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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 syntheses[7,8] and many synthetic studies[9] 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.

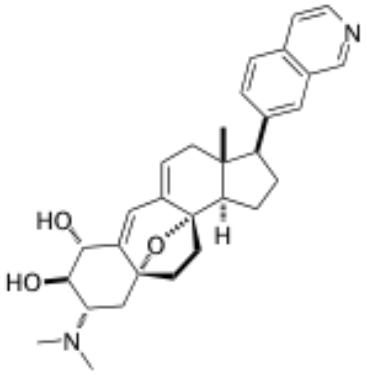


Figure 1. Cortistatin A (**1**)

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.[3-8] 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.

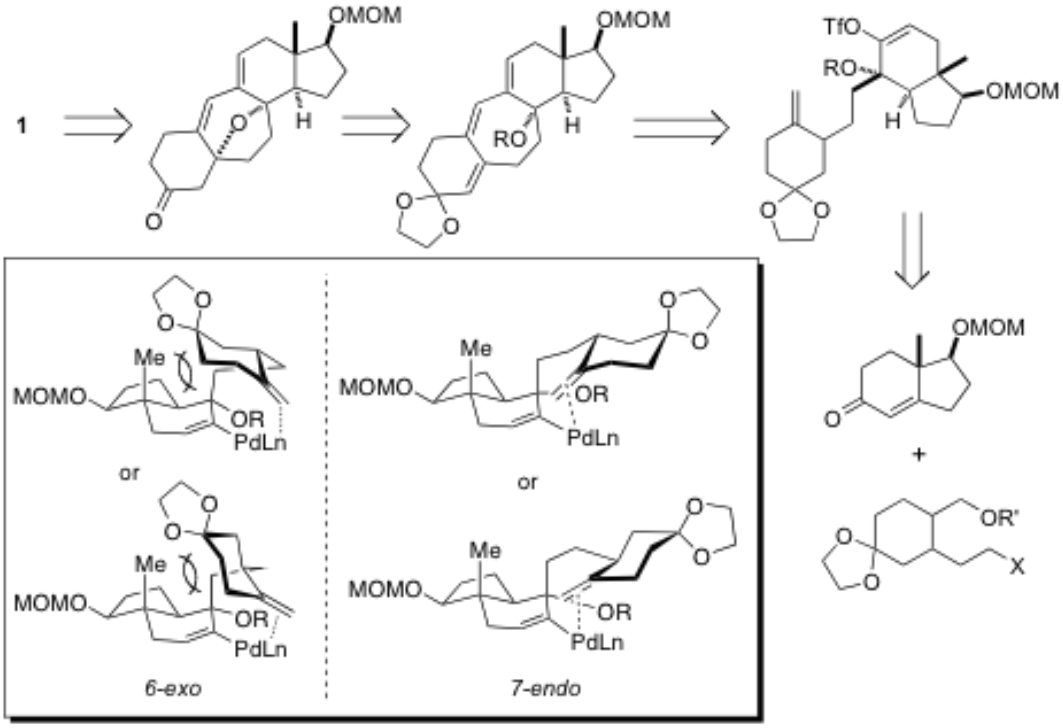
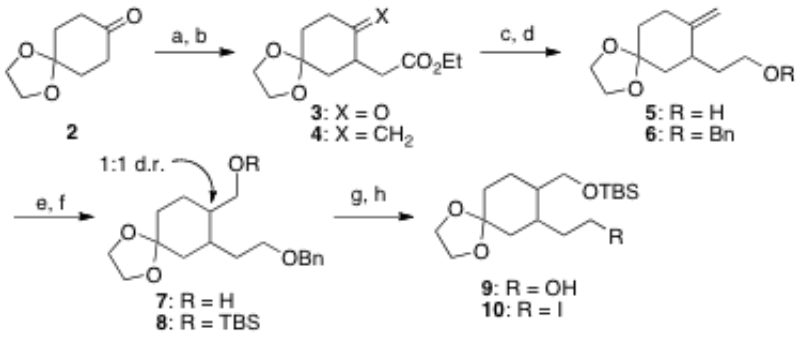


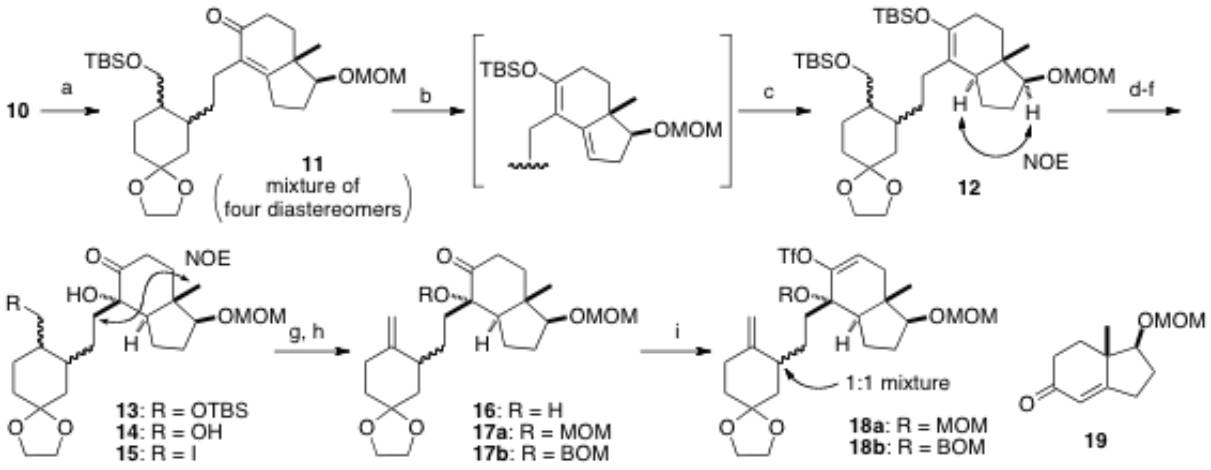
Figure 2. Retrosynthetic analysis

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. $LiAlH_4$ 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*-butyldimethylsilyl (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.



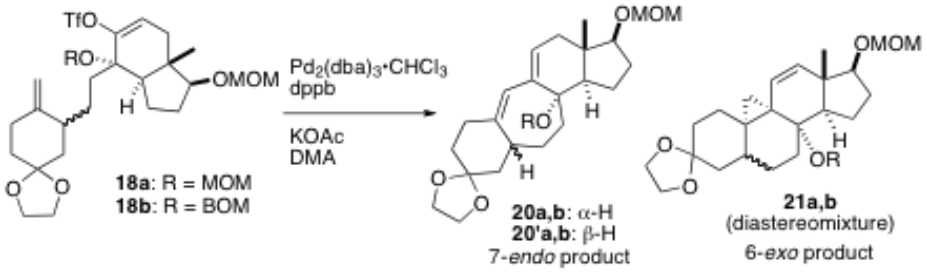
Scheme 1. Reagents and conditions: (a) LDA, ethyl bromoacetate, THF, –78 °C, 87%; (b) Ph_3PMeBr, *n*-BuLi, THF, 57%; (c) $LiAlH_4$, THF, 97%; (d) BnBr, NaH, DMF, 92%; (e) BH_3•SMe_2, THF; NaOH aq. 30% H_2O_2, quant.; (f) TBSCl, imidazole, DMAP, CH_2Cl_2, 94%; (g) H_2, Pd-C, AcOEt, 80% (93% brsm); (h) I_2, Ph_3P, imidazole, CH_2Cl_2, quant.

The A-ring fragment **10** and the CD-ring fragment **19**, prepared from commercially available (+)-Hajos-Parrish ketone in 2 steps,[11] were coupled together using Molander's method[12] 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**,[5] which was converted to a *tert*-alcohol **13** by the treatment with OsO_4 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 Et_3N 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, Et_3N, CH_2Cl_2; (c) H_2, Pd-C, AcOEt; (d) OsO_4, NMO, acetone/H_2O, 75% (3 steps); (e) TBAF, THF, 99%; (f) I_2, Ph_3P, imidazole, CH_2Cl_2, 79%; (g) DBU, THF, 84%; (h) MOMCl or BOMCl, *i*Pr_2NEt, 1,2-dichloroethane, 60 °C, 97% for **17a**, quant. for **17b**; (i) $PhNTf_2$, KHMDS, Et_3N, 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 $Pd_2(dba)_3$ and 1,4-bis(diphenylphosphino)butane (dppb) in *N*,*N*-dimethylacetamide (DMA) in the presence of potassium acetate (KOAc)[10] 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 (Et_3N 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**).



R	temp.	yield	20 : 20' : 21
MOM	70°C	60%	1 : 1 : 2.6
//	85°C	62%	1 : 1 : 6.8
BOM	70°C	29%	1 : 1 : 2.4
//	85°C	45%	1 : 1 : 2

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.

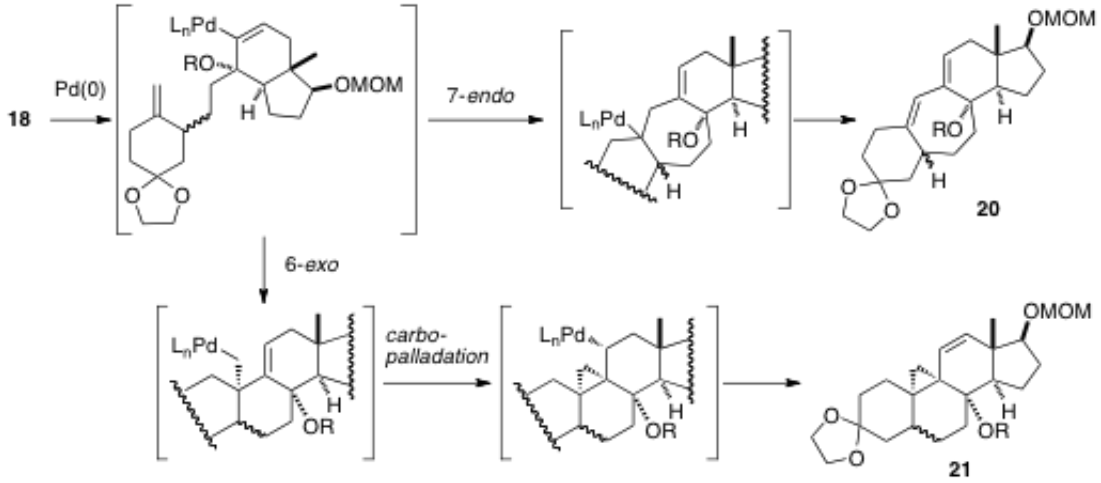


Figure 3. Plausible mechanism of Heck reaction

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,[13] which is now under investigation.

EXPERIMENTAL

A JEOL JNM LA-500 spectrometer was used to obtain ^{1}H- and ^{13}C–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, $60F_{254}$) 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*-H_2SO_4: 25 mL, AcOH: 5 mL, EtOH: 425 mL) with subsequent heating. Unless otherwise noted, all the reactions were performed under N_2 atmosphere using purchased reagents and solvents without further purification. After workup, the organic phases were dried over Na_2SO_4.

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. NH_4Cl 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 = 4:1) to give **3** (13.58 g, 87%) as a colorless oil. IR (KBr): 2982, 1730, 1709 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) 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, $CO_2CH_2C\underline{H}_3$). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 209.4, 171.9, 106.9, 64.7, 64.5, 60.3, 42.9, 40.1, 37.7, 34.4, 33.8, 14.0. Anal. Calcd for $C_{12}H_{18}O_5$: 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. NH_4Cl 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 **4** (7.66 g, 57%) as a colorless oil. IR (KBr): 2945, 1736, 1649 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 4.68 (1H, s, C=C$\underline{H}_2$), 4.54 (1H, s, C=C$\underline{H}_2$), 4.08-4.02 (2H, m, $CO_2C\underline{H}_2CH_3$), 3.89-3.86 (4H, m, $OC\underline{H}_2C\underline{H}_2O$), 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, $CO_2CH_2C\underline{H}_3$). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 172.3, 149.0 ($\underline{C}$=CH_2), 108.2 (C=$\underline{C}H_2$), 106.5, 64.2, 64.1, 60.0, 41.1, 37.6, 36.6, 36.0, 32.1, 14.0. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. 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. NH_4Cl 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=C$\underline{H_2}$), 4.66 (1H, s, C=C$\underline{H_2}$), 3.96-3.91 (4H, m, OC$\underline{H_2}$C$\underline{H_2}$O), 3.65 (2H, t-like, C$\underline{H_2}$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=C$\underline{H_2}$), 4.67 (1H, s, C=C$\underline{H_2}$), 4.50 (1H, d, *J* = 11.5 Hz, OC$\underline{H_2}$Ph), 4.46 (1H, d, *J* = 11.5 Hz, OC$\underline{H_2}$Ph), 3.91 (4H, s, OC$\underline{H_2}$C$\underline{H_2}$O), 3.53-3.51 (2H, m, C$\underline{H_2}$OCH_2Ph), 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_2OPh), 68.2 (CH_2OCH_2Ph), 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_2O_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_4Cl 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, OC$\underline{H_2}$Ph), 3.86-3.81 (4H, m, OC$\underline{H_2}$C$\underline{H_2}$O), 3.60-3.39 (4H, m, C$\underline{H_2}$OCH_2Ph, C$\underline{H_2}$OH), 2.42 (1H, brs), 1.98-2.05 (1H, m), 1.88-1.15 (9H, m). ^{13}C-NMR (125 MHz,

$CDCl_3$) 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 $C_{18}H_{26}O_4$: 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*-butyl)dimethylsilane (8)

Imidazole (2.20 g, 32.4 mmol), TBSCl (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 CH_2Cl_2 (16 mL), and the whole mixture was stirred for 24 h at rt. Sat. NH_4Cl aq. was added to the mixture at 0 °C, and the whole mixture was extracted with CH_2Cl_2. Removal of the solvent from the CH_2Cl_2 extract under reduced pressure gave a crude product, which was purified by SiO_2 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}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.33-7.24 (5H, m, Ph), 4.52-4.45 (2H, m, OC$\underline{H_2}$Ph), 3.92-3.87 (4H, m, OC$\underline{H_2}$C$\underline{H_2}$O), 3.75-3.42 (4H, m, C$\underline{H_2}$OCH$_2$Ph, C$\underline{H_2}$OTBS), 2.07-2.03 (1H, m), 1.95-1.20 (9H, m), 0.89 (9H, s, C$(CH_3)_3$), 0.04 (6H, s, Si$(CH_3)_2$). ^{13}C-NMR (125 MHz, $CDCl_3$) 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($\underline{C}H_3)_3$), 23.9, 18.2 (1/2C), 18.1 (1/2C), –5.4 ($SiCH_3$), –5.5 ($SiCH_3$). Anal. Calcd for $C_{24}H_{40}O_4Si$: 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 $C_{24}H_{40}O_4SiNa$. Found: 443.2582.

2-(8-((*t*ert-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 SiO_2 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}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.89-3.84 (4H, m, OC$\underline{H_2}$C$\underline{H_2}$O), 3.66-3.41 (4H, m, C$\underline{H_2}$OTBS, C$\underline{H_2}$OH), 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$(CH_3)_3$), -0.01 (6H, s, Si$(CH_3)_2$). ^{13}C-NMR (125 MHz, $CDCl_3$) 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), 31.3 (1/2C), 27.1, 25.8 (3C, C($\underline{C}H_3)_3$), 24.0, 18.2 (1/2C), 18.1 (1/2C), -5.5 (2C,

$Si(CH_3)_2$). Anal. Calcd for $C_{17}H_{34}O_4Si$: 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 $C_{17}H_{34}O_4SiNa$. 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_2Cl_2 (120 mL) at 0 °C, and the whole mixture was stirred for 3 h at rt. Sat. $NaHSO_3$ aq. and NH_4Cl aq. were added to the mixture, and the whole mixture was extracted with CH_2Cl_2. Removal of the solvent from the CH_2Cl_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, $OC\underline{H_2}C\underline{H_2}O$), 3.58-3.44 (2H, m, $C\underline{H_2}OTBS$), 3.27-3.13 (2H, m, $C\underline{H_2}I$), 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, $C(\underline{C}H_3)_3$), 24.2 (1/2C), 18.1 ($\underline{C}(CH_3)_3$), 5.4 (1/2C, $\underline{C}H_2I$), 3.7 (1/2C, $\underline{C}H_2I$), -5.45 ($SiCH_3$), -5.51 ($SiCH_3$). Anal. Calcd for $C_{17}H_{33}IO_3Si$: 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 $C_{17}H_{33}IO_3SiNa$. Found: 463.1155.

(1*S*,7a*S*)-4-(2-(8-((*tert*-Butyldimethylsilyloxy)methyl)-1,4-dioxaspiro[4.5]decan-7-yl)ethyl)-1-(methoxymethoxy)-7a-methyl-2,3,7,7a-tetrahydro-1*H*-inden-5(6*H*)-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 soluton 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_4Cl aq. was added to the mixture, and the whole mixture was extracted with CH_2Cl_2. Removal of the solvent from the CH_2Cl_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, $OC\underline{H_2}OCH_3$), 4.62 (1H, d, *J* = 6.7 Hz, $OC\underline{H_2}OCH_3$), 3.93-3.86 (4H, m, $OC\underline{H_2}C\underline{H_2}O$), 3.72-3.50 (3H, m), 3.34 (3H, s, $OCH_2OC\underline{H_3}$), 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 ($\underline{C}$=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($\underline{C}H_3)_3$), 25.1, 25.0, 23.91, 23.85, 23.74, 23.71, 21.9, 18.23, 18.15, 16.08, 16.05, –5.4 ($SiCH_3$), –5.5 ($SiCH_3$). Anal. Calcd for $C_{29}H_{50}O_6Si$: 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 $C_{29}H_{50}O_6SiNa$. Found: 545.3299.

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

Et_3N (0.94 mL, 6.86 mmol) and TBSOTf (1.18 mL, 5.15 mmol) were succesively added to the solution of **11** (1.79 g, 3.43 mmol) in anhydrous CH_2Cl_2 (30 mL) at 0 °C, and the whole mixture was stirred for 1.5 h. Sat. NH_4Cl aq. was added to the mixture at 0 °C, and the whole mixture was extracted with CH_2Cl_2. Removal of the solvent from the CH_2Cl_2 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), OsO_4 (4 wt.% in H_2O, 1.9 mL, 0.686 mmol) were added to the solution of the above product in acetone-H_2O (8:1, 36 mL), and the whole mixture was stirred for 12 h at 50 °C. Then sat. Na_2SO_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 = 3:1) to give **13** (mixture of diastereomers, 1.39 g, 75%) as a colorless oil. IR (KBr): 2936, 2884, 1711, 1472 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 4.56 (1H, d, *J* = 6.7 Hz, $OC\underline{H}_2OCH_3$), 4.53 (1H, d, *J* = 6.7 Hz, $OC\underline{H}_2OCH_3$), 3.88-3.84 (5H, m, $OC\underline{H}_2C\underline{H}_2O$, O<u>H</u>), 3.49-3.42 (3H, m, $C\underline{H}_2$OTBS, C<u>H</u>OMOM), 3.28 (3H, s, $OCH_2OC\underline{H}_3$), 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), 1.49-1.21 (7H, m), 1.12 (3H, s, CH_3), 0.82 (9H, s, $C(CH_3)_3$), –0.03 (6H, s, $Si(CH_3)_2$). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 214.7, 109.1, 95.9 ($O\underline{C}H_2OCH_3$), 85.4, 80.4, 64.1, 64.0, 60.0, 56.7, 55.1 ($OCH_2O\underline{C}H_3$), 42.8, 38.5, 37.1, 36.8, 36.7, 34.5, 31.4, 31.2, 30.7, 28.3, 25.8 (3C, C($\underline{C}H_3)_3$), 25.1, 23.9, 22.5, 19.0, 18.1, 14.0, 12.4, –5.5 ($SiCH_3$), –5.6 ($SiCH_3$). Anal. Calcd for $C_{29}H_{52}O_7Si$: C, 64.41; H, 9.69. Found: C, 64.15; H, 9.53. ESI MS: *m/z* 563 $(M+Na)^+$. HR-ESI MS: *m/z* 563.3380, calcd for $C_{29}H_{52}O_7SiNa$. Found: 563.3403.

(1*S*,3a*R*,4*S*,7a*S*)-4-Hydroxy-4-(2-(8-(hydroxymethyl)-1,4-dioxaspiro[4.5]decan-7-yl)ethyl)-1-(methoxymethoxy)-7a-methylhexahydro-1*H*-inden-5(6*H*)-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. NH_4Cl 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 diastereomers, 1.09 g, 99%) as a colorless oil. IR (KBr): 3480, 2936, 1711, 1449 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 4.50 (1H, d, *J* = 6.7 Hz, $OC\underline{H_2}OCH_3$), 4.47 (1H, d, *J* = 6.7 Hz, $OC\underline{H_2}OCH_3$), 4.02-3.91 (1H, m), 3.82-3.78 (4H, m, $OC\underline{H_2}C\underline{H_2}O$), 3.52-3.30 (3H, m, $C\underline{H_2}OH$, $C\underline{H}OMOM$), 3.22 (3H, s, $OCH_2OC\underline{H_3}$), 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, CH_3). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 215.0, 214.9, 214.6, 109.0, 108.78, 108.76, 108.7, 95.7, 85.2, 80.7, 80.6, 80.4, 80.3, 64.4, 64.3, 64.1, 64.0, 63.94, 63.90, 63.8, 63.6, 60.8, 60.1, 59.9, 56.6, 56.5, 55.0, 42.8, 42.7, 42.6, 42.2, 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 $C_{23}H_{38}O_7$: 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 $C_{23}H_{38}O_7Na$. Found: 449.2565.

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

PPh_3 (572 mg, 2.18 mmol), imidazole (242 mg, 3.63 mmol), and I_2 (553 mg, 2.18 mmol) were successively added to the solution of **14** (774 mg, 1.82 mmol) in anhydrous CH_2Cl_2 (20 mL) at 0 °C, and the whole mixture was stirred for 3 h at rt. Sat. $NaHSO_3$ aq. and NH_4Cl aq. were added to the mixture, and the whole mixture was extracted with CH_2Cl_2. Removal of the solvent from the CH_2Cl_2 extract under reduced pressure gave a crude product, which was purified by SiO_2 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}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 4.61 (1H, d, *J* = 6.7 Hz, $OC\underline{H_2}OCH_3$), 4.58 (1H, d, *J* = 6.7 Hz, $OC\underline{H_2}OCH_3$), 3.94-3.89 (5H, m, $OC\underline{H_2}C\underline{H_2}O$, $O\underline{H}$), 3.52-3.48 (1H, m, $C\underline{H}OMOM$), 3.34 (3H, s, $OCH_2OC\underline{H_3}$), 3.29-3.08 (2H, m, $C\underline{H_2}I$), 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, CH_3), 1.17 (3/2H, s, CH_3), 0.89-0.81 (2H, m). ^{13}C-NMR (125 MHz, $CDCl_3$) 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 ($\underline{C}H_2I$). Anal. Calcd for $C_{23}H_{37}IO_6$: C, 51.50; H, 6.95; 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 $C_{23}H_{37}IO_6Na$. Found: 559.1542.

(1*S*,3a*R*,4*S*,7a*S*)-4-Hydroxy-1-(methoxymethoxy)-7a-methyl-4-(2-(8-methylene-1,4-dioxaspiro[4.5]-

decan-7-yl)ethyl)hexahydro-1*H*-inden-5(6*H*)-one (16)

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. NH_4Cl 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 = 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}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 4.75 (1/2H, s, C=C$\underline{H_2}$), 4.74 (1/2H, s, C=C$\underline{H_2}$), 4.65 (1/2H, s, C=C$\underline{H_2}$), 4.61 (1H, d, *J* = 6.4 Hz, OC$\underline{H_2}$OCH$_3$), 4.57 (1H, d, *J* = 6.4 Hz, OC$\underline{H_2}$OCH$_3$), 4.55 (1/2H, s, C=C$\underline{H_2}$), 3.96-3.92 (5H, m, OC$\underline{H_2}$C$\underline{H_2}$O, O$\underline{H}$), 3.49 (1H, t, *J* = 8.7 Hz, C$\underline{H}$OMOM), 3.33 (3H, s, OCH$_2$OC$\underline{H_3}$), 2.68 (1H, td, *J* = 14.2, 6.1 Hz), 2.45-2.40 (1H, m), 2.30-2.02 (5H, m), 1.90-1.48 (10H, m), 1.40-1.20 (3/2H, m), 1.15 (3/2H, s, CH_3), 1.13 (3/2H, s, CH_3), 0.92-0.85 (1/2H, m). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 215.0, 150.2 (C=CH_2), 108.8, 108.7, 107.0, 106.5, 96.0 (O$\underline{C}$H$_2$OCH$_3$), 85.53, 85.50, 80.7, 64.4, 64.2, 56.9, 55.3 (OCH$_2$O$\underline{C}$H$_3$), 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 $C_{23}H_{36}O_6Na$. Found: 431.2419.

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

*i*Pr$_2$NEt (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 $ClCH_2CH_2Cl$ (5 mL), and the whole mixture was stirred for 24 h at 60 °C. Further *i*Pr$_2$NEt (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. NH_4Cl aq. was added to the mixture, and the whole mixture was extracted with CH_2Cl_2. Removal of the solvent from the CH_2Cl_2 extract under reduced pressure gave a crude product, which was purified by SiO_2 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}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 4.74 (1H, s, C=C$\underline{H_2}$), 4.70 (1/2H, s, C=C$\underline{H_2}$), 4.63 (2H, s, OC$\underline{H_2}$OCH$_3$), 4.61 (1H, d, *J* = 6.4 Hz, OC$\underline{H_2}$OCH$_3$), 4.57 (1H, d, *J* = 6.4 Hz, OC$\underline{H_2}$OCH$_3$), 4.55 (1/2H, s, C=C$\underline{H_2}$), 3.96-3.90 (4H, s, OC$\underline{H_2}$C$\underline{H_2}$O), 3.56 (1H, t, *J* = 8.6 Hz, C$\underline{H}$OMOM), 3.35 (3H, s, OCH$_2$OC$\underline{H_3}$), 3.32 (3H, s, OCH$_2$OC$\underline{H_3}$), 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, CH_3), 1.10 (3/2H, s, CH_3), 0.98-0.93 (1/2H, m). ^{13}C-NMR (125 MHz, $CDCl_3$) 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 $C_{25}H_{40}O_7Na$. Found: 475.2717.

(1*S*,3a*R*,4*S*,7a*S*)-4-(Benzyloxymethoxy)-1-(methoxymethoxy)-7a-methyl-4-(2-(8-methylene-1,4-dioxaspiro[4.5]decan-7-yl)ethyl)hexahydro-1*H*-inden-5(6*H*)-one (17b)

iPr_2NEt (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 $ClCH_2CH_2Cl$ (1.5 mL), and the whole mixture was stirred for 24 h at 60 °C. Further *i*Pr_2NEt (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. NH_4Cl aq. was added to the mixture, and the whole mixture was extracted with CH_2Cl_2. Removal of the solvent from the CH_2Cl_2 extract under reduced pressure gave a crude product, which was purified by SiO_2 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}. ^{1}H-NMR (500 MHz, $CDCl_3$) 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), 3.96-3.92 (4H, m, $OC\underline{H_2}C\underline{H_2}O$), 3.55 (1H, t, *J* = 8.6 Hz, C<u>H</u>OMOM), 3.32 (3H, s, $OCH_2OC\underline{H_3}$), 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, CH_3), 1.02-0.95 (1H, m). ^{13}C-NMR (125 MHz, $CDCl_3$) 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, 69.8, 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 $C_{31}H_{44}O_7$: 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 $C_{31}H_{44}O_7Na$. Found: 551.3007.

(1*S*,3a*R*,4*S*,7a*S*)-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-1*H*-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 $PhNTf_2$ (1.56 g, 4.36 mmol) in anhydrous THF (5.0 mL) and Et_3N (5.0 mL) at 60 °C, and the whole mixture was stirred at 60 °C for 15 min. Then $PhNTf_2$ (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. NH_4Cl 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 **18a** (mixture of two diastereomers, 629 mg, 99%) as a colorless oil. IR (KBr): 2946, 2884, 1647, 1412 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 5.92 (1H, dd, *J* = 5.5, 2.4 Hz, C=C<u>H</u>), 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, $OC\underline{H_2}C\underline{H_2}O$), 3.67 (1H, t, *J* = 8.7 Hz, C<u>H</u>OMOM), 3.37 (3H, s, $OCH_2OC\underline{H_3}$), 3.34 (3H, s, $OCH_2OC\underline{H_3}$), 2.33-2.07 (7H, m), 2.00-1.72 (7H, m), 1.62-1.36 (4H, m), 0.91 (3H, s, CH_3). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 150.2, 150.1, 149.8, 149.7, 121.8, 118.3 (*C*F_3, 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 $C_{26}H_{39}F_3O_9S$: 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 $C_{26}H_{39}F_3O_9SNa$. Found: 607.2148.

(1*S*,3a*R*,4*S*,7a*S*)-4-(Benzyloxymethoxy)-1-(methoxymethoxy)-7a-methyl-4-(2-(8-methylene-1,4-dioxaspiro[4.5]decan-7-yl)ethyl)-2,3,3a,4,7,7a-hexahydro-1*H*-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 $PhNTf_2$ (242 mg, 0.678 mmol) in anhydrous THF (0.8 mL) and Et_3N (0.8 mL) at 60 °C, and the whole mixture was stirred at 60 °C for 15 min. Then $PhNTf_2$ (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. NH_4Cl 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 **18b** (mixture of two diastereomers, 112 mg, quant.) as a colorless oil. IR (KBr): 2946, 2884, 1647, 1412 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.34-7.23 (5H, m, Ph), 5.92-5.88 (1H, m, C=C<u>H</u>), 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, O<u>CH$_2$</u>C<u>H$_2$</u>O), 3.61 (1H, t, *J* = 8.8 Hz, C<u>H</u>OMOM), 3.30 (3H, s, $OCH_2OC\underline{H_3}$), 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, CH_3). ^{13}C-NMR (125 MHz, $CDCl_3$) 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 (*C*F_3, 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 $C_{32}H_{43}F_3O_9S$: 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 $C_{32}H_{43}F_3O_9SNa$. Found: 683.2527.

General procedure for intramolecular Heck reaction

$Pd_2(dba)_3$•$CHCl_3$ (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. NH_4Cl 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 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 ($MeOH/H_2O$ = 80:20 containing 1% Et_3N).

20a: IR (KBr): 2942, 1730, 1443, 1354 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 5.82 (1H, d-like, C=C<u>H</u>), 5.69 (1H, s, C=C<u>H</u>), 4.63 (1H, d, *J* = 6.7 Hz, OC<u>H$_2$</u>OCH$_3$), 4.60 (1H, d, *J* = 6.7 Hz, OC<u>H$_2$</u>OCH$_3$), 4.47 (1H, d, *J* = 7.3 Hz, OC<u>H$_2$</u>OCH$_3$), 4.31 (1H, d, *J* = 7.3 Hz, OC<u>H$_2$</u>OCH$_3$), 3.98-3.94 (4H, m, OC<u>H$_2$</u>C<u>H$_2$</u>O), 3.68 (1H, t, *J* = 8.9 Hz, C<u>H</u>OMOM), 3.34 (3H, s, OCH$_2$OC<u>H$_3$</u>), 3.31 (3H, s, OCH$_2$OC<u>H$_3$</u>), 2.55-2.48 (1H, m, C<u>H</u>C=CH), 2.37 (1H, t-like, CH$_2$C<u>H$_2$</u>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, $CDCl_3$) δ: 143.1 (C10), 137.5 (C9), 131.9 (C11), 122.5 (C19), 108.7 (C3), 95.9 (O<u>C</u>H$_2$OCH$_3$), 91.3 (O<u>C</u>H$_2$OCH$_3$), 86.4 (C17), 84.4 (C8), 64.4 (OCH$_2$<u>C</u>H$_2$O), 64.2 (OCH$_2$<u>C</u>H$_2$O), 55.7 (OCH$_2$O<u>C</u>H$_3$), 55.2 (OCH$_2$O<u>C</u>H$_3$), 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 $C_{25}H_{38}O_6Na$. Found: 457.2605.

20'a: IR (KBr): 2646, 1732, 1439, 1366 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 5.80-5.78 (1H, m, C=C<u>H</u>CH$_2$), 5.60 (1H, s, C=C<u>H</u>C=CH), 4.63 (1H, d, *J* = 6.7 Hz, OC<u>H$_2$</u>OCH$_3$), 4.60 (1H, d, *J* = 6.7 Hz, OC<u>H$_2$</u>OCH$_3$), 4.49 (1H, d, *J* = 7.3 Hz, OC<u>H$_2$</u>OCH$_3$), 4.25 (1H, d, *J* = 7.3 Hz, OC<u>H$_2$</u>OCH$_3$), 3.98-3.94 (4H, m, OC<u>H$_2$</u>C<u>H$_2$</u>O), 3.68 (1H, t, *J* = 8.8 Hz, C<u>H</u>OMOM), 3.35 (3H, s, OCH$_2$OC<u>H$_3$</u>), 3.33 (3H, s, OCH$_2$OC<u>H$_3$</u>), 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, $CDCl_3$) δ: 144.0 (C10), 137.2 (C9), 131.7 (C11), 120.0 (C19), 109.8 (C3), 95.9 (O<u>C</u>H$_2$OCH$_3$), 91.3 (O<u>C</u>H$_2$OCH$_3$), 86.5 (C17), 85.4 (C8), 64.3 (2C, OCH$_2$<u>C</u>H$_2$O), 55.7 (OCH$_2$O<u>C</u>H$_3$), 55.2 (OCH$_2$O<u>C</u>H$_3$), 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 $C_{25}H_{38}O_6Na$. Found: 457.2605.

21a (mixture of two diastereomers): IR (KBr): 2946, 1443, 1358 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.21 (1/2H, d, *J* = 9.2 Hz, C=C<u>H</u>), 6.19 (1/2H, d, *J* = 9.2 Hz, C=C<u>H</u>), 5.25 (1/2H, d, *J* = 9.7 Hz, C=C<u>H</u>), 5.17 (1/2H, d, *J* = 9.8 Hz, C=C<u>H</u>), 4.87 (1/2H, d, *J* = 7.3 Hz, OC<u>H$_2$</u>OCH$_3$), 4.82 (1/2H, d, *J* = 7.3 Hz, OC<u>H$_2$</u>OCH$_3$), 4.67-4.62 (2H, m, OC<u>H$_2$</u>OCH$_3$), 4.49 (1/2H, d, *J* = 7.3 Hz, OC<u>H$_2$</u>OCH$_3$), 4.46 (1/2H, d, *J* = 7.4 Hz, OC<u>H$_2$</u>OCH$_3$), 3.96-3.93 (4H, m, OC<u>H$_2$</u>C<u>H$_2$</u>O), 3.79-3.72 (1H, m, C<u>H</u>OMOM), 3.36 (3H, s, OCH$_2$OC<u>H$_3$</u>), 3.33 (3H, s, OCH$_2$OC<u>H$_3$</u>), 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, $CDCl_3$) δ: 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, O<u>C</u>H$_2$OCH$_3$), 96.1 (1/2C, O<u>C</u>H$_2$OCH$_3$), 92.1 (1/2C, O<u>C</u>H$_2$OCH$_3$), 92.0 (1/2C, O<u>C</u>H$_2$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$_2$<u>C</u>H$_2$O), 64.28 (1/2C, OCH$_2$<u>C</u>H$_2$O), 64.2 (1/2C, OCH$_2$<u>C</u>H$_2$O), 64.1 (1/2C, OCH$_2$<u>C</u>H$_2$O), 55.4 (1/2C,

$OCH_2O\underline{C}H_3$), 55.3 (1/2C, $OCH_2O\underline{C}H_3$), 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, calcd for $C_{25}H_{38}O_6Na$. 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 ($MeOH/H_2O$ = 90:10).

20b: IR (KBr): 2934, 1453, 1364 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.35-7.27 (5H, m, Ph), 5.82 (1H, d-like, C=C$\underline{H}$), 5.70 (1H, s, C=C$\underline{H}$), 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, $OC\underline{H_2}C\underline{H_2}O$), 3.66 (1H, t, *J* = 8.9 Hz, C$\underline{H}$OMOM), 3.34 (3H, s, $OCH_2OC\underline{H_3}$), 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, CH_3). ^{13}C-NMR (125 MHz, $CDCl_3$) 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 ($O\underline{C}H_2OCH_3$), 89.6 ($O\underline{C}H_2OCH_2Ph$), 86.5 (C17), 84.7 (C8), 69.8 ($O\underline{C}H_2Ph$), 64.4 ($OCH_2\underline{C}H_2O$), 64.2 ($OCH_2\underline{C}H_2O$), 55.2 ($OCH_2O\underline{C}H_3$), 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, calcd for $C_{31}H_{42}O_6Na$. Found: 533.2915.

20'b: IR (KBr): 2946, 1441, 1366 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.47-7.27 (5H, m, Ph), 5.79-5.78 (1H, m, C=C$\underline{H}$), 5.60 (1H, s, C=C$\underline{H}$), 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, $OC\underline{H_2}C\underline{H_2}O$), 3.66 (1H, t, *J* = 8.8 Hz, C$\underline{H}$OMOM), 3.34 (3H, s, $OCH_2OC\underline{H_3}$), 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, CH_3). ^{13}C-NMR (125 MHz, $CDCl_3$) 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 ($O\underline{C}H_2OCH_3$), 89.4 ($O\underline{C}H_2OCH_2Ph$), 86.6 (C17), 85.6 (C8), 69.8 ($O\underline{C}H_2Ph$), 64.3 ($OCH_2\underline{C}H_2O$), 55.2 ($OCH_2O\underline{C}H_3$), 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, calcd for $C_{31}H_{42}O_6Na$. Found: 533.2915.

21b (mixture of two diastereomers): IR (KBr): 2944, 1453, 1368 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.35-7.26 (5H, m, Ph), 6.21 (1/2H, d, *J* = 9.2 Hz, C=C$\underline{H}$), 6.19 (1/2H, d, *J* = 9.2 Hz, C=C$\underline{H}$), 5.25 (1/2H, d, *J* = 9.5 Hz, C=C$\underline{H}$), 5.17 (1/2H, d, *J* = 9.5 Hz, C=C$\underline{H}$), 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$_3$) δ: 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$_3$), 90.3 (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$_2$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 $C_{31}H_{42}O_6Na$. Found: 533.2914.

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