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Divergent synthesis of the tetracyclic ethers of 6-*X*-7-6 ring systems

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Abstract—Ladder-shaped polyether natural products show diverse biological activities with extreme potency. As the initial phase of detailed SAR studies of bioactive polyethers, we set out to construct structurally simple mimics. This paper details the divergent synthesis of 6-*X*-7-6 tetracycles (*X*=7, 8, or 9) starting from a simple 6-membered ether. Key reactions in the synthesis include (i) the direct formation of an *O*,*S*-acetal by the coupling of an alcohol with an α-chlorosulfide, (ii) the construction of a 7-membered ring by radical cyclization, and (iii) cyclization to the 7, 8 or 9-membered ring via a ring-closing metathesis reaction. The neutral reaction conditions of our strategy enable the synthesis of a wide variety of substrates. The results of this study can be applied for the rapid construction of artificial polyether compounds with diversified molecular shapes and sizes.

1. Introduction

The structures of many ladder-shaped polyethers from marine sources have been recently determined using extensive modern spectroscopic techniques (Fig. 1).[1] The most notable feature of these compounds lies in their gigantic architectures that comprise *trans*/*syn*-fused ethers of 5 to 9-membered rings. All these molecules possess the extremely potent biological activities, i.e. neurotoxicity, cytotoxicity, and antifungal activity. However, the biological aspects of these molecules have not been fully investigated due to the inadequate amounts of the isolated materials.

The receptor protein has been identified for only ciguatoxins (CTX)[2,3] and brevetoxins (BTX),[4,5] which are selective activators of voltage-sensitive sodium channels (VSSC) in nerves, heart, and muscle.[6,7] The specific binding site on the channels is designated as site 5, although its precise location within the VSSC has not been identified.[8] Very recently, we have shown that gambieric acid-A (**3**)[9] and gambierol (**4**)[10,11] can inhibit the binding of BTX to site 5, and that the inhibitory activities of natural polyethers **1**–**4** are proportional to the size of the polycyclic regions of the molecules; in other words, it is likely that, despite the distinct difference in the backbone, **1**–**4** share a common binding site.[12]

The structural requirements for the sodium channel ligands, as well as other biological activities, appear to be complex. As a logical starting point for detailed SAR studies of polyethers, we set out to construct structurally simple mimics with various molecular sizes and shapes.[13] Using these biological probes can hopefully deepen our understanding of the essential topographical features for the potent activities of these marine natural products. Herein, we present the efficient syntheses of 6-*X*-7-6 tetracycles **9**–**12**, which can serve as modules for various artificial polyethers, using a novel assembly of structural fragments (Scheme 1).[14,15]

2. Synthesis plan of 6-*X*-7-6 tetracyclic ethers

To efficiently attain the diversified structures of reasonable molecular sizes, our plan involved a unified strategy starting from simple ether **5** (Scheme 1). Secondary alcohol **6** and α-chlorosulfide **7**,[16] both of which were derived from **5**, were to be coupled through the activation of **7** using a silver salt. This type of *O*,*S*-acetal formation was developed by Mukaiyama[17] and Hindsgaul[18] groups within the context of their syntheses of oligosaccharides, and was successfully applied to the synthesis of fused-polyether molecules in our laboratory.[14] To construct the 7-*X* ring system (**9**–**12**, *X*=7, 8, or 9), the resulting *O*,*S*-acetal **8** would be subjected to the radical cyclization/ring-closing olefin metathesis (RCM)[19,20] strategy, of which utility was demonstrated in our total synthesis of CTX3C (**1**).[3] Structurally diverse decacycles **13**, whose sizes are comparable to those of the natural products, could be attained by applying the same coupling

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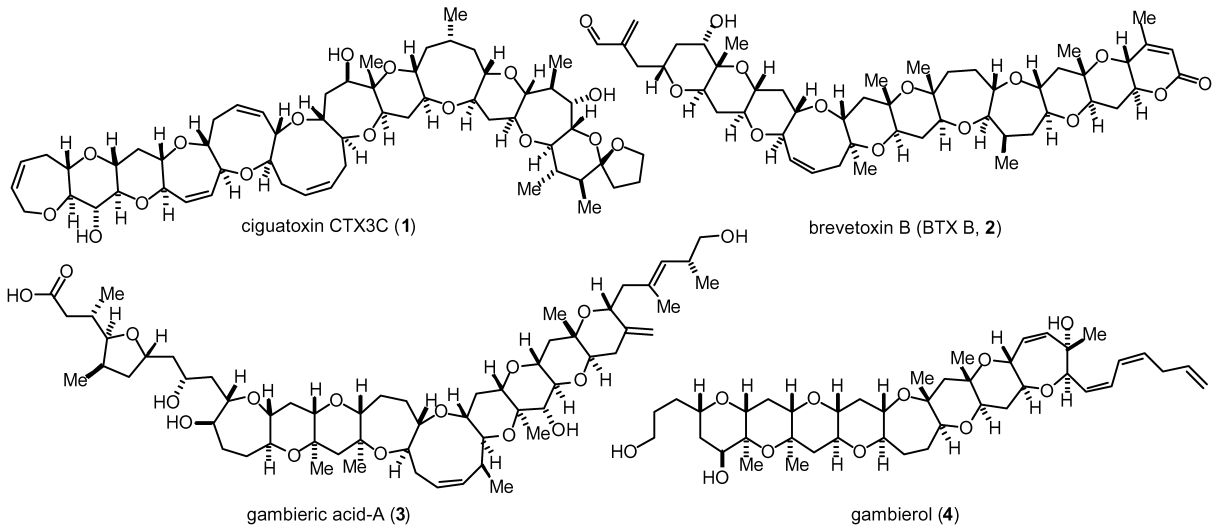
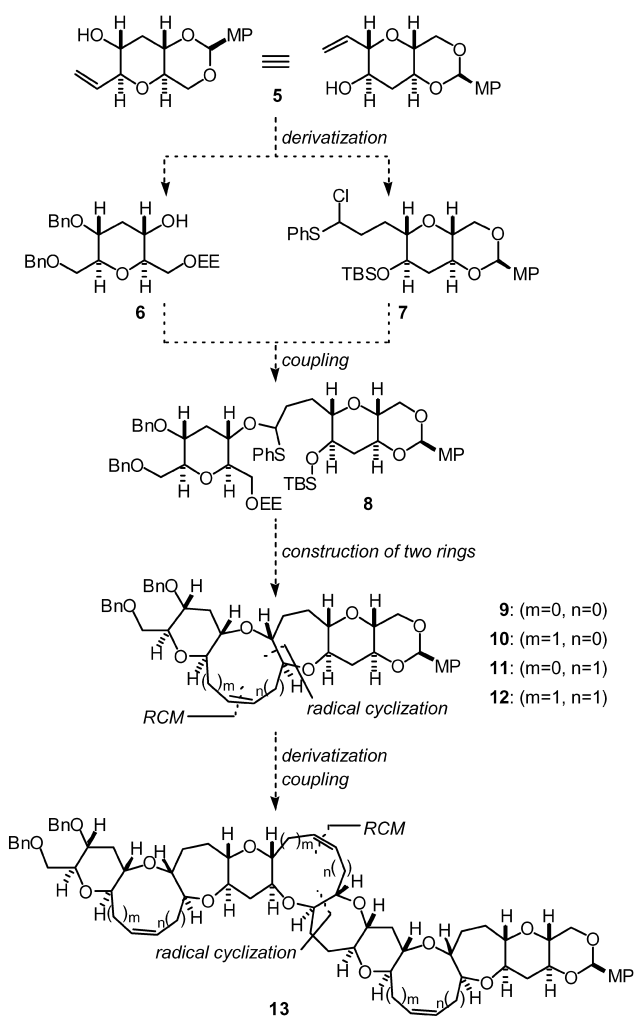


Figure 1. Various ladder-shaped polyethers from marine sources.

method to tetracycles **9**–**12**. Our synthetic methodology would, therefore, allow for the efficient preparation of a number of fused-polyether mimics starting from the common ether **5**.



Scheme 1. Synthesis plan of polyether mimics.

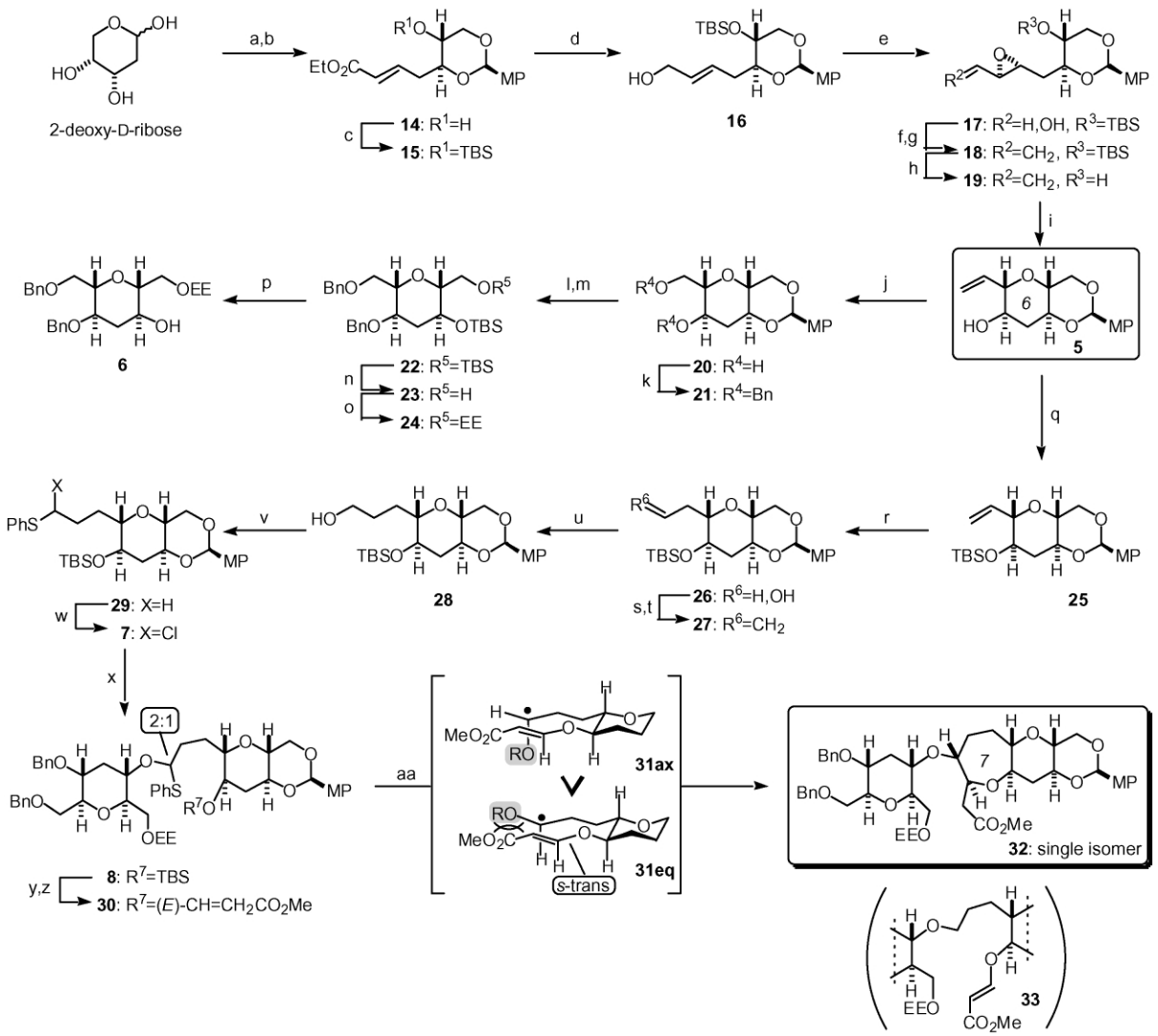
3. Synthesis of O-linked oxacycle

Compound **5** was prepared using the 6-*endo*-selective epoxide-opening reaction, developed by Nicolaou, as a key reaction (Scheme 2).[21,22] Wittig reaction of 2-deoxy-D-ribose, followed by acetalization, gave *p*-methoxybenzylidene (MP) acetal **14** in 82% yield. After TBS-protection of the secondary alcohol of **14**, ester **15** was reduced to allylic alcohol **16**, which in turn was subjected to Sharpless asymmetric epoxidation[23] to afford epoxide **17** in 84% overall yield (3 steps). Swern oxidation of alcohol **17** and subsequent Wittig methylenation led to olefin **18** in 74% yield for 2 steps. Following the fluoride-mediated removal of the TBS group of **18**, the resulting alcohol **19** was exposed to acidic conditions using PPTS in CH_2Cl_2 to provide the desired 6-membered ether **5** (74% yield, 2 steps).

The right-hand piece **6** was prepared from **5** mainly through protective group manipulations. Ozone oxidation of **5**, followed by reduction with $NaBH_4$, afforded diol **20**, which was subsequently protected with Bn groups to yield bis-Bn ether **21** (79% yield, 2 steps). Removal of the MP acetal group from **21**, followed by TBS-protection/deprotection sequence, provided primary alcohol **23** in 73% yield for 3 steps. Lastly, ethoxyethyl (EE) ether formation from **23** and the subsequent TBS removal produced secondary alcohol **6** in 83% yield (2 steps).

Conversely, the left-hand piece **29** was afforded by the modification of the *exo*-olefin of **5**. TBS-protection (**25**, 98% yield) and subsequent hydroboration/oxidation (83% yield) of **5** afforded alcohol **26**, which was subjected to SO_3·pyridine oxidation, then Wittig olefination to produce olefin **27** in 78% yield (2 steps). A second hydroboration (**27**→**28**), followed by an oxidative work-up, led to primary alcohol **28** in 77% yield. Finally, alcohol **28** was converted to the requisite phenylsulfide **29** using $(PhS)_2$ and *n*-Bu_3P (92% yield).[24]

The coupling between **6** and **29** was realized by the direct method to form *O*,*S*-acetal **8**. Initially, the chloride



Scheme 2. *Reagents and conditions*: (a) $Ph_3PCH{=}CO_2Et$, THF, reflux; (b) *p*-MeOPhCH$(OMe)_2$, CSA, CH_2Cl_2, 82% (2 steps); (c) TBSCl, imidazole, DMF; (d) DIBAL, CH_2Cl_2, −78°C; (e) diethyl-D-tartrate, Ti(O*i*-Pr)$_4$, MS4A, *t*-BuOOH, CH_2Cl_2, −30°C, 84% (3 steps); (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°C; (g) $MePPh_3^+Br^-$, NaHMDS, THF, 0°C, 74% (2 steps); (h) TBAF, THF; (i) PPTS, CH_2Cl_2, 0°C, 74% (2 steps); (j) O_3, CH_2Cl_2/MeOH (5:1), −78°C, then $NaBH_4$; (k) BnBr, NaH, THF/DMF (5:1), 79% (2 steps); (l) CSA, CH_2Cl_2/MeOH (1:1); (m) TBSCl, imidazole, DMF; (n) CSA, MeOH, 0°C, 73% (3 steps); (o) EVE, PPTS, CH_2Cl_2; (p) TBAF, THF, 83% (2 steps); (q) TBSCl, imidazole, DMF, 98%; (r) 9-BBN dimer, THF, then NaOH, H_2O_2, 83%; (s) SO_3·pyridine, DMSO, Et_3N, CH_2Cl_2; (t) $MePPh_3^+Br^-$, *t*-BuOK, THF, 0°C, 78% (2 steps); (u) 9-BBN dimer, THF, then NaOH, H_2O_2, 77%; (v) $(PhS)_2$, *n*-Bu_3P, pyridine, 92%; (w) NCS, CCl_4; (x) **6** (1.2 equiv.), AgOTf, 2,6-di-*t*-butyl-4-methylpyridine (DTBMP), MS4A, CH_2Cl_2, −78 to −30°C, 86%; (y) TBAF, THF, room temperature; (z) methyl propiolate, 4-methylmorpholine (NMM), CH_2Cl_2, 82% (2 steps); (aa) *n*-Bu_3SnH, AIBN, toluene, 80 °C, 97% (**32**/**33**=3.2:1).

substituent was introduced to sulfide **29** by treatment with *N*-chlorosuccinimide in CCl_4; the resulting α-chlorosulfide **7** was activated by silver triflate[18] in the presence of **6** (1.2 equiv.) and 2,6-di-*t*-butyl-4-methylpyridine to deliver the desired *O*,*S*-acetal **8** in 86% yield as a 2:1 mixture of epimers at the acetal carbon. The thiophenyl group of **8**, which could also be potentially activated by the silver salt, was stable under the coupling conditions. Moreover, the inertness of the acid-labile protective groups (EE, MP) of **8** demonstrated the neutral nature and high chemoselectivity of this reaction.

To prepare for the formation of 7-membered ring, TBS ether **8** was transformed to β-alkoxyacrylate **30** via a two-step sequence: (i) TBAF in THF, and (ii) methyl propiolate and 4-methylmorpholine in CH_2Cl_2 (82% yield, 2 steps). Treatment of **30** (as a 2:1 mixture of diastereomers) with *n*-Bu_3SnH in the presence of AIBN at 80°C gave 7-membered ring **32** as a single diastereomer along with a small amount of the non-cyclized product **33** (**32**/**33**=3.2:1, 97% combined yield).[25,26] Therefore, two stereocenters were introduced with complete selectivity in this one reaction. Moreover, the chirality of the acetal carbon was inconsequential to the stereochemical outcome of the radical cyclization, and thus stereoselective synthesis of *O*,*S*-acetal **8** was not necessary. These features are especially important for the facile and efficient assembly of complex natural and artificial products.

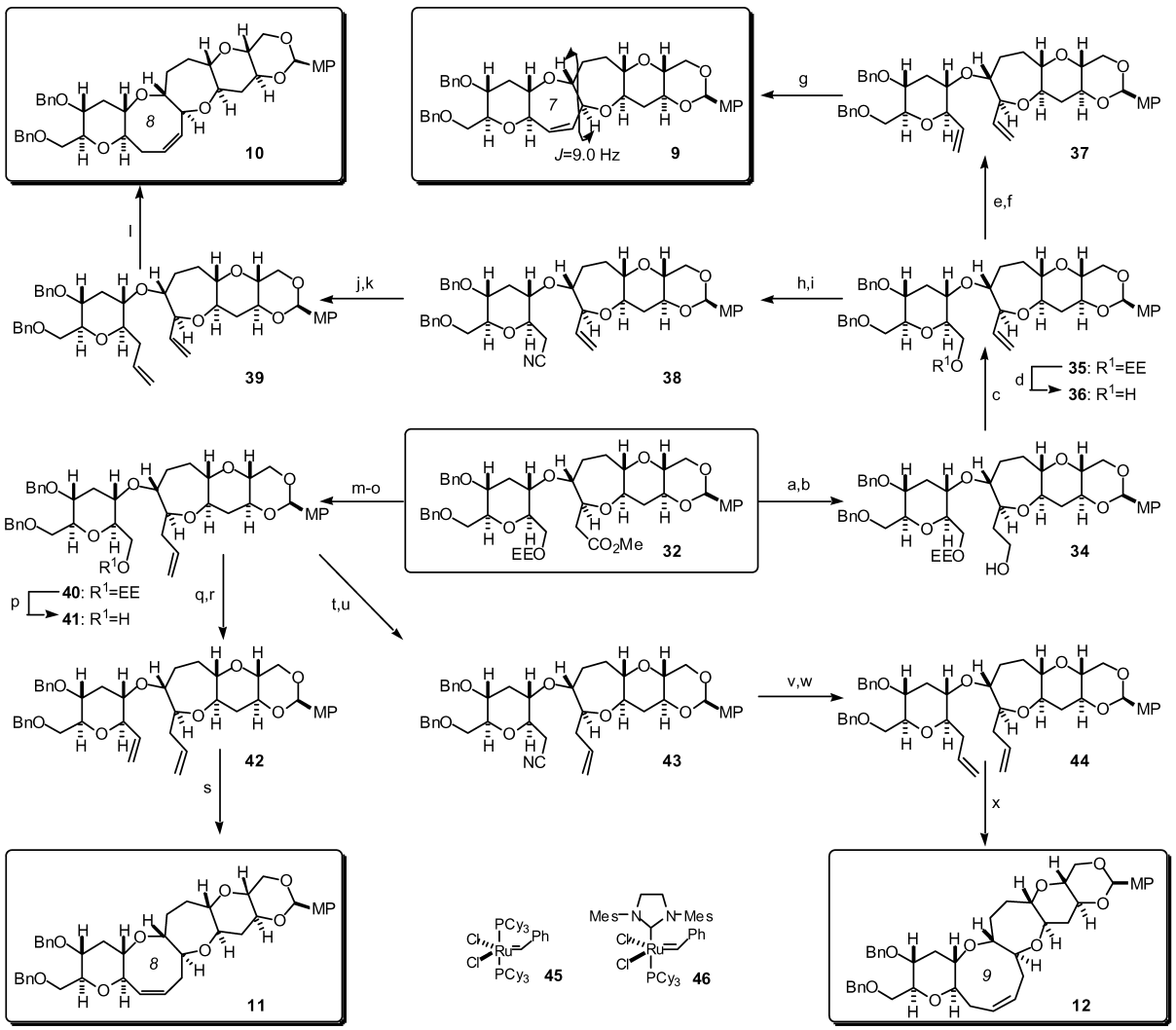
The stereoselectivity of the cyclization can be explained as follows. Initially the stereochemical information of the acetal carbon was lost upon formation of the radical intermediate **31**. The β-(*E*)-alkoxyacrylate favored the extended *s-trans* over *s*-cis-conformation. Furthermore, the steric interactions between the bulky alkoxy group and the *s-trans*-alkoxyacrylate of the pseudo-equatorial **31eq**

resulted in the preference of the pseudo-axial **31ax**, from which the desired isomer **32** was the only possible outcome among the four possible isomers.[3,14,25]

4. Synthesis of 6-*X*-7-6 ring system using RCM

The tetracycles **9**–**12** were synthesized from O-linked oxacycle **32** via RCM as a key tactic (Scheme 3). Firstly, 6-7-7-6 ring system was synthesized. Stepwise reduction of **32** using DIBAL then $NaBH_4$ afforded alcohol **34** in 70% yield for 2 steps. Treatment of alcohol **34** with 2-nitrophenyl selenocyanate and tributylphosphine produced the corresponding 2-nitrophenyl selenide, which was converted to olefin **35** through elimination via hydroperoxide oxidation (85% yield).[27] Although the removal of the EE group of **35** under acidic conditions caused partial cleavage of the MP-acetal, reformation was subsequently performed via trans-acetalization to give alcohol **36** in 74% yield (2 steps). Alcohol **36** was then successively subjected to SO_3·pyridine oxidation and Wittig methylenation to generate diene **37** (74% yield, 2 steps). Although inert to RCM reaction using **45**,[28] diene **37** was cyclized using second-generation Grubbs catalyst **46**[29] to give the 6-7-7-6 *trans*-fused polycyclic ether system **9** in 31% yield. The indicated proton-proton coupling constant in **9** (J=9.0 Hz) verified the *trans*-relationship established in the radical cyclization.

Next, two olefinic isomers (**10** and **11**) for 6-8-7-6 ring systems were constructed. For the synthesis of isomer **10**, alcohol **36** was converted to nitrile **38** via tosylation followed by displacement with NaCN (quantitative). DIBAL reduction of the nitrile group of **38** and subsequent Wittig olefination afforded the diene **39** in 50% yield along with the recovery of the starting nitrile (20%). Diene **39** was subjected to RCM in the presence of **45** to deliver the 6-8-7-6 fused polycyclic ether **10** in 91% yield. Conversely, for the synthesis of isomer **11**, ester **32** was transformed to olefin **40**



Scheme 3. *Reagents and conditions*: (a) DIBAL, CH_2Cl_2, −78°C; (b) $NaBH_4$, MeOH, 70% (2 steps); (c) 2-nitrophenyl selenocyanate, *n*-Bu_3P, pyridine, THF, then $NaHCO_3$, H_2O_2, 40°C, 85%; (d) PPTS, MeOH, then *p*-MeOPhCH(OMe)$_2$, PPTS, CH_2Cl_2, 74%; (e) SO_3·pyridine, DMSO, Et_3N, CH_2Cl_2; (f) $MePPh_3^+Br^-$, NaHMDS, THF, 0°C, 74% (2 steps); (g) **46**, CH_2Cl_2, 40°C, 31%; (h) *p*-TsCl, pyridine, MS4A, 100%; (i) NaCN, DMSO, 50°C, 100%; (j) DIBAL, CH_2Cl_2, −78°C; (k) $MePPh_3^+Br^-$, NaHMDS, THF, 0°C, 50% (2 steps), recovered **38**: 20%; (l) **45**, CH_2Cl_2, 40°C, 91%; (m) DIBAL, CH_2Cl_2, −90°C; (n) SO_3·pyridine, DMSO, Et_3N, CH_2Cl_2; (o) $MePPh_3^+Br^-$, NaHMDS, THF, 0°C, 69% (3 steps); (p) PPTS, MeOH, then *p*-MeOPhCH(OMe)$_2$, PPTS, CH_2Cl_2, 89%; (q) SO_3·pyridine, DMSO, Et_3N, CH_2Cl_2; (r) $MePPh_3^+Br^-$, NaHMDS, THF, 0°C, 66% (2 steps); (s) **45**, CH_2Cl_2, 35°C, 93%; (t) *p*-TsCl, pyridine, MS4A, 89%; (u) NaCN, DMSO, 50°C, 93%; (v) DIBAL, CH_2Cl_2, −78°C; (w) $MePPh_3^+Br^-$, NaHMDS, THF, 0°C, 75% (2 steps); (x) **45**, CH_2Cl_2, 40°C, 78%.

via 3 steps (69% yield): (i) DIBAL reduction of **32**, (ii) SO_3·pyridine oxidation and (iii) Wittig methylenation. Removal of the EE ether of **40** and subsequent reformation of the MP-acetal afforded alcohol **41** (89% yield), which was oxidized to the aldehyde, then converted to diene **42** through Wittig olefination (66% yield, 2 steps). Diene **42** was treated with **45** at 35°C to undergo RCM, leading to the 8-membered ring **11** in 93% yield.

Lastly, the 6-9-7-6 system of **12** was prepared as follows. Nitrile **43** was obtained from alcohol **41** by tosylation followed by cyanation (93% yield). DIBAL reduction of the nitrile group of **43** to the aldehyde and subsequent Wittig olefination gave diene **44** (75% yield, 2 steps), which was in turn subjected to RCM using **45** as a catalyst to generate the 6-9-7-6 *trans*-fused polycyclic ether system **12** (78% yield). Intriguingly, ^{1}H NMR signals of the 9-membered ring of **12** were severely broadened at room temperature due to slow conformational change, while such a dynamic behavior was not observed in the NMR spectra of the other ring systems (**9**–**11**).[30]

5. Conclusion

An efficient and applicable coupling strategy was developed, based on the direct construction of the *O*,*S*-acetal from the alcohol and the α-chlorosulfide. The neutral nature of the coupling strategy enabled the synthesis of a wide variety of substrates with sensitive functionalities. Application of this method to the divergent synthesis of 6-*X*-7-6 tetracyclic systems (*X*=7, 8, or 9) was demonstrated starting with a 6-membered ether as the common intermediate. We believe that the results from this study can greatly contribute to rapid constructions of ladder-shaped synthetic polyethers with the sizes of natural products. Further studies toward the synthesis of artificial polyether compounds with tailored biological activity are currently underway in our laboratory.

6. Experimental

6.1. General

All reactions sensitive to air or moisture were carried out under argon or nitrogen atmosphere in dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. THF was distilled from sodium/benzophenone, diethyl ether (Et_2O) from $LiAlH_4$, dichloromethane (CH_2Cl_2), pyridine, triethylamine (Et_3N), and toluene from calcium hydride, and DMF and DMSO from calcium hydride under reduced pressure. All other reagents were used as supplied unless otherwise stated.

Analytical thin-layer chromatography (TLC) was performed using E. Merck Silica gel 60 F254 pre-coated plates. Column chromatography was performed using 100–210 μm Silica Gel 60N (Kanto Chemical Co., Inc.), and for flash chromatography 40–50 μm Silica Gel 60N (Kanto Chemical Co., Inc.) was used.

^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 200 (200 MHz), or a Varian INOVA 500 (500 MHz) spectrometer. Chemical shifts are reported in δ (ppm) using residual $CHCl_3$ as an internal standard of δ 7.26 and δ 77.00 for ^{1}H and ^{13}C NMR, respectively. Signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. IR spectra were recorded on a Perkin–Elmer Spectrum BX FT-IR spectrometer. MALDI-TOF mass spectra were measured on a Applied Biosystems Voyager DE STR SI-3 instrument, and ESI-TOFMS were on Applied Biosystems Mariner. Optical rotations were recorded on a JASCO DIP-370 polarimeter. Melting points were measured on a Yanaco MP-S3 micro melting point apparatus.

6.1.1. Alcohol 14. A solution of 2-deoxy-D-ribose (100 g, 746 mmol) and (carbethoxymethylene)triphenyphosphorane (549 g, 1.58 mol) in THF (750 mL) was heated to reflux overnight. After concentration, the crude mixture was dissolved in CH_2Cl_2 (800 mL). To the solution were added *p*-methoxybenzaldehyde dimethyl acetal (165 mL, 889 mmol) and CSA (34.6 g 149 mmol) at room temperature. After 1 day, the reaction mixture was quenched with Et_3N (30 mL), concentrated, and subjected to column chromatography (hexane/EtOAc=10/1–3/1) to give alcohol **14** as a colorless oil (196 g, 82%): $[\alpha]_D^{27}=-44.75°$ (*c* 1.63, $CHCl_3$); IR (film) ν 3464, 2978, 1716, 1655, 1081, 1034, 613 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (2H, d, *J*=9.0 Hz), 7.07 (1H, dt, *J*=16.0, 7.0 Hz), 6.89 (2H, d, *J*=9.0 Hz), 5.96 (1H, dt, *J*=16.0, 1.5 Hz), 5.44 (1H, s), 4.25 (1H, dd, *J*=10.5, 4.5 Hz), 4.19 (2H, q, *J*=7.0 Hz), 3.81 (3H, s), 3.69 (1H, ddd, *J*=10.5, 7.0, 3.5 Hz), 3.64 (1H, td, *J*=10.5, 4.5 Hz), 3.57 (1H, t, *J*=10.5 Hz), 2.79 (1H, dddd, *J*=15.5, 7.0, 3.5, 1.5 Hz), 2.56 (1H, dtd, *J*=15.5, 7.0, 1.5 Hz), 1.29 (3H, t, *J*=7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.52, 159.97, 144.59, 129.97, 127.35, 123.82, 113.82, 113.56, 100.83, 80.32, 71.13, 65.18, 60.33, 55.24, 34.49, 14.18; MALDI-TOF-MS, calcd $C_{17}H_{22}O_6Na$ $[M+Na]^+$ 345.131, found 345.128.

6.1.2. Epoxide 17. To a solution of alcohol **14** (196 g, 399 mmol) and imidazole (41 g, 600 mmol) in DMF (200 mL) was added TBSCl (63.1 g, 419 mmol). After 12 h, additional TBSCl (12.0 g, 79 mmol) was introduced. The reaction mixture was quenched with MeOH (200 mL), and concentrated. The residue was subjected to column chromatography (hexane/EtOAc=15/1–5/1) to give TBS ether **15** as a colorless oil, which was used in the next reaction without further purification: IR (film) ν 2955, 1720, 1656, 1174, 837, 777 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (2H, d, *J*=9.0 Hz), 7.06 (1H, dt, *J*=15.5, 7.5 Hz), 6.88 (2H, d, *J*=9.0 Hz), 5.93 (1H, dt, *J*=15.5, 7.5 Hz), 5.44 (1H, s), 4.19 (2H, q, *J*=7.0 Hz), 4.17 (1H, dd, *J*=10.5, 4.5 Hz), 3.80 (3H, s), 3.66 (1H, td, *J*=8.0, 3.0 Hz), 3.58 (1H, td, *J*=10.5, 4.5 Hz), 3.55 (1H, t, *J*=10.5 Hz), 2.74 (1H, dddd, *J*=15.5, 8.0, 3.0, 1.5 Hz), 2.45 (1H, dtd, *J*=15.5, 8.0, 1.5 Hz), 1.29 (3H, t, *J*=7.0 Hz), 0.90 (9H, s), 0.11 (3H, s), 0.09 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.31, 159.88, 144.73, 130.05, 127.27, 123.55, 113.48, 100.71, 80.83, 71.53, 66.17, 60.15, 55.18, 34.34, 25.60, 17.79, 14.20, −4.17, −4.85; MALDI-TOF-MS, calcd $C_{23}H_{36}O_6SiNa$ $[M+Na]^+$ 459.217, found 459.199.

To a solution of the above TBS ether **15** in CH_2Cl_2

(533 mL) at −78°C was added DIBAL (878 mL, 878 mmol, 1.0 M in hexane) over 1 h. The reaction mixture was quenched with MeOH (12 mL), and allowed to warm to room temperature. After saturated aqueous potassium sodium tartrate (300 mL) was added, the mixture was diluted with EtOAc (300 mL), and stirred overnight. The aqueous layer was extracted with EtOAc (×2). The combined organic layer was dried over $MgSO_4$, concentrated, and subjected to column chromatography (hexane/EtOAc=10/1–4/1) to give allylic alcohol **16** as a colorless oil, which was used in the next reaction without further purification: IR (film) ν 3413, 2955, 1614, 1518, 1463, 1390, 1252, 837 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39 (2H, d, J=9.0 Hz), 6.87 (2H, d, J=9.0 Hz), 5.83 (1H, dt, J=15.5, 6.5 Hz), 5.74 (1H, dt, J=15.5, 5.5 Hz), 5.43 (1H, s), 4.15 (1H, dd, J=9.5, 2.5 Hz), 4.09 (2H, d, J=5.5 Hz), 3.79 (3H, s), 3.60–3.55 (2H, m), 3.53 (1H, t, J=9.5 Hz), 2.61 (1H, dd, J=13.5, 6.5 Hz), 2.30 (1H, dt, J=15.5, 6.5 Hz), 0.89 (9H, s), 0.10 (3H, s), 0.08 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.83, 131.53, 130.31, 128.29, 127.29, 114.24, 113.48, 100.69, 81.78, 71.57, 66.04, 55.20, 34.25, 25.63, 17.82, −4.17, −4.81; MALDI-TOF-MS, calcd $C_{21}H_{34}O_5SiNa$ $[M+Na]^+$ 417.207, found 417.205.

To a suspension of diethyl-D-tartrate (17 mL, 100 mmol), titanium(IV) tetraisopropoxide (26 mL, 88 mmol) and powdered molecular sieves 4A in CH_2Cl_2 (300 mL) at −30°C was added the solution of the above alcohol **16** in CH_2Cl_2 (800 mL) dropwise over 30 min. After 30 min, *t*-butylhydroperoxide (183 mL, 735 mmol, 4.0 M in CH_2Cl_2) was added. The reaction mixture was stored at −30°C for 27 h. Then, the reaction mixture was filtrated. The filtrate was diluted with EtOAc (600 mL), washed with aqueous saturated $Na_2S_2O_3$, and dried over $MgSO_4$. The residue was subjected to column chromatography (hexane/EtOAc=15/1–4/1) to give epoxide **17** as a pale yellow oil (139.35 g, 84% for 3 steps): $[\alpha]_D^{18}$=−36.75° (*c* 1.68, $CHCl_3$); IR (film) ν 2956, 1519, 1464, 1105, 1035, 779 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (2H, d, J=9.0 Hz), 6.88 (2H, d, J=9.0 Hz), 5.46 (1H, s), 4.17 (1H, dd, J=10.5, 4.5 Hz), 3.91 (1H, ddd, J=12.5, 5.5, 2.5 Hz), 3.80 (3H, s), 3.69–3.63 (2H, m), 3.62 (1H, ddd, J=12.5, 7.0, 5.0 Hz), 3.54 (1H, t, J=10.5 Hz), 3.22 (1H, td, J=5.0, 2.5 Hz), 2.96 (1H, dt, J=5.0, 2.5 Hz), 2.02 (1H, ddd, J=14.5, 5.0, 3.0 Hz), 1.96 (1H, ddd, J=14.5, 7.0, 6.0 Hz), 1.79 (1H, t, J=5.5 Hz), 0.88 (9H, s), 0.10 (3H, s), 0.09 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.94, 130.18, 127.29, 113.58, 100.74, 79.85, 71.74, 65.81, 61.68, 57.78, 55.25, 52.87, 33.31, 25.64, 17.82, −4.26, −4.83; MALDI-TOF-MS, calcd $C_{21}H_{34}O_6SiNa$ $[M+Na]^+$ 433.202, found 433.210.

6.1.3. Vinyl epoxide 18. To a solution of oxalyl chloride (16.6 mL, 195 mmol) and DMSO (20.6 mL, 292 mmol) in CH_2Cl_2 (600 mL) at −78°C were added alcohol **17** (40 g, 97.4 mmol) in CH_2Cl_2 (370 mL) and then Et_3N (67.8 mL, 487 mmol). After 1 h, the reaction mixture was washed with saturated aqueous NH_4Cl, and then diluted with hexane/EtOAc (1 L), and washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and concentrated to give the epoxy aldehyde, which was used in the next reaction without purification.

To a suspension of methyltriphenylphosphonium bromide (52.2 g, 122 mmol) in THF (100 mL) at 0°C was added sodium bis(trimethylsilyl)amide (122 mL, 122 mmol, 1.0 M in THF). To the resultant bright yellow ylide at 0°C was added the above aldehyde in THF (150 mL) over 10 min. After 10 min, the reaction mixture was quenched with acetone (10 mL), diluted with hexane/EtOAc (100 mL), and washed with water (×2). The organic layer was dried over $MgSO_4$ and concentrated. The residue was subjected to column chromatography (hexane/EtOAc=8/1–2/1) to give olefin **18** as a colorless oil (30 g, 74% for 2 steps): $[\alpha]_D^{18}$=−60.61° (*c* 2.12, $CHCl_3$); IR (film) ν 2956, 2929, 1463, 1389, 1172, 1111, 1036, 778 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 (2H, d, J=9.0 Hz), 6.89 (2H, d, J=9.0 Hz), 5.59 (1H, ddd, J=17.5, 10.0, 7.5 Hz), 5.47 (1H, s), 5.47 (1H, dd, J=17.5, 1.5 Hz), 5.27 (1H, dd, J=10.0, 1.5 Hz), 4.18 (1H, dd, J=10.5, 4.5 Hz), 3.80 (3H, s), 3.70 (1H, td, J=9.5, 4.0 Hz), 3.68 (1H, td, J=9.5, 4.5 Hz), 3.55 (1H, dd, J=10.5, 9.5 Hz), 3.15 (1H, dd, J=7.5, 4.0 Hz), 3.12 (1H, td, J=5.5, 4.0 Hz), 2.00 (2H, m) 0.88 (9H, s), 0.10 (3H, s), 0.09 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.92, 135.72, 130.22, 127.30, 119.31, 113.56, 100.69, 79.87, 71.75, 65.87, 58.21, 57.21, 55.26, 33.78, 25.66, 17.84, −4.27, −4.81; MALDI-TOF-MS, calcd $C_{22}H_{34}O_5SiNa$ $[M+Na]^+$ 429.207, found 429.218.

6.1.4. Pyran 5. To a solution of olefin **18** (30 g, 74 mmol) in THF (74 mL) at room temperature was added TBAF (81.4 mL, 81.4 mmol, 1.0 M in THF) dropwise. After 30 min, the reaction mixture was diluted with ether (100 mL), washed with water (×2), dried over $MgSO_4$, and concentrated. The residue was subjected to short column chromatography to give the hydroxy epoxide **19**, which was used in the next reaction without further purification.

The above hydroxy epoxide **19** in CH_2Cl_2 (740 mL) was treated with PPTS (14.8 g, 59.2 mmol) at 0°C. After 3 h, Et_3N (11.4 mL, 65 mmol) was added and the solvent was evaporated. The residue was subjected to column chromatography (hexane/EtOAc=5/1–2/1), and then recrystallized from hexane/EtOAc to give pyran **5** as a colorless crystal (15.8 g, 74% for 2 steps): mp 165–166.8°C; $[\alpha]_D^{29}$=−10.45° (*c* 0.91, $CHCl_3$); IR (film) ν 2931, 1433, 1359, 1301, 824, 747, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44–7.40 (2H, m), 6.93–6.87 (2H, m), 5.86 (1H, ddd, J=16.5, 10.0, 7.0 Hz), 5.50 (1H, s), 5.45 (1H, dd, J=16.5, 1.0 Hz), 5.38 (1H, dd, J=10.0, 1.0 Hz), 4.32 (1H, dd, J=10.5, 5.0 Hz), 3.80 (3H, s), 3.69 (1H, t, J=10.5 Hz), 3.67 (1H, dd, J=8.0, 7.0 Hz), 3.58 (1H, ddd, J=12.0, 9.0, 4.5 Hz), 3.52 (1H, ddd, J=12.0, 8.0, 4.5 Hz), 3.41 (1H, ddd, J=10.5, 9.0, 5.0 Hz), 2.52 (1H, dt, J=12.0, 4.5 Hz), 1.74 (1H, q, J=12.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.16, 134.99, 127.48, 119.99, 113.72, 101.66, 83.89, 76.52, 73.01, 69.22, 68.91, 55.31, 37.07; ESI-MS, calcd $C_{16}H_{21}O_5$ $[M+H]^+$ 293.138, found 293.098.

6.1.5. Bis-Bn ether 21. Ozone was bubbled through a solution of pyran **5** (4.39 g, 15 mmol) in CH_2Cl_2/MeOH (5:1, 456 mL) at −78°C until the color of solution turned pale purple. Then, the reaction mixture was treated with $NaBH_4$ (2.84 g, 75 mmol), and the cooling bath was removed. After being stirred at room temperature overnight,

the reaction mixture was diluted with ether-EtOAc, washed with saturated aqueous NH_4Cl and brine. The organic layer was concentrated, and the residue was subjected to short column chromatography to give diol **20**, which was used in the next reaction without further purification.

A solution of the above diol **20** in THF/DMF (5:1, 46 mL) was treated with NaH (1.37 g 60% in oil, 34.3 mmol) and BnBr (3.58 mL, 30.1 mmol) at 0°C. After being stirred for 13 h at room temperature, the reaction mixture was diluted with ether and washed with saturated aqueous NH_4Cl and brine. The organic layer was dried over $MgSO_4$ and concentrated. The residue was subjected to column chromatography (hexane/EtOAc=15/1–5/1) to give bis-Bn ether **21** as a colorless solid (5.63 g, 79% for 2 steps): $[\alpha]_D^{17}=-59.56°$ (*c* 0.82, $CHCl_3$); IR (film) ν 2869, 1615, 1518, 1454, 1096, 1029, 830 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35–7.11 (12H, m), 6.82–6.78 (2H, m), 5.38 (1H, s), 4.53 (1H, d, *J*=12.0 Hz), 4.49 (1H, d, *J*=11.0 Hz), 4.46 (1H, d, *J*=12.0 Hz), 4.33 (1H, d, *J*=11.0 Hz), 4.24 (1H, dd, *J*=10.0, 5.0 Hz), 3.71 (3H, s), 3.67 (1H, dd, *J*=10.5, 2.0 Hz), 3.63 (1H, t, *J*=10.0 Hz), 3.60 (1H, dd, *J*=10.5, 4.5 Hz), 3.54 (1H, dt, *J*=10.5, 4.5 Hz), 3.45 (1H, td, *J*=10.5, 2.0 Hz), 3.43 (1H, t, *J*=10.0, 5.0 Hz), 3.30 (1H, dt, *J*=10.5, 4.5 Hz), 2.53 (1H, dt, *J*=10.5, 4.5 Hz), 1.59 (1H, q, *J*=10.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.10, 138.10, 137.84, 129.94, 128.55, 128.34, 127.86, 127.77, 127.76, 127.63, 127.43, 113.67, 101.51, 80.51, 76.22, 73.51, 73.22, 72.22, 71.08, 69.25, 69.09, 55.27, 34.89; MALDI-TOF-MS, calcd $C_{29}H_{32}O_6Na$ $[M+Na]^+$ 499.209, found 499.210.

6.1.6. Alcohol 23. To a solution of MP-acetal **21** (4.20 g, 8.80 mmol) in MeOH/CH_2Cl_2 (10 mL, 1:1) was added CSA (0.410 g, 1.76 mmol). After 1.2 h, Et_3N (3 mL) was added, and the solution was evaporated to give the crude diol, which was used in the next reaction without purification.

A solution of the above diol in DMF (10 mL) was treated with imidazole (2.520 g, 36.9 mmol) and TBSCl (5.04 g, 33.4 mmol) at room temperature, and the resultant solution was stirred for 3 h. The mixture was diluted with EtOAc (100 mL), washed with saturated aqueous NH_4Cl and brine, dried over $MgSO_4$, and concentrated to give the bis-TBS ether **22**, which was directly used in the next reaction.

To a solution of the bis-TBS ether **22** in MeOH (20 mL) was added CSA (0.480 g, 1.76 mmol) at 0°C. The solution was stirred at 0°C for 20 min, and Et_3N (2 mL) was added. The mixture was concentrated, and the residue was subjected to flash chromatography (hexane/EtOAc=5/1) to give alcohol **23** as a colorless oil (2.90 g, 73% for 3 steps): $[\alpha]_D^{30}=-4.37°$ (*c* 0.70, $CHCl_3$); IR (film) ν 3466, 2929, 2857, 1454, 1253, 1090, 837 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.24 (10H, m), 4.63–4.54 (3H, m), 4.42 (1H, d, *J*=11.1 Hz), 3.83 (1H, dd, *J*=9.7, 2.8 Hz), 3.78 (1H, d, *J*=9.7 Hz), 3.71–3.65 (1H, m), 3.62 (1H, dd, *J*=11.1, 4.2 Hz), 3.60–3.52 (1H, m), 3.48 (1H, ddd, *J*=14.6, 11.1, 4.2 Hz), 3.44–3.42 (1H, m), 3.25–3.20 (1H, m), 2.23–2.19 (1H, m), 2.2 (1H, brs), 1.5 (1H, q, *J*=14.6 Hz), 0.89 (9H, s), 0.076 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.36, 128.63, 128.08, 128.01, 82.30, 80.04, 73.76, 73.72, 73.69, 72.40, 71.52, 69.53, 66.69, 62.77, 39.38, 25.98, 25.96, 18.13, −3.95, −4.65; MALDI-TOF-MS, calcd for $C_{27}H_{40}O_5SiNa$ $[M+Na]^+$ 495.254, found 495.243.

6.1.7. Alcohol 6. To a solution of compound **23** (116.5 mg, 0.246 mmol) and EVE (118 μL, 1.23 mmol) in CH_2Cl_2 (3 mL) was added PPTS (12.4 mg, 49.2 μmol). After 1 h, the reaction mixture was diluted with EtOAc (20 mL), and washed with saturated aqueous NH_4Cl and brine. The organic layer was dried over $MgSO_4$, and concentrated to give crude EE ether **24**.

A solution of the above compound **24** in THF (2 mL) was treated with TBAF (1 M solution in THF, 0.59 mL, 0.59 mmol). After being stirred for 3 h, the mixture was diluted with EtOAc (20 mL), washed with saturated aqueous NH_4Cl and brine, dried over $MgSO_4$, and concentrated. The residue was subjected to flash chromatography (hexane/EtOAc=1.8/1) to give alcohol **6** as a colorless oil (88.2 mg, 83% for 2 steps): ^1H NMR (500 MHz, $CDCl_3$) δ 7.33–7.20 (10H, m), 4.77 (1/2H, q, *J*=6.6 Hz), 4.72 (1/2H, q, *J*=6.6 Hz), 4.64–4.55 (3H, m), 4.42 (1H, d, *J*=13.2 Hz), 3.92 (1/2H, dd, *J*=10.5, 3.8 Hz), 3.62 (1/2H, dd, *J*=10.5, 3.8 Hz), 3.79–3.71 (1H, m), 3.70–3.60 (3H, m), 3.53–3.41 (3.5H, m), 3.36–3.27 (1.5H, m), 2.63–2.56 (1H, m), 1.48 (1H, dq, *J*=11.8, 1.3 Hz), 1.32 (3H, d, *J*=6.6 Hz), 1.22 (3H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.25, 138.00, 128.36, 128.3, 127.8, 127.79, 127.75, 127.69, 127.55, 127.53, 100.38, 100.06, 80.18, 19.99, 79.23, 78.47, 73.45, 73.43, 72.11, 71.95, 70.94, 70.93, 63.39, 69.28, 67.88, 66.76, 66.59, 61.79, 61.76, 37.54, 37.26, 19.69, 15.21, 15.16; MALDI-TOF-MS, calcd for $C_{25}H_{34}O_6Na$ $[M+Na]^+$ 453.225, found 453.206.

6.1.8. TBS ether 25. To a solution of alcohol **5** (4.38 g, 1.5 mmol) in DMF (15 mL) were added imidazole (3.06 g, 4.5 mmol) and TBSCl (4.52 g, 0.75 mol) at room temperature. The resultant mixture was stirred for 1.5 h. The solution was diluted with EtOAc (100 mL), washed with saturated aqueous NH_4Cl and brine, dried over $MgSO_4$, and concentrated. The residue was subjected to flash chromatography (hexane/EtOAc=8/1) to give the TBS ether **25** as a colorless oil (5.973 g, 98%): $[\alpha]_D^{32}=-42.75°$ (*c* 0.68, $CHCl_3$); IR (film) ν 2955, 2858, 1617, 1518, 1251, 1090, 1039, 837 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (2H, d, *J*=9.3 Hz), 6.9 (2H, d, *J*=9.3 Hz), 5.92–5.83 (1H, m), 5.49 (1H, s), 5.36 (1H, d, *J*=16.0 Hz), 5.26 (1H, d, *J*=12.0 Hz), 4.34 (1H, dd, *J*=10.0, 6.7 Hz), 3.81 (3H, s), 3.72–3.63 (2H, m), 3.57–3.49 (2H, m), 3.42 (1H, dt, *J*=10.0, 6.7 Hz), 2.42 (1H, m), 1.77 (1H, q, *J*=10.0 Hz), 0.879 (9H, s), 0.071 (3H, s), 0.051 (3H, s); ^{13}C NMR (125 MHz, $CHCl_3$) δ 160.09, 135.54, 129.92, 127.45, 117.78, 113.67, 101.58, 83.15, 76.39, 72.78, 70.44, 69.34, 55.26, 38.98, 25.68, 17.93, −4.29, −4.63; MALDI-TOF-MS, calcd for $C_{22}H_{36}O_6SiNa$ $[M+Na]^+$ 429.207, found 429.203.

6.1.9. Alcohol 26. To a solution of olefin **25** (0.407 g, 1 mmol) in THF (5 mL) was added 9-BBN dimer (0.537 g, 2.2 mmol). The solution was stirred for 38 h at room temperature. Then, the reaction mixture was cooled to 0°C, and quenched with water (0.5 mL). After 10 min, 10% NaOH solution (6 mL) and 30% H_2O_2 (3 mL) were added. The mixture was stirred for 30 h at room temperature, and then diluted with EtOAc (80 mL). The organic layer was

washed with brine, dried over $MgSO_4$, and concentrated. The residue was subjected to flash chromatography (hexane/EtOAc=15/1–6/1) to give alcohol **26** as a colorless oil (0.351 g, 83%): $[\alpha]_D^{28}=-52.87°$ (*c* 0.40, $CHCl_3$); IR (film) ν 2955, 2858, 1615, 1518, 1251, 1089, 1036, 836, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 (2H, d, *J*=9.6 Hz), 6.82 (2H, d, *J*=9.6 Hz), 5.40 (s, 1H), 4.2 (1H, dd, *J*=9.7, 4.1 Hz), 3.71–3.73 (2H, m), 3.72 (3H, s), 3.55 (1H, t, *J*=9.7 Hz), 3.48–3.42 (2H, m), 3.36 (1H, dt, *J*=9.6, 4.1 Hz), 3.34–3.26 (1H, m), 2.35–2.28 (1H, m), 2.06–1.99 (1H, m), 1.62 (1H, q, *J*=9.6 Hz), 1.60–1.53 (1H, m), 0.798 (9H, s), 0.006 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.41, 130.07, 127.72, 113.97, 101.93, 83.39, 76.56, 73.42, 70.52, 69.44, 55.56, 39.01, 34.29, 25.95, 18.15, −3.85, −4.51. MALDI-TOF-MS, calcd for $C_{22}H_{36}O_6SiNa$ $[M+Na]^+$ 447.217, found 447.208.

6.1.10. Olefin 27. To a solution of alcohol **26** (4.067 g, 9.58 mmol) in CH_2Cl_2 (40 mL) were added DMSO (4.08 mL, 57.5 mmol), Et_3N (13.35 mL, 95.78 mmol) and SO_3·pyridine (3.81 g, 23.95 mmol) at room temperature. The reaction solution was stirred for 3 h and then diluted with EtOAc (100 mL). The mixture was washed with saturated aqueous $NaHCO_3$, saturated aqueous NH_4Cl and brine, dried over $MgSO_4$, and concentrated. The residue was used in the next reaction without further purification.

To a suspension of methyltriphenylphosphonium bromide (11.98 g, 33.52 mmol) in THF (40 mL) was added *t*-BuOK (3.225 g, 28.73 mmol) at 0°C. The resultant bright yellow ylide was stirred at 0°C for further 20 min, and the above aldehyde in THF (20 mL) was added to this mixture. The reaction mixture was stirred for 1.5 h at room temperature, and then quenched with saturated aqueous NH_4Cl, and diluted with EtOAc (100 mL). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was subjected to flash chromatography (hexane/EtOAc=8/1) to give olefin **27** as a colorless solid (3.15 g, 78% for 2 steps): $[\alpha]_D^{28}=-49.12°$ (*c* 0.86, $CHCl_3$); IR (film) ν 2955, 2858, 1616, 1518, 1251, 1090, 836, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (2H, d, *J*=11.1 Hz), 6.87 (2H, d, *J*=11.1 Hz), 4.28 (1H, dd, *J*=12.7, 4.2 Hz), 3.81 (3H, s), 3.68 (1H, dd, *J*=13.9, 11.2 Hz), 3.55–3.46 (2H, m), 3.37–3.32 (1H, m), 3.31–3.25 (1H, m), 2.62–2.56 (1H, m), 2.42–2.36 (1H, m), 2.22–2.13 (1H, m), 1.50 (1H, q, *J*=13.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.36, 135.14, 130.24, 127.74, 117.01, 113.96, 101.86, 82.41, 76.84, 73.32, 70.12, 69.67, 55.56, 39.15, 36.14, 25.99, 18.17, −3.73, −4.49; MALDI-TOF-MS, calcd for $C_{23}H_{36}O_5SiNa$ $[M+Na]^+$ 443.223, found 443.219.

6.1.11. Alcohol 28. To a solution of olefin **27** (3.15 g, 7.50 mmol) in THF (30 mL) was added 9-BBN dimer (4.03 g, 16.5 mmol). The solution was stirred at room temperature for 4 days. Then, the reaction mixture was cooled to 0°C, and quenched with water (5 mL). After 10 min, 10% NaOH solution (45 mL) and 30% H_2O_2 (22 mL) were added. The mixture was stirred for 30 h at room temperature, and then diluted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was subjected to flash chromatography (hexane/EtOAc=8/1–3/1) to give alcohol **28** as a colorless oil (2.54 g, 77%): $[\alpha]_D^{31}=-47.87°$ (*c* 0.82, $CHCl_3$); IR (film) ν 3391, 2930, 2858, 1616, 1518, 1251, 1090, 1036, 836, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (2H, d, *J*=8.5 Hz), 6.89 (2H, d, *J*=8.5 Hz), 5.48 (1H, s), 4.27 (1H, dd, *J*=11.1, 4.2 Hz), 3.81 (3H, s), 3.71–3.62 (3H, m), 3.54–3.45 (2H, m), 3.39–3.33 (1H, m), 3.23 (1H, dt, *J*=8.3, 2.7 Hz), 2.62–2.56 (1H, m), 2.02–1.95 (1H, m), 1.89–1.82 (1H, brs), 1.78–1.66 (3H, m), 1.44–1.39 (1H, m), 0.89 (9H, s), 0.092 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.28, 130.06, 127.63, 113.87, 101.80, 82.89, 76.69, 73.25, 70.36, 69.41, 63.11, 55.47, 39.07, 29.06, 28.36, 25.87, 18.07, −3.90, −4.60.

6.1.12. Phenylsulfide 29. To a solution of alcohol **28** (216.6 mg, 0.326 mmol) and PhSSPh (213 mg, 0.975 mmol) in pyridine (1 mL) was added *n*-Bu_3P (250 μL, 0.326 mmol). The resultant yellow solution was stirred until the starting material disappeared (ca. 24 h). EtOAc (10 mL) was added, and the solution was washed with NH_4Cl and brine, dried over $MgSO_4$, and concentrated. The residue was subjected to flash chromatography (hexane/EtOAc=20/1–15/1) to give phenylsulfide **29** as a pale yellow oil (159.2 mg, 92%): $[\alpha]_D^{24}=-43.9°$ (*c* 0.516, $CHCl_3$); IR (film) ν 2954, 1518, 1471, 1388, 1251, 1172, 1090, 864, 836 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 (2H, d, *J*=8.5 Hz), 7.33 (2H, d, *J*=7.0 Hz), 7.28 (2H, t, *J*=7.0 Hz), 7.16 (1H, t, *J*=7.0 Hz), 6.88 (2H, d, *J*=8.5 Hz), 5.46 (1H, s), 4.25 (1H, dd, *J*=10.0, 5.0 Hz), 3.79 (3H, s), 3.62 (1H, t, *J*=10.0 Hz), 3.48 (1H, ddd, *J*=11.5, 10.0, 4.5 Hz), 3.45 (1H, ddd, *J*=11.5, 9.0, 4.5 Hz), 3.31 (1H, td, *J*=10.0, 5.0 Hz), 3.19 (1H, td, *J*=9.0, 2.5 Hz), 2.94 (2H, td, *J*=7.5, 2.5 Hz), 2.36 (1H, dt, *J*=11.5, 4.5 Hz), 2.00 (1H, dddd, *J*=13.5, 9.0, 6.5, 2.5 Hz), 1.71 (2H, m), 1.68 (1H, q, *J*=11.5 Hz), 1.43 (1H, dtd, *J*=13.5, 9.0, 4.5 Hz), 0.89 (9H, s), 0.07 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.10, 136.81, 129.97, 128.90, 128.81, 127.46, 125.68, 113.69, 101.61, 82.21, 76.62, 73.03, 70.40, 69.38, 55.23, 38.92, 33.59, 30.79, 25.72, 25.16, 17.91, −4.12, −4.78; MALDI-TOF-MS, calcd $C_{29}H_{42}O_5SSiNa$ $[M+Na]^+$ 553.242, found 553.322.

6.1.13. *O*,*S*-Acetal 8. To a solution of phenylsulfide **29** (320.3 mg, 0.603 mmol) in CCl_4 (5 mL) was added NCS (88.6 mg, 0.664 mmol) at room temperature. After being stirred for 20 min, the reaction mixture was filtrated and concentrated to give the crude α-chlorosulfide **7**, which was used in the next reaction without purification.

To a solution of alcohol **6** (311.9 mg, 0.730 mmol) and powdered molecular sieves 4A in CH_2Cl_2 (5 mL) were added AgOTf (190.0 mg, 0.724 mmol) and DTBMP (253.0 mg, 1.21 mmol) at −75°C. After 10 min, the crude α-chlorosulfide **7** in CH_2Cl_2 (5 mL) was added slowly, and the resultant mixture was stirred for 2 h below −30°C. The reaction mixture was then passed through a short plug of silica gel. The residue was subjected to flash chromatography to give *O*,*S*-acetal **8** (hexane/EtOAc=7/1) as a pale yellow oil (498.0 mg, 86%, 2:1 diastereomeric mixture at the acetal carbon): ^1H NMR (500 MHz, $CDCl_3$) δ 7.53–7.48 (2H, m), 7.40 (1H, d, *J*=9.1 Hz), 7.38–7.18 (13H, m), 6.88 (2H, d, *J*=9.1 Hz), 5.43 (1H, s), 4.96–4.88 (1H, m), 4.82–4.70 (2H, m), 4.63–4.50 (3H, m), 4.43 (1H, dd, *J*=12.3, 4.2 Hz), 4.42–4.37 (2H, m), 4.33 (1H, dd, *J*=11.2, 4.1 Hz), 4.27 (1H, dd, *J*=12.3, 5.4 Hz), 4.21 (1H, dd,

J=12.3, 4.1 Hz), 3.94 (1/2H, d, J=13.2 Hz), 3.86 (1/2H, d, J=13.2 Hz), 3.81 (3H, s), 3.50–3.36 (10H, m), 3.33–3.22 (1H, m), 3.17–3.08 (1H, m), 2.53–2.44 (1H, m), 2.38–2.30 (2H, m), 2.13–2.02 (1H, m), 1.89–1.80 (1H, m), 1.48–1.40 (1H, m), 1.34 (3H, d, J=11.2 Hz), 1.20 (3H, m), 0.89 (9H, s), 0.08 (6H, s); MALDI-TOF-MS, calcd for $C_{54}H_{74}O_{11}$-SSiNa $[M+Na]^+$ 981.461, found 981.397.

6.1.14. β-Alkoxyacrylate 30. A solution of **8** (498.0 mg, 0.519 mmol) in THF (10 mL) was treated with TBAF (0.79 mL, 0.79 mmol, 1 M in THF solution), and the mixture was stirred at room temperature for 12 h. The solvent was evaporated, and the residue was subjected to flash chromatography (hexane/EtOAc=1/1) to give the alcohol, which was used in the next reaction without purification.

To a solution of the above alcohol in CH_2Cl_2 (5 mL) were added methyl propiolate (0.71 mL, 7.91 mmol) and NMM (0.54 mL, 5.44 mmol). After being stirred for 1.5 h, the mixture was concentrated, and directly subjected to flash chromatography (hexane/EtOAc=7/1–3/1) to give β-alkoxyacrylate **30** as a colorless solid (395.4 mg, 82% for 2 steps): IR (film) ν 2934, 1714, 1644, 1587, 1518, 1250, 1100, 831, 751 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (2H, m), 7.41 (1H, d, J=12.5 Hz), 7.32 (2H, d, J=9.0 Hz), 7.28–7.11 (13H, m), 6.81 (2H, d, J=9.0 Hz), 5.38 (1/4H, s), 5.37 (1/4H, s), 5.36 (1/2H, s), 5.27 (1H, d, J=12.5 Hz), 4.72 (1/2H, m), 4.66 (1/2H, m), 4.56–4.42 (3.5H, m), 4.40 (1/4H, d, J=11.2 Hz), 4.39 (1/4H, d, J=11.2 Hz), 4.31 (1/2H, d, J=11.3 Hz), 4.27 (1/4H, d, J=11.3 Hz), 4.26 (1/4H, d, J=11.3 Hz), 4.17 (1/2H, dt, J=15.0, 5.0 Hz), 4.11 (1/2H, dt, J=14.2, 4.8 Hz), 3.90–3.45 (6H, m), 3.68–3.55 (1H, m), 3.45–3.32 (1H, m), 3.44–3.12 (7H, m), 3.68 (3H, s), 3.62 (1H, s), 3.61 (1H, s), 3.60 (1H, s), 2.52–2.38 (2H, m), 1.90–1.75 (2H, m), 1.75–1.56 (2H, m), 1.55–1.35 (2H, m), 1.23–1.14 (3H, m), 1.11 (3H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.80, 167.71, 167.58, 160.78, 160.62, 159.90, 138.13, 137.86, 137.64, 133.62, 133.42, 133.20, 133.12, 132.86, 129.44, 128.80, 128.68, 128.06, 128.00, 127.64, 127.55, 127.46, 127.30, 127.22, 113.43, 101.60, 101.31, 100.02, 99.72, 99.37, 98.13, 97.99, 90.11, 85.51, 85.31, 80.18, 80.01, 79.88, 79.77, 79.37, 79.20, 78.95, 75.72, 75.65, 75.47, 73.19, 73.06, 72.79, 72.69, 72.01, 71.88, 71.09, 70.77, 69.25, 69.03, 68.96, 68.87, 68.78, 68.56, 64.72, 64.29, 63.77, 63.41, 61.36, 60.73, 60.42, 60.11, 55.00, 50.95, 36.56, 34.65, 34.55, 33.56, 32.43, 32.36, 32.02, 31.94, 31.35, 29.71, 27.95, 27.79, 25.98, 22.43, 20.79, 19.93, 19.67, 15.12, 13.95; MALDI-TOF-MS, calcd for $C_{52}H_{64}O_{13}SNa$ $[M+Na]^+$ 951.396, found 951.359.

6.1.15. Oxepane 32. To a solution of alkoxyacrylate **30** (1.036 g, 1.115 mmol) and n-Bu_3SnH (0.6 mL+0.9 mL, 5.576 mmol) in toluene (280 mL) was added AIBN (154.0 mg, 0.938 mmol) in two portions. After being stirred for 9 h at 80°C, the reaction mixture was concentrated, and subjected to flash chromatography (hexane/EtOAc=6/1–3/1) to give an inseparable 3.2:1 mixture of the desired oxepane **32** and the reduced byproduct **33** as a colorless solid (883.4 mg, 97%): IR (film) ν 2935, 2870, 1738, 1617, 1518, 1030, 830, 786 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 (2H, d, J=9.0 Hz), 7.38–7.20 (10H, m), 6.90 (2H, d, J=8.5 Hz), 5.47 (3H, s), 4.77 (1H, m), 4.66–4.52 (3H, m), 4.45 (1H, d, J=11.5 Hz), 4.29 (1H, m), 3.94 (1H, dt, J=9.5, 5.5 Hz), 3.81 (3H, s), 3.69 (3H, s), 3.79–3.62 (5H, m), 3.59 (1H, dt, J=9.5, 5.0 Hz), 3.57–3.43 (3H, m), 3.45–3.21 (4H, m), 3.22–3.14 (1H, m), 2.62–2.54 (1H, m), 2.55–2.44 (2H, m), 2.33 (1H, ddd, J=16.0, 8.5, 4.0 Hz), 1.95–1.80 (3H, m), 1.77 (1H, q, J=11.0 Hz), 1.65 (1H, q, J=11.0 Hz), 1.46 (1H, q, J=11.0 Hz), 1.33 (1.5H, d, J=5.3 Hz), 1.31 (1.5H, d, J=5.3 Hz), 1.20 (3H, t, J=7.0 Hz); MALDI-TOF-MS, calcd for $C_{46}H_{60}O_{13}Na$ $[M+Na]^+$ 843.393, found 843.405.

6.1.16. Alcohol 34. A solution of oxepane **32** and by-product **33** (465.7 mg, 3.2:1 mixture, 0.567 mmol) in CH_2Cl_2 (10 mL) was treated with DIBAL (1.1 mL, 1.13 mmol, 1.01 M in toluene) at −78°C for 30 min. The reaction mixture was quenched with saturated aqueous NH_4Cl, allowed to warm to room temperature, and diluted with EtOAc. To this solution was added saturated aqueous potassium sodium tartrate, and the resultant mixture was stirred for 1 h. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to give a mixture of the aldehyde and the alcohol, which was subjected to the next reaction without purification.

To a solution of the crude mixture in MeOH (20 mL) was added $NaBH_4$ (53.6 mg, 1.42 mmol). After being stirred for 1 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with brine, dried over $MgSO_4$, and concentrated. The residue was subjected to flash chromatography (hexane/EtOAc=2/1–1/1) to give alcohol **34** (316.7 mg) as a colorless oil, which was contaminated with the by-product arose from **33**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (2H, d, J=8.5 Hz), 7.29–7.11 (10H, m), 6.81 (2H, d, J=8.6 Hz), 5.39 (1H, s), 4.53 (1H, d, J=12.0 Hz), 4.49 (1H, d, J=11.5 Hz), 4.46 (1H, d, J=12.0 Hz), 4.35 (1H, d, J=11.3 Hz), 4.21 (1/2H, dd, J=10.3, 5.0 Hz), 4.18 (1/2H, dd, J=10.3, 5.0 Hz), 3.80 (1H, m), 3.71 (3H, s), 3.72–3.54 (6H, m), 3.54–3.35 (6H, m), 3.35–3.14 (6H, m), 3.14–3.06 (1H, m), 2.53–2.38 (2H, m), 2.36–2.17 (1H, m), 1.85–1.70 (3H, m), 1.71–1.56 (2H, m), 1.60 (1H, q, J=11.3 Hz), 1.45–1.32 (1H, m), 1.24 (1.5H, d, J=7.0 Hz), 1.23 (1.5H, d, J=7.0 Hz), 1.13 (1.5H, t, J=6.8 Hz), 1.11 (1.5H, t, J=7.0 Hz); MALDI-TOF-MS, calcd for $C_{45}H_{60}O_{12}Na$ $[M+Na]^+$ 815.398, found 815.360.

6.1.17. Olefin 35. A solution of the above alcohol **34** (55.1 mg, 69.5 μmol) in THF (2 mL) containing 2-nitrophenyl selenocyanate (117.9 mg, 0.519 mmol) and pyridine (56 μL, 0.692 mmol) was treated with tri-n-butylphosphine (129 μL, 0.519 mmol) dropwise at room temperature. After 1 h, saturated aqueous $NaHCO_3$ (109 mg, 1.30 mmol) was added, and then H_2O_2 (0.18 mL, 34.5% water solution) was added dropwise at 0°C. The ice bath was removed, and the solution was stirred for additional 1 h at 40°C. The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ and diluted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was subjected to flash chromatography (hexane/EtOAc=6/1–5/1) to give olefin **35** as an orange oil (45.6 mg, 85%): IR (film) ν 2933, 1615, 1518, 1496, 1303, 1250, 1171, 1029, 829 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (2H, d, J=8.7 Hz), 7.26–7.15 (10H, m), 6.82 (2H, d, J=8.7 Hz), 5.76 (1H, ddd, J=17.0, 10.4, 5.5 Hz), 5.40 (1H, s), 5.25 (1H, brd, J=17.0 Hz), 5.06 (1H, brd, J=10.4 Hz), 4.72 (1H, q,

J=5.3 Hz), 4.54 (1H, d, J=12.2 Hz), 4.51 (1H, d, J=11.6 Hz), 4.47 (1H, d, J=12.2 Hz), 4.36 (1H, d, J=11.3 Hz), 4.22 (1H, dd, J=10.4, 4.8 Hz), 4.02 (1H, br), 3.72 (3H, s), 3.73–3.56 (7H, m), 3.46–3.35 (4H, m), 3.36–3.30 (1H, m), 3.31–3.21 (3H, m), 3.15 (1H, td, J=10.0, 4.5 Hz), 2.47 (1H, dt, J=11.5, 4.4 Hz), 2.33 (1H, dt, J=11.3, 4.2 Hz), 1.83–1.72 (3H, m), 1.72–1.65 (1H, m), 1.65 (1H, q, J=11.3 Hz), 1.39 (1H, q, J=11.3 Hz), 1.23 (3H, d, J=5.3 Hz), 1.13 (3H, t, J=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.03, 138.32, 138.05, 137.45, 129.93, 128.36, 128.27, 127.72, 127.69, 127.50, 127.43, 115.21, 113.63, 101.48, 99.72, 84.29, 82.00, 81.15, 80.25, 80.12, 78.26, 76.83, 73.41, 72.87, 72.18, 71.96, 71.25, 69.37, 69.30, 63.06, 61.48, 55.26, 36.79, 36.50, 26.15, 24.78, 19.92, 15.29; MALDI-TOF-MS, calcd for $C_{45}H_{58}O_{11}Na$ $[M+Na]^+$ 797.387, found 797.395.

6.1.18. Alcohol 36. A solution of the EE ether **35** (253 mg, 0.328 mmol) in MeOH (23 mL) was treated with PPTS (16.5 mg, 65.7 μmol) at room temperature, and the mixture was stirred for 1 h. Then the solution was concentrated, and the residue was used in the next reaction without purification.

To a solution of the above residue in CH_2Cl_2 (10 mL) were added *p*-methoxybenzaldehyde dimethyl acetal (73 μL, 0.393 mmol) and PPTS (15.6 mg, 62.1 μmol) at room temperature. After being stirred for 40 min, the reaction mixture was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with brine, dried over $MgSO_4$, and concentrated. Silica gel was added to the solution of the crude product in hexane, and the resultant suspension was stirred overnight, and then subjected to flash chromatography (hexane/EtOAc=2/1–1/1) to give alcohol **36** as a colorless solid (170 mg, 74%): $[\alpha]_D^{28}=-58.46°$ (c 1.45, $CHCl_3$); IR (film) ν 3482, 2934, 1615, 1518, 1363, 1249, 1171, 1082, 928, cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (2H, d, J=8.5 Hz), 7.27–7.18 (8H, m), 7.16–7.12 (2H, m), 6.80 (2H, d, J=8.6 Hz), 5.74 (1H, ddd, J=17.0, 10.5, 5.5 Hz), 5.39 (1H, s), 5.23 (1H, dt, J=17.0, 1.3 Hz), 5.06 (1H, dt, J=10.4, 1.3 Hz), 4.51 (1H, d, J=12.0 Hz), 4.49 (1H, d, J=11.3 Hz), 4.44 (1H, d, J=12.0 Hz), 4.32 (1H, d, J=11.3 Hz), 4.21 (1H, dd, J=10.3, 4.7 Hz), 3.95 (1H, m), 3.80 (1H, dd, J=11.6, 2.4 Hz), 3.70 (3H, s), 3.67 (1H, dd, J=10.5, 1.5 Hz), 3.64–3.53 (4H, m), 3.45–3.22 (6H, m), 3.19 (1H, m), 3.13 (1H, m), 2.47 (1H, dt, J=12.1, 4.0 Hz), 2.33 (1H, dt, J=11.5, 4.0 Hz), 1.83–1.71 (3H, m), 1.70–1.61 (1H, m), 1.64 (1H, q, J=11.3 Hz), 1.39 (1H, q, J=11.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.97, 137.92, 137.88, 137.27, 129.89, 128.33, 128.30, 127.77, 127.72, 127.65, 127.63, 127.39, 115.40, 113.57, 101.41, 84.46, 81.96, 81.24, 80.64, 79.69, 78.55, 73.37, 72.85, 72.08, 72.02, 71.18, 69.23, 69.14, 62.05, 55.20, 36.71, 36.23, 26.12, 25.04; MALDI-TOF-MS, calcd for $C_{41}H_{50}O_{10}Na$ $[M+Na]^+$ 725.330, found 725.328.

6.1.19. Diene 37. To a solution of alcohol **36** (47.5 mg, 67.6 μmol) in CH_2Cl_2 (2 mL), DMSO (1 mL) and Et_3N (1 mL) was added SO_3·pyridine (53.8 mg, 0.338 mmol). After 2 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$, diluted with EtOAc, washed with brine, dried over $MgSO_4$ and concentrated to give the crude aldehyde, which was directly used in the next reaction.

The above aldehyde was dissolved in THF (1.5 mL) and added to a suspension of methyltriphenylphosphonium bromide (289.8 mg, 0.811 mmol) and sodium bis(trimethylsilyl)amide (0.68 mL, 0.68 mmol, 1.0 M in THF solution) in THF (1.5 mL) at 0°C. After being stirred for 10 min, the reaction mixture was quenched with saturated aqueous NH_4Cl, diluted with EtOAc, washed with brine, dried over $MgSO_4$, and concentrated. The residue was subjected to flash chromatography (hexane/EtOAc=10/1–6/1) to give diene **37** as a colorless solid (35.0 mg, 74% for 2 steps): $[\alpha]_D^{24}=-35.32°$ (c 1.27, $CHCl_3$); IR (film) δ 3031, 1615, 1588, 1518, 1303, 1171, 1103, 829 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (2H, d, J=8.6 Hz), 7.29–7.13 (10H, m), 6.81 (2H, d, J=8.6 Hz), 5.85 (1H, ddd, J=17.1, 10.5, 6.5 Hz), 5.69 (1H, ddd, J=17.0, 10.5, 5.4 Hz), 5.40 (1H, s), 5.35 (1H, brd, J=17.0 Hz), 5.21 (1H, brd, J=10.5 Hz), 5.20 (1H, dt, J=17.0, 1.5 Hz), 5.03 (1H, dt, J=10.5, 1.4 Hz), 4.56 (1H, d, J=12.2 Hz), 4.51 (1H, d, J=11.3 Hz), 4.48 (1H, d, J=12.2 Hz), 4.35 (1H, d, J=11.3 Hz), 4.21 (1H, dd, J=10.4, 4.7 Hz), 3.99 (1H, m), 3.72 (3H, s), 3.71–3.55 (4H, m), 3.54 (1H, br), 3.50–3.36 (3H, m), 3.35 (1H, ddd, J=9.3, 4.0, 1.7 Hz), 3.26 (1H, td, J=9.5, 4.8 Hz), 3.14 (1H, dt, J=10.0, 4.6 Hz), 3.08 (1H, m), 2.47 (1H, dt, J=11.8, 4.5 Hz), 2.31 (1H, dt, J=11.5, 4.3 Hz), 1.85–1.70 (3H, m), 1.67–1.55 (1H, m), 1.63 (1H, q, J=11.4 Hz), 1.44 (1H, q, J=11.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.05, 138.28, 138.04, 137.21, 135.84, 129.95, 128.36, 128.30, 127.80, 127.72, 127.54, 127.45, 118.24, 115.08, 113.64, 101.49, 83.89, 81.85, 81.84, 81.52, 79.87, 77.61, 76.83, 76.31, 73.46, 72.82, 72.10, 71.28, 69.33, 69.06, 55.28, 36.91, 36.75, 26.14, 24.10; MALDI-TOF-MS, calcd for $C_{42}H_{50}O_9Na$ $[M+Na]^+$ 721.335, found 721.271.

6.1.20. 6-7-7-6 Ring system 9. To a solution of compound **37** (19.2 mg, 27.5 μmol) in CH_2Cl_2 (13 mL) was added second-generation Grubbs catalyst (**46**, 6.1 mg, 7.2 μmol) at room temperature. After being stirred for 13 h at 40°C, the reaction mixture was quenched with Et_3N (0.20 mL) and stirred for 2 h at room temperature. Concentration and flash chromatography (hexane/EtOAc=6.5/1–4/1) gave the 6-7-7-6 ring system **9** as a colorless solid (5.8 mg, 31%): $[\alpha]_D^{21}=-52.44°$ (c 0.33, $CHCl_3$); IR (film) ν 2929, 1614, 1517, 1369, 1249, 1173, 1038, 828 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (2H, d, J=8.6 Hz); 7.30–7.16 (8H, m), 7.14 (2H, brd, J=7.0 Hz), 6.82 (2H, d, J=8.6 Hz), 5.74 (1H, dt, J=12.3, 3.0 Hz), 5.58 (1H, dt, J=12.3, 2.2 Hz), 5.40 (1H, s), 4.55 (1H, d, J=12.3 Hz), 4.50 (1H, d, J=11.3 Hz), 4.49 (1H, d, J=12.2 Hz), 4.32 (1H, d, J=11.3 Hz), 4.21 (1H, dd, J=10.4, 4.7 Hz), 4.01 (1H, brd, J=9.0 Hz), 3.77 (1H, br), 3.73 (3H, s), 3.69 (1H, dd, J=10.0, 1.4 Hz), 3.58 (1H, dd, J=10.4, 9.5 Hz), 3.57 (1H, d, J=9.8 Hz), 3.50–3.35 (3H, m), 3.32–3.20 (3H, m), 3.15 (1H, ddd, J=10.5, 8.5, 4.3 Hz), 3.09 (1H, m), 2.43 (1H, dt, J=11.9, 4.4 Hz), 2.36 (1H, dt, J=11.9, 4.3 Hz), 1.91–1.84 (2H, m), 1.87–1.75 (2H, m), 1.67 (1H, q, J=11.4 Hz), 1.45 (1H, q, J=11.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.10, 138.21, 137.99, 134.76, 130.63, 129.85, 128.38, 128.33, 127.85, 127.76, 127.72, 127.58, 127.46, 113.69, 101.60, 84.61, 83.81, 83.67, 82.45, 80.64, 79.80, 77.38, 73.59, 73.48, 72.03, 70.92, 69.28, 69.13, 55.30, 37.02, 36.76, 30.95, 27.60; MALDI-TOF-MS, calcd for $C_{40}H_{46}O_9Na$ $[M+Na]^+$ 693.304, found 693.232.

6.1.21. Nitrile 38. To a solution of alcohol **36** (87.0 mg, 0.124 mmol) in pyridine (2 mL) were added powdered molecular sieves 4A and *p*-toluenesulfonyl chloride (377.7 mg, 1.98 mmol) in three portions. After being stirred for 2 days, the reaction mixture was quenched with saturated aqueous $NaHCO_3$, diluted with EtOAc, washed with brine, dried over $MgSO_4$, and concentrated. The residue was subjected to flash chromatography (hexane/EtOAc=4/1–2/1) to give the tosylate as a colorless solid (106 mg, 100%): $[\alpha]_D^{25}=-160.38°$ (*c* 1.48, $CHCl_3$); IR (film) ν 2933, 1615, 1518, 1496, 1362, 1250, 1096, 976, 815 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.81 (2H, d, *J*=9.0 Hz), 7.43 (2H, d, *J*=8.5 Hz), 7.37–7.22 (12H, m), 6.90 (2H, d, *J*=8.5 Hz), 5.76 (1H, ddd, *J*=17.0, 10.3, 5.7 Hz), 5.50 (1H, s), 5.31 (1H, brd, *J*=17.0 Hz), 5.13 (1H, d, *J*=10.5 Hz), 4.58 (1H, d, *J*=12.3 Hz), 4.56 (1H, d, *J*=11.3 Hz), 4.52 (1H, d, *J*=12.0 Hz), 4.43 (1H, d, *J*=11.3 Hz), 4.33–4.23 (3H, m), 4.01 (1H, br), 3.81 (3H, s), 3.73–3.57 (4H, m), 3.54 (1H, ddd, *J*=11.8, 9.0, 4.2 Hz), 3.47–3.39 (2H, m), 3.40–3.32 (4H, m), 3.23 (1H, q, *J*=7.8 Hz), 2.54 (1H, m), 2.47–2.39 (4H, m), 1.88–1.70 (4H, m), 1.73 (1H, q, *J*=11.5 Hz), 1.43 (1H, q, *J*=11.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.98, 144.72, 143.32, 139.22, 138.13, 137.80, 137.13, 132.86, 129.92, 129.73, 129.57, 12835, 128.30, 127.93, 127.77, 127.73, 127.70, 127.54, 127.42, 126.34, 115.74, 113.58, 101.42, 84.29, 81.89, 81.12, 80.37, 78.38, 77.92, 73.43, 72.90, 71.0, 71.61, 71.35, 69.24, 68.93, 68.90, 55.23, 36.72, 36.19, 26.09, 25.07, 21.57; MALDI-TOF-MS, calcd for $C_{48}H_{56}O_{12}SNa$ $[M+Na]^+$ 879.339, found 879.324.

To a solution of the above tosylate (106 mg, 0.124 mmol) in DMSO (3 mL) was added sodium cyanide (31.6 mg, 0.645 mmol) and then heated to 50°C for 1 day. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, diluted with EtOAc, washed with brine, dried over $MgSO_4$, and concentrated. The residue was subjected to flash chromatography (hexane/EtOAc=5/1–3/1) to give nitrile **38** as a colorless solid (88.2 mg, 100%): $[\alpha]_D^{28}=-38.87°$ (*c* 1.20, $CHCl_3$); IR (film) ν 2935, 2871, 1615, 1518, 1250, 928, 830, 736 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (2H, d, *J*=8.5 Hz), 7.40–7.23 (10H, m), 6.90 (2H, d, *J*=8.6 Hz), 5.83 (1H, ddd, *J*=16.7, 10.3, 6.0 Hz), 5.49 (1H, s), 5.35 (1H, d, *J*=16.7 Hz), 5.21 (1H, d, *J*=10.2 Hz), 4.64 (1H, d, *J*=12.3 Hz), 4.58 (1H, d, *J*=11.4 Hz), 4.58 (1H, d, *J*=12.3 Hz), 4.46 (1H, d, *J*=11.4 Hz), 4.31 (1H, dd, *J*=10.3, 4.7 Hz), 4.03 (1H, brt, *J*=5.0 Hz), 3.81 (3H, s), 3.78 (1H, d, *J*=10.7 Hz), 3.73–3.63 (3H, m), 3.57–3.44 (2H, m), 3.49–3.36 (3H, m), 3.40–3.30 (1H, m), 3.35–3.27 (1H, m), 3.24 (1H, dt, *J*=9.3, 5.2 Hz), 2.82 (1H, dd, *J*=16.8, 3.6 Hz), 2.72 (1H, dd, *J*=16.6, 5.5 Hz), 2.56 (1H, dt, *J*=11.7, 4.3 Hz), 2.44 (1H, dt, *J*=11.3, 4.3 Hz), 1.92–1.76 (4H, m), 1.75 (1H, q, *J*=11.5 Hz), 1.47 (1H, q, *J*=11.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.00, 138.03, 137.72, 137.13, 129.84, 129.58, 128.38, 128.30, 127.83, 127.74, 127.72, 127.56, 127.40, 126.33, 117.19, 116.16, 113.59, 101.45, 84.78, 82.02, 81.59, 80.61, 79.22, 76.78, 75.64, 75.22, 73.44, 72.95, 71.72, 71.49, 69.20, 68.86, 55.23, 36.70, 36.22, 26.16, 25.79, 21.29; MALDI-TOF-MS, calcd for $C_{42}H_{49}NO_9Na$ $[M+Na]^+$ 734.330, found 734.336.

6.1.22. Diene 39. A solution of nitrile **38** (60.1 mg, 84.4 μmol) in CH_2Cl_2 (3 mL) was treated with DIBAL (167 μL, 169 μmol, 1.01 M in toluene) at −78°C for 40 min. The reaction mixture was quenched with saturated aqueous NH_4Cl, allowed to warm to room temperature, and diluted with EtOAc. To the mixture was added saturated aqueous potassium sodium tartrate, and the resultant solution was stirred for 1 h. The mixture was diluted with EtOAc, washed with brine, dried over $MgSO_4$, and concentrated to give the crude aldehyde, which was directly used in the next reaction.

The above aldehyde was dissolved in THF (2 mL) and added to a suspension of methyltriphenylphosphonium bromide (361.8 mg, 1.01 mmol) and sodium bis(trimethylsilyl)amide (0.84 mL, 1.0 M in THF solution) in THF (2 mL) at 0°C. After being stirred for 10 min, the reaction mixture was allowed to warm to room temperature, and stirred for another 20 min, and then quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with brine, dried over $MgSO_4$, and concentrated. The residue was subjected to flash chromatography (hexane/EtOAc=5/1–4/1) to give diene **39** as a colorless solid (30.2 mg, 50%) along with 20% of recovered nitrile **38**: $[\alpha]_D^{26}=-43.24°$ (*c* 1.355, $CHCl_3$); IR (film) ν 3069, 2936, 1638, 1518, 1497, 1303, 1030, 910, 829 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (2H, d, *J*=8.7 Hz), 7.39–7.23 (10H, m), 6.91 (2H, d, *J*=8.7 Hz), 5.97 (1H, ddt, *J*=17.7, 10.2, 6.8 Hz), 5.83 (1H, ddd, *J*=17.0, 10.5, 5.7 Hz), 5.49 (1H, s), 5.32 (1H, brd, *J*=17.0 Hz), 5.19–5.08 (3H, m), 4.65 (1H, d, *J*=12.2 Hz), 4.59 (2H, d, *J*=12.0 Hz), 4.44 (1H, d, *J*=11.3 Hz), 4.31 (1H, dd, *J*=10.3, 4.7 Hz), 4.08 (1H, br), 3.81 (3H, s), 3.77 (1H, dd, *J*=11.0, 1.5 Hz), 3.72–3.65 (2H, m), 3.63 (1H, br), 3.55–3.43 (3H, m), 3.41–3.32 (2H, m), 3.30–3.20 (2H, m), 3.15 (1H, ddd, *J*=11.0, 9.3, 4.4 Hz), 2.62 (1H, br), 2.53 (1H, dt, *J*=11.7, 4.3 Hz), 2.43 (1H, dt, *J*=11.5, 4.3 Hz), 2.29 (1H, dt, *J*=14.3, 7.3 Hz), 1.95–1.79 (3H, m), 1.79–1.70 (1H, m), 1.74 (1H, q, *J*=11.5 Hz), 1.46 (1H, q, *J*=11.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.05, 138.46, 138.09, 137.37, 135.04, 129.94, 128.35, 128.27, 127.70, 127.65, 127.45, 116.74, 115.42, 113.64, 101.49, 84.54, 82.03, 81.29, 80.29, 80.12, 78.40, 76.85, 75.76, 73.34, 72.90, 72.40, 71.25, 69.31, 69.19, 55.28, 36.77, 36.64, 36.04, 26.17, 25.09; MALDI-TOF-MS, calcd for $C_{43}H_{52}O_9Na$ $[M+Na]^+$ 735.350, found 735.272.

6.1.23. 6-8-7-6 Ring system 10. To a solution of diene **39** (37.6 mg, 11.1 μmol) in CH_2Cl_2 (19 mL) was added $(PCy_3)_2Cl_2Ru{=}CHPh$ (**45**, 9.1 mg, 27.2 μmol) at 40°C. After being stirred for 13 h, the reaction mixture was quenched with Et_3N (0.19 mL), and stirred for 3 h at room temperature. Concentration and flash chromatography (hexane/EtOAc=6/1–3/1) gave the 6-8-7-6 ring system **10** as a colorless solid (32.8 mg, 91%): $[\alpha]_D^{25}=-131.22°$ (*c* 1.61, $CHCl_3$); IR (film) δ 2935, 1615, 1589, 1496, 1384, 1251, 1095, 990, 830 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (2H, d, *J*=8.5 Hz); 7.28–7.16 (8H, m), 7.12 (2H, d, *J*=7.3 Hz), 6.81 (2H, d, *J*=8.6 Hz), 5.70 (1H, dd, *J*=11.0, 6.0 Hz), 5.63 (1H, dd, *J*=11.8, 8.5 Hz), 5.39 (1H, s), 4.52 (1H, d, *J*=12.3 Hz), 4.50 (1H, d, *J*=11.2 Hz), 4.47 (1H, d, *J*=12.3 Hz), 4.28 (1H, d, *J*=11.2 Hz), 4.21 (1H, dd, *J*=11.4, 4.8 Hz), 4.07 (1H, brt, *J*=7.5 Hz), 3.72 (3H, s), 3.65 (1H, d, *J*=10.6 Hz), 3.59 (1H, t, *J*=10.1 Hz), 3.51 (1H, dd, *J*=10.6, 5.0 Hz), 3.47–3.37 (2H, m), 3.34–3.21 (5H, m), 3.17 (1H, ddd, *J*=12.2, 9.3, 3.9 Hz), 3.10 (1H, dt, *J*=9.8, 5.3 Hz), 2.64

(1H, ddd, J=14.3, 9.5, 4.9 Hz), 2.40 (1H, dt, J=11.3, 4.3 Hz), 2.38–2.29 (2H, m), 2.00–1.89 (2H, m), 1.90–1.76 (2H, m), 1.66 (1H, q, J=11.3 Hz), 1.44 (1H, q, J=10.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.07, 138.32, 138.00, 135.53, 129.843, 128.35, 128.27, 127.78, 127.66, 127.64, 127.50, 127.44, 124.71, 113.65, 101.57, 84.06, 84.03, 83.04, 82.36, 82.04, 80.63, 76.87, 73.62, 73.34, 72.92, 70.83, 69.49, 69.27, 55.28, 37.01, 36.79, 31.32, 30.34, 27.47; MALDI-TOF-MS, calcd for $C_{41}H_{48}O_9Na$ $[M+Na]^+$ 707.320, found 707.315.

6.1.24. Olefin 40. A solution of the mixture of **32** and by-product **33** (93.7 mg, 3.2:1 mixture, 0.114 mmol) in CH_2Cl_2 (3 mL) was treated with DIBAL (0.14 mL, 0.137 mmol, 1.01 M in toluene) at −90°C for 40 min. The reaction mixture was quenched with saturated aqueous NH_4Cl, diluted with EtOAc, and then saturated aqueous potassium sodium tartrate was added. The solution was allowed to warm to room temperature and stirred for 1 h. The organic layer was extracted with EtOAc, washed with brine, dried over $MgSO_4$, and concentrated. The residue was used in the next reaction without purification.

To a solution of the residue in CH_2Cl_2 (2 mL), DMSO (1 mL) and Et_3N (1 mL) was added SO_3·pyridine (93.6 mg, 0.588 mmol). After 2 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The organic layer was extracted with ether, washed with brine, dried over $MgSO_4$ and concentrated to give the aldehyde, which was used in the next reaction without purification.

To a suspension of methyltriphenylphosphonium bromide (488.7 mg, 1.37 mmol) and sodium bis(trimethylsilyl)amide (1.1 mL, 1.0 M in THF solution) in THF (1.5 mL) was added the above aldehyde in THF (2 mL) at 0°C. After being stirred for 10 min, the reaction mixture was quenched with saturated aqueous NH_4Cl. The organic layer was extracted with EtOAc, washed with brine, dried over $MgSO_4$, and concentrated. The residue was subjected to flash chromatography (hexane/EtOAc=4/1) to give olefin **40** as a colorless solid (61.7 mg, 69% for 3 steps): IR (film) ν 3065, 3030, 2870, 1641, 1615, 1588, 1366, 1311, 1250, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (2H, d, J=8.5 Hz), 7.29–7.17 (10H, m), 6.81 (2H, d, J=8.6 Hz), 5.74 (1H, m), 5.39 (1H, s), 5.01 (2H, m), 4.71 (1H, q, J=5.5 Hz), 4.54 (1H, d, J=12.2 Hz), 4.49 (1H, d, J=11.5 Hz), 4.47 (1H, d, J=12.5 Hz), 4.36 (1H, d, J=12.2 Hz), 4.21 (1H, dd, J=10.3, 4.8 Hz), 3.83 (1/2H, dd, J=10.7, 1.2 Hz), 3.72 (3H, s), 3.71–3.53 (4H, m), 3.68–3.57 (1H, m), 3.53–3.42 (3.5H, m), 3.45–3.35 (3H, m), 3.33 (1H, m), 3.30–3.15 (3H, m), 3.16–3.08 (1H, m), 2.44 (1H, m), 2.29 (1H, dt, J=10.6, 5.0 Hz), 2.19–2.07 (2H, m), 1.85–1.67 (3H, m), 1.67–1.61 (1H, m), 1.60 (1H, q, J=10.6 Hz), 1.36 (1H, q, J=11.0 Hz), 1.25 (1.5H, d, J=5.3 Hz), 1.23 (1.5H, d, J=5.3 Hz), 1.13 (1.5H, t, J=7.0 Hz), 1.12 (1.5H, t, J=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.01, 138.30, 138.28, 138.05, 134.81, 134.67, 129.92, 128.35, 128.27, 127.73, 127.70, 127.51, 127.40, 117.33, 117.21, 113.62, 101.44, 99.89, 99.77, 83.96, 83.90, 81.89, 81.85, 80.44, 80.35, 80.27, 80.08, 80.06, 79.06, 79.01, 76.84, 76.81, 73.42, 73.40, 72.85, 72.10, 72.04, 71.69, 71.23, 69.33, 69.30, 64.88, 63.26, 61.44, 60.39, 55.26, 39.42, 36.59, 36.50, 26.13, 26.09, 25.27, 19.93, 19.87, 15.30; MALDI-TOF-MS, calcd for $C_{46}H_{60}O_{11}Na$ $[M+Na]^+$ 811.403, found 811.405.

6.1.25. Alcohol 41. A solution of compound **40** (61.7 mg, 78.2 μmol) in MeOH (3 mL) was treated with PPTS (4.6 mg, 18.3 μmol) at room temperature, and the resultant mixture was stirred for 1 h. After concentration, the residue was directly used in the next reaction.

To a solution of the above residue in CH_2Cl_2 (3 mL) were added p-methoxybenzaldehyde dimethyl acetal (29 μL, 0.156 mmol) and PPTS (3.8 mg, 15.12 μmol) at room temperature. After being stirred for 1.5 h, the reaction mixture was quenched with saturated aqueous NH_4Cl. The organic layer was extracted with EtOAc, washed with brine, dried over $MgSO_4$, and concentrated. The residue was subjected to flash chromatography (hexane/EtOAc=3/1–2/1) to give alcohol **41** as a colorless solid (49.7 mg, 89%): $[\alpha]_D^{27}$=−50.45° (c 1.02, $CHCl_3$); IR (film) ν 3470 (br), 2933, 2870, 1615, 1304, 1250, 1172, 735, 699, 648 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (2H, d, J=8.5 Hz), 7.29–7.13 (10H, m), 6.82 (2H, d, J=8.7 Hz), 5.74 (1H, ddt, J=16.8, 10.2, 6.8 Hz), 5.40 (1H, s), 5.02 (2H, m), 4.52 (1H, d, J=11.5 Hz), 4.50 (1H, d, J=11.5 Hz), 4.45 (1H, d, J=12.0 Hz), 4.34 (1H, d, J=11.3 Hz), 4.21 (1H, dd, J=10.3, 4.8 Hz), 3.80 (1H, dd, J=11.0, 2.3 Hz), 3.72 (3H, s), 3.68 (1H, d, J=9.8 Hz), 3.64–3.55 (2H, m), 3.51–3.31 (7H, m), 3.29–3.16 (3H, m), 3.15–3.08 (1H, m), 2.46 (1H, m), 2.31 (1H, dt, J=10.5, 4.2 Hz), 2.14 (2H, m), 1.84–1.69 (3H, m), 1.67–1.60 (1H, m), 1.60 (1H, q, J=11.5 Hz), 1.38 (1H, q, J=10.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.02, 137.93, 137.90, 134.67, 129.94, 128.39, 128.39, 127.86, 127.73, 127.41, 117.41, 113.63, 101.45, 84.07, 81.84, 80.58, 80.54, 79.71, 79.16, 76.82, 73.46, 72.87, 72.05, 71.82, 71.21, 69.30, 69.20, 62.23, 55.27, 39.43, 36.58, 36.28, 26.14, 25.35; MALDI-TOF-MS, calcd for $C_{42}H_{52}O_{10}Na$ $[M+Na]^+$ 739.345, found 739.288.

6.1.26. Diene 42. To a solution of compound **41** (49.7 mg, 69.33 μmol) in CH_2Cl_2 (2 mL), DMSO (1 mL) and Et_3N (1 mL) was added SO_3·pyridine (111.1 mg, 0.698 mmol). After 3 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with brine, dried over $MgSO_4$ and concentrated to give the aldehyde, which was used in the next reaction without purification.

The above aldehyde was dissolved in THF (2.5 mL) and added to a suspension of methyltriphenylphosphonium bromide (297.1 mg, 0.832 mmol) and sodium bis(trimethylsilyl)amide (0.69 mL, 0.69 mmol, 1.0 M in THF solution) in THF (2.2 mL) at 0°C. After being stirred for 10 min at 0°C, the reaction mixture was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with brine, dried over $MgSO_4$, and concentrated. The residue was subjected to flash chromatography (hexane/EtOAc=8/1–1/1) to give diene **42** as a colorless solid (32.8 mg, 66% for 2 steps): $[\alpha]_D^{24}$=−41.07° (c 1.05, $CHCl_3$); IR (film) ν 2934, 1497, 1454, 1365, 1172, 927, 829 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (2H, d, J=8.5 Hz), 7.24–7.06 (10H, m), 6.75 (2H, d, J=8.5 Hz), 5.78 (1H, ddd, J=17.2, 10.5, 6.5 Hz), 5.66 (1H, ddt, J=16.8, 10.5, 7.0 Hz), 5.34 (1H, s), 5.28 (1H, d, J=17.0 Hz), 5.15 (1H, d, J=10.5 Hz),

4.94 (1H, d, J=16.8 Hz), 4.91 (1H, d, J=10.5 Hz), 4.51 (1H, d, J=12.3 Hz), 4.44 (1H, d, J=11.3 Hz), 4.42 (1H, d, J=12.3 Hz), 4.29 (1H, d, J=11.3 Hz), 4.15 (1H, dd, J=10.3, 5.0 Hz), 3.67 (3H, s), 3.65 (4H, m), 3.43–3.24 (5H, m), 3.24–3.14 (2H, m), 3.05 (1H, m), 2.97 (1H, m), 2.38 (1H, dt, J=11.8, 4.0 Hz), 2.23 (1H, dt, J=11.5, 4.5 Hz), 2.05 (2H, m), 1.77–1.62 (3H, m), 1.58–1.44 (1H, m), 1.54 (1H, q, J=11.3 Hz), 1.36 (1H, q, J=11.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.02, 138.26, 138.02, 135.91, 134.91, 129.93, 128.36, 128.30, 127.82, 127.74, 127.54, 127.42, 118.24, 117.08, 113.63, 101.46, 83.98, 81.87, 81.77, 81.09, 79.85, 78.93, 76.87, 76.02, 73.45, 72.86, 72.03, 71.24, 69.32, 69.04, 55.27, 39.25, 37.07, 36.56, 26.11, 24.88; MALDI-TOF-MS, calcd for $C_{43}H_{53}O_9$ $[M+H]^+$ 713.369, found 713.363.

6.1.27. 6-8-7-6 Ring system 11. To a solution of diene **42** (32.8 mg, 46.0 μmol) in CH_2Cl_2 (12 mL) was added $(PCy_3)_2Cl_2Ru$=CHPh (**45**, 10.9 mg, 12.2 μmol) in two portions over 20 h at 35°C. The reaction mixture was quenched with Et_3N (0.16 mL), and concentrated. The residue was subjected to flash chromatography (hexane/EtOAc=8/1–7/1) to give the 6-8-7-6 ring system **11** as a colorless solid (29.3 mg, 93%): $[\alpha]_D^{24}$=+44.07° (c 1.03, $CHCl_3$); IR (film) ν 2938, 1454, 1365, 1283, 1170, 1028, 827, 813, 756 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (2H, d, J=8.6 Hz), 7.29–7.12 (10H, m), 6.81 (2H, d, J=8.6 Hz), 5.71 (1H, dd, J=11.0, 4.8 Hz), 5.64 (1H, m), 5.39 (1H, s), 4.56 (1H, d, J=12.3 Hz), 4.51 (1H, d, J=11.5 Hz), 4.48 (1H, d, J=12.3 Hz), 4.32 (1H, d, J=11.2 Hz), 4.18 (1H, dd, J=11.3, 4.9 Hz), 3.83 (1H, m), 3.72 (3H, s), 3.67 (1H, dd, J=10.0, 1.2 Hz), 3.62–3.46 (3H, m), 3.48–3.37 (3H, m), 3.26 (1H, m), 3.24–3.15 (3H, m), 3.13 (1H, m), 2.62 (1H, m), 2.45 (1H, dt, J=12.0, 4.5 Hz), 2.32 (1H, dt, J=11.3, 4.0 Hz), 2.32–2.24 (1H, m), 1.96 (1H, m), 1.89 (1H, m), 1.83–1.71 (2H, m), 1.61 (1H, q, J=11.5 Hz), 1.42 (1H, q, J=11.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.05, 138.25, 138.05, 133.94, 129.87, 128.35, 128.29, 127.80, 127.68, 127.52, 127.44, 126.24, 113.65, 101.51, 84.22, 81.53, 80.37, 79.72, 79.69, 79.42, 78.29, 73.42, 73.12, 72.05, 70.92, 69.24, 69.03, 55.28, 37.74, 36.62, 32.46, 30.46, 29.33; MALDI-TOF-MS, calcd for $C_{41}H_{48}O_9Na$ $[M+Na]^+$ 707.319, found 707.330.

6.1.28. Nitrile 43. To a solution of alcohol **41** (29.3 mg, 40.9 μmol) in pyridine (1.5 mL) were added powdered molecular sieves 4A and p-toluenesulfonyl chloride (76.4 mg, 0.401 mmol) in four portions. After being stirred for 3 days, the reaction mixture was quenched with saturated aqueous $NaHCO_3$, diluted with EtOAc, washed with brine, dried over $MgSO_4$, and concentrated. The residue was subjected to flash chromatography (hexane/EtOAc=4/1–3/1) to give the tosylate as a colorless solid (31.9 mg, 89%): $[\alpha]_D^{24}$=−25.02° (c 1.02, $CHCl_3$); IR (film) ν 2933, 2870, 1615, 1250, 1176, 1095, 978, 931, 829 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (2H, d, J=8.0 Hz), 7.43 (2H, d, J=9.0 Hz), 7.37–7.21 (12H, m), 6.90 (2H, d, J=8.5 Hz), 5.80 (1H, ddt, J=17.0, 10.2, 7.0 Hz), 5.50 (1H, s), 5.10 (2H, m), 4.58 (1H, d, J=12.0 Hz), 4.56 (1H, d, J=12.0 Hz), 4.52 (1H, d, J=12.2 Hz), 4.43 (1H, d, J=11.3 Hz), 4.30 (1H, dd, J=10.3, 4.8 Hz), 3.81 (3H, s), 3.70 (1H, dd, J=11.0, 1.3 Hz), 3.68 (1H, t, J=10.3 Hz), 3.62 (1H, dd, J=11.0, 4.6 Hz), 3.57–3.50 (3H, m), 3.41 (1H, m), 3.38–3.26 (7H, m), 3.20 (1H, m), 2.52 (1H, dt, J=11.7, 4.5 Hz), 2.45–2.39 (1H, m), 2.41 (3H, s), 2.22 (1H, dt, J=14.0, 6.5 Hz), 2.13 (1H, dt, J=14.0, 6.5 Hz), 1.86–1.76 (3H, m), 1.75–1.66 (1H, m), 1.68 (1H, q, J=11.4 Hz), 1.39 (1H, q, J=11.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.00, 144.72, 138.21, 137.83, 134.56, 132.92, 129.97, 129.75, 128.39, 128.33, 127.99, 127.82, 127.76, 127.58, 127.43, 117.57, 113.61, 101.42, 83.68, 81.64, 80.45, 80.23, 78.84, 77.93, 73.51, 72.88, 71.65, 71.34, 71.14, 69.28, 69.00, 68.90, 55.27, 39.48, 36.59, 36.16, 26.08, 25.20, 21.62; MALDI-TOF-MS, calcd for $C_{49}H_{58}O_{12}SNa$ $[M+Na]^+$ 893.354, found 893.276.

To a solution of the above tosylate (98.3 mg, 0.113 mmol) in DMSO (3 mL) was added sodium cyanide (33.3 mg, 0.679 mmol). After being stirred for 18 h at 50°C, the reaction mixture was quenched with saturated aqueous $NaHCO_3$, diluted with EtOAc, washed with brine, dried over $MgSO_4$, and concentrated. The residue was subjected to flash chromatography (hexane/EtOAc=4/1–3/1) to give nitrile **43** as a colorless solid (76.0 mg, 93%): $[\alpha]_D^{23}$=−43.64° (c 1.22, $CHCl_3$); IR (film) ν 2934, 1615, 1518, 1365, 1172, 1029, 927, 830 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (2H, d, J=8.5 Hz), 7.28–7.12 (10H, m), 6.80 (2H, d, J=8.5 Hz), 5.73 (1H, ddt, J=14.0, 10.2, 7.0 Hz), 5.38 (1H, s), 5.04 (1H, d, J=14.0 Hz), 5.01 (1H, d, J=10.2 Hz), 4.54 (1H, d, J=12.2 Hz), 4.47 (1H, d, J=12.2 Hz), 4.46 (1H, d, J=11.4 Hz), 4.34 (1H, d, J=11.4 Hz), 4.19 (1H, dd, J=10.3, 4.7 Hz), 3.70 (3H, s), 3.67 (1H, d, J=10.8 Hz), 3.61–3.53 (2H, m), 3.50 (1H, br), 3.46 (1H, td, J=6.5, 3.2 Hz), 3.43–3.33 (2H, m), 3.34–3.28 (1H, m), 3.27–3.19 (2H, m), 3.21–3.13 (2H, m), 3.15–3.06 (1H, m), 2.69 (1H, dd, J=16.7, 3.6 Hz), 2.60 (1H, dd, J=16.7, 5.5 Hz), 2.45 (1H, dt, J=12.0, 4.0 Hz), 2.30 (1H, dt, J=11.5, 4.2 Hz), 2.19 (1H, dt, J=14.0, 6.5 Hz), 2.07 (1H, dt, J=14.0, 7.0 Hz), 1.75–1.65 (3H, m), 1.66–1.58 (1H, m), 1.58 (1H, q, J=11.5 Hz), 1.34 (1H, q, J=11.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.99, 138.06, 137.72, 134.26, 129.86, 128.38, 128.31, 127.83, 127.75, 127.73, 127.56, 127.38, 117.85, 117.12, 113.59, 101.42, 83.97, 81.60, 80.65, 80.58, 79.11, 75.54, 74.90, 73.46, 72.84, 71.67, 71.45, 69.22, 68.88, 55.23, 39.55, 36.55, 36.13, 26.09, 25.46, 21.35; MALDI-TOF-MS, calcd for $C_{43}H_{51}NO_9Na$ $[M+Na]^+$ 748.346, found 748.357.

6.1.29. Diene 44. A solution of nitrile **43** (60.9 mg, 83.9 μmol) in CH_2Cl_2 (3 mL) was treated with DIBAL (166 μL, 167.8 μmol, 1.01 M in toluene) at −78°C, and the resultant solution was stirred at −78°C for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl, allowed to warm to room temperature, and then diluted with EtOAc. To this mixture was added saturated aqueous potassium sodium tartrate and the mixture was stirred for 1 h. The solution was extracted with EtOAc, washed with brine, dried over $MgSO_4$, and concentrated. The crude aldehyde was subjected to the next reaction without purification.

The aldehyde was dissolved in THF (3 mL) and added to a suspension of methyltriphenylphosphonium bromide (299.7 mg, 0.839 mmol) and sodium bis(trimethylsilyl)-amide (0.67 mL, 1.0 M in THF solution) in THF (3 mL) at 0°C. After being stirred for 10 min at 0°C, the reaction

mixture was allowed to warm to room temperature, and stirred for another 20 min, and then quenched with saturated aqueous NH_4Cl. The organic layer was extracted with EtOAc, washed with brine, dried over $MgSO_4$, and concentrated. The residue was subjected to flash chromatography (hexane/EtOAc=9/1–7/1) to give diene **44** as a colorless solid (45.6 mg, 75% for 2 steps): $[\alpha]_D^{24}=-38.54°$ (*c* 1.02, $CHCl_3$); IR (film) ν 2934, 1639, 1616, 1518, 1249, 1172, 1096, 915, 829 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (2H, d, *J*=8.5 Hz), 7.29–7.14 (10H, m), 6.81 (2H, d, *J*=8.5 Hz), 5.88 (1H, ddt, *J*=16.7, 10.1, 6.7 Hz), 5.73 (1H, ddt, *J*=16.7, 10.2, 6.7 Hz), 5.39 (1H, s), 5.07–4.97 (4H, m), 4.55 (1H, d, *J*=12.3 Hz), 4.494 (1H, d, *J*=12.3 Hz), 4.486 (1H, d, *J*=11.3 Hz), 4.35 (1H, d, *J*=11.3 Hz), 4.21 (1H, dd, *J*=10.4, 4.8 Hz), 3.71 (3H, s), 3.67 (1H, dd, *J*=10.5, 1.6 Hz), 3.59 (1H, dd, *J*=10.4, 5.3 Hz), 3.57 (1H, d, *J*=10.5 Hz), 3.50–3.44 (2H, m), 3.45–3.33 (2H, m), 3.31–3.21 (3H, m), 3.19–3.08 (2H, m), 3.00 (1H, ddd, *J*=10.8, 9.2, 4.5 Hz), 2.51 (1H, m), 2.42 (1H, dt, *J*=11.5, 4.4 Hz), 2.30 (1H, dt, *J*=11.5, 4.4 Hz), 2.22–2.08 (3H, m), 1.84–1.69 (3H, m), 1.67–1.57 (1H, m), 1.60 (1H, q, *J*=11.5 Hz), 1.34 (1H, q, *J*=11.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.02, 138.43, 138.07, 135.04, 134.70, 129.92, 128.34, 128.27, 127.71, 127.66, 127.45, 127.41, 117.35, 116.70, 113.62, 101.45, 84.12, 81.90, 80.43, 80.27, 80.05, 79.08, 76.84, 75.50, 73.33, 72.87, 72.32, 71.21, 69.30, 69.15, 55.26, 39.50, 36.65, 36.59, 36.12, 26.13, 25.43; MALDI-TOF-MS, calcd for $C_{44}H_{54}O_9Na$ $[M+Na]^+$ 749.366, found 749.310.

6.1.30. 6-9-7-6 Polyether 12. To a solution of compound **44** (54.4 mg, 74.9 μmol) in CH_2Cl_2 (30 mL) was added $(PCy_3)_2Cl_2Ru$=CHPh (**45**, 22.4 mg, 27.2 μmol) in three portions over 32 h at 40°C. The reaction mixture was quenched with Et_3N (0.40 mL), concentrated, and subjected to flash chromatography (hexane/EtOAc=8/1–5/1) to give compound **12** as a colorless solid (40.7 mg, 78%): $[\alpha]_D^{26}=-37.09°$ (*c* 1.28, $CHCl_3$); IR (film) ν 2935, 1614, 1518, 1495, 1172, 1092, 826, 747 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, −20°C) δ 7.44 (2H, d, *J*=8.3 Hz), 7.40–7.29 (8H, m), 7.17 (2H, m), 6.92 (2H, d, *J*=8.4 Hz), 5.82–5.65 (2H, m), 5.50 (1H, s), 4.65 (1H, d, *J*=12.3 Hz), 4.60 (1H, d, *J*=11.0 Hz), 4.57 (1H, d, *J*=12.3 Hz), 4.34 (1H, d, *J*=11.0 Hz), 4.31 (1H, dd, *J*=10.3, 4.6 Hz), 3.82 (3H, s), 3.78–3.65 (3H, m), 3.64–3.48 (3H, m), 3.45–3.36 (2H, m), 3.39–3.24 (3H, m), 3.20 (1H, m), 3.11 (1H, t, *J*=9.4 Hz), 2.83–2.69 (2H, m), 2.55 (1H, m), 2.45 (1H, m), 2.38–2.24 (2H, m), 2.06–1.78 (4H, m), 1.72 (1H, q, *J*=9.1 Hz), 1.59 (1H, q, *J*=9.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, −20°C) δ 159.79, 137.84, 137.66, 137.42, 129.41, 129.34, 128.68, 128.33, 128.05, 127.94, 127.87, 127.75, 127.67, 127.31, 113.51, 101.48, 101.40, 91.12, 85.14, 85.04, 82.99, 81.39, 80.22, 79.79, 78.35, 73.23, 73.11, 72.29, 71.09, 69.05, 68.52, 55.23, 38.51, 36.56, 36.23, 32.93, 31.63, 28.93, 27.40; MALDI-TOF-MS, calcd for $C_{42}H_{50}O_9Na$ $[M+Na]^+$ 721.335, found 721.329.

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