5, 11.5 Hz, 1H), 2.00 (dd, *J* = 12.8, 5.0 Hz, 1H), 1.91–1.71 (m, 5H), 1.37–1.29 (m, 2H), 1.25 (s, 3H), 1.05 (d, *J* = 6.9 Hz, 3H), 1.07–1.02 (m, 21H), 0.97 (s, 3H), 0.93 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ□205.6,

173.6, 100.6, 79.3, 78.5 (br), 75.2 (br), 74.4, 70.8, 62.9, 47.9, 44.0, 42.2, 40.0, 39.34, 39.28, 36.7 (br), 35.3 (br), 25.0 (br), 20.5 (br), 18.23 (3C), 18.16 (3C), 14.1, 13.1, 12.8 (3C); HRMS (ESI) calcd for $C_{30}H_{54}O_8SiNa$ [$(M + Na)^+$] 593.3480; found 593.3482.

(1S,3R,5R,7R,9S,13S,14S,15S)-3-Methoxy-5,8,8,14-tetramethyl-4,11-dioxo-15-((triisopropylsilyl)oxy)-10,17,18-trioxatricyclo[11.3.1.1^{3,7}]octadecane-9-carbaldehyde (***39***).

To a solution of alcohol **38** (97.5 mg, 0.171 mmol) in CH_2Cl_2 (1.7 mL) at 0 °C were added $NaHCO_3$ (44.0 mg, 0.524 mmol) and Dess–Martin periodinane (109.4 mg, 0.2579 mmol), and the resultant mixture was stirred at room temperature for 6 h 20 min. The reaction was quenched with a 1:1 mixture of saturated aqueous $NaHCO_3$ solution and saturated aqueous Na_2SO_3 solution. The resultant mixture was extracted with *t*-BuOMe, and the organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10% to 20% EtOAc/hexanes) gave aldehyde **39** (85.4 mg, 88%) as a colorless amorphous solid: $[\alpha]_D^{26}$ −22.0 (*c* 0.64, $CHCl_3$); IR (film) 2943, 2867, 1733, 1462, 1372, 1251, 1165, 1092, 881, 827, 755, 679 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.62 (s, 1H), 5.17 (br s, 1H), 3.78 (br d, *J* = 11.5 Hz, 1H), 3.51 (ddd, *J* = 10.1, 9.6, 4.6 Hz, 1H), 3.38 (m, 1H), 3.27 (s, 3H), 3.19 (ddd, *J* = 11.9, 9.6, 2.3 Hz, 1H), 2.91 (m, 1H), 2.58 (dd, *J* = 11.9, 2.3 Hz, 1H), 2.44 (dd, *J* = 11.9, 11.9 Hz, 1H), 2.10 (dd, *J* = 12.4, 5.6 Hz, 1H), 1.92–1.86 (m, 3H), 1.66 (ddd, *J* = 12.4, 12.4, 12.4 Hz, 1H), 1.40–1.29 (m, 2H), 1.27 (s, 3H), 1.15 (s, 3H), 1.06 (d, *J* = 6.9 Hz, 3H),

1.07–1.01 (m, 21H), 0.94 (d, J = 6.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ□205.3, 198.7, 172.3, 100.6, 79.6 (br), 78.9, 77.5 (br), 74.3, 71.1, 48.2, 44.2, 42.2, 40.2, 39.4, 38.8, 36.4 (br), 35.9 (br), 23.6 (br), 21.5 (br), 18.24 (3C), 18.16 (3C), 14.1, 13.1, 12.8 (3C); HRMS (ESI) calcd for $C_{30}H_{52}O_8SiNa$ [$(M + Na)^+$] 591.3324; found 591.3323.

*(1S,3R,5R,7R,9R,13S,14S,15S)-9-((E)-2-Iodovinyl)-3-methoxy-5,8,8,14-tetramethyl-15-((triisopropylsilyl)oxy)-10,17,18-trioxatricyclo[11.3.1.1^{3,7}]octadecane-4,11-dione (**40**).* To a suspension of $CrCl_2$ (977.9 mg, 7.957 mmol) in THF (4 mL) at 0 °C was added a solution of aldehyde **39** (90.6 mg, 0.159 mmol) and CHI_3 (1.566 g, 3.977 mmol) in THF (2 mL + 1 mL and 1 mL rinse), and the resultant mixture was stirred at room temperature for 2 h 50 min. The reaction was quenched with saturated aqueous Na_2SO_3 solution. The resultant mixture was extracted with EtOAc, and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, first round, 1% EtOAc/hexanes containing 1% Et_3N; second round, 1% EtOAc/hexanes containing 1% Et_3N) gave (*E*)-vinyl iodide **40** (89.3 mg, 81%, *E/Z* >20:1) as a colorless amorphous solid: $[\alpha]_D^{27}$ −31.4 (*c* 0.74, $CHCl_3$); IR (film) 2942, 2867, 1737, 1714, 1456, 1373, 1320, 1247, 1162, 1096, 1026, 998, 882, 829, 680 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.52 (dd, J = 14.2, 7.8 Hz, 1H), 6.38 (d, J = 14.2 Hz, 1H), 5.44 (br d, J = 7.8 Hz, 1H), 3.79 (br d, J = 12.4 Hz, 1H), 3.50 (ddd, J = 10.1, 10.1, 4.6 Hz, 1H), 3.40 (br dd, J = 10.6, 10.6 Hz, 1H), 3.27 (s, 3H), 3.18 (br dd, J = 11.5, 10.1 Hz,

1H), 2.84 (m, 1H), 2.47 (br d, *J* = 11.5 Hz, 1H), 2.26 (dd, *J* = 11.5, 11.5 Hz, 1H), 2.02 (dd, *J* = 12.4, 5.5 Hz, 1H), 1.90–1.79 (m, 3H), 1.71 (ddd, *J* = 12.4, 12.4, 12.4 Hz, 1H), 1.37–1.28 (m, 2H), 1.23 (br s, 3H), 1.05 (d, *J* = 6.4 Hz, 3H), 1.05–1.02 (m, 21H), 0.92 (d, *J* = 6.4 Hz, 3H), 0.88 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.4, 172.1, 141.8, 100.5, 80.9, 79.3, 77.6 (br), 76.5 (br), 74.3, 70.8, 47.8, 44.1, 42.2, 40.1, 39.8, 39.3, 36.8 (br), 35.3 (br), 25.3 (br), 19.7 (br), 18.23 (3C), 18.15 (3C), 14.1, 13.1, 12.8 (3C); HRMS (ESI) calcd for $C_{31}H_{53}O_7ISiNa$ [$(M + Na)^+$] 715.2497; found 715.2496.

*(1S,4R,5R,7R,9R,13S,14R,15S)-4,15-Dihydroxy-9-((E)-2-iodovinyl)-5,8,8,14-tetramethyl-10,17,18-trioxatricyclo[11.3.1.1^{4,7}]octadecane-3,11-dione (**4**).* To a solution of TIPS ether **40** (67.7 mg, 0.0977 mmol) in THF/H_2O (1:1, v/v, 3.6 mL) at room temperature was added TFA (0.9 mL), and the resultant solution was stirred at room temperature for 42 h 10 min. The reaction was quenched with a 1:1 mixture of saturated aqueous $NaHCO_3$ solution and brine. The resultant mixture was stirred at room temperature for 1 h. The resultant mixture was extracted with EtOAc, and the organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 40% to 50% EtOAc/hexanes containing 1% Et_3N) gave alcohol **4** (49.8 mg, 98%) as a colorless amorphous solid: $[\alpha]_D^{25}$ −49.1 (*c* 1.00, $CHCl_3$); IR (film) 3470, 2969, 2934, 2878, 1713, 1606, 1377, 1309, 1232, 1164, 1128, 1071, 1015, 754 cm^{-1}; ^{1}H NMR (600 MHz, CD_3CN) δ 6.52 (dd, *J* = 14.3, 7.4 Hz,

1H), 6.39 (dd, *J* = 14.3, 0.9 Hz, 1H), 4.94 (dd, *J* = 7.4, 0.9 Hz, 1H), 4.61 (br s, 1H), 4.03 (dd, *J* = 11.5, 5.0 Hz, 1H), 3.64 (m, 1H), 3.27–3.21 (m, 2H), 2.97 (dd, *J* = 13.7, 9.2 Hz, 1H), 2.76 (m, 1H), 2.53 (dd, *J* = 12.8, 2.7 Hz, 1H), 2.15 (dd, *J* = 12.9, 11.5 Hz, 1H), 2.06 (dd, *J* = 13.7, 1.0 Hz, 1H), 1.99 (ddd, *J* = 11.9, 6.9, 5.0 Hz, 1H), 1.86 (ddd, *J* = 11.9, 4.6, 1.8 Hz, 1H), 1.56 (ddd, *J* = 11.9, 11.5, 11.5 Hz, 1H), 1.25 (ddd, *J* = 11.9, 11.5, 11.5 Hz, 1H), 1.06 (m, 1H), 0.89 (d, *J* = 6.4 Hz, 3H), 0.86 (d, *J* = 6.9 Hz, 3H), 0.802 (s, 3H), 0.799 (s, 3H); ^{13}C NMR (150 MHz, CD_3CN) δ207.3, 172.2, 142.6, 103.9, 83.4, 81.6, 80.1, 79.8, 75.0, 72.5, 44.4, 42.7, 42.3, 40.4, 39.7, 39.4, 34.2, 19.4, 17.7, 13.6, 12.8; HRMS (ESI) calcd for $C_{21}H_{31}IO_7Na$ [$(M + Na)^+$] 545.1007; found 545.1024.

*Glycoside **41**.* To a suspension of alcohol **4** (3.5 mg, 6.7 μmol), disaccharide thioglycoside **5a** (8.4 mg, 15.7 μmol), and activated 4 Å molecular sieves (35.0 mg) in MeCN (0.6 mL) at –40 °C was added a solution of NBS (6.0 mg, 34 μmol) in MeCN (0.4 mL). The resultant mixture was stirred at –40 °C for 30 min then allowed to warm to –20 °C and stirred at –20 °C for 1 h 35 min. The reaction mixture was then allowed to warm to –10 °C and stirred at –10 °C for 55 min. The reaction was quenched with Et_3N. The resultant mixture was extracted with EtOAc, and the organic layer was washed with saturated aqueous Na_2SO_3 solution and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, first round, 10% to 20% to 30% to 50% to 80% EtOAc/hexanes; second round, 14% acetone/hexanes) gave glycoside **41** (2.6 mg, 41%) as a colorless amorphous

solid: $[\alpha]_D^{24}$ –71.8 (*c* 0.75, $CHCl_3$); IR (film) 3481, 2972, 2932, 1736, 1714, 1456, 1371, 1321, 1166, 1097, 1038, 755 cm^{-1}; ^1H NMR (600 MHz, CD_3CN) δ 7.37–7.23 (m, 5H), 6.52 (dd, *J* = 14.2, 7.3 Hz, 1H), 6.39 (d, *J* = 14.2 Hz, 1H), 5.21 (d, *J* = 3.2 Hz, 1H), 4.93 (d, *J* = 7.3 Hz, 1H), 4.80 (d, *J* = 11.5 Hz, 1H), 4.60 (s, 1H), 4.52 (d, *J* = 11.5 Hz, 1H), 4.31 (d, *J* = 7.8 Hz, 1H), 4.14 (br q, *J* = 6.4 Hz, 1H), 4.02 (dd, *J* = 11.4, 5.0 Hz, 1H), 3.93 (dd, *J* = 11.0, 5.0 Hz, 1H), 3.73 (br s, 1H), 3.63 (br dd, *J* = 11.9, 9.2 Hz, 1H), 3.50–3.39 (m, 3H, overlapped) 3.48 (s, 3H), 3.41 (s, 3H), 3.40 (s, 3H), 3.34–3.26 (m, 2H, overlapped), 3.31 (s, 3H), 3.12 (ddd, *J* = 10.1, 10.1, 5.0 Hz, 1H), 3.06 (dd, *J* = 10.1, 10.1 Hz, 1H), 2.95 (dd, *J* = 13.7, 9.2 Hz, 1H), 2.87 (dd, *J* = 9.2, 7.8 Hz, 1H), 2.75 (m, 1H), 2.54 (dd, *J* = 12.8, 2.8 Hz, 1H), 2.15 (dd, *J* = 12.6, 11.2 Hz, 1H), 2.08 (br d, *J* = 13.7 Hz, 1H), 2.04 (ddd, *J* = 11.9, 4.6, 2.3 Hz, 1H), 1.98 (m, 1H), 1.55 (ddd, *J* = 11.8, 11.8, 11.4 Hz, 1H), 1.36 (ddd, *J* = 11.9, 11.9, 11.9 Hz, 1H), 1.27 (m, 1H), 1.04 (d, *J* = 6.4 Hz, 3H), 0.92 (d, *J* = 6.4 Hz, 3H), 0.89 (d, *J* = 6.4 Hz, 3H), 0.80 (s, 6H); ^{13}C NMR (150 MHz, CD_3CN) δ 207.2, 172.1, 142.6, 140.3, 129.1 (2C), 128.9 (2C), 128.3, 106.2, 103.9, 98.0, 85.4, 83.4, 82.6, 81.6, 81.3, 80.2, 79.8, 79.2, 78.9, 78.8, 78.2, 75.6, 74.8, 66.8, 63.6, 60.8, 58.8, 58.5, 58.1, 43.0, 42.7, 41.5, 40.3, 39.7, 39.4, 34.2, 19.4, 17.7, 16.8, 13.6, 12.8; HRMS (ESI) calcd for $C_{43}H_{63}IO_{15}Na$ $[(M + Na)^+]$ 969.3104; found 969.3072.

*Alcohol **42**.* To a solution of glycoside **41** (7.5 mg, 7.9 μmol) in CH_2Cl_2 (0.8 mL) and H_2O (0.15 mL) was added DDQ (49.0 mg, 0.216 mmol), and the resultant solution was stirred at room

temperature for 17 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution. The resultant mixture was extracted with CH_2Cl_2, and the organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10% to 20% to 30% acetone/hexanes) gave alcohol **42** (5.3 mg, 78%) as a colorless amorphous solid: $[\alpha]_D^{22}$ –70.4 (*c* 0.53, $CHCl_3$); IR (film) 3481, 2972, 2932, 1736, 1714, 1458, 1372, 1321, 1168, 1099, 1038, 754 cm^{-1}; ^1H NMR (600 MHz, CD_3CN) δ 6.52 (dd, *J* = 14.4, 7.2 Hz, 1H), 6.39 (dd, *J* = 14.4, 0.7 Hz, 1H), 5.21 (d, *J* = 3.4 Hz, 1H), 4.93 (d, *J* = 7.2 Hz, 1H), 4.60 (s, 1H), 4.31 (d, *J* = 7.6 Hz, 1H), 4.13 (br q, *J* = 6.5 Hz, 1H), 4.02 (dd, *J* = 11.4, 5.2 Hz, 1H), 3.93 (dd, *J* = 11.2, 5.0 Hz, 1H), 3.79 (m, 1H), 3.63 (br dd, *J* = 11.7, 9.1 Hz, 1H), 3.48 (s, 3H), 3.43 (dd, *J* = 10.0, 9.2 Hz, 1H), 3.38 (s, 3H), 3.38–3.21 (m, 3H, overlapped), 3.34 (s, 3H), 3.31 (s, 3H), 3.29 (ddd, *J* = 11.3, 10.2, 2.7 Hz, 1H), 3.12 (ddd, *J* = 10.0, 10.1, 5.0 Hz, 1H), 3.07 (dd, *J* = 11.2, 10.0 Hz, 1H), 2.96 (dd, *J* = 13.7, 9.1 Hz, 1H), 2.87 (dd, *J* = 9.2, 7.6 Hz, 1H), 2.75 (m, 1H), 2.67 (dd, *J* = 3.1, 0.7 Hz, 1H), 2.55 (dd, *J* = 12.7, 2.7 Hz, 1H), 2.16 (dd, *J* = 12.7, 11.3 Hz, 1H), 2.08 (br d, *J* = 13.7 Hz, 1H), 2.05 (ddd, *J* = 12.7, 4.6, 1.9 Hz, 1H), 1.99 (ddd, *J* = 11.7, 6.9, 5.2 Hz, 1H), 1.56 (ddd, *J* = 11.7, 11.7, 11.4 Hz, 1H), 1.36 (ddd, *J* = 12.7, 11.7, 11.7 Hz, 1H), 1.28 (m, 1H), 1.07 (d, *J* = 6.5 Hz, 3H), 0.92 (d, *J* = 6.2 Hz, 3H), 0.89 (d, *J* = 6.5 Hz, 3H), 0.80 (s, 6H); ^{13}C NMR (150 MHz, CD_3CN) δ 207.2, 172.1, 142.6, 106.2, 103.9, 97.8, 85.4, 83.4, 82.6, 81.6, 80.2, 79.9, 79.8, 79.3, 78.9, 78.1, 74.8, 69.3, 66.1, 63.6, 60.8, 58.8, 58.5, 57.0, 43.0, 42.7, 41.5, 40.3, 39.7,

39.4, 34.2, 19.4, 17.7, 16.4, 13.6, 12.8; HRMS (ESI) calcd for $C_{36}H_{57}IO_{15}Na$ [$(M + Na)^+$] 879.2634; found 879.2652.

*Polycavernoside A (**1**).* To a solution of alcohol **42** (1.6 mg, 1.9 μmol) and dienylstannane **6a** (17.4 mg, 45.2 μmol) in degassed DMF (0.5 mL) was added a solution of $PdCl_2(MeCN)_2$ (0.01 M solution in degassed DMF, 50 μL, 0.5 μmol), and the resultant solution was stirred at room temperature for 12 h. The reaction was quenched with H_2O. The resultant mixture was extracted with Et_2O, and the organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, first round, 0% to 30% acetone/hexanes; second round, 0% to 20% acetone/hexanes) gave polycavernoside A (**1**) (0.7 mg, 45%). Further purification by reverse phase HPLC [COSMOSIL 5C18-AR-II (20 mm ID × 400 mm), solvent: 80% MeCN/H_2O; flow rate: 6.0 mL/min] gave pure **1** as a white solid: $[\alpha]_D^{23}$ –47.2 (*c* 0.07, MeCN); IR (film) 2961, 2929, 1733, 1716, 1541, 1457, 1169, 1098, 1038, 997 cm^{-1}; ^1H NMR (600 MHz, CD_3CN) δ 6.20–6.14 (m, 2H), 6.11 (dd, *J* = 15.1, 10.3 Hz, 1H), 6.02 (ddd, *J* = 15.1, 10.3, 1.0 Hz, 1H), 5.69 (dd, *J* = 15.1, 6.9 Hz, 1H), 5.58 (dd, *J* = 15.2, 7.6 Hz, 1H), 5.21 (d, *J* = 3.8 Hz, 1H), 5.00 (d, *J* = 7.6 Hz, 1H), 4.58 (d, *J* = 0.7 Hz, 1H), 4.32 (d, *J* = 7.5 Hz, 1H), 4.14 (br q, *J* = 6.9 Hz, 1H), 4.05 (dd, *J* = 11.4, 5.2 Hz, 1H), 3.93 (dd, *J* = 11.0, 4.8 Hz, 1H), 3.80 (m, 1H), 3.64 (br dd, *J* = 11.0, 9.0 Hz, 1H), 3.48 (s, 3H), 3.44 (dd, *J* = 9.3, 8.6 Hz, 1H), 3.38 (s, 3H), 3.37–3.31 (m, 3H, overlapped), 3.34 (s, 3H), 3.31 (s, 3H), 3.30 (ddd, *J* = 11.0, 11.0, 2.9 Hz, 1H), 3.13 (ddd, *J* =

10.0, 8.6, 4.8 Hz, 1H), 3.07 (dd, *J* = 11.0, 10.0 Hz, 1H), 2.97 (dd, *J* = 13.7, 7.5 Hz, 1H), 2.88 (dd, *J* = 9.3, 7.5 Hz, 1H), 2.76 (m, 1H), 2.67 (dd, *J* = 3.3, 0.9 Hz, 1H), 2.52 (dd, *J* = 12.6, 2.9 Hz, 1H), 2.30 (m, 1H), 2.15 (dd, J = 12.6, 11.0 Hz, 1H), 2.12–2.03 (m, 2H), 1.99 (ddd, *J* = 11.7, 6.8, 5.2 Hz, 1H), 1.56 (ddd, *J* = 11.7, 11.7, 11.4 Hz, 1H), 1.36 (ddd, *J* = 11.8, 11.8, 11.8 Hz, 1H), 1.28 (m, 1H), 1.07 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 6H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.79 (s, 3H), 0.78 (s, 3H); ^{13}C NMR (150 MHz, CD_3CN) δ 207.4, 172.1, 143.7, 135.3, 134.8, 130.6, 128.7, 128.1, 106.2, 103.9, 97.8, 85.4, 83.7, 82.7, 79.9, 79.8, 79.3, 78.9 (2C), 78.1, 74.8, 69.3, 66.1, 63.6, 60.8, 58.8, 58.5, 57.0, 43.0, 42.7, 41.5, 40.5, 40.2, 39.5, 34.3, 31.9, 22.4 (2C), 19.4, 17.9, 16.4, 13.6, 12.8; HRMS (ESI) calcd for $C_{43}H_{68}O_{15}Na$ [$(M + Na)^+$] 847.4450; found 847.4471.

*(2S,3R,4R,5S,6R)-3,4,5-Trimethoxy-2-methyl-6-(phenylthio)tetrahydro-2H-pyran (**43**).* To a solution of triol **45** (1.53 g, 5.97 mmol) in DMF (30 mL) at 0 °C was added NaH (60% in mineral oil, 1.07 g, 26.8 mmol), and the resultant mixture was stirred at room temperature for 25 min. To this mixture at 0 °C was added methyl iodide (2.20 mL, 35.3 mmol), and the resultant mixture was stirred at room temperature for 2 h 20 min. The reaction was quenched with saturated aqueous NH_4Cl solution at 0 °C. The mixture was extracted with Et_2O, and the organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10% to 30% EtOAc/hexanes) gave methyl ether **43** (1.68 g, 94%) as a colorless oil: $[\alpha]_D^{21}$ +15.1 (*c* 1.00,

$CHCl_3$); IR (film) 2979, 2831, 1479, 1439, 1271, 1156, 1129, 1045, 984, 863, 745 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.56–7.53 (m, 2H), 7.29–7.27 (m, 2H), 7.24–7.20 (m, 1H), 4.47 (d, *J* = 9.6 Hz, 1H), 3.60 (s, 3H), 3.59 (s, 3H), 3.53 (s, 3H), 3.50 (qd, *J* = 6.4, 0.9 Hz, 1H), 3.41 (m, 1H), 3.39 (dd, *J* = 9.6, 9.1 Hz, 1H), 3.20 (dd, *J* = 9.1, 3.2 Hz, 1H), 1.33 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 134.4, 131.6 (2C), 128.7 (2C), 127.1, 87.6, 86.1, 79.0, 78.5, 74.4, 61.8, 61.1, 58.3, 17.0; HRMS (ESI) calcd for $C_{15}H_{22}O_4SNa$ [$(M + Na)^+$] 321.1131; found 321.1139.

*(3R,4S,5R,6S)-5-Methoxy-6-(phenylthio)tetrahydro-2H-pyran-3,4-diol (**47**).* To a solution of alcohol **46** (2.63 g, 7.38 mmol) in DMF at 0 °C was added NaH (60% in mineral oil, 0.45 g, 11.3 mmol), and the resultant mixture was stirred at room temperature for 20 min. To this mixture at 0 °C was added methyl iodide (1.0 mL, 16 mmol), and the resultant mixture was stirred at 0 °C for 40 min. The reaction was quenched with saturated aqueous NH_4Cl solution. The resultant mixture was extracted with Et_2O. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give crude methyl ether (2.95 g) as a colorless amorphous solid. This material was immediately used in the next reaction without purification: ^1H NMR (600 MHz, $CDCl_3$) δ 7.55–7.51 (m, 2H), 4.32–7.27 (m, 3H), 4.47 (d, *J* = 9.2 Hz, 1H), 3.93 (dd, *J* = 11.0, 4.6 Hz, 1H), 3.77–3.70 (m, 2H), 3.59 (s, 3H), 3.37 (dd, *J* = 10.5, 9.2 Hz, 1H), 3.30 (s, 3H), 3.26 (s, 3H), 3.14 (dd, *J* = 9.2, 9.2 Hz, 1H), 1.32 (s, 3H), 1.27 (s, 3H).

To a solution of the above methyl ether (2.95 g) in CH_2Cl_2 (50 mL) was added TFA/H_2O (10:1,

v/v, 11 mL), and the resultant solution was stirred at room temperature for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution at 0 °C. The resultant mixture was stirred at room temperature for 20 min. The mixture was extracted with EtOAc, and the organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 30% to 50% to 60% to 70% EtOAc/hexanes) gave diol **47** (1.76 g, 93% for the two steps) as a pale yellow solid: $[\alpha]_D^{24}$ –69.7 (*c* 1.00, $CHCl_3$); IR (film) 2931, 2349, 1476, 1297, 1057, 947, 888, 742 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.53–7.50 (m, 2H), 7.33–7.26 (m, 3H), 4.77 (d, *J* = 7.8 Hz, 1H), 4.18 (dd, *J* = 11.4, 4.6 Hz, 1H), 3.70 (ddd, *J* = 8.3, 7.8, 4.6 Hz, 1H), 3.64 (dd, *J* = 7.8, 7.8 Hz, 1H), 3.62 (s, 3H), 3.35 (dd, *J* = 11.4, 8.3 Hz, 1H), 3.16 (dd, *J* = 7.8, 7.8 Hz, 1H), two protons missing due to H/D exchange; ^{13}C NMR (150 MHz, $CDCl_3$) δ 133.9, 131.6 (2C), 129.0 (2C), 127.6, 87.1, 81.8, 76.1, 69.4, 67.4, 60.5; HRMS (ESI) calcd for $C_{12}H_{16}O_4SNa$ [$(M + Na)^+$] 279.0662; found 279.0676.

*(3R,4S,5R,6S)-4-Hydroxy-5-methoxy-6-(phenylthio)tetrahydro-2H-pyran-3-yl pivalate (**44**).* To a solution of diol **47** (1.59 g, 6.20 mmol) in pyridine (30 mL) at –40 °C was added pivaloyl chloride (1.50 g, 12.2 mmol). The resultant solution was allowed to warm to –20 °C and stirred at the same temperature for 7 h 15 min. The reaction was quenched with H_2O at –20 °C. The resultant mixture was extracted with EtOAc, and the organic layer was washed with 1 M aqueous HCl solution and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure.

Purification of the residue by flash column chromatography (silica gel, 20 % EtOAc/hexanes) gave pivalate **44** (2.02 g, 96%) as a colorless oil: $[\alpha]_D^{21}$ –67.4 (*c* 1.00, $CHCl_3$); IR (film) 3460, 2973, 2933, 1732, 1479, 1282, 1161, 1119, 1052, 745, 691 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.54–7.51 (m, 2H), 7.33–7.26 (m, 3H), 4.81 (ddd, *J* = 9.2, 8.7, 5.5 Hz, 1H), 4.63 (d, *J* = 9.2 Hz, 1H), 4.14 (dd, *J* = 11.5, 5.5 Hz, 1H), 3.75 (dd, *J* = 9.2, 8.7 Hz, 1H), 3.64 (s, 3H), 3.29 (dd, *J* = 11.5, 9.1 Hz, 1H), 3.13 (dd, *J* = 8.7, 8.7 Hz, 1H), 1.20 (s, 9H), one proton missing due to H/D exchange; ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.4, 133.3, 132.0 (2C), 129.0 (2C), 127.7, 87.6, 82.0, 75.7, 71.1, 65.9, 61.0, 38.9, 27.0 (3C); HRMS (ESI) calcd for $C_{17}H_{24}O_5SNa$ [$(M + Na)^+$] 363.1237; found 363.1239.

*(3R,4S,5R,6S)-5-Methoxy-6-(phenylthio)-4-(((2S,3S,4R,5R,6S)-3,4,5-trimethoxy-6-methyl-tetrahydro-2H-pyran-2-yl)oxy)tetrahydro-2H-pyran-3-yl pivalate (**48**) and (3R,4S,5R,6S)-5-Methoxy-6-(phenylthio)-4-(((2R,3S,4R,5R,6S)-3,4,5-trimethoxy-6-methyl-tetrahydro-2H-pyran-2-yl)oxy)tetrahydro-2H-pyran-3-yl pivalate (**49**).* To a suspension of NIS (982.2 mg, 4.366 mmol) and activated 4 Å molecular sieves (2.54 g) in CH_2Cl_2 (30 mL) at –78 °C was added a solution of thioglycoside **43** (1.1734 g, 3.9323 mmol) and alcohol **44** (1.4402 g, 4.2305 mmol) in CH_2Cl_2 (5 mL + 1.5 mL and 1.5 mL rinse) followed by TfOH (20 μL, 0.23 mmol). The resultant mixture was stirred at –78 °C for 3.5 h. The reaction was quenched with Et_3N at 0 °C. To this mixture was added a 1:1 mixture of saturated aqueous $NaHCO_3$ and saturated aqueous Na_2SO_3

solution, and the resultant mixture was stirred at room temperature for 30 min. The mixture was filtered through a pad of Celite, and the filtrate was extracted with EtOAc. The organic layer was washed with H_2O and brine, dried over dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, first round: 2% to 3% acetone/benzene; second round: 2% acetone/benzene then EtOAc) gave α-linked disaccharide **48** (1.283 g, 62%) as a colorless amorphous solid, along with β-linked disaccharide **49** (0.1337 g, 7%) as a colorless amorphous solid. Data for **48** $[\alpha]_D^{23}$ –24.8 (*c* 1.00, $CHCl_3$); IR (film) 2979, 2830, 1729, 1479, 1279, 1157, 1099, 1040, 991, 745 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.52–7.49 (m, 2H), 7.31–7.23 (m, 3H), 5.31 (d, *J* = 3.2 Hz, 1H), 4.98 (d, *J* = 6.4 Hz, 1H), 4.86 (ddd, *J* = 6.4, 6.0, 4.2 Hz, 1H), 4.29 (dd, *J* = 12.4, 4.2 Hz, 1H), 4.07 (br q, *J* = 6.4 Hz, 1H), 3.93 (dd, *J* = 6.4, 6.4 Hz, 1H), 3.62 (dd, *J* = 10.6, 3.2 Hz, 1H), 3.59 (s, 3H), 3.57 (dd, *J* = 10.6, 2.8 Hz, 1H), 3.54 (s, 3H), 3.52 (s, 3H), 3.51 (s, 3H), 3.43 (m, 1H), 3.39 (dd, *J* = 6.4, 6.4 Hz, 1H), 3.36 (dd, *J* = 12.4, 6.0 Hz, 1H), 1.23 (d, *J* = 6.4 Hz, 3H), 1.19 (s, 9H).; ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.7, 134.6, 131.5 (2C), 128.9 (2C), 127.3, 97.3, 87.0, 80.7, 80.2, 79.2, 77.7, 75.8, 69.9, 67.1, 63.3, 61.8, 59.5, 58.9, 58.0, 38.8, 27.1 (3C), 16.6; HRMS (ESI) calcd for $C_{26}H_{40}O_9SNa$ $[(M + Na)^+]$ 551.2285; found 551.2290. Data for **49**: $[\alpha]_D^{22}$ –57.5 (*c* 1.00, $CHCl_3$); IR (film) 2977, 2932, 2831, 1731, 1480, 1281, 1162, 1116, 1092, 1067, 744 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.50–7.47 (m, 2H), 7.29–7.25 (m, 2H), 7.23–7.20 (m, 1H), 5.23 (d, *J* = 4.2 Hz, 1H), 4.77 (ddd, *J* = 4.6, 4.6, 3.5 Hz, 1H), 4.46 (dd, *J* = 12.6,

3.5 Hz, 1H), 4.44 (d, *J* = 7.8 Hz, 1H), 3.99 (dd, *J* = 4.6, 4.6 Hz, 1H), 3.62 (s, 3H), 3.60 (s, 3H), 3.52 (s, 3H), 3.53–3.47 (m, 3H), 3.45 (s, 3H), 3.35 (br d, *J* = 3.2 Hz, 1H), 3.30 (dd, *J* = 9.6, 7.8 Hz, 1H), 3.11 (dd, *J* = 9.6, 3.2 Hz, 1H), 1.31 (d, *J* = 6.4 Hz, 3H), 1.22 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.9, 135.7, 130.8 (2C), 128.8 (2C), 126.9, 102.7, 85.7, 84.3, 80.4, 79.2, 78.8, 73.1, 70.5, 68.5, 61.9, 61.1, 61.0, 58.9, 58.6, 38.8, 27.1 (3C), 16.5; HRMS (ESI) calcd for $C_{26}H_{40}O_9SNa$ [$(M + Na)^+$] 551.2285; found 551.2291.

*(3R,4S,5R,6S)-5-Methoxy-6-(phenylthio)-4-(((2S,3S,4R,5R,6S)-3,4,5-trimethoxy-6-methyl-tetrahydro-2H-pyran-2-yl)oxy)tetrahydro-2H-pyran-3-yl acetate (**5b**).* To a solution of disaccharide **48** (1.26 g, 2.39 mmol) in CH_2Cl_2 (15 mL) at –20 °C was added DIBALH (1.04 M solution in *n*-hexane, 5.0 mL, 5.2 mmol), and the resultant solution was stirred at –20 °C for 3 h 20 min. The reaction was quenched with MeOH. The resultant mixture was diluted with EtOAc and saturated aqueous potassium sodium tartrate solution and vigorously stirred at room temperature for 2 h. The mixture was extracted with EtOAc, and the organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 50% EtOAc/hexanes) gave alcohol **S1** (0.976 g, 92%) as a colorless solid: $[\alpha]_D^{21}$ –103.9 (*c* 0.50, $CHCl_3$); IR (neat) 2929, 2360, 1456, 1363, 1131, 1068, 1025, 739 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54–7.51 (m, 2H), 7.33–7.25 (m, 3H), 5.13 (d, *J* = 4.1 Hz, 1H), 4.67 (d, *J* = 8.7 Hz, 1H), 4.25 (br, 1H), 4.16 (dd, *J* = 11.9, 5.0 Hz, 1 H), 4.12 (br q, *J* = 6.4 Hz,

1H), 3.72 (dd, *J* = 10.1, 4.1 Hz, 1H), ca. 3.63 (m, 1H overlapped), 3.63 (s, 3H), 3.61 (s, 3H), 3.57 (dd, *J* = 10.1, 2.7 Hz, 1H), 3.53 (s, 3H), 3.51 (m, 1H), 3.49 (s, 3H), 3.47 (dd, *J* = 7.8, 7.3 Hz, 1H), 3.28 (dd, *J* = 11.9, 9.2 Hz, 1H), 3.19 (dd, *J* = 8.7, 7.8 Hz, 1H), 1.29 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 134.0, 131.8 (2C), 128.9 (2C), 127.5, 98.8, 87.8, 80.2, 79.7, 78.8, 77.2, 77.1, 68.8, 67.8 (2C), 61.8, 60.9, 58.1, 57.9, 16.5; HRMS (ESI) calcd for $C_{21}H_{32}O_8SNa$ [$(M + Na)^+$] 467.1710; found 467.1708.

To a solution of the above alcohol **S1** (0.976 g, 2.20 mmol) in pyridine (20 mL) at 0 °C was added acetic anhydride（0.80 mL, 8.5 mmol), and the resultant solution was stirred at 50 °C for 11.5 h. The reaction mixture was concentrated under reduced pressure. The residue was diluted with EtOAc, washed with washed with 1 M aqueous HCl solution, saturated aqueous $NaHCO_3$ solution, and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 40% EtOAc/hexanes) gave disaccharide **5b** (992.4 g, 93%) as a colorless amorphous solid: $[\alpha]_D^{22}$ –157.3 (*c* 1.00, $CHCl_3$); IR (film) 2933, 2831, 1742, 1367, 1236, 1132, 1092, 1041, 746 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53–7.50 (m, 2H), 7.32–7.24 (m, 3H), 5.28 (d, *J* = 3.7 Hz, 1H), 4.86 (ddd, *J* = 8.2, 7.8, 5.0 Hz, 1H), 4.72 (d, *J* = 8.3 Hz, 1H), 4.21 (dd, *J* = 11.9, 5.0 Hz, 1H), 3.98 (br q, *J* = 6.9 Hz, 1H), 3.86 (dd, *J* = 8.3, 7.8 Hz, 1H), 3.61 (dd, *J* = 10.6, 3.7 Hz, 1H), 3.61 (s, 3H), 3.59 (s, 3H), 3.53 (s, 3H), 3.52 (m, overlapped 1H), 3.51 (s, 3H), 3.43 (m, 1H), 3.31 (dd, *J* = 8.2, 7.8 Hz, 1H), 3.27 (dd, *J* = 11.9,

7.8 Hz, 1H), 2.06 (s, 3H), 1.23 (d, J = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.0, 133.6, 131.7 (2C), 128.8 (2C), 127.4, 98.0, 87.5, 81.4, 80.3, 79.0, 78.4, 77.5, 70.3, 66.6, 64.9, 61.7, 60.3, 59.2, 57.8, 20.9, 16.4; HRMS (ESI) calcd for $C_{23}H_{34}O_9SNa$ [$(M + Na)^+$] 509.1816; found 509.1808.

*Glycoside **50**.* To a solution of alcohol **4** (11.2 mg, 21.4 μmol) and disaccharide thioglycoside **5b** (25.8 mg, 53.0 μmol) in MeCN (0.6 mL) was added activated 4 Å molecular sieves (58.9 mg), and the resultant suspension was cooled to –40 ºC. To this mixture was added a solution of NBS (18.9 mg, 106 μmol) in MeCN (0.3 mL + 0.1 mL rinse), and the resultant suspension was stirred at –40 ºC for 10 min, allowed to warm to –10 ºC over 2 h 10 min, and stirred at –10 ºC for further 30 min. The reaction was quenched with Et_3N, and the resultant mixture was filtered through a pad of Celite (eluted with EtOAc). The filtrate was diluted with EtOAc and washed with saturated aqueous Na_2SO_3 solution and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10 to 20% acetone/hexanes) gave glycoside **50** (9.9 mg, 51%) as a colorless amorphous: $[\alpha]_D^{25}$ –77.9 (*c* 1.00, $CHCl_3$); IR (film) 3480, 3249, 2933, 1715, 1369, 1238, 1166, 1092, 1044, 753 cm^{-1}; ^{1}H NMR (600 MHz, CD_3CN) δ 6.52 (dd, J = 14.2, 7.3 Hz, 1H), 6.39 (d, J = 14.2 Hz, 1H), 5.24 (d, J = 2.3 Hz, 1H), 4.93 (d, J = 7.3 Hz, 1H), 4.60 (ddd, J = 9.7, 9.2, 5.5 Hz, 1H), 4.59 (s, 1H), 4.39 (d, J = 7.8 Hz, 1H), 4.02 (dd, J = 11.3, 5.4 Hz, 1H), 3.89 (br q, J = 6.9 Hz, 1H), 3.84 (dd, J =

11.9, 5.5 Hz, 1H), 3.68 (dd, *J* = 9.2, 9.2 Hz, 1H), 3.63 (br dd, *J* = 10.4, 10.4 Hz, 1H), 3.49 (s, 3H), 3.43 (s, 3H), ca. 3.42 (m, 1H, overlapped), 3.38 (s, 3H), 3.38–3.31 (m, 3H, overlapped), 3.26 (s, 3H), 3.29 (ddd, *J* = 10.4, 10.4, 2.7 Hz, 1H), 3.14 (dd, *J* = 11.9, 9.7 Hz, 1H), 2.99 (dd, *J* = 9.2, 7.8 Hz, 1H), 2.96 (dd, *J* = 13.8, 9.2 Hz, 1H), 2.75 (m, 1H), 2.55 (dd, *J* = 12.9, 2.8 Hz, 1H), 2.16 (dd, *J* = 12.4, 11.5 Hz, 1H), 2.09–2.03 (m, 2H), 1.99 (m, 1H), 1.96 (s, 3H), 1.55 (ddd, *J* = 11.9, 11.9, 11.9 Hz, 1H), 1.36 (ddd, *J* = 11.9, 11.9, 11.9 Hz, 1H), 1.28 (m, 1H), 1.10 (d, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 6.4 Hz, 3H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.80 (s, 6H); ^{13}C NMR (150 MHz, CD_3CN) δ 207.2, 172.1, 171.0, 142.6, 105.8, 103.9, 98.1, 85.1, 83.4, 82.7, 81.6, 80.7, 80.2, 79.8, 79.7, 78.4, 77.0, 74.8, 71.5, 67.0, 62.9, 61.6, 60.9, 59.0, 57.8, 43.0, 42.7, 41.4, 40.3, 39.7, 39.4, 34.2, 21.2, 19.4, 17.7, 16.7, 13.6, 12.8; HRMS (ESI) calcd for $C_{38}H_{59}IO_{16}Na$ [$(M + Na)^+$] 921.2740; found 921.2735.

*Polycavernoside B (**2**).* To a solution of vinyl iodide **50** (7.96 mg, 8.86 μmol) and vinylstannane **6b** (63.7 mg, 177 μmol) in degassed DMF (500 μL) was added $PdCl_2(MeCN)_2$ (0.01 M solution in degassed DMF, 200 μL, 2 μmol), and the resultant solution was stirred at room temperature in the dark for 14 h. The reaction mixture was diluted with *t*-BuOMe and washed with H_2O and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, first round, 5 to 20% acetone/hexanes; second round, 20% acetone/hexanes) gave polycavernoside B (**2**) (4.3 mg, 58%) as a colorless amorphous solid: $[\alpha]_D^{25}$ –66.8 (*c* 0.50, $CHCl_3$); IR (film) 3481, 2963, 1736, 1368,

1237, 1092, 1044, 753 cm^{-1}; ^1H NMR (600 MHz, CD_3CN) δ 6.12 (dd, *J* = 15.1, 10.6 Hz, 1H), 5.99 (dd, *J* = 15.1, 10.6 Hz, 1H), 5.66 (dd, *J* = 15.1, 6.8 Hz, 1H), 5.51 (dd, *J* = 15.1, 7.8 Hz, 1H), 5.24 (d, *J* = 2.3 Hz, 1H), 4.97 (d, *J* = 7.8 Hz, 1H), 4.60 (ddd, *J* = 9.6, 9.2, 5.5 Hz, 1H), 4.58 (s, 1H), 4.39 (d, *J* = 7.4 Hz, 1H), 4.05 (dd, *J* = 11.4, 5.5 Hz, 1H), 3.89 (br q, *J* = 6.4 Hz, 1H), 3.84 (dd, *J* = 11.4, 5.5 Hz, 1H), 3.68 (dd, *J* = 9.2, 9.1 Hz, 1H), 3.63 (br dd, *J* = 10.3, 10.3 Hz, 1H), 3.49 (s, 3H), 3.43 (s, 3H), ca. 3.42 (m, 1H, overlapped), 3.38 (s, 3H), 3.37–3.31 (m, 3H, overlapped), 3.36 (s, 3H), 3.29 (br ddd, *J* = 11.5, 10.1, 2.8 Hz, 1H), 3.14 (dd, *J* = 11.4, 9.6 Hz, 1H), 2.99 (dd, *J* = 9.2, 7.4 Hz, 1H), ca. 2.98 (m, 1H, overlapped), 2.76 (m, 1H), 2.52 (dd, *J* = 12.9, 2.8 Hz, 1H), 2.29 (m, 1H), 2.14 (dd, *J* = 12.9, 11.5 Hz, 1H), 2.11–2.04 (m, 2H), 1.99 (m, 1H), 1.96 (s, 3H), 1.56 (ddd, *J* = 11.5, 11.5, 11.5 Hz, 1H), 1.36 (ddd, *J* = 11.9, 11.9, 11.9 Hz, 1H), 1.28 (m, 1H), 1.10 (d, *J* = 6.4 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 6H), 0.93 (d, *J* = 6.4 Hz, 3H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.79 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (150 MHz, CD_3CN) δ 207.4, 172.2, 171.0, 143.5, 135.7, 127.4, 127.2, 105.8, 103.9, 98.1, 85.1, 83.7, 82.8, 80.7, 79.8, 79.7, 79.0, 78.4, 77.0, 74.8, 71.5, 67.0, 62.9, 61.6, 60.9, 59.0, 57.8, 43.0, 42.7, 41.4, 40.5, 40.1, 39.5, 34.3, 31.7, 22.4, 22.3, 21.1, 19.4, 17.8, 16.7, 13.6, 12.8; HRMS (ESI) calcd for $C_{43}H_{68}O_{16}Na$ [$(M + Na)^+$] 863.4400; found 863.4409.

ACCOSIATED CONTENTS

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

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

AUTHOR INFORMATION

Corresponding Author

*E-mail: masasaki@m.tohoku.ac.jp

ORCID

Makoto Sasaki: 0000-0003-2964-7986

Notes

The authors declare no competing financial interest.

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