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Synthetic studies on a marine polyether toxin, gambierol: stereoselective synthesis of the EFGH ring system via *B*-alkyl Suzuki coupling

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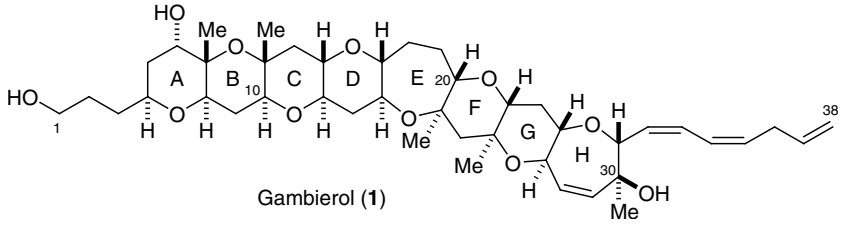
Abstract—A synthetic route to the EFGH ring system (**3**) of gambierol (**1**), a marine polyether toxin isolated from the dinoflagellate *Gambierdiscus toxicus*, has been developed. The present synthesis features convergent coupling of the F and H rings followed by ring-closure of the G ring based on the *B*-alkyl Suzuki reaction of lactone-derived enol phosphates. An angular methyl group at C23 was stereoselectively introduced by treatment of sulfone **32** with trimethylaluminum. Installation of a tertiary alcohol at C21 was accomplished through stereoselcetive dihydroxylation of *exo*-methylene **36** followed by selective formation of the primary *p*-toluensulfonate and treatment of the resultant monotosylate **40** with lithium aluminum hydride. Finally, formation of the E ring as a lactone form completed the synthesis of **3**.

1. Introduction

A variety of polyether natural products that present extremely potent biological activities have been isolated from the marine dinoflagellates.[1] Gambierol (**1**) was isolated as a toxic constituent from cultured cells of the ciguatera causative dinoflagellate, *Gambierdiscus toxicus*, and showed toxicity against mice (LD_{50} 50 μg kg^{-1}, mice, i.p.).[2] The symptoms caused in mice resemble those shown by ciguatoxins, implying the possibility that gambierol is also implicated in ciguatera fish poisoning, which is one of the most widespread seafood poisonings. The gross structure, including relative stereochemistry, has been determined by Yasumoto and co-workers on the basis of extensive NMR analysis (Fig. 1).[2] Recently, the absolute configuration has been unambiguously established by inversion of the C6–OH group and application of the chiral anisotropic reagent.[3] Its characteristic polyether structure, potent biological activity, and extremely limited availability from natural sources make gambierol an intriguing synthetic target molecule.[4] We have recently reported a powerful coupling strategy for the convergent assembly of a polyether structure based on *B*-alkyl Suzuki coupling of lactone-derived enol phosphates and disclosed its potential in the synthesis of ciguatoxin fragments.[5,6] In this paper, we describe in detail a stereocontrolled construction of the EFGH ring system (**3**) of gambierol based on the *B*-alkyl Suzuki coupling strategy.[7]



Gambierol (**1**)

Figure 1. Structure of gambierol (**1**).

Keywords: marine metabolites; polyethers; suzuki reactions; toxins.

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2. Results and discussion

2.1. Synthetic plan

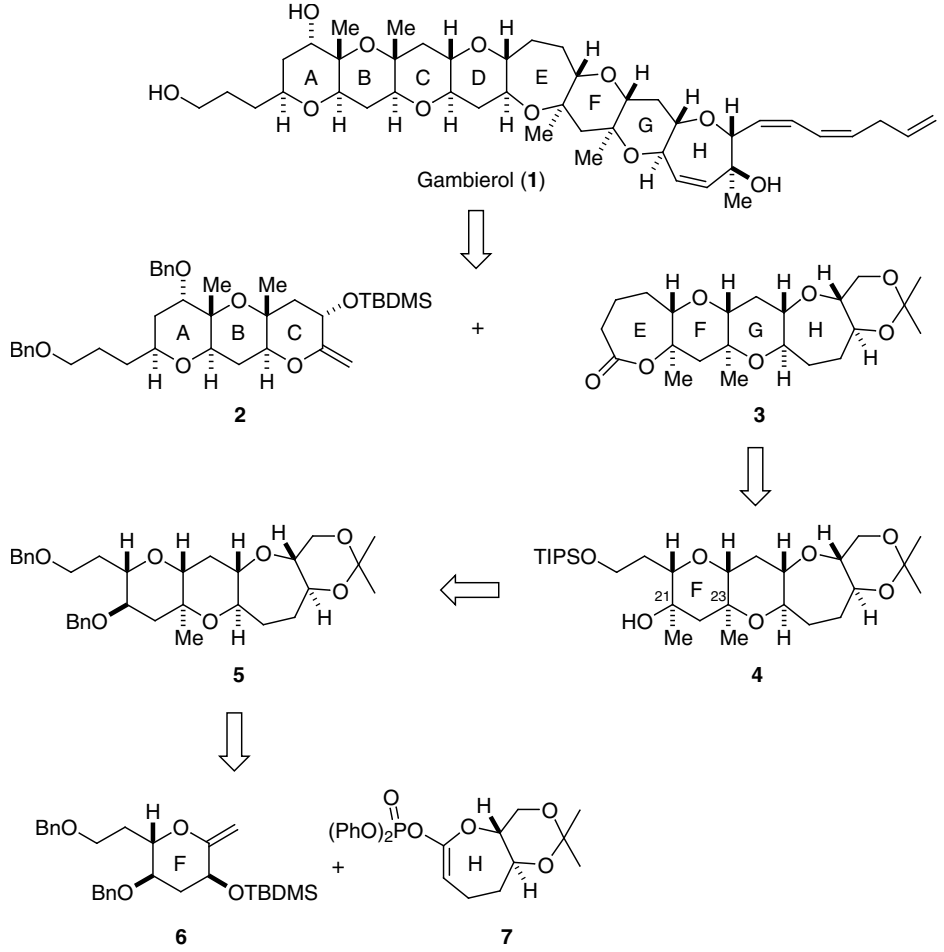
A convergent synthetic approach to gambierol (**1**) involves construction of two fragments representing the ABC and EFGH ring systems (**2** and **3**, respectively) and their coupling through *B*-alkyl Suzuki reaction (Scheme 1). The latter compound could be readily derived from tricyclic FGH ring system **4**. A formidable challenge in synthesizing **4** was the introduction of the 1,3-diaxial dimethyl groups at the C21 and C23 positions on the F ring. Although a few methods have been reported for the synthesis of a *trans*-fused tetrahydropyran ring system having axial-oriented methyl substituents flanking the ether oxygen,[8] there has been no report for the synthesis of 1,3-diaxial dimethyl-substituted terahydropyrans at the angular positions adjacent to the ring methylene. We envisaged the installation of a tertiary alcohol at C21 onto a tricyclic substrate wherein the C23 angular methyl substituent was already in place. The precursor tricyclic ether **5** could be obtained by *B*-alkyl Suzuki coupling of the F and H ring fragments (**6** and **7**, respectively) followed by ring-closure of the G ring.

2.2. Synthesis of *exo*-olefin 6

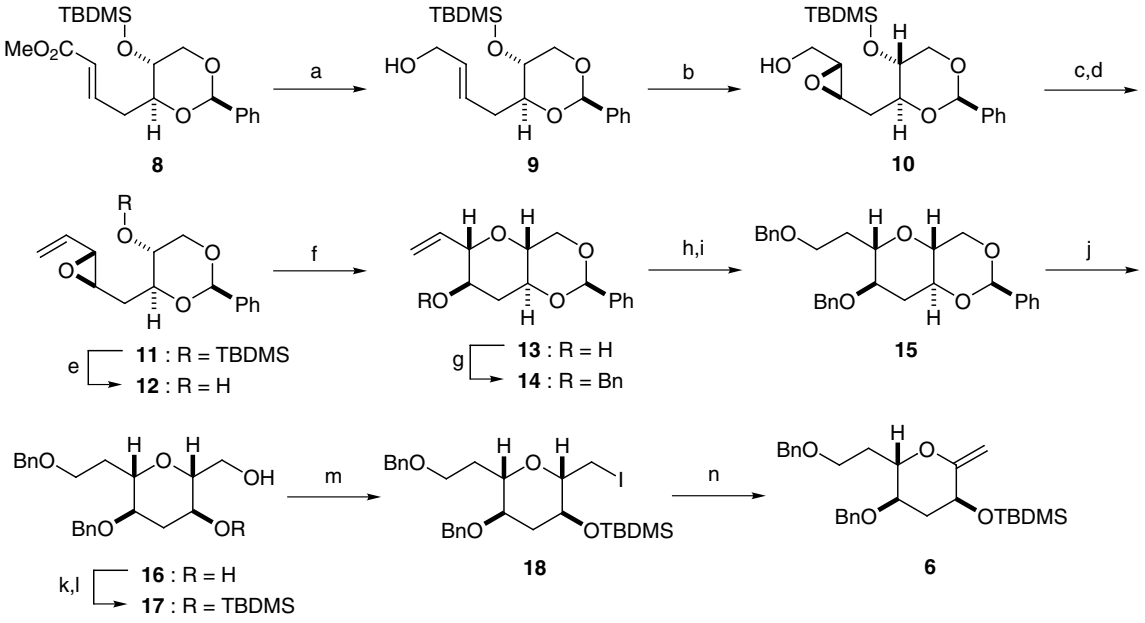
Synthesis of *exo*-olefin **6**, representing the F ring of **1**, followed the procedure of Nicolaou[9] starting from the known α, β-unsaturated ester **8** (Scheme 2).[10] DIBALH reduction of **8** gave allylic alcohol **9**, which was subjected to sharpless asymmetric epoxidation with (−)-diethyl tartrate as the chiral auxiliary to provide epoxy alcohol **10** in 87% yield. Oxidation with SO_3·pyridine and DMSO followed by Wittig methylenation generated vinyl epoxide **11** in 86% yield for the two steps, which was desilylated with tetra-*n*-butylammonium fluoride (TBAF) to give alcohol **12** in 98% yield. Upon treatment with PPTS tetrahydropyran **13** was regio- and stereoselectively formed in 94% yield. The secondary alcohol was then protected as the benzyl ether **14**. Hydroboration of **14** with 9-BBN-H followed by oxidative workup provided primary alcohol (95%), which was then benzylated to give bis(benzyl) ether **15** in 76% yield. Following removal of the benzylidene acetal, the resultant diol **16** was converted to primary alcohol **17** by silylation of both hydroxyl groups and subsequent selective mono-desilylation (camphorsulfonic acid, methanol–CH_2Cl_2, 0°C). Iodination of the primary hydroxyl group in **17** gave primary iodide **18** (95%), which upon treatment with potassium *t*-butoxide in THF at 0°C furnished the desired *exo*-olefin **6** in 96% yield.

2.3. *B*-Alkyl Suzuki coupling of 6 and 7

In our previously reported *B*-alkyl Suzuki coupling reactions,[5b,c] excess amounts (2 equiv.) of the phosphate coupling partners and elevated reaction temperature were



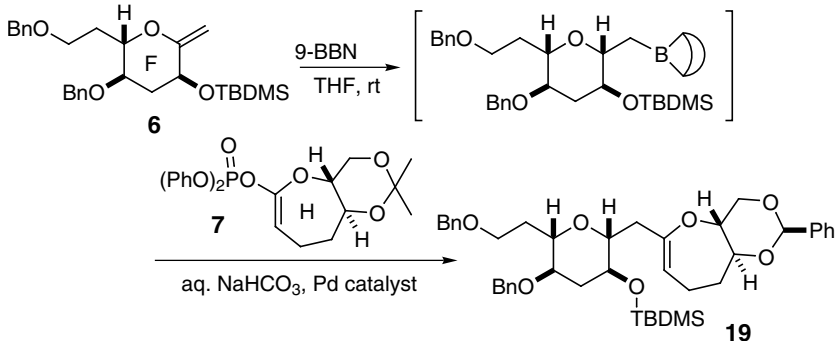
Scheme 1. Retrosynthetic analysis of gambierol.



Scheme 2. *Reagents and conditions*: (a) DIBALH, CH_2Cl_2, −78°C, quant.; (b) *t*-BuOOH, Ti(O*i*-Pr)$_4$, (−)-diethyl tartrate, 4 Å molecular sieves, CH_2Cl_2, −20°C, 87%; (c) SO_3·pyridine, Et_3N, DMSO, CH_2Cl_2, 0°C; (d) $Ph_3P^+CH_3Br^-$, NaHMDS, THF, 0°C, 86% (two steps); (e) *n*-Bu_4NF, THF, rt, 98%; (f) PPTS, CH_2Cl_2, rt, 94%; (g) NaH, BnBr, Bu_4NI, DMF, rt, 97%; (h) 9-BBN-H, THF, rt, then NaOH, H_2O_2, rt, 95%; (i) KH, BnBr, Bu_4NI, THF, reflux, 76%; (j) *p*-TsOH·H_2O, MeOH–CH_2Cl_2, rt, 90%; (k) TBDMSCl, imidazole, DMF, 50°C; (l) CSA, MeOH–CH_2Cl_2, 0°C, 96% (two steps); (m) I_2, PPh_3, imidazole, benzene, rt, 95%; (n) *t*-BuOK, THF, 0°C, 96%.

required to realize the coupling reaction in high yield. These problems prompted us to explore the optimum reaction conditions for the hydroboration–Suzuki coupling of *exo*-olefin **6** and enol phosphate **7**.[5b] Hydroboration of the *B*-alkyl Suzuki coupling partner **6** (9-BBN-H, THF, room temperature) and direct subjection of the resultant alkylborane to 1.2 equiv. of enol phosphate **7** under the previously reported conditions (aqueous 1 M $NaHCO_3$ (3 equiv.), tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$, 10 mol%), DMF, 50°C, 20 h)[5b] afforded the desired cross-coupled product **19** in 87% yield (Table 1, entry 1). Use of dichloro[1,1′-bis(diphenylphosphino)ferrocene]palladium(II) ($PdCl_2$(dppf)) as a catalyst improved the yield of **19** (entry 2) and allowed the coupling reaction to proceed at room temperature in high yield (entry 3).[11] On the other hand, use of dichlorobis(tricyclohexylphosphine)palladium(II) ($PdCl_2(PCy_3)_2$)[12] with an electron-rich phosphine ligand lowered the yield of the coupling reaction (entry 4).[13] It has been recently reported by Buchwald and co-workers that palladium(II) acetate/*o*-(di-*tert*-butylphosphino)biphenyl **20** efficiently promotes the room-temperature Suzuki coupling of less reactive aryl chlorides;[11e,f] however, this catalyst system was also less effective in the present case (entry 5).

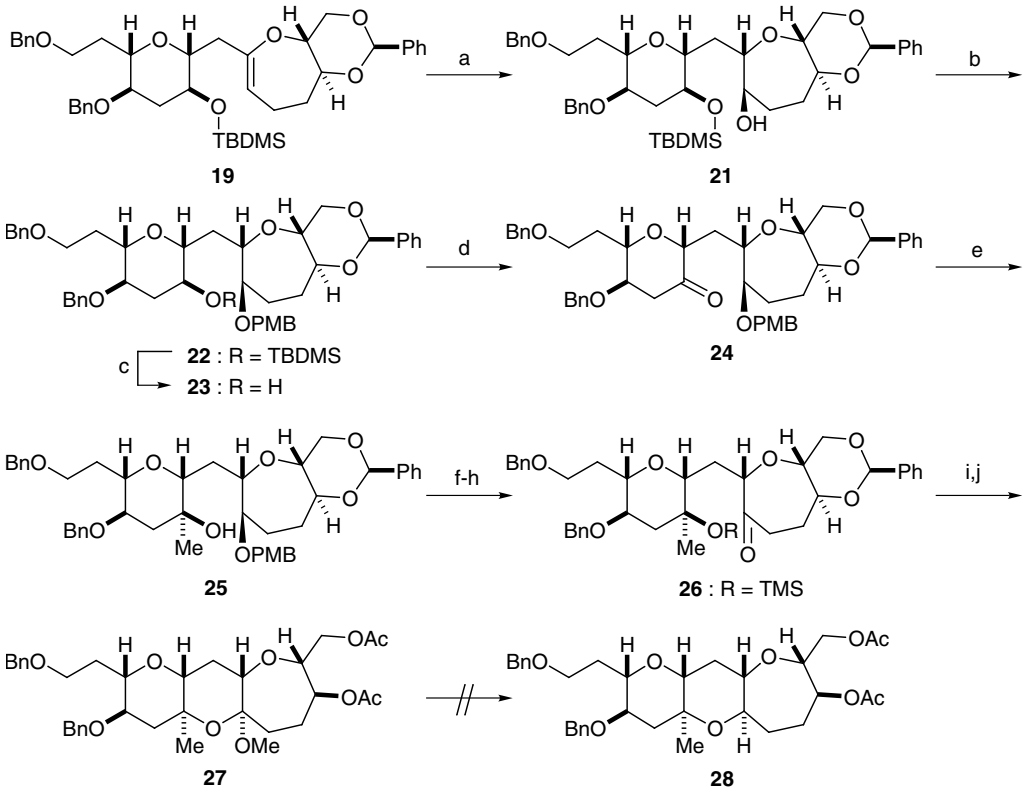
Table 1. *B*-Alkyl Suzuki coupling of *exo*-olefin **6** and enol phosphate **7**



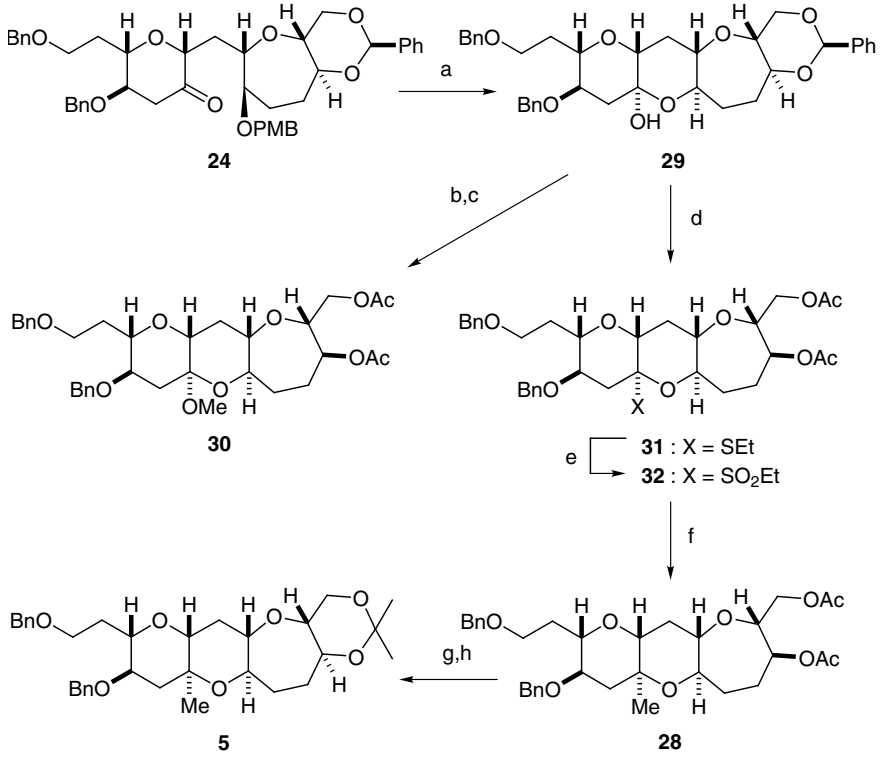
Entry	Pd catalyst	Conditions	Yield (%)
1	$Pd(PPh_3)_4$	DMF, 50°C, 20 h	87
2	$PdCl_2$(dppf)	DMF, 50°C, 20 h	93
3	$PdCl_2$(dppf)	DMF, rt, 24 h	97
4	$PdCl_2(PCy_3)_2$	DMF, 50°C, 20 h	50
5[a]	$Pd(OAc)_2$/**20**	Dioxane, rt, 24 h	58

Reactions were carried out using 10 mol% of Pd catalyst, 3 equiv. of aqueous 1 M $NaHCO_3$, and 1.2 equiv. of enol phosphate **5**; reaction times have not been minimized.

[a] 20 mol% of ligand **20** was used.



Scheme 3. *Reagents and conditions*: (a) BH_3·THF, THF, −30°C, NaOH, H_2O_2, rt→40°C, 77% (isomer, 10%); (b) KH, PMBCl, *n*-Bu_4NI, THF, rt, 88%; (c) *n*-Bu_4NF, THF, rt, quant.; (d) TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, rt, 94%; (e) MeMgBr, toluene, −78°C; (f) TMSOTf, 2,6-lutidine, CH_2Cl_2, 0°C; (g) DDQ, CH_2Cl_2–pH 7.0 phosphate buffer, rt; (h) TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, rt; (i) *p*-TsOH·H_2O, MeOH–CH_2Cl_2, rt, 80% (five steps); (j) Ac_2O, DMAP, CH_2Cl_2, rt, 70%.



Scheme 4. *Reagents and conditions*: (a) DDQ, CH_2Cl_2–pH 7.0 phosphate buffer, rt; (b) *p*-TsOH·H_2O, $CHCl_3$–MeOH, rt; (c) Ac_2O, DMAP, Et_3N, CH_2Cl_2, rt, 97% from **24**; (d) EtSH, $Zn(OTf)_2$, $NaHCO_3$, CH_2Cl_2, rt; then Ac_2O, DMAP, 88% from **24**; (e) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, rt, 96%; (f) Me_3Al, CH_2Cl_2, −78°C→rt, 90%; (g) NaOMe, MeOH–CH_2Cl_2, rt; (h) $Me_2C(OMe)_2$, PPTS, DMF– CH_2Cl_2, rt, 98% (two steps).

2.4. Synthesis of tricyclic ether 5

In our first synthetic strategy, we planned to introduce an angular methyl group at C23 via hydride reduction of mixed methyl ketal **27** (Scheme 3). Hydroboration of **19** with thexylborane (THF, 0°C) was very slow, and the desired alcohol **21** was obtained in 67% yield after 4 days. More practically, hydroboration of **19** with borane–THF complex (THF, −30°C, overnight, then NaOH, H_2O_2) provided **21** in 77% yield along with 10% of its diastereomer, which were easily separable by column chromatography on silica gel. Protection of the secondary alcohol as the *p*-methoxybenzyl (PMB) ether **22** followed by removal of the silyl group gave alcohol **23** in 88% overall yield. Oxidation of the resultant alcohol with tetrapropylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO)[14] provided ketone **24** in 94% yield. Treatment of **24** with methylmagnesium bromide in toluene at −78°C provided tertiary alcohol **25** stereoselectively.[15] Protection of the tertiary alcohol as its trimethylsilyl ether followed by oxidative removal of the PMB group with DDQ and oxidation of the resulting secondary alcohol with TPAP/NMO provided ketone **26**. Exposure of **26** to *p*-toluenesulfonic acid in methanol effected formation of a mixed methyl ketal and removal of the benzylidene group to give the diol (80% overall yield from **24**), which was then acetylated to yield diacetate **27** in 70% yield. However, reduction of **27** with triethylsilane in the presence of boron trifluoride etherate in CH_2Cl_2 or CH_3CN at low temperature (−40→0°C) resulted in no reaction, whereas at room temperature significant decomposition was observed and the desired product **28** was not obtained. The presence of an angular methyl group at C23[16] would hinder the axial attack of hydride nucleophile from the bottom face of the oxocarbenium ion generated from **27**.

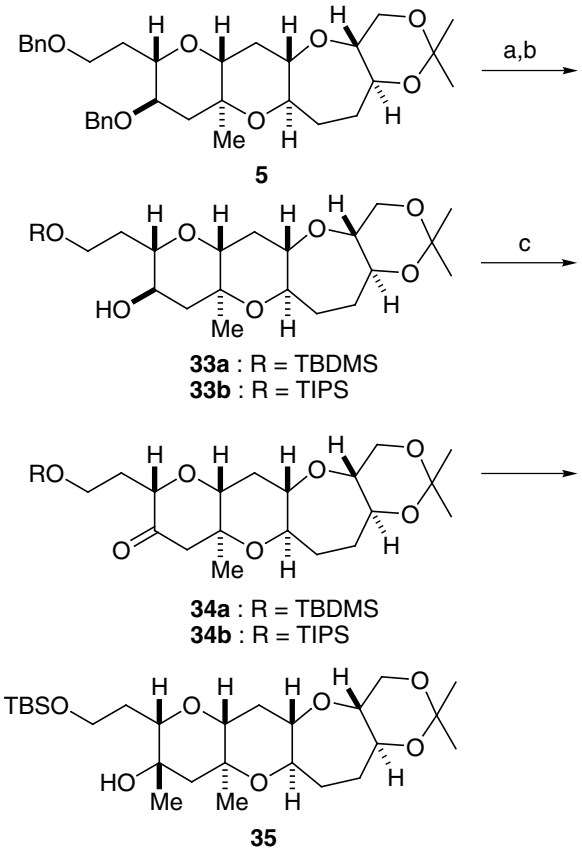
Having failed to reduce mixed methyl ketal **27** to obtain **28**, we explored the possibility of introduction of the methyl group via methylation of the oxocarbenium ion generated from mixed methyl ketal **30** (Scheme 4). Oxidative removal of the PMB group of **24** followed by acidic treatment in methanol and subsequent acetylation led to diacetate **30** in 79% overall yield. However, upon treatment of **30** with trimethylaluminum or dimethylzinc in the presence of boron trifluoride etherate,[17] none of the desired methylated product **28** was obtained.

Figure 2. Stereochemical assignment of tricyclic ether **28**. Double-ended arrows denote NOEs.

To circumvent this obstacle, we converted **24** to mixed ethylthio ketal **31**. Following removal of the PMB group of **24**, treatment of the resulting hemiketal **29** with ethanethiol and zinc triflate in the presence of $NaHCO_3$ in CH_2Cl_2[18] and in situ acetylation provided mixed thioketal **31** in 88 % overall yield. Oxidation of **31** with *m*-CPBA then gave the corresponding sulfone **32** in 96% yield. Reaction of **32** with trimethylaluminum (CH_2Cl_2, −78°C to rt)[19] led exclusively to the desired **28** in 90% yield. The relative configuration of **28** was unambiguously established by NOE experiments (Fig. 2). Finally, routine protecting group manipulation allowed for conversion of **28** to acetonide **5** in 98% overall yield.

2.5. Installation of tertiary alcohol at C21

With the desired **5** in hand, our attention was next directed to stereoselective construction of the tertiary alcohol at the C21 position. Removal of the benzyl groups of **5**, followed by selective silylation of the primary alcohol (TBDMSCl or TIPSCl, imidazole, CH_2Cl_2, rt), provided alcohol **33** in high yield (Scheme 5). Oxidation of the secondary alcohol with TPAP/NMO gave ketone **34** in near quantitative yield. Unfortunately, all attempts to install C21 tertiary alcohol by nucleophilic addition to ketone **34a** were unsuccessful. Direct methylation using methylmagnesium bromide, methyllithium, and trimethylaluminum occurred from the top face to yield the undesired isomer **35** exclusively or as the major product. Nucleophilic epoxidation using



Scheme 5. *Reagents and conditions*: (a) H_2, $Pd(OH)_2$/C, EtOAc, rt; (b) TBDMSCl or TIPSCl, imidazole, CH_2Cl_2, rt, 74% (two steps) for **33a**, 89% (two steps) for **33b**; (c) TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, rt, 99% for **34a**, quant. for **34b**.

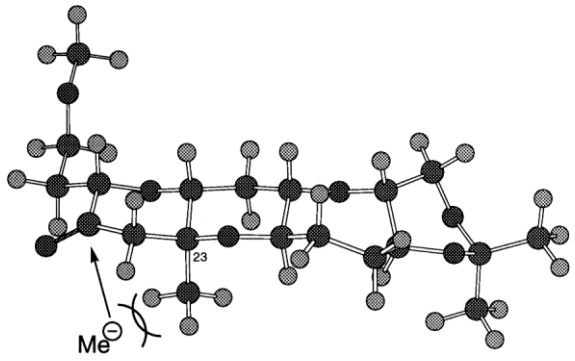
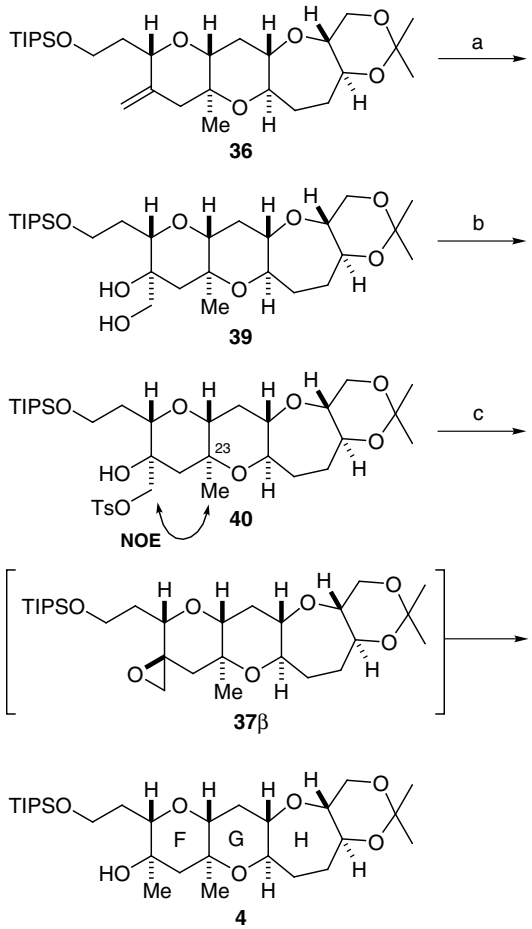


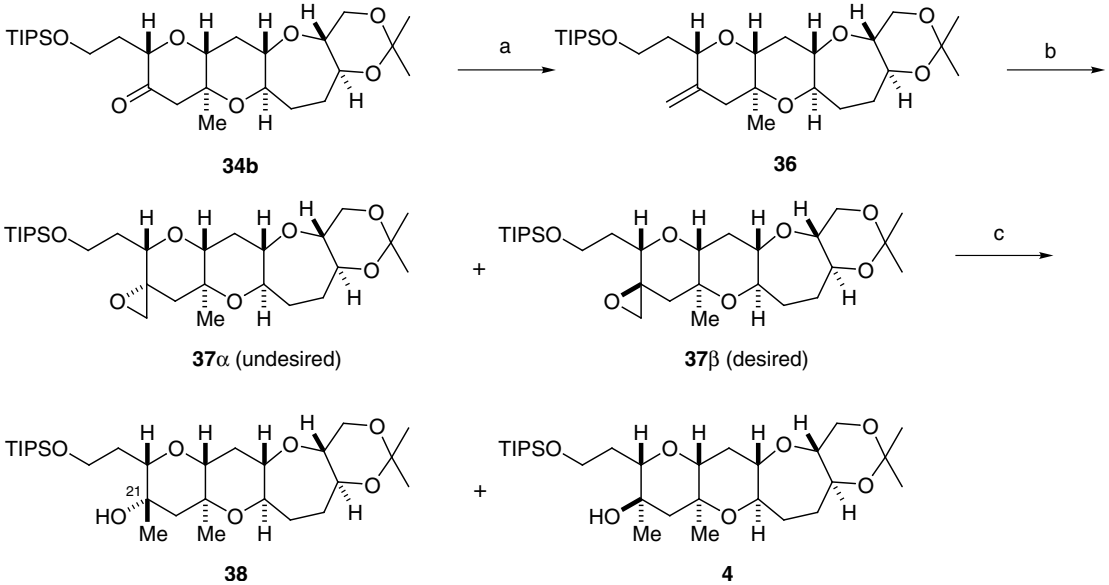
Figure 3.

dimethyloxosulfonium methylide[20] followed by reduction with lithium triethylborohydride also provided **35** as a single stereoisomer. These results can be explained by the serious steric congestion of the angular methyl group at C23 (Fig. 3).

Under these circumstances, we explored an alternative method for the construction of C21 tertiary alcohol. It was anticipated that epoxidation of *exo*-olefin **37**, derived from ketone **34b**, would proceed stereoselectively to give the β-epoxide which, upon hydride reduction, would furnish the desired tertiary alcohol **4** (Scheme 6). Thus, methylenation of ketone **34b** with Wittig reagent (6 equiv. of $Ph_3P^+BrCH_3^-$, 5.6 equiv. of NaHMDS, THF, −78°C→rt, 3.5 h) provided **36** in 92% yield. However, epoxidation of **36** with *m*-CPBA ($NaHCO_3$, CH_2Cl_2, rt, 2 days) yielded an inseparable mixture of epoxides **37** (**37**α/**37**β=2:3), which was reduced with lithium triethylborohydride (THF, rt) giving an inseparable mixture of the desired tertiary alcohol **4** and its C21 diastereomer **38** (**4**/**38**=3:2) in 68% combined yield along with 28% of recovered **36**. Epoxidation at the elevated temperature in the presence of a radical inhibitor, 4,4′-thiobis(6-*t*-butyl-*m*-cresol),[21] did not improve the facial selectivity.



Scheme 7. *Reagents and conditions*: (a) OsO_4 (3 equiv.), NMO (10 equiv.), *t*-BuOH–H_2O, rt, 1.5 d, then aq. $NaHSO_3$, pyridine, rt, 96%; (b) *p*-TsCl, DMAP, $(CH_2Cl)_2$, rt, 99%; (c) $LiAlH_4$, THF, 0°C→rt, 3 h, 75%.

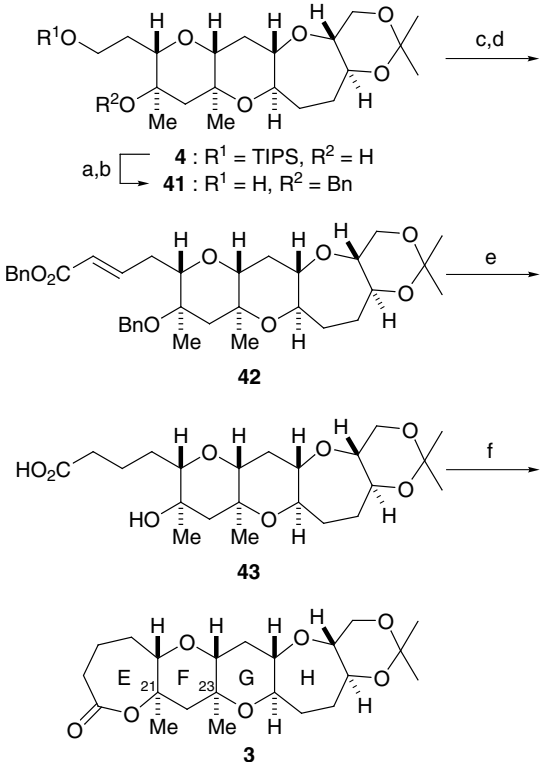


Scheme 6. *Reagents and conditions*: (a) $Ph_3P^+CH_3Br^-$ (6 equiv.), NaHMDS (5.6 equiv.), THF, −78°C→rt, 3.5 h, 92%; (b) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, rt, 2 days; (c) $LiEt_3BH$, THF, rt, 68% (two steps, **4**/**38**=3:2).

After several experiments, we found that dihydroxylation of **36** proceeded stereoselectively to give diol **39** as a single stereoisomer in near quantitative yield (Scheme 7). In this reaction, excess amounts of reagents (3 equiv. of OsO_4 and 10 equiv. of NMO) and prolonged reaction time were required to obtain a high yield of **39**. Selective tosylation of the primary hydroxyl group gave primary monotosylate **40** in virtually quantitative yield. The relative stereochemistry at C21 was established by an NOE between the oxymethylene and C23 angular methyl groups as shown in Scheme 7. Reduction of **40** with lithium aluminum hydride in THF at 0°C yielded epoxide **37**β which, upon warming to room temperature, delivered the desired tertiary alcohol **4** in 75% yield.[22] To our knowledge, the present synthesis of **4** constitutes the first example for the construction of 1,3-diaxial dimethyl-substituted tetrahydropyran at the angular position adjacent to the ring methylene.

2.6. Final conversion to the EFGH ring system

Final transformation of **4** into the target EFGH ring system (**3**) is outlined in Scheme 8. Protection of the tertiary alcohol of **4** as its benzyl ether followed by desilylation provided alcohol **41** in 87% yield for the two steps. Oxidation of the primary alcohol with SO_3·pyridine and DMSO followed by Wittig homologation using benzyl (triphenylphophoranylidene)acetate provided α,β-unsaturated benzyl ester **42** in 86% overall yield. Removal of the benzyl protecting groups and hydrogenation of the double bond gave hydroxy acid **43**, which was lactonized under Yamaguchi conditions (2,4,6-trichlorobenzoyl chloride, triethylamine, THF–toluene; then DMAP, toluene, 110°C)[23] to furnish the target EFGH ring system **3** in 93% yield for the two steps. Stereochemistry at the quaternary center at C21 was unambiguously established by NOE between the angular methyl groups at C21 and C23.



Scheme 8. *Reagents and conditions*: (a) KH, BnBr, THF, rt; (b) *n*-Bu_4NF, THF, rt, 87% (two steps); (c) SO_3·pyridine, Et_3N, DMSO, CH_2Cl_2, 0°C; (d) $Ph_3P{=}CHCO_2Bn$, $(CH_2Cl)_2$, rt, 86% (two steps); (e) H_2, $Pd(OH)_2$/C, EtOAc, rt; (f) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF–toluene (1:1), rt, then DMAP, toluene, 110°C, 93% (two steps).

3. Conclusions

We have completed the synthesis of the EFGH ring system of gambierol. In the present synthesis we have demonstrated that $PdCl_2$(dppf) promotes the room-temperature *B*-alkyl Suzuki coupling of lactone-derived enol phosphate in high yield. The mild reaction conditions described herein should tolerate the presence of a wide variety of functional groups and thus enhance the practicality and usefulness of the *B*-alkyl Suzuki coupling-based strategy for the synthesis of a polyether system. Also, 1,3-diaxial dimethyl groups with serious steric congestion were successfully introduced. Further efforts directed toward a total synthesis of gambierol are under way and will be reported in due course.

4. Experimental

4.1. General methods

All moisture and/or air sensitive reactions were conducted under an atmosphere of argon or nitrogen with dry solvents under anhydrous conditions unless otherwise noted. Anhydrous THF and dimethylsulfoxide (DMSO) were purchased from Kanto Chemical and Aldrich, respectively. Benzene, toluene, dichloromethane, methanol, triethylamine, and pyridine were distilled from calcium hydride. Other solvents and reagents purchased were of the highest commercial quality and used without further purification unless otherwise noted. All reactions were monitored by thin-layer chromatography (TLC) with pre-coated silica gel plates (E. Merck, Silica gel 60 F_{254}). Column chromatography was performed on Kanto Chemical silica gel 60N (spherical, neutral). NMR spectra were recorded on a JEOL A500 or Bruker DRX-500 instrument and referenced to a residual solvent. Chemical shifts are reported in δ (ppm). Coupling constants are reported in Hertz (Hz). The following abbreviations were used to designate the multiplicities: s=singlet, d=doublet, t=triplet, m=multiplet, br=broad. IR spectra were recorded on a JASCO FT/IR-420 instrument. Low- and high-resolution mass spectra were recorded on a JEOL JMS-SX102L mass spectrometer under fast atom bombardment (FAB) conditions with *m*-nitrobenzyl alcohol (NBA) as the matrix.

4.1.1. Allylic alcohol 9. To a solution of α,β-unsaturated ester **8**[9] (7.92 g, 20.2 mmol) in CH_2Cl_2 (80 mL) at −78°C was added DIBALH (1.0 M solution in toluene, 50.5 mL, 50.5 mmol). After being stirred at −78°C for 2 h, the reaction was quenched with saturated aqueous potassium sodium tartrate. The reaction mixture was diluted with EtOAc and vigorously stirred at room temperature until the layers were separated. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica

gel, 25→35% EtOAc/hexane) to give allylic alcohol **9** (7.34 g, quant.) as a colorless oil: $[\alpha]_D^{26}=-57.6$ (*c* 2.08, benzene); IR (film) 3413, 2954, 2929, 2857, 1462, 1398, 1362, 1254, 1108, 1029, 974, 838, 778, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47–7.45 (m, 2H), 7.36–7.31 (m, 3H), 5.82 (ddd, 1H, *J*=15.6, 6.7, 6.7 Hz), 5.74 (ddd, 1H, *J*=15.6, 5.5, 5.5 Hz), 5.46 (s, 1H), 4.17 (m, 1H), 4.08 (d, 2H, *J*=5.5 Hz), 3.62–3.52 (m, 3H), 2.61 (dd, 1H, *J*=14.7, 6.7 Hz), 2.30 (dt, 1H, *J*=14.7, 6.7 Hz), 0.89 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.9, 131.6, 128.8, 128.4, 128.2, 126.0, 100.8, 81.9, 71.7, 66.1, 63.6, 34.3, 25.7, 17.9; HRMS calcd for $C_{20}H_{34}O_4SiNa$ $[(M+Na)^+]$ 387.1968, found 387.1971.

4.1.2. Epoxide 10. To a solution of allylic alcohol **9** (4.27 g, 11.7 mmol) and 4 Å molecular sieves (1.63 g) in CH_2Cl_2 (40 mL) at −20°C were added (−)-DET (0.40 mL, 2.3 mmol) and Ti(O*i*-Pr)$_4$ (0.52 mL, 1.8 mmol). After being stirred at −20°C for 30 min, *t*-BuOOH (5.7 M solution in isooctane, 5.10 mL, 29.1 mmol) was added to the mixture and the resulting mixture was stirred at −20°C for 4 h. The reaction mixture was allowed to warm to room temperature and filtered through Celite. The filtrate was diluted with EtOAc, washed with saturated aqueous Na_2SO_4 and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 25→35% EtOAc/hexane) to give epoxide **10** (3.90 g, 87%) as a colorless oil: $[\alpha]_D^{26}=-35.6$ (*c* 0.47, benzene); IR (film) 3445, 2928, 2857, 1460, 1388, 1254, 1106, 1029, 838, 778, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.48–7.45 (m, 2H), 7.38–7.31 (m, 3H), 5.49 (s, 1H), 4.19 (dd, 1H, *J*=10.7, 4.6 Hz), 3.90 (ddd, 1H, *J*=12.5, 5.5, 4.6 Hz), 3.71–3.59 (m, 3H), 3.56 (dd, 1H, *J*=10.7, 9.5 Hz), 3.23 (dt, 1H, *J*=5.5, 2.4 Hz), 2.97 (dt, 1H, *J*=4.9, 2.4 Hz), 2.02 (m, 1H), 1.64 (dd, 1H, *J*=7.3, 5.5 Hz), 0.88 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.7, 128.9, 128.3, 126.0, 100.8, 80.0, 71.8, 65.9, 61.7, 57.8, 52.9, 33.4, 25.8, 17.9, −4.2, −4.8; HRMS calcd for $C_{20}H_{32}O_5SiNa$ $[(M+Na)^+]$ 403.1917, found 403.1945.

4.1.3. Olefin 11. To a solution of epoxide **10** (6.30 g, 16.6 mmol) and Et_3N (11.6 mL, 83.2 mmol) in CH_2Cl_2–DMSO (3:1, 80 mL) at 0°C was added SO_3·pyridine (10.55 g, 66.29 mmol) and the resulting mixture was stirred at 0°C for 30 min. The reaction mixture was diluted with EtOAc, washed with 1 M aqueous HCl, saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated to give crude aldehyde, which was used in the next reaction without further purification.

To a suspension of $Ph_3P^+CH_3Br^-$ (11.85 g, 33.17 mmol) in THF (50 mL) at 0°C was added NaHMDS (1.0 M solution in THF, 30.0 mL, 30.0 mmol) and the resulting ylide solution was stirred at 0°C for 30 min. To the solution was added dropwise a solution of the above aldehyde in THF (40 mL). After being stirred at 0°C for 30 min, the reaction was quenched with saturated aqueous NH_4Cl. The resulting mixture was diluted with ether, washed with water and brine, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, 10% EtOAc/hexane) to give olefin **11** (5.38 g, 86% for two steps) as a colorless oil: $[\alpha]_D^{26}=-49.7$ (*c* 0.45, benzene); IR (film) 2955, 2929, 2857, 1462, 1399, 1254, 1112, 1029, 984, 884, 838, 778, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47–7.45 (m, 2H), 7.36–7.32 (m, 3H), 5.58 (ddd, 1H, *J*=17.7, 10.1, 7.3 Hz), 5.49 (s, 1H), 5.46 (d, 1H, *J*=17.7 Hz), 5.26 (d, 1H, *J*=10.1 Hz), 4.18 (dd, 1H, *J*=10.7, 4.6 Hz), 3.69 (m, 1H), 3.56 (dd, 1H, *J*=10.7, 9.8 Hz), 3.16–3.07 (m, 2H), 2.04–1.93 (m, 2H), 0.88 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.8, 135.7, 128.9, 128.2, 126.0, 119.2, 100.8, 80.0, 71.9, 65.9, 58.2, 57.2, 33.8, 25.7, 17.9; HRMS calcd for $C_{21}H_{32}O_4SiNa$ $[(M+Na)^+]$ 399.1968, found 399.1974.

4.1.4. Hydroxy epoxide 12. To a solution of olefin **11** (5.38 g, 14.3 mmol) in THF (100 mL) was added TBAF (1.0 M solution in THF, 21.5 mL, 21.5 mmol). After being stirred at room temperature for 45 min, the reaction mixture was diluted with EtOAc, washed with saturated aqueous NH_4Cl and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 40→50% EtOAc/hexane) to give hydroxy epoxide **12** (3.68 g, 98%) as a colorless oil: $[\alpha]_D^{25}=-19.0$ (*c* 0.42, benzene); IR (film) 3444, 2858, 1456, 1397, 1074, 1027, 984, 925, 873, 752, 699, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.48–7.46 (m, 2H), 7.37–7.31 (m, 3H), 5.58 (ddd, 1H, *J*=17.4, 10.1, 7.0 Hz), 5.55 (s, 1H), 5.47 (d, 1H, *J*=17.4 Hz), 5.28 (d, 1H, *J*=10.1 Hz), 4.30 (dd, 1H, *J*=10.7, 5.2 Hz), 3.88 (m, 1H), 3.75 (m, 1H), 3.60 (m, 1H), 3.24–3.17 (m, 2H), 2.41 (br, 1H), 2.27 (ddd, 1H, *J*=15.0, 3.7, 3.4 Hz), 1.93 (ddd, 1H, *J*=15.0, 7.0, 5.8 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.7, 135.1, 129.0, 128.3, 126.1, 119.8, 101.1, 79.6, 71.1, 65.0, 58.3, 57.0, 34.2; HRMS calcd for $C_{15}H_{18}O_4Na$ $[(M+Na)^+]$ 285.1103, found 285.1126.

4.1.5. Tetrahydropyran 13. To a solution of hydroxy epoxide **12** (3.62 g, 13.8 mmol) in CH_2Cl_2 (140 mL) was added PPTS (1.71 g, 6.80 mmol). After being stirred at room temperature for 3.5 h, the reaction was quenched with Et_3N and the mixture was concentrated. The residue was purified by column chromatography (silica gel, 50% EtOAc/hexane) to give tetrahydropyran **13** (3.40 g, 94%) as a colorless solid: mp 143–145°C (hexane/EtOAc); $[\alpha]_D^{25}=-25.4$ (*c* 0.07, $CHCl_3$); IR (film) 3361, 2873, 1456, 1369, 1100, 1011, 750, 697, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.49–7.46 (m, 2H), 7.37–7.34 (m, 3H), 5.84 (ddd, 1H, *J*=17.4, 10.4, 7.0 Hz), 5.52 (s, 1H), 5.44 (d, 1H, *J*=17.4 Hz), 5.37 (d, 1H, *J*=10.4 Hz), 4.33 (dd, 1H, *J*=10.4, 4.9 Hz), 3.72–3.63 (m, 2H), 3.59 (ddd, 1H, *J*=11.6, 8.9, 4.3 Hz), 3.51 (m, 1H), 3.42 (ddd, 1H, *J*=11.3, 9.2, 4.9 Hz), 2.52 (ddd, 1H, *J*=11.6, 4.9, 4.3 Hz), 1.73 (ddd, 1H, *J*=11.6, 11.6, 11.3 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 135.0, 129.1, 128.3, 126.2, 120.0, 101.7, 83.9, 76.6, 73.0, 69.3, 68.9, 37.0; HRMS calcd for $C_{15}H_{18}O_4Na$ $[(M+Na)^+]$ 285.1103, found 285.1079.

4.1.6. Benzyl ether 14. To a solution of tetrahydropyran **13** (10.69 g, 40.80 mmol) in DMF (300 mL) at 0°C was added NaH (60% oil dispersion, 3.26 g, 81.5 mmol), and the resulting solution was stirred at room temperature for 30 min. The reaction mixture was cooled to 0°C, treated with BnBr (7.28 mL, 61.2 mmol) and *n*-Bu_4NI (1.51 g, 4.09 mmol), and allowed to warm to room temperature. After being stirred at room temperature for 100 min, the

reaction was quenched with MeOH. The reaction mixture was diluted with ether, washed with water and brine, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, 10% EtOAc/hexane) to give benzyl ether **14** (13.86 g, 97%) as a colorless solid: mp 95.5–97.5°C (hexane/Et_20); $[\alpha]_D^{25}=-59.8$ (*c* 1.01, $CHCl_3$); IR (film) 2879, 1454, 1381, 1093, 1012, 990, 930, 755, 697, 651 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.49–7.47 (m, 2H), 7.36–7.31 (m, 8H), 5.98 (ddd, 1H, *J*=17.3, 10.7, 5.9 Hz), 5.50 (s, 1H), 5.42 (d, 1H, *J*=17.3 Hz), 5.28 (d, 1H, *J*=10.7 Hz), 4.61 (d, 1H, *J*=11.7 Hz), 4.52 (d, 1H, *J*=11.7 Hz), 4.33 (dd, 1H, *J*=10.3, 4.8 Hz), 3.83 (dd, 1H, *J*=9.2, 5.9 Hz), 3.68 (dd, 1H, *J*=10.3, 10.2 Hz), 3.51 (m, 1H), 3.44 (m, 1H), 3.34 (m, 1H), 2.60 (ddd, 1H, *J*=11.5, 4.3, 4.3 Hz), 1.73 (ddd, 1H, *J*=11.5, 11.4, 11.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.9, 137.4, 135.4, 129.0, 128.4, 128.3, 127.8, 126.1, 117.8, 101.6, 81.3, 76.5, 72.8, 71.4, 69.3, 35.2; HRMS calcd for $C_{22}H_{24}O_4Na$ $[(M+Na)^+]$ 375.1572, found 375.1569.

4.1.7. Bis(benzyl) ether 15. To a solution of benzyl ether **14** (2.45 g, 6.96 mmol) in THF (70 mL) was added 9-BBN dimmer (2.21 g, 9.06 mmol) and the resulting mixture was stirred at room temperature for 105 min. After cooling to 0°C, the reaction was quenched with water (10 mL) and then treated with 3 M aqueous NaOH (30 mL) and 30% H_2O_2 (25 mL) and the resulting mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was diluted with EtOAc, washed with water, saturated aqueous Na_2SO_3 and brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 50% EtOAc/hexane) to give primary alcohol (2.43 g, 95%) as a viscous oil, which was used in the next reaction without further purification. ^1H NMR (500 MHz, $CDCl_3$) δ 7.47–7.45 (m, 2H), 7.37–7.27 (m, 8H), 5.50 (s, 1H), 4.65 (d, 1H, *J*=11.6 Hz), 4.46 (d, 1H, *J*=11.6 Hz), 4.27 (dd, 1H, *J*=10.4, 4.9 Hz), 3.80–3.27 (m, 2H), 3.63 (dd, 1H, *J*=10.4, 10.1 Hz), 3.56 (ddd, 1H, *J*=8.9, 8.9, 3.1 Hz), 3.48 (m, 1H), 3.42–3.32 (m, 2H), 2.64 (ddd, 1H, *J*=11.3, 4.3, 4.0 Hz), 2.16 (m, 1H), 1.75–1.60 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.5, 137.3, 129.1, 128.5, 128.3, 128.0, 127.9, 126.1, 101.7, 81.1, 76.4, 75.8, 73.1, 70.9, 69.2, 61.0, 34.6, 34.4.

To a suspension of KH (30% oil dispersion, 418.7 mg, 3.132 mmol) in THF at room temperature was added dropwise a solution of the above alcohol (442.4 mg, 1.196 mmol) in THF (7 mL). After being stirred at room temperature for 20 min, the mixture was treated with BnBr (213 μL, 1.79 mmol) and *n*-Bu_4NI (44.4 mg, 0.120 mmol) and the resultant solution was refluxed for 1 h. The reaction was quenched by careful addition of MeOH at 0°C, and the reaction mixture was diluted with EtOAc, washed with saturated aqueous NH_4Cl and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 10→20% EtOAc/hexane) to give bis(benzyl) ether **15** (415.8 mg, 76%) as a colorless oil: $[\alpha]_D^{25}=-84.1$ (*c* 0.18, benzene); IR (film) 3031, 2868, 1496, 1454, 1363, 1096, 1027, 748, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47–7.46 (m, 2H), 7.35–7.24 (m, 13H), 5.48 (s, 1H), 4.62 (d, 1H, *J*=11.6 Hz), 4.52 (d, 1H, *J*=12.1 Hz), 4.46 (d, 1H, *J*=11.6 Hz), 4.45 (d, 1H, *J*=12.1 Hz), 4.23 (dd, 1H, *J*=10.4, 4.9 Hz), 3.62–3.57 (m, 3H), 3.47–3.45 (m, 2H), 3.31–3.29 (m, 2H), 2.60 (ddd, 1H, *J*=11.4, 4.3, 4.2 Hz), 2.28 (m, 1H), 1.70–1.60 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.7, 138.0, 137.6, 129.0, 128.4, 128.3, 127.9, 127.8, 127.6, 127.5, 126.2, 101.7, 78.2, 76.8, 76.4, 73.0, 72.9, 71.0, 69.4, 66.6, 34.9, 32.2; HRMS calcd for $C_{29}H_{32}O_5Na$ $[(M+Na)^+]$ 483.2147, found 483.2169.

4.1.8. Diol 16. To a solution of bis(benzyl) ether **15** (3.76 g, 8.17 mmol) in MeOH–CH_2Cl_2 (1:1, 80 mL) was added *p*-TsOH·H_2O (0.46 g, 2.4 mmol) and the resulting mixture was stirred at room temperature for 3 h. The reaction was quenched with Et_3N, and the reaction mixture was concentrated. The residue was purified by column chromatography (silica gel, 80% EtOAc/hexane) to give diol **16** (2.74 g, 90%) as a colorless amorphous solid: $[\alpha]_D^{25}=-77.5$ (*c* 0.15, benzene); IR (film) 3393, 2925, 2868, 1456, 1097, 738, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.24 (m, 10H), 4.60 (d, 1H, *J*=11.6 Hz), 4.52 (d, 1H, *J*=12.1 Hz), 4.47–4.42 (m, 2H), 3.77 (m, 1H), 3.71 (m, 1H), 3.62–3.54 (m, 3H), 3.37 (ddd, 1H, *J*=9.1, 9.1, 2.6 Hz), 3.20–3.13 (m, 2H), 2.54 (ddd, 1H, *J*=11.3, 4.6, 4.6 Hz), 2.26 (m, 1H), 1.62 (m, 1H), 1.46 (ddd, 1H, *J*=11.3, 11.3, 11.3 Hz); HRMS calcd for $C_{22}H_{28}O_5Na$ $[(M+Na)^+]$ 395.1834, found 395.1829.

4.1.9. Alcohol 17. To a solution of diol **16** (2.49 g, 6.69 mmol) in DMF (60 mL) were added imidazole (1.82 g, 26.7 mmol) and TBDMSCl (3.03 g, 20.1 mmol), and the resulting mixture was stirred at 50°C for 9 h. The reaction mixture was cooled to room temperature, diluted with ether, washed with 1 M HCl, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$ and concentrated to give bis(silyl) ether, which was used in the next reaction without further purification.

A solution of the above bis(silyl) ether in MeOH–CH_2Cl_2 (1:1, 80 mL) was treated with CSA (311.4 mg, 1.341 mmol) at 0°C. After being stirred at 0°C for 80 min, the reaction was quenched with Et_3N and concentrated. The residue was purified by column chromatography (silica gel, 20% EtOAc/hexane) to give alcohol **17** (3.11 g, 96% for two steps) as a colorless oil: $[\alpha]_D^{26}=-24.6$ (*c* 0.21, benzene); IR (film) 3468, 2928, 2857, 1454, 1362, 1254, 1095, 860, 837, 776, 747, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.24 (m, 10H), 4.58 (d, 1H, *J*=11.6 Hz), 4.52 (d, 1H, *J*=11.9 Hz), 4.46 (d, 1H, *J*=11.6 Hz), 4.44 (d, 1H, *J*=11.9 Hz), 3.75 (m, 1H), 3.62–3.45 (m, 4H), 3.36 (ddd, 1H, *J*=9.2, 9.2, 2.8 Hz), 3.18–3.10 (m, 2H), 2.36 (ddd, 1H, *J*=11.6, 4.6, 4.6 Hz), 2.25 (m, 1H), 1.64 (m, 1H), 1.44 (ddd, 1H, *J*=11.6, 11.3, 11.3 Hz), 0.85 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 138.1, 128.40, 128.35, 127.83, 127.76, 127.6, 127.5, 81.5, 77.5, 76.2, 72.9, 71.1, 66.8, 66.7, 62.7, 39.1, 32.2, 25.7, 17.9, −4.2, −4.9; HRMS calcd for $C_{28}H_{42}O_5SiNa$ $[(M+Na)^+]$ 509.2699, found 509.2695.

4.1.10. Iodide 18. To a solution of alcohol **17** (2.59 g, 5.33 mmol) in benzene (50 mL) were added imidazole (547 mg, 8.04 mmol), PPh_3 (2.10 g, 8.01 mmol), and I_2 (1.76 g, 6.93 mmol), and the resulting mixture was stirred at room temperature for 25 min. The reaction was quenched with saturated aqueous Na_2SO_3, and the resulting mixture

was diluted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 5% EtOAc/hexane) to give iodide **18** (3.01 g, 95%) as a colorless oil: $[\alpha]_D^{28}=-15.6$ (*c* 0.12, benzene); IR (film) 2927, 2856, 1455, 1362, 1254, 1092, 837, 776, 741, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35–7.24 (m, 10H), 4.58–4.45 (m, 4H), 3.69–3.64 (m, 2H), 3.44 (dd, 1H, *J*=10.4, 2.8 Hz), 3.39 (ddd, 1H, *J*=9.5, 9.5, 2.4 Hz), 3.33 (ddd, 1H, *J*=11.0, 8.5, 4.6 Hz), 3.18–3.12 (m, 2H), 2.91 (ddd, 1H, *J*=8.9, 7.3, 2.8 Hz), 2.33 (ddd, 1H, *J*=11.9, 4.6, 4.6 Hz), 2.25 (m, 1H), 1.65 (m, 1H), 1.45 (ddd, 1H, *J*=11.9, 11.0, 11.0 Hz), 0.85 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.8, 133.7, 128.7, 128.5, 128.4, 128.3, 127.80, 127.77, 127.75, 127.4, 80.3, 77.6, 76.4, 73.0, 71.3, 70.3, 66.7, 39.0, 32.1, 25.7, 8.1, −4.0, −4.5; HRMS calcd for $C_{28}H_{41}IO_4SiNa$ $[(M+Na)^+]$ 619.1717, found 619.1730.

4.1.11. *exo*-Olefin 6. To a solution of iodide **18** (2.95 g, 4.95 mmol) in THF (50 mL) at 0°C was added KO*t*-Bu (2.78 g, 24.8 mmol), and the resulting solution was stirred at 0°C for 3 h. The reaction mixture was diluted with EtOAc, washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 5% EtOAc/hexane containing 2% Et_3N) to give *exo*-olefin **6** (2.22 g, 96%) as a colorless oil: $[\alpha]_D^{27}=-85.8$ (*c* 0.24, benzene); IR (film) 2928, 2857, 1661, 1455, 1362, 1254, 1221, 1133, 1095, 1005, 864, 837, 776, 746, 697 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.30–7.29 (m, 2H), 7.20–7.07 (m, 8H), 4.81 (d, 1H, *J*=1.6 Hz), 4.78 (d, 1H, *J*=1.6 Hz), 4.40 (d, 1H, *J*=12.2 Hz), 4.35 (d, 1H, *J*=11.8 Hz), 4.33 (d, 1H, *J*=12.2 Hz), 4.20 (d, 1H, *J*=11.8 Hz), 4.05 (m, 1H), 3.82 (ddd, 1H, *J*=9.0, 9.0, 2.7 Hz), 3.72–3.69 (m, 2H), 3.28 (ddd, 1H, *J*=10.5, 9.5, 4.6 Hz), 2.45–2.34 (m, 2H), 1.89 (m, 1H), 1.70 (ddd, 1H, *J*=11.3, 11.1, 11.1 Hz), 0.96 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.9, 138.7, 138.1, 128.4, 128.3, 127.82, 127.76, 127.6, 127.5, 92.1, 79.8, 75.6, 73.0, 71.0, 66.8, 66.6, 39.2, 32.4, 25.8, 18.2, −4.9 (2C); HRMS calcd for $C_{28}H_{40}O_4SiNa$ $[(M+Na)^+]$ 491.2594, found 491.2573.

4.1.12. Coupling product 19. *exo*-Olefin **6** (288.6 mg, 0.6167 mmol) was treated with 9-BBN (0.5 M solution in THF, 3.21 mL, 3.21 mmol) and the resulting solution was stirred at room temperature for 3 h. The solution was treated with 1 M aqueous $NaHCO_3$ (1.85 mL, 1.85 mmol) and the resultant mixture was stirred at room temperature for 15 min. The mixture was then treated with a solution of cyclic ketene acetal phosphate **7** (358.7 mg, 0.7473 mmol) in DMF (6 mL) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (50.4 mg, 0.0617 mmol). After being stirred at room temperature for 24 h, the reaction mixture was diluted with ether, washed with brine, dried over Na_2SO_4, and concentrated. The residue was dissolved in THF (20 mL) and cooled to 0°C. The resultant solution was treated with 3 M aqueous NaOH (1 mL) and 30% H_2O_2 (800 mL) and stirred at room temperature for 30 min. The reaction mixture was diluted with EtOAc, washed with saturated aqueous Na_2SO_3 and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 5% EtOAc/hexane containing 2% Et_3N) to give coupling product **19** (419.6 mg, 97%) as a colorless oil: $[\alpha]_D^{28}=+22.1$ (*c* 0.56, benzene); IR (film) 2928, 2856, 1683, 1455, 1362, 1254, 1092, 837, 748, 697 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.65–7.63 (m, 2H), 7.36–7.35 (m, 2H), 7.25–7.23 (m, 2H), 7.20–7.06 (m, 9H), 5.35 (s, 1H), 4.98 (dd, 1H, *J*=7.9, 4.0 Hz), 4.49 (d, 1H, *J*=11.9 Hz), 4.46 (d, 1H, *J*=11.9 Hz), 4.41 (d, 1H, *J*=11.6 Hz), 4.36 (dd, 1H, *J*=8.9, 3.4 Hz), 4.28 (d, 1H, *J*=11.6 Hz), 3.76–3.72 (m, 2H), 3.66–3.59 (m, 2H), 3.58–3.49 (m, 2H), 3.42 (ddd, 1H, *J*=9.8, 8.9, <1 Hz), 3.30 (ddd, 1H, *J*=11.0, 8.9, 4.6 Hz), 3.14 (ddd, 1H, *J*=11.0, 9.2, 4.6 Hz), 2.73 (dd, 1H, *J*=14.7, <1 Hz), 2.48 (m, 1H), 2.40 (ddd, 1H, *J*=11.9, 4.6, 4.6 Hz), 2.13–1.96 (m, 3H), 1.90 (m, 1H), 1.80 (m, 1H), 1.61–1.48 (m, 2H), 0.94 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 157.5, 139.6, 139.1, 138.9, 128.8, 128.52, 128.50, 128.3, 128.2, 127.9, 127.7, 127.5, 126.8, 109.4, 101.1, 82.9, 80.2, 77.7, 76.9, 75.1, 73.2, 71.0, 70.9, 69.5, 67.2, 40.1, 38.4, 33.1, 32.6, 25.9, 21.4, 18.1, −3.8, −4.6; HRMS calcd for $C_{42}H_{56}O_7SiNa$ $[(M+Na)^+]$ 723.3693, found 723.3694.

4.1.13. Alcohol 21. To a solution of coupling product **19** (419.6 mg, 0.5994 mmol) in THF (6 mL) at −30°C was added $BH_3\cdot THF$ (1.08 M solution in THF, 2.78 mL, 2.57 mmol), and the resulting solution was stirred at −30°C overnight. The reaction was quenched with water (1 mL), and the resulting mixture was treated with 3 M aqueous NaOH (3 mL) and 30% H_2O_2 (2 mL) and stirred at room temperature for 1 h and then at 40°C for 0.5 h. After being cooled to room temperature, the reaction mixture was diluted with EtOAc, washed with saturated aqueous Na_2SO_3 and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 10→30% EtOAc/hexane) to give alcohol **21** (329.9 mg, 77%) and its isomer (41.4 mg, 10%) as colorless oils. **21**: $[\alpha]_D^{28}=-9.92$ (*c* 0.24, benzene); IR (film) 3446, 2929, 2856, 1614, 1513, 1456, 1362, 1288, 1249, 1100, 1031, 836, 747, 698 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.66–7.65 (m, 2H), 7.34–7.33 (m, 2H), 7.24–7.23 (m, 2H), 7.19–7.09 (m, 9H), 5.33 (s, 1H), 4.42–4.39 (m, 2H), 4.27–4.24 (m, 2H), 3.78–3.74 (m, 2H), 3.69 (ddd, 1H, *J*=5.3, 5.3, 3.8 Hz), 3.62–3.46 (m, 5H), 3.42–3.28 (m, 3H), 3.06 (ddd, 1H, *J*=11.0, 9.3, 4.4 Hz), 2.42–2.37 (m, 2H), 2.09 (m, 1H), 1.98–1.72 (m, 4H), 1.67–1.60 (m, 2H), 1.56–1.48 (m, 2H), 0.95 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 139.2, 139.1, 139.0, 128.9, 128.8, 128.5, 128.42, 128.37, 128.23, 128.18, 128.0, 127.1, 101.2, 83.9, 82.1, 79.0, 78.1, 76.7, 75.5, 73.3, 73.0, 71.1, 70.6, 70.2, 66.8, 40.1, 37.0, 32.6, 28.7, 27.5, 25.9, 18.1, −3.8, −4.6; HRMS calcd for $C_{42}H_{58}O_8SiNa$ $[(M+Na)^+]$ 741.3799, found 741.3770. *Isomer*. $[\alpha]_D^{28}=+31.4$ (*c* 0.69, benzene); IR (film): 3446, 2928, 2857, 1455, 1362, 1286, 1253, 1102, 1028, 837, 775, 748, 698 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.65–7.64 (m, 2H), 7.34–7.33 (m, 2H), 7.24–7.07 (m, 11H), 5.33 (s, 1H), 4.43–4.33 (m, 4H), 4.26 (d, 1H, *J*=11.6 Hz), 3.82 (m, 1H), 3.70–3.63 (m, 2H), 3.57–3.34 (m, 6H), 3.26 (m, 1H), 3.12 (m, 1H), 2.45–2.34 (m, 2H), 2.26 (m, 1H), 2.07 (m, 1H), 1.95–1.67 (m, 4H), 1.60–1.45 (m, 3H), 0.96 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 139.2, 139.1, 139.0, 128.8, 128.5, 128.3, 128.2, 127.90, 127.87, 127.7, 127.5, 126.8, 101.0, 81.2, 79.4, 79.3, 77.9, 76.9, 76.6, 73.1, 70.93, 70.86, 70.3, 67.2, 67.1, 39.9, 36.0,

32.8, 32.2, 31.6, 25.9, 18.0, −4.0, −4.5; MS *m/z* [(M+Na)$^+$] 741.

4.1.14. PMB ether 22. To a suspension of KH (30% oil dispersion, 319.0 mg, 2.393 mmol) in THF (5 mL) was added dropwise a solution of alcohol **21** (318.6 mg, 0.4437 mmol) in THF (5 mL) and the mixture was stirred at room temperature for 20 min. The mixture was treated with PMBCl (120 μL, 0.885 mmol) and a catalytic amount of *n*-Bu_4NI, and stirred at room temperature for 1.5 h. The reaction was quenched with MeOH at 0°C and the mixture was diluted with ether, washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 10% EtOAc/hexane) to give PMB ether **22** (325.4 mg, 88%) as a colorless oil: $[\alpha]_D^{28}$=−8.33 (*c* 0.43, benzene); IR (film) 2927, 2856, 1541, 1456, 1358, 1251, 1098, 1027, 837, 747, 697 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 7.68–7.66 (m, 2H), 7.32–7.09 (m, 15H), 6.82–6.80 (m, 2H), 5.41 (s, 1H), 4.45–4.35 (m, 4H), 4.33–4.15 (m, 4H), 3.94 (ddd, 1H, *J*=10.1, 9.8, 5.5 Hz), 3.73–3.64 (m, 3H), 3.58–3.43 (m, 3H), 3.34–3.25 (m, 4H), 3.10–3.00 (m, 2H), 2.46 (m, 1H), 2.40–2.30 (m, 2H), 2.04–1.87 (m, 3H), 1.85–1.74 (m, 2H), 1.67 (m, 1H), 1.48 (ddd, 1H, *J*=11.6, 11.0, 11.0 Hz), 0.94 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 159.7, 139.4, 139.2, 139.1, 130.8, 129.6, 128.7, 128.3, 128.2, 127.93, 127.85, 127.78, 127.6, 126.9, 114.2, 101.2, 82.0, 81.5, 79.5, 79.0, 77.8, 76.7, 73.12, 73.07, 71.1, 70.5, 70.2, 70.0, 67.2, 54.8, 40.1, 37.5, 33.0, 26.6, 25.9, 21.9, 18.0, −3.8, −4.6; HRMS calcd for $C_{50}H_{66}O_9SiNa$ [(M+Na)$^+$] 861.4374, found 861.4365.

4.1.15. Alcohol 23. To a solution of PMB ether **22** (298.9 mg, 0.3567 mmol) in THF (5 mL) was added TBAF (1.0 M solution in THF, 1.07 mL, 1.07 mmol), and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was concentrated and the residue was purified by column chromatography (silica gel, 60% EtOAc/hexane) to give alcohol **23** (261.0 mg, quant.) as a colorless oil: $[\alpha]_D^{28}$=−35.6 (*c* 0.33, benzene); IR (film) 3446, 2927, 2863, 1614, 1512, 1456, 1248, 1098, 1027, 820, 748, 698 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 7.68–7.66 (m, 2H), 7.31–7.08 (m, 15H), 6.82–6.80 (m, 2H), 5.36 (s, 1H), 4.42 (d, 1H, *J*=11.9 Hz), 4.40–4.37 (m, 2H), 4.34 (d, 1H, *J*=11.9 Hz), 4.27–4.20 (m, 2H), 4.16 (d, 1H, *J*=11.6 Hz), 4.12 (m, 1H), 3.81 (ddd, 1H, *J*=9.8, 9.5, 5.2 Hz), 3.72–3.63 (m, 2H), 3.54–3.43 (m, 3H), 3.38 (ddd, 1H, *J*=11.0, 9.2, 5.2 Hz), 3.30 (s, 3H), 3.19 (m, 1H), 3.11–3.02 (m, 2H), 2.45 (m, 1H), 2.39 (ddd, 1H, *J*=11.6, 4.0, 4.0 Hz), 1.95–1.70 (m, 6H), 1.54 (m, 1H), 1.37 (ddd, 1H, *J*=11.6, 11.3, 11.3 Hz); ^{13}C NMR (125 MHz, C_6D_6) δ 159.8, 139.4, 139.05, 138.98, 130.8, 129.4, 128.8, 128.6, 128.53, 128.49, 128.3, 128.2, 127.9, 127.8, 127.7, 127.5, 126.9, 114.2, 101.2, 82.0, 81.3, 80.4, 79.3, 77.9, 76.8, 74.0, 73.0, 70.7, 70.2, 69.9, 69.3, 67.1, 54.8, 38.7, 38.1, 32.9, 26.7, 22.9; HRMS calcd for $C_{44}H_{52}O_9Na$ [(M+Na)$^+$] 747.3509, found 747.3509.

4.1.16. Ketone 24. To a solution of alcohol **23** (252.8 mg, 0.3492 mmol) in CH_2Cl_2 (5 mL) were added 4 Å molecular sieves (211.0 mg), NMO (81.6 mg, 0.697 mmol) and a catalytic amount of TPAP, and the resulting mixture was stirred at room temperature for 70 min. The mixture was directly subjected to column chromatography (silica gel, 40% EtOAc/hexane) to give ketone **24** (237.6 mg, 94%) as a colorless oil: $[\alpha]_D^{28}$=+1.39 (*c* 0.35, benzene); IR (film) 2931, 2862, 1733, 1611, 1513, 1454, 1364, 1289, 1249, 1099, 1029, 822, 739, 699 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 7.68–7.66 (m, 2H), 7.29–7.27 (m, 2H), 7.19–7.06 (m, 13H), 6.78–6.76 (m, 2H), 5.38 (s, 1H), 4.34–4.28 (m, 3H), 4.26 (d, 1H, *J*=11.9 Hz), 4.20–4.15 (m, 2H), 4.12 (d, 1H, *J*=11.6 Hz), 4.08 (d, 1H, *J*=11.9 Hz), 3.87–3.78 (m, 3H), 3.54–3.35 (m, 6H), 3.29 (s, 3H), 2.64 (dd, 1H, *J*=15.0, 4.3 Hz), 2.37 (dd, 1H, *J*=15.0, 5.5 Hz), 2.23 (m, 1H), 2.05–1.85 (m, 4H), 1.80–1.65 (m, 2H), 1.52 (m, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 207.4, 159.7, 139.1(×2), 138.3, 130.8, 129.3, 128.7, 128.61, 128.58, 128.53, 128.3, 128.2, 127.9, 127.8, 127.7, 126.9, 114.1, 101.2, 82.0, 80.44, 80.42, 78.7, 77.8, 77.5, 73.4, 73.1, 70.5, 70.2, 70.0, 66.6, 54.7, 41.2, 35.9, 34.2, 26.6, 22.5; HRMS calcd for $C_{44}H_{50}O_9Na$ [(M+Na)$^+$] 745.3353, found 745.3362.

4.1.17. Mixed methyl ketal 30. To a solution of ketone **24** (47.2 mg, 0.0654 mmol) in CH_2Cl_2–pH 7 buffer (9:1, 1 mL) at 0°C was added DDQ (27.4 mg, 0.121 mmol). After being stirred at room temperature for 40 min, the reaction mixture was cooled to 0°C and quenched with saturated aqueous $NaHCO_3$. The reaction mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated. The crude hemiketal **29** thus obtained was used without further purification.

To a solution of the crude **29** in MeOH–$CHCl_3$ (2:1, 1.5 mL) was added a small crystal of *p*-TsOH·H_2O. After being stirred at room temperature overnight, the reaction was quenched with Et_3N. The resulting mixture was concentrated and purified by column chromatography (silica gel, 5←10% MeOH/$CHCl_3$) to give dihydroxy mixed methyl ketal (28.2 mg, 82%) as a colorless foam.

To a solution of the above diol (26.8 mg, 0.0508 mmol) in CH_2Cl_2 (1 mL) at 0°C were added DMAP (62.2 mg, 0.509 mmol) and Ac_2O (25 μL, 0.26 mmol). After being stirred at 0°C for 30 min, the reaction was quenched with MeOH. The reaction mixture was diluted with EtOAc, washed with 1 M aqueous HCl, saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 40% EtOAc/hexane) gave mixed methyl ketal **30** (29.5 mg, 97%) as a colorless clear oil: ^{1}H NMR (500 MHz, C_6D_6) δ 7.32–7.30 (m, 2H), 7.22–7.06 (m, 8H), 5.08 (m, 1H), 4.43–4.34 (m, 3H), 4.27 (d, 1H, *J*=11.9 Hz), 4.18 (dd, 1H, *J*=11.6 6.7 Hz), 4.06 (dd, 1H, *J*=11.6, 4.9 Hz), 3.80–3.59 (m, 4H), 3.41 (ddd, 1H, *J*=11.0, 9.8, 4.3 Hz), 3.32 (ddd, 1H, *J*=12.8, 11.9, 4.6 Hz), 3.13 (ddd, 1H, *J*=11.3, 11.0, 4.9 Hz), 3.04 (dd, 1H, *J*=12.2, 4.0 Hz), 2.92 (s, 3H), 2.55 (dd, 1H, *J*=12.8, 4.6 Hz), 2.47 (m, 1H), 2.26 (ddd, 1H, *J*=12.2, 11.6, 11.3 Hz), 2.03 (m, 1H), 1.90–1.55 (m, 11H), 1.35 (dd, 1H, J=12.8, 11.9 Hz); ^{13}C NMR (C_6D_6, 125 MHz) δ 170.0, 169.3, 139.5, 138.8, 128.53, 128.46, 128.3, 128.2, 127.9, 127.8, 127.5, 95.6, 81.6, 80.5, 78.5, 77.7, 75.5, 73.5, 73.3, 72.9, 71.2, 66.9, 65.1, 46.8, 35.0, 32.7, 31.9, 27.0, 25.2, 20.6, 20.3; MS (FAB) *m/z* 596 [(M+Na)$^+$].

4.1.18. Mixed thioketal 31. To a solution of ketone **24** (929.6 mg, 1.286 mmol) in CH_2Cl_2–pH 7 phosphate buffer (9:1, 30 mL) at 0°C was added DDQ (525.7 mg, 2.316 mmol), and the resulting mixture was stirred at room temperature for 40 min. The reaction was quenched with saturated aqueous $NaHCO_3$ at 0°C, and the mixture was diluted with water and extracted with EtOAc (×2). The organic layer was dried over Na_2SO_4 and concentrated to give crude hemiketal **29**, which was used in the next reaction without further purification.

To a solution of the above crude **29** in CH_2Cl_2 (30 mL) were added solid $NaHCO_3$ (109.2 mg, 1.300 mmol), EtSH (1.91 mL, 25.8 mmol) and $Zn(OTf)_2$ (140.5 mg, 0.3865 mmol). After being stirred at room temperature overnight, the mixture was treated with Et_3N (7.18 mL, 51.5 mmol), DMAP (786.2 mg, 6.435 mmol) and Ac_2O (3.64 mL, 38.6 mmol), and the resulting mixture was stirred at room temperature for 4 h. The reaction was quenched with MeOH at 0°C, and the mixture was diluted with EtOAc, washed with 1 M aqueous HCl, saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 40% EtOAc/hexane) to give mixed thioketal **31** (723.1 mg, 88% for three steps) as a colorless oil: $[\alpha]_D^{28}$=+54.0 (*c* 0.15, benzene); IR (film) 2927, 2868, 1740, 1455, 1370, 1237, 1100, 1068, 1036, 743, 699 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.32–7.31 (m, 2H), 7.24–7.23 (m, 2H), 7.17–7.07 (m, 6H), 5.08 (m, 1H), 4.44–4.38 (m, 2H), 4.36 (d, 1H, *J*=11.9 Hz), 4.33 (d, 1H, *J*=11.9 Hz), 4.17 (dd, 1H, *J*=11.6, 6.4 Hz), 4.07–3.96 (m, 3H), 3.79–3.70 (m, 2H), 3.70–3.62 (m, 2H), 3.14 (m, 1H), 3.06 (m, 1H), 2.63 (dd, 1H, *J*=12.5, 4.6 Hz), 2.44 (m, 1H), 2.35–2.17 (m, 3H), 2.02 (m, 1H), 1.97–1.53 (m, 12H), 1.09 (t, 3H, *J*=7.6 Hz); ^{13}C NMR (125 MHz, C_6D_6) δ 170.0, 169.3, 139.5, 139.0, 128.54, 128.47, 128.40, 128.3, 128.1, 127.9, 127.5, 87.5, 81.6, 80.5, 79.7, 79.5, 76.7, 73.6, 73.5, 73.0, 71.6, 66.8, 65.1, 41.3, 33.3, 32.9, 27.0, 25.0, 20.6, 20.3, 20.1, 14.9; HRMS calcd for $C_{35}H_{46}O_9SNa$ [$(M+Na)^+$] 665.2760, found 665.2763.

4.1.19. Sulfone 32. To a solution of mixed thioketal **31** (628.6 mg, 0.9791 mmol) in CH_2Cl_2 (25 mL) were added solid $NaHCO_3$ (404.0 mg, 4.809 mmol) and *m*-CPBA (80% purity, 518.8 mg, 2.405 mmol), and the resulting mixture was stirred at room temperature for 75 min. The mixture was diluted with EtOAc, washed with saturated aqueous Na_2SO_3 and brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 50% EtOAc/hexane) to give sulfone **32** (640.4 mg, 96%) as a colorless oil, which was used in the next reaction without further purification: ^1H NMR (500 MHz, C_6D_6) δ 7.33–7.31 (m, 2H), 7.25–7.23 (m, 2H), 7.18–7.05 (m, 6H), 5.08 (m, 1H), 4.44–4.39 (m, 2H), 4.37 (d, 1H, *J*=12.2 Hz), 4.34 (d, 1H, *J*=11.6 Hz), 4.17 (dd, 1H, *J*=11.6, 6.4 Hz), 4.08–3.97 (m, 3H), 3.79–3.71 (m, 2H), 3.70–3.63 (m, 2H), 3.14 (ddd, 1H, *J*=11.3, 9.8, 4.9 Hz), 3.06 (ddd, 1H, *J*=12.5, 4.0 Hz), 2.67 (dd, 1H, *J*=12.5, 4.9 Hz), 2.43 (m, 1H), 2.34–2.19 (m, 3H), 2.02 (ddd, 1H, *J*=11.6, 4.3, 4.0 Hz), 1.97–1.55 (m, 12H), 1.09 (t, 3H, *J*=7.6 Hz); ^{13}C NMR (125 MHz, C_6D_6) δ 170.0, 169.3, 139.5, 139.0, 128.53, 128.46, 128.3, 128.2, 127.8, 127.5, 87.5, 81.6, 80.5, 79.7, 79.5, 76.7, 73.6, 73.5, 73.0, 71.6, 66.8, 65.1, 41.3, 33.3, 32.9, 27.0, 25.0, 20.6, 20.3, 20.1, 14.9.

4.1.20. Tricyclic ether 28. To a solution of the above sulfone **32** (50.6 mg, 0.0738 mmol) in CH_2Cl_2 (3.7 mL) at −78°C was added Me_3Al (1.0 M solution in hexane, 365 μL, 0.365 mmol), and the resulting mixture was allowed to warm gradually to room temperature over a period of 5 h. The reaction was quenched by the addition of saturated aqueous potassium sodium tartrate, and the reaction mixture was diluted with EtOAc, washed with saturated aqueous potassium sodium tartrate and brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 40% EtOAc/hexane) to give tricyclic ether **28** (39.5 mg, 90%) as a colorless oil: $[\alpha]_D^{28}$=−25.2 (*c* 0.19, benzene); IR (film) 3062, 3031, 2945, 2871, 1740, 1496, 1455, 1370, 1236, 1096, 1052, 804, 738, 699 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.31–7.30 (m, 2H), 7.22–7.21 (m, 2H), 7.17–7.05 (m, 6H), 5.09 (m, 1H), 4.42–4.35 (m, 3H), 4.21–4.15 (m, 2H), 4.06 (dd, 1H, *J*=11.6, 4.9 Hz), 3.74–3.69 (m, 2H), 3.65 (m, 1H), 3.57 (m, 1H), 3.36 (ddd, 1H, *J*=9.8, 9.5, 4.9 Hz), 3.27 (ddd, 1H, *J*=10.7, 10.7, 4.9 Hz), 3.09 (ddd, 1H, *J*=11.3, 9.8, 4.9 Hz), 2.95 (dd, 1H, *J*=12.5, 3.7 Hz), 2.42 (m, 1H), 2.32 (dd, 1H, *J*=11.6, 4.9 Hz), 2.05 (m, 1H), 1.85–1.53 (m, 13H), 1.08 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 169.9, 169.3, 139.4, 138.9, 128.54, 128.51, 128.49, 128.3, 128.0, 127.8, 127.7, 127.5, 81.6, 81.1, 79.3, 78.8, 76.7, 73.7, 73.6, 73.0, 72.4, 70.9, 67.0, 65.1, 43.9, 33.1, 32.9, 27.7, 25.1, 20.6, 20.3, 15.9; HRMS calcd for $C_{34}H_{44}O_9Na$ [$(M+Na)^+$] 619.2883, found 619.2899.

4.1.21. Acetonide 5. To a solution of tricyclic ether **28** (39.5 mg, 0.0663 mmol) in MeOH–CH_2Cl_2 (1:1, 4 mL) was added NaOMe (1 M solution in MeOH, 20 μL, 0.020 mmol), and the resulting mixture was stirred at room temperature for 35 min. The reaction was quenched by the addition of Amberlyst ion-exchange resin. Filtration of the resin followed by concentration gave crude diol, which was used in the next reaction without further purification.

A solution of the above crude diol in CH_2Cl_2–DMF (2:3, 5 mL) was treated with $Me_2C(OMe)_2$ (324 μL, 2.64 mmol) and a catalytic amount of PPTS, and the resulting mixture was stirred at room temperature overnight. The mixture was diluted with ether, washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 30% EtOAc/hexane) to give acetonide **5** (35.8 mg, 98% for two steps) as a colorless oil: $[\alpha]_D^{28}$=−32.7 (*c* 0.87, benzene); IR (film) 2990, 2942, 2873, 1455, 1371, 1268, 1200, 1094, 1029, 737, 698 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.31–7.29 (m, 2H), 7.24–7.22 (m, 2H), 7.15–7.06 (m, 6H), 4.43–4.33 (m, 3H), 4.18 (d, 1H, *J*=11.6 Hz), 3.93 (dd, 1H, *J*=11.3, 5.5 Hz), 3.75–3.57 (m, 5H), 3.44 (m, 1H), 3.32–3.24 (m, 2H), 2.98 (dd, 1H, *J*=12.8, 4.0 Hz), 2.92 (ddd, 1H, *J*=11.0, 9.2, 4.0 Hz), 2.42 (m, 1H), 2.31 (dd, 1H, *J*=11.3, 4.9 Hz), 2.04 (ddd, 1H, *J*=11.6, 4.3, 4.3 Hz), 2.03–1.90 (m, 2H), 1.85–1.74 (m, 3H), 1.69 (ddd, 1H, *J*=12.2, 11.9, 11.6 Hz), 1.57 (dd, 1H, *J*=11.9, 11.3 Hz), 1.47 (s, 3H), 1.29 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 139.4, 139.0, 128.52, 128.49, 128.0, 127.8, 127.7, 127.5,

98.5, 80.9, 79.3, 78.7, 76.8, 75.8, 73.5, 73.2, 73.0, 72.2, 70.9, 67.0, 63.5, 44.0, 33.2, 32.6, 30.2, 29.8, 28.9, 19.4, 15.7; HRMS calcd for $C_{33}H_{44}O_7Na$ [$(M+Na)^+$] 575.2985, found 575.3016.

4.1.22. Alcohol 33b. To a solution of acetonide **5** (217.5 mg, 0.3940 mmol) in EtOAc (10 mL) was added 20% $Pd(OH)_2$/C (72.2 mg), and the resulting mixture was stirred under hydrogen atmosphere overnight. The catalyst was filtered off, and the filtrate was concentrated to give crude diol, which was used in the next reaction without further purification.To a solution of the above crude diol in CH_2Cl_2 (10 mL) were added imidazole (65.6 mg, 0.964 mmol) and TIPSCl (100 μL, 0.467 mmol), and the resulting mixture was stirred at room temperature for 4 h. Additional imidazole (85.3 mg, 1.25 mmol) and TIPSCl (150 μL, 0.701 mmol) were added and the mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with EtOAc, washed with 1 M aqueous HCl, saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 35% EtOAc/hexane) to give alcohol **33b** (185.5 mg, 89% for two steps) as a colorless oil: $[\alpha]_D^{27}=-7.91$ (*c* 0.29, benzene); IR (film) 3445, 2943, 2867, 1462, 1380, 1268, 1093, 1052, 882, 747, 682 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 3.89 (dd, 1H, *J*=11.3, 5.8 Hz), 3.86–3.75 (m, 2H), 3.70 (m, 1H), 3.62 (dd, 1H, *J*=11.3, 8.9 Hz), 3.52–3.42 (m, 2H), 3.34 (m, 1H), 3.25 (ddd, 1H, *J*=9.2, 8.9, 5.8 Hz), 3.08 (dd, 1H, *J*=12.8, 4.0 Hz), 3.01 (ddd, 1H, *J*=11.0, 9.2, 4.9 Hz), 2.57 (br, 1H), 2.25 (dd, 1H, *J*=11.6, 4.9 Hz), 2.17 (ddd, 1H, *J*=11.9, 4.9, 4.0 Hz), 2.08 (m, 1H), 1.98–1.88 (m, 2H), 1.83–1.72 (m, 4H), 1.64 (dd, 1H, *J*=11.6, 11.3 Hz), 1.44 (s, 3H), 1.28 (s, 3H), 1.16–1.00 (m, 24H); ^{13}C NMR (125 MHz, C_6D_6) δ 98.5, 82.3, 80.9, 78.9, 75.8, 73.5, 73.2, 72.3, 69.9, 63.5, 60.7, 47.1, 37.4, 32.8, 30.2, 29.8, 28.8, 19.5, 18.1, 15.7, 12.2; HRMS calcd for $C_{28}H_{52}O_7SiNa$ [$(M+Na)^+$] 551.3380, found 551.3355.

4.1.23. Ketone 34b. To a solution of alcohol **33b** (185.5 mg, 0.3513 mmol) in CH_2Cl_2 (10 mL) were added 4 Å molecular sieves (167.7 mg), NMO (88.5 mg, 0.755 mmol) and a catalytic amount of TPAP. The resulting mixture was stirred at room temperature for 30 min and directly subjected to column chromatography (silica gel, EtOAc) to give ketone **34b** (183.5 mg, 99%) as a colorless oil: $[\alpha]_D^{27}=-2.70$ (*c* 0.11, benzene); IR (film) 2943, 2867, 1718, 1558, 1541, 1507, 1457, 1375, 1267, 1095, 881, 747, 682 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 3.98 (dd, 1H, *J*=8.9, 3.7 Hz), 3.92–3.85 (m, 2H), 3.77 (m, 1H), 3.67 (ddd, 1H, *J*=9.2, 6.7, 6.7 Hz), 3.61 (dd, 1H, *J*=11.3, 9.2 Hz), 3.28–3.20 (m, 3H), 2.94 (ddd, 1H, *J*=11.3, 9.5, 4.9 Hz), 2.78 (d, 1H, *J*=15.0 Hz), 2.44 (m, 1H), 2.28 (d, 1H, *J*=15.0 Hz), 2.18 (ddd, 1H, *J*=11.9, 4.9, 4.6 Hz), 1.92 (m, 1H), 1.86–1.66 (m, 5H), 1.45 (s, 3H), 1.28 (s, 3H), 1.21–1.00 (m, 24H); ^{13}C NMR (125 MHz, C_6D_6) δ 205.2, 98.5, 80.4, 80.3, 77.5, 75.8, 73.8, 73.4, 73.2, 63.5, 59.3, 54.4, 33.5, 32.7, 30.0, 29.7, 28.8, 19.4, 18.2, 16.1, 12.3; HRMS calcd for $C_{28}H_{50}O_7SiNa$ [$(M+Na)^+$] 549.3224, found 549.3227.

4.1.24. *exo*-Olefin 36. To a suspension of $Ph_3P^+CH_3Br^-$ (493.5 mg, 1.382 mmol) in THF (10 mL) at 0°C was added NaHMDS (1.0 M solution in THF, 1.30 mL, 1.30 mmol) and the resulting ylide solution was stirred at 0°C for 20 min. To the solution cooled to −78°C was added a solution of ketone **34b** (120.8 mg, 0.2297 mmol) in THF (7 mL), and the mixture was allowed to warm gradually to room temperature over a period of 3.5 h. The reaction was quenched with saturated aqueous NH_4Cl, and the mixture was diluted with EtOAc, washed with water and brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 10% EtOAc/hexane) to give *exo*-olefin **36** (110.8 mg, 92%) as a colorless oil: ^1H NMR (500 MHz, C_6D_6) δ 4.78 (s, 1H), 4.68 (s, 1H), 4.11 (m, 1H), 4.03 (ddd, 1H, *J*=9.8, 9.2, 4.9 Hz), 3.88 (dd, 1H, *J*=11.3, 5.5 Hz), 3.83 (ddd, 1H, *J*=9.8, 6.4, 4.0 Hz), 3.71 (ddd, 1H, *J*=9.2, 7.0, 6.7 Hz), 3.62 (dd, 1H, *J*=11.3, 9.2 Hz), 3.44 (ddd, 1H, *J*=8.9, 8.5, 4.0 Hz), 3.28–3.20 (m, 2H), 3.06 (ddd, 1H, *J*=11.3, 8.9, 4.9 Hz), 2.43 (d, 1H, *J*=12.5 Hz), 2.35 (d, 1H, *J*=12.5 Hz), 2.22 (ddd, 1H, *J*=11.9, 4.9, 4.0 Hz), 2.10 (m, 1H), 2.00–1.89 (m, 2H), 1.85–1.74 (m, 4H), 1.44 (s, 3H), 1.28 (s, 3H), 1.18–1.05 (m, 24H); ^{13}C NMR (125 MHz, C_6D_6) δ 145.9, 110.3, 98.4, 80.9, 79.1, 75.7, 74.3, 73.3, 73.2, 63.5, 59.9, 48.7, 35.2, 33.1, 30.4, 30.3, 29.8, 28.8, 19.5, 18.3, 15.1, 12.3.

4.1.25. Diol 39. To a solution of *exo*-olefin **36** (49.4 mg, 0.0943 mmol) in *t*-BuOH–H_2O (1:1, 5 mL) were added NMO (110.5 mg, 0.9432 mmol) and OsO_4 (71.1 mg, 0.280 mmol), and the resulting mixture was stirred at room temperature for 1.5 days. To the mixture were added saturated aqueous $NaHSO_3$ (10 mL) and pyridine (3 mL), and the resultant mixture was stirred at room temperature for 1 h. The mixture was diluted with EtOAc, washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 50% EtOAc/hexane) to give diol **39** (50.7 mg, 96%) as a colorless oil: $[\alpha]_D^{28}=-19.1$ (*c* 0.32, $CHCl_3$); IR (film) 3438, 2943, 2867, 1462, 1381, 1268, 1200, 1095, 1067, 922, 882, 749, 682, 516 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 3.93–3.81 (m, 3H), 3.70 (m, 1H), 3.67–3.56 (m, 3H), 3.49–3.42 (m, 2H), 3.24 (ddd, 1H, *J*=9.2, 8.9, 5.5 Hz), 3.10 (dd, 1H, *J*=12.8, 4.0 Hz), 3.02 (ddd, 1H, *J*=10.7, 9.2, 5.2 Hz), 2.50 (d, 1H, *J*=12.8 Hz), 2.16 (ddd, 1H, *J*=11.6, 5.2, 4.0 Hz), 2.08 (m, 1H), 1.99–1.87 (m, 2H), 1.81–1.69 (m, 3H), 1.63 (d, 1H, *J*=12.8 Hz), 1.56 (m, 1H), 1.45 (s, 3H), 1.29 (s, 3H), 1.18 (s, 3H), 1.15–1.05 (m, 21H); ^{13}C NMR (125 MHz, C_6D_6) δ 98.5, 83.7, 81.0, 80.7, 76.0, 73.3, 73.1, 72.1, 71.9, 65.2, 63.5, 61.0, 48.0, 32.44, 32.39, 30.1, 29.8, 28.8, 19.5, 18.2, 15.3, 12.3; HRMS calcd for $C_{29}H_{54}O_8SiNa$ [$(M+Na)^+$] 581.3486, found 581.3491.

4.1.26. Monotosylate 40. To a solution of diol **39** (144.3 mg, 0.2586 mmol) in $(CH_2Cl)_2$ (10 mL) were added DMAP (317.9 mg, 2.602 mmol) and *p*-TsCl (246.9 mg, 1.295 mmol), and the resulting mixture was stirred at room temperature overnight. The mixture was diluted with EtOAc, washed with 1 M aqueous HCl, saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 20→40% EtOAc/hexane) to give monotosylate **40** (182.4 mg, 99%) as a colorless oil: $[\alpha]_D^{27}=-38.5$ (*c* 0.07, benzene); IR (film) 2943, 2867, 1457, 1369, 1267, 1177, 1096, 986, 882, 839, 750, 669, 553 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.75–7.73 (m, 2H), 6.66–6.64 (m,

2H), 4.37 (d, 1H, J=10.7 Hz), 4.33 (d, 1H, J=10.7 Hz), 3.88 (dd, 1H, J=11.3, 5.8 Hz), 3.78 (ddd, 1H, J=10.1, 10.1, 4.3 Hz), 3.72–3.59 (m, 4H), 3.40 (ddd, 1H, J=8.9, 8.5, 4.3 Hz), 3.21 (ddd, 1H, J=8.9, 8.9, 5.8 Hz), 3.04 (dd, 1H, J=12.8, 3.7 Hz), 2.96 (ddd, 1H, J=10.9, 8.9, 4.9 Hz), 2.62 (d, 1H, J=13.1 Hz), 2.51 (br, 1H), 2.09 (ddd, 1H, J=11.3, 4.9, 3.7 Hz), 1.97–1.85 (m, 3H), 1.79 (s, 3H), 1.79–1.62 (m, 2H), 1.58 (d, 1H, J=13.1 Hz), 1.44 (s, 3H), 1.33 (m, 1H), 1.28 (s, 3H), 1.18–0.97 (m, 24H); HRMS calcd for $C_{36}H_{60}O_{10}SSiNa$ [$(M+Na)^+$] 735.3574, found 735.3587.

4.1.27. FGH ring system 4. To a solution of monotosylate **40** (41.6 mg, 0.0584 mmol) in THF (4 mL) at 0°C was added $LiAlH_4$ (22.5 mg, 0.593 mmol). The resulting mixture was stirred at 0°C for 1 h and then allowed to warm to room temperature for 2 h. The reaction was quenched with EtOAc at 0°C, and the mixture was treated with 3 M aqueous NaOH (0.3 mL) and vigorously stirred at room temperature until a white gel was precipitated. Filtration and concentration followed by column chromatography (silica gel, 30% EtOAc/hexane) gave FGH ring system **4** (23.8 mg, 75%) as a colorless oil: $[\alpha]_D^{27}=-39.2$ (c 0.20, benzene); IR (film) 3445, 2943, 2867, 1459, 1382, 1270, 1200, 1096, 1065, 930, 882, 749, 682 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 3.94–3.86 (m, 2H), 3.84 (m, 1H), 3.71 (m, 1H), 3.64 (dd, 1H, J=11.3, 8.9 Hz), 3.51–3.46 (m, 2H), 3.24 (ddd, 1H, J=8.9, 8.9, 5.4 Hz), 3.07 (dd, 1H, J=12.8, 4.0 Hz), 3.02 (ddd, 1H, J=11.0, 9.2, 5.2 Hz), 2.17 (ddd, 1H, J=11.6, 5.2, 4.0 Hz), 2.05–1.90 (m, 4H), 1.84–1.66 (m, 5H), 1.62 (m, 1H), 1.60 (s, 3H), 1.45 (s, 3H), 1.18–1.03 (m, 27H); ^{13}C NMR (125 MHz, C_6D_6) δ 98.4, 85.1, 80.5, 76.0, 73.2, 73.1, 72.0, 70.1, 63.5, 61.1, 54.6, 33.1, 32.5, 30.2, 29.8, 28.8, 24.7, 19.5, 18.2, 15.8, 12.3; HRMS calcd for $C_{29}H_{54}O_7SiNa$ [$(M+Na)^+$] 565.3537, found 565.3527.

4.1.28. Alcohol 41. To a solution of FGH ring system **4** (121.9 mg, 0.2249 mmol) in THF (5 mL) at 0°C was added excess amount of KH (30% oil dispersion, ca. 300 mg) and the resulting mixture was stirred at 0°C for 20 min. The mixture was treated with BnBr (135 μL, 1.13 mmol) at 0°C, allowed to warm to room temperature, and stirred for 50 min. The reaction was quenched with MeOH at 0°C, and the reaction mixture was diluted with EtOAc, washed with water and brine, dried over Na_2SO_4, and concentrated to give crude benzyl ether, which was used in the next reaction without further purification.To a solution of the above benzyl ether in THF (5 mL) was added TBAF (1.0 M solution in THF, 680 μL, 0.680 mmol) and the resulting mixture was stirred at room temperature for 45 min. The reaction mixture was diluted with EtOAc, washed with saturated aqueous NH_4Cl and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 30→50% EtOAc/hexane) to give alcohol **41** (93.3 mg, 87% for two steps) as a colorless oil: $[\alpha]_D^{27}=+29.1$ (c 0.15, benzene); IR (film) 3481, 2942, 2876, 1456, 1382, 1268, 1200, 1096, 1066, 878, 736, 698 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.25–7.08 (m, 5H), 4.20 (d, 1H, J=11.0 Hz), 4.15 (d, 1H, J=11.0 Hz), 3.96 (dd, 1H, J=11.3, 5.5 Hz), 3.79–3.69 (m, 3H), 3.66 (dd, 1H, J=11.3, 9.2 Hz), 3.60 (dd, 1H, J=9.8, 2.4 Hz), 3.46 (ddd, 1H, J=9.2, 8.9, 4.0 Hz), 3.27 (ddd, 1H, J=9.2, 9.2, 5.5 Hz), 2.92 (dd, 1H, J=12.8, 3.7 Hz), 2.87 (ddd, 1H, J=11.0, 9.2, 5.2 Hz), 2.08 (d, 1H, J=11.9 Hz), 2.03–1.74 (m, 8H), 1.48 (s, 3H), 1.31 (s, 3H), 1.12 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 139.5, 128.5, 128.30, 128.26, 127.7, 127.6, 98.5, 85.9, 80.9, 80.3, 76.0, 74.9, 73.3, 73.1, 71.8, 63.53, 63.47, 61.6, 50.5, 32.2 (2C), 30.2, 29.9, 28.9, 21.1, 19.4, 15.9; HRMS calcd for $C_{27}H_{41}O_7$ [$(M+H)^+$] 477.2852, found 477.2896.

4.1.29. α,β-Unsaturated ester 42. To a mixture of alcohol **41** (82.9 mg, 0.174 mmol) and Et_3N (120 μL, 0.861 mmol) in CH_2Cl_2–DMSO (1:1, 5 mL) at 0°C was added SO_3·pyridine (111.5 mg, 0.7006 mmol). The resulting mixture was stirred at 0°C for 1.5 h. The mixture was diluted with EtOAc, and the organic layer was washed with 1 M aqueous HCl, saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated to give crude aldehyde, which was used in the next reaction without further purification.

A solution of the above aldehyde in $(CH_2Cl)_2$ (5 mL) was treated with $Ph_3P{=}CHCO_2Bn$ (107.2 mg, 0.2612 mmol) and the resulting mixture was stirred at room temperature overnight. The mixture was directly subjected to column chromatography (silica gel, 25% EtOAc/hexane) to give α,β-unsaturated benzyl ester **42** (89.2 mg, 86% for two steps) as a colorless oil: $[\alpha]_D^{27}=-4.37$ (c 0.41, benzene); IR (film) 3445, 2943, 2861, 1718, 1653, 1456, 1381, 1325, 1267, 1172, 1096, 738, 697 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.30 (ddd, 1H, J=15.6, 7.5, 6.5 Hz), 7.25–7.02 (m, 10H), 5.99 (d, 1H, J=15.6 Hz), 5.09 (s, 2H), 4.17 (d, 1H, J=11.0 Hz), 4.13 (d, 1H, J=11.0 Hz), 3.96 (dd, 1H, J=11.3, 5.5 Hz), 3.72 (m, 1H), 3.64 (dd, 1H, J=11.3, 8.9 Hz), 3.48–3.40 (m, 2H), 3.27 (ddd, 1H, J=8.9, 8.9, 5.5 Hz), 2.88–2.77 (m, 2H), 2.43 (m, 1H), 2.14–1.73 (m, 8H), 1.57 (ddd, 1H, J=12.2, 11.9, 11.6 Hz), 1.48 (s, 3H), 1.30 (s, 3H), 1.09 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 166.0, 147.3, 139.5, 136.9, 128.5, 128.3, 128.1, 127.7, 127.6, 123.0, 98.5, 85.1, 80.9, 80.4, 76.0, 74.8, 73.3, 73.2, 71.8, 66.0, 63.53, 63.48, 50.5, 32.2, 32.0, 30.3, 29.9, 28.9, 20.8, 19.4, 16.0; HRMS calcd for $C_{36}H_{46}O_8Na$ [$(M+Na)^+$] 629.3090, found 629.3047.

4.1.30. EFGH ring system 3. To a solution of α,β-unsaturated ester **42** (33.4 mg, 55.1 μmol) in EtOAc (2 mL) was added a catalytic amount of 20% $Pd(OH)_2/C$, and the resulting mixture was stirred at room temperature under hydrogen atmosphere overnight. The catalyst was removed by filtration through Celite and the filtrate was concentrated to give crude hydroxy carboxylic acid **43**, which was azeotropically dried with toluene and used in the next step.

To a solution of the above hydroxy carboxylic acid **43** in THF–toluene (1:1, 2 mL) were added Et_3N (76 μL, 0.55 mmol) and 2,4,6-trichlorobenzoylchloride (34 μL, 0.22 mmol), and the resulting mixture was stirred at room temperature for 45 min and then diluted with toluene (10 mL). The reaction mixture was added dropwise to a refluxing solution of DMAP (80.2 mg, 0.671 mmol) in toluene (10 mL) over a period of 45 min. The mixture was stirred under reflux for 1 h. The mixture was cooled to room temperature, concentrated and diluted with EtOAc. The organic layer was washed with 1 M aqueous HCl, saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column

chromatography (silica gel, 50→60% EtOAc/hexane) to give EFGH ring system **3** (20.9 mg, 93% for two steps) as a colorless amorphous solid: $[\alpha]_D^{28}=+29.3$ (*c* 0.79, $CHCl_3$); IR (film) 2947, 2883, 1712, 1456, 1382, 1278, 1197, 1110, 1078, 912, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.85 (dd, 1H, *J*=11.6, 5.5 Hz), 3.70 (m, 1H), 3.56 (dd, 1H, *J*=11.6, 8.9 Hz), 3.48 (ddd, 1H, *J*=9.2, 8.9, 4.0 Hz), 3.39 (dd, 1H, *J*=11.6, 3.1 Hz), 3.32 (ddd, 1H, *J*=8.9, 8.9, 5.5 Hz), 3.24 (ddd, 1H, *J*=11.0, 9.2, 5.2 Hz), 3.09 (dd, 1H, *J*=12.8, 3.7 Hz), 2.82 (m, 1H), 2.55 (m, 1H), 2.14 (d, 1H, *J*=12.8 Hz), 2.08 (ddd, 1H, *J*=11.9, 5.2, 3.7 Hz), 2.06–1.52 (m, 13H), 1.41 (s, 3H), 1.34 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 98.6, 84.8, 80.7, 80.61, 80.57, 75.9, 72.7, 72.6, 71.5, 63.1, 53.2, 37.1, 31.6, 30.3, 29.6, 29.2, 28.3, 22.2, 20.8, 19.6, 15.9; HRMS calcd for $C_{22}H_{34}O_7Na$ $[(M+Na)^+]$ 433.2202; found 433.2211.

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