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Synthetic studies of yessotoxin, a polycyclic ether implicated in diarrhetic shellfish poisoning: convergent synthesis of the BCDE ring system via an alkyne intermediate

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Abstract—A convergent synthetic route to the BCDE ring system of yessotoxin, a polycyclic ether marine toxin related to diarrhetic shellfish poisoning, has been developed. The key feature of the present synthesis is the alkylation of acetylene with the B and E ring units, which were prepared from a common intermediate. The alkyne functionality was directly converted to a 1,2-diketone by ruthenium oxidation. Acid treatment of the diketone led to the formation of a tetracyclic dihemiketal structure. *O*-Methylation of the hydroxyl groups of the dihemiketal and reductive etherification completed the synthesis of the BCDE ring system of yessotoxin.

1. Introduction

Polycyclic ether marine toxins produced by marine dinoflagellates consist of bioactive agents, the skeletons of which incorporate regular oxygenated heterocycles,[1] and their unique architecture and potent biological activities have attracted the attention of numerous organic chemists. Yessotoxin (**1**) was isolated from the digestive glands of diarrhetic shellfish poisoning-infested scallops, *Patinopecten yessoensis*, in 1993 as one of the causative toxins of diarrhetic shellfish poisoning.[2] Its planar structure and relative stereochemistry have been elucidated by spectroscopic methods to have a ladder-shape polycyclic skeleton with an unsaturated side-chain and two sulfate ester groups.[2,3] The absolute configuration was determined by the NMR method using a chiral anisotropic reagent.[4] The *trans*-fused polyether skeleton has led researchers to believe that an iterative[5] or convergent approach[6] might be the best way to synthesize the six-membered ring systems contained in yessotoxin. We have recently reported a convergent strategy for the synthesis of polytetrahydropyrans using alkyne intermediates.[7] The same approach has also been reported independently by Murai's[8] and Nakata's[9] groups at almost the same time. In this paper, we describe in detail a stereocontrolled construction of the BCDE ring system of yessotoxin based on our alkyne strategy.

2. Result and discussion

2.1. Retrosynthetic analysis

A synthetic plan to the BCDE ring system **2** of yessotoxin involves the synthesis of 1,2-diketone **3** (Scheme1). Simultaneous double six-membered hemiketal ring formation from **3** followed by reductive elimination of the two hemiketal hydroxyl groups would be expected to provide the *trans*-fused ring system **2**. In turn, the 1,2-diketone **3** would be prepared by direct oxidation of the corresponding acetylene derivative **4**. Disassembly of **4** at the indicated strategic bonds leads to the B-ring **5** and E-ring **6** units and acetylene. We next envisaged synthesizing the B- and E-ring units from a common intermediate, ketone **7**, which could be prepared by an oxiranyl anion strategy developed in our laboratory using triflate **8** and an oxiranyl anion **9**.[10] These disconnections allow for a highly convergent approach, and the successful execution of the synthetic strategy for **2** is described below.

2.2. Synthesis of the B ring

The initial steps for the synthesis of the B ring, based on an oxiranyl anion strategy[5b] are shown in Scheme 2. One-pot regioselective activation and protection of two hydroxyl groups of 1,3-*O*-di-*t*-butylsilylene-L-erythritol (**10**)[11] was accomplished with triflic anhydride followed by triethylsilyl triflate to afford the TES-protected triflate **8** in 95% yield. Reaction of the triflate with the oxiranyl anion generated from racemic epoxy sulfone **11** (a ca. 1:3 mixture of *cis*- and *trans*-isomers) and *n*-butyllithium in THF–HMPA at −100°C gave the coupled product **12** in 91% yield. As the

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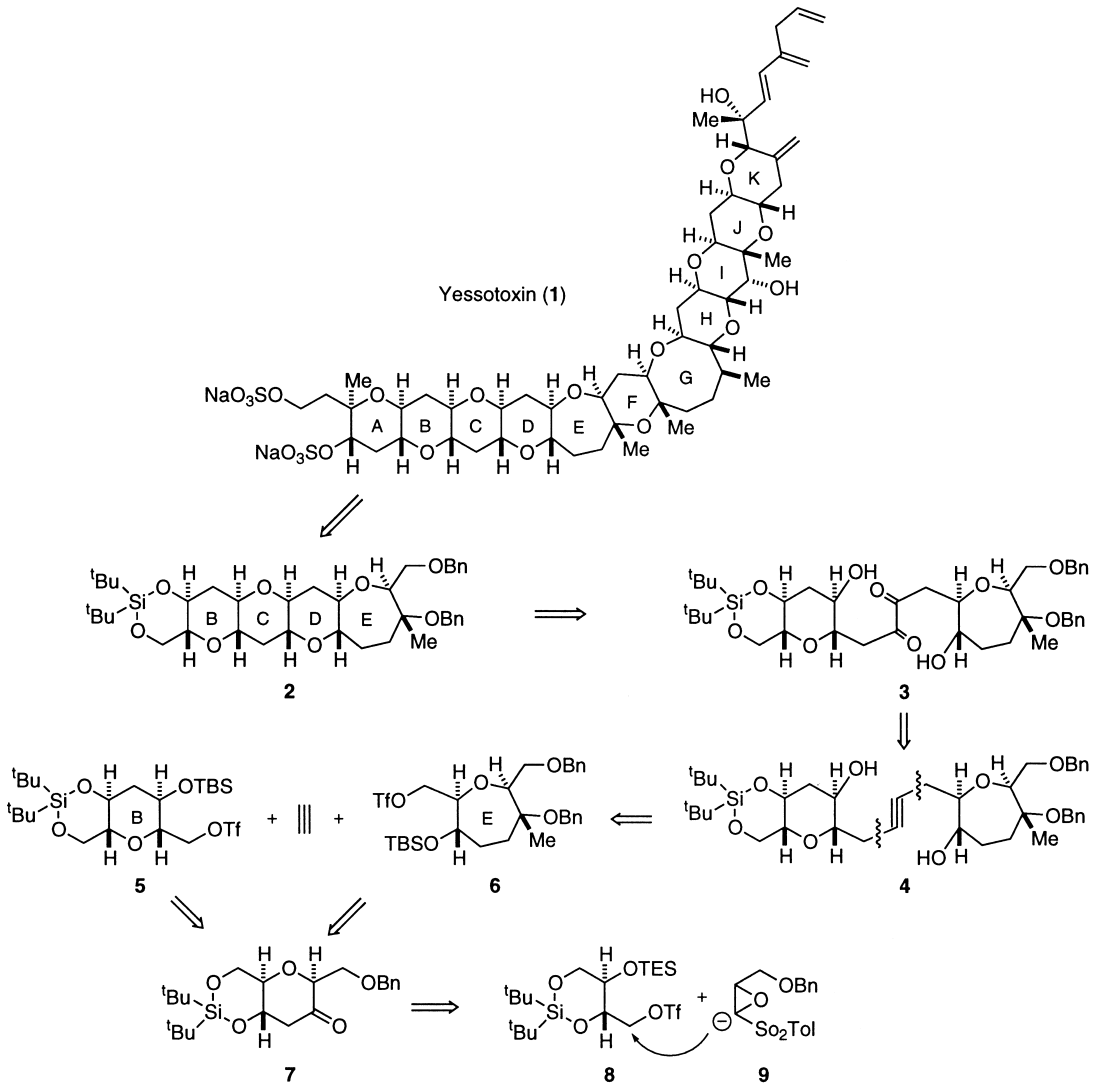
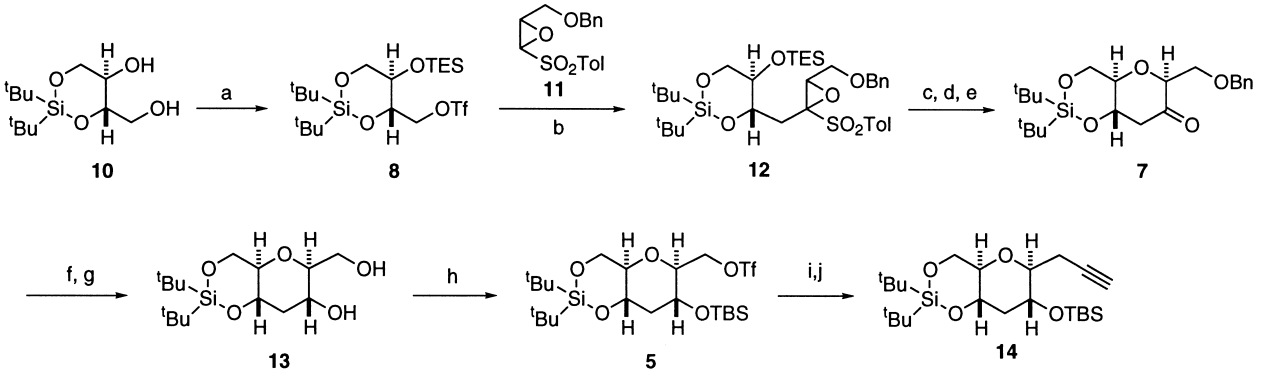
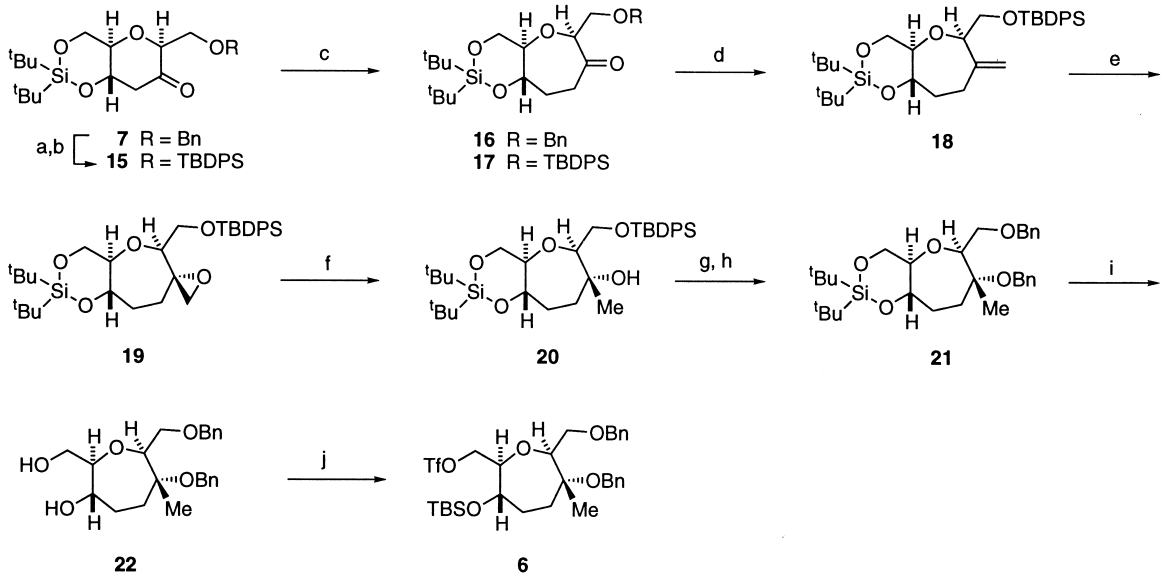


Scheme 1. Retrosynthetic analysis of yessotoxin (**1**).

product is a mixture of four diastereoisomers around the stereochemistry of the epoxide functionality, cyclization of **12** to a tetrahydropyran ring was carried out in a stepwise manner according to the previously reported method.[12] Thus, detriethylsilylation of **12** with TsOH followed by exposure to $MgBr_2{\cdot}OEt_2$ gave a mixture of hydroxy bromoketones, which was then treated with DBU to afford an equilibrium mixture of cyclized products. The desired, thermodynamically more stable ketone **7** was isolated in 79% overall yield along with a 9% yield of its epimer having



Scheme 2. *Reagents and conditions*: (a) Tf_2O, 2,6-lutidine, CH_2Cl_2, −78°C, 30 min, then TESOTf, 95%; (b) *n*-BuLi, THF–HMPA, −100°C, 40 min, 91%; (c) $TsOH{\cdot}H_2O$, MeOH, room temperature, 2 h, 98%; (d) $MgBr_2{\cdot}OEt_2$, CH_2Cl_2, 0°C, 1 h, 97%; (e) DBU, CH_2Cl_2, 0°C, 1 h, 83%; (f) $NaBH_4$, CH_2Cl_2–MeOH, −78°C, 30 min, 95%; (g) H_2, $Pd(OH)_2$–C, EtOAc, 40 min, 100%; (h) Tf_2O, 2,6-lutidine, THF, −78°C, 30 min, then TBSOTf, −78→0°C, 94%; (i) $Me_3SiC{\equiv}CH$, *n*-BuLi, THF–HMPA, −78°C, 2.5 h; (j) 5% KOH, MeOH, room temperature, 1.5 h, 74% (two steps).



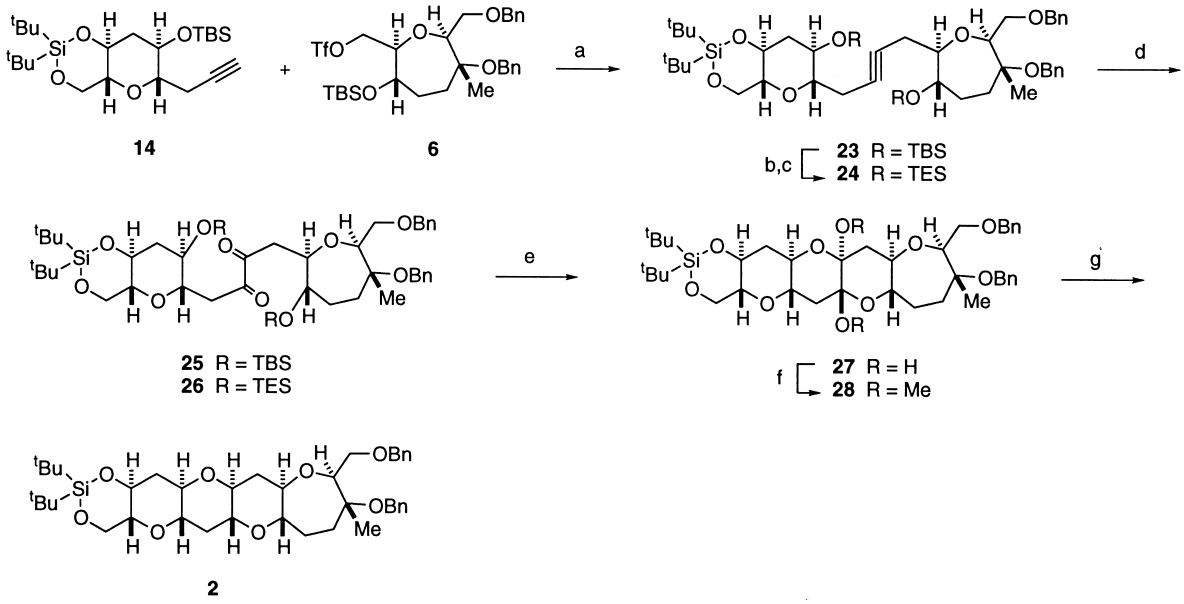
Scheme 3. *Reagents and conditions*: (a) H_2, $Pd(OH)_2$–C, EtOAc, 100%; (b) TBDPSCl, imidazole, DMF, room temperature, 100%; (c) Me_3SiCHN_2, $BF_3{\cdot}OEt_2$, MS 3A, CH_2Cl_2, −78°C; PPTS, MeOH, room temperature, 72%; (d) Tebbe reagent, THF, 0°C, 95%; (e) Oxone, CF_3COCH_3, $NaHCO_3$, 0.4 mM EDTA·Na_2, acetone–MeCN, 0°C, 87%; (f) $LiBHEt_3$, THF, 0°C, 98%; (g) 10% KOH, MeOH, room temperature, 88%; (h) BnBr, KH, THF, 0°C, 96%; (i) Bu_4NF, THF, room temperature, 89%; (j) Tf_2O, 2,6-lutidine, CH_2Cl_2, −78°C, then TBSOTf, −78→0°C, 93%.

an axial side chain. Stereoselective reduction of ketone **7** with sodium borohydride in CH_2Cl_2–MeOH at −78°C and subsequent debenzylation by hydrogenolysis gave diol **13** in 95% yield. In order to introduce an acetylene unit into **13**, the diol was transformed into the TBS-protected triflate **5**. Coupling reaction of **5** with lithium trimethylsilylacetylide in THF–HMPA[13] followed by selective removal of the trimethylsilyl group with 5% KOH in methanol led to the completion of the B-ring unit **14** having a terminal alkynyl group.

2.3. Synthesis of the E ring

Elaboration of the six-membered ketone **7** to a seven-membered ketone requires one-carbon homologation of the tetrahydropyran ring (Scheme 3). The reaction conditions of this ring expansion reaction have been established previously.[14] However, reaction of **7** with trimethylsilyldiazomethane in the presence of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at −78°C gave the desired seven-membered ketone **16** in only 43% yield after acid treatment of the intermediary α-trimethylsilyl ketone. The side-reactions were competitive spiro-epoxide formation on the carbonyl group of **7** and debenzylation by $BF_3{\cdot}OEt_2$, and a debenzylated TMS-substituted spiro-epoxide derivative was isolated in 38% yield. Then, the benzyl group of **7** was replaced by a bulky *t*-butyldiphenylsilyl group and the resulting **15** was subjected to the ring expansion reaction. In this case, the reaction proceeded more satisfactorily to afford **17** in 72% yield along with 5% yield of its regioisomeric ketone. With the desired ketone **17** in hand, our attention was directed to stereoselective installation of a methyl group at the carbonyl carbon. Unfortunately, direct introduction of the β-oriented methyl group by nucleophilic addition to the ketone was unsuccessful. Methylation using trimethylaluminum, methylmagnesium bromide, and methyllithium took place mainly from the less hindered α-side of the molecule with selectivity of ca. 4:1. The desired tertiary alcohol **20** was obtained as a minor product.

We next explored an alternative method to construct the methyl group having β-configuration: spiro-epoxide formation and reductive opening. The ketone **17** was converted into *exo*-methylene **18** in 95% yield using the Tebbe reagent.[15] Epoxidation of **18** with *m*-CPBA, however, led to only 3:2 selectivity of α- and β-epoxides, although the major isomer was the desired product **19**. In order to effect a predominant α-attack, use of a reagent that demands more steric requirements in a transition state is one way to this end. In this regard, dioxirane oxidation occurred to us. Epoxidation of olefins with dioxiranes is believed to proceed via a spiro transition state rather than a planar transition state.[16] The spiro transition state should induce more steric interactions between the substituents of an olefin and a dioxirane and therefore, would favor the approach of an oxidizing reagent from the less hindered side of the olefin. In this case, reaction of **18** with methyl(trifluoromethyl)dioxirane generated in situ from Oxone® and 1,1,1-trifluoroacetone[17] led to spiro-epoxide formation with 10:1 selectivity, and the desired α-epoxide **19** was isolated in 87% yield. Reductive opening of the oxirane ring with lithium triethylborohydride gave the desired tertiary alcohol **20** quantitatively. The TBDPS ether of **20** was then selectively removed in the presence of the silylene-protective group by exposure to 10% NaOH in methanol[18] to furnish a diol, which was protected as the benzyl ether by treatment with potassium hydride and benzyl bromide, giving **21** in 84% yield. With the right-hand side fully protected, it was possible to begin manipulation of the left side. Thus, the silylene group of **21** was deprotected with Bu_4NF in THF to give diol **22**. Regioselective triflation of the primary hydroxyl group followed by silylation of the secondary hydroxyl group in one-pot yielded the E-ring triflate **6** in 83% overall yield from **21**.



Scheme 4. *Reagents and conditions*: (a) *n*-BuLi, THF–HMPA, −78°C, 71%; (b) $TsOH{\cdot}H_2O$, CH_2Cl_2–MeOH, room temperature, 93%; (c) TESOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 95%; (d) $RuO_2{\cdot}H_2O$, $NaIO_4$, CCl_4–MeCN–pH 7 buffer, room temperature, 65%; (e) $TsOH{\cdot}H_2O$, $CHCl_3$, 0°C, 89%; (f) MeI, NaH, DMF, 0°C, 55%; (g) Et_3SiH, TMSOTf, CH_2Cl_2, 0°C, 51%.

2.4. Synthesis of the BCDE ring system

Convergent synthesis of the target ring system **2** is shown in Scheme 4. Coupling reaction of the lithium acetylide generated from acetylene **14** with triflate **6** gave the disubstituted acetylene **23** in 71% yield. Oxidation of the acetylene to the corresponding 1,2-diketone was carried out according to the reported procedure. Thus, oxidation of the acetylene **23** with a catalytic amount of $RuO_2{\cdot}H_2O$ and 3 equiv. of $NaIO_4$ in CCl_4–CH_3CN–H_2O[19] afforded the 1,2-diketone **25** in 74% yield. Selective deprotection of the TBS group with TsOH in $CHCl_3$ at 55°C and the following spontaneous double hemiketal ring formation to **27** was unsuccessful, giving a complex mixture of products. Treatment with trimethyl orthoformate in the presence of TsOH also led to a mixture of *O*-methyl ethers of cyclic and acyclic ketals. The difficulty in the formation of *trans*-fused dihemikatal rings may be attributed to the higher reaction temperature required for the deprotection of the TBS groups and the configurational problem of the hydroxyl group on the seven-membered ring which adopts an axial-like quasi-equatorial configuration.

In order to carry out the deprotection of the silyl groups and the following dihemikatal ring formation under mild conditions, the TBS groups of acetylene **23** were replaced with TES ethers by treatment with TsOH in methanol followed by triethylsilylation, giving **24** in 88% overall yield. Ruthenium oxidation of **24** gave diketone **26** in 65% yield. The expected six-membered dihemiketal formation proceeded smoothly by the treatment of the diketone with TsOH in chloroform at 0°C to give **27** in 89% yield. *O*-Methylation of the two hemiketal hydroxyl groups under basic conditions with MeI and NaH in DMF gave the desired di-*O*-methyl ketal **28** in 55% yield along with two other stereoisomers (13 and 5% yields) attributed to the configuration of the methoxy groups. The stereochemical assignment of two methoxy groups of **28** was established by NOESY experiments. Direct treatment of **26** with $TsOH{\cdot}H_2O$ and trimethyl orthoformate in chloroform afforded a lower yield of the desired product **28** and increased amounts of other isomers. Final reductive etherification of **28** with triethylsilane in the presence of trimethylsilyl triflate[20] at room temperature resulted in the formation of the desired *trans*-fused tetracyclic ether ring system in 50% yield, but the concomitant elimination of the benzyloxy group at a quaternary center to an *exo*-methylene group was observed. This elimination reaction was suppressed by carrying out the reduction at 0°C, and the synthesis of the target BCDE ring system **2** of yessotoxin was accomplished in 55% yield.

3. Conclusion

Stereocontrolled convergent synthesis of the BCDE ring system of yessotoxin was developed starting from 1,3-*O*-di-*t*-butylsilylene-L-erythritol. In the present synthesis, we have demonstrated that the six-membered ketone **7** prepared by an oxiranyl anion strategy is a useful common intermediate for the synthesis of the B- and E-ring units. Connection of both ring units via acetylene, followed by ruthenium oxidation of the triple bond to the corresponding 1,2-diketone, double hemiketal formation, and reductive etherification enabled a convergent synthesis of the tetracyclic ether ring system composed of six- and seven-membered rings. These studies are expected to facilitate the projected total synthesis of yessotoxin and related compounds.

4. Experimental

4.1. General

IR spectra were recorded in $CHCl_3$ solution on a JASCO

FTIR-420 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL A-400 or A-600 spectrometer in $CDCl_3$ solution using TMS and $CDCl_3$ (77.00 ppm) as internal standards, respectively. Mass spectra were obtained on JEOL JMS-700 and HX-110 mass spectrometers. Optical rotations were determined on a JASCO DIP-370 digital polarimeter. Air- and moisture-sensitive reactions were carried out under an argon atmosphere in anhydrous conditions. Flash chromatography was carried out with E. Merck silica gel 60 (230–400 mesh). The term 'dried' refers to the drying of an organic solution over $MgSO_4$ followed by filtration.

4.1.1. Triflate 8. To a stirred solution of diol **10**[11] (1.40 g, 5.34 mmol) in dry CH_2Cl_2 (14 mL) at −78°C under argon was added 2,6-lutidine (1.85 mL, 16.03 mmol) and triflic anhydride (0.94 mL, 5.61 mmol). After stirring at −78°C for 30 min, TESOTf (1.42 mL, 6.41 mmol) was added and stirring was continued for another 30 min. The reaction mixture was poured into water and extracted with EtOAc. The combined extracts were washed with saturated aqueous $NaHCO_3$, water, and brine, dried, and evaporated. Purification by flash chromatography (3% EtOAc/hexane) gave **8** (2.59 g, 95%) as a pale yellow oil; $[\alpha]_D^{25}=-38.5°$ (*c* 0.22, $CHCl_3$); IR ($CHCl_3$) δ 1473, 1413, 1225, 1207 cm^{-1}; ^{1}H NMR (600 MHz) δ 0.61 (6H, q, *J*=8.1 Hz), 0.95 (9H, t, *J*=8.1 Hz, 1.00 (9H, s), 1.04 (9H, s), 3.79 (2H, m), 4.06 (2H, m), 4.61 (1H, dd, *J*=10.3, 4.4 Hz), 4.68 (1H, dd, *J*=10.3, 2.2 Hz).

4.1.2. Ketone 7. *Alkylation reaction*. A solution of triflate **8** (2.59 g, 5.09 mmol) and a 1:3 mixture of racemic *cis*- and *trans*-epoxy sulfone **11** (2.43 g, 7.65 mmol) in HMPA (2.66 mL, 15.29 mmol) and dry THF (34 mL) under argon was cooled to −100°C and treated with *n*-BuLi (4.78 mL of 1.6 M solution in hexane, 7.65 mmol). After stirring at −100°C for 40 min, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was warmed to 0°C and extracted with EtOAc. The combined extracts were washed with water and brine, dried, and evaporated. Purification by flash chromatography (6% EtOAc/hexane) gave **12** (3.15 g, 91%).

Detriethylsilylation. The product **12** (3.15 g, 4.65 mmol) obtained above was dissolved in MeOH (31 mL) and $TsOH\cdot H_2O$ (18 mg, 0.093 mmol) was added. After stirring at room temperature for 2 h, the reaction was quenched with Et_3N (0.1 mL) and the solvent was evaporated. The residue was purified by flash chromatography (30% EtOAc/hexane) to give a 1:1 mixture of hydroxy epoxy sulfones (2.55 g, 98%).

Bromoketone formation. To a stirred solution of the hydroxy epoxy sulfones (2.55 g, 4.54 mmol) in CH_2Cl_2 (45 mL) was added $MgBr_2\cdot OEt_2$ (1.41 g, 5.44 mmol) at 0°C. After stirring at room temperature for 1 h, the reaction mixture was poured into water and extracted with CH_2Cl_2. The combined extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried, and evaporated. Purification by flash chromatography (25% EtOAc/hexane) gave a 1:1 mixture of bromoketones (2.14 g, 97%).

Cyclization. To a stirred solution of the bromoketones (2.14 g, 4.39 mmol) in CH_2Cl_2 (30 mL) at 0°C was added DBU (0.69 mL, 4.61 mmol). After stirring at 0°C for 1 h, the reaction was quenched with saturated aqueous NH_4Cl and the mixture was extracted with CH_2Cl_2. The combined extracts were washed with water, dried, and evaporated. Purification by flash chromatography (3⟶15% EtOAc/hexane) gave **7** (1.49 g, 83%) as a solid and its C(8)-epimer (162 mg, 9%) as an oil. **7**: mp 101–102°C; $[\alpha]_D^{25}=-12.08°$ (*c* 0.59, $CHCl_3$); IR ($CHCl_3$) 1725, 1473, 1114 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.00 (9H, s), 1.05 (9H, s), 2.44 (1H, dd, *J*=16.1, 10.7 Hz), 3.04 (1H, dd, *J*=16.1, 5.9 Hz), 3.63 (1H, ddd, *J*=10.3, 10.3, 4.9 Hz), 3.66 (1H, dd, *J*=10.7, 5.9 Hz), 3.87 (1H, dd, *J*=10.7, 2.9 Hz), 3.95 (1H, t, *J*=10.3 Hz), 4.06 (1H, dd, *J*=6.3, 2.9 Hz), 4.18 (1H, ddd, *J*=10.7, 10.3, 5.9 Hz), 4.31 (1H, dd, *J*=10.3, 4.9 Hz), 4.53 and 4.57 (each 1H, d, *J*=12.1 Hz), 7.27–7.36 (5H, m); ^{13}C NMR (100 MHz) δ 19.90, 22.59, 26.98 (3×C), 27.37 (3×C), 48.22, 66.54, 68.33, 72.49, 73.71, 76.05, 82.61, 127.73 (2×C), 127.76 (2×C), 128.39, 137.83, 203.93; EIMS *m/z* 406 (M^+). Anal. Calcd for $C_{22}H_{34}O_5Si$: C, 64.99; H, 8.43. Found: C, 64.62; H, 8.69.

4.1.3. Diol 13. To a stirred solution of **7** (1.49 g, 3.67 mmol) in CH_2Cl_2 (15 mL) and MeOH (15 mL) at −78°C was added $NaBH_4$ (300 mg, 7.93 mmol), and the reaction mixture was stirred at −78°C for 30 min. The reaction mixture was poured into water and extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated. Purification by flash chromatography (20% EtOAc/hexane) gave an alcohol (1.42 g, 95%) as a crystalline solid: mp 77–79°C; $[\alpha]_D^{25}=-6.16°$ (*c* 0.53, $CHCl_3$). A mixture of the alcohol (800 mg, 1.96 mmol) and 20% $Pd(OH)_2/C$ (160 mg) in EtOAc (14 mL) was stirred at room temperature for 40 min under a hydrogen atmosphere. The reaction mixture was passed through a short column of Celite and eluted with EtOAc. Concentration of the eluate gave **13** (622 mg, 100%) as a crystalline solid: mp 211–212°C; $[\alpha]_D^{25}=-37.4°$ (*c* 0.50, $CHCl_3$); IR (KBr) 3587, 3420 cm^{-1}; ^{1}H NMR (600 MHz, acetone-d_6) δ 0.98 (9H, s), 1.02 (9H, s), 1.51 (1H, q, *J*=11.7 Hz), 2.40 (1H, ddd, *J*=11.7, 4.4, 4.4 Hz), 3.20 (1H, ddd, *J*=8.8, 5.9, 2.9 Hz), 3.31 (1H, ddd, *J*=9.5, 9.5, 5.1 Hz), 3.53 (1H, t, *J*=6.4 Hz, OH), 3.55–3.62 (2H, m), 3.74 (1H, t, *J*=10.3 Hz), 3.77 (2H, m), 4.07 (1H, dd, *J*=10.3, 5.1 Hz), 4.10 (1H, d, *J*=5.1 Hz, OH); ^{13}C NMR (150 MHz, acetone-d_6) δ 20.43, 23.11, 27.47 (3×C), 27.79 (3×C), 42.74, 63.13, 66.58, 67.66, 73.43, 77.66, 83.68; EIMS *m/z* 318 (M^+). Anal. Calcd for $C_{15}H_{30}O_5Si$: C, 56.57; H, 9.50. Found: C, 56.43; H, 9.76.

4.1.4. Triflate 5. To a stirred solution of **13** (504 mg, 1.585 mmol) in dry THF (10 mL) and 2,6-lutidine (740 μL, 6.340 mmol) at −78°C was added Tf_2O (290 μL, 1.743 mmol). After stirring at −78°C for 30 min, TBSOTf (540 μL, 2.377 mmol) was added, and the reaction mixture was allowed to warm to 0°C over 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$, and the mixture was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated. The residue was purified by flash chromatography (3% EtOAc in hexane) to give triflate **5** (844 mg, 94%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.09 (3H, s), 0.13 (3H, s), 0.89 (9H, s), 0.99 (9H, s), 1.04 (9H, s), 1.54 (1H, q, *J*=12.0 Hz), 2.43 (1H, ddd, *J*=12.0, 4.4, 4.4 Hz), 3.33

(1H, ddd, *J*=9.9, 9.9, 4.8 Hz), 3.45 (1H, ddd, *J*=7.3, 5.5, 1.8 Hz), 3.60 (1H, ddd, *J*=10.6, 9.2, 4.4 Hz), 3.76 (1H, ddd, *J*=11.4, 9.5, 4.4 Hz), 3.79 (1H, t, *J*=10.3 Hz), 4.14 (1H, dd, *J*=10.3, 4.8 Hz), 4.50 (1H, dd, *J*=10.6, 5.5 Hz), 4.69 (1H, dd, *J*=10.6, 1.8 Hz).

4.1.5. Acetylene 14. To a stirred solution of trimethylsilylacetylene (156 μL, 1.106 mmol) in dry THF (2 mL) at 0°C was added *n*-BuLi (710 μL of a 1.56 M solution in hexane, 1.106 mmol), and the reaction mixture was stirred at 0°C for 30 min. After cooling the mixture to −78°C, HMPA (290 μL, 1.660 mmol) and a solution of **5** (312 mg, 0.553 mmol) in dry THF (2 mL) were added, and the mixture was warmed gradually to 0°C over 2.5 h. The reaction was quenched with saturated aqueous NH_4Cl, and the mixture was extracted with Et_2O. The extract was washed with water and brine, dried, and concentrated. The residue was dissolved in MeOH (5 mL) and 5% KOH (0.5 mL), and the solution was stirred at room temperature for 1.5 h. The reaction mixture was extracted with EtOAc, and the extract was washed with water and brine, dried, and concentrated. Purification of the residue by flash chromatography (4% EtOAc in hexane) gave **14** (180 mg, 74%) as a colorless oil: $[\alpha]_D^{24}=-46.7°$ (*c* 0.93, $CHCl_3$); IR ($CHCl_3$) 3309, 2122, 1472 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.11 (3H, s), 0.12 (3H, s), 0.89 (9H, s), 0.99 (9H, s), 1.05 (9H, s), 1.52 (1H, q, *J*=11.7 Hz), 1.98 (1H, t, *J*=2.9 Hz), 2.37 (1H, ddd, *J*=11.7, 4.4, 4.4 Hz), 2.42 (1H, ddd, *J*=16.9, 5.9, 2.9 Hz), 2.61 (1H, ddd, *J*=16.9, 2.9, 2.9 Hz), 3.24 (1H, ddd, *J*=8.8, 5.9, 3.7 Hz), 3.32 (1H, ddd, *J*=10.3, 10.3, 5.1 Hz), 3.59 (1H, ddd, *J*=11.7, 9.5, 5.1 Hz), 3.77 (1H, ddd, *J*=11.7, 9.5, 4.4 Hz), 3.83 (1H, t, *J*=10.3 Hz), 4.16 (1H, dd, *J*=10.3, 5.1 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ −4.86, −4.07, 17.86, 19.95, 21.59, 22.60, 25.72 (3×C), 27.09 (3×C), 27.46 (3×C), 42.21, 66.87, 68.52, 69.88, 72.23, 77.30, 79.99, 80.73; HREIMS *m*/*z* Calcd for $C_{23}H_{44}O_4Si_2$ (M^+) 440.2776. Found 440. 2749.

4.1.6. Ketone 15. A mixture of **7** (924 mg, 2.276 mmol) and 20% $Pd(OH)_2$/C (92 mg) in EtOAc (23 mL) was stirred under a hydrogen atmosphere for 1 h. The reaction mixture was filtered through a short pad of Celite, and the filtrate was concentrated. To a solution of the residue in DMF (4.5 mL) was added imidazole (310 mg, 4.552 mmol) and TBDPSCl (0.65 mL, 2.504 mmol) at 0°C. After stirring at room temperature for 3 h, the reaction mixture was extracted with Et_2O, and the extract was washed with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated. Flash chromatography (5% EtOAc in hexane) gave **15** (1.26 g, 100%) as an oil: $[\alpha]_D^{25}=-22.2°$ (*c* 2.39, $CHCl_3$); IR ($CHCl_3$) 1726, 1472 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.01 (9H, s), 1.02 (9H, s), 1.05 (9H, s), 2.42 (1H, dd, *J*=16.9, 11.0 Hz), 3.04 (1H, dd, *J*=16.9, 5.9 Hz), 3.58 (1H, ddd, *J*=9.5, 9.5, 5.1 Hz), 3.90 (1H, t, *J*=10.2 Hz), 3.95 (2H, m), 4.00 (1H, dd, *J*=11.0, 2.2 Hz), 4.19 (1H, ddd, *J*=9.5, 9.5, 5.9 Hz), 4.23 (1H, dd, *J*=10.2, 5.1 Hz), 7.35–7.43 (6H, m), 7.65–7.68 (4H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.26, 19.60, 22.63, 26.69 (3×C), 27.00 (3×C), 27.40 (3×C), 48.21, 63.21, 66.61, 72.20, 75.37, 83.58, 127.60 (4×C), 129.66 (2×C), 133.31, 133.39, 135.64 (4×C), 205.15; HREIMS *m*/*z* Calcd for $C_{31}H_{46}O_5Si_2$ 554.2881. Found 554.2898.

4.1.7. Ketone 17. To a stirred solution of ketone **15** (894 mg, 1.614 mmol) and molecular sieves 3A (4.5 g) in dry CH_2Cl_2 (16 mL) at −78°C were added $BF_3{\cdot}OEt_2$ (218 μL, 1.775 mmol) and Me_3SiCHN_2 (2.42 mL of a 2.0 M solution in hexane, 4.841 mmol), and the mixture was stirred at −78°C for 20 min. The reaction was quenched with saturated aqueous $NaHCO_3$, and the mixture was extracted with hexane. The extract was washed with water and brine, dried, and concentrated. The residue was dissolved in MeOH (20 mL) and PPTS (50 mg) was added to the solution. After stirring at room temperature for 4 h, Et_3N (0.1 mL) was added, and the mixture was concentrated. Flash chromatography (6% Et_2O in hexane) gave **17** (666 mg, 72%) as an oil: $[\alpha]_D^{25}=-75.8°$ (*c* 2.09, $CHCl_3$); IR ($CHCl_3$) 1716, 1472 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.96 (9H, s), 1.01 (9H, s), 1.08 (9H, s), 1.58 (1H, br q, *J*=12.5 Hz), 2.28 (1H, m), 2.43 (1H, dd, *J*=12.5, 7.3 Hz), 2.97 (1H, br t, *J*=12.5 Hz), 3.21 (1H, ddd, *J*=10.3, 10.3, 5.1 Hz), 3.84–3.95 (4H, m), 4.05 (1H, ddd, *J*=10.3, 10.3, 4.4 Hz), 4.10 (1H, dd, *J*=10.3, 5.1 Hz), 7.36–7.42 (6H, m), 7.62–7.69 (4H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.21, 19.87, 22.63, 26.68 (3×C), 27.00 (3×C), 27.47 (3×C), 32.46, 38.28, 65.87, 66.97, 77.41, 81.28, 88.02, 127.60 (2×C), 127.67 (2×C), 129.71, 129.74, 132.93, 133.13, 135.61 (2×C), 135.68 (2×C), 214.87; HREIMS *m*/*z* Calcd for $C_{32}H_{48}O_5Si_2$ 568.3038. Found 568.3011.

4.1.8. *exo*-Olefin 18. To a stirred solution of **17** (784 mg, 1.380 mmol) in dry THF (14 mL) at 0°C was added the Tebbe reagent (3.04 mL of a 0.5 M solution in toluene, 1.518 mmol), and the mixture was stirred at 0°C for 35 min. The reaction mixture was diluted with Et_2O (20 mL), and 1% NaOH was added until orange–yellow precipitate formed. The mixture was extracted with Et_2O, and the extract was washed with water and brine, dried, and concentrated. Flash chromatography (3% EtOAc in hexane) gave **18** (739 mg, 95%) as an oil: $[\alpha]_D^{25}=-37.9°$ (*c* 2.74, $CHCl_3$); IR ($CHCl_3$) 1472, 1428 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.96 (9H, s), 1.03 (9H, s), 1.04 (9H, s), 1.33 (1H, m), 2.11 (2H, m), 2.22 (1H, m), 3.23 (1H, ddd, *J*=10.3, 10.3, 5.1 Hz), 3.51 (1H, dd, *J*=11.0, 5.1 Hz), 3.66 (1H, dd, *J*=11.0, 6.6 Hz), 3.79 (1H, ddd, *J*=11.0, 11.0, 5.8 Hz), 3.81 (1H, t, *J*=11.0 Hz), 4.02 (1H, dd, *J*=11.0, 5.1 Hz), 4.16 (1H, br t, *J*=5.9 Hz), 4.74 (1H, s), 4.98 (1H, s), 7.35–7.42 (6H, m), 7.65–7.67 (4H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.21, 19.82, 22.58, 26.82 (3×C), 27.10 (3×C), 27.50 (3×C), 28.02, 39.61, 66.96 (2×C), 76.79, 77.77, 84.25, 113.05, 127.56 (4×C), 129.59 (2×C), 133.62, 133.80, 135.71 (4×C), 150.34; HREIMS *m*/*z* Calcd for $C_{33}H_{50}O_4Si_2$ 566.3245. Found 566.3271.

4.1.9. Epoxide 19. To a stirred solution of **18** (610 mg, 1.078 mmol) in acetone (30 mL) and MeCN (10 mL) at 0°C were added successively $EDTA{\cdot}Na_2$ (9 mL of a 0.4 mM aqueous solution), 1,1,1-trifluoroacetone (3 mL), $NaHCO_3$ (1.36 g, 16.166 mmol), and Oxone® (3.31 g, 5.388 mmol). After stirring at 0°C for 5 h, the reaction mixture was diluted with EtOAc and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (4% EtOAc in hexane) to give **19** (546 mg, 87%) and its epimer (56 mg, 9%). **19**: $[\alpha]_D^{28}=-28.3°$ (*c* 1.26, $CHCl_3$); IR ($CHCl_3$) 1472, 1428,

1114 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.99 (9H, s), 1.03 (9H, s), 1.04 (9H, s), 1.21 (1H, ddd, J=13.9, 5.1, 2.9 Hz), 1.81 (1H, m), 2.00 (1H, m), 2.05 (1H, ddd, J=13.9, 13.9, 2.2 Hz), 2.68 (1H, d, J=4.4 Hz), 2.80 (1H, d, J=4.4 Hz), 3.31 (1H, t, J=5.1 Hz), 3.59–3.66 (3H, m), 3.77 (1H, t, J=10.3 Hz), 3.81 (1H, ddd, J=10.3, 10.3, 5.1 Hz), 4.00 (1H, dd, J=10.3, 5.1 Hz), 7.36–7.44 (6H, m), 7.62–7.65 (4H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.15, 19.90, 22.53, 25.56, 26.81 (3×C), 27.13 (3×C), 27.45 (3×C), 32.58, 51.98, 60.38, 65.06, 66.79, 75.72, 77.63, 83.95, 127.69 (4×C), 129.81 (2×C), 133.11, 133.23, 135.61 (4×C); HREIMS m/z Calcd for $C_{33}H_{50}O_5Si_2$ 582.3194. Found 582.3225.

4.1.10. Alcohol 20. To a stirred solution of **19** (623 mg, 1.070 mmol) in dry THF (9 mL) at 0°C was added lithium triethylborohydride (1.2 mL of a 1.0 M solution in THF, 1.20 mmol), the solution was stirred at 0°C for 30 min. The reaction was quenched with water, and the mixture was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated. Flash chromatography (10% EtOAc in hexane) gave **20** (612 mg, 98%) as an oil: $[\alpha]_D^{26}$=+11.6° (c1.28, $CHCl_3$); IR ($CHCl_3$) 3507, 1472, 1103 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.99 (9H, s), 1.01 (9H, s), 1.06 (9H, s), 1.16 (3H, s), 1.64 (1H, m), 1.81–1.93 (3H, m), 2.72 (1H, br s, OH), 3.33 (1H, ddd, J=10.3, 10.3, 5.1 Hz), 3.59 (1H, t, J=7.3 Hz), 3.67 (1H, t, J=10.3 Hz), 3.68 (1H, m), 3.71 (2H, d, J=10.3 Hz), 4.43 (1H, dd, J=10.3, 5.1 Hz), 7.39–7.46 (6H, m), 7.67–7.69 (4H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.03, 20.00, 22.52, 24.24, 26.81 (3×C), 27.19 (3×C), 27.48 (3×C), 30.14, 38.09, 63.82, 67.84, 74.49, 79.02, 83.66, 85.32, 127.83 (2×C), 127.87 (2×C), 129.97, 130.04, 132.59, 132.65, 135.55 (2×C), 135.63 (2×C); HREIMS m/z Calcd for $C_{33}H_{52}O_5Si_2$ 584.3350. Found 582.3371.

4.1.11. Dibenzyl ether 21. To a stirred solution of **20** (592 mg, 1.014 mmol) in MeOH (30 mL) was added 10% KOH (5.2 mL), and the solution was stirred at room temperature for 2.5 h. After the reaction was neutralized with 3N HCl, the mixture was concentrated to one-third of the volume and extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated. Flash chromatography (10% Et_2O in hexane) gave a diol (309 mg, 88%). The diol (221 mg, 0.639 mmol) and benzyl bromide (0.61 mL, 5.110 mmol) was dissolved in dry THF (6.4 mL), and then excess KH in mineral oil was added at 0°C. After stirring at room temperature for 1 h, the reaction was quenched carefully with saturated aqueous NH_4Cl and extracted with Et_2O. The extract was washed with water and brine, dried, and concentrated. Flash chromatography (5% EtOAc in hexane) gave **21** (322 mg, 96%) as an oil: $[\alpha]_D^{25}$=+10.7° (c 1.0, $CHCl_3$); IR ($CHCl_3$) 1496, 1472, 1104 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (9H, s), 1.04 (9H, s), 1.12 (3H, s), 1.51 (1H, dd, J=15.6, 11.2 Hz), 1.87 (1H, m), 1.95 (1H, m), 2.12 (1H, dd, J=15.6, 7.8 Hz), 3.45 (1H, dd, J=10.2, 8.8 Hz), 3.50 (1H, ddd, J=10.2, 9.8, 4.9 Hz), 3.74 (1H, ddd, J=9.8, 9.8, 3.9 Hz), 3.77 (1H, dd, J=10.2, 2.0 Hz), 3.82 (1H, t, J=10.2 Hz), 3.84 (1H, dd, J=8.8, 2.0 Hz), 4.23 (1H, dd, J=10.2, 4.9 Hz), 4.39 and 4.44 (each 1H, d, J=11.2 Hz), 4.55 and 4.57 (each 1H, d, J=12.2 Hz), 7.23–7.33 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.97, 20.63, 22.57, 27.18 (3×C), 27.56 (3×C), 30.20, 31.78, 63.38, 67.90, 70.68, 73.10, 78.93, 79.06, 83.75, 86.46, 127.09, 127.22, 127.33 (2×C), 127.40 (2×C), 128.29 (2×C), 128.32 (2×C), 138.62, 139.20; HREIMS m/z Calcd for $C_{31}H_{46}O_5Si$ 526.3112. Found 526.3137.

4.1.12. Diol 22. To a stirred solution of **21** (322 mg, 0.612 mmol) in THF (4 mL) was added Bu_4NF (1.83 mL of a 1.0 M solution in THF, 1.836 mmol), the solution was stirred at room temperature for 5 h. The solvent was evaporated, and the residue was purified by flash chromatography (80% EtOAc in hexane) to give **22** (211 mg, 89%) as an oil: $[\alpha]_D^{24}$=−11.3° (c 1.0, $CHCl_3$); IR ($CHCl_3$) 3486 (br), 1497 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.15 (3H, s), 1.59 (1H, dd, J=14.7, 9.5 Hz), 1.78 (1H, br, OH), 1.82 (1H, m), 1.89 (1H, m), 2.08 (1H, dd, J=14.7, 9.5 Hz), 2.87 (1H, br, OH), 3.44 (1H, ddd, J=8.8, 8.8, 3.7 Hz), 3.53 (2H, m), 3.59 (1H, dd, J=11.0, 8.1 Hz), 3.73 (1H, dd, J=10.3, 2.2 Hz), 3.80 (1H, dd, J=9.5, 2.2 Hz), 3.83 (1H, dd, J=11.0, 2.9 Hz), 4.39 and 4.43 (each 1H, d, J=11.0 Hz), 4.54 and 4.56 (each 1H, d, J=11.7 Hz), 7.26–7.35 (10H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.67, 30.24, 31.11, 63.39, 64.74, 70.47, 72.50, 73.20, 78.58, 86.59, 88.87, 127.06 (2×C), 127.26 (2×C), 127.62 (2×C), 128.30 (2×C), 128.41 (2×C), 138.06, 139.15; HREIMS m/z Calcd for $C_{23}H_{30}O_5$ 386.2092. Found 386.2084.

4.1.13. Triflate 6. The procedure for compound **5** was employed with compound **22** (66 mg, 0.171 mmol) and CH_2Cl_2 as a solvent. Purification by flash chromatography (4% EtOAc in hexane) gave **6** (100 mg, 93%) as a pale yellow oil: $[\alpha]_D^{22}$=+10.2° (c 0.25, $CHCl_3$); IR ($CHCl_3$) 1497, 1413 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.06 (3H, s), 0.07 (3H, s), 0.87 (9H, s), 1.14 (3H, s), 1.50 (1H, dd, J=15.4, 11.0 Hz), 1.73 (1H, ddd, J=14.2, 8.8, 3.7 Hz), 1.91 (1H, ddd, J=14.2, 10.3, 10.3 Hz), 2.07 (1H, dd, J=15.4, 9.5 Hz), 3.46 (1H, dd, J=9.5, 8.1 Hz), 3.60 (1H, ddd, J=8.8, 8.8, 3.7 Hz), 3.64 (1H, ddd, J=8.1, 5.1, 2.2 Hz), 3.77 (1H, dd, J=10.2, 1.5 Hz), 3.81 (1H, d, J=8.8 Hz), 4.40 and 4.42 (each 1H, d, J=11.0 Hz), 4.52 (1H, dd, J=10.3, 5.1 Hz), 4.53 and 4.59 (each 1H, d, J=11.7 Hz), 4.70 (1H, dd, J=10.3, 2.2 Hz), 7.27–7.36 (10H, m).

4.1.14. Alkyne 23. A solution of **14** (62 mg, 0.141 mmol), **6** (45 mg, 0.070 mmol), and HMPA (0.1 mL) in dry THF (0.9 mL) was cooled to −78°C and treated with n-BuLi (97 μL of a 1.6 M solution in hexane, 0.155 mmol). After stirring at −78°C for 30 min, the reaction mixture was warmed to −20°C over 30 min and stirred for 1 h. The reaction was quenched with NH_4Cl, and the mixture was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated. Flash chromatography (5% EtOAc in hexane) gave **23** (47 mg, 71%) as an oil: $[\alpha]_D^{22}$=−32.8° (c 1.69, $CHCl_3$); IR ($CHCl_3$) 1472, 1252, 1093 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.07 (3H, s), 0.08 (3H, s), 0.09 (3H, s), 0.10 (3H, s), 0.88 (9H, s), 0.89 (9H, s), 0.99 (9H, s), 1.04 (9H, s), 1.16 (3H, s), 1.50 (2H, q, J=11.2 Hz), 1.69 (1H, ddd, J=10.2, 9.3, 2.4 Hz), 1.83 (1H, ddd, J=8.8, 5.4, 5.4 Hz), 2.15 (1H, dd, J=14.2, 9.8 Hz), 2.29 (1H, br dd, J=16.6, 6.8 Hz), 2.36 (1H, ddd, J=12.2, 4.4, 4.4 Hz), 2.43 (2H, m), 2.61 (1H, br dd, J=16.6, 2.4 Hz), 3.20 (1H, ddd, J=8.8, 7.3, 2.9 Hz), 3.30 (1H, ddd, J=10.2,

10.2, 4.9 Hz), 3.51 (3H, m), 3.76 (1H, ddd, *J*=11.2, 9.3, 4.4 Hz), 3.80 (1H, dd, *J*=10.3, 2.0 Hz), 3.81 (1H, t, *J*=9.8 Hz), 3.86 (1H, m), 3.90 (1H, dd, *J*=8.3, 2.0 Hz), 4.15 (1H, dd, *J*=9.8, 4.9 Hz), 4.42 (2H, s), 4.54 and 4.61 (each 1H, d, *J*=12.7 Hz), 7.23–7.35 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.79, −4.60, −4.27, −4.09, 17.86 (2×C), 19.77, 19.95, 22.14, 22.59, 24.28, 25.75 (3×C), 25.81 (3×C), 27.09 (3×C), 27.44 (3×C), 28.38, 30.76, 42.30, 63.21 (2×C), 66.96, 68.87, 70.81, 72.28, 73.02, 74.14, 78.05, 78.09, 78.43, 80.88, 83.98, 85.52, 126.99 (2×C), 127.04 (2×C), 127.24, 127.37, 128.19 (2×C), 128.26 (2×C), 138.95, 139.54; HRFABMS *m/z* Calcd for $C_{52}H_{87}O_8Si_3$ (MH^+) 923.5704. Found 923.5743.

4.1.15. Alkyne 24. A solution of **23** (63 mg, 0.068 mmol) and $TsOH{\cdot}H_2O$ (26 mg, 0.136 mmol) in CH_2Cl_2 (0.3 mL) and MeOH (0.7 mL) was stirred at room temperature for 7 h. After addition of Et_3N (0.1 mL), the reaction mixture was concentrated. The residue was purified by flash chromatography (40% EtOAc in hexane) to give a diol (44.3 mg, 93%). The diol (32.8 mg, 0.047 mmol) was dissolved in CH_2Cl_2 (1 mL), and then 2,6-lutidine (28 μL, 0.236 mmol) and TESOTf (43 μL, 0.189 mmol) were added at 0°C. After stirring at 0°C for 30 min, the reaction mixture was extracted with EtOAc. The extract was washed with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated. Flash chromatography (6% EtOAc in hexane) gave acetylene **24** (41.4 mg, 95%): $[\alpha]_D^{21}=-33.8°$ (*c* 0.84, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.58–0.65 (12H, m), 0.96 (18H, t, *J*=7.8 Hz), 0.99 (9H, s), 1.04 (9H, s), 1.16 (3H, s), 1.52 (2H, m), 1.70 (1H, m), 1.84 (1H, ddd, *J*=14.6, 8.3, 8.3 Hz), 2.16 (1H, dd, *J*=14.2, 10.3 Hz), 2.28 (1H, br dd, *J*=16.6, 7.3 Hz), 2.36 (1H, ddd, *J*=12.2, 4.4, 4.4 Hz), 2.47 (2H, m), 2.64 (1H, dd, *J*=16.6, 2.4 Hz), 3.20 (1H, ddd, *J*=8.8, 7.3, 2.9 Hz), 3.29 (1H, ddd, *J*=10.2, 10.2, 4.9 Hz), 3.47–3.56 (3H, m), 3.74 (1H, ddd, *J*=11.2, 8.8, 4.4 Hz), 3.81 (1H, t, *J*=10.3 Hz), 3.82 (1H, dd, *J*=10.2, 2.0 Hz), 3.85 (1H, m), 3.91 (1H, dd, *J*=8.3, 2.0 Hz), 4.15 (1H, dd, *J*=9.8, 4.9 Hz), 4.42 (2H, s), 4.54 and 4.61 (each 1H, d, *J*=12.7 Hz), 7.21–7.35 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.03 (6×C), 6.86 (3×C), 6.91 (3×C), 19.74, 19.95, 22.60, 24.38, 27.09 (3×C), 27.46 (3×C), 28.46, 30.85, 42.41, 63.21, 66.95, 69.02, 70.83, 72.31, 73.05 (2×C), 74.27, 77.26, 78.00, 78.05, 78.45, 81.00, 83.91, 85.61, 127.00 (2×C), 127.04, 127.24 (2×C), 127.38, 128.21 (2×C), 128.24 (2×C), 138.98, 139.58; HRFABMS *m/z* Calcd for $C_{52}H_{87}O_8Si_3$ (MH^+) 923.5704. Found 923.5681.

4.1.16. 1,2-Diketone 26. To a suspension of **24** (38.8 mg, 0.0421 mmol) in CCl_4 (0.4 mL), MeCN (0.4 mL), and pH 7 phosphate buffer (0.6 mL) were added $NaIO_4$ (22.5 mg, 0.1052 mmol) and $RuO_2{\cdot}H_2O$ (0.8 mg). After stirring at room temperature for 4 h, additional $NaIO_4$ (10.4 mg) was added, and stirring was continued for 4 h. The reaction mixture was extracted with hexane and the extract was washed with aqueous $Na_2S_2O_3$ and brine, dried, and concentrated. Flash chromatography (7% EtOAc in hexane) gave **26** (26 mg, 65%) as a yellow oil: $[\alpha]_D^{25}=-28.0°$ (*c* 0.68, $CHCl_3$); IR ($CHCl_3$) 1715, 1472, 1093 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.59 (12H, m), 0.94 (18H, m), 0.97 (9H, s), 1.02 (9H, s), 1.09 (3H, s), 1.50 (1H, m), 1.51 (1H, q, *J*=11.7 Hz), 1.72 (1H, ddd, *J*=14.7, 9.5, 3.7 Hz), 1.88 (1H, ddd, *J*=14.7, 5.3, 5.3 Hz), 2.07 (1H, dd, *J*=15.4, 9.5 Hz), 2.35 (1H, ddd, *J*=11.7, 4.4, 4.4 Hz), 2.85 (1H, dd, *J*=16.9, 6.8 Hz), 2.94 (1H, dd, *J*=15.4, 9.5 Hz), 3.01 (1H, dd, *J*=15.4, 2.9 Hz), 3.04 (1H, dd, *J*=16.9, 3.0 Hz), 3.27 (1H, ddd, *J*=9.5, 9.5, 5.1 Hz), 3.36 (1H, dd, *J*=10.3, 8.1 Hz), 3.42 (1H, ddd, *J*=10.3, 10.3, 4.4 Hz), 3.53 (1H, ddd, *J*=8.1, 8.1, 2.9 Hz), 3.62 (1H, dd, *J*=10.3, 1.5 Hz), 3.66 (1H, t, *J*=10.3 Hz), 3.69 (2H, m), 3.80 (1H, dd, *J*=8.1, 2.2 Hz), 3.90 (1H, ddd, *J*=8.1, 8.1, 2.9 Hz), 4.00 (1H, dd, *J*=10.5, 4.4 Hz), 4.38 and 4.40 (each 1H, d, *J*=11.3 Hz), 4.47 and 4.49 (each 1H, d, *J*=12.5 Hz), 7.22–7.31 (10H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 5.01 (3×C), 5.07 (3×C), 6.83 (3×C), 6.86 (3×C), 19.98 (2×C), 22.62, 27.05 (3×C), 27.43 (3×C), 29.59, 31.07, 38.66, 40.57, 42.41, 63.19, 66.66, 70.01, 70.26, 72.22 (2×C), 72.59, 76.15, 78.13, 78.60, 84.27, 84.69, 126.95 (4×C), 127.06, 127.23, 127.49 (2×C), 128.21 (2×C), 138.67, 139.39, 197.28, 197.41; HRFABMS *m/z* Calcd for $C_{52}H_{87}O_{10}Si_3$ (MH^+) 955.5602. Found 955.5647.

4.1.17. Dimethyl ketal 28. A solution of **26** (24.2 mg, 0.0253 mmol) and $TsOH{\cdot}H_2O$ (9.6 mg, 0.0507 mmol) in $CHCl_3$ (1.0 mL) was stirred at 0°C for 1 h. The reaction was quenched with three drops of Et_3N, and the solvent was evaporated. Flash chromatography (20% acetone in hexane) gave **27** (16.9 mg, 89%). To a stirred solution of **27** (15.0 mg) in DMF (1.0 mL) at 0°C were added MeI (0.1 mL) and NaH (60% in mineral oil, 20 mg), the reaction mixture was stirred at 0°C for 35 min. The reaction was quenched with saturated aqueous NH_4Cl, and the mixture was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated. Flash chromatography (25% Et_2O in hexane) gave **28** (8.5 mg, 55%) as a solid: mp 188–189°C; $[\alpha]_D^{20}=-17.7°$ (*c* 0.71, $CHCl_3$); IR ($CHCl_3$) 1473, 1365, 1278, 1102 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.99 (9H, s), 1.04 (9H, s), 1.16 (3H, s), 1.57 (1H, m), 1.66 (1H, q, *J*=11.7 Hz), 1.75 (1H, m), 1.90 (1H, t, *J*=12.5 Hz), 2.00 (1H, m), 2.03 (1H, t, *J*=11.7 Hz), 2.15 (1H, dd, *J*=12.5, 4.2 Hz), 2.19 (1H, dd, *J*=15.4, 8.1 Hz), 2.30 (1H, dd, *J*=12.5, 4.4 Hz), 2.34 (1H, ddd, *J*=11.7, 4.4, 4.4 Hz), 3.20 (3H, s), 3.25 (3H, s), 3.27 (1H, ddd, *J*=11.7, 8.8, 5.1 Hz), 3.33 (1H, ddd, *J*=10.3, 10.3, 5.1 Hz), 3.37–3.47 (3H, m), 3.50 (1H, dd, *J*=10.3, 8.1 Hz), 3.78 (1H, dd, *J*=10.3, 2.4 Hz), 3.82 (1H, t, *J*=10.3 Hz), 3.84 (2H, m), 4.13 (1H, dd, *J*=10.3, 4.4 Hz), 4.40 and 4.46 (each 1H, d, *J*=11.7 Hz), 4.57 and 4.59 (each 1H, d, *J*=11.7 Hz), 7.25–7.34 (10H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.94, 20.99, 22.60, 26.96, 27.05 (3×C), 27.40 (3×C), 29.11, 30.80, 33.09, 37.82, 47.03, 47.10, 63.27, 66.74, 68.43, 70.70, 72.97, 73.09, 75.62, 76.01, 78.04, 78.99, 81.77, 87.39, 98.13, 98.46, 126.95, 127.14, 127.24, 127.29, 128.23, 128.26, 128.31, 128.36, 129.45, 129.54, 138.80, 139.29; HRFABMS *m/z* Calcd for $C_{42}H_{63}O_{10}Si$ (MH^+) 755.4187. Found 755.4162.

4.1.18. BCDE ring system 2. To a stirred solution of **28** (8.4 mg, 0.0111 mmol) in dry CH_2Cl_2 (0.2 mL) at 0°C were added Et_3SiH (16.5 μL, 0.111 mmol) and TMSOTf (8.8 μL, 0.0446 mmol), the reaction mixture was stirred at 0°C for 45 min. The reaction was quenched with $NaHCO_3$, and the mixture was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated. Flash chromatography (15% acetone in hexane) gave **2**

(3.9 mg, 51%) as a solid: mp 182–183°C; $[\alpha]_D^{21}=-25.2°$ (*c* 0.1, $CHCl_3$); IR ($CHCl_3$) 1454, 1077 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.98 (9H, s), 1.04 (9H, s), 1.13 (3H, s), 1.44 (1H, q, *J*=11.0 Hz), 1.54 (3H, q, *J*=11.8 Hz), 1.82 (1H, m), 1.90 (1H, ddd, *J*=13.9, 10.3, 10.3 Hz), 2.17 (1H, dd, *J*=15.4, 8.1 Hz), 2.30 (1H, ddd, *J*=8.1, 3.7, 3.7 Hz), 2.44 (1H, ddd, *J*=11.0, 4.4, 4.4 Hz), 2.48 (1H, ddd, *J*=11.0, 3.7, 3.7 Hz), 3.03–3.10 (4H, m), 3.14 (1H, ddd, *J*=11.0, 9.5, 4.4 Hz), 3.31 (1H, ddd, *J*=10.3, 10.3, 3.7 Hz), 3.33 (1H, ddd, *J*=9.5, 9.5, 5.1 Hz), 3.48 (1H, dd, *J*=10.3, 8.8 Hz), 3.77 (1H, dd, *J*=10.3, 1.5 Hz), 3.81 (2H, t, *J*=10.3 Hz), 3.84 (1H, ddd, *J*=11.0, 8.8, 4.4 Hz), 4.14 (1H, dd, *J*=10.3, 5.1 Hz), 4.38 and 4.44 (each 1H, d, *J*=11.7 Hz), 4.56 and 4.61 (each 1H, d, *J*=12.5 Hz), 7.24–7.34 (10H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.94, 20.76, 22.65, 23.22, 27.05 (3×C), 27.43 (3×C), 32.40, 35.14, 36.85, 38.35, 63.31, 66.77, 70.77, 72.71 (2×C), 73.20, 76.61, 77.05, 77.38, 77.74, 78.97, 83.15, 84.22, 87.01, 127.01 (2×C), 127.21 (2×C), 127.41 (2×C), 128.28 (2×C), 128.34 (2×C), 138.70, 139.28; HRFABMS *m/z* Calcd for $C_{40}H_{59}O_8Si$ (MH^+) 695.3976. Found 695.3989.

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