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SYNTHESIS OF THE 37-*epi*-HIJ RING SYSTEM OF ADRIATOXIN

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Abstract – A stereoselective synthesis of the 37-*epi*-HIJ ring system of adriatoxin, a diarrheic shellfish toxin of mussels, was achieved. The present synthesis involves installation of the tertiary alcohol structure of the I ring via a spiro-epoxide and subsequent formation of the J ring dihydropyran followed by the stereoselective oxidation of an enolic double bond and sulfation of an anomeric hydroxy group.

INTRODUCTION

Adriatoxin (**1**) is a trisulfated polycyclic ether isolated as a diarrheic shellfish toxin along with yessotoxin and its congeners from the digestive glands of mussels, *Mytilus galloprovincialis,* infested by toxic dinoflagellates in Italy.[1] The decacyclic skeleton is identical with that of the A-J ring system of yessotoxin, a diarrheic shellfish toxin originally isolated from scallops in Japan.[2] Contamination of bivalves by these toxins poses a worldwide problem to human health as well as to the shellfish industry. Their characteristic molecular architectures and potent biological activities[3] make adriatoxin and yessotoxin challenging synthetic targets, and efficient methods have been developed involving intramolecular diacetalization of diketone and reductive etherification,[4] α-cyano ether formation and ring-closing metathesis,[5] and intramolecular allylation of an α-chloroacetoxy ether and ring-closing metathesis.[6] As part of our studies directed towards the synthesis of these diarrheic toxins, we have recently reported iterative[7] and convergent[8] syntheses of the ABCDEF ring system of adriatoxin and yessotoxin based on an oxiranyl anion strategy.[9] We report herein our synthetic studies of the HIJ ring system (**2**) of adriatoxin.

It is clear that stereocontrolled construction of the I ring, which has a 4-hydroxy-3-methyltetrahydropyran structure, and a monosulfated *cis*-1,2-diol structure of the J ring are the keys in the synthesis of **2** (Figure 1).

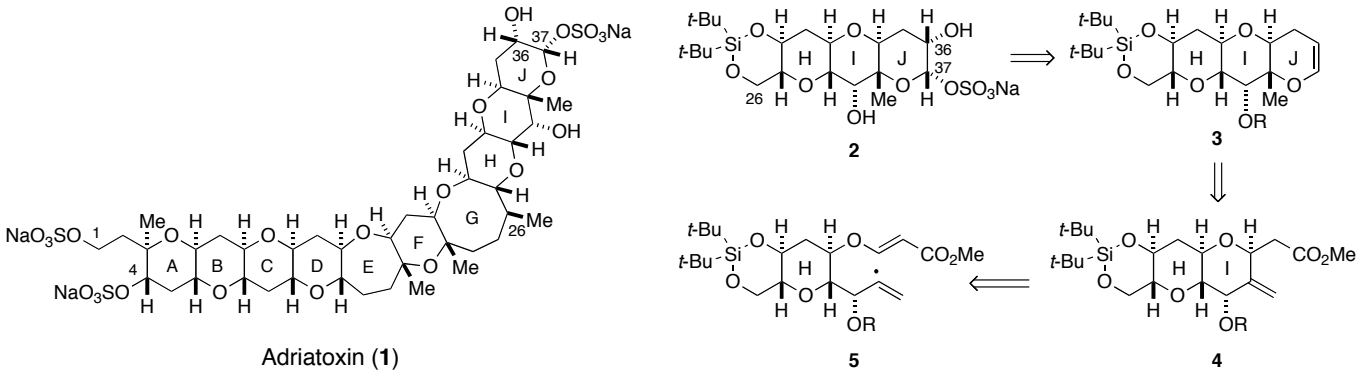
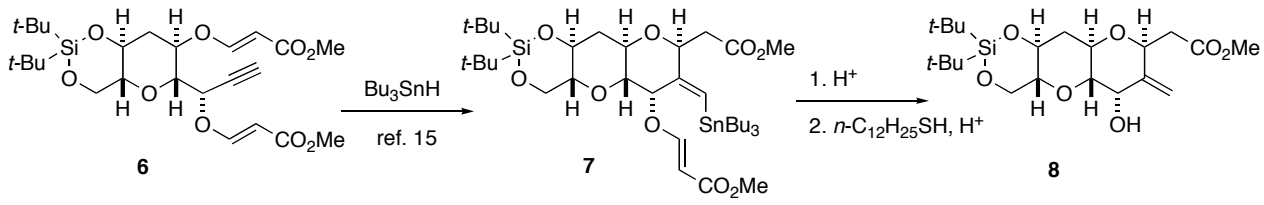


Figure 1 Structure of adriatoxin (**1**) and retrosynthetic analysis of the HIJ ring system (**2**)

The synthesis of a polycyclic ether ring system including a 4-hydroxy-3-methyltetrahydropyran has recently been reported by using intramolecular hetero-Michael addition and reductive etherification.[10] We envisioned that an efficient and straightforward construction of the I ring would be accessible by the 6-*exo*-*trig* cyclization of vinyl radical (**5**) generated from an acetylenic β-alkoxyacrylate, and the product (**4**) would then be transformed into dihydropyran (**3**). Stereocontrolled dihydroxylation of **3** and sulfation of an anomeric hydroxy group would provide the HIJ fragment (**2**). Although the intramolecular addition of acyl,[11] ketyl,[12] or vinyl radicals[13] to β-alkoxyacrylates has proven to be a useful method for the synthesis of tetrahydropyrans, the influence of an alkoxy group of **5** adjacent to the radical center on cyclization has not been explored. The alkoxy group should occupy the α-axial position in the transition state, which might disturb the cyclization.[14] In this context, we have recently revealed that the radical cyclization of acetylenic β-alkoxyacrylates proceeded in good yields irrespective of the stereochemistry of the propargylic position. Application of the radical cyclization to **6** provided allylic alcohol (**8**), which is a useful precursor of the HIJ ring system (Scheme 1).[15]



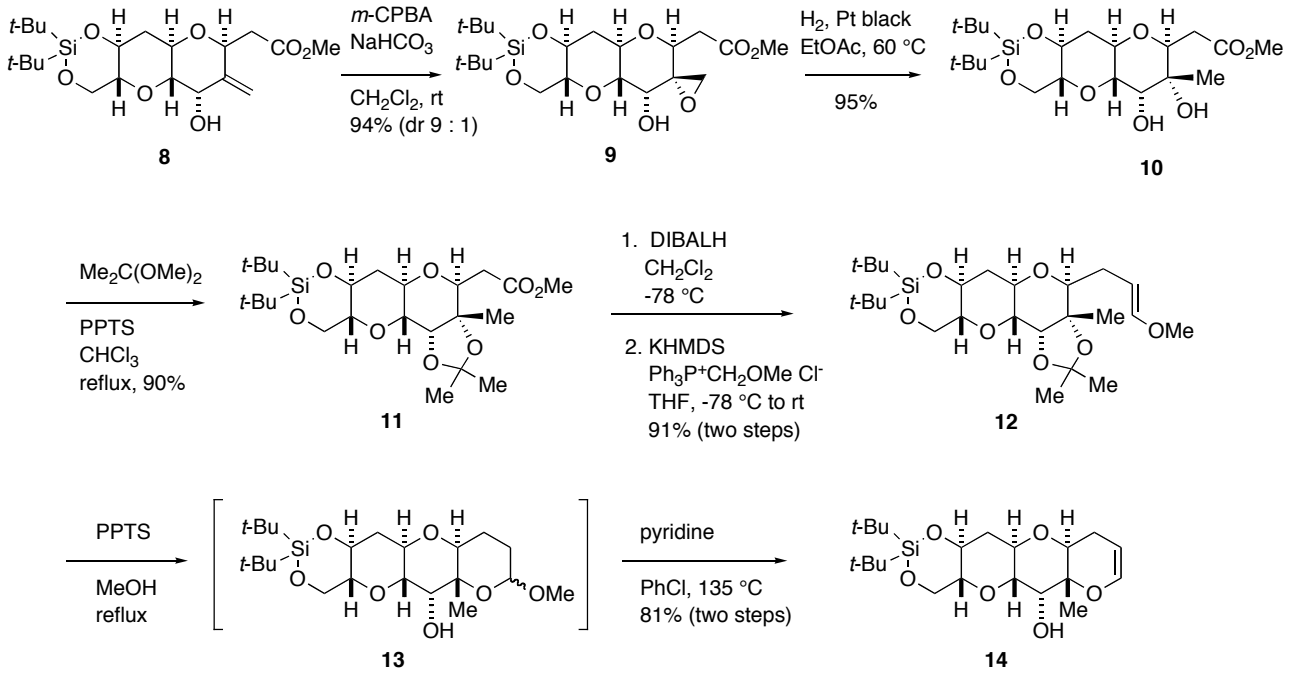
Scheme 1

RESULTS AND DISCUSSION

Synthesis of the HIJ ring (**2**) started with allylic alcohol (**8**) (Scheme 2). To install a tertiary alcohol structure, **8** was subjected to hydroxy-directed epoxidation with *m*-CPBA to give α-epoxide (**9**) in good selectivity. Treatment of **9** with lithium triethylborohydride led to reduction of the ester and epoxide to

give cleanly a triol albeit in moderate yield. Then, a chemoselective reduction of the spiro-epoxide by catalytic hydrogenation was examined.[16] After several experiments, it was discovered that hydrogenolysis of the epoxide with platinum black in EtOAc at 60 °C yielded dihydroxy ester (**10**) in high yield. The resulting *cis*-diol was protected with 2,2-dimethoxypropane to give acetonide **(11**) in 90% yield.

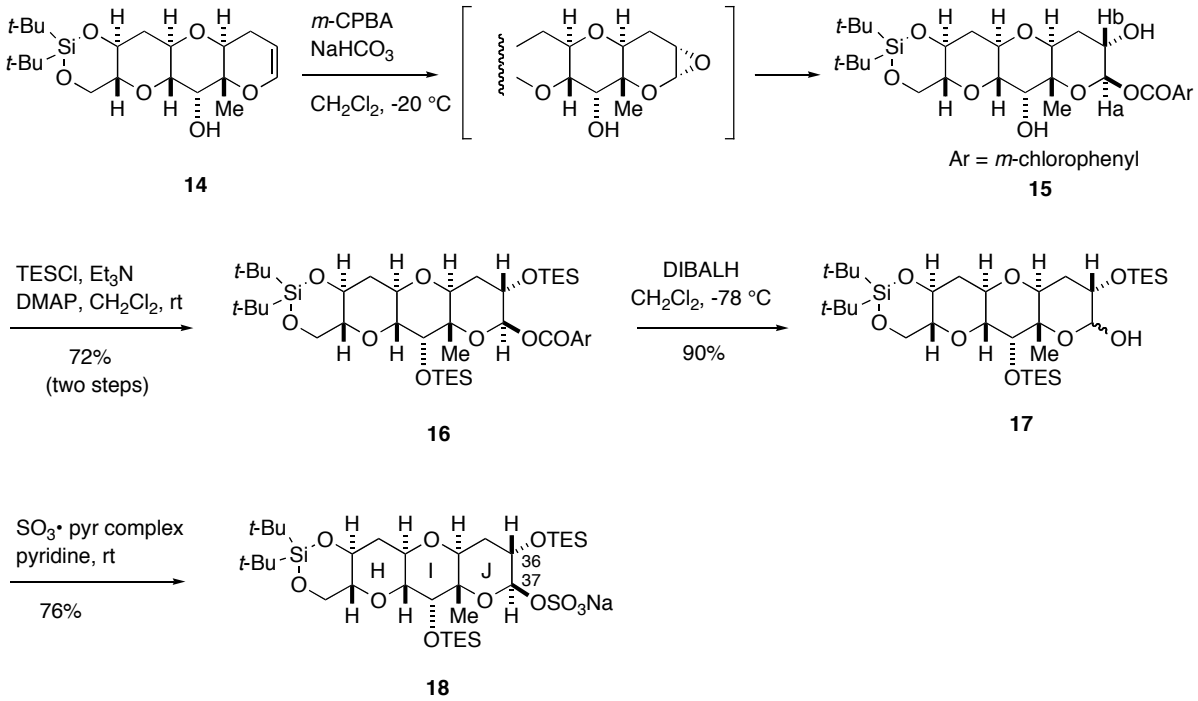
In order to construct the J ring, **11** was reduced with DIBALH and subsequent Wittig reaction of the resulting aldehyde gave enol ether (**12**). Conversion of the enol ether to dihydropyran (**14**) was carried out by a one-pot procedure.[17] Thus, heating **12** with PPTS in MeOH at reflux led to dimethyl acetal formation of the side chain, deprotection of the acetonide, and acetal formation successively to give cyclic methyl acetal (**13)**; following the formation of **13** by TLC, chlorobenzene and pyridine were added to the reaction flask and the mixture was heated at 135 °C. This protocol resulted in the formation of dihydropyran (**14**) in 81% overall yield.



Scheme 2

Finally, stereoselective oxidation of the double bond of **14** and sulfation of an anomeric center were investigated (Scheme 3). Treatment of **14** with *m*-CPBA led to the direct formation of dihydroxy 3-chlorobenzoate (**15**) as a major isomer (dr 9:1). The stereochemistry of the newly introduced 1,2-hydroxy benzoate structure of **15** was assigned to be *trans*-diaxial based on ^{1}H NMR analysis. Thus, the proton signals of Ha and Hb of **15** were observed at δ 6.20 as a singlet and at δ 4.18 as a triplet (J = 2.6 Hz), respectively, indicating that the configurations of Ha and Hb are both equatorial. The stereoselective formation of **15** can be rationalized by epoxidation from the less hindered α-side of the J

ring due to the presence of the β-axial methyl group followed by the *trans*-diaxial ring opening. This *m*-CPBA oxidation is advantageous in that the 1,2-dihydroxylation of the enolic double bond and the following chemoselective protection of the anomeric hydroxy group were achieved in one step. Protection of the two secondary hydroxy groups of **15** with triethylsilyl chloride followed by reduction with DIBALH gave a 1:4 mixture of α- and β-hemiacetals (**17**) in 90% yield. Introduction of sulfuric ester at the anomeric position was accomplished with SO_3·pyridine,[18] and the product was purified by ODS-silica gel chromatography to afford the unstable TES-protected HIJ ring system (**18**) in 76% yield. The stereochemistry of the anomeric center was determined by the NOE experiment. A 7.6% NOE was observed between H36 (δ 4.17, t, J = 2.4 Hz) and H37 (δ 5.46, s), while no NOE was observed between H37 and C33-methyl (δ 1.41, s). Moreover, the signals of H36 and C33-methyl appeared at a lower field than those of adriatoxin (H36, δ 3.42; C33-Me, δ 1.34) due to the β-oriented sulfate ester. The α-equatorial orientation of the sulfate of adriatoxin has been established by the presence of an NOE between H37 (no *J*-value was provided) and C33-methyl. These results revealed that the configuration of the anomeric sulfate group of **18** was β-axial and **18** was a C37-isomer of **2**. The predominant formation of the axial sulfate ester would be explained by the anomeric effect and the steric hindrance of the C36-triethylsilyloxy group.



Scheme 3

In conclusion, a synthetic route of the HIJ ring system of adriatoxin was developed by installation of the tertiary alcohol structure of the I ring via a spiro-epoxide and the subsequent formation of the J ring

dihydropyran followed by the stereoselective oxidation of an enolic double bond. However, sulfation of an anomeric hydroxy group provided a C37-isomer of the HIJ ring (**2**). Further studies toward the synthesis of **1**, including consideration of the stereochemical issues are in progress.

EXPERIMENTAL

General: IR spectra were recorded in $CHCl_3$ solution on a JASCO FTIR-420 spectrometer. ^1H 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. EI and FAB mass spectra were obtained on JEOL JMS-700 and HX-110 mass spectrometers, respectively. Optical rotations were determined on a JASCO DIP-370 digital polarimeter. All air- and moisture-sensitive reactions were carried out under an argon atmosphere in dry, freshly distilled solvents under 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.

Spiro epoxide (9). To a stirred solution of **8** (854 mg, 1.99 mmol) in CH_2Cl_2 (20 mL) were added *m*-CPBA (690 mg, 3.99 mmol) and $NaHCO_3$ (670 mg, 87.98 mmol), and the reaction mixture was stirred at room temperature for 15 h. The reaction was quenched with aqueous saturated $Na_2S_2O_3$ and the mixture was extracted with EtOAc. The extract was washed with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated in vacuo. Purification by flash chromatography (6→10% EtOAc in hexane) gave **9** (833 mg, 94%) as a colorless oil. $[\alpha]^{25}_D$ -40.3 (*c* 0.45, $CHCl_3$); IR ($CHCl_3$) 3587, 1740, 1473, 1439, 1104, 1052 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (9H, s), 1.04 (9H, s), 1.52 (1H, q, *J* = 11.7 Hz), 2.25 (1H, dd, *J* = 15.6, 8.8 Hz), 2.28 (1H, s, OH), 2.30 (1H, dd, *J* = 15.6, 4.4 Hz), 2.53 (1H, ddd, *J* = 11.7, 4.4, 4.4 Hz), 2.67 and 2.92 (each 1H, d, *J* = 3.9 Hz), 2.29 (1H, dd, *J* = 9.8, 2.9 Hz), 3.40 (1H, ddd, *J* = 9.8, 9.8, 4.9 Hz), 3.70 (3H, s), 3.83-3.90 (2H, m), 3.88 (1H, t, *J* = 10.2 Hz), 4.14 (1H, dd, *J* = 10.2, 4.9 Hz), 4.72 (1H, dd, *J* = 8.8, 4.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 22.6, 27.0 (3xC), 27.4 (3xC), 33.6, 38.2, 48.7, 51.9, 58.9, 66.6, 69.1, 70.0, 72.2, 77.2, 77.8, 79.6, 171.0; EIMS *m/z* 444 (M^+); HREIMS *m/z* calcd for $C_{21}H_{36}O_8Si$ (M^+) 444.2177, found 444.2185.

Diol (10). A mixture of **9** (599 mg, 1.350 mmol) and Pt black (240 mg) in EtOAc (14 mL) was stirred vigorously under a hydrogen atmosphere at 80 °C for 3.5 h. The reaction mixture was diluted with EtOAc and filtered through a short pad of Celite. The filtrate was concentrated in vacuo and the residue was purified by flash chromatography (35→50% EtOAc in hexane) to give **10** (572 mg, 95%) as a solid. Mp 222-224 °C, $[\alpha]^{25}_D$ -30.2 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3550, 1736, 1473, 1099, 1052 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (9H, s), 1.03 (9H, s), 1.31 (3H, s), 1.49 (1H, q, *J* = 11.7 Hz), 2.37 (1H, d, *J* = 1.5 Hz, OH), 2.40 (1H, dd, *J* = 15.6, 9.8 Hz), 2.47 (1H, ddd, *J* = 11.7, 4.4, 4.4 Hz), 2.69 (1H, dd, *J* = 15.6, 2.9 Hz), 2.97 (1H, s, OH), 3.40 (1H, ddd, *J* = 10.3, 10.3, 4.9 Hz), 3.61 (1H, ddd, *J* = 11.7, 9.8, 4.4 Hz), 3.71 (3H,

s), 3.78 (1H, ddd, *J* = 10.7, 9.3, 4.4 Hz), 3.82 (1H, t, *J* = 10.3 Hz), 3.83 (1H, br s), 4.04 (1H, dd, *J* = 9.8, 2.9 Hz), 4.13 (1H, dd, *J* = 10.3, 4.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 19.9, 22.6, 27.0 (3xC), 27.4 (3xC), 34.2, 38.1, 51.8, 66.7, 69.5, 71.2, 72.4, 73.8, 75.7, 77.9, 78.0, 172.5; EIMS *m/z* 446 (M^+); HREIMS *m/z* calcd for $C_{21}H_{38}O_8Si$ (M^+) 446,2336, found 446.2348.

Acetonide (11). A solution of **10** (201 mg, 0.451 mmol), PPTS (5.7 mg, 0.023 mmol), and 2,2-dimethoxypropane (0.11 mL, 0.903 mmol) in $CHCl_3$ (6.0 mL) was heated at 60°C for 2 h. After cooling to room temperature, Et_3N (0.2 mL) was added to the solution. The reaction mixture was concentrated in vacuo and the residue was purified by flash chromatography (30% EtOAc in hexane) to give **11** (196 mg, 90%) as a solid. Mp 210-212°C, $[\alpha]^{25}_D$ -9.3 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 1738, 1473, 1382, 1105, 1057 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (9H, s), 1.02 (9H, s), 1.26 (3H, s), 1.39 (3H, s), 1.56 (3H, s), 1.48 (1H, q, *J* = 11.7 Hz), 2.38 (1H, dd, *J* = 15.1, 10.3 Hz), 2.51 (1H, ddd, *J* = 11.7, 4.4, 4.4 Hz), 2.53 (1H, dd, *J* = 15.1, 2.9 Hz), 3.26 (1H, dd, *J* = 10.2, 3.4 Hz), 3.32 (1H, ddd, *J* = 10.3, 9.3, 4.9 Hz), 3.67 (1H, ddd, *J* = 11.2, 9.8, 4.4 Hz), 3.70 (3H, s), 3.88 (1H, ddd, *J* = 11.2, 9.3, 4.4 Hz), 4.00 (1H, t, *J* = 10.3 Hz), 4.05 (1H, dd, *J* = 10.3, 2.9 Hz), 4.12 (1H, d, *J* = 3.4 Hz), 4.16 (1H, dd, *J* = 10.3, 4.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.2, 19.9, 22.6, 27.0 (3xC), 27.1, 27.4 (3xC), 28.2, 34.3, 38.4, 51.8, 66.5, 70.6, 72.0, 76.9, 77.3, 78.9, 79.1, 80.1, 110.4, 171.8; EIMS *m/z* 486 (M^+); HREIMS *m/z* calcd for $C_{24}H_{42}O_8Si$ (M^+) 486.2649, found 446.2653.

Enol ether (12). To a stirred solution of **11** (235 mg, 0.484 mmol) in CH_2Cl_2 at -78 °C was added DIBALH (0.61 mL of a 0.95 M solution in hexane, 0.580 mmol), and the reaction mixture was stirred at -78 °C for 35 min. The reaction was quenched with MeOH and the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with EtOAc and washed with saturated aqueous potassium sodium tartrate, water, and brine. The organic layer was dried and concentrated in vacuo to give aldehyde, which was used in the next reaction without purification.

To a suspension of methoxymethyltriphenylphosphonium chloride (663 mg, 1.93 mmol) in THF (4.0 mL) at 0 °C was added KHMDS (2.74 mL of a 0.67 M solution in toluene, 1.84 mmol) and the mixture was stirred for 30 min. The yellow suspension was cooled to -78 °C and a solution of the aldehyde in THF (4.8 mL) was added to the suspension. After stirring at -78 °C for 40 min, the reaction mixture was warmed to room temperature and stirring was continued for 40 min. 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 in vacuo. Flash chromatography (10→25% EtOAc in hexane) gave **12** (213 mg, 91%) as a colorless oil. $[\alpha]^{25}_D$ -27.9 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 1656, 1473, 1381, 1104, 1049 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (9H, s), 1.03 (9H, s), 1.26 (3H, s), 1.39 (3H, s), 1.52 (3H, s), 1.51(1H, q, *J* = 11.7 Hz), 1.97 (1H, m), 2.16 (1H, m), 2.58 (1H, ddd, *J* = 11.7, 4.4, 4.4 Hz), 3.27 (1H, dd, *J* = 9.8, 3.4 Hz), 3.35-3.42 (2H, m), 3.52 (3H, s), 3.60 (1H, ddd, *J* = 11.7, 10.3, 4.4 Hz), 3.89 (1H, ddd, *J*

= 11.7, 9.3, 4.4 Hz), 4.00 (1H, t, *J* = 10.2 Hz), 4.09 (1H, d, *J* = 3.4 Hz), 4.16 (1H, dd, *J* = 10.2, 4.9 Hz), 4.82 (1H, ddd, *J* = 12.7, 8.3, 6.4 Hz), 6.35 (1H, d, *J* = 12.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.3, 19.9, 22.6, 27.0 (3xC), 27.1, 27.4 (3xC), 28.4, 38.5, 55.9, 66.5, 70.3, 72.1, 77.2, 77.5, 78.9, 79.3, 80.9, 81.4, 99.7, 110.0, 148.2; EIMS *m/z* 484 (M^+); HREIMS *m/z* calcd for $C_{25}H_{44}O_7Si$ (M^+) 484,2856, found 484.2859.

Cyclic enol ether (14). A solution of **12** (252 mg, 0.520 mmol) and PPTS (130 mg, 0.520 mmol) in MeOH (5.2 mL) was refluxed for 2.5 h. After cooling the solution to room temperature, chlorobenzene (5.2 mL) was added and MeOH was removed under reduced pressure. To this solution was added pyridine (0.084 mL, 1.04 mmol) and the solution was heated at 135 °C for 70 min. The reaction mixture was cooled to room temperature and Et_3N (0.2 mL) was added. The mixture was concentrated in vacuo and the residue was purified by flash chromatography (30% EtOAc in hexane) to give **14** (167 mg, 78%) as a solid. Mp 211-214 °C, $[\alpha]^{25}_D$ -7.84 (*c* 0.25, $CHCl_3$); IR ($CHCl_3$) 3580, 1646, 1473, 1243, 1106, 1077 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (9H, s), 1.04 (9H, s), 1.21 (3H, s), 1.53 (1H, q, *J* = 11.7 Hz), 1.98 (1H, dddd, *J* = 16.1, 11.2, 2.4, 2.4 Hz), 2.25 (1H, ddd, *J* = 16.1, 5.8, 5.8 Hz), 2.48 (1H, ddd, *J* = 11.7, 4.4, 4.4 Hz), 3.30 (1H, dd, *J* = 9.8, 2.9 Hz), 3.38 (1H, ddd, *J* = 10.2, 10.2, 4.9 Hz), 3.75 (1H, ddd, *J* = 11.7, 9.8, 4.4 Hz), 3.87 (1H, ddd, *J* = 11.2, 9.3, 4.4 Hz), 3.91 (1H, dd, *J* = 11.2, 5.8 Hz), 3.93 (1H, t, *J* = 10.2 Hz), 4.04 (1H, d, *J* = 2.4 Hz), 4.17 (1H, dd, *J* = 10.2, 4.9 Hz), 4.68 (1H, ddd, *J* = 5.9, 5.9, 2.0 Hz), 6.19 (1H, ddd, *J* = 5.9, 2.4, 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.3, 19.9, 22.6, 23.3, 27.1 (3xC), 27.4 (3xC), 38.4, 66.7, 70.1, 70.2, 72.2, 72.3, 78.3, 78.4, 98.6, 140.6; EIMS *m/z* 412 (M^+); HREIMS *m/z* calcd for $C_{21}H_{36}O_6Si$ (M^+) 412.2281, found 412.2280.

***m*-Chlorobenzoate (16)**. To a stirred mixture of **14** (166.8 mg, 0.0.405 mmol) and $NaHCO_3$ (102 mg, 1.215 mmol) in CH_2Cl_2 (4.0 mL) at -20 °C was added *m*-CPBA (105 mg, 0.607 mmol), and the reaction mixture was stirred at -20 °C for 30 min. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ and the mixture was extracted with EtOAc. The extract was washed with water, saturated aqueous $NaHCO_3$, and brine, dried, and concentrated in vacuo. Flash chromatography (60% EtOAc in hexane) gave **15** (203 mg) as a solid. Mp 187-189 °C; IR (KBr) 3586, 3461, 1738, 1473, 1253 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 0.99 (9H, s), 1.05 (9H, s), 1.44 (3H, s), 1.57 (1H, q, *J* = 11.3 Hz), 1.97 (1H, m), 2.25 (1H, ddd, *J* = 13.1, 13.1, 3.3 Hz), 2.43 (1H, ddd, *J* = 11.3, 4.4, 4.4 Hz), 2.82 (1H, br, OH), 3.44 (1H, ddd, *J* = 9.3, 9.3, 5.1 Hz), 3.47 (1H, dd, *J* = 9.8, 2.9 Hz), 3.74 (1H, ddd, *J* = 11.7, 9.9, 4.0 Hz), 3.77 (1H, m), 3.81 (1H, t, *J* = 10.2 Hz), 3.85 (1H, br s, OH), 3.87 (1H, ddd, *J* = 11.0, 9.2, 4.8 Hz), 4.09 (1H, dd, *J* = 9.9, 4.8 Hz), 4.18 (1H, t, *J* = 2.6 Hz), 4.43 (1H, dd, *J* = 13.2, 4.0 Hz), 6.21 (1H, s), 7.56-8.03 (4H, Ar).

To a solution of **15** (203 mg) in CH_2Cl_2 (4.0 mL) were added Et_3N (0.85 mL, 6.072 mmol), DMAP (5.0 mg), and TESCl (0.51 mL, 3.036 mmol), and the reaction mixture was stirred at room temperature for 19 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and the mixture was extracted with

CH_2Cl_2. The extract was washed with water and brine, dried, and concentrated in vacuo. Flash chromatography (5→10% Et_2O in hexane) gave **16** (184 mg, 72% in two steps) as a colorless oil. $[\alpha]^{25}_D$ -1.96 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 1726, 1575, 1472, 1067, 1006 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.49-0.68 (12H, m), 0.94 (18 H, q, *J* = 7.8 Hz), 0.99 (9H, s), 1.04 (9H, s), 1.41 (3H, s), 1.51 (1H, q, *J* = 11.7 Hz), 1.89 (1H, ddd, *J* = 12.7, 3.4, 3.4 Hz), 2.03 (1H, ddd, *J* = 12.7, 12.7, 2.9 Hz), 2.47 (1H, ddd, *J* = 11.7, 4.4, 4.4 Hz), 3.25 (1H, dd, *J* = 9.8, 2.4 Hz), 3.33 (1H, ddd, *J* = 9.8, 9.8, 4.9 Hz), 3.69-3.80 (2H, m), 3.79 (1H, t, *J* = 10.2 Hz), 3.86 (1H, d, *J* = 2.4 Hz), 4.05 (1H, s), 4.12 (1H, dd, *J* = 10.2, 4.9 Hz), 4.41 (1H, dd, *J* = 12.7, 3.4 Hz), 6.10 (1H, s), 7.39-7.99 (4H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.6 (2xC), 5.1 (2xC), 6.4 (2xC), 6.7 (2xC), 6.8 (2xC), 6.9 (2xC), 19.1, 19.9, 22.7, 27.1 (3xC), 27.4 (3xC), 29.0, 38.5, 66.8, 67.9, 69.1, 71.5, 72.7, 73.3, 77.7, 78.6, 96.9, 127.8, 129.7, 129.8, 131.9, 133.2, 134.7, 163.7; EIMS *m/z* 783 (M^+-C_2H_5); HREIMS *m/z* calcd for $C_{38}H_{64}ClO_9Si_3$ (M^+-C_2H_5) 783.3547, found 783.3543.

37-epi-HIJ ring (18). To a solution of the *m*-chlorobenzoate (32.1 mg, 0.0395 mmol) in CH_2Cl_2 (0.5 mL) at -78°C was added DIBALH (0.125 mL of a 0.95 M solution in hexane, 0.119 mmol), and the reaction mixture was stirred at -78 °C for 40 min. The reaction was quenched with MeOH and the mixture was warmed to room temperature. After stirring for 20 min, saturated aqueous potassium sodium tartrate was added to the mixture and the mixture was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated in vacuo to give **17** (24.0 mg, 90%).

To a solution of **17** obtained above (24.0 mg, 0.0355 mmol) in pyridine (0.5 mL) was added a SO_3·pyrdine complex (31 mg, 0.197 mmol) and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was made alkaline (pH 9) with 1 N NaOH, diluted with 0.5 N NH_4OH (1.0 mL), and subjected to chromatography (ODS-silica gel, eluted successively with 0.5 N NH_4OH, 20→50→90% MeOH in 0.5 N NH_4OH). Fractions containing the HIJ fragment (silica gel TLC: Rf = 0.55, 14% MeOH in EtOAc) were combined and concentrated in vacuo to give **18** (23.4 mg, 76%). $[\alpha]^{25}_D$ -10.6 (*c* 1.0, MeOH); ^1H NMR (400 MHz, CD_3OD) δ 0.57-0.71 (12H, m), 0.93-1.00 (18 H, m), 0.99 (9H, s), 1.04 (9H, s), 1.41 (3H, s), 1.50 (1H, q, *J* = 11.7 Hz), 1.73 (1H, d, *J* = 12.7 Hz, H35eq), 2.03 (1H, ddd, *J* = 12.7, 12.7, 2.4 Hz, H35ax), 2.41 (1H, ddd, *J* = 11.7, 4.4, 4.4 Hz), 3.30 (1H, m), 3.38 (1H, ddd, *J* = 9.8, 9.8, 5.4 Hz), 3.67 (1H, ddd, *J* = 11.7, 9.3, 3.9 Hz), 3.76 (1H, m), 3.78 (1H, t, *J* = 10.2 Hz), 3.88 (1H, d, *J* = 2.4 Hz), 4.10 (1H, dd, *J* = 10.2, 4.9 Hz), 4.17 (1H, t, *J* = 2.4 Hz), 4.35 (1H, dd, *J* = 12.7, 3.4 Hz, H34ax), 5.46 (1H, s); ^{13}C NMR (100 MHz, CD_3OD) δ 5.5 (2xC), 5.7, 6.0, 6.1 (2xC), 7.2 (2xC), 7.4, 7.5 (2xC), 7.6, 19.5, 20.8, 23.6, 27.6 (3xC), 27.9 (3xC), 29.6, 39.5, 68.0, 69.6, 71.4, 72.8, 74.4, 75.0, 77.9, 78.9, 79.9, 101.1; FABMS *m/z* 799 ($M+Na^+$); HRFABMS *m/z* calcd for $C_{33}H_{65}O_{11}SSi_3Na_2$ ($M+Na^+$) 799.3246, found 799.3257.

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