SYNTHETIC STUDY OF CARBOCYCLIC CORE OF CORTISTATIN A, AN ANTI-ANGIOGENIC STEROIDAL ALKALOID FROM MARINE SPONGE

Naoyuki Kotoku,* Yuji Sumii, Takeshi Hayashi, and Motomasa Kobayashi*

Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-oka, Suita, Osaka 565-0871, Japan. E-mail: kotoku@phs.osaka-u.ac.jp; kobayasi@phs.osaka-u.ac.jp

Abstract – Synthesis of carbocyclic core of cortistatin A (1), a novel anti-angiogenic steroidal alkaloid from Indonesian marine sponge, was investigated. Intramolecular Heck cyclization using substrate 18 achieved construction of 7-membered B-ring structure. The presence of steric hindrance around the reaction center was found to favor endo cyclization pathway in this substrate.

INTRODUCTION

Angiogenesis, a formation of new blood capillaries from preexisting blood vessels, is critical for tumor growth and metastasis. A growing tumor needs an extensive network of capillaries to provide nutrients and oxygen etc. In addition, the new blood vessels provide a way for tumor cells to enter in the circulation and to metastasize to another organ. Therefore, substances that inhibit angiogenesis have a considerable potential to be novel therapeutic agents for the treatment of cancer.1

In the course of our study on the bioactive substances from marine organisms, we focused on a search for selective growth inhibitors against human umbilical vein endothelial cells (HUVECs) as anti-angiogenic substances and found cortistatins,2 a family of novel abeo-9(10-19)-androstane-type steroidal alkaloids, from the Indonesian marine sponge of Corticium simplex. Cortistatin A (1, Figure 1), a major constituent, showed remarkably selective anti-proliferative activity against HUVECs and also inhibited migration and tubular formation of HUVECs induced by VEGF or bFGF.2a The unique structure and characteristic biological properties of this compound attracted many synthetic chemists, and four total syntheses,3-6 two formal syntheses7,8 and many synthetic studies9 have been reported so far. Here we report about the construction of carbocyclic core of 1 through Pd-catalyzed 7-endo-type intramolecular cyclization reaction.
RESULTS AND DISCUSSION

Cortistatin A (1) has a characteristic rearranged steroid skeleton, particular with 8-oxabicyclo[3.2.1]octene system in B-ring. Synthetic methods of this complex ring system were highlighted in all the reported total syntheses of 1 to date, such as ring-expansion of cyclopropane or enyne cycloisomerization, etc.\(^3\text{–}^8\) We planned to investigate another approach, that is, direct ring closure through intramolecular Heck-type reaction and subsequent oxo-bridge formation (Figure 2). In the cyclization intermediate of Heck reaction, 7-endo pathway was expected to be sterically more accessible than 6-exo pathway.\(^10\) And, cyclization precursor was divided into two fragments of A-ring fragment and CD-ring fragment.

Figure 2. Retrosynthetic analysis
Firstly, the A-ring fragment was prepared as follows (Scheme 1). Commercial 1,4-cyclohexanedione mono(ethylene ketal) (2) was alkylated with ethyl bromoacetate to give a keto-ester 3, and subsequent Wittig reaction provided an exo-methylene 4 in moderate yield. LiAlH₄ treatment of 4 and protection of the resulting alcohol moiety of 5 by benzyl group gave compound 6. The exo-methylene of 6 was transformed to hydroxymethyl group by hydroboration/oxidation method to give compound 7 as a 1:1 mixture of two diastereomers, which indicates that hydroboration occurred with no stereoselectivity. Then, the hydroxyl group of 7 was protected as tert-butylidimethylsilyl (TBS) ether to give compound 8. The compound 8 was further converted to a desired A-ring fragment 10 in a racemic form through debenzylation and phosphine-mediated substitution reaction.

Scheme 1. Reagents and conditions: (a) LDA, ethyl bromoacetate, THF, –78 °C, 87%; (b) Ph₃PMeBr, n-BuLi, THF, 57%; (c) LiAlH₄, THF, 97%; (d) BnBr, NaH, DMF, 92%; (e) BH₃•SMe₂, THF; NaOH aq. 30% H₂O₂, quant.; (f) TBSCl, imidazole, DMAP, CH₂Cl₂, 94%; (g) H₂, Pd-C, AcOEt, 80% (93% brsm); (h) I₂, Ph₃P, imidazole, CH₂Cl₂, quant.

The A-ring fragment 10 and the CD-ring fragment 19, prepared from commercially available (+)-Hajos-Parrish ketone in 2 steps, were coupled together using Molander’s method to give compound 11 as a mixture of four diastereomers. Hydrogenation of the dienol silyl ether derived from 11 occurred stereoselectively to provide compound 12, which was converted to a tert-alcohol 13 by the treatment with OsO₄ with almost complete diastereoselectivity. The stereochemistry of the newly formed tert-alcohol moiety was determined by NOE experiment. Then removal of the TBS group and subsequent iodination of the primary hydroxyl group of 14 gave compound 15, which was further converted to an objective cyclization precursor 18 (1:1 diastereomeric mixture) by the treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), protection of the tert-alcohol moiety, and enol triflate formation with the use of N-phenyltrifluoromethanesulfonimide in the presence of Et₃N and KHMDS at elevated temperature. In order to investigate steric effect against the 6-exo/7-endo selectivity of Heck cyclization, the tert-alcohol moiety of 16 was protected as methoxymethyl (MOM) or benzyloxymethyl (BOM) ether.
Scheme 2. Reagents and conditions: (a) 19, NaH, DMSO, THF, 56%; (b) TBSOTf, Et3N, CH2Cl2; (c) H2, Pd-C, AcOEt; (d) OsO4, NMO, acetone/H2O, 75% (3 steps); (e) TBAF, THF, 99%; (f) I2, Ph3P, imidazole, CH2Cl2, 79%; (g) DBU, THF, 84%; (h) MOMCl or BOMCl, iPr2NEt, 1,2-dichloroethane, 60 °C, 97% for 17a, quant. for 17b; (i) PhNTf2, KHMDS, Et3N, THF, 60 °C, 99% for 18a, quant. for 18b.

Palladium-catalyzed intramolecular cyclization of substrates 18a or 18b was investigated (Scheme 3). The desired cyclization reaction occurred with palladium catalyst generated by the combination of Pd2(dba)3 and 1,4-bis(diphenylphosphino)butane (dpbb) in N,N-dimethylacetamide (DMA) in the presence of potassium acetate (KOAc) to give a mixture of 7-endo- and 6-exo-cyclization products (20 and 21), respectively. The use of monodentate ligand such as triphenylphosphine provided solely 6-exo-product 21, and organic base (Et3N etc.) gave diminished reaction yield (data not shown). It revealed that the bulkiness of protecting group of the tert-alcohol moiety in 18 affected endo/exo selectivity. Thus, the use of 18a as a substrate at 70 °C gave 20a, 20’a and 21a with the ratio of 1:1:2.6, and the same reaction at higher temperature (85 °C) provided lower 7-endo selectivity (1:3.4). In the case of 18b, the reaction at 85 °C proceeded with acceptable yield and 1:1:2 product ratio (20b, 20'b and 21b).

Scheme 3. Intramolecular Heck reaction

Plausible mechanism of the intramolecular Heck reaction was shown in Figure 3. 7-Endo-trig cyclization toward exo-methylene and subsequent β-elimination provided the desired product 20 having conjugated
diene system. While, the undesired product 21 having cyclopropane ring might be formed through 6-exo-trig cyclization, following carbopalladation toward 9,11-olefin, and β-elimination. Contrary to our expectation, the 6-exo-cyclization was more favored than the 7-endo-one in this substrate. However, the bulky protecting group of the tert-alcohol moiety might inhibit the formation of the 6-exo-cyclization intermediate to provide the improved, but not satisfactory, 7-endo selectivity.

Figure 3. Plausible mechanism of Heck reaction

In summary, a synthesis of the carbocyclic core of cortistatin A (1) was achieved through 7-endo intramolecular Heck reaction. This methodology will lead to the total synthesis of 1 and its analogs, which is now under investigation.

**EXPERIMENTAL**

A JEOL JNM LA-500 spectrometer was used to obtain 1H- and 13C–NMR data using tetramethylsilane as an internal standard. Mass spectra were obtained with a Waters Q-Tof Ultima API using MeOH as a solvent. HPLC was performed using a Hitachi L-6000 pump equipped with Hitachi L-4000H UV detector. Silica gel (Merck, 60-230 mesh) and pre-coated thin layer chromatography (TLC) plates (Merck, 60F254) were used for column chromatography and TLC. Spots on TLC plates were detected by spraying phosphomolybdic acid solution (5 g phosphomolybdic acid in 100 mL of EtOH) and acidic p-anisaldehyde solution (p-anisaldehyde: 25 mL, c-H2SO4: 25 mL, AcOH: 5 mL, EtOH: 425 mL) with subsequent heating. Unless otherwise noted, all the reactions were performed under N2 atmosphere using purchased reagents and solvents without further purification. After workup, the organic phases were dried over Na2SO4.

**Ethyl 2-(8-oxo-1,4-dioxaspiro[4.5]decan-7-yl)acetate (3)**
n-BuLi (2.69 M in hexane, 25.3 mL, 68.0 mmol) was added to a solution of diisopropylamine (9.61 mL, 68.0 mmol) in dry THF (100 mL) at –78 °C, and the whole mixture was stirred for 15 min at –78 °C and further 15 min at rt. Then 2 (10.1 g, 64.7 mmol, in 50 mL of dry THF) was added to the mixture via cannula at –78 °C, and the whole mixture was stirred for 1 h at –78 °C. Then HMPA (11.3 mL, 64.7 mmol) and ethyl bromoacetate (7.88 mL, 71.2 mmol) were added dropwise to the mixture at –78 °C, and the whole mixture was stirred at –78 °C. After 3 h, sat. NH₄Cl aq. was added to the mixture at 0 °C, and the whole mixture was extracted with AcOEt. Removal of the solvent from the AcOEt extract under reduced pressure gave a crude product, which was purified by SiO₂ column (n-hexane/AcOEt = 4:1) to give 3 (13.58 g, 87%) as a colorless oil. IR (KBr): 2982, 1730, 1709 cm⁻¹. ¹H-NMR (500 MHz, CDCl₃) δ: 4.10-3.93 (6H, m), 3.13 (1H, quint, J = 6.7 Hz), 2.69-2.62 (2H, m), 2.33 (1H, ddd, J = 14.3, 4.9, 2.7 Hz), 2.13 (1H, dd, J = 16.8, 6.1 Hz), 2.07-1.97 (2H, m), 1.92 (1H, td, J = 13.5, 5.1 Hz), 1.75 (1H, t, J = 13.3 Hz), 1.19 (3H, t, J = 7.1 Hz, CO₂CH₂CH₃). ¹³C-NMR (125 MHz, CDCl₃) δ: 209.4, 171.9, 106.9, 64.7, 60.3, 42.9, 40.1, 37.7, 34.4, 33.8, 14.0. Anal. Calcd for C₁₂H₁₈O₅: C, 59.49; H, 7.49. Found: C, 59.38; H, 7.40.

Ethyl 2-(8-methylene-1,4-dioxaspiro[4.5]decan-7-yl)acetate (4)
n-BuLi (2.69 M in hexane, 33.4 mL, 89.7 mmol) was added dropwise to the solution of methyltriphenylphosphonium bromide (30.1 g, 84.1 mmol) in dry THF (100 mL) at 0 °C, and the whole mixture was stirred for 15 min at 0 °C. Then 3 (13.6 g, 56.1 mmol, in 60 mL of dry THF) was added to the mixture via cannula. After stirring for 1 h at rt, sat. NH₄Cl aq. was added to the mixture at 0 °C, and the whole mixture was extracted with AcOEt. Removal of the solvent from the AcOEt extract under reduced pressure gave a crude product, which was purified by SiO₂ column (n-hexane/AcOEt = 5:1) to give 4 (7.66 g, 57%) as a colorless oil. IR (KBr): 2982, 1736, 1649 cm⁻¹. ¹H-NMR (500 MHz, CDCl₃) δ: 4.68 (1H, s, C=CH₂), 4.54 (1H, s, C=CH₂), 4.08-4.02 (2H, m, CO₂CH₂CH₃), 3.89-3.86 (4H, m, OCH₂CH₂O), 2.75 (1H, m), 2.55 (1H, dd, J = 15.1, 7.3 Hz), 2.28-2.23 (3H, m), 1.82-1.78 (1H, m), 1.72-1.69 (1H, m), 1.57-1.51 (1H, m), 1.33 (1H, t, J = 11.5 Hz), 1.17 (3H, t, J = 7.3 Hz, CO₂CH₂CH₃). ¹³C-NMR (125 MHz, CDCl₃) δ: 172.3, 149.0 (C=CH₂), 108.2 (C=CH₂), 106.5, 64.2, 64.1, 60.0, 41.1, 37.6, 36.6, 36.0, 32.1, 14.0. Anal. Calcd for C₁₃H₂₀O₄: C, 65.94; H, 7.49. Found: C, 65.23; H, 8.25.

2-(8-Methylene-1,4-dioxaspiro[4.5]decan-7-yl)ethanol (5)
4 (8.89 g, 37.0 mmol, in 50 mL of dry THF) was added dropwise via dropping funnel to a suspension of lithium aluminum hydride (1.38 g, 37.0 mmol) in dry THF (300 mL) at 0 °C, and the whole mixture was stirred for 1 h at rt. Water (1.3 mL), 15% NaOH aq. (1.3 mL), and sat. NH₄Cl aq. were successively added to the mixture, and the whole mixture was extracted with AcOEt. Removal of the solvent from the AcOEt
extract under reduced pressure gave a crude product, which was purified by SiO$_2$ column (n-hexane/AcOEt = 1:1) to give 5 (7.13 g, 97%) as a colorless oil. IR (KBr): 3347, 2946, 1647 cm$^{-1}$. 

$^1$H-NMR (500 MHz, CDCl$_3$) δ: 4.75 (1H, s, C=CH$_2$), 4.66 (1H, s, C=CH$_2$), 3.96-3.91 (4H, m, OCH$_2$CH$_2$O), 3.65 (2H, t-like, CH$_2$OH), 2.42-2.37 (1H, m), 2.31 (1H, td, J = 13.0, 5.0 Hz), 2.25-2.20 (1H, m), 2.00-1.93 (1H, m), 1.89 (1H, brs), 1.86 (1H, ddd, J = 18.0, 5.0, 2.0 Hz), 1.77-1.72 (1H, m), 1.64-1.50 (2H, m), 1.43-1.39 (1H, m). $^{13}$C-NMR (125 MHz, CDCl$_3$) δ: 150.1 (C=CH$_2$), 108.7 (C=CH$_2$), 106.8, 64.3, 64.1, 60.8, 41.5, 36.7, 36.2, 35.1, 32.1. Anal. Calcd for C$_{11}$H$_{18}$O$_3$: C, 66.64; H, 9.15. Found: C, 66.74; H, 9.17.

7-(2-(Benzyloxy)ethyl)-8-methylene-1,4-dioxaspiro[4.5]decane (6)

NaH (60% in oil, 1.55 g, 38.7 mmol) was added to the solution of 5 (6.40 g, 32.2 mmol) in dry DMF (60 mL) at 0 °C, and the whole mixture was stirred for 30 min at rt. Benzyl bromide (5.76 mL, 48.4 mmol) was added to the mixture, and the whole was stirred for 24 h at rt. Sat. NaHCO$_3$ aq. was added to the mixture at 0 °C, and the whole mixture was extracted with AcOEt. Removal of the solvent from the AcOEt extract under reduced pressure gave a crude product, which was purified by SiO$_2$ column (n-hexane/AcOEt = 5:1) to give 6 (8.54 g, 92%) as a colorless oil. IR (KBr): 2946, 1647, 1454 cm$^{-1}$. 

$^1$H-NMR (500 MHz, CDCl$_3$) δ: 7.34-7.33 (5H, m, Ph), 4.76 (1H, s, C=CH$_2$), 4.67 (1H, s, C=CH$_2$), 4.50 (1H, d, J = 11.5 Hz, OCH$_2$Ph), 4.46 (1H, d, J = 11.5 Hz, OCH$_2$Ph), 3.91 (4H, s, OCH$_2$CH$_2$O), 3.53-3.51 (2H, m, CH$_2$OCH$_2$Ph), 2.47 (1H, m), 2.34-2.26 (2H, m), 2.07-2.03 (1H, m), 1.90-1.87 (1H, m), 1.80-1.75 (1H, m), 1.66-1.62 (2H, m), 1.42-1.38 (1H, m). $^{13}$C-NMR (125 MHz, CDCl$_3$) δ: 149.8 (C=CH$_2$), 138.4 (Ph), 128.1 (2C, Ph), 127.4 (2C, Ph), 127.2 (Ph), 108.5 (C=CH$_2$), 106.6, 72.7 (OCH$_2$OPh), 68.2 (CH$_2$OCH$_2$Ph), 64.1, 64.0, 41.3, 36.7, 36.2, 32.02, 31.99. Anal. Calcd for C$_{18}$H$_{24}$O$_3$: C, 74.97; H, 8.39. Found: C, 75.07; H, 8.43.

(7-(2-(Benzyloxy)ethyl)-1,4-dioxaspiro[4.5]decan-8-yl)methanol (7)

BH$_3$•SMe$_2$ (2.0 M in THF, 54.1 mL, 108 mmol) was added to the solution of 6 (10.4 g, 36.1 mmol) in THF (36 mL) at 0 °C, and the whole mixture was stirred for 10 h at rt. 3.0 M NaOH (36.1 mL, 108 mmol) and 30% H$_2$O$_2$ (13.0 mL, 126 mmol) were added to the mixture at 0 °C, and the whole mixture was stirred for additional 4 h at rt. Sat. NH$_4$Cl aq. was added to the mixture, and the whole mixture was extracted with AcOEt. Removal of the solvent from the AcOEt extract under reduced pressure gave a crude product, which was purified by SiO$_2$ column (n-hexane/AcOEt = 1:2) to give 7 (mixture of two diastereomers, 11.1 g, quant.) as a colorless oil. IR (KBr): 3480, 2936, 2874, 1454 cm$^{-1}$. 

$^1$H-NMR (500 MHz, CDCl$_3$) δ: 7.30-7.21 (5H, m, Ph), 4.47-4.41 (2H, m, OCH$_2$Ph), 3.86-3.81 (4H, m, OCH$_2$CH$_2$O), 3.60-3.39 (4H, m, CH$_2$OCH$_2$Ph, CH$_2$OH), 2.42 (1H, brs), 1.98-2.05 (1H, m), 1.88-1.15 (9H, m). $^{13}$C-NMR (125 MHz,
CDCl₃ δ: 138.12 (1/2C, Ph), 138.08 (1/2C, Ph), 128.3 (2C, Ph), 127.6 (2C, Ph), 127.5 (Ph), 109.0 (1/2C), 108.8 (1/2C), 73.0 (1/2C), 72.9 (1/2C), 69.0 (1/2C), 68.1 (1/2C), 64.7 (1/2C), 64.1 (1/2C), 64.0 (1/2C), 63.8 (1/2C), 61.1, 40.3 (1/2C), 39.6 (1/2C), 34.0 (1/2C), 33.6 (1/2C), 33.3 (1/2C), 32.8 (1/2C), 31.6 (1/2C), 31.4 (1/2C), 30.4 (1/2C), 26.9 (1/2C), 23.8 (1/2C), 22.5 (1/2C). Anal. Calcd for C₁₈H₂₆O₄: C, 70.56; H, 8.55. Found: C, 70.26; H, 8.44.

((7-(2-(Benzyloxy)ethyl)-1,4-dioxaspiro[4.5]decan-8-yl)methoxy)(tert-butyldimethylsilane (8)

Imidazole (2.20 g, 32.4 mmol), TBSCI (2.93 g, 19.4 mmol), and DMAP (395 mg, 3.24 mmol) were successively added to the solution of 7 (4.95 g, 16.2 mmol) in anhydrous CH₂Cl₂ (16 mL), and the whole mixture was stirred for 24 h at rt. Sat. NH₄Cl aq. was added to the mixture at 0 °C, and the whole mixture was extracted with CH₂Cl₂. Removal of the solvent from the CH₂Cl₂ extract under reduced pressure gave a crude product, which was purified by SiO₂ column (n-hexane/AcOEt = 5:1) to give 8 (mixture of two diastereomers, 6.37 g, 94%) as a colorless oil. IR (KBr): 2928, 2859, 1456 cm⁻¹.

¹H-NMR (500 MHz, CDCl₃) δ: 7.33-7.24 (5H, m, Ph), 4.52-4.45 (2H, m, OCH₂Ph), 3.92-3.87 (4H, m, OCH₂CH₂O), 3.75-3.42 (4H, m, CH₂OCH₂Ph, CH₂OTBS), 2.07-2.03 (1H, m), 1.95-1.20 (9H, m), 0.89 (9H, s, C(CH₃)₃), 0.04 (6H, s, Si(CH₃)₂).

¹³C-NMR (125 MHz, CDCl₃) δ: 138.6 (1/2C), 138.5 (1/2C), 128.2 (2C), 127.44, 127.41, 127.3, 109.1 (1/2C), 108.9 (1/2C), 72.8 (1/2C), 72.7 (1/2C), 68.7 (1/2C), 68.1 (1/2C), 65.3 (1/2C), 64.1 (1/2C), 64.0 (1/2C), 63.9 (1/2C), 61.1, 43.3 (1/2C), 40.1 (1/2C), 39.0 (1/2C), 37.1 (1/2C), 34.1 (1/2C), 33.3 (1/2C), 32.8 (1/2C), 31.2 (1/2C), 27.0, 25.8 (3C, C(CH₃)₃), 23.9, 18.2 (1/2C), 18.1 (1/2C), -5.4 (SiCH₃), -5.5 (SiCH₃). Anal. Calcd for C₂₄H₄₀O₄Si: C, 68.53; H, 9.58. Found: C, 68.31; H, 9.50. ESI MS: m/z 443 (M+Na)+. HR-ESI MS: m/z 443.2594, calcd for C₂₄H₄₀O₄SiNa. Found: 443.2582.

2-(8-((tert-Butyldimethylsilyloxy)methyl)-1,4-dioxaspiro[4.5]decan-7-yl)ethanol (9)

Pd-C (10%, 3.80 g) was added to the solution of 8 (19.0 g, 45.2 mmol) in AcOEt (45 mL), and the whole mixture was stirred for 24 h under hydrogen atmosphere. The reaction mixture was filtered through Celite pad, eluting with AcOEt. Removal of the solvent from the filtrate under reduced pressure gave a crude product, which was purified by SiO₂ column (n-hexane/AcOEt = 1:2) to give 9 (mixture of two diastereomers, 12.0 g, 80%) as a colorless oil. Unreacted 8 (2.66 g) was also recovered (93% based on recovered starting material). IR (KBr): 3441, 2936, 1472 cm⁻¹. ¹H-NMR (500 MHz, CDCl₃) δ: 3.89-3.84 (4H, m, OCH₂CH₂O), 3.66-3.41 (4H, m, CH₂OTBS, CH₂OH), 2.51 (1H, brs), 2.05-1.92 (1H, m), 1.76-1.68 (3H, m), 1.61-1.43 (5H, m), 1.42-1.20 (1H, m), 0.82 (9H, s, C(CH₃)₃), -0.01 (6H, s, Si(CH₃)₂).

¹³C-NMR (125 MHz, CDCl₃) δ: 109.2 (1/2C), 108.9 (1/2C), 65.5 (1/2C), 64.1 (1/2C), 64.0 (1/2C), 63.9 (1/2C), 61.6 (1/2C), 61.1 (1/2C), 60.2, 43.2 (1/2C), 40.2 (1/2C), 39.1 (1/2C), 37.2 (1/2C), 34.0 (1/2C), 33.7 (1/2C), 33.2 (1/2C), 27.1, 25.8 (3C, C(CH₃)₃), 24.0, 18.2 (1/2C), 18.1 (1/2C), -5.5 (2C,
Si(CH$_3$)$_2$). Anal. Calcd for C$_{17}$H$_{34}$O$_4$Si: C, 61.77; H, 10.37. Found: C, 61.37; H, 10.05. ESI MS: m/z 353 (M+Na$^+$). HR-ESI MS: m/z 353.2124, calcd for C$_{17}$H$_{34}$O$_4$SiNa. Found: 353.2085.

tert-Butyl(7-(2-iodoethyl)-1,4-dioxaspiro[4.5]decan-8-yl)methoxy)dimethylsilane (10)
PPh$_3$ (11.4 g, 43.5 mmol), imidazole (4.93 g, 72.5 mmol), and I$_2$ (4.93 g, 72.5 mmol) were successively added to the solution of 9 (12.0 g, 36.2 mmol) in anhydrous CH$_2$Cl$_2$ (120 mL) at 0 °C, and the whole mixture was stirred for 3 h at rt. Sat. NaHSO$_3$ aq. and NH$_4$Cl aq. were added to the mixture, and the whole mixture was extracted with CH$_2$Cl$_2$. Removal of the solvent from the CH$_2$Cl$_2$ extract under reduced pressure gave a crude product, which was purified by SiO$_2$ column (n-hexane/AcOEt = 4:1) to give 10 (mixture of two diastereomers, 15.9 g, quant.) as a colorless oil. IR (KBr): 2928, 2884, 1472 cm$^{-1}$. $^1$H-NMR (500 MHz, CDCl$_3$) δ: 3.89-3.87 (4H, m, OC$_2$H$_4$), 3.58-3.44 (2H, m, C$_2$H$_4$OTBS), 3.27-3.13 (2H, m, C$_2$H$_4$I), 2.15-1.35 (10H, m), 0.85 (9H, s, C(CH$_3$)$_3$), 0.00 (6H, s, Si(CH$_3$)$_2$). $^{13}$C-NMR (125 MHz, CDCl$_3$) δ: 108.9 (1/2C), 108.6 (1/2C), 65.2 (1/2C), 64.9 (1/2C), 64.3 (1/2C), 64.2 (1/2C), 64.1 (1/2C), 64.0 (1/2C), 42.8 (1/2C), 38.8 (1/2C), 38.6 (1/2C), 37.7 (1/2C), 37.5 (1/2C), 37.1 (1/2C), 36.3 (1/2C), 34.8 (1/2C), 34.1 (1/2C), 31.7 (1/2C), 26.8 (1/2C), 25.9 (3C, C(CH$_3$)$_3$), 24.2 (1/2C), 18.1 (C(CH$_3$)$_3$), 5.4 (1/2C, CH$_2$I), 3.7 (1/2C, CH$_2$I), -5.45 (Si(CH$_3$)$_2$), -5.51 (Si(CH$_3$)$_2$). Anal. Calcd for C$_{17}$H$_{33}$IO$_3$Si: C, 46.36; H, 7.55; I, 28.81. Found: C, 46.32; H, 7.27; I, 28.68. ESI MS: m/z 463 (M+Na$^+$). HR-ESI MS: m/z 463.1141, calcd for C$_{17}$H$_{33}$IO$_3$SiNa. Found: 463.1155.

(1S,7aS)-4-(2-(8-(tert-Butyl(dimethyl)silyl)oxy)methyl)-1,4-dioxaspiro[4.5]decan-7-yl)ethyl-1-(methoxymethoxy)-7a-methyl-2,3,7,7a-tetrahydro-1H-inden-5(6H)-one (11)
NaH (60% in oil, 1.52 g, 37.9 mmol) was added to DMSO (40 mL), and the mixture was stirred for 1.5 h at 50 °C. The mixture was diluted with THF (40 mL), and a solution of 19 (7.97 g, 37.9 mmol) in DMSO (100 mL) was added dropwise to the mixture at 0 °C. After 2 h with stirring, a solution of 10 (15.9 g, 36.1 mmol) in THF (40 mL) was added to the mixture via cannula, and the whole mixture was stirred for 24 h with gradually warming to rt. Sat. NH$_4$Cl aq. was added to the mixture, and the whole mixture was extracted with CH$_2$Cl$_2$. Removal of the solvent from the CH$_2$Cl$_2$ extract under reduced pressure gave a crude product, which was purified by SiO$_2$ column (n-hexane/AcOEt = 4:1) to give 11 (mixture of diastereomers, 13.8 g, 56%) as a colorless oil. IR (KBr): 2936, 2884, 1665, 1470 cm$^{-1}$. $^1$H-NMR (500 MHz, CDCl$_3$) δ: 4.66 (1H, d, J = 6.7 Hz, OCH$_2$OCH$_3$), 4.62 (1H, d, J = 6.7 Hz, OCH$_2$OCH$_3$), 3.93-3.86 (4H, m, OCH$_2$CH$_2$O), 3.72-3.50 (3H, m), 3.34 (3H, s, OCH$_2$OCH$_3$), 2.59-2.47 (2H, m), 2.40-2.31 (2H, m), 2.14-2.03 (4H, m), 1.83-1.72 (5H, m), 1.61-1.13 (7H, m), 1.09 (3H, s, CH$_3$), 0.84 (9H, s, C(CH$_3$)$_3$), 0.00 (6H, s, Si(CH$_3$)$_2$). $^{13}$C-NMR (125 MHz, CDCl$_3$) δ: 197.8 (C=O), 166.8, 133.7, 133.6, 109.3, 109.2, 96.0, 85.6, 85.5, 65.2, 64.2, 64.1, 64.0, 60.3, 55.2, 44.6, 42.8, 39.8, 38.7, 37.03, 36.97, 36.9, 36.3, 34.24, 34.17,
33.4, 31.4, 30.9, 30.6, 27.2, 27.1, 27.0, 25.9 (3C, C(CH₃)₃), 25.1, 25.0, 23.91, 23.85, 23.74, 23.71, 21.9, 18.23, 18.15, 16.08, 16.05, −5.4 (SiCH₃), −5.5 (SiCH₃). Anal. Calcd for C₂₉H₅₀O₆Si: C, 66.63; H, 9.64. Found: C, 66.23; H, 9.38. ESI MS: m/z 545 (M+Na)⁺. HR-ESI MS: m/z 545.3274, calcd for C₂₉H₅₀O₆SiNa. Found: 545.3299.

(1S,3aR,4S,7aS)-4-(2-(8-(tert-Butyldimethylsilyloxy)methyl)-1,4-dioxaspiro[4.5]decan-7-yl)ethyl)-4-hydroxy-1-(methoxymethoxy)-7a-methylhexahydro-1H-inden-5(6H)-one (13)

Et₃N (0.94 mL, 6.86 mmol) and TBSOTf (1.18 mL, 5.15 mmol) were successively added to the solution of 11 (1.79 g, 3.43 mmol) in anhydrous CH₂Cl₂ (30 mL) at 0 °C, and the whole mixture was stirred for 1.5 h. Sat. NH₄Cl aq. was added to the mixture at 0 °C, and the whole mixture was extracted with CH₂Cl₂. Removal of the solvent from the CH₂Cl₂ extract under reduced pressure gave a crude product, which was used in the next reaction without further purification.

Pd-C (10%, 3.8 g) was added to the solution of the above product in AcOEt (20 mL), and the whole mixture was stirred for 5 h under hydrogen atmosphere. The reaction mixture was filtered through Celite pad, eluting with AcOEt. Removal of the solvent from the filtrate under reduced pressure gave a crude product 12, which was used in the next reaction without further purification.

NMO (804 mg, 6.86 mmol), OsO₄ (4 wt.% in H₂O, 1.9 mL, 0.686 mmol) were added to the solution of the above product in acetone-H₂O (8:1, 36 mL), and the whole mixture was stirred for 12 h at 50 °C. Then sat. Na₂SO₃ aq. was added to the mixture at 0 °C, and the whole mixture was extracted with AcOEt. Removal of the solvent from the AcOEt extract under reduced pressure gave a crude product, which was purified by SiO₂ column (n-hexane/AcOEt = 3:1) to give 13 (mixture of diastereomers, 1.39 g, 75%) as a colorless oil. IR (KBr): 2936, 2884, 1711, 1472 cm⁻¹. ¹H-NMR (500 MHz, CDCl₃) δ: 4.56 (1H, d, J = 6.7 Hz, OCH₂OCH₃), 4.53 (1H, d, J = 6.7 Hz, OCH₂OCH₃), 3.88-3.84 (5H, m, OCH₂OCH₃, OH), 3.49-3.42 (3H, m, C₆H₄OTBS, CHOMOM), 3.28 (3H, s, OCH₂OCH₃), 2.62 (1H, td, J = 14.2, 6.1 Hz), 2.37-2.33 (1H, m), 2.10-1.96 (2H, m), 1.80-1.54 (10H, m), 1.12 (3H, s, CH₃), 0.82 (9H, s, C(CH₃)₃), −0.03 (6H, s, Si(CH₃)₂). ¹³C-NMR (125 MHz, CDCl₃) δ: 214.7, 109.1, 95.9 (OCH₂OCH₃), 85.4, 80.4, 64.1, 64.0, 60.0, 56.7, 55.1 (OCH₂OCH₃), 42.8, 38.5, 37.1, 36.8, 36.7, 34.5, 31.4, 31.2, 30.7, 28.3, 25.8 (3C, C(CH₃)₃), 25.1, 23.9, 22.5, 19.0, 18.1, 14.0, 12.4, −5.5 (SiCH₃), −5.6 (SiCH₃). Anal. Calcd for C₂₉H₅₀O₆Si: C, 64.15; H, 9.53. ESI MS: m/z 563 (M+Na)⁺. HR-ESI MS: m/z 563.3380, calcd for C₂₉H₅₀O₆SiNa. Found: 563.3403.

(1S,3aR,4S,7aS)-4-Hydroxy-4-(2-(8-(hydroxymethyl)-1,4-dioxaspiro[4.5]decan-7-yl)ethyl)-1-(methoxymethoxy)-7a-methylhexahydro-1H-inden-5(6H)-one (14)

TBAF (1.0 M in THF, 5.2 mL, 5.2 mmol) was added to the solution of 13 (1.39 g, 2.57 mmol) in THF (36
mL) at 0 °C, and the whole mixture was stirred for 10 h at rt. Sat. NH₄Cl aq. was added to the mixture, and the whole mixture was extracted with AcOEt. Removal of the solvent from the AcOEt extract under reduced pressure gave a crude product, which was purified by SiO₂ column (n-hexane/AcOEt = 1:2) to give 7 (mixture of diastereomers, 1.09 g, 99%) as a colorless oil. IR (KBr): 3480, 2936, 1711, 1449 cm⁻¹. 

¹H-NMR (500 MHz, CDCl₃) δ: 4.50 (1H, d, J = 6.7 Hz, OCH₂OCH₃), 4.47 (1H, d, J = 6.7 Hz, OCH₂OCH₃), 4.02-3.91 (1H, m), 3.82-3.78 (4H, m, OCH₂CH₂O), 3.52-3.30 (3H, m, CH₂OH, CHOMOM), 3.22 (3H, s, OCH₂OC₃H₃), 2.75-2.50 (2H, m), 2.30-2.25 (1H, m), 2.05-1.80 (3H, m), 1.75-1.46 (9H, m), 1.45-1.13 (7H, m), 1.06 (3H, s, CH₃). 

¹³C-NMR (125 MHz, CDCl₃) δ: 215.0, 214.9, 214.6, 109.0, 108.7, 108.6, 108.4, 108.3, 64.4, 64.3, 64.1, 64.0, 63.94, 63.93, 63.8, 63.6, 60.8, 60.1, 59.9, 56.6, 56.5, 55.0, 42.8, 42.6, 42.3, 39.8, 39.7, 39.4, 38.1, 37.2, 37.1, 36.9, 36.6, 36.0, 35.8, 35.6, 34.4, 34.3, 33.9, 33.7, 31.4, 31.3, 30.9, 30.6, 30.5, 29.1, 28.7, 28.1, 26.7, 26.5, 25.9, 25.7, 25.5, 24.6, 23.2, 22.4, 20.7, 18.9, 18.8. Anal. Calcd for C₂₃H₃₈O₇: C, 64.76; H, 8.98. Found: C, 64.31; H, 8.82. ESI MS: m/z 449 (M+Na)⁺. HR-ESI MS: m/z 449.2515, calcd for C₂₃H₃₈O₇Na. Found: 449.2565.

(1S,3aR,4S,7aS)-4-Hydroxy-4-(2-(8-(iodomethyl)-1,4-dioxaspiro[4.5]decan-7-yl)ethyl)-1-(methoxymethoxy)-7a-methylhexahydro-1H-inden-5(6H)-one (15)

PPh₃ (572 mg, 2.18 mmol), imidazole (242 mg, 3.63 mmol), and I₂ (553 mg, 2.18 mmol) were successively added to the solution of 14 (774 mg, 1.82 mmol) in anhydrous CH₂Cl₂ (20 mL) at 0 °C, and the whole mixture was stirred for 3 h at rt. Sat. NaHSO₃ aq. and NH₄Cl aq. were added to the mixture, and the whole mixture was extracted with CH₂Cl₂. Removal of the solvent from the CH₂Cl₂ extract under reduced pressure gave a crude product, which was purified by SiO₂ column (n-hexane/AcOEt = 3:1) to give 15 (mixture of diastereomers, 770 mg, 79%) as a colorless oil. IR (KBr): 2936, 2884, 1711, 1449 cm⁻¹. 

¹H-NMR (500 MHz, CDCl₃) δ: 4.61 (1H, d, J = 6.7 Hz, OCH₂OCH₃), 4.58 (1H, d, J = 6.7 Hz, OCH₂OCH₃), 3.94-3.89 (5H, m, OCH₂CH₂O, OH), 3.52-3.48 (1H, m, CHOMOM), 3.34 (3H, s, OCH₂OCH₂), 3.29-3.08 (2H, m, CH₂I), 2.75-2.65 (1H, m), 2.47-2.40 (1H, m), 2.18-1.92 (3H, m), 1.83-1.60 (9H, m), 1.55-1.30 (5H, m), 1.19 (3/2H, s, CH₃), 1.17 (3/2H, s, CH₃), 0.89-0.81 (2H, m). 

¹³C-NMR (125 MHz, CDCl₃) δ: 215.1, 215.0, 108.7, 108.6, 106.2, 106.1, 96.0, 85.49, 85.46, 80.6, 80.5, 64.4, 64.3, 64.2, 64.1, 57.0, 56.9, 56.8, 55.3, 43.0, 42.9, 41.8, 40.2, 40.1, 39.6, 39.4, 38.8, 38.7, 38.6, 36.9, 36.8, 36.4, 34.7, 34.6 (2C), 33.9, 33.7, 31.6, 31.1, 30.2, 30.1, 29.5, 29.3, 28.4, 26.9, 26.2, 25.6, 25.0, 22.6, 19.2, 14.7, 14.1, 13.5, 12.7, 12.6, 6.2 (CH₂I). Anal. Calcd for C₂₃H₃₇IO₆: C, 51.50; H, 6.69; I, 23.66. Found: C, 51.42; H, 6.66; I, 23.09. ESI MS: m/z 559 (M+Na)⁺. HR-ESI MS: m/z 559.1533, calcd for C₂₃H₃₇IO₆Na. Found: 559.1542.

(1S,3aR,4S,7aS)-4-Hydroxy-1-(methoxymethoxy)-7a-methyl-4-(2-(8-methylene-1,4-dioxaspiro[4.5]-
DBU (1.51 mL, 10.1 mmol) was added to the solution of 15 (676 mg, 1.26 mmol) in anhydrous THF (10 mL), and the whole mixture was stirred for 12 h at 60 °C. Sat. NH₄Cl aq. was added to the mixture at 0 °C, and the whole mixture was extracted with AcOEt. Removal of the solvent from the AcOEt extract under reduced pressure gave a crude product, which was purified by SiO₂ column (n-hexane/AcOEt = 3:1) to give 16 (mixture of two diastereomers, 431.2 mg, 84%) as a colorless oil. IR (KBr): 3488, 2946, 1711, 1647, 1449 cm⁻¹. ¹H-NMR (500 MHz, CDCl₃) δ: 4.75 (1/2H, s, C=C₂H₂), 4.74 (1/2H, s, C=CH₂), 4.65 (1/2H, s, C=CH₂), 4.61 (1H, d, J = 6.4 Hz, OCH₂OCH₃), 4.57 (1H, d, J = 6.4 Hz, OCH₂OCH₃), 4.55 (1/2H, s, C=C₂H₂), 3.96-3.92 (5H, m, OCH₂C₂H₂O, O₂H), 3.49 (1H, t, J = 8.7 Hz, C₂HOMOM), 3.33 (3H, s, OCH₂OCH₃), 2.68 (1H, td, J = 14.2, 6.1 Hz), 2.45-2.40 (1H, m), 2.30-2.20 (5H, m), 1.90-1.48 (10H, m), 1.40-1.20 (3/2H, m), 1.15 (3/2H, s, CH₃), 1.13 (3/2H, s, CH₃), 0.92-0.85 (1/2H, m). ¹³C-NMR (125 MHz, CDCl₃) δ: 215.0, 150.2 (C=CH₂), 108.8, 108.7, 107.0, 106.5, 96.0 (OCH₂OCH₃), 85.53, 85.50, 80.7, 64.4, 64.2, 56.9, 55.3 (OCH₂OCH₃), 43.0, 42.1, 42.0, 40.3, 40.1, 36.9, 36.5, 36.2, 34.6, 32.4, 31.1, 31.0, 28.4, 25.7, 25.6, 19.1, 12.6, 12.5. ESI MS: m/z 431 (M+Na)⁺. HR-ESI MS: m/z 431.2410, calcd for C₂₃H₃₆O₆Na. Found: 431.2419.

(1S,3aR,4S,7aS)-1,4-Bis(methoxymethoxy)-7a-methyl-4-(2-(8-methylene-1,4-dioxaspiro[4.5]decan-7-y1)ethyl)hexahydro-1H-inden-5(6H)-one (17a)

dr₂NEt (0.511 mL, 2.81 mmol) and MOMCl (0.171 mL, 2.25 mmol) were added to the solution of 16 (459 mg, 1.13 mmol) in CH₂Cl₂ (5 mL), and the whole mixture was stirred for 24 h at 60 °C. Further iPr₂NEt (0.204 mL, 1.13 mmol) and MOMCl (0.086 mL, 1.13 mmol) were added to the mixture, and the whole mixture was stirred for additional 24 h at 60 °C. Sat. NH₄Cl aq. was added to the mixture, and the whole mixture was extracted with CH₂Cl₂. Removal of the solvent from the CH₂Cl₂ extract under reduced pressure gave a crude product, which was purified by SiO₂ column (n-hexane/AcOEt = 4:1) to give 17a (mixture of two diastereomers, 493 mg, 97%) as a colorless oil. IR (KBr) : 2946, 2884, 1713, 1647, 1449 cm⁻¹. ¹H-NMR (500 MHz, CDCl₃) δ: 4.74 (1H, s, C=C₂H₂), 4.70 (1/2H, s, C=C₂H₂), 4.63 (2H, s, OCH₂OCH₃), 4.61 (1H, d, J = 6.4 Hz, OCH₂OCH₃), 4.57 (1H, d, J = 6.4 Hz, OCH₂OCH₃), 4.55 (1/2H, s, C=C₂H₂), 3.96-3.90 (4H, s, OCH₂C₂H₂O), 3.56 (1H, t, J = 8.6 Hz, CHOMOM), 3.35 (3H, s, OCH₂OCH₃), 3.32 (3H, s, OCH₂OCH₃), 2.55 (1H, td, J = 14.6, 6.1 Hz), 2.40-2.35 (1H, m), 2.28-2.06 (5H, m), 1.98-1.93 (1H, m), 1.90-1.65 (7H, m), 1.60-1.45 (3H, m), 1.40-1.32 (3/2H, m), 1.12 (3/2H, s, CH₃), 1.10 (3/2H, s, CH₃), 0.98-0.93 (1/2H, m). ¹³C-NMR (125 MHz, CDCl₃) δ: 210.9, 150.2, 149.9, 108.9, 108.8, 106.7, 106.3, 96.0, 92.6, 92.5, 87.43, 87.40, 85.6, 85.5, 64.3, 64.2, 55.8, 55.7, 55.2, 51.5, 51.4, 43.5, 42.3, 42.2, 40.3, 40.0, 37.1, 36.5, 36.3, 35.4, 32.7, 32.6, 30.8, 30.7, 27.9, 25.4, 25.3, 19.2, 12.8, 12.7. ESI MS: m/z 475 (M+Na)⁺. HR-ESI MS: m/z 475.2672, calcd for C₂₅H₄₀O₇Na. Found: 475.2717.
(1S,3aR,4S,7aS)-4-(Benzyloxymethoxy)-1-(methoxymethoxy)-7a-methyl-4-(2-(8-methylene-1,4-dioxaspiro[4.5]decan-7-yl)ethyl)hexahydro-1H-inden-5(6H)-one (17b)

iPr₂NEt (0.217 mL, 1.20 mmol) and BOMCl (0.133 mL, 0.958 mmol) were added to the solution of 16 (196 mg, 0.479 mmol) in ClCH₂CH₂Cl (1.5 mL), and the whole mixture was stirred for 24 h at 60 °C. Further iPr₂NEt (0.217 mL, 1.20 mmol) and BOMCl (0.133 mL, 0.958 mmol) were added to the mixture, and the whole mixture was stirred for additional 24 h at 60 °C. Sat. NH₄Cl aq. was added to the mixture, and the whole mixture was extracted with CH₂Cl₂. Removal of the solvent from the CH₂Cl₂ extract under reduced pressure gave a crude product, which was purified by SiO₂ column (n-hexane/AcOEt = 4:1) to give 17b (mixture of two diastereomers, 253 mg, quant.) as a colorless oil. IR (KBr): 2946, 2884, 1713, 1456 cm⁻¹. 

¹H-NMR (500 MHz, CDCl₃) δ: 7.34-7.26 (5H, m, Ph), 4.85 (1H, d, J = 7.3 Hz), 4.78-4.71 (4H, m), 4.60 (1H, d, J = 6.7 Hz), 4.57 (1H, d, J = 6.7 Hz), 4.49 (1H, d, J = 11.6 Hz), 4.38-4.32 (4H, m, OCH₂CH₂O), 3.55 (1H, t, J = 8.6 Hz, CHOMOM), 3.32 (3H, s, OCH₂OC₃H₇), 3.30 (3H, s, OCH₂OC₃H₇), 2.55 (1H, td, J = 15.3, 6.1 Hz), 2.40-2.35 (1H, m), 2.32-2.02 (5H, m), 1.98-1.70 (7H, m), 1.60-1.45 (3H, m), 1.37 (1H, t, J = 12.2 Hz), 1.30-1.22 (1H, m), 1.13 (3H, s, CH₃), 1.02-0.95 (1H, m). ¹³C-NMR (125 MHz, CDCl₃) δ: 210.8, 149.9, 138.0 (Ph), 128.3 (2C, Ph), 127.7 (2C, Ph), 127.5 (Ph), 108.9, 106.8, 96.0, 90.7, 87.6, 85.6, 69.9, 64.3, 64.2, 55.2, 51.3, 43.5, 42.3, 40.1, 37.1, 36.3, 35.4, 32.7, 31.5, 30.8, 27.9, 25.5, 22.6, 19.3, 14.1, 12.8. Anal. Calcd for C₃₁H₄₄O₇: C, 70.43; H, 8.39. Found: C, 70.24; H, 8.25. ESI MS: m/z 551 (M+Na)⁺. HR-ESI MS: m/z 551.2985, calcd for C₃₁H₄₄O₇Na. Found: 551.3007.

(1S,3aR,4S,7aS)-1,4-Bis(methoxymethoxy)-7a-methyl-4-(2-(8-methylene-1,4-dioxaspiro[4.5]decan-7-yl)ethyl)-2,3,3a,4,7,7a-hexahydro-1H-inden-5-yl trifluoromethanesulfonate (18a)

KHMDS (0.5 M in THF, 6.54 mL, 3.27 mmol) was added dropwise to the solution of 17a (493 mg, 109 mmol) and PhNTf₂ (1.56 g, 4.36 mmol) in anhydrous THF (5.0 mL) and Et₃N (5.0 mL) at 60 °C, and the whole mixture was stirred at 60 °C for 15 min. Then PhNTf₂ (779 mg, 2.18 mmol) and KHMDS (3.27 mL, 1.64 mmol) were further added to the mixture, and the whole was stirred for additional 15 min. Sat. NH₄Cl aq. was added to the mixture at 0 °C, and the whole mixture was extracted with AcOEt. Removal of the solvent from the AcOEt extract under reduced pressure gave a crude product, which was purified by SiO₂ column (n-hexane/AcOEt = 5:1) to give 18a (mixture of two diastereomers, 629 mg, 99%) as a colorless oil. IR (KBr): 2946, 1647, 1412 cm⁻¹. 

¹H-NMR (500 MHz, CDCl₃) δ: 5.92 (1H, dd, J = 5.5, 2.4 Hz, C=CH), 4.79 (1H, d, J = 8.6 Hz), 4.77 (1H, s), 4.72 (1/2H, s), 4.68 (1/2H, s), 4.62 (1H, d, J = 6.7 Hz), 4.58 (1H, d, J = 6.7 Hz), 4.52 (1H, d, J = 7.9 Hz), 3.99-3.93 (4H, m, OCH₂CH₂O), 3.67 (1H, t, J = 8.7 Hz, CHOMOM), 3.37 (3H, s, OCH₂OCH₃), 3.34 (3H, s, OCH₂OCH₃), 2.33-2.07 (7H, m), 2.00-1.72 (7H, m), 1.62-1.36 (4H, m), 0.91 (3H, s, CH₃). ¹³C-NMR (125 MHz, CDCl₃) δ: 150.2, 150.1, 149.8, 149.7, 121.8, 118.3 (CF₃, q, J = 320 Hz), 108.9, 106.7, 106.6, 96.0, 91.24, 91.21, 85.4, 79.1, 79.0, 64.3, 64.2,
55.8, 55.7, 55.3, 48.9, 48.8, 43.5, 43.4, 42.1, 42.0, 40.8, 40.7, 36.6, 36.5, 36.4, 32.6, 32.5, 32.0, 27.7, 26.13, 26.10, 20.4, 20.3, 13.9, 13.8. Anal. Calcd for C_{26}H_{39}F_{3}O_{9}S: C, 53.41; H, 6.72. Found: C, 53.01; H, 6.49.

ESI MS: m/z 607 (M+Na)^+. HR-ESI MS: m/z 607.2165, calcd for C_{26}H_{39}F_{3}O_{9}SNa. Found: 607.2148.

(1S,3aR,4S,7aS)-4-(Benzyloxymethoxy)-1-(methoxymethoxy)-7a-methyl-4-(2-(8-methylene-1,4-dioxoaspiro[4.5]decan-7-yl)ethyl)-2,3,3a,4,7,7a-hexahydro-1H-inden-5-yl trifluoromethanesulfonate (18b)

KHMDS (0.5 M in THF, 1.02 mL, 0.508 mmol) was added dropwise to the solution of 17b (89.5 mg, 0.169 mmol) and PhNTf2 (242 mg, 0.678 mmol) in anhydrous THF (0.8 mL) and Et3N (0.8 mL) at 60 °C, and the whole mixture was stirred at 60 °C for 15 min. Then PhNTf2 (121 mg, 0.339 mmol) and KHMDS (0.508 mL, 0.254 mmol) were further added to the mixture, and the whole was stirred for additional 15 min. Sat. NH4Cl aq. was added to the mixture at 0 °C, and the whole mixture was extracted with AcOEt. Removal of the solvent from the AcOEt extract under reduced pressure gave a crude product, which was purified by SiO2 column (n-hexane/AcOEt = 5:1) to give 18b (mixture of two diastereomers, 112 mg, quant.) as a colorless oil. IR (KBr): 2946, 2884, 1647, 1412 cm^{-1}. 1H-NMR (500 MHz, CDCl3) δ: 7.34-7.23 (5H, m, Ph), 5.92-5.88 (1H, m, C=C), 4.86 (1H, d, J = 8.5 Hz), 4.77-4.67 (4H, m), 4.58 (1H, d, J = 6.7 Hz), 4.54 (1H, d, J = 6.7 Hz), 4.50 (1H, d, J = 11.8 Hz), 3.95-3.92 (4H, m, OCH2C2H2O), 3.61 (1H, t, J = 8.8 Hz, CHOMOM), 3.30 (3H, s, OCH2OCH2), 2.35-2.28 (2H, m), 2.23-2.10 (4H, m), 2.05-1.95 (2H, m), 1.85-1.70 (5H, m), 1.60-1.45 (3H, m), 1.42-1.35 (1H, m), 1.28-1.22 (1H, m), 0.89 (3H, s, CH3). 13C-NMR (125 MHz, CDCl3) δ: 150.2, 150.1, 149.7, 137.8, 137.7, 128.4 (2C), 127.9 (2C), 127.8, 127.6, 121.9, 118.3 (CF3, q, J = 320 Hz), 108.8, 106.8, 106.7, 96.0, 89.3, 89.2, 85.3, 79.3, 79.2, 69.9, 64.3, 64.2, 55.2, 48.9, 48.8, 43.5, 42.0, 41.9, 40.8, 40.7, 36.5, 36.4, 32.5, 32.4, 31.9, 31.5, 27.6, 26.1, 22.6, 20.5, 20.4, 14.0, 13.9, 13.8. Anal. Calcd for C_{32}H_{43}F_{3}O_{9}S: C, 58.17; H, 6.56. Found: C, 58.28; H, 6.57. ESI MS: m/z 683 (M+Na)^+. HR-ESI MS: m/z 683.2478, calcd for C_{32}H_{43}F_{3}O_{9}SNa. Found: 683.2527.

General procedure for intramolecular Heck reaction

Pd2(dba)3•CHCl3 (0.03 mmol) was added to the solution of dppb (0.06 mmol) in DMA (1 mL), and the whole mixture was stirred for 30 min. Then the solution of triflate 18 (0.1 mmol) in DMA (1 mL) and KOAc (0.3 mmol) were added to the mixture, and the whole mixture was stirred for 2 days at the indicated temperature. Sat. NH4Cl aq. was added to the mixture at 0 °C, and the whole mixture was extracted with AcOEt. Removal of the solvent from the AcOEt extract under reduced pressure gave a crude product, which was purified by SiO2 column to give a mixture of cyclized products (20 and 21). These products were further purified by reversed-phase HPLC.

20a, 20’a and 21a (R = MOM)

Following the general procedure, 18a (104 mg, 0.178 mmol) was converted to a mixture of 20a, 20’a and...
21a (46.3 mg, 60%, 20a/20’a/21a = 1:1:2.6), which were further purified by reversed-phase HPLC (MeOH/H$_2$O = 80:20 containing 1% Et$_3$N).

20a: IR (KBr): 2942, 1730, 1443, 1354 cm$^{-1}$. $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$: 5.82 (1H, d-like, C=CH), 5.69 (1H, s, C=CH), 4.63 (1H, d, $J = 6.7$ Hz, OCH$_2$OCH$_3$), 4.60 (1H, d, $J = 6.7$ Hz, OCH$_2$OCH$_3$), 4.47 (1H, d, $J = 7.3$ Hz, OCH$_2$OCH$_3$), 4.31 (1H, d, $J = 7.3$ Hz, OCH$_2$OCH$_3$), 3.98-3.94 (4H, m, OCH$_2$CH$_2$O), 3.68 (1H, t, $J = 8.9$ Hz, CHOMOM), 3.34 (3H, s, OCH$_2$OCH$_3$), 3.31 (3H, s, OCH$_2$OCH$_3$), 2.55-2.48 (1H, m, CH=C=CH), 2.37 (1H, t-like, CH$_2$CH$_2$C=CH), 2.25-2.04 (6H, m), 1.75-1.65 (6H, m), 1.62-1.55 (2H, m), 1.43-1.33 (2H, m), 0.84 (3H, s, CH$_3$). $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$: 143.1 (C10), 137.5 (C9), 131.9 (C11), 122.5 (C19), 108.7 (C3), 95.9 (OCH$_2$OCH$_3$), 91.3 (OCH$_2$OCH$_3$), 86.4 (C17), 84.4 (C8), 64.4 (OCH$_2$CH$_2$O), 64.2 (OCH$_2$CH$_2$O), 55.7 (OCH$_2$OCH$_3$), 55.2 (OCH$_2$OCH$_3$), 48.5 (C14), 43.4 (C4), 43.0 (C13), 40.0 (C12), 38.3 (C5), 34.9 (C2), 34.3 (C1), 34.0 (C7), 32.2 (C6), 27.6 (C16), 19.1 (C15), 14.0 (C18). ESI MS: $m/z$ 457 (M+Na$^+$). HR-ESI MS: $m/z$ 457.2566, calcd for C$_{25}$H$_{38}$O$_6$Na. Found: 457.2605.

20’a: IR (KBr): 2646, 1732, 1439, 1366 cm$^{-1}$. $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$: 5.80-5.78 (1H, m, C=CHCH$_2$), 5.60 (1H, s, C=CH=CH), 4.63 (1H, d, $J = 6.7$ Hz, OCH$_2$OCH$_3$), 4.60 (1H, d, $J = 6.7$ Hz, OCH$_2$OCH$_3$), 4.49 (1H, d, $J = 7.3$ Hz, OCH$_2$OCH$_3$), 4.25 (1H, d, $J = 7.3$ Hz, OCH$_2$OCH$_3$), 3.98-3.94 (4H, m, OCH$_2$CH$_2$O), 3.68 (1H, t, $J = 8.8$ Hz, CHOMOM), 3.35 (3H, s, OCH$_2$OCH$_3$), 3.33 (3H, s, OCH$_2$OCH$_3$), 2.53 (1H, d-like), 2.30-2.25 (2H, m), 2.19-2.03 (7H, m), 1.90-1.85 (1H, m), 1.75-1.47 (7H, m), 0.85 (3H, s, CH$_3$). $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$: 144.0 (C10), 137.2 (C9), 131.7 (C11), 120.0 (C19), 109.8 (C3), 95.9 (OCH$_2$OCH$_3$), 91.3 (OCH$_2$OCH$_3$), 86.5 (C17), 85.4 (C8), 64.3 (2C, OCH$_2$CH$_2$O), 55.7 (OCH$_2$OCH$_3$), 55.2 (OCH$_2$OCH$_3$), 48.9 (C14), 43.0 (C13), 40.1 (C12), 39.6 (C4), 38.9 (C5), 37.0 (C1), 34.5 (C2), 30.9 (C7), 28.2 (C6), 27.6 (C16), 19.0 (C15), 13.9 (C18). ESI MS: $m/z$ 457 (M+Na$^+$). HR-ESI MS: $m/z$ 457.2566, calcd for C$_{25}$H$_{38}$O$_6$Na. Found: 457.2605.

21a (mixture of two diastereomers): IR (KBr): 2946, 1443, 1358 cm$^{-1}$. $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$: 6.21 (1/2H, d, $J = 9.2$ Hz, C=CH), 6.19 (1/2H, d, $J = 9.2$ Hz, C=CH), 5.25 (1/2H, d, $J = 9.7$ Hz, C=CH), 5.17 (1/2H, d, $J = 9.8$ Hz, C=CH), 4.87 (1/2H, d, $J = 7.3$ Hz, OCH$_2$OCH$_3$), 4.82 (1/2H, d, $J = 7.3$ Hz, OCH$_2$OCH$_3$), 4.67-4.62 (2H, m, OCH$_2$OCH$_3$), 4.49 (1/2H, d, $J = 7.3$ Hz, OCH$_2$OCH$_3$), 4.46 (1/2H, d, $J = 7.4$ Hz, OCH$_2$OCH$_3$), 3.96-3.93 (4H, m, OCH$_2$CH$_2$O), 3.79-3.72 (1H, m, CHOMOM), 3.36 (3H, s, OCH$_2$OCH$_3$), 3.33 (3H, s, OCH$_2$OCH$_3$), 2.36-2.20 (3/2H, m), 2.15-1.92 (2H, m), 1.88-1.35 (10H, m), 1.28-1.20 (3/2H, m), 1.17-1.03 (2H, m), 1.01 (3/2H, m, CH$_3$), 0.87 (3/2H, s, CH$_3$), 0.52 (1/2H, d, $J = 4.9$ Hz, cyclopropane-CH$_2$), 0.46 (1/2H, d, $J = 4.3$ Hz, cyclopropane-CH$_2$). $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$: 138.0 (1/2C, C12), 137.4 (1/2C, C12), 132.7 (1/2C, C11), 132.5 (1/2C, C11), 109.6 (1/2C, C3), 109.2 (1/2C, C3), 96.2 (1/2C, OCH$_2$OCH$_3$), 96.1 (1/2C, OCH$_2$OCH$_3$), 92.1 (1/2C, OCH$_2$OCH$_3$), 92.0 (1/2C, OCH$_2$OCH$_3$), 83.3 (1/2C, C17), 83.1 (1/2C, C17), 79.44 (1/2C, C8), 79.41 (1/2C, C8), 64.31 (1/2C, OCH$_2$CH$_2$O), 64.28 (1/2C, OCH$_2$CH$_2$O), 64.2 (1/2C, OCH$_2$CH$_2$O), 64.1 (1/2C, OCH$_2$CH$_2$O), 55.4 (1/2C,
OCH₃OCH₃), 55.3 (1/2C, OCH₂OCH₃), 50.7 (1/2C, C14), 50.5 (1/2C, C14), 44.4, 44.2, 41.9, 38.9, 36.7, 34.7, 33.9, 33.8, 32.9, 32.5, 32.2, 32.1, 30.5, 30.4, 30.3, 27.7, 27.5, 23.7 (1/2C, C19), 22.9, 21.8, 19.9, 19.5 (1/2C, C19), 13.7 (1/2C, C18), 13.5 (1/2C, C18). ESI MS: m/z 457 (M+Na)+. HR-ESI MS: m/z 457.2566, calc'd for C₂₅H₃₈O₆Na. Found: 457.2605.

20b, 20'b and 21b (R = BOM)

Following the general procedure, 18b (19.3 mg, 0.0292 mmol) was converted to a mixture of 20b, 20'b and 21b (6.7 mg, 45%, 20b/20'b/21b = 1:1:2), which were further purified by reversed-phase HPLC (MeOH/H₂O = 90:10).

20b: IR (KBr): 2934, 1453, 1364 cm⁻¹. ¹H-NMR (500 MHz, CDCl₃) δ: 7.35-7.27 (5H, m, Ph), 5.82 (1H, d-like, C=CH), 5.70 (1H, s, C=CH), 4.77 (1H, d, J = 11.6 Hz), 4.63 (1H, d, J = 6.7 Hz), 4.60 (1H, d, J = 6.7 Hz), 4.57 (1H, d, J = 7.3 Hz), 4.43 (1H, d, J = 7.3 Hz), 4.39 (1H, d, J = 11.6 Hz), 4.00-3.93 (4H, m, OCH₂CH₂O), 3.66 (1H, t, J = 8.9 Hz, CHOMOM), 3.34 (3H, s, OCH₂OCH₃), 2.56-2.49 (1H, m), 2.37 (1H, t-like), 2.24-1.98 (6H, m), 1.73-1.60 (6H, m), 1.59-1.55 (2H, m), 1.54-1.34 (2H, m), 0.84 (3H, s, CH₃). ¹³C-NMR (125 MHz, CDCl₃) δ: 143.1 (C10), 138.5 (Ph), 137.5 (C9), 132.0 (C11), 128.3 (2C, Ph), 127.6 (2C, Ph), 127.4 (Ph), 122.5 (C19), 108.7 (C3), 95.9 (OCH₂OCH₃), 89.6 (OCH₂OCH₂Ph), 86.5 (C17), 84.7 (C8), 69.8 (OCH₂Ph), 64.4 (OCH₂CH₂O), 64.2 (OCH₂CH₂O), 55.2 (OCH₂OCH₃), 48.4 (C14), 43.4 (C4), 43.0 (C13), 40.0 (C12), 38.4 (C5), 34.9 (C2), 34.4 (C1), 34.0 (C7), 32.3 (C6), 27.6 (C16), 19.2 (C15), 14.0 (C18). ESI MS: m/z 533 (M+Na)+. HR-ESI MS: m/z 533.2879, calc'd for C₃₁H₄₂O₆Na. Found: 533.2915.

20'b: IR (KBr): 2946, 1441, 1366 cm⁻¹. ¹H-NMR (500 MHz, CDCl₃) δ: 7.47-7.27 (5H, m, Ph), 5.79-5.78 (1H, m, C=CH), 5.60 (1H, s, C=CH), 4.75 (1H, d, J = 11.9 Hz), 4.63 (1H, d, J = 6.7 Hz), 4.60 (1H, d, J = 6.7 Hz), 4.57 (1H, d, J = 7.7 Hz), 4.46 (1H, d, J = 7.7 Hz), 4.42 (1H, d, J = 11.9 Hz), 4.00-3.96 (4H, m, OCH₂CH₂O), 3.66 (1H, t, J = 8.8 Hz, CHOMOM), 3.34 (3H, s, OCH₂OCH₃), 2.54 (1H, d-like), 2.34-2.26 (2H, m), 2.19-1.98 (7H, m), 1.89-1.85 (1H, m), 1.79-1.68 (3H, m), 1.60-1.45 (4H, m), 0.86 (3H, s, CH₃). ¹³C-NMR (125 MHz, CDCl₃) δ: 144.1 (C10), 138.3 (Ph), 137.2 (C9), 131.7 (C11), 128.4 (2C, Ph), 127.8 (2C, Ph), 127.5 (Ph), 120.0 (C19), 109.8 (C3), 95.9 (OCH₂OCH₃), 89.4 (OCH₂OCH₂Ph), 86.6 (C17), 85.6 (C8), 69.8 (OCH₂Ph), 64.3 (OCH₂CH₂O), 55.2 (OCH₂OCH₃), 48.8 (C14), 43.0 (C13), 40.0 (C12), 39.6 (C4), 39.0 (C5), 37.0 (C1), 34.5 (C2), 30.9 (C7), 28.2 (C6), 27.6 (C16), 19.1 (C15), 13.9 (C18). ESI MS: m/z 533 (M+Na)+. HR-ESI MS: m/z 533.2879, calc'd for C₃₁H₄₂O₆Na. Found: 533.2915.

21b (mixture of two diastereomers): IR (KBr): 2944, 1453, 1368 cm⁻¹. ¹H-NMR (500 MHz, CDCl₃) δ: 7.35-7.26 (5H, m, Ph), 6.21 (1/2H, d, J = 9.2 Hz, C=CH), 6.19 (1/2H, d, J = 9.2 Hz, C=CH), 5.25 (1/2H, d, J = 9.5 Hz, C=CH), 5.17 (1/2H, d, J = 9.5 Hz, C=CH), 4.97 (1/2H, d, J = 7.6 Hz), 4.93 (1/2H, d, J = 4.9 Hz), 4.79-4.52 (4H, m), 4.46 (1/2H, d, J = 4.6 Hz), 4.43 (1/2H, d, J = 4.6 Hz), 3.98-3.92 (4H, m,
OCH$_2$CH$_2$O), 3.78-3.72 (1H, m, CHOMOM), 3.372 (3/2H, s, OCH$_2$OCH$_3$), 3.370 (3/2H, s, OCH$_2$OCH$_3$), 2.47-2.42 (1H, m), 2.24-2.07 (1H, m), 2.07-1.77 (2H, m), 1.77-1.51 (10H, m), 1.50-1.05 (3H, m), 1.02 (3/2H, s, CH$_3$), 0.88 (3/2H, s, CH$_3$), 0.53 (1/2H, d, $J = 4.5$ Hz, cyclopropane-CH$_2$), 0.47 (1/2H, d, $J = 4.8$ Hz, cyclopropane-CH$_2$). $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$: 138.4 (Ph), 138.0 (1/2C, C12), 137.5 (1/2C, C12), 132.6 (1/2C, C11), 132.4 (1/2C, C11), 128.3 (2C, Ph), 127.62 (Ph), 127.57 (Ph), 127.4 (Ph), 109.6 (1/2C, C3), 109.2 (1/2C, C3), 96.2 (1/2C, OCH$_2$OCH$_3$), 96.1 (1/2C, OCH$_2$OCH$_3$), 90.1 (1/2C, OCH$_2$OCH$_2$Ph), 90.1 (1/2C, OCH$_2$OCH$_2$Ph), 83.4 (1/2C, C17), 83.1 (1/2C, C17), 79.71 (1/2C, C8), 79.67 (1/2C, C8), 69.7 (1/2C, OCH$_2$Ph), 69.5 (1/2C, OCH$_2$Ph), 64.33 (1/2C, OCH$_2$CH$_2$O), 64.30 (1/2C, OCH$_2$CH$_3$O), 64.25 (1/2C, OCH$_2$CH$_2$O), 64.2 (1/2C, OCH$_2$CH$_2$O), 55.33 (1/2C, OCH$_2$OCH$_3$), 55.31 (1/2C, OCH$_2$OCH$_3$), 50.6 (1/2C, C14), 50.4 (1/2C, C14), 44.5, 44.2, 42.0, 38.9, 36.8, 34.7, 34.0, 33.8, 32.9, 32.5, 32.24, 32.19, 30.5, 30.40, 30.35, 27.7, 27.5, 27.3, 23.7 (1/2C, C19), 22.9, 21.9, 20.1, 19.6 (1/2C, C19), 19.1, 13.8 (1/2C, C18), 13.5 (1/2C, C18). ESI MS: $m/z$ 533 (M+Na)$^+$. HR-ESI MS: $m/z$ 533.2879, calcd for C$_{31}$H$_{42}$O$_6$Na. Found: 533.2914.

ACKNOWLEDGEMENTS

This study was financially supported by the Uehara memorial Foundation, and by the Grant-in-Aid for Scientific research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan.

REFERENCES


