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A general strategy for the convergent synthesis of fused polycyclic ethers via *B*-alkyl Suzuki coupling: synthesis of the ABCD ring fragment of ciguatoxins

Makoto Sasaki,[a,b,*] Makoto Ishikawa,[a] Haruhiko Fuwa[a] and Kazuo Tachibana[a]

[a]*Department of Chemistry, Graduate School of Science, The University of Tokyo, and CREST, Japan Science and Technology Corporation (JST), Hongo, Bunkyo-ku, Tokyo 113-0033, Japan*
[b]*Department of Biomolecular Science, Graduate School of Life Science, Tohoku University, Tsutsumidori-Amamiya, Aoba-ku, Sendai 981-8555, Japan*

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Abstract—A new method for convergent coupling of fused polycyclic ethers has been developed, which relies on *B*-alkyl Suzuki cross-coupling of lactone-derived enol triflates or phosphates. The strategy was successfully applied to a convergent synthesis of the ABCD ring fragment **4** of ciguatoxins, the causative toxin for ciguatera fish poisoning. The synthetic route includes a convergent union of the B and D rings (**18** and **29c**, respectively) by the *B*-alkyl Suzuki coupling, introduction of a double bond into the D ring followed by reductive closure of the tetrahydropyran C ring to afford the BCD ring system **51**, and, finally, ring-closing metathesis reaction to construct the oxepene A ring.

1. Introduction

The polycyclic ether class of marine natural products, exemplified by brevetoxins, ciguatoxins, and maitotoxin, has received much attention due to the biological potency and structural complexity of these molecules.[1] Among the most remarkable polycyclic ethers are ciguatoxin (CTX, **1**) and its congeners. These are the principal toxins for ciguatera seafood poisoning that is prevalent in circum tropical areas with more than 20,000 victims annually and continues to be a serious public health problem.[2] The causative toxins originate in an epiphytic dinoflagellate *Gambierdiscus toxicus*[3] and are accumulated in fish through the food chain, thus causing human intoxication. These dinoflagellate toxins undergo oxidative changes in fish, yielding the principal toxins, ciguatoxin and a number of congeners. Ciguatoxin (**1**) was first isolated from the moray eel *Gymnothorax javanicus* by Scheuer's group in 1980.[4] The structure of **1**, except for the absolute configuration and relative stereochemistry at C2, was elucidated using a purified sample of only 0.35 μg by Yasumoto and co-workers in 1989.[5] The ciguatoxin molecule consists of 12 *trans*-fused polycyclic ethers, ranging from six- to nine-membered, and a spirally attached five-membered cyclic ether at one end. So far, 22 ciguatoxin congeners, including CTX3C **2**[6] and 51-hydroxyCTX3C **3**,[7] have been identified from toxic fish and/or *G. toxicus*, and the structures were elucidated by extensive NMR analysis and/or CID FAB/MS/MS experiments using a minute amount of samples.[8] More recently, the absolute configuration of **1** was successfully determined as shown in Fig. 1 by Yasumoto and co-workers.[9]

The ciguatoxins are extremely potent neurotoxins that bind to voltage-sensitive Na^+-channels (VSSC) and inhibit depolarization to allow inward Na^+ influx to continue;[10] however, the mechanism for the binding of ciguatoxins to VSSC has not yet been clarified. The binding site on VSSC was reported to be shared by brevetoxins, another class of structurally related marine toxins.[11] It is noteworthy that the binding affinity of **1** was shown to be some 10 times more potent than that of brevetoxins, despite their structural similarity.[11b] However, the precise location of the receptor site of the ciguatoxins and brevetoxins on VSSC has not been fully identified.[12] The scarcity of ciguatoxins from natural sources has also precluded further investigations on their interactions with VSSC. Thus, a practical total synthesis currently provides the only potential source of useful amounts of these intriguing molecules. In addition, structure–activity relationship studies of structural analogues not accessible by degradation or functionalization of the natural toxins may provide useful information for understanding the detailed structural basis necessary for their high-affinity binding to VSSC.

Keywords: marine metabolites; polyethers; ring-closing metathesis; Suzuki reactions; toxins.

* Corresponding author. Tel.: +81-3-5841-4357; fax: +81-3-5841-8380; e-mail: msasaki@chem.s.u-tokyo.ac.jp

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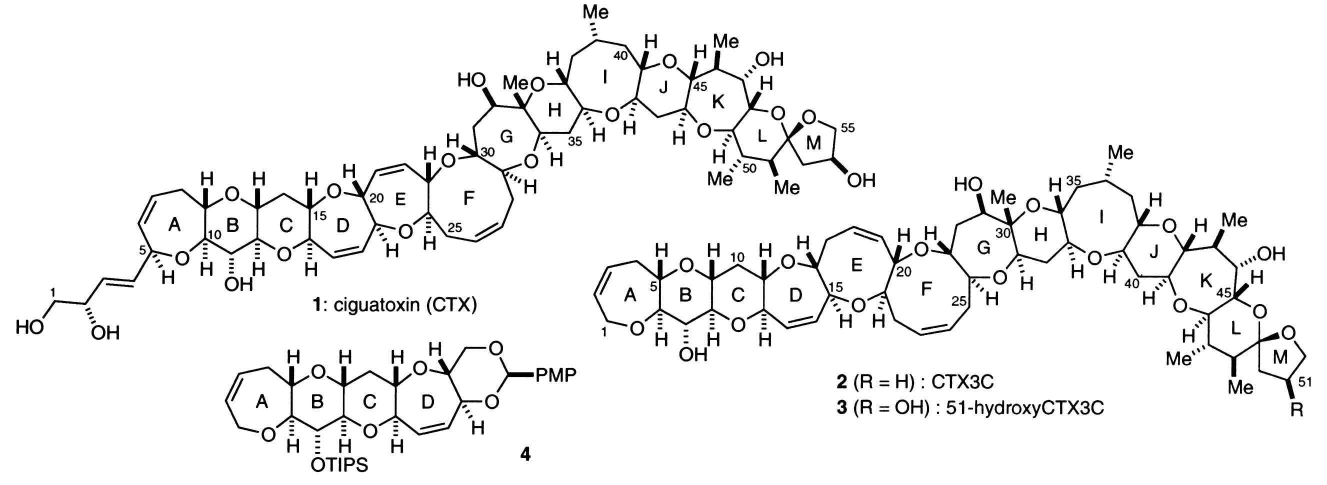

1: ciguatoxin (CTX)

2 (R = H) : CTX3C

3 (R = OH) : 51-hydroxyCTX3C

4

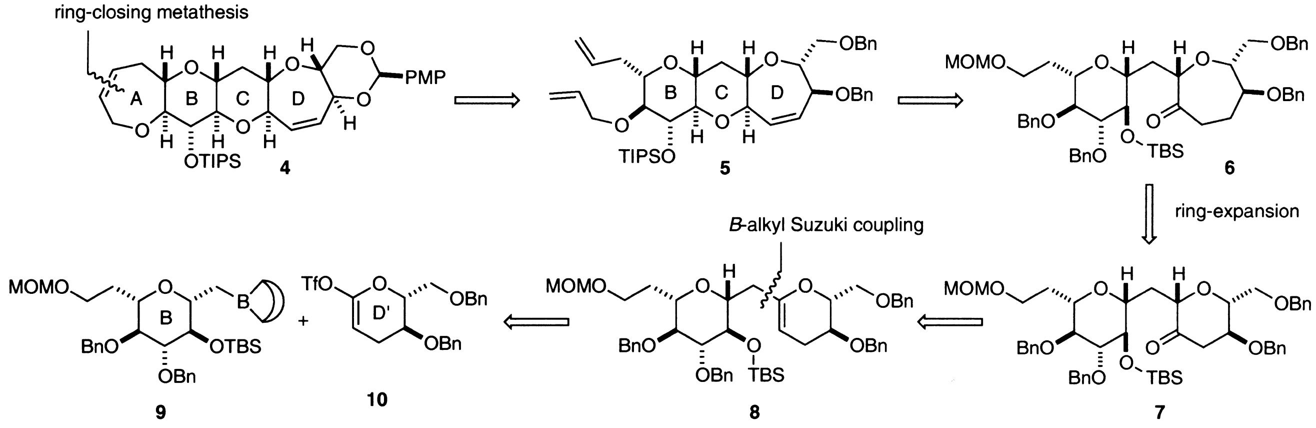
Figure 1. Structures of ciguatoxin (CTX, **1**), its congeners (CTX3C, **2**; 51-hydroxyCTX3C, **3**), and the ABCD ring fragment **4**.

The complex molecular architecture and their potential as tools for biological studies of ciguatoxins, as well as their limited availability from natural sources, make these toxins attractive targets for total synthesis, and thus a number of synthetic efforts, including ours,[13,14] have been reported.[15–17] Our own investigations in this area have focused on development of a practical methodology for the convergent assembly of polycyclic ethers.[18] We have recently reported an efficient and general strategy for the convergent synthesis of polycyclic ether frameworks via palladium-catalyzed Suzuki coupling of alkylboranes with lactone-derived enol triflates.[14a,19–21] However, the *B*-alkyl Suzuki coupling of lactone-derived enol triflates was limited to reactions of six-membered rings, and seven-membered enol triflates could not be utilized as the coupling partners due to their instability under the reaction conditions. In order to overcome this problem, we have disclosed *B*-alkyl Suzuki coupling of lactone-derived enol phosphates, superior substrates to the corresponding triflates with respect to their stability and handling.[14b–e,22] It was noteworthy that the method enabled convergent coupling of medium-ring ethers with a variety of ring sizes. In this contribution, we describe full details of our *B*-alkyl Suzuki coupling of lactone-derived enol phosphates and its successful application to the convergent synthesis of the ABCD ring fragment **4** of representative ciguatoxin analogues, CTX3C (**2**) and 51-hydroxyCTX3C (**3**).[23]

2. Results and discussion

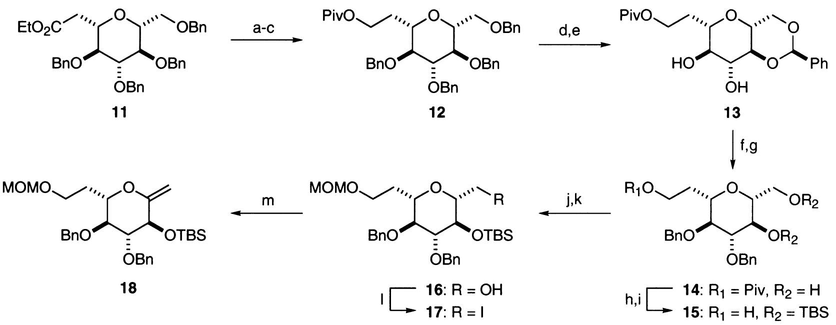
2.1. Synthesis plan

We have previously shown that a polytetrahydropyran ring system, the most frequently encountered structural unit in polycyclic ether natural products, can be constructed efficiently by *B*-alkyl Suzuki coupling of lactone-derived enol triflates followed by stereoselective hydroboration and reductive ring-closure (Eq. (1)). We envisioned that such a sequence would provide convenient entry to the ABCD ring system of the ciguatoxins. Our initial approach to the ABCD ring fragment **4** is outlined retrosynthetically in Scheme 1. We reasoned that the oxepene ring A could be accessed from a precursor triene **5** by a ring-closing metathesis reaction. The ring-closing metathesis reaction has rapidly become an important and powerful transformation in organic synthesis,[24] and its utility has been demonstrated in the construction of medium-ring ethers.[13f,16,25] We envisioned that seven-membered ketone **6** would serve as a key precursor for the synthesis of **5**; introduction of a



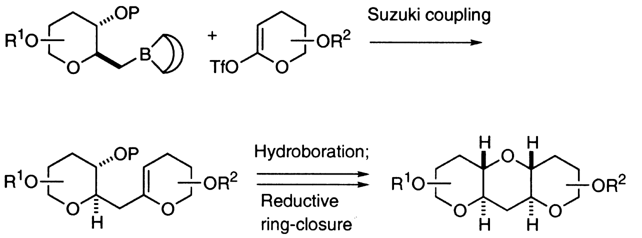
4 5 6 7 8 9 10

Scheme 1. Retrosynthetic analysis of ABCD ring fragment **4** of CTX3C.



Scheme 2. *Reagents and conditions*: (a) DIBALH, CH_2Cl_2, −78°C; (b) $NaBH_4$, MeOH, 0°C; (c) PivCl, NEt_3, DMAP, CH_2Cl_2, rt, quant. (three steps); (d) H_2, $Pd(OH)_2/C$, EtOAc/MeOH, rt; (e) CSA, $PhCH(OMe)_2$, DMF/CH_2Cl_2, rt, 80% (two steps); (f) BnBr, NaHMDS, TBAI, DMF, 0°C; (g) CSA, MeOH/CH_2Cl_2, rt, 84% (two steps); (h) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0°C; (i) DIBALH, CH_2Cl_2, −78°C, 87% (two steps); (j) MOMCl, *i*-Pr_2NEt, TBAI, CH_2Cl_2, rt; (k) CSA, MeOH/CH_2Cl_2, 0°C, 91% (two steps); (l) I_2, PPh_3, imidazole, PhH, rt, quant.; (m) *t*-BuOK, THF, 0°C, 96%.

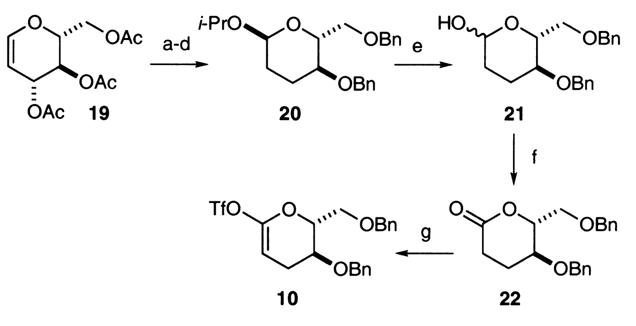
double bond into the D ring of **6** followed by reductive closure of the C ring would lead to **5**. The key intermediate **6** would arise by ring-expansion[26] of six-membered ketone **7**, which should be readily derived from **8**. In turn, enol ether **8** would be obtained by Suzuki coupling of alkylborane **9**, generated from the corresponding *exo*-olefin, with six-membered lactone-derived enol triflate **10**.



(1)

2.2. Synthesis of the BCD ring framework: *B*-alkyl Suzuki coupling-ring expansion strategy

The synthesis of *exo*-olefin **18**, representing the B ring, began with the known ester **11**[27] (Scheme 2). Reduction of the ester in **11** by a two-step sequence (DIBALH, then $NaBH_4$) was followed by protection of the resultant primary alcohol to give pivalate ester **12** in quantitative yield. Removal of the benzyl groups by hydrogenolysis and subsequent protection as the benzylidene acetal gave diol **13** in 84% yield for the two steps. Benzylation followed by removal of the benzylidene acetal group yielded diol **14**, which, upon bis-silylation and reductive removal of the pivalate ester, provided primary alcohol **15** in 87% overall yield. Protection as its methoxymethyl (MOM) ether and selective removal of the primary *t*-butyldimethylsilyl (TBS) group afforded alcohol **16** (91% yield for the two steps), which upon iodination gave primary iodide **17**. Finally, treatment with a base (KO*t*-Bu, THF, 0°C) completed the synthesis of the B ring *exo*-olefin **18** in 96% overall yield from **16**.

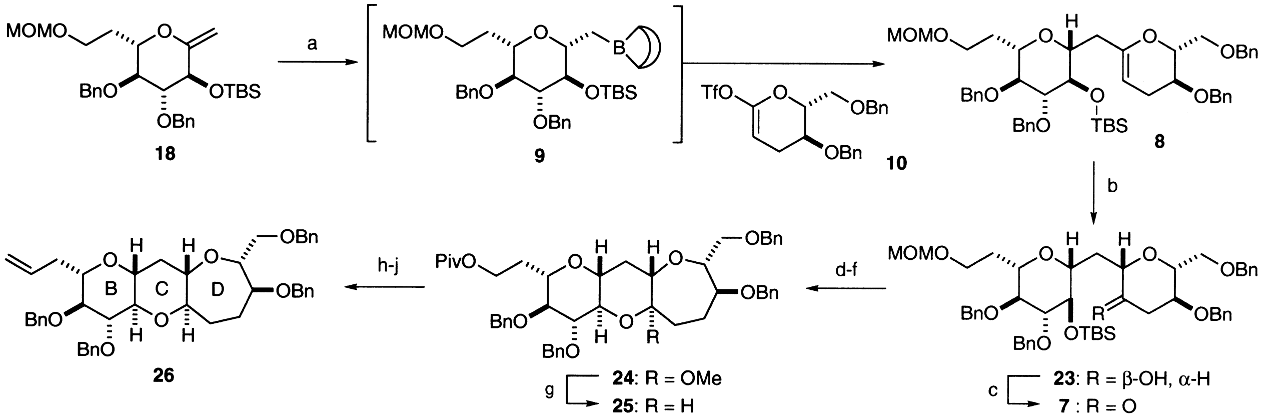


Scheme 3. *Reagents and conditions*: (a) $BF_3 \cdot OEt_2$, *i*-PrOH, CH_2Cl_2, 0°C→rt; (b) H_2, 10% Pd/C, EtOAc/MeOH, rt; (c) NaOMe, MeOH, rt; (d) NaH, BnBr, *n*-Bu_4NI, THF/DMF (2:1), 0°C, 85% (four steps); (e) 80% HOAc, 1 M HCl, 50–60°C; (f) TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, rt, 66% (two steps); (g) KHMDS, $PhNTf_2$, THF/HMPA, −78→0°C.

The synthesis of enol triflate **10** started with tri-*O*-acetyl-D-glucal (**19**) as summarized in Scheme 3. *O*-Glycosidation of **19** with 2-propanol in the presence of $BF_3 \cdot OEt_2$ (CH_2Cl_2, 0°C) and hydrogenation of the double bond,[28] followed by replacement of the acetyl groups with benzyl groups, afforded bis(benzyl) ether **20**. Acidic hydrolysis produced hemiacetal **21**, which was then oxidized with catalytic tetra-*n*-propylammonium perruthenate (TPAP)[29] and *N*-methylmorpholine-*N*-oxide (NMO) to afford lactone **22**. Finally, lactone **22** was converted to enol triflate **10** according to the procedure of Murai (KHMDS, $PhNTf_2$, THF/HMPA, −78°C).[30] Due to its unstable nature, the unpurified **10** was immediately used in the next Suzuki coupling.

Hydroboration of *exo*-olefin **18** with 2.6 equiv. of 9-BBN (THF, rt→60°C) afforded the corresponding alkylborane **9**, which was in situ treated with aqueous Cs_2CO_3 and then enol triflate **10** in the presence of $Pd_2(dba)_3 \cdot CHCl_3$ (dba= dibenzylideneacetone) and triphenylarsine in DMF at room temperature (Scheme 4). The desired cross-coupled product **8** was obtained in excellent yield. The use of $Pd_2(dba)_3 \cdot CHCl_3$ as a palladium(0) catalyst instead of $PdCl_2(dppf)$ (dppf=1,1′-bis(diphenylphosphino)ferrocene) that was used in the original report[14a] improved the yield of the coupling reaction. Further hydroboration of the enol ether within **8** with thexylborane (THF, 0°C) proceeded stereoselectively to give, after oxidative workup, alcohol **23** in 92% yield as the sole product. Oxidation of the secondary alcohol with TPAP/NMO[29] afforded ketone **7** in quantitative yield.

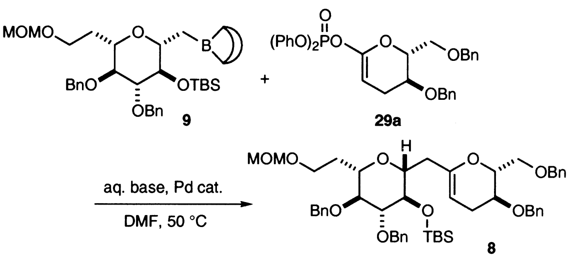
With the desired **7** in hand, we focused on the possibility of



Scheme 4. *Reagents and conditions*: (a) **18**, 9-BBN, THF, rt→60°C; then 3 M aq. Cs_2CO_3, **10**, $Pd_2(dba)_3$·$CHCl_3$, Ph_3As, DMF, rt, 91%; (b) $ThexylBH_2$, THF, 0°C; then 3 M NaOH, 30% H_2O_2, rt, 92%; (c) TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, rt, 99%; (d) $TMSCHN_2$, Me_3Al, CH_2Cl_2, −78°C; (e) *p*-TsOH·H_2O, MeOH/CH_2Cl_2, 55°C; (f) PivCl, Et_3N, DMAP, CH_2Cl_2, rt; (g) Et_3SiH, BF_3·OEt_2, CH_3CN, 0°C, 78% (four steps); (h) DIBALH, CH_2Cl_2, −78°C, 96%; (i) SO_3·Pyr, DMSO, Et_3N, CH_2Cl_2, 0°C; (j) Ph_3PCH_3Br, NaHMDS, THF, 0°C, 88% (two steps).

ring expansion leading to seven-membered ketone **6**.[26] This transformation was best accomplished by treatment with trimethylsilyldiazomethane ($TMSCHN_2$) in the presence of trimethylaluminum in CH_2Cl_2 at −78°C (Scheme 4). The crude reaction product[31] was then treated with *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O) in methanol/CH_2Cl_2 at 55°C to effect removal of the MOM and TBS protecting groups with concomitant formation of a mixed methyl ketal.[32] Subsequent protection of the primary alcohol gave pivalate ester **24**. Axial hydride reduction of the methyl ketal at C12[33] with Et_3SiH and BF_3·OEt_2 (CH_2Cl_2, 0°C)[27] afforded tricyclic ether **25** as the sole product in 78% overall yield from **7**. Reductive removal of the pivalate ester followed by Parikh–Doering oxidation[34] and Wittig methylenation of the derived aldehyde afforded terminal olefin **26** in 79% yield for the three steps.

Table 1. Suzuki coupling of alkylborane **9** with enol phosphate **29a** (Eq. (3))



(3)

Entry	Base[a]	Pd cat.	Co-ligand	**29a** (eq)	Yield (%)
1[b]	Cs_2CO_3	$Pd_2(dba)_3$·$CHCl_3$	Ph_3As	1.0	0
2[b]	Cs_2CO_3	$Pd_2(dba)_3$·$CHCl_3$	(2-Furyl)$_3$P	1.0	0
3[b]	K_3PO_4	$Pd(PPh_3)_4$	–	1.0	46
4	K_3PO_4	$Pd(PPh_3)_4$	–	1.0	56
5	$NaHCO_3$	$Pd(PPh_3)_4$	–	1.0	72
6	$NaHCO_3$	$Pd(PPh_3)_4$	–	1.4	84
7	$NaHCO_3$	$Pd(PPh_3)_4$	–	2.0	98

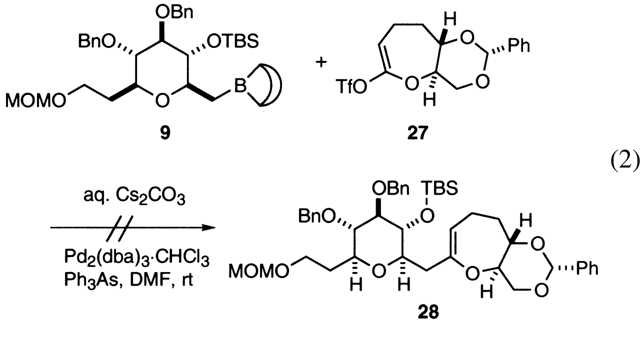
All reactions were carried out with aq. base (3 equiv.), Pd(0) cat. (10 mol%), and co-ligand (0.4 equiv.) in DMF.

[a] 3 M Cs_2CO_3; 3 M K_3PO_4; 1 M $NaHCO_3$.

[b] Reaction was carried out at room temperature.

2.3. Suzuki coupling of lactone-derived enol phosphate

While the BCD ring system **26** was successfully synthesized via the *B*-alkyl Suzuki coupling of six-membered enol triflate **10** and subsequent ring-expansion protocol, overall efficiency was lacking. Accordingly, an alternative and more direct approach that uses *B*-alkyl Suzuki coupling of seven-membered enol triflates was investigated. However, we encountered difficulty in using seven-membered enol triflate **27** as a substrate in the *B*-alkyl Suzuki coupling (Eq. (2)), mainly due to its instability under the aqueous basic conditions. Therefore, we explored *B*-alkyl Suzuki coupling of lactone-derived enol phosphates, superior substrates to the corresponding triflates with respect to their stability and handling.

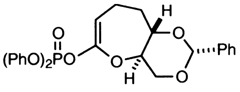
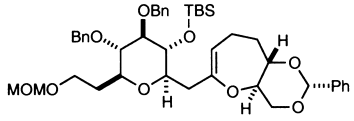
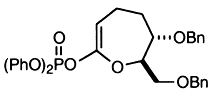
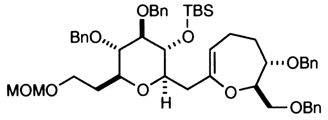
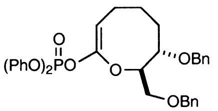
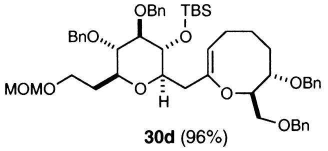
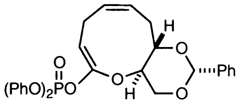
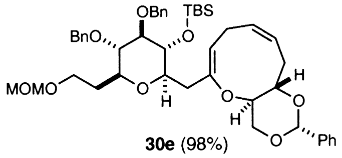


(2)

The use of lactone-derived enol phosphates in organic synthesis was first demonstrated by Kane and co-workers in their total synthesis of zoapatanol.[35] More recently, Nicolaou and co-workers have reported that six- to nine-membered enol phosphates derived from the corresponding lactones undergo palladium-catalyzed Stille coupling,[36] which has been used as the key reaction in their total synthesis of brevetoxin A.[37] However, at the time that we initiated our studies, Suzuki coupling of enol phosphates had not been reported.[38]

To test the feasibility of utilizing lactone-derived enol phosphates in *B*-alkyl Suzuki coupling, we first examined the

Table 2. Suzuki coupling of alkylborane **9** with enol phosphates with a variety of ring sizes

Entry	Phosphate	Product (yield)
1	 **29b**	 **28** (94%)
2	 **29c**	 **30c** (97%)
3	 **29d**	 **30d** (96%)
4	 **29e**^{b}	 **30e** (98%)

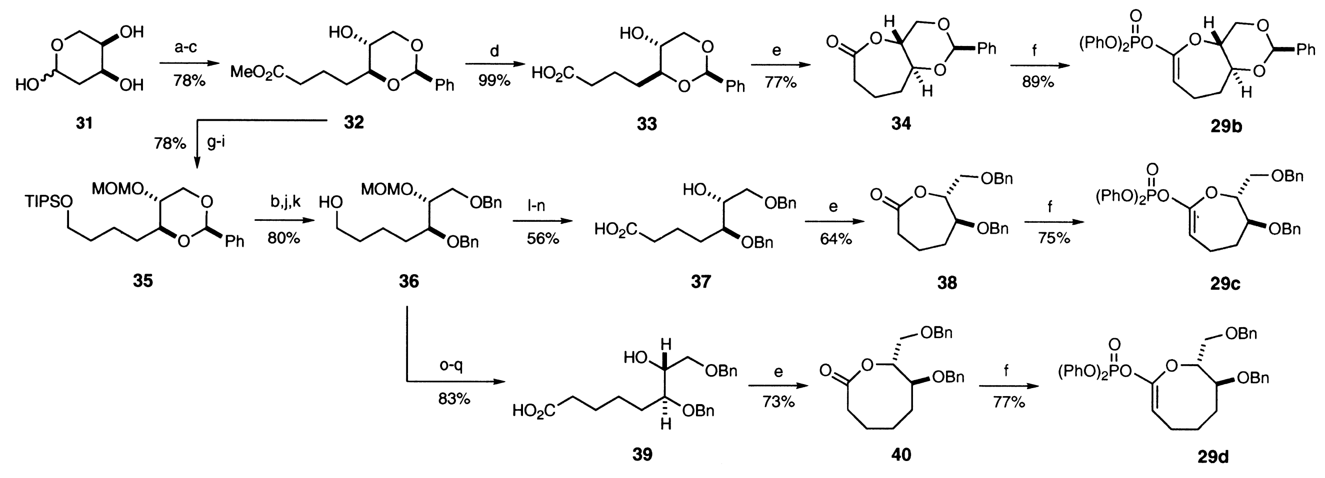
All reactions were carried out with aq. $NaHCO_3$ (3 equiv.) and $Pd(PPh_3)_4$ (10 mol%) in DMF at 50°C.

[a] See, Ref. 36.

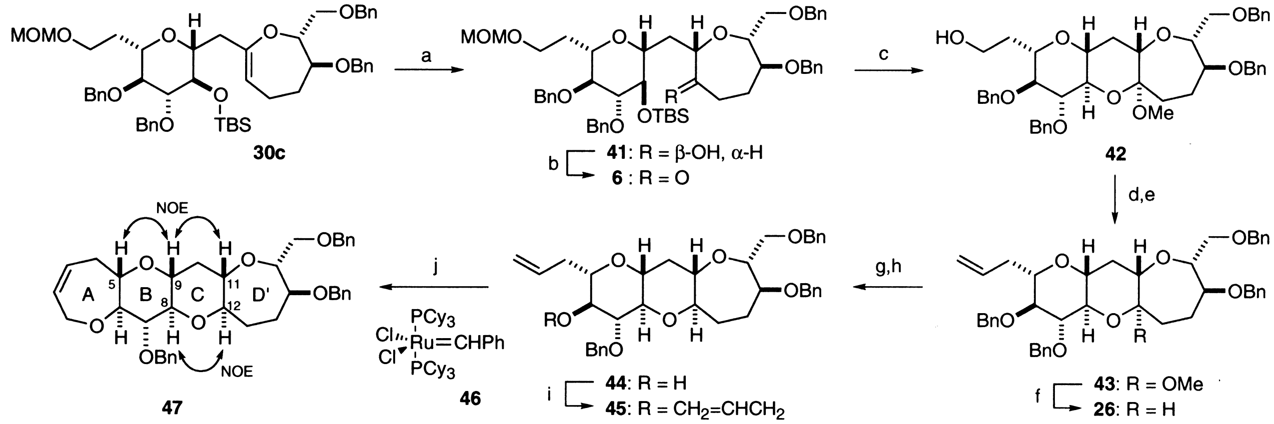
reaction of alkylborane **9** with phosphate **29a** as a model system (Eq. (3), Table 1). Enol phosphate **29a** was prepared from lactone **22** following the procedure of Nicolaou (KHMDS, $(PhO)_2P(O)Cl$, THF/HMPA, −78°C).[36] Alkylborane **9**, generated in situ from **18** with 9-BBN as described above, reacted with **29a** under the conditions that we have described for the Suzuki coupling of enol triflate **10** (Cs_2CO_3, $Pd_2(dba)_3 \cdot CHCl_3$, Ph_3As, DMF, room temperature). However, the desired coupling product **8** could not be obtained at all (entry 1). Tri(2-furyl)phosphine was also ineffective in the present coupling reaction (entry 2). Considering the low reactivity of enol phosphate **29a** compared with triflate **10**, it was supposed that phosphate **29a** could not undergo oxidative addition to a palladium(0) species having a less electron-donating ligand such as triphenylarsine or tri(2-furyl)phosphine.[39] In contrast, the most commonly used system (aqueous K_3PO_4, $Pd(PPh_3)_4$, DMF) in Suzuki couplings[19,20] afforded **8**, albeit in modest yield (46–56%, entries 3 and 4). Presumably, hydrolysis of **29a** would occur competitively under these conditions due to the slow rate of oxidative addition of less reactive **29a** to the palladium(0) complex. Use of $NaHCO_3$ as a weaker base proved to be the most effective (entry 5). Increasing the amounts of **29a** further improved the yield of coupling product (entry 6). Finally, the best result was obtained when 2 equiv. of **29a** was employed, giving **8** in nearly quantitative yield (entry 7).

To ascertain the generality and scope of the *B*-alkyl Suzuki coupling of lactone-derived enol phosphates, a variety of substrates of different ring sizes were allowed to react with **9** under the optimal conditions described earlier. As shown in Table 2, seven- to nine-membered enol phosphates **29b–e** reacted smoothly with **9** to afford the desired cross-coupled products **28** and **30c–e** in excellent yields. Since the seven-membered enol triflate decomposed even under these mild conditions using $NaHCO_3$ as a base,[40] the use of a phosphate leaving group is critical for this coupling reaction. Moreover, since eight- and nine-membered lactone-derived enol triflates are known to be rather unstable and difficult to prepare or isolate,[41] the present *B*-alkyl Suzuki coupling of medium-ring enol phosphates is promising for the synthesis of polycyclic ether natural products.

The syntheses of seven- and eight-membered enol phosphates **29b–d** are outlined in Scheme 5. The synthesis of seven-membered enol phosphate **29b** began with 2-deoxy-D-ribose (**31**), which was converted to hydroxy ester **32** in a three-step sequence. Hydrolysis of the methyl ester within **32** afforded hydroxy acid **33**, which was lactonized under Yamaguchi conditions[42] to give seven-membered lactone **34**. Conversion of **34** to enol phosphate **29b** was accomplished by the procedure of Nicolaou (KHMDS, $(PhO)_2P(O)Cl$, THF, HMPA, −78°C).[36] Another seven-membered enol phosphate **29c** was prepared from **32**. Protection as its MOM ether followed by reduction of the ester and silylation of the derived alcohol afforded TIPS ether **35**. After removal of the benzylidene acetal by hydrogenolysis, benzylation of the derived alcohols was followed by desilylation to afford primary alcohol **36**, which was then converted to hydroxy acid **37** by a three-step sequence. Yamaguchi lactonization followed by enol phosphate formation afforded **29c** following the same procedure as described for the conversion of **33** to **29b**. Construction of eight-membered enol phosphate **29d** started with alcohol **36**, which was transformed to hydroxy acid **39** by tosylation, displacement with KCN, and hydrolysis of the cyanide. Hydroxy acid **39** was readily converted to enol phosphate **29d** by the same procedure described earlier.



Scheme 5. *Reagents and conditions*: (a) $Ph_3P{=}CHCO_2Me$, THF, reflux; (b) H_2, 10% Pd/C, EtOAc/MeOH, rt; (c) $PhCH(OMe)_2$, CSA, CH_2Cl_2, rt; (d) KOH, THF/MeOH/H_2O, 50°C; (e) 2,4,6-$Cl_3PhCOCl$, Et_3N, THF, rt; then DMAP, benzene, 80°C; (f) KHMDS, $(PhO)_2P(O)Cl$, THF/HMPA, −78°C; (g) MOMCl, *i*-Pr_2NEt, TBAI, CH_2Cl_2, rt; (h) $LiAlH_4$, THF, 0°C; (i) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0°C→rt; (j) NaH, BnBr, TBAI, DMF, rt; (k) TBAF, THF, rt; (l) SO_3·Pyr, Et_3N, DMSO, CH_2Cl_2, 0°C; (m) BF_3·OEt_2, Me_2S, CH_2Cl_2, 0°C; (n) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, *t*-BuOH/H_2O, rt; (o) *p*-TsCl, Et_3N, DMAP, CH_2Cl_2, rt; (p) KCN, DMSO, 80°C; (q) aq. HCl, MeOH; then aq. KOH, MeOH, 70°C.



Scheme 6. *Reagents and conditions*: (a) $ThexylBH_2$, THF, −10→0°C; then 3 M NaOH, 30% H_2O_2, rt, 83% (+recovered **30c**, 10%); (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78→0°C; (c) *p*-TsOH, MeOH/CH_2Cl_2, 55°C, 82% (two steps); (d) SO_3·Pyr, DMSO, Et_3N, CH_2Cl_2, 0°C; (e) Ph_3PCH_3Br, NaHMDS, THF, 0°C, 79% (two steps); (f) Et_3SiH, BF_3·OEt_2, $MeCN/CH_2Cl_2$, 0°C, 86%; (g) I_2, CH_2Cl_2, 0°C; (h) Zn, HOAc, Et_2O/MeOH, 0°C, 96% (two steps); (i) NaHMDS, allyl bromide, DMF, 0°C→rt, 78%; (j) Grubbs' catalyst **46**, CH_2Cl_2, rt, quant.

2.4. Synthesis of the ABCD ring system 47

Hydroboration of the enol ether **30c** with thexylborane (THF, −10→0°C), followed by oxidation, afforded the desired alcohol **41** in 83% yield along with a 10% yield of recovered **30c** (Scheme 6). The stereoselectivity of the hydroboration of **30c** can be explained by approach of the thexylborane onto the double bond from the α-face in the most stable conformer **A** (Fig. 2), generated by conformational search using MM2* force field in MacroModel version 5.5. Oxidation of the secondary alcohol under Swern conditions provided ketone **6**, which upon treatment with *p*-TsOH·H_2O in methanol afforded hydroxy mixed methyl ketal **42** in 82% yield for the two steps. Oxidation of the primary alcohol[34] followed by Wittig reaction afforded olefin **43** (79%, two steps), which was then reduced with Et_3SiH and BF_3·OEt_2 to give tricycle **26** as the sole product in 86% yield.

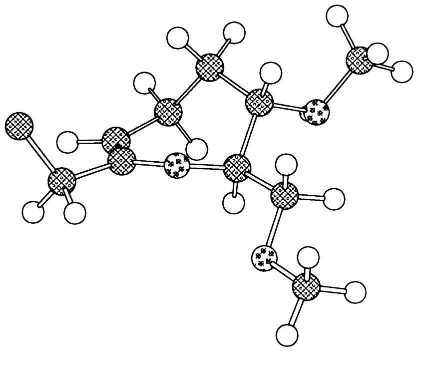
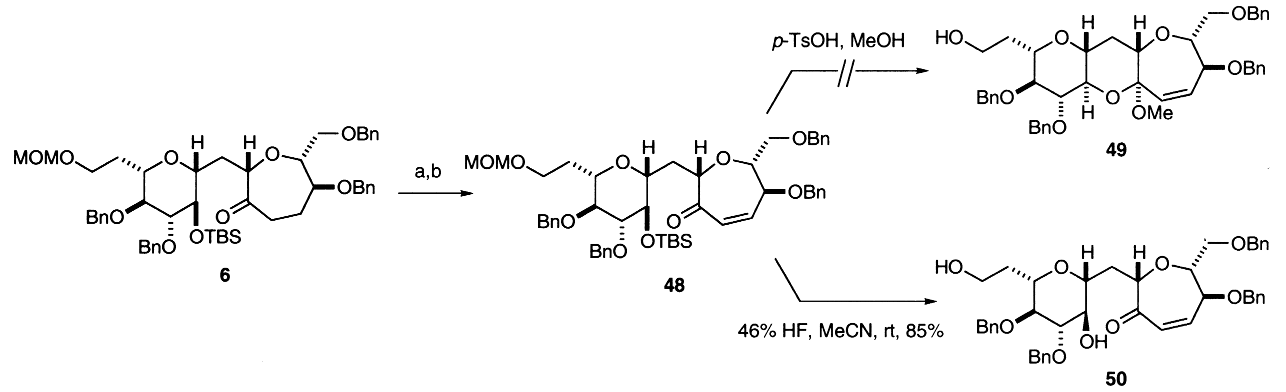


Figure 2.

In order to construct the oxepene ring A, we decided to use a ring-closing metathesis reaction. To this end, regioselective removal of the benzyl group at C6 of **26** was carried out according to the method of Cipolla.[43] Thus, treatment of **26** with I_2 effected debenzylative iodoetherification to give an iodoether, which was then treated with zinc powder in the presence of acetic acid to afford alcohol **44** in 84% overall yield. Subsequent allylation of the derived secondary



Scheme 7. *Reagents and conditions*: (a) LiHMDS, TMSCl, Et_3N, CH_2Cl_2, −78°C; (b) $Pd(OAc)_2$, MeCN, rt, 96% (two steps).

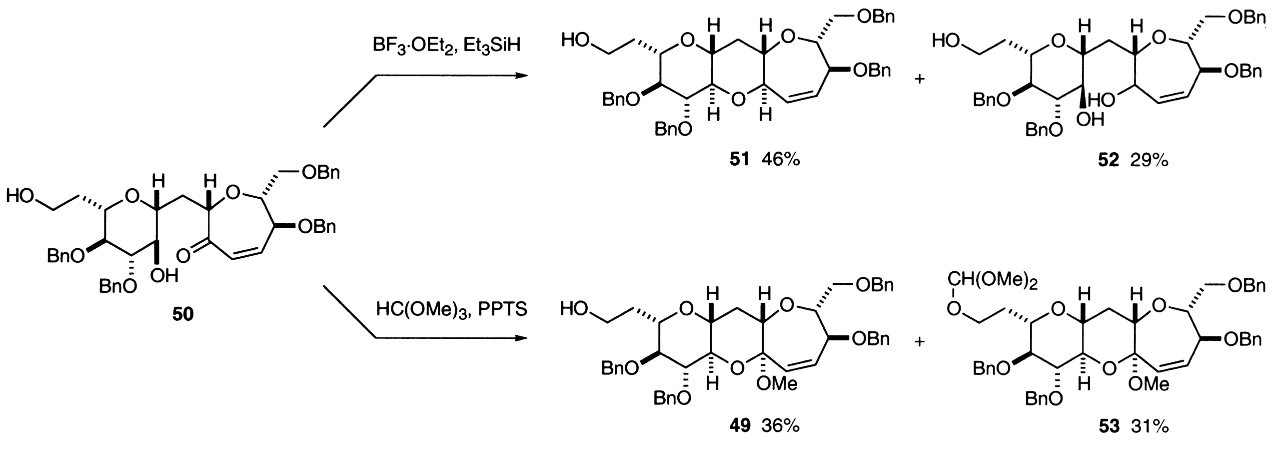
alcohol gave diene **45** (78% yield), setting the stage for the ring-closing metathesis reaction. Exposure of **45** to Grubbs' catalyst **46**[44] furnished the desired ABCD ring framework **47** in nearly quantitative yield. The relative configuration of **47** was firmly established by NOEs between H-5/H-9, H-8/H-12, and H-9/H-11. Thus, a concise and rapid synthesis of the ABCD ring polyether skeleton **47** was achieved in 10 steps and 30% overall yield from **18**.

2.5. Synthesis of the ABCD ring fragment 4

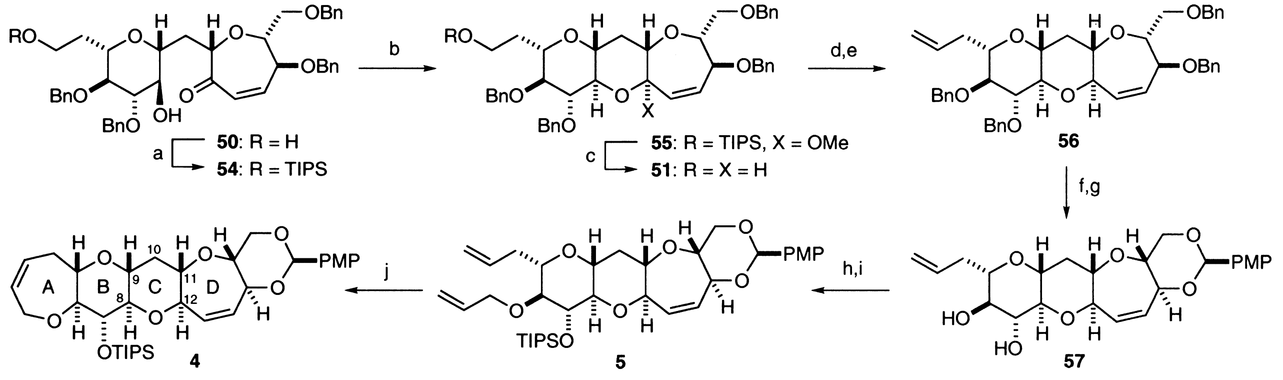
For the synthesis of the ABCD ring fragment **4**, we required introduction of a double bond into the oxepane D ring of **6**. Initial attempts to install the double bond by selenenylation-oxidative elimination sequence[45] proved unsuccessful. Selenenylation of ketone **6** under acidic or basic conditions resulted in no reaction or only a low yield of enone **48**. Moreover, separation of the desired **48** from the recovered ketone **6** was troublesome. Accordingly, we sought an alternative method for introduction of the double bond. After some experimentation, it was discovered that the Ito–Saegusa protocol[46] gave the best result (Scheme 7). Thus, ketone **6** was converted to the kinetic enol silyl ether (LiHMDS, CH_2Cl_2, −78°C, then TMSCl, Et_3N), which was then treated with a stoichiometric amount of $Pd(OAc)_2$ in MeCN at room temperature to yield enone **48** in excellent yield. The next stage of our synthetic plan called for the conversion of **48** to mixed methyl ketal **49** for the construction of the C ring. However, treatment of **48** with *p*-TsOH in methanol did not provide the desired **49** but resulted in decomposition. After extensive experimentation,[47] we found that an 83% yield of a 7:1 mixture of hydroxy ketone **50** and the corresponding hemiketal (not shown) could be obtained upon treatment of **48** with 46% aqueous HF in MeCN at room temperature.

Treatment of a mixture of **50** and the hemiketal with Et_3SiH in the presence of $BF_3{\cdot}OEt_2$ afforded less than 50% of the desired tricyclic ether **51**, and diol **52** was significantly produced (Scheme 8). Hirama and co-workers have reported that reduction of a mixed methyl ketal rather than that of the corresponding hemiketal with Et_3SiH and $BF_3{\cdot}OEt_2$ gave reproducibly a higher yield of the reduction product.[18e] However, treatment of **50** with $HC(OMe)_3$ in the presence of PPTS (CH_2Cl_2, rt) afforded an approximately 1:1 mixture of **49** and the orthoester **53** in modest yield. Finally, this problem was addressed by the first selective protection of the primary alcohol within **50** as the triisopropylsilyl (TIPS) ether **54** (87%) and subsequent treatment with $HC(OMe)_3$ in the presence of PPTS, giving mixed methyl ketal **55** (Scheme 9). Exposure of **55** to Et_3SiH and $BF_3{\cdot}OEt_2$ effected reduction of the mixed methyl ketal with concomitant desilylation to furnish tricyclic ether **51** as the sole product in 94% yield from **54**.

Oxidation of the primary alcohol within **51** with SO_3·pyridine[34] followed by Wittig methylenation of the derived aldehyde afforded olefin **56** in 91% overall yield. Removal



Scheme 8.



Scheme 9. *Reagents and conditions*: (a) TIPSCl, Et_3N, DMAP, CH_2Cl_2, rt, 87%; (b) PPTS, $HC(OMe)_3$, toluene, 45°C; (c) Et_3SiH, $BF_3{\cdot}OEt_2$, $MeCN/CH_2Cl_2$ (2:1), 0°C, 94% (two steps); (d) $SO_3{\cdot}Pyr$, DMSO, Et_3N, CH_2Cl_2, 0°C; (e) Ph_3PCH_3Br, NaHMDS, THF, 0°C, 91% (two steps); (f) LiDBB, THF, −78°C; (g) CSA, *p*-$MeOC_6H_4CH(OMe)_2$, CH_2Cl_2/DMF (3:1), rt, 59% (two steps); (h) TIPSOTf, 2,6-lutidine, CH_2Cl_2/DMF (3:1), 0°C; (i) NaHMDS, allyl bromide, DMF, rt, quant. (two steps); (j) Grubbs' catalyst **46**, CH_2Cl_2, rt, 97%.

of the benzyl groups with lithium di-*tert*-butylbiphenilide (LiDBB)[48] and selective protection of the derived tetraol as its mono-*p*-methoxybenzylidene acetal provided **57** in 59% yield for the two steps. Regioselective protection of the hydroxyl group at C7 of diol **57** as its TIPS ether followed by allylation of the remaining alcohol gave triene **5** in 94% overall yield. Finally, ring-closing metathesis reaction of **5** with Grubbs' catalyst **46** proceeded cleanly in the presence of the D ring double bond to furnish the targeted ABCD ring fragment **4** in 97% yield. The relative configuration of **4** was unambiguously established by $^1H-^1H$ coupling constant analysis.[49]

3. Conclusion

We have developed a general and high-yielding method for the convergent synthesis of polycyclic ethers based on *B*-alkyl Suzuki reaction of lactone-derived enol phosphates. The synthesis enables the coupling of medium-ring ethers of different ring sizes. The potential of the *B*-alkyl Suzuki coupling-based approach to the assemblage of polycyclic ether structures was demonstrated by its successful application to the convergent synthesis of the ABCD ring fragment **4** of ciguatoxin analogues.

4. Experimental

4.1. General methods

All reactions sensitive to air or moisture were carried out under an atmosphere of argon or nitrogen in freshly distilled, dry solvents under anhydrous conditions unless otherwise noted. Anhydrous THF and *N*,*N*-dimethylformamide (DMF) were purchased from Kanto Chemical Co. Inc. and used without further drying. Diethyl ether (Et_2O) was dried from sodium/benzophenone under argon, benzene, dichloromethane (CH_2Cl_2), *N*,*N*-diisopropylethylamine, methanol, toluene, triethylamine, and pyridine from calcium hydride, dimethylsulfoxide (DMSO) and hexamethylphosphoric triamide (HMPA) from calcium hydride under reduced pressure. All other reagents purchased were of the highest commercial quality and used without further purification unless otherwise noted. Analytical thin-layer chromatography was performed using E. Merck silica gel 60 F254 plates (0.25-mm thickness). Column chromatography was performed using Kanto Chemical silica gel 60N (40–100 mesh, spherical, neutral) and for flash column chromatography Fuji Silysia silica gel BW-300 (200–400 mesh) or E. Merck Kieselgel silica gel 60 (230–400 mesh) was used. Optical rotations were recorded on a JASCO DIP-350 digital polarimeter. IR spectra were recorded on a JASCO FT/IR-420 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a JEOL A500 or Bruker DRX-500 spectrometer, and chemical shift values are reported in ppm (d) downfield from tetramethylsilane with reference to internal residual solvent (^1H NMR, $CHCl_3$ (7.24), C_6HD_5 (7.15), C_5HD_4N (8.50); ^{13}C NMR, $CDCl_3$ 77.0, C_6D_6 128.0, C_5D_5N 135.5). Coupling constants (*J*) are reported in hertz (Hz). The following abbreviations are used to designate the multiplicities: s=singlet, d=doublet, t=triplet, m=multiplet, br=broad. Low- and high-resolution mass spectra were recorded on a JEOL JMS-SX102 mass spectrometer under fast atom bombardment (FAB) conditions using *m*-nitrobenzyl alcohol (NBA) as a matrix.

4.1.1. Pivalate 12. To a solution of ester **11**[27] (42.48 g, 69.64 mmol) in CH_2Cl_2 (400 mL) at −78°C was added dropwise diisobutylaluminum hydride (1.0 M in toluene, 105 mL, 105 mmol). The resultant solution was stirred at −78°C for 1 h before the reaction was quenched with saturated aqueous potassium sodium tartrate (400 mL). The mixture was extracted with ethyl acetate (900 mL), washed with H_2O (200 mL) and brine (400 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude aldehyde was used in the next reaction without chromatographic purification.

To a solution of the above aldehyde in methanol (280 mL) at 0°C was added $NaBH_4$ (2.1 g, 56 mmol). The resultant solution was stirred at 0°C for 30 min before the reaction was quenched with water (10 mL). The solvent was removed in vacuo, and the residue was dissolved in ethyl acetate (1.5 L), washed with saturated aqueous NH_4Cl (400 mL) and brine (400 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude alcohol was used in the next reaction without purification.

To a solution of the above alcohol in CH_2Cl_2 (400 mL) were successively added triethylamine (29.1 mL, 209 mmol), dimethylaminopyridine (2.55 g, 13.9 mmol), and pivaloyl chloride (17.15 mL, 139.3 mmol). The resultant solution was stirred at room temperature overnight. The reaction mixture was extracted with ether (1.5 mL), washed with 1 M HCl (400 mL), saturated aqueous $NaHCO_3$ (400 mL), and brine (400 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (30% ether/hexanes) gave pivalate **12** (45.9 g, quant. for the three steps) as a colorless oil: $[\alpha]_D^{27}=-63.7$ (*c* 0.81, C_6H_6); IR (film) 3089, 3063, 3030, 2971, 2903, 2869, 1951, 1873, 1808, 1727, 1605, 1586, 1540, 1496, 1479, 1454, 1397, 1361, 1283, 1208, 1158, 1099, 941, 908, 735, 697, 614, 461 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.33–7.13 (m, 20H), 4.89 (s, 2H), 4.87 (d, J=9.2 Hz, 1H), 4.80 (d, J=10.7 Hz, 1H), 4.64 (d, J=11.0 Hz, 1H), 4.61 (d, J=12.5 Hz, 1H), 4.55 (d, J=11.0 Hz, 1H), 4.50 (d, J=12.2 Hz, 1H), 4.22–4.13 (m, 2H), 3.70–3.63 (m, 4H), 3.37–3.24 (m, 3H), 2.16 (m, 1H), 1.69 (m, 1H), 1.16 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.4, 138.6, 138.3, 138.2, 138.1, 128.4, 128.3, 128.0, 127.8, 127.7, 127.6, 87.3, 82.2, 79.0, 78.5, 76.1, 75.5, 75.2, 74.9, 73.5, 69.0, 61.1, 38.7, 31.0, 27.2; HRMS (FAB) calcd for $C_{41}H_{48}O_7Na$ $[(M+Na)^+]$ 675.3298, found 675.3302.

4.1.2. Diol 13. To a solution of pivalate **12** (45.75 g, 70.17 mmol) in ethyl acetate/methanol (1:2, v/v, 500 mL) was added 20% $Pd(OH)_2/C$ (5.0 g), and the resulting mixture was stirred at room temperature under hydrogen atmosphere overnight. The catalyst was removed by filtration through a pad of Celite, and the filtrate was concentrated to give crude tetraol, which was used in the next reaction without purification.

To a solution of the above tetraol in CH_2Cl_2/DMF (20:7, v/v, 135 mL) were added benzaldehyde dimethylacetal (15.7 mL, 105 mmol) and camphorsulfonic acid (1.61 g, 6.93 mmol). The resultant solution was stirred at room temperature overnight before the reaction was quenched with triethylamine. The solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel (50–70% ethyl acetate/hexanes) to give diol **13** (21.23 g, 80% for the two steps) as a colorless oil: $[\alpha]_D^{27}=-36.3$ (*c* 5.19, C_6H_6); IR (film) 3445, 3069, 3036, 2973, 2872, 1961, 1815, 1727, 1540, 1480, 1455, 1385, 1286, 1165, 1127, 1100, 1015, 971, 940, 916, 876, 762, 737, 699, 680, 654, 605, 538 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.51–7.31 (m, 5H), 5.45 (s, 1H), 4.24 (dd, J=10.4, 4.9 Hz, 1H), 4.18 (m, 1H), 4.11 (m, 1H), 3.63–3.57 (m, 3H), 3.37 (dd, J=9.2, 9.2 Hz, 1H), 3.33–3.29 (m, 2H), 3.22 (dd, J=8.8, 8.8 Hz, 1H), 2.12 (m, 1H), 1.66 (m, 1H), 1.19 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.6, 137.0, 129.2, 128.2, 126.3, 101.7, 81.0, 77.2, 75.0, 74.3, 70.1, 68.7, 61.0, 38.6, 31.0, 27.1; HRMS (FAB) calcd for $C_{20}H_{28}O_7Na$ $[(M+Na)^+]$ 403.1733, found 403.1733.

4.1.3. Diol 14. To a solution of diol **13** (21.06 g, 55.42 mmol) in DMF (300 mL) at 0°C were added tetra-*n*-butylammonium iodide (2.05 g, 5.54 mmol) and sodium bis(trimethylsilyl)amide (1.0 M solution in THF, 166.3 mL, 166.3 mmol). After being stirred at 0°C for 5 min, the mixture was treated with benzyl bromide (16.48 mL, 138.5 mmol). The resultant solution was stirred at 0°C for 1 h and allowed to warm to room temperature. After 3 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was extracted with ether (1.5 L), washed with saturated aqueous NH_4Cl (400 mL), water (400 mL), and brine (400 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude bis(benzyl) ether was used in the next reaction without chromatographic purification.

A solution of the above bis(benzyl) ether in CH_2Cl_2/methanol (1:1, v/v, 200 mL) was treated with camphorsulfonic acid (2.6 g, 11 mmol). The resultant solution was stirred at room temperature for 5 h before the reaction was quenched with triethylamine. The solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel (8% methanol/$CHCl_3$) to provide diol **14** (22.00 g, 84% for the two steps) as a colorless solid: $[\alpha]_D^{27}=-39.0$ (*c* 0.36, C_6H_6); IR (film) 3356, 3064, 3032, 2968, 2933, 2871, 1727, 1497, 1479, 1454, 1397, 1361, 1282, 1210, 1153, 1097, 1038, 996, 886, 738, 698, 647, 530 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.23 (m, 10H), 4.94 (d, J=11.6 Hz, 1H), 4.87 (d, J=11.0 Hz, 1H), 4.74 (d, J=11.6 Hz, 1H), 4.65 (d, J=11.0 Hz, 1H), 4.20 (m, 1H), 4.14 (m, 1H), 3.80 (m, 1H), 3.67 (m, 1H), 3.55–3.47 (m, 2H), 3.37 (ddd, J=2.4, 9.5, 9.5 Hz, 1H), 3.25–3.19 (m, 2H), 2.19 (m, 1H), 1.62 (m, 1H), 1.17 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.6, 138.5, 137.8, 128.7, 128.5, 128.1, 128.0, 127.8, 86.7, 82.1, 79.0, 75.8, 75.3, 75.2, 71.1, 62.8, 60.6, 38.8, 31.1, 27.2; HRMS (FAB) calcd for $C_{27}H_{36}O_7Na$ $[(M+Na)^+]$ 495.2359, found 495.2378.

4.1.4. Alcohol 15. To a solution of diol **14** (2.00 g, 4.24 mmol) and 2,6-lutidine (1.98 mL, 16.9 mmol) in CH_2Cl_2 (42 mL) at 0°C was added *t*-butyldimethylsilyl trifluoromethanesulfonate (2.63 mL, 11.4 mmol). The resultant solution was stirred at 0°C for 2 h before the reaction was quenched with methanol (2 mL). The mixture was extracted with ether (200 mL), washed with 1 M HCl (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude bis(silyl) ether was used in the next reaction without purification.

To a solution of the above bis(silyl) ether in CH_2Cl_2 (42 mL) at −78°C was added DIBALH (1.0 M solution in toluene, 10.6 mL, 10.6 mmol). The resultant solution was stirred at −78°C for 2 h before the reaction was quenched with saturated aqueous potassium sodium tartrate. The mixture was stirred vigorously at room temperature for 1 h. The mixture was extracted with ethyl acetate (200 mL), washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (10–15% ethyl acetate/hexanes) gave alcohol **15** (2.27 g, 87% for the two steps) as a colorless solid: $[\alpha]_D^{27}=+24.7$ (*c* 0.22, C_6H_6); IR (film) 3420, 2960, 2928, 2856, 1497, 1471, 1409, 1359, 1260, 1152, 1092, 1027, 939, 859, 835, 800, 732, 696 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.11 (m, 10H), 4.95 (d, J=11.9 Hz, 1H), 4.80 (d, J=11.9 Hz, 1H), 4.73 (d, J=10.7 Hz, 1H), 4.54 (d, J=11.0 Hz, 1H), 3.84 (dd, J=11.0, 2.1 Hz, 1H), 3.77 (m, 2H), 3.61 (dd, J=11.0, 6.4 Hz, 1H), 3.56–3.42 (m, 3H), 3.26 (dd, J=9.2, 9.2 Hz, 1H), 2.01 (m, 1H), 1.70 (m, 1H), 0.88 (s, 9H), 0.86 (s, 9H), −0.03 (s, 3H),

−0.07 (s, 3H), −0.27 (s, 3H), −0.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.9, 137.8, 128.4, 128.2, 127.9, 127.8, 127.1, 126.6, 86.8, 82.9, 81.2, 80.2, 75.2, 75.0, 71.2, 63.0, 62.1, 33.7, 25.9, 25.8, 18.3, 18.0, −3.8, −4.6, −5.3, −5.34; HRMS (FAB) calcd for $C_{34}H_{56}O_6Si_2Na$ [(M+Na)$^+$] 639.3513, found 639.3527.

4.1.5. Alcohol 16. To a solution of alcohol **15** (23.64 g, 38.38 mmol) and tetra-*n*-butylammonium iodide (2.84 g, 7.69 mmol) in CH_2Cl_2 (30 mL) at 0°C were added diisopropylethylamine (23.4 mL, 134.3 mmol) followed by chloromethyl methyl ether (7.3 mL, 95.9 mmol). The resultant solution was stirred at room temperature overnight. The mixture was diluted with ether (1 L), washed with 1 M HCl (300 mL), saturated aqueous $NaHCO_3$ (300 mL), and brine (300 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude methoxymethyl ether was used in the next reaction without purification.

To a solution of the above methoxymethyl ether in CH_2Cl_2/methanol (1:3, v/v, 400 mL) at 0°C was added camphorsulfonic acid (4.46 g, 19.2 mmol). The resultant solution was stirred at 0°C for 1 h before the reaction was quenched with triethylamine. The solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel (20–40% ethyl acetate/hexanes) to give alcohol **16** (19.09 g, 91% for the two steps) as a colorless oil: $[\alpha]_D^{27}=-5.95$ (*c* 0.14, C_6H_6); IR (film) 3483, 3030, 2952, 2927, 2884, 2856, 1497, 1471, 1455, 1359, 1252, 1211, 1153, 1107, 1059, 918, 858, 836, 778, 733, 697, 672, 411 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34–7.13 (m, 10H), 4.93 (d, *J*=11.9 Hz, 1H), 4.81 (d, *J*=11.9 Hz, 1H), 4.74 (d, *J*=10.7 Hz, 1H), 4.60–4.56 (m, 3H), 3.80 (m, 1H), 3.79–3.56 (m, 3H), 3.54 (dd, *J*=8.9, 8.9 Hz, 1H), 3.49–3.44 (m, 2H), 3.33 (s, 3H), 3.27–3.22 (m, 2H), 2.15 (m, 1H), 1.64 (m, 1H), 0.85 (s, 9H), 0.06 (s, 3H), −0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.9, 137.8, 128.4, 128.2, 127.9, 127.8, 127.1, 126.6, 96.3, 87.0, 83.0, 80.3, 76.2, 75.2, 75.1, 71.3, 64.0, 62.5, 55.2, 32.0, 25.9, 18.0, −3.8, −4.7; HRMS (FAB) calcd for $C_{30}H_{46}O_7SiNa$ [(M+Na)$^+$] 569.2911, found 569.2899.

4.1.6. Iodide 17. To a solution of alcohol **16** (1.83 g, 3.35 mmol) and imidazole (342.3 mg, 5.03 mmol) in benzene (50 mL) were added triphenylphosphine (1.32 g, 5.03 mmol) followed by iodine (1.11 g, 4.36 mmol). The resultant solution was stirred at room temperature for 45 min before the reaction was quenched with saturated aqueous Na_2SO_3 (10 mL). The mixture was extracted with ether (300 mL), washed with brine (80 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (5–15% ethyl acetate/hexanes) gave iodide **17** (2.25 g, quant.) as a colorless oil, which was used in the next reaction without further purification.

4.1.7. *exo*-Olefin 18. To a solution of the above iodide **17** in THF (40 mL) at 0°C was added potassium *t*-butoxide (940.2 mg, 8.38 mmol). The resultant solution was stirred at 0°C for 4 h. The mixture was diluted with ether, washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (10% ethyl acetate/hexanes) gave *exo*-olefin **18** (1.70 g, 96%) as a colorless oil: $[\alpha]_D^{27}=-34.4$ (*c* 0.44, C_6H_6); IR (film) 3089, 3063, 3031, 2953, 2928, 2884, 2857, 1661, 1497, 1472, 1454, 1388, 1360, 1253, 1210, 1151, 1098, 1027, 919, 863, 837, 778, 734, 697, 556 cm^{-1}; ^{1}H NMR (C_6D_6, 500 MHz) δ 7.33–7.00 (m, 10H), 4.84 (d, *J*=11.8 Hz, 1H), 4.81 (s, 1H), 4.75 (d, *J*=11.2 Hz, 1H), 4.71 (d, *J*=11.8 Hz, 1H), 4.50–4.46 (m, 3H), 4.14 (d, *J*=8.2 Hz, 1H), 3.82 (ddd, *J*=2.7, 9.3, 9.3 Hz, 2H), 3.71 (m, 1H), 3.55 (dd, *J*=8.2, 8.2 Hz, 1H), 3.36 (dd, *J*=9.7, 8.2 Hz, 1H), 3.16 (s, 3H), 2.25 (m, 1H), 1.74 (m, 1H), 0.96 (s, 9H), 0.08 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (C_6D_6, 125 MHz) δ 160.9, 139.7, 139.3, 128.9, 128.7, 128.6, 128.2, 127.9, 127.8, 97.0, 94.7, 87.1, 82.9, 77.8, 75.3, 75.2, 73.5, 64.3, 55.3, 33.4, 26.4, 18.6, −4.1, −4.4; HRMS (FAB) calcd for $C_{30}H_{44}O_6SiNa$ [(M+Na)$^+$] 551.2805, found 551.2794.

4.1.8. Bis(benzyl) ether 20. To a solution of tri-*O*-acetyl-D-glucal **19** (5.10 g, 18.7 mmol) in CH_2Cl_2 (30 mL) at 0°C were added isopropyl alcohol (5.80 mL, 75.5 mmol) and boron trifluoride etherate (3.20 mL, 25.2 mmol). The resultant mixture was stirred at 0°C for 20 min and at room temperature for 40 min. The reaction was quenched with saturated aqueous $NaHCO_3$ (30 mL), and the mixture was diluted with ethyl acetate (200 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (80 mL) and brine (80 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude isopropyl glycoside was used in the next reaction without chromatographic purification.

To a solution of the above glycoside in ethyl acetate/ethanol (1:1, v/v, 50 mL) was added 10% Pd/C (0.60 g), and the mixture was stirred at room temperature under hydrogen atmosphere overnight. The catalyst was removed by filtration through a pad of Celite, and the filtrate was concentrated to give crude diacetate, which was used in the next reaction without purification.

To a solution of the above diacetate in methanol (50 mL) was added sodium methoxide (1.0 M solution in methanol, 5.69 mL, 5.60 mmol). The resultant solution was stirred at room temperature for 30 min. The reaction was quenched with amberlyst-15, and the resin was removed by filtration. The solvent was removed in vacuo to give crude diol, which was used in the next reaction without purification.

To a solution of the above diol in THF/DMF (2:1, v/v, 150 mL) at 0°C were added tetra-*n*-butylammonium iodide (0.72 g, 1.9 mmol) and sodium hydride (60% dispersion in mineral oil, 3.00 g, 75.0 mmol). The resultant mixture was stirred at 0°C for 10 min and then at room temperature for 30 min. The mixture was recooled to 0°C and treated with benzyl bromide (6.10 mL, 51.2 mmol). After 10 min, the resultant mixture was allowed to warm to room temperature, and the stirring was continued overnight. The reaction was quenched with methanol (20 mL) at 0°C, and the mixture was extracted with ether (300 mL), washed with water (100 mL) and brine (100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (10% ethyl acetate/hexanes) gave bis(benzyl) ether **20** (5.89 g, 85% for the four steps) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.93 (brs, 1H), 4.64 (d, *J*=12.2 Hz, 1H), 4.57 (d, *J*=11.3 Hz, 1H), 4.51 (d, *J*=12.2 Hz, 1H), 4.38 (d, *J*=11.3 Hz, 1H), 3.92 (dd, *J*=5.8, 6.3 Hz, 1H), 3.82 (m, 1H), 3.76 (dd, J=3.9, 10.4 Hz, 1H), 3.64 (dd, J=2.1, 10.4 Hz, 1H), 3.53 (ddd, J=4.3, 4.9, 10.1 Hz, 1H), 2.01 (m, 1H), 1.86–1.72 (m, 3H), 1.18 (d, J=6.3 Hz, 3H), 1.11 (d, J=5.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 138.4, 93.9, 73.4, 73.1, 71.3, 70.8, 69.3, 67.7, 29.4, 24.0, 23.3, 21.3.

4.1.9. Lactone 22. A solution of bis(benzyl) ether **20** (3.85 g, 10.4 mmol) in 80% acetic acid/1 M HCl (4:1, v/v, 100 mL) was heated at 60°C for 2 days. The reaction mixture was cooled to room temperature and poured into cold saturated aqueous $NaHCO_3$ (300 mL). The aqueous layer was extracted with ethyl acetate (300 mL×3), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (50–60% ethyl acetate/hexanes) gave lactol **21** (1.01 g, 78%) as a white solid.

To a solution of lactol **21** (1.31 g, 4.00 mmol) in acetonitrile (10 mL) were added 4 Å molecular sieves (2.05 g) and N-methylmorpholine-N-oxide (0.70 g, 5.9 mmol). After 20 min, tetra-n-propylammonium perruthenate (76.8 mg, 0.218 mmol) was added, and the resultant mixture was stirred at room temperature for 4.5 h. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel (40% ethyl acetate/hexanes) to give lactone **22** (1.01 g, 78%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28–7.18 (m, 10H), 4.52 (d, 1H, J=11.9 Hz), 4.92 (d, 1H, J=11.9 Hz), 4.43 (d, 1H, J=11.9 Hz), 4.43 (d, 1H, J=11.9 Hz), 4.38 (m, 1H), 3.82 (m, 1H), 3.64 (dd, 1H, J=3.7, 10.7 Hz), 3.60 (dd, 1H, J=4.0, 10.7 Hz), 2.63 (ddd, 1H, J=6.4, 9.5, 17.4 Hz), 2.40 (ddd, 1H, J=5.8, 6.1, 17.4 Hz), 2.02 (m, 1H), 1.92 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 137.6, 137.5, 128.5, 128.4, 128.4, 127.9, 127.8, 127.8, 127.7, 80.9, 73.6, 71.1, 70.5, 69.3, 26.7, 23.4.

4.1.10. Enol triflate 10. To a solution of lactone **22** (3.40 g, 10.43 mmol) in THF (50 mL) at −78°C were added HMPA (2.72 mL, 15.6 mmol) followed by potassium bis(trimethylsilyl)amide (0.5 M solution in toluene, 27.2 mL, 13.5 mmol). After 30 min at −78°C, N-phenytrifluoromethanesulfonimide (4.47 g, 12.5 mmol) in THF (15 mL) was added to the solution, and the resultant mixture was stirred at 0°C for 1.5 h. Volatiles were removed in vacuo and the residue was extracted with hexane (15 mL×6). The organic extracts were combined and concentrated to give crude enol triflate **10**, which was used immediately in the next reaction without purification.

4.1.11. Enol ether 8. *exo*-Olefin **18** (3.72 g, 7.05 mmol) was treated with 9-BBN (0.5 M solution in THF, 36.6 mL, 18.3 mmol), and the resultant solution was stirred at room temperature for 1 h and then heated to reflux for 2 h. The solution was cooled to room temperature and treated with 3 M aqueous Cs_2CO_3 (7.05 mL, 21.2 mmol). After 15 min, the above enol triflate **10** in DMF (20 mL) followed by tris(dibenzylideneacetone)dipalladium(0)–chloroform adduct complex (364.6 mg, 0.352 mmol) and triphenylarsine (863.0 mg, 2.82 mmol) were added to the solution. After being stirred at room temperature for 14 h, the reaction mixture was extracted with ether (500 mL), washed with brine (200 mL×2), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (10–40% ethyl acetate/hexanes) provided enol ether **8** (15.35 g, 91%) as a colorless oil: $[\alpha]_D^{31}=+53.7$ (c 0.55, C_6H_6); IR (film) 3032, 2925, 1684, 1458, 1360, 1308, 1254, 1105, 847, 739, 694 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24–7.11 (m, 20H), 4.83 (d, J=11.9 Hz, 1H), 4.71 (d, J=11.6 Hz, 1H), 4.63 (d, J=10.7 Hz, 1H), 4.52 (d, J=11.9 Hz, 1H), 4.49–4.42 (m, 4H), 4.40 (s, 2H), 4.38 (m, 1H), 3.85 (m, 1H), 3.68–3.62 (m, 3H), 3.54 (m, 1H), 3.41 (m, 1H), 3.33 (m, 1H), 3.24 (m, 1H), 3.20–3.16 (m, 4H), 3.13 (dd, J=9.2, 8.9 Hz, 1H), 2.47 (dd, J=14.7, <1 Hz, 1H), 2.22 (m, 1H), 2.04–1.95 (m, 2H), 1.82 (dd, J=14.7, 9.8 Hz, 1H), 1.52 (m, 1H), 0.82 (s, 9H), −0.05 (s, 3H), −0.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.6, 143.3, 139.0, 138.5, 138.1, 130.5, 129.0, 128.4, 128.3, 128.1, 127.9, 127.7, 127.6, 127.55, 127.79, 127.0, 126.7, 125.4, 96.5, 94.0, 87.0, 83.5, 77.8, 76.9, 76.0, 75.2, 75.1, 75.0, 73.3, 71.1, 70.6, 69.3, 64.5, 55.0, 41.9, 36.6, 32.4, 27.2, 26.8, 26.0, 25.7, 24.7, 18.0, −3.6, −4.1; HRMS (FAB) calcd for $C_{50}H_{66}O_9SiNa$ [(M+Na)$^+$] 861.4374, found 861.4402.

4.1.12. Alcohol 23. To a solution of 2,3-dimethyl-2-butene (5.06 mL, 42.6 mmol) in THF (5 mL) at 0°C was added borane·THF (1.0 M solution in THF, 42.6 mL, 42.6 mmol). The resultant solution was stirred at 0°C for 2 h. To a solution of enol ether **8** (5.95 g, 7.10 mmol) in THF (70 mL) at 0°C was added the above solution of thexylborane in THF, and the resulting solution was stirred at 0°C for 2 h. The reaction was quenched with water (5 mL), and the mixture was treated with 3 M aqueous NaOH (40 mL) followed by 30% aqueous H_2O_2 (30 mL). The resultant solution was stirred at room temperature for 1.5 h and then heated at 45°C for 0.5 h. The reaction mixture was cooled to room temperature, extracted with ethyl acetate (500 mL), washed with saturated aqueous Na_2SO_3 (200 mL) and brine (200 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (20% ethyl acetate/hexanes) gave alcohol **23** (5.61 g, 92%) as a colorless oil: $[\alpha]_D^{27}=+12.4$ (c 0.075, C_6H_6); IR (film) 3458, 3063, 3031, 2927, 2856, 1652, 1496, 1454, 1360, 1310, 1251, 1209, 1107, 1056, 918, 858, 836, 777, 734, 697, 668 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 7.37–6.91 (m, 20H), 4.99 (d, J=12.2 Hz, 1H), 4.79 (d, J=12.2 Hz, 1H), 4.66 (d, J=11.1 Hz, 1H), 4.57–4.42 (m, 6H), 4.30 (d, J=11.8 Hz, 1H), 3.77 (ddd, J=9.4, 9.4, 4.8 Hz, 1H), 3.67–3.57 (m, 4H), 3.53–3.47 (m, 3H), 3.46 (m, 1H), 3.41 (dd, J=8.8, 8.8 Hz, 1H), 3.19 (dd, J=9.4, 9.4 Hz, 1H), 3.18 (s, 3H), 2.67 (ddd, J=11.4, 4.4, 4.4 Hz, 1H), 2.36 (ddd, J=14.7, 5.1, 1.5 Hz, 1H), 2.17 (m, 1H), 2.03 (ddd, J=14.7, 8.9, 3.6 Hz, 1H), 1.62 (ddd, J=11.4, 11.4, 11.4 Hz, 1H), 1.52 (m, 1H), 1.02 (s, 9H), 0.16 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 139.7, 135.9, 139.2, 138.7, 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.2, 126.7, 96.7, 87.1, 83.2, 81.4, 80.0, 77.4, 76.4, 75.0, 74.9, 74.8, 73.6, 73.0, 70.9, 70.2, 69.0, 64.2, 55.1, 38.9, 35.0, 32.3, 26.4, 18.4, −3.2, −4.0; HRMS (FAB) calcd for $C_{50}H_{68}O_{10}SiNa$ [(M+Na)$^+$] 879.4479, found 879.4476.

4.1.13. Ketone 7. To a solution of alcohol **23** (5.61 g, 6.55 mmol) in CH_2Cl_2 (30 mL) were added 4 Å molecular sieves (2 g) and N-methylmolpholine-N-oxide (1.15 g, 9.82 mmol), and the solution was stirred at room temperature for 5 min. Tetra-*n*-propylammonium perruthenate (115.2 mg, 0.33 mmol) was added, and the resultant solution was stirred at room temperature for 1 h. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel (40% ethyl acetate/hexanes) to give ketone **7** (5.57 g, 99%) as a colorless oil: $[\alpha]_D^{27}=-5.25$ (c 0.05, C_6H_6); IR (film) 3030, 2927, 2855, 1734, 1496, 1472, 1453, 1359, 1251, 1207, 1108, 1027, 915, 858, 836, 777, 733, 697, 674 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.37–6.87 (m, 20H), 4.99 (d, J=12.1 Hz, 1H), 4.80 (d, J=12.1 Hz, 1H), 4.71 (d, J=11.0 Hz, 1H), 4.62–4.50 (m, 3H), 4.38–4.28 (m, 2H), 4.23 (dd, J=6.7, 4.0 Hz, 1H), 4.18 (d, J=11.9 Hz, 1H), 3.94–3.87 (m, 4H), 3.81–3.70 (m, 3H), 3.55–3.47 (m, 4H), 3.45 (dd, J=8.8, 8.8 Hz, 1H), 3.29 (dd, J=9.2, 9.2 Hz, 1H), 3.19 (s, 3H), 2.86 (dd, J=14.9, 3.9 Hz, 1H), 2.63 (ddd, J=14.0, 6.9, 2.5 Hz, 1H), 2.57 (dd, J=14.9, 4.8 Hz, 1H), 2.21 (m, 1H), 2.13 (ddd, J=14.0, 10.1, 4.0 Hz, 1H), 1.76 (m, 1H), 0.98 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 207.9, 139.7, 138.9, 138.8, 138.5, 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.2, 126.7, 96.7, 87.3, 83.5, 79.8, 79.0, 77.2, 76.4, 75.9, 75.1, 75.1, 74.9, 73.5, 70.7, 70.6, 64.3, 55.0, 41.3, 33.9, 32.7, 26.3, 18.3, −3.4, −3.9; HRMS (FAB) calcd for $C_{50}H_{66}O_{10}SiNa$ $[(M+Na)^+]$ 877.4323, found 877.4343.

4.1.14. Tricyclic ether 25. To a solution of ketone **7** (173.8 mg, 0.204 mmol) in CH_2Cl_2 (2 mL) at −78°C were added trimethylaluminum (0.98 M solution in hexane, 0.26 mL, 0.25 mmol) and trimethylsilyldiazomethane (2.0 M solution in hexane, 0.15 mL, 0.30 mmol). The resultant solution was stirred at −78°C for 6 h before the reaction was quenched with saturated aqueous $NaHCO_3$. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in methanol/CH_2Cl_2 (3:1, v/v, 2.6 mL) and treated with *p*-toluenesulfonic acid monohydrate (58.1 mg, 0.301 mmol). The resultant solution was stirred at room temperature for 2 days and then heated to reflux for 4 h. The solution was cooled to 0°C, and the reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with ethyl acetate, washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude alcohol was used in the next reaction without chromatographic purification.

To a solution of the above alcohol in CH_2Cl_2 (2 mL) were successively added triethylamine (0.09 mL, 0.61 mmol), dimethylaminopyridine (12.4 mg, 0.102 mmol), and pivaloyl chloride (0.05 mL, 0.41 mmol). The resultant solution was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate, washed with 1 M HCl, saturated aqueous $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was filtered through a short column chromatography on silica gel (10–30% ethyl acetate/hexanes) to give mixed methyl ketal **24**, which was used in the next reaction without further purification.

To a solution of the above mixed methyl ketal **24** in acetonitrile (3 mL) at 0°C were successively added triethylsilane (0.25 mL, 1.57 mmol) and boron trifluoride etherate (0.075 mL, 0.59 mmol). The resultant solution was stirred at 0°C for 2 h before the reaction was quenched with saturated aqueous $NaHCO_3$. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (10% ethyl acetate/hexanes) gave tricyclic ether **25** (123.1 mg, 78% for the four steps) as a colorless amorphous solid: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.80–7.24 (m, 20H), 4.98–4.90 (m, 2H), 4.74 (d, J=11.3 Hz, 1H), 4.61 (d, J=10.1 Hz, 1H), 4.54 (m, 1H), 4.32 (d, J=11.9 Hz, 1H), 4.20–4.07 (m, 2H), 3.76 (ddd, J=4.9, 4.9, 4.9 Hz, 1H), 3.69 (m, 1H), 3.57 (dd, J=8.9, 8.9 Hz, 1H), 3.44 (m, 1H), 3.36–3.28 (m, 2H), 3.21 (dd, J=8.9, 8.9 Hz, 1H), 3.16–3.08 (m, 1H), 3.04 (m, 1H), 2.35 (ddd, J=11.6, 4.6, 4.3 Hz, 1H), 2.14 (m, 1H), 2.05 (m, 1H), 1.95–1.85 (m, 2H), 1.71–1.59 (m, 2H), 1.51 (ddd, J=11.6, 11.6, 11.6 Hz, 1H), 1.17 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.5, 138.9, 138.4, 138.3, 138.2, 128.4, 128.3, 127.9, 127.7, 127.6, 127.5, 84.1, 83.6, 82.3, 81.8, 81.5, 79.6, 78.2, 77.3, 76.4, 75.2, 74.9, 73.2, 71.4, 70.6, 61.1, 38.7, 37.0, 31.3, 27.2, 26.3, 23.6.

4.1.15. Olefin 26. To a solution of pivalate ester **25** (58.4 mg, 0.0751 mmol) in CH_2Cl_2 (1 mL) at −78°C was added diisobutylaluminum hydride (1.0 M solution in toluene, 0.23 mL, 0.23 mmol). The resultant solution was stirred at −78°C for 3 h before the reaction was quenched with saturated aqueous potassium sodium tartrate. The mixture was diluted with ethyl acetate and stirred vigorously at room temperature for 2.5 h. The resultant mixture was diluted with ethyl acetate, washed with water and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (30–40% ethyl acetate/hexanes) gave primary alcohol (49.9 mg, 96%) as a colorless oil.

To a solution of the above alcohol in CH_2Cl_2/DMSO (4:1, v/v, 1 mL) at 0°C were successively added triethylamine (0.05 mL, 0.36 mmol) and $SO_3\cdot$pyridine complex (45.8 mg, 0.288 mmol). The resultant solution was stirred at 0°C for 2 h. The mixture was diluted with ethyl acetate, washed with 1 M HCl, saturated aqueous $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude aldehyde was used in the next reaction without purification.

To a suspension of methyltriphenylphosphonium bromide (77.1 mg, 0.216 mmol) in THF (1 mL) at 0°C was added sodium bis(trimethylsilyl)amide (1.0 M solution in THF, 0.2 mL, 0.2 mmol). The resultant solution was stirred at 0°C for 30 min. A solution of the above aldehyde in THF/CH_2Cl_2 (3:10, v/v, 1.3 mL) was added to the ylide solution, and the resulting mixture was stirred at 0°C for 1 h. The reaction was quenched with saturated aqueous NH_4Cl, and the mixture was diluted with ethyl acetate, washed with water and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (5–20% ethyl acetate/hexanes) gave olefin **26** (43.9 mg, 88% for the two steps) as a white solid: $[\alpha]_D^{31}=+4.65°$ (c 0.97, $CHCl_3$); IR (film) 3030, 2866, 1954, 1732, 1643, 1495, 1452, 1363, 1211, 1072, 910, 741, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36–7.26 (m, 20H), 5.87 (ddt, J=17.2, 10.1, 6.6 Hz, 1H), 5.09–5.04

(m, 2H), 4.97 (d, J=11.2 Hz, 1H), 4.93 (d, J=10.8 Hz, 1H), 4.75 (d, J=11.2 Hz, 1H), 4.61 (d, J=10.9 Hz, 1H), 4.54 (d, J=12.6 Hz, 1H), 4.53 (s, 2H), 4.33 (d, J=11.8 Hz, 1H), 3.77 (ddd, J=4.9, 4.9, 4.9 Hz, 1H), 3.70 (m, 1H), 3.59 (dd, J=8.6, 8.6 Hz, 1H), 3.47–3.44 (m, 2H), 3.37–3.26 (m, 3H), 3.15–3.07 (m, 3H), 2.57 (m, 1H), 2.37 (ddd, J=11.5, 4.3, 4.3 Hz, 1H), 2.25 (m, 1H), 2.05 (m, 1H), 1.91–1.89 (m, 2H), 1.67 (m, 1H), 1.55 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.0, 138.5, 138.4, 138.3, 134.7, 128.35, 128.32, 128.27, 128.0, 127.9, 127.62, 127.59, 127.53, 127.45, 116.9, 84.2, 83.7, 82.4, 81.9, 81.0, 79.7, 79.0, 78.3, 75.1, 74.9, 74.0, 73.2, 71.6, 70.7, 37.1, 36.1, 26.4, 23.7; HRMS (FAB) calcd for $C_{44}H_{50}O_7Na$ [(M+Na)$^+$] 713.3454, found 713.3450.

4.1.16. Enol phosphate 29a. To a solution of lactone **22** (1.19 g, 3.65 mmol) in THF (20 mL) were added HMPA (1.90 mL, 10.9 mmol) and diphenylphosphoryl chloride (1.52 mL, 7.30 mmol). The resultant solution was cooled to −78°C and treated with potassium bis(trimethylsilyl)-amide (0.5 M solution in toluene, 9.50 mL, 4.75 mmol). After being stirred at −78°C for 30 min, the reaction mixture was diluted with ether and 2% NH_4OH. The mixture was stirred at room temperature for 30 min before dilution with ethyl acetate. The organic layer was separated, washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (25% ethyl acetate/hexanes) gave enol phosphate **29a** (1.52 g, 75%) as a pale yellow oil, which was used in the next cross-coupling reaction without further purification: ^{1}H NMR (C_6D_6) δ 7.39–77.34 (m, 4H), 7.28–7.24 (m, 2H), 7.20–7.05 (m, 8H), 6.97–6.90 (m, 4H), 6.83–6.77 (m, 2H), 4.46 (m, 1H), 4.37 (d, J=11.9 Hz, 1H), 4.31 (d, J=11.9 Hz, 1H), 4.26 (d, J=11.9 Hz, 1H), 4.20 (d, J=11.9 Hz, 1H), 4.10 (ddd, J=7.6, 4.6, 3.1 Hz, 1H), 3.70–3.61 (m, 2H), 3.52 (dd, J=11.0, 3.1 Hz, 1H), 2.00 (m, 1H), 1.89 (m, 1H); HRMS (FAB) calcd for $C_{32}H_{31}O_7PNa$ [(M+Na)$^+$] 581.1705, found 581.1724.

4.2. General procedure for Suzuki coupling of enol phosphates

exo-Olefin **18** (103.7 mg, 0.1964 mmol) was treated with 9-BBN (0.5 M solution in THF, 1.00 mL, 0.500 mmol). The resultant solution was stirred at room temperature for 1 h and then heated at 60°C for 2 h. After being cooled to room temperature, the reaction mixture was treated with 1 M aqueous $NaHCO_3$ (0.59 mL, 0.59 mmol) and stirred at room temperature for 15 min. To this mixture were added a solution of enol phosphate **29a** (221.0 mg, 0.3961 mmol) in DMF (2.5 mL) followed by tetrakis(triphenylphosphine)palladium(0) (23.2 mg, 0.0201 mmol). The resultant solution was stirred at 50°C for 20 h. The mixture was cooled to room temperature and diluted with ether, washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in THF (5 mL), cooled to 0°C, and treated with 3 M aqueous NaOH (0.50 mL) and 30% H_2O_2 (0.25 mL). The resulting mixture was stirred at room temperature for 1 h, diluted with ethyl acetate, washed with saturated aqueous Na_2SO_3 and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (10% ethyl acetate/hexanes) gave coupling product **8** (160.8 mg, 98%) as a colorless clear oil.

4.2.1. Hydroxy ester 32. To a solution of 2-deoxy-D-ribose (**31**) (10.00 g, 74.55 mmol) in THF (200 mL) was added methyl triphenylphosphoranylidene acetate (27.4 g, 82.0 mmol). The resultant solution was heated under reflux for 3 h. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel (10–15% methanol/$CHCl_3$) to give α,β-unsaturated ester as a brownish viscous oil, which was used in the next reaction without further purification.

To a solution of the above α,β-unsaturated ester in ethyl acetate/methanol (1:1, v/v, 250 mL) was added 10% Pd/C (2.0 g). The resulting mixture was stirred at room temperature under hydrogen atmosphere overnight. The catalyst was removed by filtration through a pad of Celite, and the filtrate was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (400 mL) and treated with benzaldehyde dimethylacetal (16.8 mL, 112 mmol) and camphorsulfonic acid (5.20 g, 22.4 mmol). The resultant solution was stirred at room temperature overnight before the reaction was quenched with triethylamine. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel (10–40% ethyl acetate/hexanes) to give hydroxy ester **32** (16.33 g, 78% for the three steps) as a colorless clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.35 (m, 2H), 7.27–7.21 (m, 3H), 5.35 (s, 1H), 4.15 (dd, J=10.1, 4.3 Hz, 1H), 3.57–3.42 (m, 6H), 2.30–2.24 (m, 2H), 1.90 (brd, J=5.2 Hz, 1H), 1.86–1.80 (m, 2H), 1.66 (m, 1H), 1.54 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 137.7, 128.8, 128.4, 128.3, 128.2, 126.0, 100.9, 81.5, 71.2, 65.7, 51.6, 33.8, 30.9, 20.4.

4.2.2. Hydroxy acid 33. To a solution of hydroxy ester **32** (959.4 mg, 3.4264 mmol) in THF/methanol/water (1:1:1, v/v, 30 mL) was added KOH (340 mg, 6.06 mmol). After being stirred at 50°C for 45 min, the reaction mixture was acidified with 1 M aqueous HCl. The mixture was diluted with brine, and the aqueous layer was extracted with ethyl acetate repeatedly. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was passed through a short column of silica gel (10% methanol/$CHCl_3$) to give hydroxy acid **33** (904.2 mg, 99%) as a colorless amorphous solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46–7.45 (m, 2H), 7.36–7.31 (m, 3H), 5.46 (s, 1H), 4.26 (dd, J=10.5, 4.7 Hz, 1H), 3.64–3.52 (m, 3H), 2.46–2.38 (m, 2H), 2.01–1.90 (m, 2H), 1.79 (m, 1H), 1.66 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.0, 137.8, 128.9, 128.2, 126.1, 101.0, 81.5, 71.2, 65.8, 33.5, 30.9, 20.3.

4.2.3. Seven-membered lactone 34. To a solution of hydroxy acid **33** (2.16 g, 8.12 mmol) in THF (50 mL) were added triethylamine (1.58 mL, 11.3 mmol) and 2,4,6-trichlorobenzoyl chloride (1.40 mL, 8.96 mmol). After being stirred at room temperature overnight, the reaction mixture was diluted with benzene (50 mL) and transferred via cannula to a refluxing solution of dimethylaminopyridine (1.50 g, 12.3 mmol) in benzene (400 mL) over a period of 4 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was diluted with ethyl acetate, washed with 1 M aqueous HCl, saturated aqueous $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (40–50% ethyl acetate/hexanes) gave lactone **34** (1.56 g, 77%) as a colorless amorphous solid: ^1H NMR (500 MHz, $CDCl_3$) δ 7.47–7.42 (m, 2H), 7.38–7.34 (m, 3H), 5.48 (s, 1H), 4.40 (dd, J=11.3, 5.8 Hz, 1H), 4.26 (ddd, J=9.5, 9.5, 5.8 Hz, 1H), 3.83–3.76 (m, 2H), 2.75 (dd, J=14.4, 7.0 Hz, 1H), 2.60 (m, 1H), 2.32 (m, 1H), 2.01 (m, 1H), 1.84–1.67 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 132.6, 129.2, 128.3, 128.1, 126.1, 100.7, 78.2, 71.5, 68.1, 35.3, 34.8, 19.9.

4.2.4. Enol phosphate 29b. By the same procedure described above, lactone **34** (370.7 mg, 1.4948 mmol) afforded enol phosphate **29b** (640.6 mg, 89%) as a pale yellow oil, which was immediately used in the next coupling reaction: ^1H NMR (500 MHz, C_6D_6) δ 7.57–7.53 (m, 2H), 7.33–7.28 (m, 4H), 7.19–7.07 (m, 5H), 6.97–6.91 (m, 4H), 6.83–6.78 (m, 2H), 5.24 (s, 1H), 4.70 (m, 1H), 4.30 (dd, J=10.7, 5.5 Hz, 1H), 4.01 (ddd, J=10.1, 9.2, 5.5 Hz, 1H), 3.40 (dd, J=10.7, 10.1 Hz, 1H), 3.31 (ddd, J=10.4, 9.2, 3.4 Hz, 1H), 1.79–1.69 (m, 2H), 1.52 (m, 1H), 1.37 (m, 1H).

4.2.5. Silyl ether 35. To a solution of ester **32** (16.33 g, 58.32 mmol) in CH_2Cl_2 (300 mL) at 0°C were added diisopropylethylamine (40.6 mL, 233 mmol), tetra-*n*-butylammonium iodide (2.15 g, 5.82 mmol) and chloromethyl methyl ether (13.3 mL, 175 mmol). After being stirred at room temperature for 3 days, the reaction mixture was diluted with ethyl acetate, washed with 1 M aqeuous HCl, saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude methoxymethyl ether was used in the next reaction without purification.

To a solution of the above methoxymethyl ether in THF (300 mL) at 0°C was added lithium aluminum hydride (3.33 g, 87.7 mmol). After being stirred at 0°C for 45 min, the reaction mixture was treated with 3 M aqueous NaOH (20 mL) and stirred vigorously at room temperature until the white gel precipitated. Filtration through a pad of Celite followed by concentration gave crude alcohol, which was used in the next reaction without purification.

To a solution of the above alcohol in CH_2Cl_2 (250 mL) at 0°C were added 2,6-lutidine (9.61 mL, 83.0 mmol) and triisopropylsilyl trifluoromethanesulfonate (16.7 mL, 62.1 mmol). The resultant solution was allowed to warm to room temperature over 4 h before addition of methanol. The reaction mixture was diluted with ethyl acetate, washed with 1 M aqueous HCl, saturated aqueous $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (5–10% ethyl acetate/hexanes) gave silyl ether **35** (20.42 g, 78% for the three steps) as a colorless clear oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.48–7.45 (m, 2H), 7.36–7.29 (m, 3H), 5.46 (s, 1H), 4.68–4.64 (m, 2H), 4.40 (dd, J=10.8, 5.1 Hz, 1H), 3.72–3.67 (m, 2H), 3.65–3.58 (m, 2H), 3.48 (ddd, J=9.8, 9.8, 5.1 Hz, 1H), 3.37 (s, 3H), 1.90 (m, 1H), 1.71–1.44 (m, 5H), 1.15–0.90 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.0, 128.7, 128.2, 126.0, 100.7, 96.8, 80.4, 72.3, 70.1, 63.3, 55.7, 33.0, 31.6, 21.4, 18.0, 12.0.

4.2.6. Primary alcohol 36. To a solution of silyl ether **35** (20.42 g, 45.22 mmol) in ethyl acetate/methanol (1:1, v/v, 250 mL) was added 20% $Pd(OH)_2/C$ (1.97 g), and the mixture was stirred at room temperature under hydrogen atmosphere overnight. The catalyst was removed by filtration, and the solvent was removed in vacuo. The crude diol was used in the next reaction without chromatographic purification.

To a solution of the above diol in DMF (200 mL) at 0°C was added sodium hydride (60% dispersion in mineral oil, 7.32 g, 183 mmol). The reaction mixture was stirred at room temperature for 30 min and then cooled to 0°C. To the mixture were added benzyl bromide (16.2 mL, 136 mmol) and tetra-*n*-butylammonium iodide (1.67 g, 4.52 mmol). The resultant solution was stirred at room temperature overnight before the reaction was quenched with methanol. The mixture was diluted with ether, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude bis(benzyl) ether was used in the next reaction without purification.

To a solution of the above bis(benzyl) ether in THF (200 mL) was added tetra-*n*-butylammonium fluoride (1.0 M solution in THF, 67.8 mL, 67.8 mmol). After being stirred at room temperature overnight, the reaction mixture was concentrated in vacuo. Purification by column chromatography on silica gel (50% ethyl acetate/hexanes) gave alcohol **36** (14.03 g, 80% for the three steps) as a colorless clear oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.35–7.23 (m, 10H), 4.77 (d, J=6.7 Hz, 1H), 4.71 (d, J=6.7 Hz, 1H), 4.64 (d, J=11.3 Hz, 1H), 4.54 (d, J=12.2 Hz, 1H), 4.50 (d, J=12.2 Hz, 1H), 4.49 (d, J=11.3 Hz, 1H), 3.90 (dd, J=9.8, 4.3 Hz, 1H), 3.67–3.55 (m, 5H), 3.36 (s, 3H), 1.65–1.48 (m, 6H), 1.38 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6, 138.2, 128.3, 127.9, 127.64, 127.60, 96.4, 79.1, 77.2, 73.4, 72.4, 70.1, 62.7, 55.6, 32.7, 30.3, 21.7.

4.2.7. Hydroxy acid 37. To a solution of alcohol **36** (497.6 mg, 1.2891 mmol) in CH_2Cl_2/DMSO (1:1, v/v, 12 mL) at 0°C were successively added triethylamine (0.900 mL, 6.46 mmol) and $SO_3\cdot$pyridine complex (822.7 mg, 5.17 mmol). After being stirred at 0°C for 1 h, the reaction mixture was diluted with ether, washed with 1 M aqueous HCl, saturated aqueous $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude aldehyde was used in the next reaction without purification.

To a solution of the above aldehyde in CH_2Cl_2/dimethyl sulfide (3:1, v/v, 16 mL) at 0°C was added $BF_3\cdot OEt_2$ (0.490 mL, 3.87 mmol). The resultant solution was stirred at 0°C for 30 min before the reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with ethyl acetate, washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude hydroxy aldehyde was used in the next reaction without purification.

To a solution of the above hydroxy aldehyde in *t*-butanol/water (4:1, v/v, 15 mL) at 0°C were successively added 2-methyl-2-butene (2.70 mL, 25.5 mmol), NaH_2PO_4 (176.9 mg, 1.474 mmol) and $NaClO_2$ (79% purity, 517.0 mg, 4.516 mmol). After being stirred at room temperature for 1 h, the reaction mixture was acidified with 1 M aqueous HCl and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (3% methanol/$CHCl_3$) gave hydroxy acid **37** (259.0 mg, 56% for the three steps) as a colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.35–7.24 (m, 10H), 4.56 (s, 2H), 4.52 (s, 2H), 3.88 (ddd, *J*=6.6, 6.2, 3.7 Hz, 1H), 3.61 (dd, *J*=9.6, 3.7 Hz, 1H), 3.57 (dd, *J*=9.6, 6.6 Hz, 1H), 3.49 (m, 1H), 2.38–2.27 (m, 2H), 1.82 (m, 1H), 1.73–1.57 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.6, 138.3, 137.9, 128.5, 128.4, 127.90, 127.86, 127.7, 79.1, 73.5, 72.3, 71.5, 71.1, 33.6, 29.4, 20.3.

4.2.8. Seven-membered lactone 38. By the same procedure described above, hydroxy acid **37** (765.2 mg, 2.137 mmol) afforded lactone **38** (465.7 mg, 64%) as a pale yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.35–7.22 (m, 10H), 4.56 (d, *J*=11.6 Hz, 1H), 4.56 (s, 2H), 4.38 (d, *J*=11.6 Hz, 1H), 4.32 (ddd, *J*=8.2, 5.8, 2.8 Hz, 1H), 3.74 (dd, *J*=10.7, 2.8 Hz, 1H), 3.72–3.66 (m, 2H), 2.74 (ddd, *J*=14.3, 10.1, 7.6 Hz, 1H), 2.61 (ddd, *J*=14.3, 6.7, 4.0 Hz, 1H), 2.00–1.82 (m, 3H), 1.71 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 137.9, 137.7, 128.5, 128.4, 127.9, 127.8, 127.7, 80.8, 75.5, 73.6, 71.6, 69.8, 32.6, 28.7, 16.6.

4.2.9. Enol phosphate 29c. By the same procedure described above, lactone **38** (288.1 mg, 0.847 mmol) in THF (15 mL) afforded enol phosphate **29c** (364.0 mg, 75%) as a pale yellow oil, which was immediately used in the next coupling reaction: ^1H NMR (500 MHz, C_6D_6) δ 7.41–7.33 (m, 4H), 7.28–7.24 (m, 2H), 7.18–7.10 (m, 8H), 6.97–6.90 (m, 4H), 6.82–6.76 (m, 2H), 4.61 (m, 1H), 4.44–4.38 (m, 2H), 4.27 (d, *J*=12.2 Hz, 1H), 4.23 (d, *J*=11.6 Hz, 1H), 4.05 (d, *J*=11.6 Hz, 1H), 3.86 (m, 1H), 3.78 (dd, *J*=11.0, 2.4 Hz, 1H), 3.68 (dd, *J*=11.0, 2.4 Hz, 1H), 2.18 (m, 1H), 1.86 (m, 1H), 1.65–1.52 (m, 2H).

4.2.10. Hydroxy acid 39. To a solution of alcohol **36** (1.4874 g, 3.8533 mmol) in CH_2Cl_2 (35 mL) at 0°C were successively added triethylamine (1.60 mL, 11.5 mmol), dimethylaminopyridine (47.2 mg, 0.386 mmol) and *p*-toluenesulfonyl chloride (1.10 g, 5.77 mmol). After being stirred at room temperature overnight, the reaction mixture was diluted with ethyl acetate, washed with 1 M aqueous HCl, saturated aqueous $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (20–25% ethyl acetate/hexanes) gave tosylate (1.7550 g, 84%) as a pale yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.67–7.63 (m, 2H), 7.23–7.12 (m, 12H), 4.64 (d, *J*=6.7 Hz, 1H), 4.58 (d, *J*=6.7 Hz, 1H), 4.50 (d, *J*=11.3 Hz, 1H), 4.42 (d, *J*=12.2 Hz, 1H), 4.39 (d, *J*=12.2 Hz, 1H), 4.33 (d, *J*=11.3 Hz, 1H), 3.89–3.83 (m, 2H), 3.75 (m, 1H), 3.51 (dd, *J*=10.4, 5.8 Hz, 1H), 3.46 (dd, *J*=10.4, 4.6 Hz, 1H), 3.41 (m, 1H), 3.24 (m, 3H), 1.54–1.30 (m, 5H), 1.21 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.6, 138.4, 138.1, 133.2, 129.8, 128.4, 128.3, 127.92, 127.85, 127.7, 96.4, 78.7, 76.9, 73.3, 72.3, 70.4, 69.9, 55.6, 29.9, 28.9, 21.6; MS (FAB) $[(M+Na)^+]$ *m/z* 565.

To a solution of the above tosylate (1.755 g, 3.2380 mmol) in DMSO (30 mL) was added KCN (1.05 g, 16.1 mmol). The resultant solution was heated at 80°C overnight. After being cooled to room temperature, the reaction mixture was diluted with ether, washed with water and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (30% ethyl acetate/hexanes) gave cyanide (1.283 g, quant.) as a colorless clear oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.40–7.25 (m, 10H), 4.77 (d, *J*=6.7 Hz, 1H), 4.72 (d, *J*=6.7 Hz, 1H), 4.65 (d, *J*=11.3 Hz, 1H), 4.54 (d, *J*=12.2 Hz, 1H), 4.50 (d, *J*=12.2 Hz, 1H), 4.47 (d, *J*=11.3 Hz, 1H), 3.90 (m, 1H), 3.67–3.55 (m, 3H), 3.36 (s, 3H), 2.29–2.21 (m, 2H), 1.67–1.38 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 138.0, 128.4, 128.0, 127.7, 119.7, 96.4, 78.5, 76.8, 73.4, 72.3, 69.8, 55.6, 29.7, 25.4, 24.8, 17.1; MS (FAB) *m/z* 420 $[(M+Na)^+]$.

To a solution of the above cyanide (131.2 mg, 0.3304 mmol) in methanol (4 mL) was added 6 M aqueous HCl (2 mL). After being stirred at room temperature overnight, the reaction mixture was cooled to 0°C and treated with 6 M aqueous KOH (2 mL). Solid KOH (1.31 g, 23.3 mmol) was added to the mixture, and the resultant solution was heated at 70°C overnight. The reaction mixture was cooled to 0°C and acidified with diluted HCl. The aqueous layer was extracted with $CHCl_3$ repeatedly. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (5% methanol/$CHCl_3$) gave hydroxy acid **39** (121.2 mg, 99% for the two steps) as a colorless clear oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.24 (m, 10H), 4.58–4.48 (m, 4H), 3.89 (m, 1H), 3.61 (dd, *J*=9.6, 3.8 Hz, 1H), 3.57 (dd, *J*=9.6, 6.7 Hz, 1H), 3.49 (m, 1H), 2.37–2.25 (m, 2H), 1.67–1.46 (m, 5H), 1.38 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.0, 138.3, 137.8, 128.44, 128.36, 127.9, 127.8, 127.7, 79.3, 73.4, 72.4, 71.6, 71.0, 33.8, 29.7, 24.7, 24.5.

4.2.11. Eight-membered lactone 40. By the same procedure described above, hydroxy acid **39** (520.0 mg, 1.398 mmol) afforded lactone **40** (361.1 mg, 73%) as a colorless clear oil: ^1H NMR ($CDCl_3$) δ 7.34–7.20 (m, 10H), 4.67 (m, 1H), 4.60–4.50 (m, 3H), 4.30 (d, *J*=11.3 Hz, 1H), 3.80 (dd, *J*=10.8, 1.9 Hz, 1H), 3.69 (dd, *J*=10.8, 5.9 Hz, 1H), 3.62 (m, 1H), 2.53–2.38 (m, 2H), 1.92–1.72 (m, 4H), 1.67–1.52 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 175.8, 138.1, 137.9, 128.9, 128.7, 128.41, 128.38, 128.0, 127.8, 127.7, 127.6, 78.8, 77.9, 73.4, 71.3, 69.7, 33.0, 28.3, 28.0, 21.1.

4.2.12. Enol phosphate 29d. By the same procedure described above, lactone **40** (224.8 mg, 0.6350 mmol) afforded enol phosphate **29d** (286.4 mg, 77%) as a pale yellow oil, which was immediately used in the next coupling reaction: ^1H NMR (500 MHz, C_6D_6) δ 7.38–7.34 (m, 4H), 7.30–7.27 (m, 2H), 7.20–7.05 (m, 8H), 6.97–6.89 (m, 4H), 6.82–6.77 (m, 2H), 4.82 (ddd, *J*=7.0, 6.7, 2.4 Hz, 1H), 4.48 (m, 1H), 4.41 (d, *J*=12.2 Hz, 1H), 4.34 (d, *J*=12.2 Hz, 1H), 4.31 (d, *J*=11.6 Hz, 1H), 4.15 (d, *J*=11.6 Hz, 1H), 3.77–3.60 (m, 3H), 2.00–1.86 (m, 3H), 1.72 (m, 1H), 1.57 (m, 1H), 1.51 (m, 1H).

4.2.13. Compound 28. By the same procedure described above, *exo*-olefin **18** (102.4 mg, 0.1903 mmol) and enol phosphate **29b** (180.9 mg, 0.3769 mmol) afforded coupling product **28** (136.0 mg, 94%) as a colorless oil: $[\alpha]_D^{31}=+47.3°$ (c 0.25, C_6H_6); IR (film) $\nu_{max}=3033$, 2933, 2867, 1685, 1460, 1367, 1107, 1067, 847, 744, 694 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.66–7.64 (m, 3H), 7.38–7.36 (m, 2H), 7.22–7.02 (m, 10H), 5.38 (s, 1H), 5.03–4.95 (m, 2H), 4.79 (d, $J=11.9$ Hz, 1H), 4.70 (d, $J=11.0$ Hz, 1H), 4.62 (d, $J=10.0$ Hz, 1H), 4.60 (d, $J=10.0$ Hz, 1H), 4.51 (d, $J=11.0$ Hz, 1H), 4.42 (m, 1H), 3.85 (ddd, $J=9.5$, 9.2, 5.5 Hz, 1H), 3.78 (ddd, $J=9.5$, 6.7, 4.3 Hz, 1H), 3.67 (m, 1H), 3.64–3.58 (m, 2H), 3.57–3.42 (m, 4H), 3.27 (dd, $J=9.2$, 8.9 Hz, 1H), 3.24 (s, 3H), 2.73 (dd, $J=14.0$, <1 Hz, 1H), 2.29 (m, 1H), 2.15 (m, 1H), 2.08 (dd, $J=14.0$, 10.0 Hz, 1H), 2.03 (m, 1H), 1.94 (m, 1H), 1.67 (m, 1H), 1.60 (m, 1H), 0.96 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 156.9, 139.7, 138.8, 138.8, 128.8, 128.53, 128.46, 128.4, 128.3, 127.9, 127.7, 127.2, 126.8, 126.7, 110.4, 101.1, 96.8, 87.3, 83.8, 83.0, 78.1, 76.0, 75.7, 75.2, 75.1, 75.0, 69.5, 64.2, 54.9, 38.8, 32.9, 32.5, 26.1, 21.3, 18.3, −3.3, −4.2; HRMS (FAB) calcd for $C_{44}H_{60}O_9SiNa$ $[(M+Na)^+]$ 783.3904, found 783.3895.

4.2.14. Compound 30c. By the same procedure described above, *exo*-olefin **18** (155.5 mg, 0.2945 mmol) and enol phosphate **29c** (337.6 mg, 0.5902 mmol) afforded coupling product **30c** (243.1 mg, 97%) as a colorless oil: $[\alpha]_D^{31}=+64.3°$ (c 0.47, C_6H_6); IR (film) 3033, 2927, 1680, 1458, 1363, 1254, 1103, 847, 739, 696 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.39–7.02 (m, 20H), 5.08 (d, $J=12.2$ Hz, 1H), 4.85–4.80 (m, 2H), 4.64–4.58 (m, 2H), 4.54 (d, $J=12.5$ Hz, 1H), 4.50 (d, $J=10.7$ Hz, 1H), 4.48 (d, $J=12.4$, 1H), 4.35 (d, $J=11.9$ Hz, 1H), 4.34 (m, 1H), 3.96 (d, $J=11.6$ Hz, 1H), 3.89–3.82 (m, 2H), 3.75 (m, 1H), 3.70 (d, $J=4.3$ Hz, 1H), 3.68 (s, 2H), 3.67 (m, 1H), 3.57 (ddd, $J=9.8$, 9.8, 2.1 Hz, 1H), 3.53–3.50 (m, 2H), 3.28 (dd, $J=9.8$, 8.9 Hz, 1H), 3.23 (s, 3H), 2.90 (dd, $J=14.3$, <1 Hz, 1H), 2.61 (m, 1H), 2.32 (m, 1H), 2.22 (dd, $J=14.3$, 10.1 Hz, 1H), 2.19 (m, 1H), 1.92–1.89 (m, 2H), 1.71 (m, 1H), 0.98 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (125 MHz, C_6D_6) δ 157.1, 139.8, 139.4, 139.2, 138.9, 128.5, 128.43, 128.36, 128.3, 128.0, 127.8, 127.74, 127.66, 127.54, 127.51, 127.17, 126.7, 106.3, 96.9, 87.4, 84.1, 83.9, 77.74, 77.66, 76.1, 75.8, 75.1, 75.0, 73.2, 71.4, 70.9, 64.6, 54.9, 38.9, 33.0, 29.0, 26.3, 20.9, 18.3, −3.3, −4.0; HRMS (FAB) calcd for $C_{51}H_{68}O_9SiNa$ $[(M+Na)^+]$ 875.4530, found 875.4506.

4.2.15. Compound 30d. By the same procedure described above, *exo*-olefin **18** (117.1 mg, 0.2218 mmol) and enol phosphate **29d** (256.8 mg, 0.4382 mmol) afforded coupling product **30d** (185.2 mg, 96%) as a colorless oil: $[\alpha]_D^{31}=+47.5°$ (c 0.90, C_6H_6); IR (film) $\nu_{max}=3030$, 2931, 2867, 1662, 1458, 1363, 1254, 1105, 847, 739, 696 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.39–7.04 (m, 20H), 5.01 (d, $J=12.0$ Hz, 1H), 4.82 (d, $J=12.2$ Hz, 1H), 4.76 (dd, $J=8.9$, 6.7 Hz, 1H), 4.71 (d, $J=11.0$ Hz, 1H), 4.63–4.58 (m, 3H), 4.53–4.48 (m, 2H), 4.46 (d, $J=11.6$ Hz, 1H), 4.15 (d, $J=11.6$ Hz, 1H), 3.89 (m, 1H), 3.82 (m, 1H), 3.75 (dd, $J=10.5$, 2.3 Hz, 1H), 3.72–3.61 (m, 3H), 3.55–3.43 (m, 3H), 3.27 (dd, $J=9.0$, 9.0 Hz, 1H), 3.22 (s, 3H), 2.99 (dd, $J=13.9$, <1 Hz, 1H), 2.56 (m, 1H), 2.33 (m, 1H), 2.18–2.08 (m, 2H), 2.02–1.93 (m, 2H), 1.86 (m, 1H), 1.79 (m, 1H), 1.67 (m, 1H), 0.97 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 153.7, 139.8, 139.4, 139.2, 138.9, 128.7, 128.6, 128.5, 128.5, 128.4, 128.3, 128.0, 128.0, 127.8, 127.7, 127.6, 127.5, 127.2, 126.8, 103.5, 96.8, 87.4, 84.0, 80.2, 78.7, 77.8, 76.3, 75.8, 75.1, 75.0, 73.5, 72.4, 70.9, 64.9, 54.9, 39.2, 33.1, 26.3, 25.8, 24.4, 24.0, 18.3, −3.3, −4.0; HRMS (FAB) calcd for $C_{52}H_{70}O_9SiNa$ $[(M+Na)^+]$ 889.4687, found 889.4709.

4.2.16. Compound 30e. By the same procedure described above, *exo*-olefin **18** (106.6 mg, 0.2019 mmol) and enol phosphate **29e**[36] (202.8 mg, 0.4008 mmol) afforded coupling product **30e** (155.5 mg, 98%) as a colorless oil: $[\alpha]_D^{31}=+31.8°$ (c 0.47, C_6H_6); IR (film) $\nu_{max}=3027$, 2933, 2860, 1743, 1668, 1458, 1392, 1363, 1298, 1254, 1209, 1103, 847, 769, 742, 694 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.64–7.62 (m, 3H), 7.38–7.36 (m, 2H), 7.22–7.02 (m, 10H), 5.80–5.70 (m, 2H), 5.35 (s, 1H), 5.07 (dd, $J=7.9$, 7.3 Hz, 1H), 5.03 (d, $J=11.9$ Hz, 1H), 4.82 (d, $J=11.9$ Hz, 1H), 4.70 (d, $J=11.0$ Hz, 1H), 4.66 (d, $J=6.4$ Hz, 1H), 4.63 (d, $J=6.4$ Hz, 1H), 4.56 (dd, $J=10.4$, 4.9 Hz, 1H), 4.50 (d, $J=11.0$ Hz, 1H), 3.94 (ddd, $J=10.4$, 10.4, 4.9 Hz, 1H), 3.87–3.74 (m, 3H), 3.68 (dd, $J=10.4$, 10.4 Hz, 1H), 3.57 (ddd, $J=9.8$, 9.8, 2.1 Hz, 1H), 3.54–3.37 (m, 4H), 3.32–3.22 (m, 5H), 2.72 (dd, $J=14.7$, <1 Hz, 1H), 2.38–2.26 (m, 2H), 2.03 (dd, $J=14.7$, 10.7 Hz, 1H), 1.64 (m, 1H), 0.96 (s, 9H), 0.10 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 156.5, 139.6, 138.8, 138.7, 131.9, 129.0, 128.9, 128.5, 128.5, 128.4, 128.3, 128.2, 128.0, 127.8, 127.3, 126.8, 126.7, 124.4, 113.4, 101.7, 97.0, 87.4, 84.0, 81.2, 77.5, 76.1, 75.8, 75.8, 75.2, 75.1, 71.0, 64.4, 55.0, 39.6, 33.0, 29.7, 26.2, 23.5, 18.2, −3.5, −3.7; HRMS (FAB) calcd for $C_{46}H_{62}O_9SiNa$ $[(M+Na)^+]$ 809.4061, found 809.4037.

4.2.17. Alcohol 41. To a solution of 2,3-dimethyl-2-butene (97 μL, 0.82 mmol) in THF (0.5 mL) at 0°C was added BH_3·THF (0.98 M solution in THF, 0.83 mL, 0.82 mmol), and the resultant solution was stirred at 0°C for 2 h. To a solution of enol ether **30c** (139.0 mg, 0.163 mmol) in THF (1 mL) at −10°C was added the above solution of thexylborane in THF. The resultant solution was stirred at −10°C for 19 h, −5°C for 3 h, and then 0°C for 3 h. The reaction was quenched with water (2 mL), and the mixture was treated with 3 M aqueous NaOH (1.1 mL) followed by 30% aqueous H_2O_2 (0.6 mL). The resultant mixture was stirred at room temperature for 2 h, extracted with ethyl acetate (50 mL), washed with saturated aqueous Na_2SO_3 (15 mL) and brine (15 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (10–40% ethyl acetate/hexanes) gave alcohol **41** (117.8 mg, 83%) as a colorless oil, along with recovered **30c** (14.2 mg, 10%). **41**: $[\alpha]_D^{31}=+30.3$ (c 0.47, $CHCl_3$); IR (film) 3471, 3043, 2929, 1749, 1458, 1362, 1254, 1101, 847, 739, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36–7.14 (m, 20H), 4.95 (d, $J=11.9$ Hz, 1H), 4.82 (d, $J=11.9$ Hz, 1H), 4.75 (d, $J=10.8$ Hz, 1H), 4.60–4.46 (m, 4H), 4.59 (s, 2H), 4.35 (d, $J=11.6$ Hz, 1H), 3.74 (m, 1H), 3.68 (ddd, $J=5.1$, 4.9, 4.7 Hz, 1H), 3.64–3.56 (m, 3H), 3.53–3.50 (m, 2H), 3.47–3.43 (m, 3H), 3.40–3.32 (m, 2H), 3.32 (s, 3H), 3.23 (dd, $J=9.3$, 9.3 Hz, 1H), 2.16–2.10 (m, 2H), 1.97 (m, 1H), 1.86–1.79 (m, 2H), 1.76–1.66 (m, 2H), 1.63–1.55 (m, 1H), 0.87 (s, 9H), 0.07 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.0, 138.6, 138.5, 138.0, 128.3, 128.1, 127.8, 127.7, 127.6, 127.5, 127.0, 126.6, 125.7, 96.4, 86.9, 83.1, 82.7, 82.2, 78.5, 76.6, 76.2, 75.0, 74.9, 74.8, 73.3, 73.2, 71.4, 70.7, 64.1, 55.3, 35.5, 31.9, 28.3, 26.0, 23.6, 18.1, −3.4, −4.1; HRMS (FAB) calcd for $C_{51}H_{70}O_{10}SiNa$ $[(M+Na)^+]$ 893.4636, found 893.4620.

4.2.18. Ketone 6. To a solution of alcohol **41** (670.2 mg, 0.770 mmol) in CH_2Cl_2 (8 mL) were added 4 Å molecular sieves (385 mg) and *N*-methylmorpholine-*N*-oxide (135.4 mg, 1.54 mmol). After 5 min, tetra-*n*-propylammonium perruthenate (13.6 mg, 0.039 mmol) was added to the mixture, and the resultant solution was stirred at room temperature for 1 h. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel (35% ethyl acetate/hexanes) to give ketone **6** (661.4 mg, 99%) as a colorless oil: $[\alpha]_D^{27}=+6.0$ (*c* 0.27, C_6H_6); IR (film) 3063, 3029, 2927, 2883, 2856, 1716, 1496, 1454, 1360, 1321, 1252, 1209, 1107, 1028, 916, 859, 836, 777, 734, 697, 676 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.35–6.86 (m, 20H), 4.98 (d, J=12.2 Hz, 1H), 4.79 (d, J=12.2 Hz, 1H), 4.70 (d, J=11.0 Hz, 1H), 4.56 (s, 2H), 4.51 (d, J=11.3 Hz, 1H), 4.47–4.40 (m, 2H), 4.23 (dd, J=7.4, 4.5 Hz, 1H), 4.17 (d, J=11.4 Hz, 1H), 3.83 (m, 1H), 3.77 (m, 1H), 3.67–3.63 (m, 2H), 3.62 (m, 1H), 3.56–3.48 (m, 3H), 3.47 (m, 1H), 3.40 (dd, J=8.7, 8.7 Hz, 1H), 3.28 (dd, J=9.2, 9.2 Hz, 1H), 3.21 (s, 3H), 2.77 (ddd, J=12.9, 12.8, 3.2 Hz, 1H), 2.47 (ddd, J=13.8, 7.4, 2.6 Hz, 1H), 2.35 (ddd, J=12.9, 7.4, 2.5 Hz, 1H), 2.21 (m, 1H), 2.11 (ddd, J=13.8, 9.2, 4.5 Hz, 1H), 1.97 (m, 1H), 1.79 (m, 1H), 1.46 (dddd, J=12.8, 11.7, 11.7, 2.5 Hz, 1H), 0.98 (s, 9H), 0.15 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 213.1, 139.8, 139.2, 138.96, 138.92, 128.6, 128.5, 128.4, 128.3, 128.0, 127.8, 127.7, 127.2, 126.7, 96.8, 87.3, 85.5, 83.9, 83.3, 78.0, 76.6, 76.28, 76.25, 75.4, 74.9, 73.5, 71.43, 71.4, 64.3, 55.0, 36.7, 36.0, 32.6, 27.4, 26.3, 18.3, −3.3, −3.9; HRMS (FAB) calcd for $C_{51}H_{68}O_{10}SiNa$ $[(M+Na)^+]$ 891.4479, found 891.4470.

4.2.19. Hydroxy mixed methyl ketal 42. To a solution of oxalyl chloride (0.25 mL, 0.287 mmol) in CH_2Cl_2 (1 mL) at −78°C was added dropwise DMSO (0.027 mL, 0.380 mmol). After 10 min, a solution of **41** (81.2 mg, 0.0933 mmol) in CH_2Cl_2 (1 mL) was added to the mixture, and the resulting solution was stirred at −78°C for 40 min before addition of triethylamine (0.104 mL, 0.747 mmol). After being stirred at −78°C for 10 min, the reaction mixture was allowed to warm to 0°C over 1 h. The mixture was diluted with ethyl acetate, washed with 1 M HCl, saturated aqueous $NaHCO_3$, water, and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude ketone was used in the next reaction without chromatographic purification.

To a solution of the above ketone in methanol/CH_2Cl_2 (4:1, v/v, 1 mL) was added *p*-toluenesulfonic acid monohydrate (35.5 mg, 0.187 mmol). The resultant solution was stirred at room temperature for 18 h and then heated at 55°C for 4 h. After cooling to room temperature, the reaction was quenched with aqueous saturated $NaHCO_3$. The solution was diluted with ethyl acetate, washed with aqueous saturated $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography on silica gel (30–40% ethyl acetate/hexanes) afforded hydroxy mixed methyl ketal **42** (55.4 mg, 82% for the two steps) as a colorless oil: $[\alpha]_D^{31}=-47.4°$ (*c* 0.23, $CHCl_3$); IR (film) 3495, 3030, 2905, 1496, 1453, 1364, 1219, 1088, 737, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.22 (m, 20H), 4.96 (d, J=11.1 Hz, 1H), 4.90 (d, J=10.9 Hz, 1H), 4.75 (d, J=11.1 Hz, 1H), 4.58 (d, J=10.9 Hz, 1H), 4.54–4.48 (m, 3H), 4.37 (d, J=11.9 Hz, 1H), 3.81 (ddd, J=5.9, 5.9, 3.6 Hz, 1H), 3.73–3.70 (m, 3H), 3.57 (dd, J=9.0, 8.9 Hz, 1H), 3.51–3.44 (m, 3H), 3.39–3.35 (m, 2H), 3.26 (m, 1H), 3.26 (s, 3H), 3.12 (ddd, J=11.4, 9.6, 4.4 Hz, 1H), 2.07–1.85 (m, 6H), 1.77–1.65 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 138.4, 138.3, 138.1, 128.4, 128.3, 128.03, 128.00, 127.8, 127.7, 126.7, 99.2, 84.6, 83.7, 81.6, 80.5, 79.9, 78.7, 75.4, 75.1, 74.3, 74.2, 73.3, 71.5, 70.7, 61.2, 47.1, 34.2, 32.0, 25.9, 21.6; HRMS calcd for $C_{44}H_{52}O_9Na$ $[(M+Na)^+]$ 747.3509, found 747.3502.

4.2.20. Olefin 43. To a solution of hydroxy mixed methyl ketal **42** (49.8 mg, 68.8 μmol) and triethylamine (0.05 mL, 0.358 mmol) in CH_2Cl_2/DMSO (4:1, v/v, 1 mL) at 0°C was added SO_3·pyridine complex (43.8 mg, 0.275 mmol). The resulting solution was stirred at 0°C for 1.4 h and then at room temperature for 2 h. The reaction mixture was diluted with ethyl acetate, washed with 1 M HCl, aqueous saturated $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude aldehyde was used in the next reaction without purification.

To a suspension of methyltriphenylphosphonium bromide (73.7 mg, 0.206 mmol) in THF (1 mL) at 0°C was added sodium bis(trimethylsilyl)amide (1 M solution in THF, 0.193 mL, 0.193 mmol). After stirring for 30 min, a solution of the above aldehyde in THF/CH_2Cl_2 (5:7, v/v, 1.2 mL) was added to the ylide solution, and the resultant mixture was stirred at 0°C for 1 h before the reaction was quenched with aqueous saturated NH_4Cl. The mixture was diluted with ethyl acetate, washed with water and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography on silica gel (10–20% ethyl acetate/hexanes) afforded olefin **26** (39.3 mg, 79% for the two steps) as a colorless oil: $[\alpha]_D^{31}=-23.4°$ (*c* 0.69, $CHCl_3$); IR (film) 3024, 2902, 1637, 1495, 1454, 1363, 1215, 1080, 912, 741, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35–7.23 (m, 20H), 5.88 (ddt, J=17.2, 10.2, 6.6 Hz, 1H), 5.08–5.03 (m, 2H), 4.96 (d, J=11.1 Hz, 1H), 4.90 (d, J=10.8 Hz, 1H), 4.75 (d, J=11.1 Hz, 1H), 4.59 (d, J=10.8 Hz, 1H), 4.55–4.47 (m, 3H), 4.38 (d, J=11.8 Hz, 1H), 3.82 (ddd, J=6.0, 5.9, 3.8 Hz, 1H), 3.69 (m, 1H), 3.54 (dd, J=6.7, 6.5 Hz, 1H), 3.49 (dd, J=10.2, 6.0 Hz, 1H), 3.48 (dd, J=12.1, 4.5 Hz, 1H), 3.39 (dd, J=10.2, 5.9 Hz, 1H), 3.38–3.31 (m, 2H), 3.28 (m, 1H), 3.27 (s, 3H), 3.08 (ddd, J=11.3, 9.7, 4.3 Hz, 1H), 2.55 (m, 1H), 2.26 (m, 1H), 2.08 (ddd, J=11.0, 4.5, 4.3 Hz, 1H), 2.01–1.85 (m, 4H), 1.75 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.9, 138.5, 138.42, 138.36, 134.7, 128.4, 128.3, 128.0, 127.9, 127.64, 127.60, 127.5, 116.9, 99.1, 84.7, 84.0, 81.3, 80.8, 79.1, 78.7, 75.2, 75.1, 74.5, 74.1, 73.3, 71.6, 70.6, 47.1, 36.1, 32.0, 26.1, 21.6; HRMS (FAB) calcd for $C_{44}H_{52}O_8Na$ $[(M+Na)^+]$ 743.3560, found 743.3558.

4.2.21. Tricyclic ether 26. To a solution of olefin **43** (29.1 mg, 40.4 μmol) in CH_3CN/CH_2Cl_2 (5:3, v/v, 0.8 mL) at 0°C were added triethylsilane (0.052 mL, 0.326 mmol) followed by boron trifluoride etherate (0.015 mL, 0.118 mmol). The resultant solution was stirred at 0°C for 1.5 h before the reaction was quenched with aqueous saturated $NaHCO_3$. The mixture was diluted with ethyl acetate, washed with aqueous saturated $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography on silica gel (15–20% ethyl acetate/hexanes) afforded tricyclic ether **26** (24.1 mg, 86%).

4.2.22. Alcohol 44. To a solution of tricyclic ether **26** (24.5 mg, 35.5 μmol) in CH_2Cl_2 (1 mL) at 0°C was added iodine (90.1 mg, 0.355 mmol). The resultant solution was stirred at room temperature for 6 h before the reaction was quenched with saturated aqueous $Na_2S_2O_3$ (2 mL). The mixture was extracted with ethyl acetate (10 mL), washed with brine (3 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (5–20% ethyl acetate/hexanes) gave iodide (22.3 mg, 87%) as a colorless solid, which was used in the next reaction without further purification.

To a solution of the above iodide (22.3 mg, 30.7 μmol) in ether/methanol (2:1, v/v, 1.5 mL) were added zinc powder (18.1 mg, 0.277 mmol) and acetic acid (3 μL, 0.06 mmol). The resultant solution was stirred at room temperature overnight. Insoluble solids were filtered through a pad of Celite, and the filtrate was concentrated in vacuo. Purification by column chromatography on silica gel (5–20% ethyl acetate/hexanes) gave alcohol **44** (17.7 mg, 96%) as a colorless solid: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.15–7.37 (m, 15H), 5.81 (m, 1H), 4.90–5.08 (m, 3H), 4.60 (d, J=11.6 Hz, 1H), 4.48 (d, J=10.0 Hz, 1H), 4.46 (s, 2H), 4.28 (d, J=11.9 Hz, 1H), 3.61–3.74 (m, 2H), 3.17–3.43 (m, 6H), 2.98–3.15 (m, 3H), 2.50 (m, 1H), 2.10–2.36 (m, 2H), 1.98 (m, 1H), 1.78–1.89 (m, 2H), 1.47–1.65 (m, 2H).

4.2.23. Diene 45. To a solution of alcohol **44** (17.7 mg, 0.0295 mmol) in DMF (0.5 mL) at 0°C was added sodium bis(trimethylsilyl)amide (1.0 M solution in THF, 0.12 mL, 0.12 mmol). After 1 h, allyl bromide (8 μL, 0.09 mmol) was added, and the resultant solution was stirred at 0°C for 4 h before the reaction was quenched with saturated aqueous NH_4Cl (1 mL). The mixture was extracted with ethyl acetate (10 mL), washed with water (3 mL) and brine (3 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (10% ethyl acetate/hexanes) gave diene **45** (14.7 mg, 78%) as a colorless solid: $[\alpha]_D^{31}=-5.38$ (c 0.22, $CHCl_3$); IR (film) 3028, 2864, 1643, 1452, 1362, 1074, 914, 741, 696 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.24 (m, 15H), 5.93–5.82 (m, 2H), 5.22 (dd, J=17.0, 2.0 Hz, 1H), 5.14–5.02 (m, 3H), 4.91 (d, J=11.0 Hz, 1H), 4.71 (d, J=11.0 Hz, 1H), 4.53 (d, J=13.0 Hz, 1H), 4.52 (s, 2H), 4.36 (dddd, J=12.0, 5.8, 1.3, 1.3 Hz, 1H), 4.31 (d, J=11.5 Hz, 1H), 4.09 (dddd, J=12.0, 5.8, 1.3, 1.3 Hz, 1H), 3.74 (m, 1H), 3.67 (m, 1H), 3.48 (dd, J=8.8, 8.8 Hz, 1H), 3.46–3.39 (m, 2H), 3.33–3.26 (m, 2H), 3.13–3.01 (m, 4H), 2.54 (m, 1H), 2.34 (m, 1H), 2.23 (ddd, J=7.3, 7.3, 7.3 Hz, 1H), 2.03 (m, 1H), 1.91–1.84 (m, 2H), 1.64 (m, 1H), 1.54 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.0, 138.4, 138.3, 135.0, 134.7, 128.3, 128.26, 127.9, 127.63, 127.60, 127.55, 127.46, 116.9, 84.0, 83.7, 82.2, 81.8, 81.0, 79.8, 79.0, 78.2, 74.9, 74.2, 74.0, 73.2, 71.5, 70.6, 37.1, 36.1, 26.3, 23.6; HRMS (FAB) calcd for $C_{40}H_{48}O_7Na$ [(M+Na)$^+$] 663.3298, found 663.3290.

4.2.24. ABCD ring system 47. To a solution of diene **45** (8.2 mg, 0.013 mmol) in CH_2Cl_2 (2 mL) was added Grubbs' catalyst **46** (2.1 mg, 2.55 μmol) in CH_2Cl_2 (0.5 mL) via cannula, and the resultant solution was stirred at room temperature for 2.5 h. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel (20% ethyl acetate/hexanes) to give ABCD ring system **47** (10.2 mg, quant.) as a colorless solid: $[\alpha]_D^{31}=-0.12$ (c 0.41, $CHCl_3$); IR (film) 3028, 2865, 1739, 1450, 1365, 1086, 741, 698 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 740–7.15 (m, 15H), 5.63–5.53 (m, 2H), 5.23–5.10 (m, 2H), 4.45–4.38 (m, 3H), 4.25 (d, J=11.9 Hz, 1H), 4.16 (dd, J=15.6, 5.3 Hz, 1H), 4.01 (m, 1H), 3.84 (dd, J=15.6, 2.4 Hz, 1H), 3.73 (m, 1H), 3.67 (dd, J=8.9, 8.6 Hz, 1H), 3.52–3.38 (m, 3H), 3.35–3.29 (m, 2H), 3.15 (ddd, J=10.7, 9.2, 4.3 Hz, 1H), 2.93 (ddd, J=11.6, 9.5, 4.3 Hz, 1H), 2.64 (ddd, J=16.2, 7.6, 4.0 Hz, 1H), 2.51 (ddd, J=11.6, 4.6, 4.3 Hz, 1H), 2.33 (m, 1H), 2.16 (dddd, J=11.9, 11.9, 11.9, <1 Hz, 1H), 1.97–1.86 (m, 2H), 1.78 (ddd, J=11.6, 11.3, 11.3 Hz, 1H), 1.60 (dddd, J=14.3, 13.4, <1, <1 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 140.6, 139.11, 139.10, 131.7, 128.6, 128.4, 128.3, 127.91, 127.89, 127.8, 127.7, 127.4, 126.5, 87.9, 83.8, 82.7, 82.2, 82.1, 79.4, 78.8, 77.2, 75.2, 73.8, 73.3, 72.0, 70.8, 68.5, 38.0, 35.2, 26.7, 23.5; HRMS (FAB) calcd for $C_{38}H_{44}O_7Na$ [(M+Na)$^+$] 635.2985, found 635.2977.

4.2.25. Enone 48. To a solution of ketone **6** (661.4 mg, 0.762 mmol) in THF (7 mL) at −78°C was added lithium bis(trimethylsilyl)amide (1.0 M solution in THF, 1.53 mL, 1.53 mmol). After 20 min, triethylamine (0.21 mL, 1.53 mmol) and trimethylsilyl chloride (0.193 mL, 1.53 mmol) were added, and the resultant solution was stirred at −78°C for 10 min before the reaction was quenched with water (0.5 mL). The mixture was extracted with ethyl acetate (50 mL), washed with water (15 mL) and brine (15 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude silyl enol ether was used immediately in the next reaction without purification.

To a solution of the above silyl enol ether in acetonitrile (7 mL) was added palladium(II) acetate (427.7 mg, 1.90 mmol). The resultant solution was stirred at room temperature for 30 min. The mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo. Purification by column chromatography on silica gel (20–30% ethyl acetate/hexanes) gave enone **48** (632.5 mg, 96% for the two steps) as a colorless oil: $[\alpha]_D^{27}=+71.7$ (c 0.97, C_6H_6); IR (film) 3087, 3062, 3029, 2927, 2884, 2856, 1671, 1557, 1540, 1496, 1471, 1454, 1387, 1360, 1309, 1251, 1209, 1107, 1028, 917, 859, 836, 777, 734, 697, 677 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 7.35–7.06 (m, 20H), 6.20–6.13 (m, 2H), 4.97 (d, J=12.2 Hz, 1H), 4.77 (d, J=12.2 Hz, 1H), 4.70 (d, J=11.0 Hz, 1H), 4.56 (s, 2H), 4.59–4.50 (m, 2H), 4.44 (d, J=12.2 Hz, 1H), 4.38 (d, J=12.2 Hz, 1H), 4.33 (d, J=11.5 Hz, 1H), 4.22 (d, J=11.5 Hz, 1H), 4.18 (dd, J=3.0, 7.7 Hz, 1H), 3.88–3.73 (m, 3H), 3.70 (ddd, J=9.2, 9.2, 2.1 Hz, 1H), 3.58–3.55 (m, 2H), 3.53 (m, 1H), 3.51 (dd, J=9.2, 9.2 Hz, 1H), 3.41 (dd, J=9.2, 9.2 Hz, 1H), 3.28 (dd, J=9.2, 9.2 Hz, 1H), 3.21 (s, 3H), 2.55 (ddd, J=13.9, 7.0, 2.1 Hz, 1H), 2.27–2.18 (m, 2H), 1.80 (m, 1H), 0.97 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 204.1, 141.3, 139.8, 139.0, 138.9, 138.4, 129.8, 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 127.2, 126.7, 96.7, 87.3, 83.3, 83.2, 81.8, 76.9, 76.7, 76.5, 75.5, 75.0, 74.9, 73.6, 71.7, 70.8, 64.5, 54.9, 36.5, 32.5, 26.3, 18.3, −3.3, −3.9; HRMS (FAB) calcd for $C_{51}H_{66}O_{10}SiNa$ [$(M+Na)^+$] 889.4323, found 889.4343.

4.2.26. Keto diol 50. To a solution of enone **48** (1.61 g, 1.853 mmol) in acetonitrile (25 mL) at 0°C was added 46% aqueous HF (4.2 mL). The resultant solution was stirred at room temperature overnight. Another portion of 46% aqueous HF (2.0 mL) was added, and the stirring was continued overnight. Another portion of 46% aqueous HF (1.5 mL) was added, and the reaction mixture was stirred overnight before the reaction was quenched with saturated aqueous $NaHCO_3$ (100 mL). The mixture was extracted with ethyl acetate, washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (40–60% ethyl acetate/hexanes) gave a 7:1 equilibrium mixture of keto diol **50** and the corresponding hemiketal (1.12 g, 85%) as a colorless oil. **50**: $[\alpha]_D^{26}=+26.8$ (*c* 0.73, $CHCl_3$); IR (film) 3458, 3087, 3062, 3030, 2870, 1667, 1496, 1453, 1361, 1311, 1208, 1090, 1027, 911, 736, 698, 681, 609 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21–7.11 (m, 20H), 6.41 (m, 1H), 5.89 (m, 1H), 4.75–4.71 (m, 3H), 4.49–4.33 (m, 6H), 4.10 (ddd, *J*=7.9, 3.6, 1.6 Hz, 1H), 3.72 (ddd, *J*=8.2, 5.7, 2.6 Hz, 1H), 3.61–3.53 (m, 5H), 3.34–3.13 (m, 3H), 3.12 (dd, *J*=9.0, 8.9 Hz, 1H), 2.68 (brd, *J*=3.9 Hz, 1H), 2.13 (ddd, *J*=14.9, 3.9, 3.9 Hz, 1H), 1.93–1.78 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.4, 142.6, 138.7, 138.1, 137.8, 137.3, 128.8, 128.53, 128.49, 128.47, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 80.5, 83.3, 81.8, 81.2, 78.8, 76.5, 76.3, 75.3, 75.0, 74.4, 73.5, 71.9, 70.2, 60.6, 35.6, 34.1; HRMS (FAB) calcd for $C_{43}H_{48}O_9Na$ [$(M+Na)^+$] 731.3196, found 731.3185.

4.2.27. TIPS ether 54. To a solution of a mixture of hydroxyketone **50** and its hemiketal (3.03 g, 4.28 mmol) in CH_2Cl_2 (50 mL) at 0°C were successively added triethylamine (2.38 mL, 17.1 mmol), dimethylaminopyridine (104.5 mg, 0.285 mmol), and triisopropylsilyl chloride (1.10 mL, 5.13 mmol). The resultant solution was stirred at 0°C for 2 h and then allowed to warm to room temperature. After 20 h, additional dimethylaminopyridine (104.5 mg, 0.285 mmol) and triisopropylsilyl chloride (0.36 mL, 1.71 mmol) were added, and the stirring was continued for further 2 days. Additional dimethylaminopyridine (52.2 mg, 0.142 mmol) was added, and the mixture was stirred for 1 h before the reaction was quenched with methanol (3 mL). The mixture was extracted with ethyl acetate (400 mL), washed with saturated aqueous NH_4Cl (100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (10–40% ethyl acetate/hexanes) gave a 7:1 mixture of TIPS ether **54** and the corresponding hemiketal (3.20 g, 87%) as a colorless oil. **54**: $[\alpha]_D^{26}=+18.5$ (*c* 0.94, $CHCl_3$); IR (film) 3447, 3062, 3030, 2868, 1663, 1496, 1453, 1361, 1310, 1207, 1089, 1027, 912, 736, 697, 610 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 7.33–7.07 (m, 20H), 6.04 (dd, *J*=3.4, 12.6 Hz, 1H), 5.98 (d, *J*=12.6 Hz, 1H), 4.99 (d, *J*=11.6 Hz, 1H), 4.92 (d, *J*=11.4 Hz, 1H), 4.82 (d, *J*=11.6 Hz, 1H), 4.63–4.59 (m, 2H), 4.42 (d, *J*=12.0 Hz, 1H), 4.32 (d, *J*=12.0 Hz, 1H), 4.23 (d, *J*=11.6 Hz, 1H), 4.14 (d, *J*=11.6 Hz, 1H), 4.11–3.96 (m, 2H), 3.92 (m, 1H), 3.70 (m, 1H), 3.65–3.62 (m, 2H), 3.58 (m, 1H), 3.54 (dd, *J*=8.9, 9.0 Hz, 1H), 3.46 (m, 1H), 3.32 (dd, *J*=9.0, 9.1 Hz, 1H), 2.91 (brd, *J*=4.6 Hz, 1H), 2.50 (ddd, *J*=14.8, 3.8, 3.8 Hz, 1H), 2.30–2.17 (m, 2H), 1.73 (m, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 203.4, 141.9, 139.9, 139.4, 138.5, 138.2, 129.2, 128.7, 128.6, 128.54, 128.51, 128.4, 128.3, 128.2, 128.0, 127.91, 127.86, 127.83, 127.6, 127.5, 87.2, 83.3, 82.8, 81.4, 76.7, 76.5, 76.2, 75.3, 75.2, 74.9, 73.6, 71.7, 70.4, 60.1, 36.13, 36.10, 18.3, 18.2, 12.4; HRMS (FAB) calcd for $C_{52}H_{68}O_9Na$ [$(M+Na)^+$] 887.4530, found 887.4526.

4.2.28. Alcohol 51. A solution of a mixture of hydroxy ketone **54** and its hemiketal (1.08 g, 1.25 mmol) in toluene (13 mL) was treated with trimethyl orthoformate (2.73 mL, 25.0 mmol) and pyridinium *p*-toluenesulfonate (62.8 mg, 0.250 mmol). The resultant solution was stirred at 45°C overnight before the reaction was quenched with saturated aqueous $NaHCO_3$ (30 mL) at room temperature. The mixture was extracted with ethyl acetate (100 mL), washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude mixed methyl ketal **55** was used in the next reaction without chromatographic purification.

To a solution of the above mixed methyl ketal **55** in acetonitrile/CH_2Cl_2 (2:1, v/v, 19 mL) at 0°C were added triethylsilane (1.60 mL, 10.0 mmol) and boron trifluoride etherate (0.64 mL, 5.00 mmol). The resultant solution was stirred at 0°C for 1.5 h before the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL). The mixture was extracted with ethyl acetate (80 mL), washed with saturated aqueous $NaHCO_3$ (30 mL) and brine (30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (30–40% ethyl acetate/hexanes) gave alcohol **51** (817.0 mg, 94% for the two steps) as a colorless solid: $[\alpha]_D^{26}=-7.17$ (*c* 0.84, $CHCl_3$); IR (film) 3289, 3061, 3030, 2872, 1496, 1453, 1365, 1327, 1292, 1209, 1095, 1027, 908, 736, 696, 613 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 7.31–6.99 (m, 20H), 5.82–5.74 (m, 2H), 5.09 (d, *J*=11.6 Hz, 1H), 4.96 (d, *J*=11.6 Hz, 1H), 4.81 (d, *J*=11.6 Hz, 1H), 4.51 (d, *J*=11.3 Hz, 1H), 4.47–4.41 (m, 3H), 4.30 (d, *J*=11.6 Hz, 1H), 4.18 (dd, *J*=8.7, 1.9 Hz, 1H), 3.76–3.64 (m, 6H), 3.58 (dd, *J*=9.2, 9.2 Hz, 1H), 3.42 (m, 1H), 3.21 (dd, *J*=9.2, 9.2 Hz, 1H), 3.14 (ddd, *J*=11.4, 9.2, 4.3 Hz, 1H), 3.05 (dd, *J*=9.2, 9.2 Hz, 1H), 2.73 (ddd, *J*=11.6, 9.4, 4.2 Hz, 1H), 2.13 (ddd, *J*=11.4, 4.3, 4.3 Hz, 1H), 1.98 (m, 1H), 1.60 (m, 1H), 1.52 (ddd, *J*=11.4, 11.4, 11.4 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 139.7, 139.3, 139.2, 138.7, 132.5, 132.3, 128.6, 128.5, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 84.4, 84.0, 82.5, 81.8, 80.9, 79.1, 78.7, 78.0, 75.4, 75.0, 73.9, 73.7, 71.9, 71.4, 60.5, 37.2, 35.0; HRMS (FAB) calcd for $C_{43}H_{48}O_8Na$ [$(M+Na)^+$] 715.3247, found 715.3262.

4.2.29. Olefin 56. To a solution of alcohol **51** (105.2 mg, 0.152 mmol) and triethylamine (0.106 mL, 0.760 mmol) in CH_2Cl_2/DMSO (3:1, v/v, 2.7 mL) at 0°C was added SO_3·pyridine (96.8 mg, 0.608 mmol). The resultant solution was stirred at 0°C for 2 h. The mixture was extracted with ethyl acetate (10 mL), washed with 1 M HCl (3 mL), saturated aqueous $NaHCO_3$ (3 mL), and brine (3 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude aldehyde was used in the next reaction without purification.

To a suspension of methyltriphenylphosphonium bromide (162.9 mg, 0.456 mmol) in THF (3.0 mL) at 0°C was added sodium bis(trimethylsilyl)amide (1.0 M solution in THF, 0.46 mL, 0.46 mmol). The resultant ylide solution was stirred at 0°C for 30 min. To the solution was added a solution of the above aldehyde in CH_2Cl_2 (2 mL), and the resultant mixture was stirred at 0°C for 30 min. The reaction mixture was poured into water (5 mL), extracted with ethyl acetate (10 mL×2), washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (10–20% ethyl acetate/hexanes) gave olefin **56** (94.9 mg, 91% for the two steps) as a colorless solid: $[\alpha]_D^{26}=-0.3$ (*c* 0.33, $CHCl_3$); IR (film) 3067, 3028, 2863, 1496, 1453, 1363, 1325, 1205, 1073, 1027, 997, 913, 734, 696, 611 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.44–7.08 (m, 20H), 6.06–6.00 (m, 2H), 5.81–5.77 (m, 2H), 5.14–5.05 (m, 3H), 5.01 (d, J=11.3 Hz, 1H), 4.82 (d, J=11.5 Hz, 1H), 4.57 (d, J=11.3 Hz, 1H), 4.48–4.44 (m, 2H), 4.30 (d, J=11.6 Hz, 1H), 4.16 (dd, J=8.5, 1.6 Hz, 1H), 3.76–3.69 (m, 4H), 3.64 (dd, J=9.1, 9.0 Hz, 1H), 3.37–3.31 (m, 2H), 3.19 (m, 1H, 11H), 3.11 (dd, J=9.0, 9.1 Hz, 1H), 2.83 (ddd, J=11.5, 4.3, 9.1 Hz, 1H), 2.62 (m, 1H), 2.37–2.23 (m, 2H), 1.66 (ddd, J=11.5, 11.5, 11.5 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 139.8, 139.4, 138.7, 135.1, 132.4, 132.3, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 117.1, 84.6, 84.0, 82.7, 81.3, 81.0, 79.4, 78.8, 78.0, 75.2, 75.0, 73.8, 73.6, 71.9, 71.4, 37.4, 36.6; HRMS (FAB) calcd for $C_{44}H_{48}O_7Na$ $[(M+Na)^+]$ 711.3298, found 711.3308.

4.2.30. *p*-Methoxybenzylidene acetal 57. To a solution of di-*tert*-butylbiphenyl (1.6 g, 6.0 mmol) in THF (12 mL) at 0°C was added lithium metal (60.0 mg, 8.57 mmol), and the resultant solution was stirred at 0–25°C for 5 h. To a solution of olefin **56** (126.3 mg, 0.1835 mmol) in THF (8 mL) at −78°C was added the above lithium di-*tert*-butylbiphenylide (LiDBB) until the solution became deep blue. The resultant solution was stirred at −78°C for 1 h before the reaction was quenched with solid NH_4Cl (200 mg) and methanol (1 mL). The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel (15% methanol/$CHCl_3$) to give tetraol, which was used in the next reaction without further purification.

To a solution of the above tetraol in DMF/CH_2Cl_2 (1:3, v/v, 4 mL) were added *p*-anisaldehyde dimethylacetal (62.5 μL, 0.367 mmol) and camphorsulfonic acid (8.5 mg, 37 μmol). The resultant solution was stirred at room temperature for 6 h before the reaction was quenched with triethylamine. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel (2% methanol/$CHCl_3$) to give *p*-methoxybenzylidene acetal **57** (48.2 mg, 59% for the two steps) as a colorless oil: $[\alpha]_D^{26}=-3.16$ (*c* 0.11, $CHCl_3$); IR (film) 3489, 2859, 1615, 1517, 1457, 1382, 1303, 1284, 1250, 1172, 1089, 1040, 1001, 916, 828, 674, 579 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, J=8.7 Hz, 2H), 6.87 (d, J=7.0 Hz, 2H), 5.90 (m, 1H), 5.76 (m, 1H), 5.70 (m, 1H), 5.36 (s, 1H), 5.14 (dd, J=17.0, 1.0 Hz, 1H), 5.06 (dd, J=10.2, 1.0 Hz, 1H), 4.29 (dd, J=8.8, 2.1 Hz, 1H), 4.19 (dd, J=10.8, 5.1 Hz, 1H), 3.88 (dd, J=9.0, 2.0 Hz, 1H), 3.78 (s, 3H), 3.58 (dd, J=9.2, 9.2 Hz, 1H), 3.56–3.46 (m, 2H), 3.38–3.29 (m, 3H), 3.10 (ddd, J=11.7, 9.2, 4.2 Hz, 1H), 2.93 (dd, J=9.2, 9.2 Hz, 1H), 2.59 (m, 1H), 2.38–2.26 (m, 2H), 1.53 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.2, 134.3, 131.9, 131.3, 127.5, 117.3, 113.7, 100.8, 80.7, 80.6, 80.5, 79.0, 77.6, 76.0, 74.1, 73.9, 73.0, 69.2, 55.3, 36.4, 36.1; HRMS (FAB) calcd for $C_{24}H_{30}O_8Na$ $[(M+Na)^+]$ 469.1838, found 469.1827.

4.2.31. Triene 5. To a solution of diol **57** (206.9 mg, 0.464 mmol) and 2,6-lutidine (0.162 mL, 1.39 mmol) in DMF/CH_2Cl_2 (1:3, v/v, 4 mL) at 0°C was added triisopropylsilyl trifluoromethanesulfonate (0.25 mL, 0.93 mmol). The resultant solution was stirred at 0°C for 6 h before the reaction was quenched with methanol (1 mL). The mixture was extracted with ethyl acetate (30 mL), washed with saturated aqueous NH_4Cl (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude TIPS ether was used in the next reaction without purification.

To a solution of the above triisopropylsilyl ether in DMF (5 mL) at 0°C was added sodium bis(trimethylsilyl)amide (1.0 M solution in THF, 2.3 mL, 2.3 mmol). The resultant solution was stirred at 0°C for 30 min, and then allyl bromide (0.16 mL, 1.85 mmol) was added. The resultant solution was stirred at room temperature overnight before the reaction was quenched with saturated aqueous NH_4Cl (30 mL). The mixture was extracted with ethyl acetate (50 mL×2), washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (7% ethyl acetate/hexanes) gave triene **5** (302.7 mg, quant. for the two steps) as a colorless oil: $[\alpha]_D^{26}=+27.6$ (*c* 0.175, $CHCl_3$); IR (film) 3076, 2942, 2891, 2864, 1642, 1615, 1588, 1517, 1462, 1382, 1250, 1172, 1095, 1065, 1039, 999, 917, 882, 828, 806, 681 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.57 (d, J=8.7 Hz, 2H), 6.81 (d, J=8.6 Hz, 2H), 6.05 (m, 2H), 5.93–5.85 (m, 3H), 5.30 (dd, J=17.6, 1.7 Hz, 1H), 5.28 (s, 1H), 5.15 (dd, J=17.4, 1.5 Hz, 1H), 5.09 (dd, J=10.3, <1 Hz, 1H), 5.04 (dd, J=10.6, 1.4 Hz, 1H), 4.45 (d, J=12.6, 5.0 Hz, 1H), 4.12 (dd, J=10.1, 4.3 Hz, 1H), 4.07 (dd, J=9.2, <1 Hz, 1H), 4.04 (dd, J=12.6, 5.5 Hz, 1H), 3.91 (dd, J=9.7, 8.5 Hz, 1H), 3.80 (dd, J=8.1, <1 Hz, 1H), 3.45 (dd, J=10.1, 10.1 Hz, 1H), 3.41 (ddd, J=10.1, 9.2, 4.3 Hz, 1H), 3.28 (m, 1H), 3.26 (s, 3H), 3.07–3.02 (m, 2H), 2.86 (dd, J=9.1, 8.7 Hz, 1H), 2.77 (ddd, J=11.5, 9.1, 4.5 Hz, 1H), 2.60 (m, 1H), 2.30 (m, 1H), 2.16 (ddd, J=11.5, 4.5, 4.5 Hz, 1H), 1.55 (ddd, J=11.5, 11.5, 11.5 Hz, 1H), 1.37–1.16 (m, 21H); ^{13}C NMR (125 MHz, C_6D_6) δ 160.6, 135.5, 135.3, 132.6, 131.6, 130.9, 128.5, 128.3, 128.0, 117.0, 115.8, 113.8, 101.1, 83.3, 82.4, 81.1, 80.9, 79.5, 78.0, 77.7, 74.2, 74.1, 73.4, 69.4, 54.7, 37.2, 36.6, 18.6, 18.5, 13.7; HRMS (FAB) calcd for $C_{36}H_{54}O_8SiNa$ $[(M+Na)^+]$ 665.3486, found 665.3470.

4.2.32. ABCD ring fragment 4. To a solution of triene **5** (58.2 mg, 90.7 μmol) in CH_2Cl_2 (10 mL) was added Grubbs' catalyst **46** (37.3 mg, 45.3 μmol), and the resultant solution was stirred at room temperature for 2 h. Another portion of **46** (7.5 mg, 9.0 μmol) was added, and the stirring was continued for further 2 h. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel (5–10% ethyl acetate/hexanes) to give ABCD ring fragment **4** (53.9 mg, 97%) as a colorless oil: $[\alpha]_D^{26}=+7.54$ (c 0.08, $CHCl_3$); IR (film) 2942, 2890, 2864, 1615, 1518, 1463, 1381, 1302, 1284, 1250, 1172, 1100, 1038, 1005, 882, 810, 677, 652 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.57 (d, J=8.6 Hz, 2H), 6.81 (d, J=8.7 Hz, 2H), 5.94–5.88 (m, 2H), 5.58–5.51 (m, 2H), 5.28 (s, 1H), 4.14–4.08 (m, 2H), 4.04 (dd, J=15.4, 5.9 Hz, 1H), 3.87 (dd, J=9.0, 8.4 Hz, 1H), 3.82 (dd, J=9.0, <1 Hz, 1H), 3.70 (dd, J=15.4, 2.5 Hz, 1H), 3.47–3.39 (m, 2H), 3.26 (s, 3H), 3.21 (dd, J=9.6, 3.8 Hz, 1H), 3.12 (dd, J=9.6, 9.0 Hz, 1H), 3.10 (ddd, J=11.3, 9.0, 4.0 Hz, 1H), 2.95 (dd, J=9.2, 8.4 Hz, 1H), 2.86 (ddd, J=11.3, 9.2, 4.3 Hz, 1H), 2.54 (ddd, J=16.2, 7.9, 3.8 Hz, 1H), 2.25 (m, 1H), 2.22 (ddd, J=11.3, 4.3, 4.0 Hz, 1H), 1.59 (ddd, J=11.3, 11.3, 11.3 Hz, 1H), 1.33–1.16 (m, 21H); ^{13}C NMR (125 MHz, C_6D_6) δ 160.5, 132.4, 132.0, 130.9, 128.3, 128.0, 126.8, 113.8, 101.1, 89.1, 82.3, 81.1, 80.9, 77.8, 77.0, 76.1, 74.2, 72.9, 69.4, 68.5, 54.7, 37.3, 35.2, 18.6, 13.1; HRMS (FAB) calcd for $C_{34}H_{50}O_8SiNa$ $[(M+Na)^+]$ 637.3173, found 637.3197.

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