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Convergent synthesis of the BCDEFGHIJ-ring polyether core of gambieric acids, potent antifungal polycyclic ethers

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Abstract—A convergent synthesis of the nonacyclic BCDEFGHIJ-ring polyether core of gambieric acids, potent antifungal polycyclic ether marine natural products, has been achieved. The present synthesis involved as key features: (i) convergent union of the BCD- and GHIJ-ring fragments through esterification, (ii) construction of the E-ring as a lactone form via reductive acetylation, (iii) stereoselective allylation to establish the C26 stereocenter, and (iv) ring-closing metathesis reaction to form the nine-membered F-ring.

1. Introduction

Marine organisms provide an important source of structurally diverse secondary metabolites with unique molecular architecture and significant biological properties. Among these marine natural products, ladder-shaped polycyclic ethers have attracted considerable attention of chemists and biologists because of their complex and huge molecular structures coupled with exceptionally potent biological activities.[1] Gambieric acids A–D (**1**–**4**, Fig. 1) were isolated in 1992 by Nagai and co-workers from the culture media of the marine dinoflagellate, *Gambierdiscus toxicus*, which is well-known as the causative organism responsible for ciguatera seafood poisoning.[2] Their gross structures including the relative stereochemistry of the polycyclic ether skeleton were determined based on extensive 2D-NMR experiments.[2a,b] Structurally, gambieric acids consist of a nonacyclic fused polyether system (BCDEFGHIJ-ring) and one isolated tetrahydrofuran ring (A-ring) in the terminal chain. Their absolute configurations were subsequently determined by combining the modified Mosher method, NMR conformational analysis, and chiral fluorometric HPLC analysis.[2c]

These polycyclic ethers exhibited potent antifungal activity against filamentous fungi.[3] Especially, their growth inhibitory activity against *Aspergillus niger* by the paper disk method was 2000 times greater than that of amphotericin B, whereas they did not show either toxicity or abnormal reaction in mice up to the dose of 1 mg/kg (intraperitoneal injection).[2b,3] These useful biological aspects make them potential lead compounds for the discovery of antifungal agents. Interestingly, it has been reported that gambieric acid A enhances the cell concentration of *G. toxicus* in a dose-dependent manner with inhibition at higher concentration, suggesting the potential biological function of gambieric acid A to be an endogenous growth regulator of *G. toxicus*.[4] Moreover, Inoue et al. recently described that gambieric acid A inhibits the binding of tritiated brevetoxin-B derivative

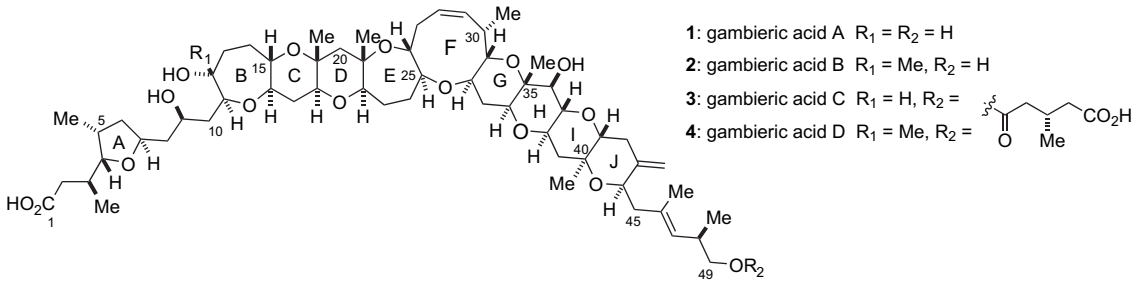

Figure 1. Structures of gambieric acids.

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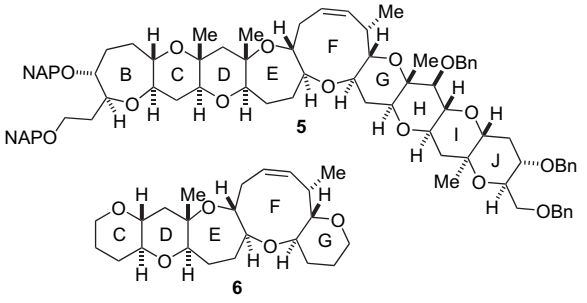


Figure 2. BCDEFGHIJ-ring polyether core **5** and CDEFG-ring system **6** of gambieric acids.

([^{3}H]PbTx-3) to site 5 of voltage-sensitive sodium channels of excitable membranes, although its binding affinity is significantly lower than those of brevetoxins and ciguatoxins.[5]

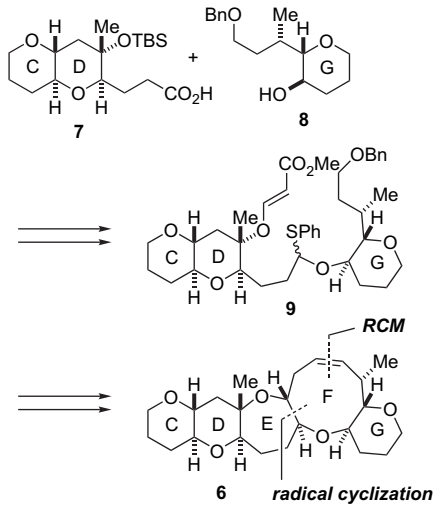
These intriguing biological properties and the molecular complexity of gambieric acids have generated considerable interest within the synthetic community, and several synthetic approaches toward the total synthesis of these polycyclic ether compounds have been reported to date.[6–8] In this paper, we describe the details of the synthesis of the nonacyclic BCDEFGHIJ-ring polyether core **5** (Fig. 2) of gambieric acids A and C.

2. Results and discussion

2.1. Synthesis of the CDEFG-ring system

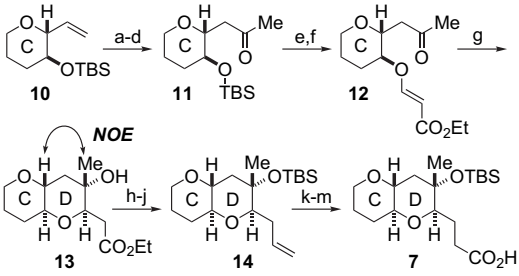
We have previously reported a convergent route to the FGH-ring system ciguatoxins.[9] The synthesis features a stereoselective intramolecular radical cyclization to construct the seven-membered G-ring and closure of the nine-membered F-ring by a ring-closing metathesis (RCM) reaction. This remarkable approach was further modified and refined by the Hirama and Inoue's group,[10] culminating in the total synthesis of ciguatoxin and its congeners.[11] We envisioned this strategy being applied to the total synthesis of gambieric acids and selected the CDEFG-ring system **6** (Fig. 2) as a prime synthetic target. Retrosynthetically, the CDEFG-ring **6** can be dissected into the CD- and G-ring segments (**7** and **8**, respectively, Scheme 1). We expected successful union of these segments and further transformations to give the desired mixed thioacetal **9**, a key intermediate, which upon radical cyclization would form the seven-membered E-ring. Finally, construction of the nine-membered F-ring by RCM would lead to the CDEFG-ring system **6**.

The synthesis of carboxylic acid **7** commenced with the known TBS ether **10**,[12] which was converted to methyl ketone **11** by a standard four-step sequence in 82% overall yield (Scheme 2). After desilylation with TBAF (94%), treatment of the resultant alcohol with ethyl propiolate in the presence of 4-methylmorpholine (NMM) produced β-(*E*)-alkoxyacrylate **12** in 87% yield. Treatment of **12** with SmI_2 in the presence of methanol (THF, 0 °C) effected reductive cyclization[13] to form the D-ring, giving bicyclic ether **13** as the sole product in excellent yield. After protection as the TBS ether, DIBALH reduction of the ester moiety to the aldehyde followed by Wittig reaction afforded



Scheme 1. First synthetic plan for CDEFG-ring system **6**.

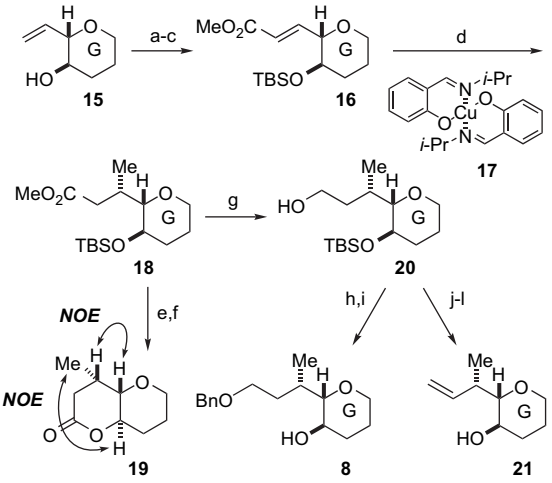
olefin **14** in 77% yield for the three steps. Hydroboration using 9-BBN-H followed by oxidative workup gave an alcohol, which was then oxidized by a two-step procedure (Parikh–Doering oxidation[14] and $NaClO_2$) to provide the desired CD-ring carboxylic acid **7** in 88% yield for the three steps.



Scheme 2. Synthesis of CD-ring **7**. Reagents and conditions: (a) 9-BBN-H, THF; aq NaOH, H_2O_2; (b) SO_3·pyr, Et_3N, DMSO/CH_2Cl_2; (c) MeMgBr, THF; (d) TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, 0 °C→rt, 82% (four steps); (e) TBAF, THF, 94%; (f) ethyl propiolate, NMM, CH_2Cl_2, 87%; (g) SmI_2, MeOH, THF, 0 °C, 99%; (h) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C→rt; (i) DIBALH, CH_2Cl_2, −78 °C; (j) NaHMDS, Ph_3PCH_3Br, THF, 77% (three steps); (k) 9-BBN-H, THF; aq NaOH, H_2O_2; (l) SO_3·pyr, Et_3N, DMSO/CH_2Cl_2; (m) $NaClO_2$, KH_2PO_4, 2-methyl-2-butene, *t*-BuOH/H_2O, 88% (three steps).

The synthesis of alcohol **8** started with the known alcohol **15**[12] (Scheme 3). Protection as the TBS ether (90%) and oxidative cleavage of the double bond (OsO_4, NMO; then $NaIO_4$), followed by Wittig reaction, afforded α,β-unsaturated ester **16** in 91% overall yield. Treatment of **16** with MeMgBr and TMSCl in the presence of bis(*N*-isopropylsalicylaldimine) copper(II) complex **17**[15] (THF, −45 °C) gave the desired 1,4-adduct **18** as the sole product in 90% yield.[16] The stereochemistry of the newly generated methyl stereocenter was confirmed by conversion to lactone **19** by deprotection of the TBS group followed by acid-catalyzed lactonization (81%, two steps) and its NMR analysis as shown. DIBALH reduction of **18** produced primary alcohol **20** (95%), which was protected as the benzyl ether and then desilylated with TBAF to give alcohol **8** in 90% yield for the two steps. Alcohol **20** was converted to a terminal olefin via

the corresponding *o*-nitrophenyl selenide by the Grieco/Nishizawa protocol (1. 2-$NO_2C_6H_4SeCN$, Bu_3P; 2. *m*-CPBA, 92% for the two steps).[17] Subsequent desilylation afforded alcohol **21** in 94% yield.



Scheme 3. Synthesis of G-rings **8** and **21**. Reagents and conditions: (a) TBSCl, imidazole, DMAP, DMF, 90%; (b) cat OsO_4, NMO, THF/H_2O; $NaIO_4$; (c) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, 91% (two steps); (d) MeMgBr, **17**, TMSCl, THF, −45 °C, 90%; (e) aq HCl, MeOH; (f) PPTS, toluene, 110 °C, 81% (two steps); (g) DIBALH, CH_2Cl_2, −78 °C, 95%; (h) KO*t*-Bu, BnBr, THF, 90%; (i) TBAF, THF, quant.; (j) 2-$NO_2C_6H_4SeCN$, Bu_3P, CH_2Cl_2; (k) *m*-CPBA, CH_2Cl_2, 0 °C, 92% (two steps); (l) TBAF, THF, 94%.

With the desired fragments **7** and **8** in hand, we next turned our attention to their coupling. Yamaguchi esterification[18] of **7** with **8** proceeded smoothly to afford ester **22** in quantitative yield (Scheme 4). Conversion to the α-acetoxy ether **23** was performed by the procedure of Rychnovsky.[19] Thus, reduction of **22** with DIBALH (CH_2Cl_2, −78 °C) followed by treatment of the resulting hemiacetal intermediate with Ac_2O, DMAP, and pyridine (−78 °C→room temperature) provided the desired acetate **23** in 98% yield. Subsequent treatment with phenylthiotrimethylsilane (TMSSPh) and TMSOTf in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) afforded the corresponding mixed thioacetal (88%), which was desilylated with TBAF to give alcohol **24** in 94% yield. The β-(*E*)-alkoxyacrylate unit was attached to the tertiary alcohol by treatment with methyl propiolate and Me_3P[20] to provide **9** albeit in modest yield (47%, 82% yield based on recovered **24**). However, radical cyclization of **9** (Bu_3SnH, AIBN, toluene, 80 °C) was sluggish and yielded a complex mixture of the desired *O*-linked oxepane **25**, its diastereomer **26**, and reduction product **27** (**25**/**26**/**27**=ca. 1:4:3), along with recovered **9**. Stereostructure of compound **25** was assigned by NOE between 21-Me[21] and 26-H and a small coupling constant, $^3J_{25,26}$=3.5 Hz. The outcome of this radical cyclization can be explained as indicated in Figure 3. Severe steric repulsion between the tertiary methyl group at C21 and β-hydrogen on the acrylate unit in the transition state structure **A** resulted in a preference for the structure **B**, which leads to **26**. A similar result has been reported by Nakata and co-workers in their SmI_2-mediated reductive cyclization.[22]

Accordingly, we next investigated an alternative route as summarized in Scheme 5. Alcohol **21** and carboxylic acid **7** were coupled through esterification under Yamaguchi conditions[18] to afford **28** in 91% yield. Reductive acetylation[19] proceeded smoothly to give an α-acetoxy ether as a 3:1 mixture of diastereomers, which was subsequently treated with TMSCN and TMSOTf in the presence of DTBMP to generate α-cyano ether **29**. Removal of the TBS group with TBAF (MeCN, 70 °C) afforded alcohol **30** in 61% yield for the three steps. The nitrile group was hydrolyzed under alkaline conditions (KOH, ethylene glycol, 150 °C) to give carboxylic acid **31** in high yield as a 1:1 mixture of isomers. Subsequent Yamaguchi lactonization[18] produced a mixture of seven-membered lactones, which was separated by flash column chromatography to give **32a** and **32b** in 38% and 40% yield, respectively. All attempts to isomerize **32b** to the

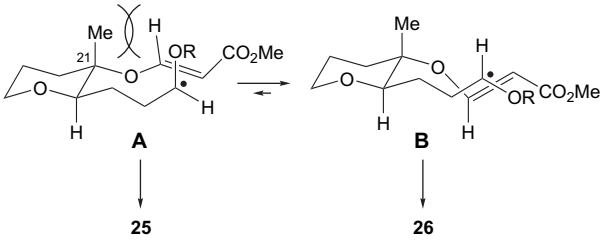
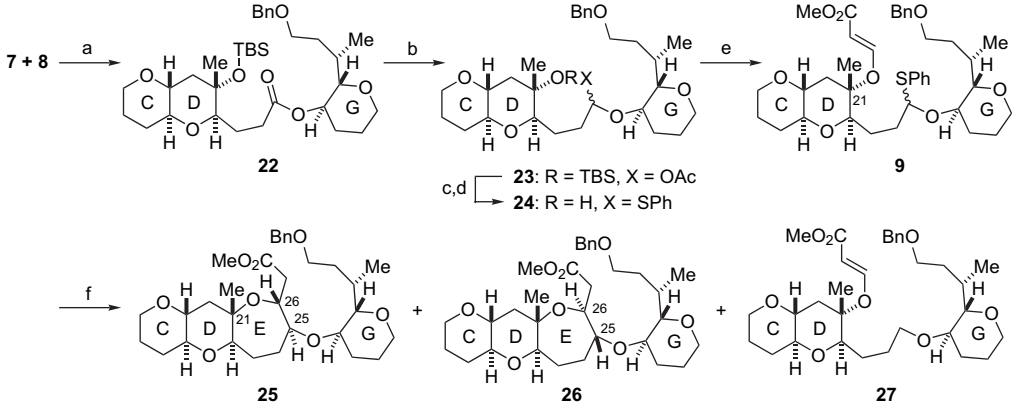
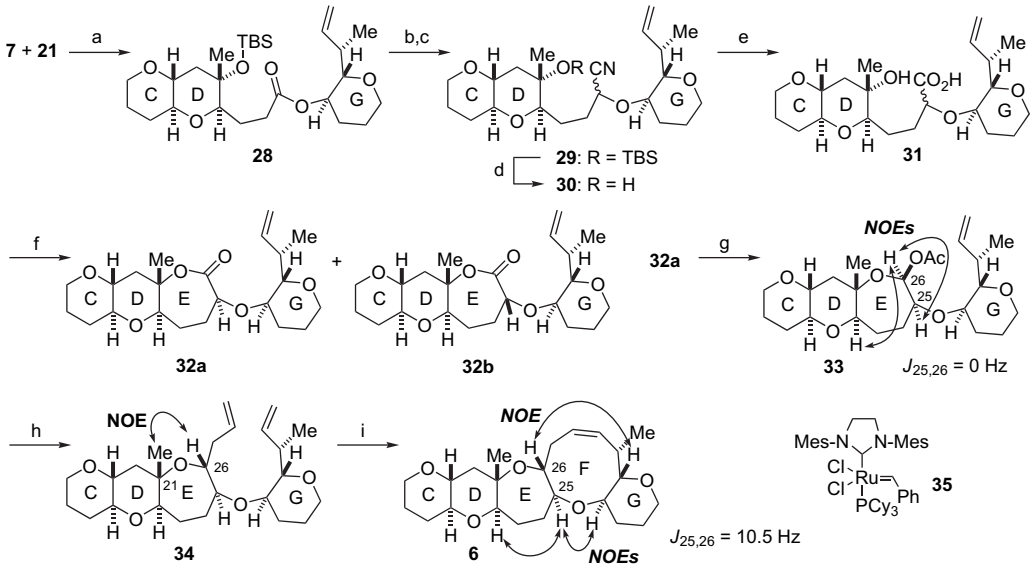


Figure 3. Possible rationale for radical cyclization.



Scheme 4. Attempted synthesis of *O*-linked oxepane **25**. Reagents and conditions: (a) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF, 40 °C; DMAP, toluene, 40 °C, quant.; (b) DIBALH, CH_2Cl_2, −78 °C; Ac_2O, DMAP, pyr, −78 °C→rt, 98%; (c) TMSSPh, TMSOTf, DTBMP, CH_2Cl_2, 0 °C→rt, 88%; (d) TBAF, MeCN, 70 °C, 94%; (e) methyl propiolate, Me_3P, CH_2Cl_2, 47% (82% based on recovered **24**); (f) Bu_3SnH, AIBN, toluene, 80 °C, 74% (**25**/**26**/**27**=ca. 1:4:3).



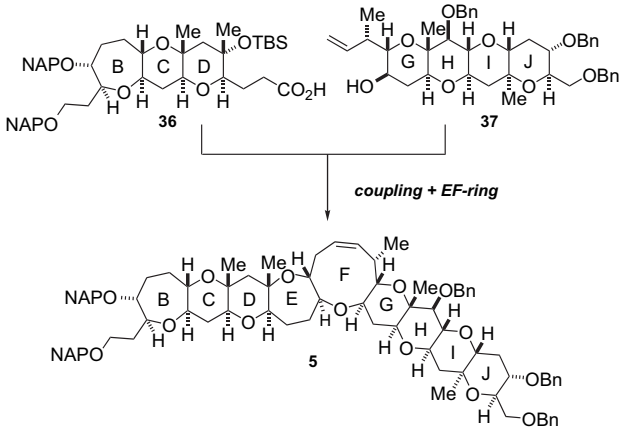
Scheme 5. Synthesis of CDEFG-ring system **6**. Reagents and conditions: (a) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF, 40 °C; DMAP, toluene, 40 °C, 91%; (b) DIBALH, CH_2Cl_2, −78 °C; Ac_2O, DMAP, pyr, −78→0 °C; (c) TMSCN, TMSOTf, DTBMP, CH_2Cl_2, −78→0 °C; (d) TBAF, MeCN, 70 °C, 61% (three steps); (e) KOH, ethylene glycol, 150 °C, 95%; (f) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF/toluene; DMAP, toluene, reflux, 38% for **32a**, 40% for **32b**; (g) DIBALH, CH_2Cl_2, −78 °C; Ac_2O, DMAP, pyr, −78→0 °C, 96%; (h) CH_2=$CHCH_2TMS$, $BF_3\cdot OEt_2$, 4 Å molecular sieves, MeCN, −40→0 °C, 66%; (i) **35**, CH_2Cl_2, 40 °C, 98%.

desired **32a** under various basic conditions were unsuccessful. Reductive acetylation (DIBALH, CH_2Cl_2, −78 °C; then Ac_2O, DMAP, pyridine, −78→0 °C)[19] of lactone **32a** produced acetate **33** in 96% yield as the sole product. The stereochemistry at C26 of **33** was assigned on the basis of NOEs and the coupling constant, $J_{25,26}$=0 Hz, as shown. Upon treatment of **33** with allyltrimethylsilane in the presence of $BF_3\cdot OEt_2$ (MeCN, −40→0 °C), stereoselective allylation took place from the opposite side of the angular methyl group at C21 to afford the requisite diene **34** in 66% yield. Stereochemistry at the C26 position was determined by NOE between 21-Me and 26-H. Finally, construction of the nine-membered F-ring was achieved by RCM using the second-generation Grubbs catalyst **35**[23] (CH_2Cl_2, 40 °C) to furnish the CDEFG-ring system **6** in 98% yield. The stereostructure of **6** was unequivocally established by NOE experiments and the coupling constant as shown in Scheme 5.

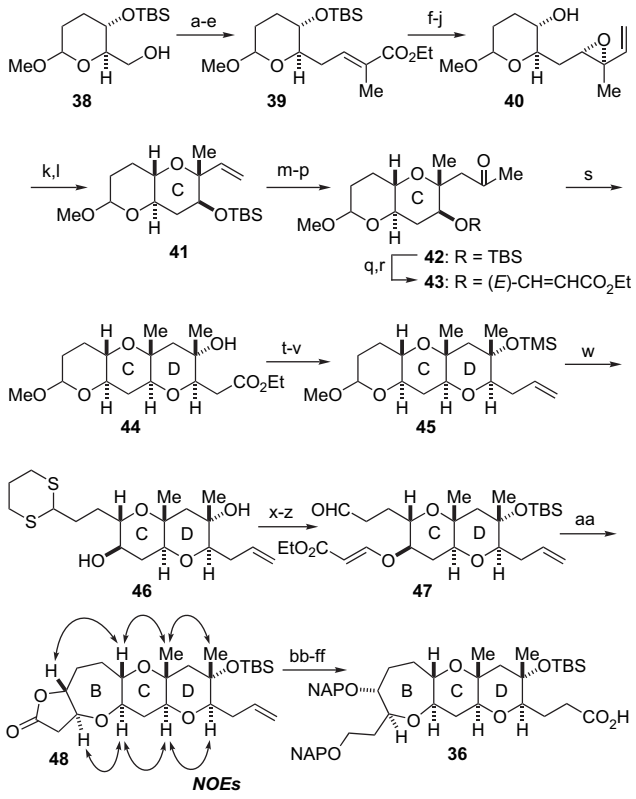
2.2. Synthesis of the BCDEFGHIJ-ring core

Having successfully developed a convergent synthetic route to the CDEFG-ring system **6**, we next applied this strategy to construct the nonacyclic BCDEFGHIJ-ring polyether core **5** of gambieric acids A and C from two complex fragments, the BCD-ring carboxylic acid **36** and the GHIJ-ring alcohol **37**, as illustrated in Scheme 6.

The synthesis of the BCD-ring fragment **36** started with the known alcohol **38**, which is available in four steps from tri-*O*-acetyl-D-glucal.[16a] Parikh–Doering oxidation[14] and Wittig olefination, followed by hydroboration with 9-BBN-H, produced a homologated alcohol in 75% overall yield (Scheme 7). The resultant primary alcohol was subjected to a second oxidation/Wittig reaction to afford α,β-unsaturated ester **39** in 90% yield for the two steps. Ester **39** was reduced with DIBALH, and the resulting allylic alcohol was subjected to Sharpless asymmetric epoxidation using (+)-diethyl tartrate (DET). Oxidation of the derived epoxy alcohol and Wittig methylenation, followed by removal of the TBS group, gave hydroxy epoxide **40** in 81% overall yield. Upon treatment of **40** with PPTS, 6-*endo* cyclization[24] proceeded smoothly to afford the C-ring tetrahydropyran **41** after TBS protection (93%, two steps). The terminal olefin of **41** was then converted to methyl ketone **42** by a standard four-step sequence, and the secondary TBS group of **42** was changed to β-(*E*)-alkoxyacrylate in two steps to give **43**. Reductive cyclization of **43** with SmI_2[13] in the presence of methanol (THF, 0 °C→room temperature) afforded the CD-ring **44** in high yield as a single diastereomer. After protection of the tertiary alcohol as the TMS ether (93%), the ethyl ester was reduced with DIBALH and the resulting aldehyde was subjected to Wittig reaction to give olefin **45** in 93% yield for the two steps. Subsequent treatment with 1,3-propanedithiol in the presence of TMSOTf (MeCN, 0 °C) effected ring-opening of the methyl acetal and



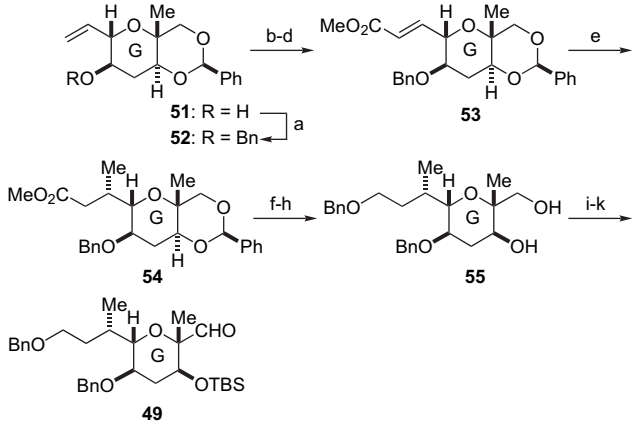
Scheme 6. Synthetic plan for BCDEFGHIJ-ring polyether core **5**.



Scheme 7. Synthesis of BCD-ring **36**. Reagents and conditions: (a) SO_3·pyr, Et_3N, DMSO/CH_2Cl_2; (b) NaHMDS, Ph_3PCH_3Br, THF, 95% (two steps); (c) 9-BBN-H, THF; aq NaOH, H_2O_2, 79%; (d) SO_3·pyr, Et_3N, DMSO/CH_2Cl_2; (e) $Ph_3P{=}C(Me)CO_2Et$, toluene, 100 °C, 90% (two steps); (f) DIBALH, CH_2Cl_2, −78 °C, 99%; (g) *t*-BuOOH, (+)-DET, Ti(O*i*-Pr)$_4$, 4 Å molecular sieves, CH_2Cl_2, −20 °C; (h) SO_3·pyr, Et_3N, DMSO/CH_2Cl_2; (i) NaHMDS, Ph_3PCH_3Br, THF, 88% (three steps); (j) TBAF, THF, 93%; (k) PPTS, CH_2Cl_2, 96%; (l) TBSOTf, 2,6-lutidine, CH_2Cl_2, 97%; (m) BH_3·SMe_2, 2-methyl-2-butene, THF; aq NaOH, H_2O_2, 98%; (n) SO_3·pyr, Et_3N, DMSO/CH_2Cl_2, 0 °C; (o) MeMgBr, THF, 88% (two steps); (p) TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, 92%; (q) TBAF, THF, 99%; (r) ethyl propiolate, NMM, CH_2Cl_2; (s) SmI_2, MeOH, THF, 0 °C→rt, 83% (two steps); (t) TMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 93%; (u) DIBALH, toluene, −78 °C; (v) NaHMDS, Ph_3PCH_3Br, THF, 93% (two steps); (w) 1,3-propanedithiol, TMSOTf, MeCN, 0 °C, 92%; (x) ethyl propiolate, NMM, CH_2Cl_2, 94%; (y) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 97%; (z) MeI, $NaHCO_3$, MeCN/H_2O, 98%; (aa) SmI_2, MeOH, THF; (bb) $LiAlH_4$, THF, 0 °C, 89% (two steps); (cc) NaH, NAPBr, Bu_4NI, DMF, 0 °C→rt, 96%; (dd) 9-BBN-H, THF; aq NaOH, H_2O_2; (ee) SO_3·pyr, Et_3N, DMSO/CH_2Cl_2; (ff) $NaClO_2$, 2-methyl-2-butene, KH_2PO_4, *t*-BuOH/H_2O, 88% (three steps).

desilylation to provide dithiane diol **46** in 92% yield. Upon exposure of **46** to ethyl propiolate and NMM, selective hetero-Michael reaction of the secondary alcohol took place and the remaining tertiary alcohol was protected as the TBS ether. The thioacetal was hydrolyzed (MeI, $NaHCO_3$, MeCN/H_2O) to produce aldehyde **47** in 89% yield from **46**. SmI_2-promoted reductive cyclization of **47** proceeded again smoothly to form the seven-membered B-ring, giving γ-lactone **48** as the sole product. The stereostructure of **48** was confirmed by NOE experiments as shown in Scheme 7. After reduction of the lactone moiety with $LiAlH_4$, the resultant diol was protected as the 2-naphthylmethyl (NAP) ethers (85% yield from **47**).[11b,25] Finally, the terminal olefin was converted to the carboxylic acid in a three-step sequence involving hydroboration with 9-BBN-H and a two-step oxidation of the resultant primary alcohol (88%, three steps), completing the synthesis of the BCD-ring fragment **36**.

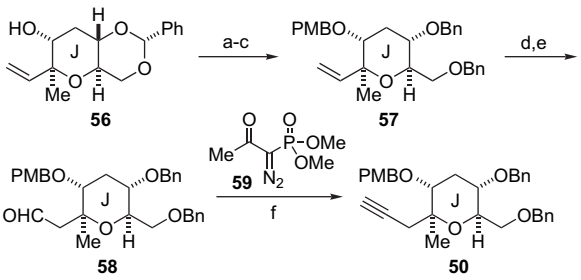
The synthesis of the GHIJ-ring fragment **37** was performed by the union of the G- and J-rings (**49** and **50**, respectively) followed by the HI-ring formation according to the acetylide–aldehyde coupling/hetero-Michael cyclization strategy developed by the Nakata group with some modifications.[26] The synthesis of the G-ring aldehyde **49** began with the known alcohol **51**,[27] which was protected as the benzyl ether to afford **52** in quantitative yield (Scheme 8). Oxidative cleavage of the double bond (OsO_4, NMO; then $NaIO_4$) followed by Wittig reaction gave α,β-unsaturated ester **53** in 80% yield for the three steps. Treatment of **53** with MeMgBr (TMSCl, Cu(II) complex **17**,[15] THF, −45 °C) gave the expected 1,4-adduct **54** in 96% yield. DIBALH reduction, benzyl protection, and hydrolysis of the benzylidene acetal provided diol **55** in 91% yield for the three steps. The secondary hydroxy group of **55** was selectively protected as the TBS ether by bis-TBS protection followed by selective deprotection of the primary TBS group (95%, two steps). The resulting primary alcohol was oxidized under Parikh–Doering conditions[14] to furnish the G-ring aldehyde **49** in 94% yield.



Scheme 8. Synthesis of G-ring **49**. Reagents and conditions: (a) NaH, BnBr, Bu_4NI, DMF, quant.; (b) cat OsO_4, NMO, THF/H_2O; (c) $NaIO_4$, THF/H_2O; (d) $Ph_3P{=}CHCO_2Me$, THF, 80% (three steps); (e) MeMgBr, **17**, TMSCl, THF, −45 °C, 96%; (f) DIBALH, CH_2Cl_2, −78 °C, quant.; (g) NaH, BnBr, Bu_4NI, DMF, 0 °C→rt; (h) TsOH, MeOH, 40→70 °C, 91% (two steps); (i) TBSOTf, 2,6-lutidine, CH_2Cl_2; (j) CSA, MeOH/CH_2Cl_2, 0 °C, 95% (two steps); (k) SO_3·pyr, Et_3N, DMSO/CH_2Cl_2, 94%.

The synthesis of the J-ring alkyne **50** is summarized in Scheme 9. Protection of the known alcohol **56**[28] as the *p*-methoxybenzyl (PMB) ether and removal of the benzylidene acetal, followed by benzylation of the resultant diol, provided **57** in 81% yield for the three steps. Hydroboration of the terminal olefin with 9-BBN-H (71%) and subsequent oxidation of the derived alcohol with tetra-*n*-propylammonium perruthenate (TPAP)/NMO[29] led to aldehyde **58** in 77% yield. Treatment of aldehyde **58** with Ohira–Bestmann reagent **59**[30] (Cs_2CO_3, *i*-PrOH, 92%) completed the synthesis of the J-ring alkyne **50**.

Reaction of the lithium acetylide, generated from alkyne **50** (*t*-BuLi, THF/HMPA, −78 °C), with aldehyde **49** provided propargyl alcohol **60** in 95% yield as a mixture of diastereomers (Scheme 10). Swern oxidation afforded ynone **61** (93%), which was treated with NaOMe (MeOH/THF, room temperature) to afford vinylogous ester **62** in 98% yield. Subsequent removal of the TBS group from **62** was best carried out by treatment with HF·pyridine/pyridine/THF



Scheme 9. Synthesis of J-ring **50**. Reagents and conditions: (a) NaH, PMBCl, Bu_4NI, DMF, 0 °C→rt; (b) CSA, MeOH, 86% (two steps); (c) NaH, BnBr, Bu_4NI, DMF, 0 °C→rt, 94%; (d) 9-BBN-H, THF; aq NaOH, H_2O_2, 71%; (e) TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, 0 °C→rt, 77%; (f) **59**, Cs_2CO_3, *i*-PrOH, 92%.

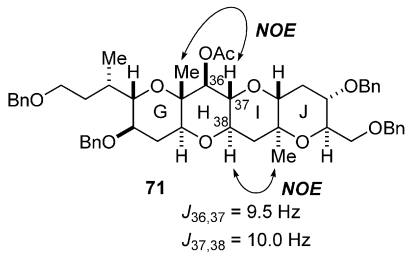
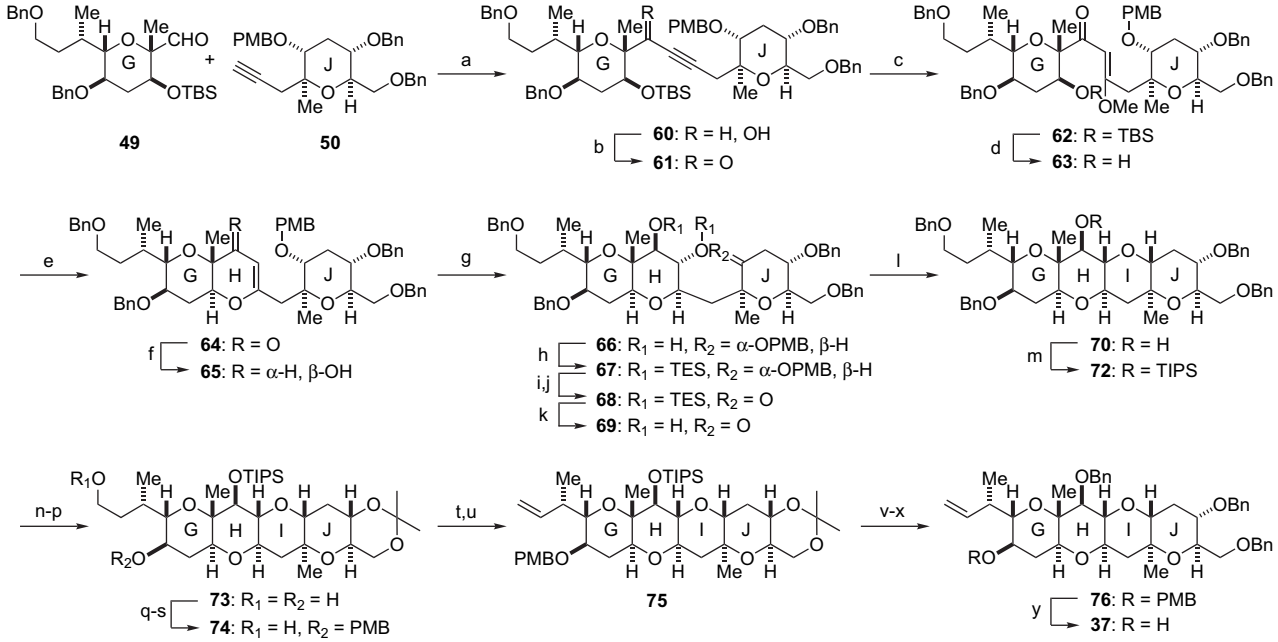


Figure 4. Stereochemical confirmation of GHIJ-ring **71**.

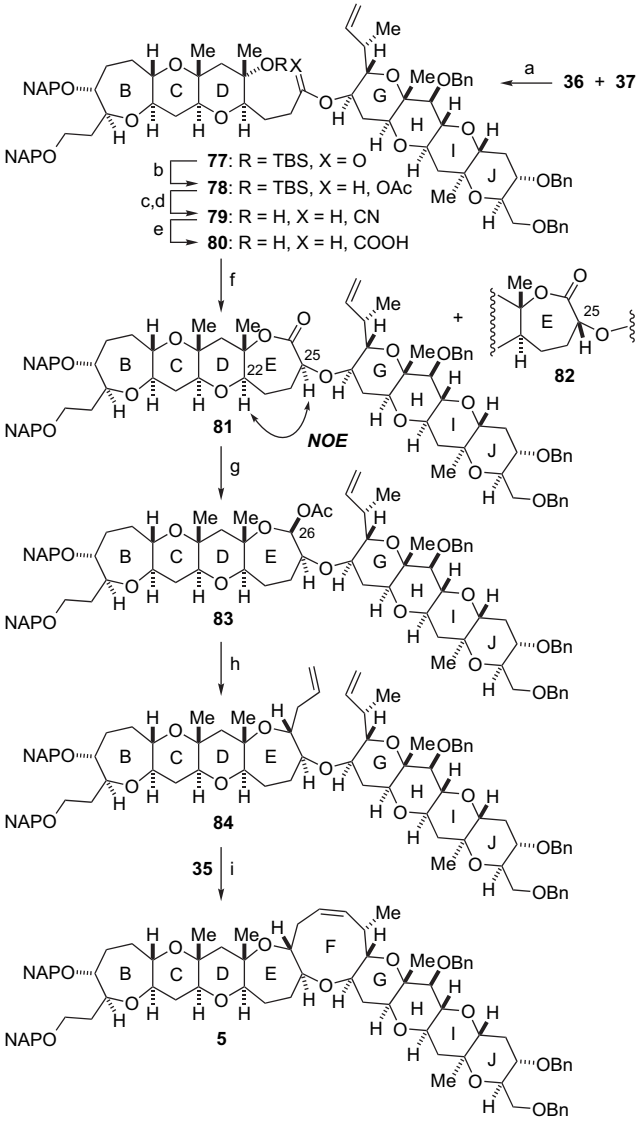
(2:1:4) at 0 °C→room temperature to give alcohol **63** in 93% yield. The use of TBAF resulted in moderate yield of **63** with recovery of **62**. The resultant alcohol **63** was treated with PPTS (toluene, 100 °C) to induce an intramolecular hetero-Michael reaction, leading to the desired dihydropyranone **64** in 87% yield. Subsequent reduction of **64** with DIBALH proceeded stereoselectively to afford equatorial-oriented β-alcohol **65** in 92% yield as the sole product. Hydroboration of the enol ether with $BH_3\cdot$THF led exclusively to diol **66** (91%), which was protected as the bis-TES ether **67** (quant.). After removal of the PMB group from **67** with DDQ, oxidation of the resultant alcohol with TPAP/NMO[29] provided ketone **68**, which was then desilylated with TBAF/HOAc to afford dihydroxy ketone **69** in 81% yield (three steps). Treatment of **69** with Et_3SiH and TMSOTf (MeCN, −10 °C) furnished the desired tetracyclic ether **70** in 83% yield. The use of large excess amounts of Et_3SiH was necessary to attain high yield of **70** in this reductive etherification; stoichiometric amounts of Et_3SiH resulted in variable yield (28–62%). The stereochemistry of **70** was established based on the ^1H NMR analysis of the corresponding acetate **71** (Ac_2O, DMAP, Et_3N, room temperature, 86%) as shown in Figure 4. A four-step sequence of standard protecting group manipulations was performed on **70** to afford diol **73** via **72** in 65% overall yield. The resulting diol **73** was then converted to primary alcohol **74** in a further three-step sequence. Alcohol **74** was then transformed to terminal olefin **75** via the corresponding *o*-nitrophenyl selenide.[17] After removal of the TIPS and acetonide groups from **75**, the resultant triol was protected as the tris-benzyl ether **76** and the PMB group was selectively removed ($BF_3\cdot OEt_2$, Et_3SiH/MeCN, 0 °C)[31] to complete the synthesis of the GHIJ-ring fragment **37**.

With the requisite key fragments **36** and **37** in hand, the stage was now set for the union of these complex fragments followed by formation of the EF-ring. Acid **36** and alcohol



Scheme 10. Synthesis of GHIJ-ring **37**. Reagents and conditions: (a) **50**, *t*-BuLi, THF/HMPA, −78 °C; then **49**, −78 °C, 95%; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C→rt, 93%; (c) NaOMe, MeOH/THF, 98%; (d) HF·pyr/pyr/THF (2:1:4), 93%; (e) PPTS, toluene, 100 °C, 87%; (f) DIBALH, toluene, −78 °C, 92%; (g) $BH_3\cdot$THF, THF, 0 °C→rt; aq NaOH, H_2O_2, 91%; (h) TESOTf, 2,6-lutidine, CH_2Cl_2, quant.; (i) DDQ, CH_2Cl_2/pH 7 buffer, 0 °C; (j) TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, 0 °C→rt; (k) TBAF, HOAc, THF, 81% (three steps); (l) TMSOTf, Et_3SiH/MeCN (1:4), −10 °C, 83%; (m) TIPSOTf, 2,6-lutidine, CH_2Cl_2; (n) H_2, Pd/C, MeOH; (o) 2,2-dimethoxypropane, CSA, DMF, 30 °C; (p) PPTS, MeOH/CH_2Cl_2, 0 °C, 65% (four steps); (q) PivCl, pyr, 0 °C, 85%; (r) NaH, PMBCl, Bu_4NI, DMF, 0 °C→rt, 78%; (s) DIBALH, CH_2Cl_2, −78 °C, 72%; (t) 2-$NO_2C_6H_4SeCN$, Bu_3P, THF; (u) *m*-CPBA, Et_3N, CH_2Cl_2, 0→35 °C, 94% (two steps); (v) TBAF, THF, 92%; (w) TsOH, MeOH, 0 °C; (x) NaH, BnBr, Bu_4NI, DMF, 0 °C→rt, 89% (two steps); (y) $BF_3\cdot OEt_2$, Et_3SiH, MeCN, 0 °C, quant.

37 were coupled by Yamaguchi esterification[18] to afford **77** in 92% yield (Scheme 11). Ester **77** was then subjected to reductive acetylation (DIBALH, CH_2Cl_2, −78 °C; then Ac_2O, DMAP, pyridine, −78→0 °C).[19] The desired α-acetoxy ether **78** was obtained albeit in moderate yield (55%) as an approximately 1:1 mixture of diastereomers. Subsequent treatment of **78** with TMSCN and TMSOTf in the presence of DTBMP afforded the corresponding α-cyano ether, which was desilylated with TBAF (MeCN, 70 °C) to give alcohol **79** in 87% yield for the two steps. The nitrile group was hydrolyzed under alkaline conditions (KOH, ethylene glycol, 150 °C) to provide carboxylic acid **80** in 86% yield as a 1:1 mixture of diastereomers. Yamaguchi lactonization[18] of **80** provided a mixture of seven-membered lactones, which



Scheme 11. Synthesis of BCDEFGHIJ-ring polyether core **5**. Reagents and conditions: (a) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF, 40 °C; DMAP, toluene, 40 °C, 92%; (b) DIBALH, CH_2Cl_2, −78 °C; Ac_2O, DMAP, pyr, −78→0 °C, 55%; (c) TMSCN, TMSOTf, DTBMP, CH_2Cl_2, −78→0 °C; (d) TBAF, MeCN, 70 °C, 87% (two steps); (e) KOH, ethylene glycol, 150 °C, 86%; (f) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF/toluene; DMAP, reflux, 36% for **81**, 32% for **82**; (g) DIBALH, CH_2Cl_2, −78 °C; Ac_2O, DMAP, pyr, −78→0 °C, 68%; (h) CH_2=$CHCH_2TMS$, $BF_3\cdot OEt_2$, 4 Å molecular sieves, MeCN, −40→−30 °C, 58%; (i) **35**, CH_2Cl_2, 40 °C, 67%.

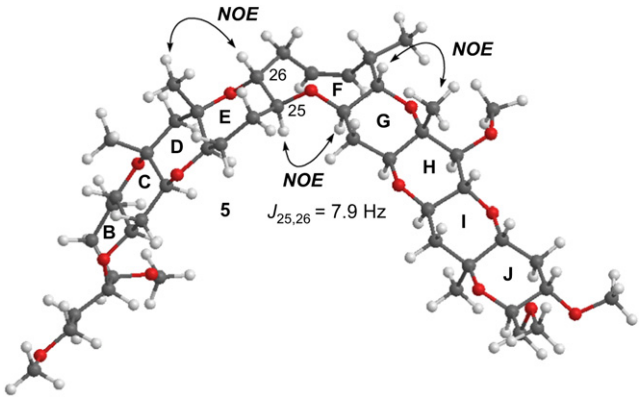


Figure 5. Stereochemical confirmation of BCDEFGHIJ-ring **5**.

was separated by flash column chromatography to afford the desired **81** and its C25 diastereomer **82** in 36% and 32% yield for the two steps, respectively. The C25 stereochemistry of **81** was unambiguously determined by NOE between 22-H and 25-H as shown in Scheme 11. Attempted isomerization of **82** to the desired **81** under basic conditions was unsuccessful as was the case with **32b**. Reductive acetylation of lactone **81** produced acetate **83** in 68% yield and ca. 10:1 diastereomeric ratio. Stereochemistry at the C26 position of **83** was tentatively assigned on the basis of the foregoing model studies (see Scheme 5). Upon treatment of **83** with allyltrimethylsilane in the presence of $BF_3\cdot OEt_2$ (4 Å molecular sieve, MeCN, −40→−30 °C), stereoselective allylation took place from the less hindered α-side of the molecule to afford diene **84** in 58% yield. Finally, RCM reaction of **84** with second Grubbs catalyst **35**[23] (CH_2Cl_2, 40 °C) led to the formation of the nine-membered F-ring, furnishing the targeted nonacyclic BCDEFGHIJ-ring polyether core **5** in 67% yield. The stereostructure of nonacycle **5** was unequivocally established by extensive NMR experiments as shown in Figure 5.

3. Conclusion

We have accomplished the synthesis of the nonacyclic BCDEFGHIJ-ring polyether core **5** of gambieric acids A and C in a convergent fashion. The synthesis involved as key features: (i) convergent union of the BCD- and GHIJ-ring fragments through esterification; (ii) construction of the seven-membered E-ring as a lactone form via reductive acetylation; (iii) stereoselective allylation to establish the C26 stereocenter; and (iv) cyclization of the nine-membered F-ring by utilizing ring-closing metathesis reaction. Further studies toward the total synthesis of gambieric acids A and C and their analogues along these lines are in progress and will be reported in due course.

4. Experimental

4.1. General methods

All reactions sensitive to air or moisture were performed under an atmosphere of argon in dry, freshly distilled

solvents under anhydrous conditions, unless otherwise noted. Anhydrous dichloromethane (CH_2Cl_2) was purchased from Kanto Chemical Co., Inc. and used directly without further drying. *N*,*N*-Dimethylformamide (DMF) was dried over active 4 Å molecular sieves. Acetonitrile (MeCN) and toluene were freshly distilled from calcium hydride under an atmosphere of argon. Tetrahydrofuran (THF) was freshly distilled over sodium/benzophenone ketyl under an atmosphere of argon. Hexamethylphosphoramide (HMPA) was distilled from calcium hydride under reduced pressure. Trimethylsilyl chloride (TMSCl) was distilled from calcium hydride. All other reagents were used as supplied unless otherwise stated. Analytical thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F_{254} pre-coated plates (0.25-mm thickness). Column chromatography was performed using Kanto Chemical silica gel 60 N (40–100 mesh, spherical, neutral), and for flash column chromatography Fuji Silysia silica gel BW-300 (200–400 mesh) was used. Optical rotations were recorded on a JASCO DIP-370 or P-1020 digital polarimeter. IR spectra were recorded on a JASCO FT/IR-4100 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity INOVA 500 or INOVA 600 spectrometer. Chemical shifts are reported in δ (ppm) from tetramethylsilane with reference to internal residual solvent [^{1}H NMR: $CHCl_3$ (7.24), C_6HD_5 (7.15); ^{13}C NMR: $CDCl_3$ (77.0), C_6D_6 (128.0)]. Coupling constants (*J*) are reported in hertz (Hz). The following abbreviations are used to designate the multiplicities: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad peak. FAB mass spectra were recorded on a JEOL JMS-700 spectrometer and ESI-TOF mass spectra were measured on a Bruker microTOFfocus spectrometer.

4.1.1. Methyl ketone 11. To a solution of olefin **10** (3.12 g, 12.9 mmol) in THF (43 mL) at 0 °C was added 9-BBN-H (0.5 M in THF, 103 mL, 51.5 mmol). The resulting mixture was stirred at room temperature for 20 h. The solution was cooled to 0 °C and treated with 10% aqueous NaOH (72 mL) followed by 30% H_2O_2 (58 mL). The resulting mixture was stirred at room temperature for 9 h before it was diluted with EtOAc. The organic layer was separated, washed with saturated aqueous Na_2SO_3 and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (30% EtOAc/hexanes) afforded alcohol (3.16 g), which was used directly in the subsequent reaction.

To a solution of the above alcohol in CH_2Cl_2/DMSO (1:1, v/v, 48 mL) at 0 °C were added Et_3N (8.0 mL, 57.4 mmol) and SO_3·pyridine (7.63 g, 47.9 mmol). The resulting mixture was stirred at room temperature for 2.5 h before it was quenched with water. The solution was diluted with EtOAc, washed with 1 M aqueous HCl, saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (30% EtOAc/hexanes) afforded aldehyde, which was used directly in the subsequent reaction.

To a solution of the above aldehyde in THF (40 mL) at 0 °C was added methylmagnesium bromide (3.0 M in Et_2O, 4.0 mL, 12.0 mmol). The resulting mixture was stirred at room temperature for 3 h before it was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (40% EtOAc/hexanes) afforded alcohol (3.04 g), which was used directly in the subsequent reaction.

To a suspension of the above alcohol and 4 Å molecular sieves in CH_2Cl_2 (36 mL) were added NMO (2.50 g, 21.3 mmol) and TPAP (0.31 g, 0.88 mmol). The resulting mixture was stirred at 0 °C for 2 h and then at room temperature for 1 h. The mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (20% EtOAc/hexanes) to afford methyl ketone **11** (2.89 g, 82% for the four steps) as a colorless oil: $[\alpha]_D^{21}$ +72.1 (*c* 0.18, $CHCl_3$); IR (film) 2929, 1359, 1253, 1098, 837, 775, 669 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.82–3.79 (m, 1H), 3.51 (ddd, *J*=9.5, 9.5, 3.0 Hz, 1H), 3.35–3.33 (m, 2H), 2.79 (dd, *J*=15.5, 2.5 Hz, 1H), 2.42 (dd, *J*=15.5, 9.5 Hz, 1H), 2.16 (s, 3H), 2.00–1.97 (m, 1H), 1.66–1.54 (m, 2H), 1.48–1.39 (m, 1H), 0.84 (s, 9H), 0.033 (s, 3H), 0.025 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.9, 79.4, 71.0, 67.8, 46.9, 33.4, 30.6, 25.7 (×3), 25.5, 17.9, −4.0, −4.8; HRMS (FAB) calcd for $C_{14}H_{29}O_3Si$ [(M+H)$^+$] 273.1886, found 273.1886.

4.1.2. β-Alkoxyacrylate 12. To a solution of methyl ketone **11** (2.89 g, 10.6 mmol) in THF (54 mL) at 0 °C was added TBAF (1.0 M in THF, 21.2 mL, 21.2 mmol). The resulting mixture was stirred at room temperature for 14 h before it was concentrated under reduced pressure. Purification by column chromatography on silica gel (70% EtOAc/hexanes) afforded alcohol (1.58 g, 94%), which was used directly in the subsequent reaction.

To a solution of the above alcohol (1.58 g, 10.0 mmol) in CH_2Cl_2 (48 mL) at 0 °C were added 4-methylmorpholine (1.48 mL, 13.5 mmol) and ethyl propiolate (3.19 mL, 31.5 mmol). The resulting mixture was stirred at room temperature for 14 h before it was concentrated under reduced pressure. Purification by column chromatography on silica gel (30% EtOAc/hexanes) afforded β-alkoxyacrylate **12** (2.22 g, 87%) as a pale yellow oil: $[\alpha]_D^{21}$ +15.8 (*c* 1.87, $CHCl_3$); IR (film) 2941, 1709, 1643, 1137, 835 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J*=12.0 Hz, 1H), 5.24 (d, *J*=12.0 Hz, 1H), 4.12 (dd, *J*=11.0, 4.0 Hz, 2H), 3.86–3.83 (m, 1H), 3.72 (ddd, *J*=9.5, 9.5, 3.5 Hz, 1H), 3.63 (ddd, *J*=10.5, 10.5, 4.5 Hz, 1H), 3.36 (ddd, *J*=11.5, 11.5, 3.5 Hz, 1H), 2.68 (dd, *J*=16.0, 3.0 Hz, 1H), 2.52 (dd, *J*=15.5, 9.0 Hz, 1H), 2.21 (m, 1H), 2.15 (s, 3H), 1.72–1.62 (m, 2H), 1.50 (dddd, *J*=12.5, 12.5, 12.5, 5.5 Hz, 1H), 1.23 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.3, 167.6, 160.8, 98.4, 79.9, 76.1, 67.6, 59.8, 45.9, 31.0, 29.4, 25.0, 14.3; HRMS (FAB) calcd for $C_{13}H_{21}O_5$ [(M+H)$^+$] 257.1389, found 257.1394.

4.1.3. Bicyclic ether 13. To a solution of β-alkoxyacrylate **12** (0.15 g, 0.59 mmol) in THF (6.3 mL) at 0 °C were added MeOH (60 μL) and SmI_2 (0.1 M in THF, 18.9 mL, 1.89 mmol). The resulting mixture was stirred at 0 °C for 15 min before it was quenched with 50% aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with brine, dried over

Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (30% EtOAc/hexanes) afforded bicyclic ether **13** (0.15 g, 99%) as a colorless solid: $[\alpha]_D^{21}$ +28.9 (*c* 2.26, $CHCl_3$); IR (film) 3437, 2940, 1736, 1298, 1105, 947 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.19–4.09 (m, 2H), 3.89–3.84 (m, 1H), 3.69 (dd, *J*=9.5, 4.0 Hz, 1H), 3.34 (ddd, *J*=11.5, 11.5, 7.0 Hz, 1H), 3.05 (ddd, *J*=9.5, 9.5, 4.5 Hz, 1H), 2.96 (ddd, *J*=12.0, 12.0, 4.5 Hz, 1H), 2.68 (dd, *J*=15.0, 3.0 Hz, 1H), 2.37 (dd, *J*=15.5, 9.0 Hz, 1H), 2.12 (dd, *J*=12.0, 4.5 Hz, 1H), 2.02 (ddd, *J*=8.0, 8.0, 3.5 Hz, 1H), 1.73–1.66 (m, 3H), 1.60–1.51 (m, 1H), 1.44–1.36 (m, 1H), 1.24 (t, *J*=7.0 Hz, 3H), 1.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 81.0, 79.0, 76.7, 70.8, 67.9, 60.7, 46.0, 34.9, 29.2, 25.5, 21.4, 14.2; HRMS (FAB) calcd for $C_{13}H_{23}O_5$ [(M+H)$^+$] 259.1545, found 259.1547.

4.1.4. Olefin 14. To a solution of bicyclic ether **13** (0.63 g, 2.44 mmol) in CH_2Cl_2 (12 mL) at 0 °C were added 2,6-lutidine (0.72 mL, 6.18 mmol) and TBSOTf (0.78 mL, 3.40 mmol). The resulting mixture was stirred at 0 °C for 1 h and at room temperature for 12 h before it was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was filtered through a plug of silica gel (20% EtOAc/hexanes) to give TBS ether, which was used directly in the subsequent reaction.

To a solution of the above TBS ether in CH_2Cl_2 (20 mL) at −78 °C was added DIBALH (0.95 M in hexane, 2.9 mL, 2.76 mmol). The resulting mixture was stirred at −78 °C for 1.5 h before it was quenched with saturated aqueous potassium sodium tartrate. The mixture was diluted with EtOAc and vigorously stirred until the layers became clear. The organic layer was separated, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The obtained crude aldehyde was used directly in the subsequent reaction without purification.

To a solution of Ph_3PCH_3Br (2.5 g, 7.00 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added NaHMDS (1.0 M in THF, 4.62 mL, 4.62 mmol). The resulting ylide solution was stirred at 0 °C for 30 min. A solution of the above crude aldehyde in THF (5.0 mL) was added and the mixture was stirred at room temperature for 9 h before it was quenched with saturated aqueous NH_4Cl. The mixture was diluted with Et_2O, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (20% EtOAc/hexanes) afforded olefin **14** (0.61 g, 77% for the three steps) as a colorless oil: $[\alpha]_D^{21}$ +48.4 (*c* 1.11, $CHCl_3$); IR (film) 2953, 1256, 1139, 1105, 836, 774, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.94–5.85 (m, 1H), 5.06 (d, *J*=17.0 Hz, 1H), 5.00 (d, *J*=10.5 Hz, 1H), 3.88–3.86 (m, 1H), 3.37–3.31 (m, 1H), 3.15–3.13 (m, 1H), 3.00–2.91 (m, 2H), 2.43 (dd, *J*=15.0, 7.5 Hz, 1H), 2.10 (dd, *J*=11.5, 4.5 Hz, 1H), 2.05–1.96 (m, 2H), 1.71–1.60 (m, 3H), 1.45–1.37 (m, 1H), 1.20 (s, 3H), 0.83 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.8, 115.7, 85.2, 78.8, 76.8, 73.5, 67.9, 46.1, 33.0, 29.3, 25.7, 25.6 (×3), 22.2, 18.0, −2.0, −2.1; HRMS (FAB) calcd for $C_{18}H_{34}O_3SiNa$ [(M+Na)$^+$] 349.2175, found 349.2177.

4.1.5. Carboxylic acid 7. To a solution of olefin **14** (1.82 g, 5.58 mmol) in THF (84 mL) at 0 °C was added 9-BBN-H (0.5 M in THF, 44 mL, 22.0 mmol). The reaction mixture was stirred at room temperature for 4 h. The mixture was cooled to 0 °C, and treated with 10% aqueous NaOH (33 mL) followed by 30% H_2O_2 (26 mL). The resulting mixture was stirred at room temperature for 12 h before it was diluted with EtOAc. The mixture was washed with saturated aqueous Na_2SO_3 and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (30% EtOAc/hexanes) afforded alcohol (1.74 g), which was used directly in the subsequent reaction.

To a solution of the above alcohol in CH_2Cl_2/DMSO (1:1, v/v, 50 mL) at 0 °C were added Et_3N (3.48 mL, 25.0 mmol) and SO_3·pyridine (3.18 g, 20.0 mmol). The resulting mixture was stirred at room temperature for 4 h before it was quenched with water. The mixture was diluted with Et_2O, washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude aldehyde was used directly in the subsequent reaction without purification.

To a solution of the above aldehyde in *t*-BuOH/water (4:1, v/v, 50 mL) at 0 °C were added 2-methyl-2-butene (2.43 mL, 22.9 mmol), KH_2PO_4 (0.69 g, 5.07 mmol), and $NaClO_2$ (1.61 g, 17.8 mmol). The resulting mixture was stirred at room temperature for 2 h before it was diluted with $CHCl_3$. The mixture was washed with 1 M aqueous HCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (10% MeOH/$CHCl_3$) afforded carboxylic acid **7** (1.75 g, 88% for the three steps) as a colorless oil: $[\alpha]_D^{21}$ +37.8 (*c* 2.69, $CHCl_3$); IR (film) 2951, 1709, 1256, 1107, 1071, 835, 774, 667 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.88–3.86 (m, 1H), 3.34 (ddd, *J*=15.5, 8.5, 6.0 Hz, 1H), 3.08 (dd, *J*=10.5, 1.5 Hz, 1H), 2.99–2.90 (m, 2H), 2.53 (ddd, *J*=16.5, 8.5, 6.5 Hz, 1H), 2.40 (ddd, *J*=15.5, 7.5, 7.5 Hz, 1H), 2.12–1.99 (m, 3H), 1.73–1.16 (m, 9H), 0.82 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.1, 84.5, 78.8, 76.7, 73.4, 67.9, 46.1, 31.6, 29.2, 25.7 (×3), 25.5, 23.6, 22.1, 17.9, −2.02, −2.07; HRMS (FAB) calcd for $C_{18}H_{35}O_5Si$ [(M+H)$^+$] 359.2254, found 359.2255.

4.1.6. α,β-Unsaturated ester 16. To a solution of alcohol **15** (0.75 g, 5.86 mmol) in DMF (12 mL) at 0 °C were added imidazole (1.24 g, 18.2 mmol), DMAP (70.9 mg, 0.58 mmol), and TBSCl (2.20 g, 14.6 mmol). The resulting solution was stirred at room temperature for 5 h before it was quenched with saturated aqueous NH_4Cl. The mixture was diluted with Et_2O, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (20% EtOAc/hexanes) afforded TBS ether (1.28 g, 90%), which was used directly in subsequent reaction.

To a solution of the above TBS ether (1.28 g, 5.29 mmol) in THF/H_2O (1:1, v/v, 20 mL) were added NMO (50 wt % in water, 2.4 mL, 10.2 mmol) and OsO_4 (0.039 M in *t*-BuOH, 6.67 mL, 0.26 mmol). The resulting solution was stirred at room temperature for 23 h before $NaIO_4$ (3.38 g, 15.8 mmol) was added. The mixture was stirred at room

temperature for further 8 h. The reaction mixture was diluted with EtOAc, washed with water, saturated aqueous Na_2SO_3, and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude aldehyde was used directly in the subsequent reaction without purification.

To a solution the above aldehyde in CH_2Cl_2 (53 mL) was added $Ph_3P{=}CHCO_2Me$ (2.30 g, 6.88 mmol). The resulting mixture was stirred at room temperature for 12 h before it was diluted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (30% EtOAc/hexanes) afforded α,β-unsaturated ester **16** (1.44 g, 91% for the two steps) as a colorless oil: $[\alpha]_D^{20}$ −40.8 (*c* 0.81, $CHCl_3$); IR (film) 2951, 1726, 1265, 1099, 838, 777 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.10 (dd, *J*=15.5, 4.5 Hz, 1H), 6.03 (dd, *J*=15.5, 1.5 Hz, 1H), 3.95–3.92 (m, 1H), 3.71 (s, 3H), 3.68–3.65 (m, 1H), 3.39–3.34 (m, 1H), 3.32–3.27 (m, 1H), 2.04–2.01 (m, 1H), 1.68–1.64 (m, 2H), 1.55–1.47 (m, 1H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 146.5, 120.4, 81.1, 71.2, 67.6, 51.5, 33.8, 25.7 (×3), 25.3, 17.9, −4.3, −4.9; HRMS (FAB) calcd for $C_{15}H_{28}O_4SiNa$ [(M+Na)$^+$] 323.1655, found 323.1660.

4.1.7. Ester 18. To a solution of bis(*N*-isopropylsalicylaldimine) copper(II) complex **17** (5 mg, 12.9 μmol) and TMSCl (0.49 mL, 3.86 mmol) in THF (3.2 mL) at −45 °C was added enoate **16** (0.39 g, 1.30 mmol) in THF (3.2 mL). Methylmagnesium bromide (3.0 M in Et_2O, 0.64 mL, 1.92 mmol) was added and the resulting mixture was stirred at −45 °C for 1.5 h before it was quenched with 1 M aqueous HCl. The mixture was diluted with Et_2O, washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (30% EtOAc/hexanes) afforded ester **18** (0.37 g, 90%) as a colorless oil: $[\alpha]_D^{20}$ −2.12 (*c* 0.24, $CHCl_3$); IR (film) 2953, 1740, 1259, 1094, 837, 775, 669 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.84–3.82 (m, 1H), 3.63 (s, 3H), 3.38 (ddd, *J*=10.0, 10.0, 4.5 Hz, 1H), 3.25 (m, 1H), 2.93–2.91 (m, 1H), 2.44–2.37 (m, 2H), 2.12 (dd, *J*=15.0, 10.5 Hz, 1H), 2.02–1.99 (m, 1H), 1.59–1.51 (m, 2H), 1.43–1.35 (m, 1H), 1.02 (d, *J*=7.5 Hz, 3H), 0.86 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 86.2, 68.0, 68.0, 51.3, 35.0, 33.9, 29.9, 25.8 (×3), 25.6, 17.9 (×2), −3.9, −4.9; HRMS (FAB) calcd for $C_{16}H_{33}O_4Si$ [(M+H)$^+$] 317.2148, found 317.2150.

4.1.8. Lactone 19. To a solution of ester **18** (2.3 mg, 7.3 μmol) in MeOH (0.07 mL) was added 1% HCl in MeOH (0.35 mL). The resulting mixture was stirred at room temperature for 2 h before being quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude alcohol was used directly in the subsequent reaction without purification.

To a solution the above alcohol in benzene (0.54 mL) was added PPTS (0.9 mg, 3.6 μmol). The resulting mixture was stirred at 80 °C for 10 h. Toluene (1.0 mL) was added and the mixture was stirred at 110 °C for further 5 h. The reaction mixture was cooled to room temperature and quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (30% EtOAc/hexanes) afforded lactone **19** (1.0 mg, 81% for the two steps) as a colorless oil: $[\alpha]_D^{20}$ +105.6 (*c* 0.07, $CHCl_3$); IR (film) 2920, 1727, 1383, 1075, 778, 661 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.12 (ddd, *J*=10.5, 10.5, 5.0 Hz, 1H), 3.98–3.95 (m, 1H), 3.47 (ddd, *J*=11.5, 11.5, 3.5 Hz, 1H), 3.36 (dd, *J*=9.0, 5.0 Hz, 1H), 2.75 (dd, *J*=18.0, 7.5 Hz, 1H), 2.45 (dd, *J*=17.5, 3.5 Hz, 1H), 2.34 (ddd, *J*=13.0, 6.5, 4.0 Hz, 1H), 2.25 (m, 1H), 1.73–1.54 (m, 3H), 1.07 (d, *J*=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.1, 72.9, 68.4, 37.5, 31.2, 30.1, 29.0, 25.1, 14.7; HRMS (EI) calcd for $C_9H_{14}O_3$ (M$^+$) 170.0943, found 170.0951.

4.1.9. Alcohol 20. To a solution of ester **18** (1.04 g, 3.29 mmol) in CH_2Cl_2 (16 mL) at −78 °C was added DIBALH (0.94 M in hexane, 10.5 mL, 9.87 mmol). The resulting mixture was stirred at −78 °C for 2 h before it was quenched with saturated aqueous potassium sodium tartrate. The mixture was vigorously stirred until the layers became clear. The organic layer was separated, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (40% EtOAc/hexanes) afforded alcohol **20** (0.90 g, 95%) as a colorless oil: $[\alpha]_D^{21}$ −25.1 (*c* 1.34, $CHCl_3$); IR (film) 2934, 1251, 1100, 836, 775, 669 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 3.70–3.55 (m, 5H), 3.00–2.95 (m, 2H), 2.34–2.31 (m, 1H), 2.02 (br, 1H), 1.84–1.82 (m, 1H), 1.76 (ddd, *J*=14.0, 14.0, 7.5 Hz, 1H), 1.70–1.64 (m, 1H), 1.41–1.32 (m, 1H), 1.29–1.18 (m, 1H), 1.10 (d, *J*=7.5 Hz, 3H), 0.95 (s, 9H), 0.08 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 87.2, 68.1, 68.1, 59.9, 34.3, 33.0, 30.0, 26.0 (×3), 25.8, 18.1, 17.2, −3.6, −4.6; HRMS (FAB) calcd for $C_{15}H_{33}O_3Si$ [(M+H)$^+$] 289.2199, found 289.2204.

4.1.10. Alcohol 8. To a solution of alcohol **20** (0.50 g, 1.74 mmol) in THF (17 mL) at 0 °C was added KO*t*-Bu (0.78 g, 6.95 mmol). The resulting solution was stirred at room temperature for 10 min before benzyl bromide (0.62 mL, 5.21 mmol) and Bu_4NI (44 mg 0.12 mmol) were added. The reaction mixture was stirred at room temperature for 1 h before it was quenched with MeOH. The mixture was diluted with Et_2O, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (40% EtOAc/hexanes) afforded benzyl ether (0.59 g, 90%) as a yellow oil: $[\alpha]_D^{17}$ −42.3 (*c* 1.18, $CHCl_3$); IR (film) 2930, 2855, 1099, 835, 775, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31–7.30 (m, 4H), 7.25 (m, 1H), 4.51–4.43 (m, 2H), 3.84 (m, 1H), 3.55–3.47 (m, 2H), 3.42 (m, 1H), 3.24 (m, 1H), 2.90 (dd, *J*=8.5, 2.0 Hz, 1H), 2.1–2.0 (m, 2H), 1.79 (m, 1H), 1.75–1.54 (m, 2H), 1.46 (m, 1H), 1.37 (m, 1H), 0.96 (d, *J*=6.5 Hz, 3H), 0.84 (s, 9H) 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 128.2 (×3), 127.5 (×2), 127.3, 87.3, 72.7, 69.2, 68.0, 67.8, 34.0, 29.51, 29.48, 25.8 (×3), 25.7, 17.9, 17.4, −3.7, −4.7; HRMS (ESI) calcd for $C_{22}H_{38}NaO_3Si$ [(M+Na)$^+$] 401.2488, found 401.2487.

To a solution of the above benzyl ether (0.56 g, 1.48 mmol) in THF (15 mL) at 0 °C was added TBAF (1.0 M in THF,

4.5 mL, 4.5 mmol). The resultant mixture was stirred at room temperature for 2 h and concentrated under reduced pressure. Purification by column chromatography on silica gel (30% EtOAc/hexanes) afforded alcohol **8** (0.39 g, quant.) as a colorless oil: $[\alpha]_D^{17}$ −28.0 (*c* 1.00, $CHCl_3$); IR (film) 3397, 2933, 2851, 1453, 1091, 737, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24–7.14 (m, 5H), 4.43–4.36 (m, 2H), 3.77 (m, 1H), 3.48 (m, 1H), 3.39–3.32 (m, 2H), 3.16 (m, 1H), 2.81 (dd, *J*=8.5, 1.5 Hz, 1H), 2.47 (m, 1H), 2.00–1.92 (m, 2H), 1.87–1.80 (m, 1H), 1.54–1.49 (m, 2H), 1.31–1.16 (m, 2H), 0.90 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 128.5 (×2), 128.3, 127.8 (×2), 127.7, 86.8, 73.2, 69.4, 68.0, 67.1, 32.5, 30.1, 30.0, 25.8, 17.9; HRMS (ESI) calcd for $C_{16}H_{24}NaO_3$ [(M+Na)$^+$] 287.1623, found 287.1603.

4.1.11. Alcohol 21. To a solution of alcohol **20** (0.89 g, 3.09 mmol) in THF (15 mL) were added *o*-nitrophenyl selenocyanate (1.05 g, 4.62 mmol) and Bu_3P (1.53 mL, 6.13 mmol). The resulting mixture was stirred at room temperature for 30 min before it was concentrated under reduced pressure. The residue was filtered through a plug of silica gel (10% EtOAc/hexanes) to give *o*-nitrophenyl selenide, which was used directly in the subsequent reaction.

To a solution the above selenide in CH_2Cl_2 (31 mL) at 0 °C was added *m*-CPBA (77%, 1.39 g, 6.20 mmol). The resulting mixture was stirred at 0 °C for 30 min before it was quenched with Et_3N. The mixture was stirred at 35 °C for further 12 h and concentrated under reduced pressure. Purification by column chromatography on silica gel (10% EtOAc/hexanes) afforded olefin (0.77 g, 92% for the two steps), which was used directly in the subsequent reaction.

To a solution of the above olefin (0.77 g, 2.85 mmol) in THF (28 mL) at 0 °C was added TBAF (1.0 M in THF, 5.6 mL, 5.6 mmol). The resulting mixture was stirred at room temperature for 15 h before it was quenched with saturated aqueous NH_4Cl. The organic layer was separated, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (40% EtOAc/hexanes) afforded alcohol **21** (0.42 g, 94%) as a yellow oil: $[\alpha]_D^{21}$ −18.9 (*c* 3.83, $CHCl_3$); IR (film) 3397, 2935, 1085, 1054, 1004, 914, 717 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.88 (ddd, *J*=17.0, 10.0, 8.0 Hz, 1H), 5.09–5.03 (m, 2H), 3.91–3.88 (m, 1H), 3.47–3.42 (m, 1H), 3.31–3.23 (m, 1H), 2.95 (dd, *J*=9.0, 2.5 Hz, 1H), 2.66 (ddd, *J*=14.5, 7.5, 6.0 Hz, 1H), 2.05 (m, 1H), 1.64–1.56 (m, 2H), 1.45 (d, *J*=4.0 Hz, 1H), 1.42–1.34 (m, 1H), 1.10 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.9, 115.1, 85.5, 67.9, 67.8, 38.6, 32.9, 25.6, 16.9; HRMS (FAB) calcd for $C_9H_{17}O_2$ [(M+H)$^+$] 157.1229, found 157.1231.

4.1.12. Ester 22. To a solution of carboxylic acid **7** (0.70 g, 1.96 mol) in THF (14 mL) at 0 °C were added Et_3N (0.70 mL, 5.02 mmol) and 2,4,6-trichlorobenzoyl chloride (0.55 mL, 3.52 mmol). The resultant mixture was stirred at room temperature for 1.5 h and concentrated under reduced pressure. The mixture was added to a solution of alcohol **8** (0.37 g, 1.40 mmol) and DMAP (0.35 g, 2.86 mmol) in THF (14 mL). The mixture was stirred at room temperature for 2 h before it was quenched with saturated aqueous NH_4Cl. The reaction mixture was diluted with EtOAc, washed with brine and saturated aqueous $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (20% EtOAc/hexanes) afforded ester **22** (0.85 g, quant.) as a colorless oil: $[\alpha]_D^{17}$ +4.0 (*c* 1.76, $CHCl_3$); IR (film) 2952, 2854, 1736, 1251, 1107, 835, 774, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31–7.24 (m, 5H), 4.73 (ddd, *J*=10.5, 10.5, 5.0 Hz, 1H), 4.48–4.42 (m, 2H), 3.89–3.85 (m, 2H), 3.50–3.41 (m, 2H), 3.36–3.28 (m, 2H), 3.15–3.13 (m, 1H), 3.03 (m, 1H), 2.94–2.88 (m, 2H), 2.49–2.43 (ddd, *J*=16.0, 9.5, 5.0 Hz, 1H), 2.28–2.22 (m, 1H), 2.16–2.08 (m, 2H), 2.02–1.96 (m, 2H), 1.87–1.82 (m, 2H), 1.69–1.47 (m, 6H), 1.44–1.36 (m, 3H), 1.18 (s, 3H), 0.96 (d, *J*=6.5 Hz, 3H), 0.83 (s, 9H), 0.07 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.8, 128.3 (×2), 127.5 (×2), 127.3 (×2), 84.5, 83.8, 78.8, 76.8, 73.4, 72.5, 68.8, 68.7, 67.9, 67.7, 46.2, 32.0, 30.5, 30.2, 29.6, 29.3, 25.7 (×3), 25.5, 25.1, 23.9, 22.2, 18.0, 16.8, −2.0, −2.1; HRMS (ESI) calcd for $C_{34}H_{56}NaO_7Si$ [(M+Na)$^+$] 627.3693, found 627.3688.

4.1.13. α-Acetoxy ether 23. To a solution of ester **22** (0.40 g, 0.66 mmol) in CH_2Cl_2 (13 mL) at −78 °C was added DIBALH (0.94 M in hexane, 2.81 mL, 2.64 mmol). The resultant mixture was stirred at −78 °C for 20 min. A solution of Ac_2O (0.75 mL, 7.93 mmol) and DMAP (1.05 g, 8.59 mmol) in CH_2Cl_2 (13 mL) was added over 80 min, and then a solution of pyridine (0.64 mL, 7.91 mmol) in CH_2Cl_2 (6 mL) was added dropwise over 40 min. The mixture was stirred at −78 °C for 19 h and allowed to warm to 0 °C. After being stirred at 0 °C for 1 h, the reaction was quenched with saturated aqueous NH_4Cl and saturated aqueous potassium sodium tartrate. The mixture was vigorously stirred until the layers became clear. The solution was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was filtered through a plug of silica gel (20% EtOAc/hexanes containing 1% Et_3N) to afford α-acetoxy ether **23** (0.42 g, 98%) as a 4:1 mixture of diastereomers; $[\alpha]_D^{17}$ −6.3 (*c* 1.39, $CHCl_3$); IR (film) 2936, 2854, 1737, 1247, 1089, 836, 774, 698 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.32–7.30 (m, 2H), 7.19–7.17 (m, 2H), 7.08 (m, 1H), 6.29 (dd, *J*=7.0, 4.0 Hz, 1H), 4.35 (m, 2H), 3.73–3.65 (m, 3H), 3.56–3.47 (m, 2H), 3.18–2.99 (m, 4H), 2.94–2.85 (m, 2H), 2.45 (m, 1H), 2.21–2.00 (m, 5H), 1.96–1.60 (m, 8H), 1.56–1.30 (m, 4H), 1.25–1.12 (m, 8H), 0.95 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 168.6, 137.6, 126.5 (×2), 126.44, 126.0, 125.4, 92.9, 83.8, 83.2, 77.3, 75.3, 72.1, 70.8, 69.8, 67.5, 65.6, 65.7, 44.8, 31.3, 28.6, 28.5, 27.8, 27.7, 24.0 (×3), 23.9, 23.6, 21.5, 20.4, 18.8, 14.3, 15.3, −3.88, −3.93; HRMS (ESI) calcd for $C_{36}H_{60}NaO_8Si$ [(M+Na)$^+$] 671.3955, found 671.3976.

4.1.14. Alcohol 24. To a solution of α-acetoxy ether **23** (0.21 g, 0.32 mmol) in CH_2Cl_2 (0.4 mL) at 0 °C were added 2,6-di-*tert*-butyl-4-methylpyridine (0.26 g, 1.27 mmol), TMSSPh (0.12 mL, 0.63 mmol) and TMSOTf (0.17 mL, 0.94 mmol). The resultant mixture was stirred at 0 °C for 5 min and allowed to warm to room temperature. After being stirred at room temperature for 2 h, the mixture was quenched with Et_3N, filtered, and concentrated under reduced pressure. The residue was filtered through a plug of silica gel (20% EtOAc/hexanes) to afford crude

mixed thioacetal (0.20 g, 88%) as a 1.5:1 mixture of diastereomers.

To a solution of the above mixed thioacetal (0.14 g, 0.20 mmol) in MeCN (2 mL) was added TBAF (0.54 g, 2.07 mmol). The resultant mixture was stirred at 70 °C for 7 h before it was concentrated under reduced pressure. Purification by column chromatography on silica gel (EtOAc) afforded alcohol **24** (0.11 g, 94%) as a ca. 1.25:1 mixture of diastereomers: $[\alpha]_D^{16}$ −5.2 (*c* 1.49, $CHCl_3$); IR (film) 3438, 2950, 2850, 1732, 1638, 1258, 1104, 750, 697 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.69–7.67 (m, 0.88H), 7.61–7.60 (m, 1.12H), 7.36–7.34 (m, 0.88H), 7.31–7.29 (m, 1.12H), 7.26 (m, 0.44H), 7.22–6.94 (m, 5.56H), 5.27 (m, 0.44H), 5.04 (m, 0.56H), 4.45–4.23 (m, 2H), 3.97 (ddd, *J*=9.5, 4.0, 4.0 Hz, 0.44H), 3.74–3.59 (m, 3.56H), 3.44–3.29 (m, 2H), 3.18–3.14 (m, 1H), 3.04–2.96 (m, 3.44H), 2.92 (m, 0.44H), 2.88–2.73 (m, 2.56H), 2.49–2.45 (m, 1.44H), 2.45–2.35 (m, 2.56H), 2.17–1.99 (m, 3.24H), 1.94–1.82 (m, 2.88H), 1.73–1.64 (m, 1H), 1.60–1.09 (m, 10.44H); ^{13}C NMR (125 MHz, C_6D_6) δ 133.5 (×2), 133.3 (×2), 129.1 (×2), 129.0 (×2), 128.6 (×2), 128.53 (×2), 128.45 (×2), 128.3 (×3), 128.0 (×2), 127.7 (×2), 127.4, 127.3 (×2), 90.0, 86.6, 85.9, 85.5, 85.2, 84.8, 79.13, 79.10, 77.4, 77.3, 74.4 (×2), 73.1, 72.9, 71.1, 70.7, 69.6, 68.4, 67.7, 67.6 (×3), 46.7 (×2), 35.3, 34.5, 31.7, 30.6, 30.5, 30.3, 29.7, 29.2, 28.5, 27.6, 25.9 (×3), 25.8, 25.5 (×2), 21.64, 21.60, 17.6, 17.5; HRMS (ESI) calcd for $C_{34}H_{48}NaO_6S$ [$(M+Na)^+$] 607.3069, found 607.3077.

4.1.15. β-Alkoxyacrylate 9. To a solution of alcohol **24** (62.1 mg, 0.106 mmol) in CH_2Cl_2 (0.1 mL) at 0 °C were added Me_3P (1.0 M in THF, 3.0 mL, 3.0 mmol) and methyl propiolate (0.15 mL, 1.69 mmol). The resultant mixture was stirred at room temperature for 11 h before it was concentrated under reduced pressure. Purification by column chromatography on silica gel (30% EtOAc/hexanes) afforded β-alkoxyacrylate **9** (33.4 mg, 47%) as a ca. 1.2:1 mixture of diastereomers, along with recovered **24** (26.3 mg, 42%) **9**: $[\alpha]_D^{17}$ −6.7 (*c* 0.62, $CHCl_3$); IR (film) 2945, 2852, 1714, 1638, 1135, 1105, 748, 696 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.82–7.79 (m, 1H), 7.69–7.68 (m, 0.9H), 7.59–7.58 (m, 1.1H), 7.35–6.93 (m, 8H), 5.67–5.64 (m, 1H), 5.25–5.18 (m, 0.55H), 4.96 (m, 0.45H), 4.44–4.36 (m, 2H), 3.95 (m, 0.45H), 3.73–3.67 (m, 1.9H), 3.62–3.58 (m, 2.65H), 3.51–3.20 (m, 5.55H), 3.17–3.12 (m, 2.1H), 3.05–2.86 (m, 3.35H), 2.61–2.48 (m, 3.25H), 2.42–2.33 (m, 1.55H), 2.24 (m, 0.55H), 2.15–1.86 (m, 5.45H), 1.72–1.04 (m, 7.2H), 0.98 (s, 1.65H), 0.96 (s, 1.35H); ^{13}C NMR (125 MHz, C_6D_6) δ 198.9, 196.9, 156.7, 156.6, 133.7 (×2), 133.5 (×2), 129.1 (×2), 129.0, 128.6, 128.5, 128.4 (×2), 128.3 (×6), 127.8 (×2), 127.7, 127.6, 127.5, 127.4 (×2), 127.3, 100.4, 100.3, 86.3 (×2), 85.5 (×2), 82.5, 82.3, 80.5 (×2), 78.9, 78.8, 76.5 (×2), 73.1, 72.9, 71.2, 69.6 (×2), 68.3, 67.7, 67.6 (×2), 50.6 (×2), 42.4 (×2), 34.6, 33.9, 31.9, 30.5 (×2), 30.3, 29.4 (×2), 29.3 (×2), 28.5, 25.6 (×3), 25.5 (×2), 18.5 (×2), 17.7, 17.6; HRMS (ESI) calcd for $C_{38}H_{52}NaO_8S$ [$(M+Na)^+$] 691.3281, found 691.3276.

4.1.16. Ester 28. To a solution of carboxylic acid **7** (0.71 g, 1.98 mmol) in THF (20 mL) at 0 °C were added Et_3N (0.41 mL, 2.94 mmol) and 2,4,6-trichlorobenzoyl chloride (0.40 mL, 2.56 mmol). The reaction mixture was stirred at 40 °C for 1.5 h before it was concentrated under reduced pressure. The mixture was dissolved in toluene (20 mL) and treated with alcohol **21** (0.31 g, 1.98 mmol) and DMAP (0.48 g, 3.93 mmol). The resulting mixture was stirred at 40 °C for 2.5 h before it was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with brine and saturated aqueous $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (20% EtOAc/hexanes) afforded ester **28** (0.90 g, 91%) as a pale yellow oil: $[\alpha]_D^{21}$ +21.7 (*c* 1.47, $CHCl_3$); IR (film) 2953, 1737, 1107, 835, 774, 667 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.78 (ddd, *J*=18.5, 17.5, 10.5 Hz, 1H), 4.99 (dd, *J*=11.0, 1.5 Hz, 1H), 4.90 (d, *J*=17.5 Hz, 1H), 4.60 (dd, *J*=12.5, 4.5 Hz, 1H), 3.93–3.86 (m, 2H), 3.38–3.27 (m, 2H), 3.17 (dd, *J*=9.5, 2.5 Hz, 1H), 3.05 (dd, *J*=10.5, 1.5 Hz, 1H), 2.97–2.90 (m, 2H), 2.50 (ddd, *J*=15.5, 10.0, 5.5 Hz, 1H), 2.41 (ddd, *J*=13.5, 7.0, 7.0 Hz, 1H), 2.27 (ddd, *J*=15.5, 10.0, 6.5 Hz, 1H), 2.18–2.15 (m, 1H), 2.11 (dd, *J*=11.5, 4.0 Hz, 1H), 2.04–1.98 (m, 2H), 1.71–1.50 (m, 6H), 1.43–1.33 (m, 2H), 1.20 (s, 3H) 1.08 (d, *J*=7.0 Hz, 3H), 0.83 (s, 9H), 0.074 (s, 3H), 0.072 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 138.9, 115.4, 84.5, 83.1, 78.9, 76.8, 73.4, 69.5, 68.0, 67.9, 46.2, 38.5, 32.1, 29.5, 29.3, 25.7 (×3), 25.6, 25.1, 24.0, 22.2, 18.0, 17.0, −2.0, −2.1; HRMS (FAB) calcd for $C_{27}H_{49}O_6Si$ [$(M+H)^+$] 497.3298, found 497.3300.

4.1.17. Alcohol 30. To a solution of ester **28** (0.29 g, 0.58 mmol) in CH_2Cl_2 (12 mL) at −78 °C was added DIBALH (0.95 M in hexane, 2.55 mL, 2.42 mmol). The resulting mixture was stirred at −78 °C for 1 h. A solution of Ac_2O (0.68 mL, 7.19 mmol) and DMAP (0.96 g, 7.86 mmol) in CH_2Cl_2 (12 mL) was added dropwise over 1 h, and then a solution of pyridine (0.57 mL, 7.37 mmol) in CH_2Cl_2 (6 mL) was added over 0.5 h. The mixture was stirred at −78 °C for 8 h and allowed to warm to 0 °C. After being stirred at 0 °C for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and saturated aqueous potassium sodium tartrate. The mixture was vigorously stirred until the layers became clear. The solution was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was filtered through a plug of silica gel (20% EtOAc/hexanes containing 1% Et_3N) to afford α-acetoxy ether (0.32 g) as a 3:1 mixture of diastereomers, which was used directly in the subsequent reaction.

To a solution of the above α-acetoxy ether (0.32 g) in CH_2Cl_2 (11 mL) at −78 °C were added 2,6-di-*tert*-butyl-4-methylpyridine (0.46 g, 2.24 mmol), TMSCN (0.15 mL, 1.20 mmol), and TMSOTf (0.30 mL, 1.66 mmol). The resulting mixture was stirred at −78 °C for 30 min and allowed to warm to 0 °C. After being stirred at 0 °C for 1 h, the mixture was quenched with Et_3N, filtered, and concentrated under reduced pressure. The residue was filtered through a plug of silica gel (30% EtOAc/hexanes) to afford crude α-cyano ether **29** (0.32 g) as a ca. 3:1 mixture of diastereomers: $[\alpha]_D^{21}$ +5.2 (*c* 0.96, $CHCl_3$); IR (film) 3074, 2934, 1462, 1250, 1106, 836, 774, 667 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.87–5.75 (m, 1H), 5.14–4.89 (m, 2H), 4.31 (dd, *J*=8.5, 5.0 Hz, 0.75H), 4.22–4.19 (m, 0.25H),

3.92–3.86 (m, 2H), 3.49–3.44 (m, 0.75H), 3.37–3.32 (m, 1.25H), 3.30–3.22 (m, 1H), 3.07–3.05 (m, 1H), 2.99–2.90 (m, 3H), 2.67 (ddd, J=6.5, 6.5, 6.5 Hz, 0.75H), 2.55 (ddd, J=6.5, 6.5, 6.5 Hz, 0.25H), 2.44–2.41 (m, 0.25H), 2.22–2.19 (m, 0.75H), 2.12–2.01 (m, 4H), 1.94–1.89 (m, 1H), 1.86–1.76 (m, 1H), 1.72–1.55 (m, 4H), 1.43–1.29 (m, 2H), 1.27–1.18 (m, 4H), 1.09–1.06 (m, 3H), 0.83 (m, 9H), 0.078 (s, 3H), 0.073 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.7, 118.5, 116.1, 109.7, 85.2, 83.9, 78.8, 76.7, 73.6, 73.4, 67.9, 64.3, 46.1, 38.0, 32.2, 29.3, 28.2, 25.69 (×3), 25.66, 25.5, 24.9, 24.0, 22.2, 17.7, −2.0, −2.1 (major isomer); HRMS (FAB) calcd for $C_{28}H_{49}NO_5SiNa$ [(M+Na)$^+$] 530.3278, found 530.3284.

To a solution of the above α-cyano ether **29** (0.32 g) in MeCN (11 mL) was added TBAF (1.35 g, 5.16 mmol). The resulting mixture was stirred at 70 °C for 29 h before it was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc) to afford alcohol **30** (0.14 g, 61% for the three steps) as a ca. 1.5:1 mixture of diastereomers: $[\alpha]_D^{21}$ −5.4 (c 0.81, $CHCl_3$); IR (film) 3443, 2938, 1455, 1383, 1105, 967, 930, 680 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89–5.78 (m, 1H), 5.15–4.95 (m, 2H), 4.34 (dd, J=7.0, 6.0 Hz, 0.6H), 4.22 (dd, J=6.5, 6.5 Hz, 0.4H), 3.92–3.87 (m, 2H), 3.47 (ddd, J=11.0, 9.5, 4.5 Hz, 0.6H), 3.38–3.32 (m, 1H), 3.31–3.23 (m, 1.4H), 3.13–3.10 (m, 1H), 3.02–2.92 (m, 3H), 2.68 (ddd, J=15.0, 7.0, 7.0 Hz, 0.6H), 2.56 (ddd, J=14.0, 7.0, 7.0 Hz, 0.4H), 2.43 (m, 0.4H), 2.20 (m, 0.6H), 2.11–2.02 (m, 3.6H), 1.91–1.81 (m, 2H), 1.74–1.35 (m, 9.4H), 1.29–1.18 (m, 3H), 1.09 (d, J=6.5 Hz, 1.8H), 1.07 (d, J=7.5 Hz, 1.2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.1, 138.7, 119.7, 118.5, 116.2, 115.4, 84.4, 84.3, 83.8, 83.7, 78.9, 78.9, 77.6, 76.7 (×2), 73.7, 71.14, 71.12, 68.1, 67.9 (×3), 67.8, 64.5, 46.0, 45.9, 38.4, 38.0, 31.8, 31.7, 30.0, 29.24, 29.23, 28.17, 25.5 (×2), 25.3, 24.9, 24.0, 23.6, 21.7, 21.6, 18.1, 17.7; HRMS (FAB) calcd for $C_{22}H_{36}NO_5$ [(M+H)$^+$] 394.2593, found 394.2594.

4.1.18. Hydroxy acid 31. To a solution of alcohol **30** (0.14 g, 0.36 mmol) in ethylene glycol (3.5 mL) was added KOH (0.20 g, 3.56 mmol). The resulting mixture was stirred at 150 °C for 14 h. The solution was cooled to room temperature and quenched with 1 M aqueous HCl. The mixture was diluted with $CHCl_3$, washed with 1 M aqueous HCl and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (20% MeOH/$CHCl_3$) afforded hydroxy acid **31** (0.14 g, 95%) as a 1:1 mixture of diastereomers: $[\alpha]_D^{21}$ +0.89 (c 1.12, $CHCl_3$); IR (film) 3416, 2938, 1728, 1105, 921, 680 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 5.90–5.81 (m, 1H), 5.09–4.95 (m, 2H), 4.05 (dd, J=7.5, 4.5 Hz, 0.5H), 3.90 (dd, J=5.5, 5.5 Hz, 0.5H), 3.85–3.82 (m, 2H), 3.40–3.23 (m, 4.5H), 3.18 (ddd, J=9.0, 4.0 Hz, 0.5H), 3.12–2.91 (m, 4H), 2.84 (ddd, J=14.5, 7.0, 7.0 Hz, 0.5H), 2.74 (ddd, J=14.0, 7.0, 7.0 Hz, 0.5H), 2.28–2.26 (m, 0.5H), 2.17–2.14 (m, 0.5H), 2.02–1.92 (m, 3.5H), 1.86–1.76 (m, 1.5H), 1.69–1.26 (m, 8H), 1.14 (s, 3H), 1.08 (d, J=6.5 Hz, 1.5H), 1.06 (d, J=6.0 Hz, 1.5H); ^{13}C NMR (125 MHz, CD_3OD) δ 178.5, 176.9, 141.1, 141.0, 116.1, 115.8, 86.2, 86.0, 85.8, 85.5, 80.2, 80.2, 79.8, 78.3 (×2), 77.9, 77.4, 75.4, 71.6, 71.6, 68.8 (×2), 68.8, 68.6, 46.7, 46.7, 39.5, 38.9, 32.2, 32.2, 31.1, 30.5, 30.33, 30.31, 26.7 (×2), 26.5, 26.2, 25.6, 25.4, 21.6, 21.5, 18.9, 18.6; HRMS (FAB) calcd for $C_{22}H_{36}O_7Na$ [(M+Na)$^+$] 435.2359, found 435.2365.

4.1.19. Lactones 32a and 32b. To a solution of hydroxy acid **31** (0.44 g, 1.07 mol) in THF/toluene (1:1, v/v, 22 mL) at 0 °C were added Et_3N (0.30 mL, 2.15 mmol) and 2,4,6-trichlorobenzoyl chloride (0.25 mL, 1.60 mmol). The resulting mixture was stirred at room temperature for 2 h before it was diluted with toluene (44 mL). This mixture was added dropwise to a refluxing solution of DMAP (0.65 g, 5.32 mmol) in toluene (107 mL) over a period of 1.5 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. Purification by column chromatography on silica gel (10–20% EtOAc/hexanes) afforded lactones **32a** (0.16 g, 38%) as a colorless oil and **32b** (0.17 g, 40%) as a solid. **32a**: $[\alpha]_D^{21}$ −49.5 (c 0.55, $CHCl_3$); IR (film) 2940, 1720, 1076, 947, 705 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (ddd, J=18.5, 10.5, 9.0 Hz, 1H), 5.07 (d, J=16.5 Hz, 1H), 5.05 (d, J=10.5 Hz, 1H), 4.40 (d, J=4.0 Hz, 1H), 3.91–3.85 (m, 2H), 3.43–3.31 (m, 3H), 3.24 (ddd, J=11.0, 11.0, 2.5 Hz, 1H), 3.04–2.95 (m, 3H), 2.65 (ddd, J=14.0, 7.0, 7.0 Hz, 1H), 2.28 (dd, J=12.5, 8.5 Hz, 1H), 2.17 (m, 1H), 2.11–2.02 (m, 2H), 1.95–1.89 (m, 1H), 1.80–1.76 (m, 2H) 1.73–1.66 (m, 5H), 1.63–1.49 (m, 3H), 1.45–1.34 (m, 2H), 1.07 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 138.9, 116.1, 84.1, 82.9, 82.4, 79.0, 78.5, 76.5, 76.4, 67.9, 67.6, 45.1, 37.7, 30.1, 29.1, 27.7, 25.4, 25.1, 24.8, 20.2, 18.1; HRMS (FAB) calcd for $C_{22}H_{35}O_6$ [(M+H)$^+$] 395.2434, found 395.2434. **32b**: $[\alpha]_D^{21}$ −13.9 (c 0.83, $CHCl_3$); IR (film) 3070, 2943, 1743, 1098, 941, 681 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.95 (ddd, J=19.0, 9.0, 9.0 Hz, 1H), 5.05 (dd, J=10.0, 1.5 Hz, 1H), 5.02 (d, J=17.0 Hz, 1H), 4.12 (dd, J=11.0, 1.5 Hz, 1H), 3.91–3.85 (m, 2H), 3.37–3.32 (m, 2H), 3.25 (ddd, J=13.5, 11.5, 2.5 Hz, 1H), 3.11–3.01 (m, 3H), 2.96 (ddd, J=12.0, 9.5, 4.0 Hz, 1H), 2.63 (ddd, J=15.0, 7.5, 7.5 Hz, 1H), 2.37–2.35 (m, 1H), 2.26 (dd, J=12.0, 3.5 Hz, 1H), 2.04–2.02 (m, 3H), 1.85–1.76 (m, 3H) 1.73–1.69 (m, 2H), 1.64–1.61 (m, 1H), 1.58–1.45 (m, 5H), 1.43–1.35 (m, 1H), 1.09 (d, J=6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 140.7, 115.2, 84.5, 80.9, 80.8, 79.1, 79.0, 77.6, 76.3, 68.0, 67.9, 45.1, 38.6, 30.4, 29.03, 29.01, 27.7, 25.7, 25.4, 19.8, 18.7; HRMS (FAB) calcd for $C_{22}H_{35}O_6$ [(M+H)$^+$] 395.2434, found 395.2433.

4.1.20. Acetate 33. To a solution of lactone **32a** (0.15 g, 0.38 mmol) in CH_2Cl_2 (7.7 mL) at −78 °C was added DIBALH (0.95 M in hexane 1.64 mL, 1.56 mmol). The resulting mixture was stirred at −78 °C for 1 h. A solution of Ac_2O (0.44 mL, 4.65 mmol) and DMAP (0.61 g, 4.99 mmol) in CH_2Cl_2 (7.7 mL) was added dropwise over 40 min, and then a solution of pyridine (0.38 mL, 4.70 mmol) in CH_2Cl_2 (3.9 mL) was added over 20 min. The resulting mixture was stirred at −78 °C for 13 h and allowed to warm to 0 °C. After being stirred at 0 °C for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and saturated aqueous potassium sodium tartrate, and vigorously stirred until the layers became clear. The mixture was diluted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel

(30% EtOAc/hexanes) afforded acetate **33** (0.16 g, 96%) as a colorless oil: $[\alpha]_D^{21}$ −26.4 (*c* 0.73, $CHCl_3$); IR (film) 2939, 1752, 1234, 1085, 1020, 943 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.96–5.89 (m, 2H), 5.02–4.98 (m, 2H), 3.88–3.86 (m, 2H), 3.77–3.56 (m, 1H), 3.36–3.30 (m, 2H), 3.27–3.21 (m, 2H), 3.06 (dd, *J*=9.5, 1.0 Hz, 1H), 3.01–2.98 (m, 2H), 2.89 (ddd, *J*=7.5, 7.5, 7.5 Hz, 1H), 2.07–2.00 (m, 8H), 1.97–1.85 (m, 2H), 1.72–1.50 (m, 4H), 1.47–1.37 (m, 3H), 1.33 (s, 3H), 1.08 (d, *J*=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 140.2, 115.2, 91.7, 85.2, 83.2, 79.9, 77.2, 76.7, 76.2, 74.3, 67.90, 67.85, 43.0, 37.2, 31.4, 29.4, 28.9, 25.6, 25.5, 24.4, 21.2, 20.8, 18.1; HRMS (FAB) calcd for $C_{24}H_{38}O_7Na$ [$(M+Na)^+$] 461.2515, found 461.2519.

4.1.21. Diene 34. To a suspension of acetate **33** (50.0 mg, 0.114 mmol) and 4 Å molecular sieves in MeCN (1.2 mL) at −40 °C was added allyltrimethylsilane (55.0 μL, 0.35 mmol). After 5 min, $BF_3\cdot OEt$ (4 μL, 32 μmol) was added. The resulting mixture was stirred at −40 °C for 2 h and allowed to warm to 0 °C. After being stirred at 0 °C for 2 h, the reaction mixture was quenched with Et_3N, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (10% EtOAc/hexanes) afforded diene **34** (31.6 mg, 66%) as a colorless oil: $[\alpha]_D^{21}$ +2.9 (*c* 1.30, $CHCl_3$); IR (film) 3072, 2938, 1454, 1436, 1086, 912, 679 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.91–5.76 (m, 2H), 5.05–4.99 (m, 4H), 3.89–3.84 (m, 2H), 3.77 (ddd, *J*=7.5, 7.5, 2.0 Hz, 1H), 3.51 (dd, *J*=2.5, 2.5 Hz, 1H), 3.34 (ddd, *J*=11.5, 11.5, 4.0 Hz, 1H), 3.23 (ddd, *J*=11.0, 11.0, 2.5 Hz, 1H), 3.11–2.95 (m, 5H), 2.66 (ddd, *J*=15.0, 5.0, 5.0 Hz, 1H), 2.23–2.21 (m, 2H), 2.10–2.02 (m, 2H), 1.94 (dd, *J*=11.0, 3.5 Hz, 1H) 1.84 (m, 1H), 1.78–1.67 (m, 3H), 1.58–1.51 (m, 5H), 1.46–1.38 (m, 1H), 1.35–1.27 (m, 4H), 1.08 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.7, 135.4, 116.8, 115.2, 85.6, 84.8, 80.5, 79.2, 77.6, 77.2, 76.0, 74.3, 68.0, 67.9, 45.1, 41.2, 37.7, 31.1, 29.5, 27.1, 25.7, 25.4, 23.7, 18.4, 16.0; HRMS (FAB) calcd for $C_{25}H_{41}O_5Si$ [$(M+H)^+$] 421.2954, found 421.2959.

4.1.22. CDEFG-ring model 6. To a solution of diene **34** (6.7 mg, 16.0 μmol) in CH_2Cl_2 (3.2 mL) was added Grubbs' catalyst **35** (3.4 mg, 4.0 μmol). The resulting mixture was stirred at 40 °C for 20 h. The reaction mixture was cooled to 0 °C, quenched with Et_3N (one drop), and concentrated under reduced pressure. Purification by column chromatography on silica gel (10% EtOAc/hexanes) afforded CDEFG-ring model **6** (6.1 mg, 98%) as a colorless oil: $[\alpha]_D^{21}$ −54.3 (*c* 1.00, $CHCl_3$); IR (film) 3090, 2937, 1462, 1376, 1095, 1039, 791, 678 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.71 (ddd, *J*=11.0, 5.0, 5.0 Hz, 1H), 5.42 (dd, *J*=11.0, 11.0 Hz, 1H), 3.86 (m, 2H), 3.80 (ddd, *J*=10.5, 3.0, 3.0 Hz, 1H), 3.34 (ddd, *J*=11.0, 11.0, 4.5 Hz, 1H), 3.24–3.12 (m, 3H), 3.10–3.05 (m, 2H), 3.03–2.98 (m, 2H), 2.93 (ddd, *J*=11.0 ,11.0, 3.5 Hz, 1H), 2.78 (ddd, *J*=14.5, 14.5, 3.5 Hz, 1H), 2.14–1.92 (m, 5H), 1.79–1.65 (m, 4H), 1.63–1.50 (m, 4H), 1.45–1.34 (m, 2H), 1.18 (s, 3H), 1.00 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.0, 126.6, 84.8, 84.0, 83.9, 82.2, 79.1, 77.0, 75.4, 75.3, 68.7, 67.9, 45.0, 32.3, 32.2, 32.1, 31.4, 29.4, 26.2, 25.6, 24.5, 16.6, 15.5; HRMS (FAB) calcd for $C_{23}H_{37}O_5$ [$(M+H)^+$] 393.2641, found 393.2644.

4.1.23. α,β-Unsaturated ester 39. To a solution of alcohol **38** (22.8 g, 82.6 mmol) in CH_2Cl_2/DMSO (1/2, v/v, 309 mL) at 0 °C were added Et_3N (34.0 mL, 244 mmol) and $SO_3\cdot$pyridine (26.2 g, 165 mmol). The resulting mixture was stirred at room temperature for 3 h before water was added. The mixture was diluted with Et_2O, washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (30% EtOAc/hexanes) afforded aldehyde, which was used directly in the subsequent reaction.

To a suspension of Ph_3PCH_3Br (42.0 g, 118 mmol) in THF (137 mL) at 0 °C was added NaHMDS (1.9 M in THF, 45.0 mL, 85.5 mmol). The resulting ylide solution was stirred at 0 °C for 30 min. A solution of the above crude aldehyde in THF (5.0 mL) was added, and the mixture was stirred at room temperature for 12.5 h before saturated aqueous NH_4Cl was added. The reaction mixture was diluted with Et_2O, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (30% EtOAc/hexanes) afforded olefin (21.4 g, 95% for the two steps) as a colorless oil.

To a solution of the above olefin (4.49 g, 16.5 mmol) in THF (163 mL) at 0 °C was added 9-BBN-H (0.5 M in THF, 130 mL, 65.0 mmol). The resulting mixture was stirred at room temperature for 18 h. The reaction mixture was cooled to 0 °C and treated with 10% aqueous NaOH (40 mL) followed by 30% H_2O_2 (73 mL). The resulting mixture was stirred at room temperature for 15 h before being diluted with EtOAc. The organic layer was separated, washed with saturated aqueous Na_2SO_3 and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (30% EtOAc/hexanes) afforded primary alcohol (3.80 g, 79%) as a colorless oil.

To a solution of the above alcohol (3.75 g, 12.9 mmol) in CH_2Cl_2/DMSO (1:1, v/v, 130 mL) at 0 °C were added Et_3N (8.9 mL, 63.9 mmol) and $SO_3\cdot$pyridine (8.20 g, 51.5 mmol). The resulting mixture was stirred at room temperature for 1 h before water was added. The mixture was diluted with Et_2O, washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude aldehyde, which was used directly in the subsequent reaction without purification.

To a solution the above aldehyde in toluene (65 mL) was added $Ph_3P{=}C(CH_3)CO_2Et$ (9.33 g, 25.7 mmol). The resulting mixture was stirred at 100 °C for 11 h before being concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (30% EtOAc/hexanes) to afford α,β-unsaturated ester **39** (4.34 g, 90% for the two steps) as a colorless oil: $[\alpha]_D^{31}$ +84.4 (*c* 1.50, $CHCl_3$); IR (film) 2953, 2931, 2894, 2857, 1712, 1257, 1129, 1091, 1058, 8337, 775, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.88 (dd, *J*=7.0, 7.0 Hz, 1H), 4.59 (d, *J*=2.5 Hz, 1H), 4.16 (dd, *J*=14.0, 6.5 Hz, 2H), 3.56 (ddd, *J*=9.5, 9.5, 3.0 Hz, 1H), 3.37 (m, 1H), 3.29 (m, 3H), 2.66 (dd, *J*=15.0, 6.5 Hz, 1H), 2.19 (m, 1H), 1.87–1.66 (m, 7H), 1.25 (dd, *J*=7.0, 7.0 Hz, 3H), 0.86 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.3, 139.3, 129.3, 97.5, 72.8, 71.1,

60.6, 54.6, 31.5, 29.6, 28.5, 26.0 (×3), 18.2, 14.5, 12.8, −3.7, −4.5; HRMS (FAB) calcd for $C_{19}H_{36}O_5SiNa$ [(M+Na)$^+$] 395.2230, found 395.2231.

4.1.24. Hydroxy epoxide 40. To a solution of α,β-unsaturated ester **39** (4.2 g, 11.3 mmol) in CH_2Cl_2 (113 mL) at −78 °C was added DIBALH (0.95 M in hexane, 59.5 mL, 56.5 mmol). The resulting solution was stirred at −78 °C for 1 h before it was quenched with saturated aqueous potassium sodium tartrate. The mixture was vigorously stirred until the layers became clear. The organic layer was separated, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (30% EtOAc/hexanes) afforded allylic alcohol (3.70 g, 99%) as a colorless oil.

To a solution of the allylic alcohol (3.70 g, 11.2 mmol) and activated powdered 4 Å molecular sieves in CH_2Cl_2 (110 mL) at −20 °C was added D-(+)-diethyl tartrate (0.58 mL, 3.39 mmol). The mixture was stirred at −20 °C for 15 min before Ti(O*i*-Pr)$_4$ (0.66 mL, 2.23 mmol) was added. The solution was stirred at the same temperature for further 30 min. *t*-BuOOH (5.5 M in isooctane, 4.08 mL, 22.4 mmol) was added, and the reaction mixture was stirred at −20 °C for 17 h before Et_2O and aqueous Na_2SO_4 were added. The resulting mixture was vigorously stirred at room temperature for 2 h before being filtered through a pad of Celite. The filtrate and washings were combined and concentrated, and the residue was filtered through a plug of silica gel (40% EtOAc/hexanes) to afford the crude epoxy alcohol, which was used directly in the subsequent reaction.

To a solution of the epoxy alcohol in CH_2Cl_2/DMSO (4:1, v/v, 70 mL) at 0 °C were added Et_3N (6.7 mL, 48.1 mmol) and SO_3·pyridine (5.34 g, 33.6 mmol). The resulting mixture was stirred at room temperature for 1.5 h before it was quenched with water. The solution was diluted with Et_2O, washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude aldehyde, which was used directly in the subsequent reaction without purification.

To a suspension of Ph_3PCH_3Br (8.4 g, 23.5 mmol) in THF (18.7 mL) at 0 °C was added NaHMDS (1.0 M in THF, 5.89 mL, 5.89 mmol). The resulting ylide solution was stirred at 0 °C for 30 min. A solution of the above crude aldehyde in THF (18.7 mL) was added, and the reaction mixture was stirred at room temperature for 1.5 h before being quenched with saturated aqueous NH_4Cl. The mixture was diluted with Et_2O, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (5% EtOAc/hexanes) afforded olefin (3.39 g, 88% for the three steps) as a colorless oil.

To a solution of the olefin (3.39 g, 9.91 mmol) in THF (50 mL) at 0 °C was added TBAF (1.0 M in THF, 19.8 mL, 19.8 mmol). The resulting mixture was stirred at room temperature for 3 h before it was quenched with saturated aqueous NH_4Cl. The organic layer was separated, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (40% EtOAc/hexanes containing 1% Et_3N) afforded hydroxy epoxide **40** (2.11 g, 93%) as a colorless oil: $[\alpha]_D^{32}$ +111.3 (*c* 0.91, $CHCl_3$); IR (film) 3415, 2937, 1441, 1383, 1127, 1053, 940, 875, 763, 665 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.64 (dd, *J*=17.5, 10.5 Hz, 1H), 5.32 (dd, *J*=15.0, 1.0 Hz, 1H), 5.17 (dd, *J*=11.0, 1.0 Hz, 1H), 4.64 (d, *J*=2.0 Hz, 1H), 3.65 (ddd, *J*=10.0, 7.0, 3.0 Hz, 1H), 3.54 (m, 1H), 3.31 (s, 3H), 3.07 (dd, *J*=7.5, 4.5 Hz, 1H), 2.06 (m, 1H), 1.87–1.71 (m, 6H), 1.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.7, 128.3, 116.2, 97.4, 71.4, 69.5, 62.0, 54.4, 30.9, 29.5, 27.3, 15.0; HRMS (ESI) calcd for $C_{12}H_{20}O_4Na$ [(M+Na)$^+$] 251.1259, found 251.1234.

4.1.25. TBS ether 41. To a solution of alcohol **40** (2.11 g, 9.25 mmol) in CH_2Cl_2 (92 mL) at 0 °C was added pyridinium *p*-toluenesulfonate (1.16 g, 4.62 mmol). The resulting mixture was stirred at room temperature for 14.5 h before being quenched with Et_3N. The solution was filtered and concentrated under reduced pressure. Purification by column chromatography on silica gel (30% EtOAc/hexanes) afforded bicyclic ether (2.02 g, 96%) as a colorless oil.

To a solution of the above bicyclic ether (2.02 g, 8.86 mmol) in CH_2Cl_2 (45 mL) at 0 °C were added 2,6-lutidine (3.09 mL, 26.5 mmol) and TBSOTf (2.99 mL, 13.0 mmol). The resulting solution was stirred at room temperature for 2 h before it was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (30% EtOAc/hexanes) afforded TBS ether **41** (2.94 g, 97%) as a colorless oil: $[\alpha]_D^{32}$ +72.0 (*c* 0.61, $CHCl_3$); IR (film) 3408, 2952, 2886, 1643, 1105, 1031, 837, 775 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (dd, *J*=17.5, 10.5 Hz, 1H), 5.26 (dd, *J*=17.5, 1.5 Hz, 1H), 5.07 (dd, *J*=10.5, 1.5 Hz, 1H), 4.62 (d, *J*=1.5 Hz, 1H), 3.56 (dd, *J*=11.5, 5.0 Hz, 1H), 3.40 (ddd, *J*=13.5, 9.5, 4.5 Hz, 1H), 3.35–3.27 (m, 4H), 1.92 (ddd, *J*=11.5, 4.5, 4.5 Hz, 1H), 1.87–1.84 (m, 1H), 1.79–1.69 (m, 3H), 1.63 (m, 1H), 1.55 (s, 3H), 0.84 (s, 9H), 0.03, (s, 3H), 0.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.5, 113.6, 98.0, 78.0, 73.1, 70.3, 68.2, 54.9, 35.4, 29.8, 26.0 (×3), 25.0, 18.1, 15.0, −3.9, −4.6; HRMS (ESI) calcd for $C_{18}H_{34}O_4SiNa$ [(M+Na)$^+$] 365.2124, found 365.2130.

4.1.26. β-Alkoxyacrylate 43. To a solution of 2-methyl-2-butene (4.5 mL, 42.5 mmol) in THF (21 mL) at 0 °C was added BH_3·SMe_2 (2.0 M in Me_2S, 21.0 mL, 42.0 mmol). The resulting solution was added to a solution of TBS ether **41** (2.84 g, 8.30 mmol) in THF (28 mL) at 0 °C. The reaction mixture was stirred at room temperature for 4 h. The solution was then cooled to 0 °C and treated with 10% aqueous NaOH (50 mL) followed by 30% H_2O_2 (39 mL). The resulting mixture was stirred at room temperature for 17 h before it was diluted with EtOAc. The organic layer was separated, washed with saturated aqueous Na_2SO_3 and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (40% EtOAc/hexanes) afforded alcohol (2.94 g, 98%) as a colorless oil.

To a solution of the alcohol in CH_2Cl_2/DMSO (1:1, v/v, 54 mL) at 0 °C were added Et_3N (5.58 mL, 40.0 mmol)

and SO_3·pyridine (5.12 g, 32.2 mmol). The resulting mixture was stirred at 0 °C for 3 h before water was added. The solution was diluted with Et_2O, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude aldehyde, which was used directly in the subsequent reaction without purification.

To a solution of the aldehyde in THF (80 mL) at 0 °C was added methylmagnesium bromide (3.0 M in Et_2O, 11.0 mL, 33.0 mmol). The resulting mixture was stirred at room temperature for 1 h before it was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (30–50% EtOAc/hexanes) afforded alcohol (2.69 g, 88% for the two steps) as a colorless oil.

To a suspension of the alcohol (6.58 g, 17.6 mmol) and 4 Å molecular sieves in CH_2Cl_2 (76 mL) at 0 °C were added NMO (5.10 g, 43.5 mmol) and TPAP (0.54 g, 1.54 mmol). The resulting mixture was allowed to warm to room temperature over 5 h before it was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (20% EtOAc/hexanes) to afford methyl ketone **42** (6.03 g, 92%) as a colorless oil.

To a solution of methyl ketone **42** (6.03 g, 16.2 mmol) in THF (81 mL) at 0 °C was added TBAF (1.0 M in THF, 32.4 mL, 32.4 mmol). The resulting solution was stirred at room temperature for 7 h before it was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (50% EtOAc/hexanes) to afford alcohol (4.16 g, 99%) as a colorless oil.

To a solution of the alcohol (1.37 g, 5.31 mmol) in CH_2Cl_2 (27 mL) at 0 °C were added 4-methylmorpholine (0.87 mL, 7.91 mmol) and ethyl propiolate (1.63 mL, 16.1 mmol). The resulting solution was stirred at room temperature for 4.5 h before it was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (30% EtOAc/hexanes) to afford β-alkoxyacrylate **43** (1.96 g), which was used directly in the subsequent reaction: $[\alpha]_D^{32}$ +60.3 (*c* 0.81, $CHCl_3$); IR (film) 2946, 2898, 1707, 1643, 1624, 1384, 1322, 1198, 1125, 1084, 1051, 1020, 845 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J*=12.0 Hz, 1H), 5.31 (d, *J*=12.0 Hz, 1H), 4.61 (d, *J*=3.0 Hz, 1H), 4.20 (dd, *J*=11.5, 4.5 Hz, 1H), 4.14 (ddd, *J*=7.5, 7.5, 7.5 Hz, 2H), 3.39–3.33 (m, 4H), 3.25 (ddd, *J*=10.0, 10.0, 5.0 Hz, 1H), 2.65 (d, *J*=12.5 Hz, 1H), 2.43 (d, *J*=12.5 Hz, 1H), 2.17–2.11 (m, 4H), 1.84 (m, 1H), 1.76–1.62 (m, 4H), 1.28 (s, 3H), 1.25 (d, *J*=6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.8, 167.6, 161.3, 98.8, 97.7, 79.8, 76.0, 70.4, 67.2, 59.9, 54.7, 51.3, 33.5, 30.5, 30.9, 24.4, 17.0, 14.3; HRMS (ESI) calcd for $C_{18}H_{28}O_7Na$ [(M+Na)$^+$] 379.1733, found 379.1759.

4.1.27. Ester 44. To a solution of the above β-alkoxyacrylate **43** (1.96 g) in THF (53 mL) at 0 °C were added MeOH (0.12 mL) and SmI_2 (0.1 M in THF, 160 mL, 16.0 mmol). The resulting mixture was stirred at 0 °C for 1 h and then at room temperature for 1 h. The reaction mixture was quenched with 50% aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (80% EtOAc/hexanes) afforded ester **44** (1.58 g, 83% for the two steps) as a colorless oil: $[\alpha]_D^{30}$ +45.4 (*c* 0.55, C_6H_6); IR (film) 3454, 2947, 2891, 1736, 1383, 1303, 1194, 1111, 1051, 1045, 924, 859, 620 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.61 (d, *J*=3.0 Hz, 1H), 4.20–4.11 (m, 2H), 3.76 (dd, *J*=9.0, 3.5 Hz, 1H), 3.70 (m, 1H), 3.41 (m, 1H), 3.32 (s, 3H), 3.23 (dd, *J*=12.5, 3.5 Hz, 1H), 2.66 (dd, *J*=14.5, 4.0 Hz, 1H), 2.43 (dd, *J*=15.5, 9.0 Hz, 1H), 2.07 (d, *J*=12.5 Hz, 1H), 1.98 (ddd, *J*=12.0, 4.0, 4.0 Hz, 1H), 1.85 (m, 1H), 1.73–1.68 (m, 6H), 1.28 (s, 3H) 1.27 (s, 3H), 1.25 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 97.8, 84.0, 81.1, 73.0, 70.3, 69.9, 69.1, 60.8, 54.5, 54.4, 34.9, 30.2, 29.8, 25.0, 24.0, 15.9, 14.2; HRMS (ESI) calcd for $C_{18}H_{30}O_7Na$ [(M+Na)$^+$] 381.1889, found 381.1857.

4.1.28. Diol 46. To a solution of ester **44** (1.56 g, 4.36 mmol) in CH_2Cl_2 (50 mL) at 0 °C were added 2,6-lutidine (1.20 mL, 10.3 mmol) and TMSOTf (1.18 mL, 6.52 mmol). The resulting mixture was stirred at 0 °C for 1 h before it was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (30% EtOAc/hexanes) afforded TMS ether (1.75 g, 93%) as a colorless oil.

To a solution of the TMS ether (1.75 g, 4.07 mmol) in toluene (40 mL) at −78 °C was added DIBALH (1.01 M in toluene, 4.74 mL, 4.79 mmol). The resulting mixture was stirred at −78 °C for 10 min before it was quenched with saturated aqueous potassium sodium tartrate. The mixture was diluted with EtOAc and vigorously stirred until the layers became clear. The organic layer was separated, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude aldehyde, which was used directly in the subsequent reaction.

To a solution of Ph_3PCH_3Br (6.08 g, 17.0 mmol) in THF (6.75 mL) at 0 °C was added NaHMDS (1.0 M in THF, 15.8 mL, 15.8 mmol). The resulting ylide solution was stirred at 0 °C for 30 min. A solution of the crude aldehyde in THF (6.75 mL) was added, and the reaction mixture was stirred at room temperature for 1 h before it was quenched with saturated aqueous NH_4Cl. The mixture was diluted with Et_2O, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (30% EtOAc/hexanes) afforded olefin **45** (1.45 g, 93% for the two steps) as a colorless oil.

To a solution of olefin **45** (166 mg, 0.432 mmol) in MeCN (4.8 mL) at 0 °C were added 1,3-propanedithiol (53.0 μL, 0.53 mmol) and TMSOTf (86.8 μL, 0.48 mmol). The resulting mixture was stirred at 0 °C for 10 min before it was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (80% EtOAc/hexanes) afforded diol **46** (154 mg, 92%) as a

colorless oil: $[\alpha]_D^{30}$ −23.2 (*c* 2.25, C_6H_6); IR (film) 3398, 2947, 1641, 1423, 1384, 1088, 1035, 910, 754, 665 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.90 (m, 1H), 5.11 (dd, *J*=17.0, 1.5 Hz, 1H), 5.05 (d, *J*=10.0 Hz, 1H), 4.02 (dd, *J*=7.0, 7.0 Hz, 1H), 3.36 (d, *J*=5.5 Hz, 2H), 3.25 (dd, *J*=10.0, 4.0 Hz, 1H), 3.04 (dd, *J*=13.0, 3.5 Hz, 1H), 2.87–2.79 (m, 4H), 2.39 (ddd, *J*=11.0, 7.0, 3.5 Hz, 1H), 2.20–2.06 (m, 4H), 2.04–1.93 (m, 3H), 1.89–1.81 (m, 1H), 1.79–1.73 (m, 1H), 1.63–1.51 (m, 4H), 1.28 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.9, 116.6, 87.0, 80.0, 73.1, 71.8, 71.1, 70.9, 54.2, 47.6, 33.6, 33.5, 31.2, 30.3 (×2), 29.4, 26.0, 24.1, 15.7; HRMS (ESI) calcd for $C_{19}H_{32}O_4S_2Na$ [(M+Na)$^+$] 411.1640, found 411.1651.

4.1.29. Aldehyde 47. To a solution of diol **46** (4.09 g, 10.5 mmol) in CH_2Cl_2 (105 mL) at 0 °C were added 4-methylmorpholine (1.94 mL, 17.6 mmol) and ethyl propiolate (1.82 mL, 18.0 mmol). The resulting mixture was stirred at room temperature for 13 h before it was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (30–50% EtOAc/hexanes) to afford β-alkoxyacrylate (4.80 g, 94%).

To a solution of the β-alkoxyacrylate (4.80 g, 9.88 mmol) in CH_2Cl_2 (99 mL) at 0 °C were added 2,6-lutidine (5.45 mL, 46.8 mmol) and TBSOTf (6.88 mL, 30.0 mmol). The resulting mixture was stirred at 0 °C for 14 h before saturated aqueous NH_4Cl was added. The mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (10% EtOAc/hexanes) afforded TBS ether (5.72 g, 97%) as a colorless oil.

To a solution of the TBS ether (5.72 g, 9.53 mmol) in MeCN/H_2O (1:1, v/v, 98 mL) were added $NaHCO_3$ (16.4 g, 0.20 mol) and methyl iodide (12.3 mL, 0.20 mol). The resulting mixture was stirred at room temperature for 19 h before it was diluted with EtOAc. The mixture was washed with saturated aqueous $Na_2S_2O_3$ and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (25% EtOAc/hexanes) afforded aldehyde **47** (4.76 g, 98%) as a pale yellow oil: $[\alpha]_D^{32}$ +64.6 (*c* 0.62, $CHCl_3$); IR (film) 2953, 2892, 1740, 1623, 1382, 1303, 1253, 1114, 1058, 1028, 840, 757, 670 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 9.27 (s, 1H), 7.53 (d, *J*=13.0 Hz, 1H), 6.15 (m, 1H), 5.56 (d, *J*=12.5 Hz, 1H), 5.23 (d, *J*=12.5 Hz, 1H), 5.15 (d, *J*=10.0 Hz, 1H), 4.12 (dd, *J*=14.0, 7.0 Hz, 2H), 3.33–3.28 (m, 2H), 3.02 (ddd, *J*=10.0, 10.0, 5.5 Hz, 1H), 2.69 (dd, *J*=12.5, 3.5 Hz, 1H), 2.47 (dd, *J*=14.0, 8.0 Hz, 1H), 2.14 (ddd, *J*=15.5, 10.5, 6.5 Hz, 1H), 2.03–1.87 (m, 3H), 1.81–1.73 (m, 2H), 1.44–1.29 (m, 3H), 1.10 (s, 3H), 1.04 (d, *J*=7.5 Hz, 3H), 0.93–0.90 (m, 12H), 0.07 (s, 3H) 0.04 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 200.0, 199.1, 160.1, 136.9, 116.4, 99.3, 88.3, 81.1, 79.3, 73.7, 72.1, 69.9, 59.8, 54.7, 39.8, 33.8, 30.7, 25.9 (×3), 25.2, 24.9, 18.2, 15.6, 14.5, −1.8, −1.9; HRMS (ESI) calcd for $C_{27}H_{46}O_7SiNa$ [(M+Na)$^+$] 533.2911, found 533.2919.

4.1.30. BCD-ring fragment 36. To a solution of aldehyde **47** (4.49 g, 8.80 mmol) in THF (88 mL) were added MeOH (0.25 mL) and SmI_2 (0.1 M in THF, 264 mL, 26.4 mmol). The resulting mixture was stirred at room temperature for 1 h before it was quenched with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (25% EtOAc/hexanes) afforded lactone **48** (3.52 g), which was used directly in the subsequent reaction.

To a solution of lactone **48** (3.52 g) in THF (88 mL) at 0 °C were added $LiAlH_4$ (0.41 g, 10.8 mmol). The resulting mixture was stirred at 0 °C for 1 h before it was quenched with saturated aqueous potassium sodium tartrate. The mixture was diluted with EtOAc and vigorously stirred until the layers became clear. The organic layer was separated, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (80% EtOAc/hexanes) afforded diol (3.70 g, 89% for the two steps) as a colorless oil.

To a solution of the diol (0.39 g, 0.83 mmol) in DMF (8.30 mL) at 0 °C was added NaH (50% in oil, 0.16 g, 3.33 mmol). The resulting solution was stirred at 0 °C for 1 h before 2-naphthylmethyl bromide (0.55 g, 2.48 mmol) and Bu_4NI (91.5 mg, 0.25 mmol) were added. The reaction mixture was stirred at room temperature for 12 h before it was quenched with saturated aqueous NH_4Cl. The mixture was diluted with Et_2O, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (30% EtOAc/hexanes) afforded bis-naphthylmethyl ether (0.60 g, 96%) as a colorless oil.

To a solution of the bis-naphthylmethyl ether (0.60 g, 0.81 mmol) in THF (4.1 mL) at 0 °C was added 9-BBN-H (0.5 M in THF, 3.30 mL, 1.65 mmol). The resulting solution was stirred at room temperature for 2 h. The mixture was cooled to 0 °C and treated with 10% aqueous NaOH (2.5 mL) followed by 30% H_2O_2 (1.7 mL). The reaction mixture was stirred at room temperature for 12 h before it was diluted with EtOAc. The mixture was washed with saturated aqueous Na_2SO_3 and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (30% EtOAc/hexanes) afforded alcohol (0.62 g), which was used directly in the subsequent reaction.

To a solution of the alcohol in CH_2Cl_2/DMSO (1:1, v/v, 8.1 mL) at 0 °C were added Et_3N (0.56 mL, 4.02 mmol) and SO_3·pyridine (0.52 g, 3.27 mmol). The resulting mixture was stirred at room temperature for 45 min before water was added. The mixture was diluted with Et_2O, washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude aldehyde, which was used directly in the subsequent reaction.

To a solution of the aldehyde in *t*-BuOH/water (4:1, v/v, 8 mL) at 0 °C were added 2-methyl-2-butene (0.39 mL, 3.68 mmol), KH_2PO_4 (0.11 g, 0.81 mmol), and $NaClO_2$ (0.26 g, 2.87 mmol). The resulting mixture was stirred at room temperature for 2 h before it was diluted with $CHCl_3$. The organic layer was separated, washed with 1 M aqueous HCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on

silica gel (10% MeOH/$CHCl_3$) afforded BCD-ring fragment **36** (0.55 g, 88% for the three steps) as a colorless oil: $[\alpha]_D^{29}$ −2.0 (*c* 4.47, $CHCl_3$); IR (film) 3374, 3055, 2929, 2856, 1710, 1383, 1252, 1149, 836, 774 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.81–7.74 (m, 8H), 7.46–7.43 (m, 6H), 4.70 (d, *J*=12.5 Hz, 1H), 4.64 (d, *J*=11.5 Hz, 1H), 4.60 (d, *J*=12.0 Hz, 1H), 4.51 (d, *J*=11.5 Hz, 1H), 3.82 (ddd, *J*=8.5, 7.5, 3.5 Hz, 1H), 3.82–3.54 (m, 3H), 3.42–3.31 (m, 2H), 3.12 (d, *J*=9.5 Hz, 1H), 3.00 (dd, *J*=13.0, 3.5 Hz, 1H), 2.59–2.54 (m, 1H), 2.43–2.36 (m, 2H), 2.06–1.95 (m, 3H), 1.89–1.77 (m, 3H), 1.73–1.47 (m, 4H), 1.38–1.23 (m, 5H), 1.20 (s, 3H), 0.82 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.4, 136.0, 135.9, 133.24, 133.21, 132.9 (×2), 128.1 (×2), 127.84, 127.83, 127.68, 127.67, 126.2 (×2), 126.09, 126.05, 125.82, 125.78, 125.73, 125.71, 87.0, 81.6, 81.2, 80.2, 79.8, 73.7, 73.3, 71.9, 70.6, 67.2, 54.4, 41.9, 35.3, 32.0, 31.4, 26.6, 25.7 (×3), 24.7, 23.7, 23.4, 17.9, 16.0, −1.9, −2.0; HRMS (ESI) calcd for $C_{47}H_{62}O_8SiNa$ [(M+Na)$^+$] 805.4112, found 805.4114.

4.1.31. α,β-Unsaturated ester 53. To a solution of alcohol **51** (9.78 g, 35.4 mmol) in DMF (118 mL) at 0 °C was added NaH (50% in oil, 2.85 g, 59.4 mmol). The resulting mixture was stirred at 0 °C for 1 h before benzyl bromide (8.65 mL, 72.7 mmol) and Bu_4NI (1.31 g, 3.55 mmol) were added. The mixture was stirred at room temperature for 16 h before it was quenched with saturated aqueous NH_4Cl. The mixture was diluted with Et_2O, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (30% EtOAc/hexanes) afforded benzyl ether **52** (13.0 g, quant.) as a colorless oil.

To a solution of the benzyl ether **52** (1.98 g, 5.41 mmol) in THF/H_2O (1:1, v/v, 21 mL) were added NMO (50 wt % in water, 3.84 mL, 16.4 mmol) and OsO_4 (0.039 M in *t*-BuOH, 8.03 mL, 0.31 mmol). The resulting mixture was stirred at room temperature for 11 h before it was diluted with EtOAc. The organic layer was separated, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude diol.

To a solution of the crude diol in THF/H_2O (1:1, v/v, 21 mL) was added $NaIO_4$ (3.49 g, 16.3 mmol). The resulting mixture was stirred at room temperature for 1 h before it was diluted with EtOAc. The mixture was washed with H_2O, saturated aqueous Na_2SO_3 and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was filtered through a plug of silica gel (50% EtOAc/hexanes) to give the crude aldehyde, which was used directly in the subsequent reaction.

To a solution the aldehyde in THF (18.2 mL) was added $Ph_3P{=}CHCO_2Me$ (1.91 g, 5.71 mmol). The resulting mixture was stirred at room temperature for 26 h before it was diluted with Et_2O. The mixture was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (30% EtOAc/hexanes) afforded α,β-unsaturated ester **53** (1.83 g, 80% for the three steps) as a colorless oil: $[\alpha]_D^{31}$ −65.9 (*c* 0.28, $CHCl_3$); IR (film) 2950, 2865, 1723, 1384, 1306, 1278, 1108, 747, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.48–7.46 (m, 2H), 7.39–7.27 (m, 8H), 7.10 (dd, *J*=15.5, 4.5 Hz, 1H), 6.11 (dd, *J*=11.5, 1.5 Hz, 1H), 5.54 (s, 1H), 4.61 (d, *J*=11.0 Hz, 1H), 4.48 (d, *J*=12.0 Hz, 1H), 4.25 (ddd, *J*=9.5, 4.0, 1.0 Hz, 1H), 3.97 (d, *J*=10.0 Hz, 1H), 3.75 (s, 3H), 3.65 (d, *J*=10.5 Hz, 1H), 3.56 (dd, *J*=13.0, 4.0 Hz, 1H), 3.32 (ddd, *J*=10.0, 5.5, 5.5 Hz, 1H), 2.40 (ddd, *J*=12.5, 4.5, 4.5 Hz, 1H), 1.85 (ddd, *J*=12.0, 12.0, 12.0 Hz, 1H), 1.51 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 145.2, 137.4, 137.3, 129.2, 128.5 (×2), 128.4 (×2), 128.0, 127.9 (×2), 126.2 (×2), 121.3, 102.8, 78.4, 76.8, 76.2, 71.9, 71.4, 69.2, 51.6, 36.5, 14.6; HRMS (ESI) calcd for $C_{25}H_{28}O_6Na$ [(M+Na)$^+$] 447.1784, found 447.1787.

4.1.32. Ester 54. To a solution of α,β-unsaturated ester **53** (1.23 g, 2.90 mmol), bis(*N*-isopropylsalicylaldimine) copper(II) complex **17** (11.0 mg, 28.4 μmol), and TMSCl (1.14 mL, 8.98 mmol) in THF (15 mL) at −45 °C was added methylmagnesium bromide (3.0 M in Et_2O, 1.51 mL, 4.53 mmol). The resulting solution was stirred at −45 °C for 3 h before it was quenched with 1 M aqueous HCl. The mixture was diluted with Et_2O, washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (20% EtOAc/hexanes) afforded ester **54** (1.23 g, 96%) as a colorless oil: $[\alpha]_D^{31}$ −114.5 (*c* 0.14, $CHCl_3$); IR (film) 2951, 2867, 1725, 1384, 1107, 1007, 747, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J*=7.5 Hz, 2H), 7.33 (d, *J*=7.5 Hz, 2H) 7.22–7.19 (m, 4H), 7.15–7.09 (m, 2H), 5.37 (s, 1H), 4.46 (d, *J*=12.5 Hz, 1H), 4.25 (d, *J*=11.5 Hz, 1H), 3.81 (d, *J*=10.0 Hz, 1H), 3.52 (dd, *J*=10.0, 2.0 Hz, 1H), 3.39–3.35 (m, 4H), 3.23 (ddd, *J*=10.0, 5.0, 5.0 Hz, 1H), 3.07 (dd, *J*=12.0, 3.5 Hz, 1H), 2.79 (m, 1H), 2.41 (dd, *J*=16.0, 4.0 Hz, 1H), 2.26–2.20 (m, 2H), 1.66 (m, 1H), 1.34 (s, 3H), 1.12 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 136.7, 136.6, 127.0, 126.7 (×2), 126.5, 126.31 (×2), 126.26 (×2), 124.8 (×2), 100.6, 76.9, 74.6, 74.5, 71.5, 68.2, 66.8, 49.0, 33.5, 28.9, 28.3, 16.1, 12.7; HRMS (ESI) calcd for $C_{26}H_{32}O_6Na$ [(M+Na)$^+$] 463.2097, found 463.1761.

4.1.33. Diol 55. To a solution of ester **54** (1.23 g, 2.80 mmol) in CH_2Cl_2 (7.3 mL) at −78 °C was added DIBALH (0.95 M in hexane, 9.19 mL, 8.73 mmol). The resulting mixture was stirred at −78 °C for 1 h before being quenched with saturated aqueous potassium sodium tartrate. The mixture was vigorously stirred until the layers became clear. The organic layer was separated, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (20% EtOAc/hexanes) afforded alcohol (1.16 g, quant.) as a colorless oil.

To a solution of the alcohol (4.33 g, 10.5 mmol) in DMF (35 mL) at 0 °C was added NaH (50% in oil, 0.76 g, 15.8 mmol). The resulting solution was stirred at 0 °C for 1.5 h before benzyl bromide (2.29 mL, 19.3 mmol) and Bu_4NI (0.19 g, 0.51 mmol) were added. The reaction mixture was stirred at room temperature for 15 h before it was quenched with saturated aqueous NH_4Cl. The mixture was diluted with Et_2O, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was filtered through a plug of silica gel (20%

EtOAc/hexanes) to give bis-benzyl ether, which was used directly in the subsequent reaction.

To a solution of the bis-benzyl ether in MeOH (35 mL) at 0 °C was added *p*-TsOH·H_2O (1.99 g, 10.5 mmol). The resulting mixture was stirred at 40–70 °C for 3 h. The reaction mixture was cooled to room temperature and quenched with Et_3N. The mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (80% EtOAc/hexanes) to afford diol **55** (3.95 g, 91% for the two steps) as a colorless oil: $[\alpha]_D^{30}$ −58.0 (*c* 0.10, $CHCl_3$); IR (film) 3417, 2933, 2873, 1455, 1383, 1065, 735, 548 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31–7.20 (m, 10H), 4.56 (d, *J*=11.0 Hz, 1H), 4.47 (m, 3H), 3.73 (ddd, *J*=12.0, 5.0, 5.0 Hz, 1H), 3.51–3.45 (m, 2H), 3.41 (dd, *J*=11.0, 3.5 Hz, 1H), 3.36 (dd, *J*=7.5, 7.5 Hz, 1H), 3.31–3.30 (m, 2H), 2.31 (ddd, *J*=8.0, 4.0, 4.0 Hz, 1H), 2.28 (d, *J*=5.0 Hz, 1H), 2.09–2.06 (m, 2H), 1.70 (m, 1H), 1.54 (m, 1H), 1.33 (m, 1H), 1.06 (s, 3H), 0.91 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 138.0, 128.4 (×2), 128.3 (×2), 127.9 (×2), 127.8, 127.6 (×2), 127.5, 76.8, 75.9, 73.2, 73.0, 70.8, 68.9, 68.3, 67.1, 33.8, 29.8, 29.6, 17.2, 12.9; HRMS (ESI) calcd for $C_{25}H_{34}O_5Na$ [$(M+Na)^+$] 437.2304, found 437.2311.

4.1.34. Aldehyde 49. To a solution of diol **55** (3.93 g, 9.49 mmol) in CH_2Cl_2 (32 mL) at 0 °C were added 2,6-lutidine (2.34 mL, 20.1 mmol) and TBSOTf (3.92 mL, 17.1 mmol). The resulting solution was stirred at room temperature for 1.5 h before it was concentrated under reduced pressure. The residue was filtered through a plug of silica gel (50% EtOAc/hexanes) to give bis-TBS ether, which was used directly in the subsequent reaction.

To a solution of the bis-TBS ether in CH_2Cl_2/MeOH (1:1, v/v, 47 mL) at 0 °C was added CSA (1.09 g, 4.69 mmol). The resulting solution was stirred at 0 °C for 2 h before it was quenched with Et_3N. The mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (80% EtOAc/hexanes) to afford primary alcohol (4.77 g, 95% for the two steps) as a colorless oil.

To a solution of the alcohol (0.16 g, 0.30 mmol) in CH_2Cl_2/DMSO (3:5, v/v, 0.74 mL) at 0 °C were added Et_3N (0.19 mL, 1.36 mmol) and SO_3·pyridine (0.18 g, 1.13 mmol). The resulting mixture was stirred at room temperature for 2.5 h before it was quenched with water. The mixture was diluted with Et_2O, washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (80% EtOAc/hexanes) afforded aldehyde **49** (0.15 g, 94%) as a colorless oil: $[\alpha]_D^{32}$ −64.1 (*c* 0.13, $CHCl_3$); IR (film) 2928, 2856, 1754, 1384, 777, 736, 698 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 9.33 (s, 1H), 7.32–7.28 (m, 4H), 7.18–7.08 (m, 6H), 4.44 (d, *J*=12.0 Hz, 1H), 4.39–4.31 (m, 3H), 3.65 (dd, *J*=11.0, 4.5 Hz, 1H), 3.49–3.45 (m, 1H), 3.41–3.36 (m, 2H), 3.30 (ddd, *J*=11.0, 4.5, 4.5 Hz, 1H), 2.39 (m, 1H), 2.20 (ddd, *J*=12.0, 5.0, 5.0 Hz, 1H), 1.95 (m, 1H), 1.65–1.52 (m, 2H), 1.26 (s, 3H), 1.01 (d, *J*=7.5 Hz, 3H), 0.92 (s, 9H), −0.00 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 197.4, 137.4, 136.9, 126.6, 126.5 (×3), 126.1 (×2), 125.9, 125.7 (×2), 125.6, 78.8, 75.3, 71.1, 70.7, 69.0, 66.9, 64.6, 33.3, 28.3, 27.7, 23.8 (×3), 16.0, 15.2, 8.8, −4.2, −4.9; HRMS (ESI) calcd for $C_{31}H_{46}O_5SiNa$ [$(M+Na)^+$] 549.3012, found 549.3020.

4.1.35. *p*-Methoxybenzyl ether 57. To a solution of alcohol **56** (2.00 g, 7.25 mmol) in DMF (24 mL) at 0 °C was added NaH (50% in oil, 0.97 g, 20.2 mmol). The resulting solution was stirred at 0 °C for 1 h before *p*-methoxybenzyl chloride (2.95 mL, 21.8 mmol) and Bu_4NI (0.54 g, 1.46 mmol) were added. The reaction mixture was stirred at room temperature for 15.5 h before being quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with Et_2O, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was filtered through a plug of silica gel (20% EtOAc/hexanes) to give *p*-methoxybenzyl ether, which was used directly in the subsequent reaction.

To a solution of the *p*-methoxybenzyl ether in MeOH (36 mL) at 0 °C was added CSA (0.17 g, 0.73 mmol). The resulting mixture was stirred at room temperature for 0.5 h before it was quenched with Et_3N. The mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (100% EtOAc) to afford diol (1.91 g, 86% for the two steps) as a colorless oil.

To a solution of the diol (1.91 g, 6.20 mmol) in DMF (20 mL) at 0 °C was added NaH (50% in oil, 1.20 g, 25.0 mmol). The resulting solution was stirred at 0 °C for 1 h before benzyl bromide (3.79 mL, 31.9 mmol) and Bu_4NI (0.69 g, 1.87 mmol) were added. The reaction mixture was stirred at room temperature for 16 h before it was quenched with saturated aqueous NH_4Cl. The mixture was diluted with Et_2O, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (20% EtOAc/hexanes) afforded *p*-methoxybenzyl ether **57** (2.85 g, 94%) as a colorless oil: $[\alpha]_D^{32}$ +24.9 (*c* 0.33, $CHCl_3$); IR (film) 2938, 2869, 1513, 1352, 1248, 1074, 736, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.19 (m, 12H), 6.85 (d, *J*=9.0 Hz, 2H), 6.02 (dd, *J*=17.5, 10.5 Hz, 1H), 5.34 (dd, *J*=17.5, 1.0 Hz, 1H), 5.08 (dd, *J*=11.0, 1.5 Hz, 1H), 4.62 (d, *J*=13.0 Hz, 1H), 4.57–4.54 (m, 2H), 4.48 (d, *J*=11.5 Hz, 1H), 4.41–4.37 (m, 2H), 3.79 (s, 3H), 3.69–3.68 (m, 2H), 3.65–3.62 (m, 1H) 3.43 (ddd, *J*=11.5, 5.0 Hz, 1H), 3.25 (dd, *J*=11.5, 4.5 Hz, 1H), 2.41 (ddd, *J*=12.0, 4.5, 4.5 Hz, 1H), 1.57 (m, 1H), 1.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.0 (×2), 138.7, 138.2, 129.1 (×2), 128.4 (×2), 128.3 (×2), 127.8 (×2), 127.69 (×2), 127.67, 127.4, 113.7 (×2), 113.1, 109.7, 78.3, 76.1, 73.4, 73.1, 72.8, 71.4, 71.1, 69.7, 55.3, 31.1, 15.2; HRMS (ESI) calcd for $C_{31}H_{36}O_5Na$ [$(M+Na)^+$] 511.2460, found 511.2448.

4.1.36. Alkyne 50. To a solution of *p*-methoxybenzyl ether **57** (2.85 g, 5.84 mmol) in THF (12 mL) at 0 °C was added 9-BBN-H (0.5 M in THF, 46.7 mL, 23.4 mmol). The resulting solution was stirred at room temperature for 2 h. The mixture was cooled to 0 °C and treated with 10% aqueous NaOH (18.0 mL) followed by 30% H_2O_2 (12.0 mL). The reaction mixture was stirred at room temperature for 18 h before it was diluted with EtOAc. The mixture was washed with saturated aqueous Na_2SO_3 and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure.

Purification by column chromatography on silica gel (40% EtOAc/hexanes) afforded primary alcohol (2.1 g, 71%) as a colorless oil.

To a suspension of the primary alcohol (2.70 g, 5.33 mmol) and 4 Å molecular sieves in CH_2Cl_2 (26 mL) were added NMO (1.25 g, 10.7 mmol) and TPAP (150 mg, 0.427 mmol). The resulting mixture was stirred at 0 °C for 5 min and then at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (30% EtOAc/hexanes) to afford aldehyde **58** (2.06 g, 77%) as a colorless oil.

To a solution of aldehyde **58** (0.83 g, 1.65 mmol) in *i*-PrOH (20 mL) at 0 °C were added dimethyl (1-diazo-2-oxopropyl)phosphonate (0.66 g, 3.44 mmol) and Cs_2CO_3 (1.53 g, 4.70 mmol). The resulting mixture was stirred at room temperature for 20 h before it was quenched with saturated aqueous NH_4Cl. The mixture was diluted with Et_2O, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (30% EtOAc/hexanes) afforded alkyne **50** (0.76 g, 92%) as a colorless oil: $[\alpha]_D^{30}$ +8.9 (*c* 3.57, C_6H_6); IR (film) 3290, 2939, 2870, 1612, 1513, 1249, 1085, 737, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25–7.11 (m, 12H), 6.76 (d, *J*=8.0 Hz, 2H), 4.58 (d, *J*=12.5 Hz, 1H), 4.48 (d, *J*=12.5 Hz, 1H), 4.47 (d, *J*=11.0 Hz, 1H), 4.45 (d, *J*=11.5 Hz, 1H), 4.33 (d, *J*=11.5 Hz, 1H), 4.30 (d, *J*=11.0 Hz, 1H), 3.69 (s, 3H), 3.62–3.58 (m, 2H), 3.52–3.47 (m, 1H), 3.40 (dd, *J*=12.0, 4.5 Hz, 1H), 3.34 (ddd, *J*=11.5, 11.5, 5.0 Hz, 1H), 2.43 (dd, *J*=17.0, 2.5 Hz, 1H), 2.38–2.33 (m, 2H), 1.85 (dd, *J*=2.5, 2.5 Hz, 1H), 1.43 (ddd, *J*=11.5, 11.5, 11.5 Hz, 1H), 1.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 138.9, 138.2, 130.4, 129.2 (×2), 128.4 (×2), 128.2 (×2), 127.71 (×2), 127.65, 127.62 (×2), 127.3, 113.7 (×2), 81.0, 76.2, 75.5, 73.8, 73.3, 72.8, 71.2, 70.9, 70.3, 69.4, 55.2, 30.5, 30.4, 15.6; HRMS (ESI) calcd for $C_{32}H_{36}O_5Na$ [(M+Na)$^+$] 523.2460, found 523.2467.

4.1.37. Propargyl ketone 61. To a solution of alkyne **50** (8.89 g, 17.8 mmol) and HMPA (5.6 mL) in THF (42.1 mL) was added *t*-BuLi (1.56 M in pentane, 10.3 mL, 16.1 mmol) at −78 °C. The resulting mixture was stirred at −78 °C for 20 min before a solution of aldehyde **49** (4.43 g, 8.42 mmol) in THF (34 mL) at −78 °C was added. The reaction mixture was stirred at −78 °C for 1.5 h before being quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (20% EtOAc/hexanes) afforded propargyl alcohol **60** (8.23 g, 95%) as a colorless oil.

To a solution of CH_2Cl_2/DMSO (1:2, v/v, 80 mL) at −78 °C was added dropwise $(COCl)_2$ (2.08 mL, 24.6 mmol). After the resulting mixture was stirred at −78 °C for 15 min, a solution of alcohol **60** (8.23 g, 8.02 mmol) in CH_2Cl_2 (13.4 mL) was added. The reaction mixture was stirred at −78 °C for 30 min before Et_3N (1.1 mL, 7.9 mmol) was added. The resulting mixture was allowed to warm to room temperature over 3 h before it was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (20% EtOAc/hexanes) afforded propargyl ketone **61** (7.63 g, 93%) as a colorless oil: $[\alpha]_D^{20}$ −20.8 (*c* 1.44, $CHCl_3$); IR (film) 2929, 1681, 1513, 1454, 1250, 1091, 837, 736, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J*=7.5 Hz, 2H), 7.31–7.08 (m, 20H), 6.82 (d, *J*=9.0 Hz, 2H), 4.62 (d, *J*=13.0 Hz, 1H), 4.54 (d, *J*=12.0 Hz, 1H), 4.48–4.45 (m, 2H), 4.40–4.30 (m, 6H), 4.23 (d, *J*=11.5 Hz, 1H), 3.80–3.74 (m, 2H), 3.67 (m, 1H), 3.50–3.41 (m, 7H), 3.32 (s, 3H), 2.68 (d, *J*=17.0 Hz, 1H), 2.60 (d, *J*=17.5 Hz, 1H), 2.47–2.32 (m, 3H), 2.08 (m, 1H), 1.75–1.70 (m, 2H), 1.52 (s, 3H), 1.27 (s, 3H), 1.09 (d, *J*=7.0 Hz, 3H), 0.97 (s, 9H), 0.20 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.9, 159.8, 157.2, 139.5, 139.3, 139.14 (×2), 139.08 (×2), 130.8, 129.4 (×2), 128.6 (×4), 128.3 (×3), 127.99 (×2), 127.97 (×2), 127.80 (×2), 127.77 (×2), 127.70 (×2), 127.6, 127.5, 114.1 (×2), 93.0, 82.7, 82.0, 77.8, 77.0, 76.0, 74.4, 73.6, 73.2, 73.1, 72.9, 71.10, 71.06 (×2), 70.1, 69.2, 68.7, 54.8, 35.7, 31.4, 31.0, 30.6, 30.0, 26.0, 18.1, 17.5, 15.8, 12.3, −4.1, −4.6; HRMS (ESI) calcd for $C_{63}H_{80}O_{10}SiNa$ [(M+Na)$^+$] 1047.5418, found 1047.5491.

4.1.38. Vinylogous ester 62. To a solution of ketone **61** (7.58 g, 7.40 mmol) in MeOH/THF (10:1, v/v, 74 mL) was added NaOMe (4.00 g, 74.0 mmol). The resulting solution was stirred at room temperature for 11 h before it was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (20% EtOAc/hexanes) to afford vinylogous ester **62** (7.63 g, 98%) as a colorless oil: $[\alpha]_D^{32}$ −41.5 (*c* 0.08, $CHCl_3$); IR (film) 2926, 2855, 1584, 1512, 1453, 1383, 1247, 1094, 837, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J*=7.5 Hz, 2H), 7.35 (d, *J*=9.0 Hz, 2H), 7.30–7.07 (m, 18H), 6.88 (d, *J*=8.0 Hz, 2H), 6.22 (s, 1H), 4.69 (d, *J*=12.5 Hz, 1H), 4.58 (d, *J*=12.5 Hz, 1H), 4.51–4.42 (m, 4H), 4.38–4.27 (m, 5H), 3.97 (dd, *J*=11.5, 5.0 Hz, 1H), 3.82–3.76 (m, 4H), 3.55 (dd, *J*=10.0, 1.5 Hz, 1H), 3.50–3.38 (m, 3H), 3.34 (m, 4H), 3.26 (s, 3H), 2.68 (d, *J*=12.5 Hz, 1H), 2.48–2.39 (m, 3H), 2.29 (m, 1H), 2.03 (m, 1H), 1.77 (m, 1H), 1.63–1.56 (m, 4H), 1.54 (s, 3H), 1.05 (d, *J*=7.0 Hz, 3H), 1.00 (s, 9H), 0.15 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.8, 174.5, 159.5, 140.0, 139.43, 139.35, 139.1, 131.6, 129.3 (×2), 129.2 (×2), 128.5 (×5), 128.33, 128.26, 127.98, 127.97, 127.89, 127.77, 127.75, 127.65, 127.57, 127.56, 127.4 (×2), 113.9 (×4), 83.2, 78.3, 78.0, 77.7, 73.6, 73.3, 73.1 (×2), 71.0, 70.8, 70.1, 69.2, 54.82, 54.79, 54.75, 54.69, 42.8, 35.8, 31.2, 30.8, 30.1, 26.1 (×3), 18.2 (×2), 17.6, 16.4, 13.1, −4.3, −4.7; HRMS (ESI) calcd for $C_{64}H_{84}O_{11}SiNa$ [(M+Na)$^+$] 1079.5681, found 1079.5741.

4.1.39. Alcohol 65. To a solution of vinylogous ester **62** (0.23 g, 0.22 mmol) in pyridine/THF (1:4, v/v, 2.8 mL) at 0 °C was added HF/pyridine complex (70% solution, 1.10 mL). The resulting mixture was stirred at room temperature for 15 h before it was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with Et_2O, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (40% EtOAc/hexanes) afforded alcohol **63** (0.19 g, 93%) as a colorless oil.

To a solution of alcohol **63** (5.91 g, 6.27 mmol) in toluene (63 mL) was added pyridinium *p*-toluenesulfonate (1.58 g, 6.29 mmol). The resulting mixture was stirred at 100 °C for 3.5 h. The reaction mixture was cooled to room temperature and quenched with Et_3N. The mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (30% EtOAc/hexanes) to afford dihydropyranone **64** (4.95 g, 87%) as a colorless oil.

To a solution of dihydropyranone **64** (0.13 g, 0.14 mmol) in toluene (1.4 mL) at −78 °C was added DIBALH (1.01 M in toluene, 0.54 mL, 0.55 mmol). The resulting mixture was stirred at −78 °C for 2 h before it was quenched with saturated aqueous potassium sodium tartrate. The mixture was vigorously stirred until the layers became clear. The organic layer was separated, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (30% EtOAc/hexanes) afforded alcohol **65** (0.12 g, 92%) as a colorless oil: $[\alpha]_D^{32}$ −34.1 (*c* 1.47, $CHCl_3$); IR (film) 3425, 2940, 2872, 1612, 1512, 1454, 1248, 1092, 1029, 737, 698 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.44 (d, *J*=7.5 Hz, 1H), 7.33–7.07 (m, 21H), 6.82 (d, *J*=10.0 Hz, 2H), 4.76 (m, 1H), 4.65 (d, *J*=12.5 Hz, 1H), 4.55 (d, *J*=12.0 Hz, 1H), 4.50 (d, *J*=11.5 Hz, 1H), 4.45 (d, *J*=11.5 Hz, 1H), 4.40–4.30 (m, 5H), 4.23–4.21 (m, 2H), 3.83–3.71 (m, 2H), 3.55–3.46 (m, 3H), 3.41–3.29 (m, 6H), 3.17 (ddd, *J*=10.5, 10.5, 4.5 Hz, 1H), 2.51–2.44 (m, 2H), 2.36 (m, 1H), 2.29 (ddd, *J*=9.5, 4.0, 4.0 Hz, 1H), 1.89 (m, 1H), 1.76 (m, 1H), 1.63 (m, 1H), 1.56–1.51 (m, 2H), 1.39 (s, 3H), 1.35–1.27 (m, 2H), 1.24 (s, 3H), 1.05 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.7, 152.4, 139.7, 139.5, 139.3, 139.0, 131.2, 129.2 (×2), 128.57 (×2), 128.55 (×2), 128.53 (×4), 128.0 (×2), 127.82 (×2), 127.78 (×2), 127.71 (×4), 127.6 (×2), 114.1 (×2), 104.3, 77.9, 77.6, 76.2, 75.0, 74.0, 73.9, 73.8, 73.5, 73.1, 73.0, 72.8, 71.0, 70.7, 70.5, 70.3, 69.2, 54.8, 44.4, 30.9, 30.7, 30.4, 30.1, 17.4, 16.3, 9.6; HRMS (ESI) calcd for $C_{57}H_{68}O_{10}Na$ [(M+Na)$^+$] 935.4710, found 935.4751.

4.1.40. Diol 66. To a solution of alcohol **65** (4.46 g, 4.89 mmol) in THF (50 mL) at 0 °C was added $BH_3\cdot$THF (0.98 M in THF, 20.2 mL, 19.8 mmol). The resulting solution was stirred at 0 °C for 30 min and then at room temperature for 2.5 h. The reaction mixture was cooled to 0 °C and treated with 10% aqueous NaOH (31 mL) followed by 30% H_2O_2 (63 mL). The solution was stirred at room temperature for 3.5 h before it was diluted with EtOAc. The organic layer was separated, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (50% EtOAc/hexanes) afforded diol **66** (4.12 g, 91%) as a colorless oil: $[\alpha]_D^{30}$ −24.9 (*c* 0.49, C_6H_6); IR (film) 3435, 2873, 1612, 1513, 1454, 1248, 1070, 737, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.27 (m, 22H), 6.89 (d, *J*=8.5 Hz, 2H), 4.64–4.41 (m, 9H), 4.37 (d, *J*=11.5 Hz, 1H), 3.27 (d, *J*=3.0 Hz, 1H), 3.82–3.74 (m, 4H), 3.65–3.54 (m, 5H), 3.49–3.42 (m, 3H), 3.30–3.24 (m, 2H), 3.03 (ddd, *J*=8.0, 8.0, 4.0 Hz, 1H), 2.71 (m, 1H), 2.55 (m, 1H), 2.37 (m, 1H), 2.26 (m, 1H), 2.18–2.16 (m, 2H), 1.85–1.79 (m, 2H), 1.63 (m, 3H), 1.26 (s, 3H), 1.17 (m, 3H), 1.02 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 138.7, 138.1, 138.0, 137.9, 130.4, 129.6 (×2), 128.35 (×2), 128.33 (×2), 128.28 (×2), 128.24, 128.23 (×2), 127.90 (×2), 127.86 (×2), 127.70, 127.66 (×3), 127.5 (×2), 127.3, 113.6 (×2), 80.2, 77.2 (×2), 76.1, 75.9, 74.5, 74.2, 73.7, 73.6, 73.4, 72.8, 72.8, 72.0, 71.3, 70.7, 70.0, 69.0, 68.5, 55.3, 44.2, 30.08, 30.05, 30.02, 29.99, 17.7, 17.1, 9.8; HRMS (ESI) calcd for $C_{57}H_{70}O_{11}Na$ [(M+Na)$^+$] 953.4816, found 953.4787.

4.1.41. Bis-TES ether 67. To a solution of diol **66** (4.12 g, 4.43 mmol) in CH_2Cl_2 (44 mL) at 0 °C were added 2,6-lutidine (1.55 mL, 13.3 mmol) and TESOTf (2.96 mL, 13.1 mmol). The resulting mixture was stirred at room temperature for 1.5 h before it was diluted with EtOAc. The mixture was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (20–50% EtOAc/hexanes) afforded bis-TES ether **67** (5.13 g, quant.) as a colorless oil: $[\alpha]_D^{29}$ +3.28 (*c* 3.11, $CHCl_3$); IR (film) 2951, 2874, 1513, 1455, 1247, 1091, 1007, 735, 697 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.56–7.54 (m, 2H), 7.49–7.46 (m, 2H), 7.43–7.13 (m, 18H), 6.94 (d, *J*=10.0 Hz, 2H), 4.84 (d, *J*=12.5 Hz, 1H), 4.72 (m, 1H), 4.64 (dd, *J*=10.5, 2.5 Hz, 1H), 4.61–4.57 (m, 2H), 4.47–4.36 (m, 4H), 4.22 (d, *J*=11.5 Hz, 1H), 4.12 (m, 1H), 4.06–4.03 (m, 2H), 3.85–3.83 (m, 2H), 3.77–3.73 (m, 2H), 3.67 (m, 1H), 3.60–3.49 (m, 3H), 3.41 (s, 3H), 3.28 (m, 1H), 2.96 (m, 1H), 2.68 (m, 1H), 2.45 (m, 1H), 2.31–2.11 (m, 4H), 1.86–1.73 (m, 3H), 1.46 (s, 3H), 1.32 (s, 3H), 1.23 (m, 21H), 1.08–0.92 (m, 12H); ^{13}C NMR (125 MHz, C_6D_6) δ 157.7, 138.0, 137.5, 137.4, 137.1, 129.8, 127.7 (×2), 126.6 (×2), 126.5 (×5), 126.3, 125.8 (×2), 125.7 (×2), 125.7 (×2), 125.6, 125.6, 125.6, 125.5, 125.4, 112.0 (×2), 81.2, 76.1, 75.4, 75.0, 74.6, 74.0, 73.7, 73.6, 72.3, 72.2, 71.6, 71.1, 71.0, 69.3, 69.1, 68.7, 67.9, 67.2, 52.8 (×2), 40.1, 30.7, 29.8, 29.5, 28.9, 16.1, 15.2, 8.1, 5.48 (×2), 5.46, 5.36, 5.0, 4.9, 4.3 (×2), 4.2, 3.6 (×2), 2.9; HRMS (ESI) calcd for $C_{69}H_{98}O_{11}Si_2Na$ [(M+Na)$^+$] 1181.6545, found 1181.6541.

4.1.42. Dihydroxy ketone 69. To a solution of bis-TES ether **67** (5.13 g, 4.43 mmol) in CH_2Cl_2/pH 7 phosphate buffer (10:1, v/v, 89 mL) at 0 °C was added DDQ (3.02 g, 13.3 mmol). The resulting mixture was stirred at 0 °C for 1 h before it was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was filtered through a plug of silica gel (20% EtOAc/hexanes) to give alcohol, which was used directly in the subsequent reaction.

To a suspension of the alcohol and 4 Å molecular sieves in CH_2Cl_2 (44 mL) were added NMO (1.04 g, 8.88 mmol) and TPAP (77.7 mg, 0.22 mmol). The resulting mixture was stirred at 0 °C for 5 min and then at room temperature for 6 h. The mixture was concentrated under reduced pressure, and the residue was filtered through a plug of silica gel (20% EtOAc/hexanes) to give ketone **68**, which was used directly in the subsequent reaction.

To a solution of the above ketone **68** in THF (44 mL) at 0 °C were added TBAF (1.0 M in THF, 26.6 mL, 26.6 mmol) and acetic acid (0.76 mL, 13.3 mmol). The resulting solution

was stirred at room temperature for 7.5 h before it was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (50% EtOAc/hexanes) afforded dihydroxy ketone **69** (2.89 g, 81% for the three steps) as a colorless oil: $[\alpha]_D^{32}$ +68.1 (*c* 1.06, $CHCl_3$); IR (film) 3454, 2952, 2887, 2857, 1462, 1360, 1253, 1107, 1031, 838, 776, 672 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.36–7.24 (m, 20H), 4.66–4.57 (m, 3H), 4.53–4.41 (m, 4H), 4.35 (m, 1H), 4.13 (dd, *J*=7.5, 3.5 Hz, 1H), 4.06 (m, 1H), 3.73 (dd, *J*=11.5, 4.0 Hz, 1H), 3.65–3.49 (m, 3H), 3.43 (m, 1H), 3.37–3.30 (m, 2H), 3.26 (m, 1H), 2.92 (dd, *J*=14.5, 4.5 Hz, 1H), 2.79 (dd, *J*=12.5, 3.5 Hz, 1H), 2.57 (dd, *J*=15.0, 4.5 Hz, 1H), 2.43–2.40 (m, 2H), 2.12–2.04 (m, 4H), 1.75 (m, 1H), 1.55 (m, 1H), 1.45–1.39 (m, 5H), 1.08 (m, 3H), 0.96 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.0, 138.6, 138.1, 137.9, 137.7, 128.4 (×2), 128.33 (×5), 128.26 (×2), 127.8 (×2), 127.7 (×3), 127.53 (×2), 127.50 (×2), 127.4 (×2), 80.7, 80.6, 76.5, 76.2, 75.9, 75.1, 74.7, 73.9, 73.7, 73.5, 73.2, 72.9, 71.0, 70.9, 70.4, 68.9, 53.7, 43.2, 41.0, 30.1, 29.9, 29.7, 28.9, 9.8; HRMS (ESI) calcd for $C_{49}H_{60}O_{10}Na$ [(M+Na)$^+$] 831.4084, found 831.4075.

4.1.43. Tetracyclic ether 70. To a solution of dihydroxy ketone **69** (52.8 mg, 65.3 μmol) in MeCN/Et_3SiH (4:1, v/v, 1.3 mL) at −10 °C was added TMSOTf (14.1 μL, 77.9 μmol). The resulting solution was stirred at −10 °C for 15 min before being quenched with Et_3N. The mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (40% EtOAc/hexanes) to afford tetracyclic ether **70** (42.8 mg, 83%) as a colorless oil: $[\alpha]_D^{29}$ −10.1 (*c* 1.07, $CHCl_3$); IR (film) 3475, 2950, 2875, 1454, 1380, 1087, 1065, 738, 698 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.34–7.15 (m, 16H), 7.12–7.08 (m, 4H), 4.52–4.46 (m, 2H), 4.45–4.33 (m, 4H), 4.31–4.28 (m, 2H), 3.79 (m, 1H), 3.76–3.71 (m, 2H), 3.55–3.46 (m, 4H), 3.39 (ddd, *J*=8.0, 8.0, 5.5 Hz, 1H), 3.33 (ddd, *J*=10.5, 5.0 Hz, 1H), 3.17 (m, 1H), 3.09 (d, *J*=9.5 Hz, 1H), 2.81 (dd, *J*=12.5, 3.5 Hz, 1H), 2.71 (dd, *J*=13.0, 4.0 Hz, 1H), 2.37 (m, 1H), 2.28–2.15 (m, 4H), 1.95 (m, 1H), 1.74–1.55 (m, 4H), 1.28 (s, 3H), 1.18 (s, 3H), 1.08 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 139.5, 139.4, 138.9, 138.9, 128.6 (×3), 128.5 (×2), 128.5 (×2), 128.3 (×3), 128.1 (×2), 127.9 (×2), 127.8 (×2), 127.7 (×2), 127.6 (×2), 83.1, 79.4, 78.2, 77.9, 76.7, 76.6, 76.2, 73.6, 73.5, 73.3, 73.1 (×2), 73.1, 72.8, 70.8, 70.6, 70.3, 69.1, 43.8, 30.6, 30.4, 30.3, 17.6, 15.9, 10.1; HRMS (ESI) calcd for $C_{49}H_{60}O_9Na$ [(M+Na)$^+$] 815.4135, found 815.4413.

4.1.44. TIPS ether 72. To a solution of tetracyclic ether **70** (2.12 g, 2.68 mmol) in CH_2Cl_2 (27 mL) at 0 °C were added 2,6-lutidine (0.62 mL, 5.32 mmol) and TIPSOTf (1.41 mL, 5.25 mmol). The resulting mixture was stirred at room temperature for 2.5 h before it was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was filtered through a plug of silica gel (20% EtOAc/hexanes) to give TIPS ether **72** (3.14 g): $[\alpha]_D^{30}$ −8.81 (*c* 1.91, $CHCl_3$); IR (film) 2943, 2864, 1455, 1100, 736, 679 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.34–7.26 (m, 9H), 7.20–7.08 (m, 11H), 4.52–4.47 (m, 3H), 4.44–4.30 (m, 7H), 3.78–3.76 (m, 2H), 3.73–3.69 (m, 2H), 3.58–3.56 (m, 2H), 3.49 (m, 1H), 3.42 (m, 1H), 3.33 (m, 1H), 3.13 (m, 1H), 2.94 (m, 1H), 2.82 (m, 1H), 2.67 (m, 1H), 2.41 (m, 1H), 2.34 (m, 1H), 2.26–2.24 (m, 2H), 1.97 (m, 1H), 1.73–1.60 (m, 2H), 1.39–1.24 (m, 24H), 1.14 (m, 6H); ^{13}C NMR (125 MHz, C_6D_6) δ 139.5, 139.3, 138.9 (×2), 128.6 (×4), 128.5 (×2), 128.3 (×3), 128.2 (×3), 128.1 (×2), 127.9 (×2), 127.7 (×2), 127.60, 127.57, 84.1, 79.5, 79.2, 78.3, 77.3, 77.0, 76.7, 73.6, 73.4, 73.3, 73.13, 73.08, 72.8, 71.2, 70.5, 70.3, 69.2, 43.8, 30.9, 30.5, 30.3, 18.83 (×3), 18.77 (×3), 17.8, 15.9, 13.3, 13.26 (×3), 10.2; HRMS (ESI) calcd for $C_{58}H_{80}O_9SiNa$ [(M+Na)$^+$] 971.5469, found 971.5493.

4.1.45. Diol 73. To a solution of the TIPS ether **72** (3.14 g) in MeOH (18 mL) was added 10% Pd/C (2.5 g). The resulting mixture was stirred at room temperature under an atmosphere of hydrogen for 17 h before it was filtered through a pad of Celite. The filtrate and washings were combined and concentrated under reduced pressure to give tetraol, which was used directly in the subsequent reaction.

To a solution of the tetraol in DMF (26.8 mL) at room temperature were added 2,2-dimethoxypropane (3.55 mL, 28.9 mmol) and CSA (3.75 g, 16.1 mmol). The resulting mixture was stirred at 30 °C for 6.5 h before being quenched with Et_3N. The mixture was concentrated under reduced pressure, and the residue was filtered through a plug of silica gel (20% EtOAc/hexanes) to give a mixture of monoacetonide and bis-acetonide, which was used directly in the subsequent reaction.

To a solution of the mixture of monoacetonide and bis-acetonide in CH_2Cl_2/MeOH (4:1, v/v, 21.8 mL) at 0 °C was added PPTS (0.27 g, 1.07 mmol). The resulting mixture was stirred at 0 °C for 1 h before being quenched with Et_3N. The mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (50% EtOAc/hexanes) to afford diol **73** (1.09 g, 65% for the four steps) as a colorless oil: $[\alpha]_D^{31}$ −17.1 (*c* 1.41, $CHCl_3$); IR (film) 3397, 2944, 2866, 1463, 1329, 1063, 1035, 757, 679 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 3.79 (dd, *J*=10.0, 4.5 Hz, 1H), 3.71 (ddd, *J*=5.0, 5.0, 5.0 Hz, 1H), 3.67–3.63 (m, 2H), 3.61–3.50 (m, 5H), 3.32–3.28 (m, 2H), 3.12 (dd, *J*=12.0, 3.5 Hz, 1H), 3.04–3.01 (m, 2H), 2.11–2.01 (m, 4H), 1.72–1.59 (m, 4H), 1.55–1.45 (m, 4H), 1.39 (s, 3H), 1.33–1.26 (m, 4H), 1.19 (s, 3H), 1.12–0.97 (m, 24H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 99.5, 84.2, 80.4, 78.6, 78.4, 77.8, 76.6, 74.4, 70.8, 67.4, 66.5, 63.5, 60.6, 42.9, 33.1, 31.9, 30.3, 29.2, 29.0, 27.6, 19.2, 18.34 (×3), 18.28 (×3), 17.2, 16.4, 12.8 (×3), 10.2; HRMS (ESI) calcd for $C_{33}H_{61}O_9Si$ [(M+H)$^+$] 629.4085, found 629.4116.

4.1.46. Olefin 75. To a solution of diol **73** (1.00 g, 1.59 mmol) in pyridine (16 mL) at 0 °C was added pivaloyl chloride (1.56 mL, 12.7 mmol). The resulting solution was stirred at 0 °C for 40 min before saturated aqueous NH_4Cl was added. The mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (40% EtOAc/hexanes) afforded pivalate ester (0.96 g, 85%) as a colorless oil: $[\alpha]_D^{29}$ −15.7 (*c* 1.22,

$CHCl_3$); IR (film) 3410, 2944, 2867, 1725, 1463, 1384, 1157, 1064, 1036, 882, 759, 677 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.11 (m, 1H), 4.00 (m, 1H), 3.79 (dd, J=10.5, 5.0 Hz, 1H), 3.67–3.50 (m, 5H), 3.34–3.25 (m, 2H), 3.13 (dd, J=12.0, 3.5 Hz, 1H), 3.04–3.01 (m, 2H), 2.15–2.08 (m, 2H), 2.02 (m, 1H), 1.96 (m, 1H), 1.87–1.77 (m, 2H), 1.71–1.59 (m, 2H), 1.55–1.37 (m, 8H), 1.27 (s, 3H), 1.19 (s, 3H), 1.16 (s, 9H), 1.10–0.98 (m, 24H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.8, 99.5, 84.1, 80.4, 78.4, 78.3, 77.6, 76.6, 74.4, 70.8, 67.4, 67.0, 63.5, 63.4, 42.9, 38.7, 33.8, 30.3, 30.0, 29.2, 29.1, 27.2 (×3), 19.2, 18.4, 18.3 (×3), 18.3 (×3), 17.2, 16.4, 12.8 (×3), 10.1; HRMS (ESI) calcd for $C_{38}H_{68}O_{10}SiNa$ [(M+Na)$^+$] 735.4479, found 735.4478.

To a solution of the pivalate ester (0.24 g, 0.34 mmol) in DMF (6.6 mL) at 0 °C was added NaH (50% in oil, 32.0 mg, 0.67 mmol). The resulting solution was stirred at 0 °C for 1 h before *p*-methoxybenzyl chloride (44.7 μL, 0.33 mmol) and Bu_4NI (36.0 mg, 97.5 μmol) were added. The reaction mixture was stirred at room temperature for 6 h before it was quenched with saturated aqueous NH_4Cl. The mixture was diluted with Et_2O, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (20% EtOAc/hexanes) afforded *p*-methoxybenzyl ether (0.22 g, 78% for two cycles) as a colorless oil.

To a solution of *p*-methoxybenzyl ether (0.20 g, 0.24 mmol) in CH_2Cl_2 (2.5 mL) at −78 °C was added DIBALH (0.95 M in hexane, 0.48 mL, 0.46 mmol). The resulting mixture was stirred at −78 °C for 30 min before it was quenched with saturated aqueous potassium sodium tartrate. The mixture was vigorously stirred until the layers became clear. The organic layer was separated, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (30% EtOAc/hexanes) afforded alcohol **74** (0.13 g, 72%) as a colorless oil.

To a solution of alcohol **74** (0.12 g, 0.16 mmol) in THF (1.6 mL) were added *o*-nitrophenyl selenocyanate (79.0 mg, 0.35 mmol) and Bu_3P (0.79 mL, 3.2 mmol). The resulting mixture was stirred at room temperature for 45 min before it was concentrated under reduced pressure. The residue was filtered through a plug of silica gel (10% EtOAc/hexanes) to give *o*-nitrophenyl selenide, which was used directly in the subsequent reaction.

To a solution the above selenide in CH_2Cl_2 (3.2 mL) at 0 °C was added *m*-CPBA (77%, 40.0 mg, 0.18 mmol). The resulting solution was stirred at 0 °C for 45 min before it was quenched with Et_3N. The mixture was stirred at 35 °C for further 12 h and concentrated under reduced pressure. Purification by column chromatography on silica gel (10% EtOAc/hexanes) afforded olefin **75** (0.11 g, 94% for the two steps) as a colorless oil: $[\alpha]_D^{32}$ −51.2 (*c* 0.04, $CHCl_3$); IR (film) 2945, 2866, 1513, 1465, 1383, 1249, 1079, 882, 673 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.22 (d, J=8.5 Hz, 2H), 6.85 (d, J=9.0 Hz, 2H), 5.74 (ddd, J=17.5, 10.0, 10.0 Hz, 1H), 4.95 (dd, J=10.5, 2.5 Hz, 1H), 4.88 (dd, J=17.5, 2.0 Hz, 1H) 4.49 (d, J=11.0 Hz, 1H), 4.32 (d, J=11.5 Hz, 1H), 3.82–3.76 (m, 4H), 3.68–3.51 (m, 4H), 3.37 (m, 1H), 3.34–3.23 (m, 2H), 3.14 (dd, J=12.5, 4.0 Hz, 1H), 3.03 (dd, J=9.0, 9.0 Hz, 1H), 2.97 (dd, J=12.5, 3.0 Hz, 1H), 2.63 (ddd, J=15.0, 7.5, 7.5 Hz, 1H), 2.27 (ddd, J=11.0, 4.5, 4.5 Hz, 1H), 2.10 (dd, J=11.0, 4.5 Hz, 1H), 2.04 (m, 1H), 1.64 (m, 2H), 1.56–1.47 (m, 4H), 1.40 (s, 3H), 1.27 (s, 3H), 1.19 (s, 3H), 1.13–1.03 (m, 24H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 140.0, 130.1, 129.6 (×2), 115.3, 113.8 (×2), 99.5, 84.1, 80.3, 78.4, 78.3, 76.5, 75.7, 74.4, 74.0, 70.8, 70.3, 67.4, 63.5, 55.2, 42.9, 38.7, 30.3, 29.9, 29.2, 19.1, 18.37, 18.34 (×3), 18.28 (×3), 18.19, 16.4, 12.8 (×3), 9.9; HRMS (ESI) calcd for $C_{41}H_{66}O_9SiNa$ [(M+Na)$^+$] 753.4374, found 753.4415.

4.1.47. Tris-benzyl ether 76. To a solution of olefin **75** (0.18 g, 0.25 mmol) in THF (2.4 mL) at 0 °C was added TBAF (1.0 M in THF, 0.99 mL, 0.99 mmol). The resulting solution was stirred at room temperature for 16 h before it was concentrated under reduced pressure. Purification by column chromatography on silica gel (30% EtOAc/hexanes) afforded alcohol (0.13 g, 92%) as a colorless oil.

To a solution of the alcohol (0.20 g, 0.35 mmol) in MeOH (3.6 mL) at 0 °C was added *p*-TsOH·H_2O (67.8 mg, 0.36 mmol). The reaction mixture was stirred at 0 °C for 1 h before being quenched with Et_3N. The mixture was concentrated under reduced pressure, and the residue was filtered through a plug of silica gel (10% MeOH/$CHCl_3$) to give triol, which was used directly in the subsequent reaction.

To a solution of the triol in DMF (3.5 mL) at 0 °C was added NaH (50% in oil, 0.10 g, 2.08 mmol). The resulting solution was stirred at 0 °C for 1 h before benzyl bromide (0.22 mL, 1.85 mmol) and Bu_4NI (39.4 mg, 0.107 mmol) were added. The reaction mixture was stirred at room temperature for 17.5 h before it was quenched with saturated aqueous NH_4Cl. The mixture was diluted with Et_2O, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (30% EtOAc/hexanes) afforded tris-benzyl ether **76** (0.25 g, 89% for the two steps) as a colorless oil: $[\alpha]_D^{30}$ −51.2 (*c* 0.04, $CHCl_3$); IR (film) 2944, 2866, 1513, 1465, 1383, 1086, 882, 673 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.32 (m, 2H), 7.25–7.11 (m, 15H), 6.79 (d, J=10.0 Hz, 2H), 5.67 (ddd, J=17.0, 9.5, 9.5 Hz, 1H), 4.91 (dd, J=10.5, 2.0 Hz, 1H), 4.88–4.84 (m, 2H), 4.66 (d, J=12.0 Hz, 1H), 4.53–4.42 (m, 4H), 4.27 (d, J=11.5 Hz, 1H), 4.26 (d, J=10.5 Hz, 1H), 3.71 (s, 3H), 3.63 (m, 1H), 3.55 (m, 2H), 3.38–3.32 (m, 3H), 3.28–3.14 (m, 3H), 3.02 (dd, J=13.0, 4.0 Hz, 1H), 2.95 (dd, J=12.5, 3.5 Hz, 1H), 2.60 (m, 1H), 2.32 (ddd, J=11.5, 4.0, 4.0 Hz, 1H), 2.24 (ddd, J=11.5, 4.5, 4.5 Hz, 1H), 2.10 (dd, J=11.0, 4.0 Hz, 1H), 1.61–1.50 (m, 3H), 1.19 (s, 3H), 1.18 (s, 3H), 1.05 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 139.8, 139.1, 138.4, 137.8, 130.0, 129.6 (×2), 128.4 (×2), 128.3 (×2), 128.2 (×2), 127.8 (×2), 127.8 (×3), 127.7 (×2), 127.5, 127.3, 115.7, 113.9 (×2), 84.2, 82.5, 79.1, 78.0, 77.7, 75.6, 74.2, 74.0, 73.3, 73.2, 72.8, 72.6, 71.0, 70.4, 69.6, 55.3 (×2), 43.2, 38.6, 30.1, 29.7, 18.8, 15.9, 10.5; HRMS (ESI) calcd for $C_{50}H_{60}O_9Na$ [(M+Na)$^+$] 827.4135, found 827.4141.

4.1.48. GHIJ-ring fragment 37. To a solution of tris-benzyl ether **76** (0.21 g, 0.26 mmol) in MeCN (5.3 mL) at 0 °C were

added Et_3SiH (0.13 mL, 0.81 mmol) and $BF_3 \cdot OEt_2$ (33 μL, 0.27 mmol). The resulting solution was stirred at 0 °C for 45 min before being quenched with Et_3N. The mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (40% EtOAc/hexanes) to afford GHIJ-ring fragment **37** (0.18 g, quant.) as a colorless oil: $[\alpha]_D^{31}$ +53.1 (*c* 0.23, $CHCl_3$); IR (film) 3407, 2876, 1642, 1383, 1066, 1029, 737, 697 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.58 (d, *J*=7.5 Hz, 2H), 7.31 (d, *J*=7.0 Hz, 2H), 7.26–7.07 (m, 11H), 5.95 (ddd, *J*=17.0, 10.0, 10.0 Hz, 1H), 5.11–5.06 (m, 3H), 4.91 (d, *J*=12.5 Hz, 1H), 4.49 (d, *J*=12.5 Hz, 1H), 4.43 (d, *J*=11.5 Hz, 1H), 4.40 (d, *J*=12.5 Hz, 1H), 4.24 (d, *J*=12.0 Hz, 1H), 3.79 (m, 1H), 3.75–3.69 (m, 2H), 3.50 (ddd, *J*=7.0, 7.0, 5.5 Hz, 1H), 3.39 (d, *J*=9.5 Hz, 1H), 3.34 (m, 1H), 3.27 (dd, *J*=10.5, 10.5 Hz, 1H), 3.19 (dd, *J*=9.5, 1.5 Hz, 1H), 3.15 (ddd, *J*=12.0, 12.0, 4.5 Hz, 1H), 2.89 (dd, *J*=12.5, 3.0 Hz, 1H), 2.79 (dd, *J*=12.5, 3.5 Hz, 1H), 2.69 (dd, *J*=7.0, 7.0 Hz, 1H), 2.30 (ddd, *J*=11.0, 4.0, 4.0 Hz, 1H), 2.26 (dd, *J*=11.0, 3.5 Hz, 1H), 2.01 (ddd, *J*=11.0, 4.5, 4.5 Hz, 1H), 1.73 (dd, *J*=12.0, 12.0 Hz, 1H), 1.68–1.54 (m, 3H), 1.31 (s, 3H), 1.22 (d, *J*=7.0 Hz, 3H), 1.16 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 138.2, 138.1, 137.4, 137.0, 126.54 (×2), 126.46 (×2), 126.43 (×2), 126.3, 125.9 (×2), 125.84, 125.80 (×2), 125.76, 125.54, 125.48, 113.6, 82.5, 81.6, 77.6, 76.2, 75.9, 75.3, 74.9, 72.5, 71.5, 71.4, 71.3, 70.8, 68.9, 68.3, 65.6, 41.9, 37.0, 31.9, 28.7, 16.6, 13.9, 8.8; HRMS (ESI) calcd for $C_{42}H_{52}O_8Na$ [(M+Na)$^+$] 707.3560, found 707.3535.

4.1.49. Ester 77. To a solution of carboxylic acid **36** (0.21 g, 0.27 mmol) in THF (2.6 mL) at 0 °C were added Et_3N (54.0 μL, 0.39 mmol) and 2,4,6-trichlorobenzoyl chloride (52 μL, 0.33 mmol). The resulting mixture was stirred at 40 °C for 1 h before it was concentrated under reduced pressure. The mixture was dissolved in toluene (2.6 mL) and treated with alcohol **37** (0.18 g, 0.26 mmol) and DMAP (65.9 mg, 0.54 mmol). The reaction mixture was stirred at 40 °C for 1.5 h before being quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with brine and saturated aqueous $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (30% EtOAc/hexanes) afforded ester **77** (0.35 g, 92%) as a solid: $[\alpha]_D^{26}$ +15.4 (*c* 0.55, $CHCl_3$); IR (film) 2926, 2855, 1738, 1383, 1251, 1068, 774, 658 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.82–7.75 (m, 8H), 7.46–7.40 (m, 8H), 7.34–7.26 (m, 11H), 7.21–7.19 (m, 2H), 5.71 (ddd, *J*=17.5, 9.5, 9.5 Hz, 1H), 5.01 (d, *J*=11.5 Hz, 1H), 4.92–4.90 (m, 2H), 4.78–4.51 (m, 9H), 4.35 (d, *J*=11.0 Hz, 1H), 3.85–3.82 (m, 1H), 3.71–3.54 (m, 7H), 3.48–3.30 (m, 5H), 3.23 (dd, *J*=8.0, 8.0 Hz, 1H), 3.13–3.08 (m, 3H), 3.00 (dd, *J*=12.0, 3.0 Hz, 1H), 2.57–2.51 (m, 1H), 2.40–2.24 (m, 4H), 2.17 (dd, *J*=11.5, 4.5 Hz, 1H), 2.07–1.78 (m, 7H), 1.73–1.50 (m, 8H), 1.28–1.23 (m, 9H), 1.21 (s, 3H), 1.11 (d, *J*=7.0 Hz, 3H), 0.83 (s, 9H), 0.08 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 139.0, 138.5, 138.4, 137.8, 136.0, 135.8, 133.23, 133.19, 132.9, 128.4 (×2), 128.3 (×2), 128.2 (×2), 128.1 (×2), 127.8 (×2), 127.7 (×2), 127.5, 127.3, 126.24 (×2), 126.21 (×2), 126.10 (×2), 126.06 (×2), 125.83 (×2), 125.78 (×2), 125.72 (×2), 125.6 (×2), 116.2, 87.2, 84.1, 82.6, 81.6, 81.2, 80.3, 79.8, 79.2, 77.8, 77.4, 76.8, 74.3, 74.2, 73.6, 73.4, 73.3, 73.2, 73.1, 72.8, 72.6, 71.9, 71.0, 70.6, 69.6, 68.6, 67.2, 54.5, 43.1, 38.7, 35.3, 32.1, 32.0, 30.1, 29.7, 26.6, 25.7 (×3), 24.8, 23.9, 23.3, 18.0, 17.9, 16.1, 15.9, 10.5, −1.9, −2.0; HRMS (FAB) calcd for $C_{89}H_{112}O_{15}SiNa$ [(M+Na)$^+$] 1471.7668, found 1471.7606.

4.1.50. Alcohol 79. To a solution of ester **77** (0.23 g, 0.16 mmol) in CH_2Cl_2 (3.2 mL) at −78 °C was added DIBALH (0.94 M in hexane, 0.34 mL, 0.32 mmol). The resulting solution was stirred at −78 °C for 1 h. A solution of Ac_2O (0.18 mL, 1.90 mmol) and DMAP (0.26 g, 2.13 mmol) in CH_2Cl_2 (3.2 mL) was added dropwise over 1 h, and then a solution of pyridine (0.16 mL, 1.98 mmol) in CH_2Cl_2 (1.6 mL) was added over 0.5 h. The reaction mixture was stirred at −78 °C for 20 h and allowed to warm to 0 °C. After being stirred at 0 °C for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and saturated aqueous potassium sodium tartrate. The mixture was vigorously stirred until the layers became clear. The solution was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was filtered through a plug of silica gel (20% EtOAc/hexanes containing 1% Et_3N) to afford α-acetoxy ether **78** (0.13 g, 55%) as an approximately 1:1 mixture of diastereomers, which was used directly in the subsequent reaction.

To a solution of the α-acetoxy ether **78** (0.12 g, 80.4 μmol) in CH_2Cl_2 (1.60 mL) at −78 °C were added 2,6-di-*tert*-butyl-4-methylpyridine (65.6 mg, 0.32 mmol), TMSCN (21.3 μL, 0.17 mmol), and TMSOTf (43.4 μL, 0.24 mmol). The resulting mixture was stirred at −78 °C for 5 min and allowed to warm to 0 °C. The reaction mixture was stirred at 0 °C for 1 h before it was quenched with Et_3N. The mixture was filtered and concentrated under reduced pressure. The residue was filtered through a plug of silica gel (30% EtOAc/hexanes) to afford α-cyano ether (0.12 g) as a 1:1 mixture of diastereomers.

To a solution of the α-cyano ether (0.12 g, 79.8 μmol) in MeCN (3.2 mL) was added TBAF (0.21 g, 0.80 mmol). The reaction mixture was stirred at 70 °C for 20 h before it was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (50% EtOAc/hexanes) to afford alcohol **79** (93.7 mg, 87% for the two steps) as a 1:1 mixture of diastereomers: $[\alpha]_D^{25}$ +1.0 (*c* 0.98, $CHCl_3$); IR (film) 3465, 3060, 2944, 1455, 1382, 1093, 753, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.81–7.72 (m, 10H), 7.46–7.40 (m, 10H), 7.35–7.20 (m, 9H), 5.84–5.70 (m, 1H), 5.21–4.90 (m, 3H), 4.77–4.51 (m, 8H), 4.37–4.35 (m, 1H), 4.30 (dd, *J*=5.5, 5.5 Hz, 0.5H), 4.20 (dd, *J*=6.0, 6.0 Hz, 0.5H), 3.87–3.85 (m, 1H), 3.72–3.53 (m, 7H), 3.49–3.30 (m, 6H), 3.26–3.22 (m, 1H), 3.12–2.97 (m, 4H), 2.65–2.63 (m, 1H), 2.54–2.48 (m, 1H), 2.42–2.40 (m, 1H), 2.29–2.27 (m, 1H), 2.19–2.17 (m, 1H), 2.09–2.01 (m, 4H), 1.89–1.69 (m, 7H), 1.66–1.43 (m, 6H), 1.27–1.23 (m, 12H), 1.16–1.13 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.7, 138.93 (×2), 138.91 (×2), 138.4 (×3), 138.3 (×2), 137.82, 137.79 (×2), 136.0, 135.9, 135.8, 133.20 (×2), 133.16 (×2), 132.88 (×2), 132.86 (×2), 128.4 (×4), 128.3 (×4), 128.2 (×2), 128.14 (×2), 128.09 (×2), 128.07 (×2), 127.8 (×5), 127.73 (×4), 127.66 (×3), 127.65 (×3), 127.61, 127.5, 127.4, 127.34, 127.32, 126.23, 126.22, 126.16, 126.14, 126.07 (×2),

126.05, 126.04, 125.81, 125.77, 125.76, 125.69 (×2), 125.68, 125.63, 125.61, 119.1, 118.1, 117.0, 116.1, 86.9, 86.8, 84.2, 84.0, 82.54, 82.46, 81.6 (×2), 81.20, 81.15, 80.31, 80.25, 79.7, 79.6, 79.2 (×2), 77.69, 77.66, 77.59, 77.55, 77.33, 77.31, 77.2, 77.0, 76.8 (×2), 75.0, 74.8, 74.3, 73.6, 73.3 (×2), 73.19, 73.15, 73.0 (×2), 72.73, 72.71, 72.58, 72.55, 71.72, 71.70, 71.0, 70.9, 70.75, 70.74, 70.6, 69.6, 68.3, 67.17, 67.12, 65.0, 60.4, 54.51, 54.47, 43.14, 43.10, 38.7, 38.3, 35.28, 35.26, 32.02, 31.96, 31.6, 31.5, 30.3, 30.0 (×2), 28.69, 28.68, 26.5, 24.2, 24.04, 24.00, 23.8, 23.3, 23.2, 21.0, 18.8, 18.6, 15.9, 15.8, 15.72, 15.69, 14.2, 14.1, 10.5, 10.4; HRMS (ESI) calcd for $C_{84}H_{99}NO_{14}Na$ [(M+Na)$^+$] 1368.6963, found 1368.7057.

4.1.51. Lactones 81 and 82. To a solution of alcohol **79** (66.5 mg, 49.4 μmol) in ethylene glycol (5 mL) was added KOH (0.39 g, 6.95 mmol). The resulting mixture was stirred at 150 °C for two days. The reaction mixture was cooled to room temperature and quenched with 3 M aqueous HCl. The mixture was diluted with $CHCl_3$, and washed with 1 M aqueous HCl and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (20% MeOH/$CHCl_3$) afforded hydroxy acid **80** (58.0 mg, 86%) as a 1:1 mixture of diastereomers, which was used directly in the subsequent reaction.

To a solution of hydroxy acid **80** (58.0 mg, 42.5 μmol) in THF/toluene (1:1, v/v, 1.8 mL) at 0 °C were added Et_3N (25.6 μL, 0.18 mmol) and 2,4,6-trichlorobenzoyl chloride (21.5 μL, 0.14 mmol). The resulting mixture was stirred at room temperature for 3 h before it was diluted with toluene (4.6 mL). This mixture was added dropwise to a refluxing solution of DMAP (28.1 mg, 0.23 mmol) in toluene (4.6 mL) over a period of 1 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. Purification by column chromatography on silica gel (20–30% EtOAc/hexanes) afforded lactones **81** (20.7 mg, 36%) and **82** (18.4 mg, 32%). **81**: $[\alpha]_D^{25}$ −4.2 (*c* 1.55, $CHCl_3$); IR (film) 2946, 2872, 2357, 1714, 1455, 1274, 1097, 751, 698 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 7.71–7.58 (m, 12H), 7.47–7.45 (m, 2H), 7.33–7.07 (m, 15H), 5.99 (ddd, *J*=18.0, 10.5, 10.5 Hz, 1H), 5.47 (d, *J*=17.5 Hz, 1H), 5.28 (d, *J*=12.0 Hz, 1H), 5.06 (d, *J*=12.0 Hz, 1H), 4.90 (d, *J*=12.0 Hz, 1H), 4.55–4.41 (m, 7H), 4.33–4.31 (m, 2H), 4.25 (d, *J*=11.5 Hz, 1H), 4.16 (m, 1H), 3.82 (m, 1H), 3.78–3.72 (m, 3H), 3.62–3.39 (m, 8H), 3.27 (m, 1H), 3.17 (m, 1H), 3.01 (m, 1H), 2.93–2.81 (m, 3H), 2.66 (dd, *J*=12.5, 3.5 Hz, 1H), 2.31–2.25 (m, 3H), 2.17–2.07 (m, 4H), 1.99 (m, 1H), 1.89–1.48 (m, 14H), 1.31 (s, 3H), 1.27 (d, *J*=7.5 Hz, 3H), 1.23 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 169.9, 140.0, 139.3, 139.2, 139.0, 136.8, 136.4, 133.9, 133.8, 133.51, 133.49, 128.6, 128.54 (×2), 128.52, 128.47 (×2), 128.45, 128.44, 128.2 (×2), 128.1 (×2), 127.9 (×4), 127.81 (×2), 127.78, 127.55, 127.54, 126.7, 126.5, 126.4, 126.3, 126.09, 126.05, 125.98 (×2), 117.3, 85.4, 84.5, 83.5, 82.3, 81.9, 81.3, 81.1, 79.7, 79.6, 79.2, 77.7, 77.5, 76.9, 76.1, 75.9, 74.6, 74.1, 73.53, 73.46, 73.3, 73.2, 72.8, 71.9, 70.9, 70.8, 70.4, 67.2, 53.9, 44.0, 38.7, 35.9, 32.5, 30.71, 30.69, 28.4, 27.1, 25.0, 23.3, 22.9, 19.2, 16.1, 16.0, 10.5; HRMS (ESI) calcd for $C_{84}H_{99}O_{15}$ [(M+H)$^+$] 1347.6984, found 1347.7243. **82**: $[\alpha]_D^{25}$ +16.8 (*c* 1.35, $CHCl_3$); IR (film) 2927, 2871, 1739, 1453, 1382, 1093, 750, 698 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 7.71–7.58 (m, 12H), 7.47–7.44 (m, 2H), 7.34–7.09 (m, 15H), 6.12 (ddd, *J*=17.5, 9.5, 9.5 Hz, 1H), 5.13–5.01 (m, 3H), 4.92 (d, *J*=12.0 Hz, 1H), 4.55–4.41 (m, 7H), 4.32 (d, *J*=12.5 Hz, 1H), 4.25 (d, *J*=11.5 Hz, 1H), 4.18–4.15 (m, 2H), 3.81–3.71 (m, 3H), 3.63–3.47 (m, 8H), 3.40 (m, 1H), 3.34–3.26 (m, 2H), 3.18 (m, 1H), 3.02 (ddd, *J*=11.0, 3.5, 3.5 Hz, 1H), 2.93 (m, 1H), 2.88 (dd, *J*=13.0, 3.5 Hz, 1H), 2.78 (dd, *J*=12.5, 4.0 Hz, 1H), 2.73 (m, 1H), 2.68–2.64 (m, 1H), 2.31–2.28 (m, 2H), 2.18–2.01 (m, 5H), 1.90–1.54 (m, 10H), 1.33 (s, 3H), 1.27 (d, *J*=7.0 Hz, 3H), 1.21 (s, 3H), 1.20 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 171.3, 141.3, 140.1, 139.4, 139.0, 136.8, 136.4, 133.8 (×2), 133.5 (×2), 128.53 (×4), 128.46 (×2), 128.41 (×2), 128.2 (×2), 128.07, 128.05, 127.9 (×2), 127.81 (×2), 127.78 (×2), 127.72, 127.5, 127.4, 126.7, 126.5, 126.4, 126.3, 126.1, 126.04, 126.00, 125.97, 115.6, 84.8, 83.8, 83.7, 81.8, 81.3, 80.8, 80.1, 80.0, 79.6, 79.5, 78.5, 77.9, 77.3, 76.9, 76.4, 74.5, 74.1, 73.5 (×2), 73.4, 73.2, 72.8, 71.7, 70.9 (×2), 70.3, 67.7, 54.0, 43.9, 39.5, 35.9, 32.4, 31.9, 31.6, 30.7, 29.6, 27.1, 23.3, 22.2, 19.7, 16.0, 15.9, 10.8; HRMS (ESI) calcd for $C_{84}H_{98}O_{15}Na$ [(M+Na)$^+$] 1369.6803, found 1369.6848.

4.1.52. Acetate 83. To a solution of lactone **81** (15.5 mg, 11.5 μmol) in CH_2Cl_2 (0.23 mL) at −78 °C was added DIBALH (0.95 M in hexane, 49.0 μL, 46.6 μmol). The resulting mixture was stirred at −78 °C for 1 h. A solution of Ac_2O (13.0 μL, 0.14 mmol) and DMAP (18.0 mg, 0.15 mmol) in CH_2Cl_2 (0.12 mL), and then a solution of pyridine (11.0 μL, 0.14 mmol) in CH_2Cl_2 (0.12 mL) were added over 30 min. The reaction mixture was stirred at −78 °C for 12 h and allowed to warm to 0 °C. The reaction mixture was stirred at 0 °C for further 1 h before it was quenched with saturated aqueous NH_4Cl and saturated aqueous potassium sodium tartrate. The resulting mixture was vigorously stirred until the layers became clear. The mixture was diluted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (30% EtOAc/hexanes containing 1% Et_3N) afforded acetate **83** (10.8 mg, 68%) as a colorless oil: $[\alpha]_D^{25}$ +1.56 (*c* 1.08, $CHCl_3$); IR (film) 2922, 2871, 1747, 1383, 1068, 750, 698 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 7.71–7.55 (m, 12H), 7.46–7.43 (m, 2H), 7.32–7.08 (m, 15H), 6.31 (s, 1H), 6.08 (m, 1H), 5.40 (m, 1H), 5.20 (dd, *J*=10.5, 2.0 Hz, 1H), 5.09 (d, *J*=12.5 Hz, 1H), 4.92 (d, *J*=12.0 Hz, 1H), 4.53–4.40 (m, 6H), 4.30 (d, *J*=12.0 Hz, 1H), 4.25 (d, *J*=11.5 Hz, 1H), 4.15 (m, 1H), 3.82–3.72 (m, 4H), 3.67–3.19 (m, 14H) 3.07–3.01 (m, 2H), 2.91 (m, 1H), 2.81 (m, 1H), 2.34–2.24 (m, 4H), 2.22–2.09 (m, 4H), 1.91–1.53 (m, 13H), 1.50 (s, 3H), 1.32 (s, 3H), 1.29 (d, *J*=7.0 Hz, 3H), 1.23 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 168.7, 140.3, 140.0, 139.3, 139.0, 136.8, 136.5, 133.88, 133.85, 133.5, 128.55 (×2), 128.53 (×3), 128.46 (×2), 128.44, 128.41, 128.2 (×2), 128.06, 128.05, 127.89 (×2), 127.87, 127.82 (×2), 127.77, 127.55 (×2), 127.50, 126.6, 126.5, 126.34, 126.29 (×2), 126.1, 126.03, 125.98, 125.95, 114.3, 93.7, 84.7, 84.5, 83.5, 82.0, 81.6, 81.4, 80.1, 79.6, 78.0, 77.80, 77.76, 77.0, 76.6, 76.3, 75.4, 74.5, 74.2, 73.53, 73.46, 73.3, 73.2 (×2), 72.8, 72.1, 70.9, 70.7, 70.4, 67.3, 53.6, 44.0, 38.3, 36.0, 32.8, 28.7, 27.2, 23.5, 23.3,

21.0, 19.3, 16.6, 16.0 (×2), 10.6; HRMS (ESI) calcd for $C_{86}H_{102}O_{16}Na$ [(M+Na)$^+$] 1413.7066, found 1413.6857.

4.1.53. BCDEFGHIJ-ring polyether core 5. To a suspension of acetate **83** (4.00 mg, 2.88 μmol) and 4 Å molecular sieves in MeCN (0.3 mL) at −40 °C was added allyltrimethylsilane (23.0 μL, 0.14 mmol). After 5 min, $BF_3\cdot OEt_2$ (one drop) was added. The resulting mixture was stirred at −40 °C and allowed to warm to −30 °C over 1 h before it was quenched with Et_3N. The mixture was filtered and concentrated under reduced pressure. Purification by column chromatography on silica gel (10% EtOAc/hexanes) afforded diene **84** (2.30 mg, 58%), which was used directly in the subsequent reaction.

To a solution of diene **84** (3.04 mg, 2.22 μmol) in CH_2Cl_2 (1.11 mL) was added the second-generation Grubbs catalyst **35** (2.81 mg, 3.31 μmol). The resulting solution was stirred at 40 °C for two days. The mixture was cooled to room temperature, quenched with Et_3N, and concentrated under reduced pressure. Purification by column chromatography on silica gel (10% EtOAc/hexanes) afforded BCDEFGHIJ-ring **5** (1.99 mg, 67%) as a colorless oil: $[\alpha]_D^{28}$ −2.5 (*c* 0.28, $CHCl_3$); IR (film) 2925, 2872, 1632, 1454, 1384, 1069, 739, 698 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 7.69–7.56 (m, 14H), 7.45–7.41 (m, 3H), 7.33–7.07 (m, 12H), 6.12 (ddd, *J*=11.0, 11.0, 5.0 Hz, 1H), 5.63 (dd, *J*=10.5, 10.5 Hz, 1H), 5.12 (d, *J*=12.5 Hz, 1H), 4.92 (d, *J*=12.5 Hz, 1H), 4.53–4.41 (m, 6H), 4.29 (d, *J*=12.0 Hz, 1H), 4.24 (d, *J*=11.5 Hz, 1H), 4.14 (m, 1H), 3.81 (m, 1H), 3.78–3.70 (m, 2H), 3.67–3.66 (m, 2H), 3.62–3.59 (m, 2H), 3.51–3.46 (m, 4H), 3.32–3.20 (m, 5H), 3.22 (dd, *J*=12.0, 3.0 Hz, 1H), 2.98 (m, 1H), 2.92–2.89 (m, 2H), 2.34–2.12 (m, 8H), 1.94–1.53 (m, 15H), 1.32 (s, 3H), 1.28 (s, 3H), 1.22 (s, 3H), 1.20 (d, *J*=7.0 Hz, 3H), 1.09 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 140.2, 139.4, 139.0, 136.8, 136.5, 134.4, 133.9 (×2), 133.5 (×2), 128.54 (×3), 128.46 (×2), 128.43 (×2), 128.3, 128.2 (×2), 128.1 (×2), 127.9 (×2), 127.80 (×3), 127.75, 127.54 (×2), 127.48, 126.5 (×2), 126.31, 126.27, 126.0 (×3), 125.94 (×2), 85.1, 85.0, 84.9, 84.7, 83.7, 83.6, 82.0, 81.4, 81.2, 79.9, 79.7, 79.2, 78.6, 77.4, 75.7, 74.6, 74.2, 74.1, 73.53 (×2), 73.48, 73.36, 73.2, 72.8, 70.9, 70.8, 70.4, 67.3, 54.5, 44.1, 35.9, 33.0, 32.9, 32.6, 32.3, 31.2, 30.7, 27.3, 24.0, 23.4, 18.3, 16.7, 16.3, 16.0, 11.2; HRMS (ESI) calcd for $C_{85}H_{100}O_{14}Na$ [(M+Na)$^+$] 1367.7011, found 1367.7224.

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