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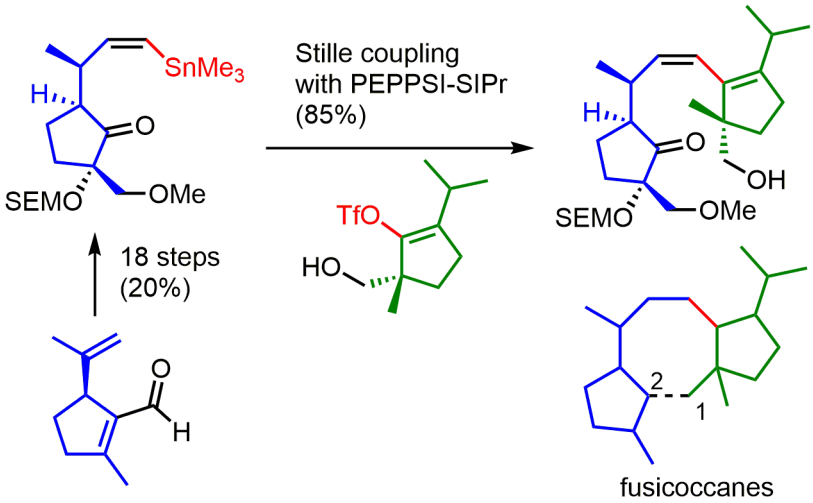

Synthesis of the 1,2-seco fusicoccane diterpene skeleton by Stille coupling reaction between the highly functionalized A and C ring segments of cotylenin A

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Abstract

1-Hydroxy-14-isopropyl-3β-methoxymethyl-7β,11β-dimethyl-3α-[((2-trimethylsilyl)ethoxy)methoxy]-1,2-secofusicocca-8,10(14)-dien-2-one, a highly functionalized 1,2-seco fusicoccane diterpene skeleton related to cotylenin A was synthesized in a convergent manner. The A ring segment, *i. e.*, (1'*R*,2*S*, 2'*E*,5*S*)-2-methoxymethyl-5-[1'-methyl-3'-(trimethylstannyl)prop-2-enyl]-2-[((2"-trimethylsilyl)ethoxy)methoxy]cyclopentanone, was synthesized in 20.1% yield over 18 steps from known (*S*)-5-isopropenyl-2-methylcyclopent-1-enecarbaldehyde. This was coupled with the C ring segment, *i. e.*, (*R*)-5-hydroxymethyl-2-isopropyl-5-methylcyclopent-1-en-1-yl trifluoromethylsulfonate, which was prepared according to our previous report. The Stille coupling reaction between alkenylstannane and sterically hindered

triflate proceeded successfully in the presence of PEPPSI-SIPr (85%), and the total yield of the target molecule was 17.1% over the longest linear sequences (19 steps) from (*S*)-5-isopropenyl-2-methylcyclopent-1-enecarbaldehyde.

1. Introduction

Cotylenin A (**1**, Figure 1) was first isolated from *Cladosporium* sp. as a plant growth regulator and its structure was later determined by Sassa and co-workers.[1,2] Because of its biological effects such as induction of differentiation in murine and human myeloid leukemia cells,[3] and apoptosis in the cooperation with interferon (INF)-α,[4] this compound has been suggested to act as anticancer agent. In *in vivo* animal studies, the combined use of **1** and INF-α shows high therapeutic efficacy in tumor-bearing mice, inoculated with human lung adenocarcinoma cells[4] and human ovarian carcinoma cells.[5]

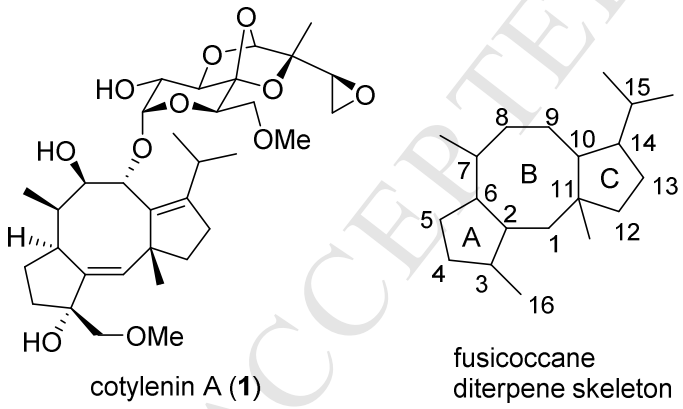
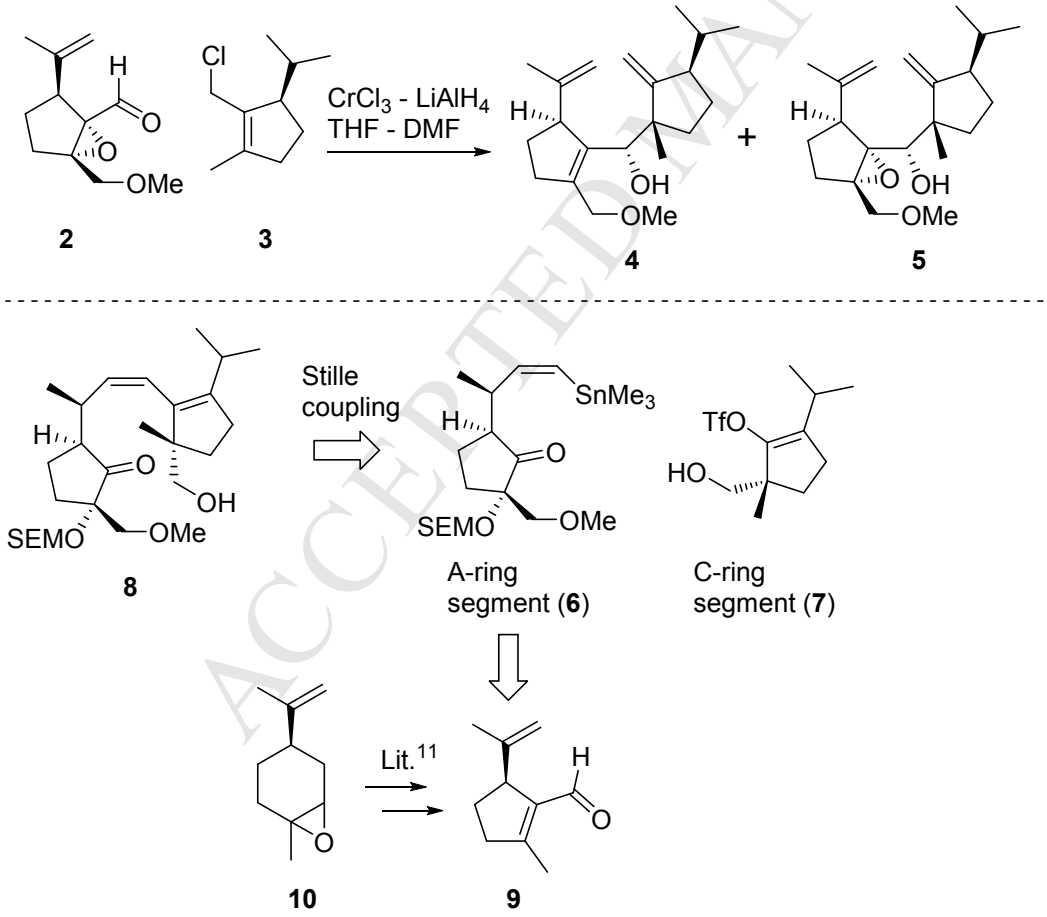


Figure 1. Structure of cotylenin A (**1**) and the numbering of the fusicoccane diterpene skeleton.

However, the original fungal strain lost its ability to proliferate with consequent of lack of production of cotylenin A (**1**).[6] This prompted synthetic chemists to develop new methodologies for the construction of carbon skeleton with proper oxygen functionalities. Convergent

approaches were reported in pioneering and intensive works by Kato, Takeshita and co-workers.[7-9] For example, the A ring and the C ring segment (**2** and **3**, respectively) were coupled between C-1 and C-11 (in fusicoccane numbering) to form 8,9-seco derivatives as in **4** and **5** (Scheme 1).[9]

In the present work, we designed an alternative convergent approach involving the coupling of A and C ring segments (**6** and **7**[10]) between C-9 and C-10 to construct highly functionalized 1,2-seco derivative **8** with correct stereochemistreis at C-3, C-6, C-7, and C-11. Herein, we describe the elaboration of coupling conditions between **7** and A ring segment **6** toward **8**. The synthesis of alkenylstannane **6** was envisaged *via* known aldehyde **9**[11] starting from commercially available (4*R*)-limonene oxide (**10**).



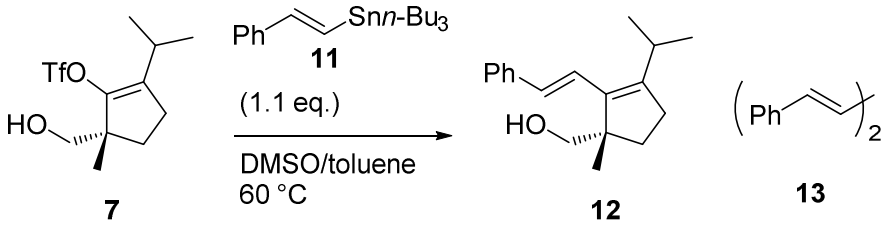
Scheme 1. Previous strategy based on bond formation between C-1 and C-11 in Kato and Takeshita's work (top), and our strategy toward **8** based on Stille cross-coupling between **6** and **7** to

form **8** (bottom).

2. Results and discussion

First, the conditions of the Stille reaction of **7** were investigated using styrylstannane (**11**), as the model substatrate. As **11** was poorly soluble in DMSO, toluene was added as a co-solvent to ensure the homogeneity of the reaction mixture. Due to the severe steric hindrance around triflate, we supposed that low reactivity of **7** would be caused by poor efficiency of oxidative addition. At first, the widely used $Pd_2(dba)_3$-$CHCl_3$ was tested (entries 1-3). In the absence of ligands, the formation of undesired dimer **13** competed with the desired cross-coupling reaction (entry 1). Addition of Ph_3As suppressed the reactivity of **7**, resulting in the predominant formation of **13** (entry 2). In the presence of more electron-donating XPhos,[12] the conversion of **7** increased; however, undesired **13** was still the major product (entry 3). On the basis of these results, we envisioned that a more electron-rich palladium catalyst would promote the coupling. As expected, in the presence of PEPPSI-IPr,[13] a palladium complex containing an *N*-heterocyclic carbene ligand, **7** was cleanly converted into the desired **12** (entry 4). In all entries, **11** was completely consumed in the reaction mixture, judged by ^{1}H NMR analysis of the crude products. We thought that PEPPSI-IPr not only accelerated the oxidative addition to **7**, but also suppressed the undesired dimerization to incline **11** to the cross-coupling with **7**.

Table 1. Optimization of the Stille coupling reaction conditions between **7** and **11**.



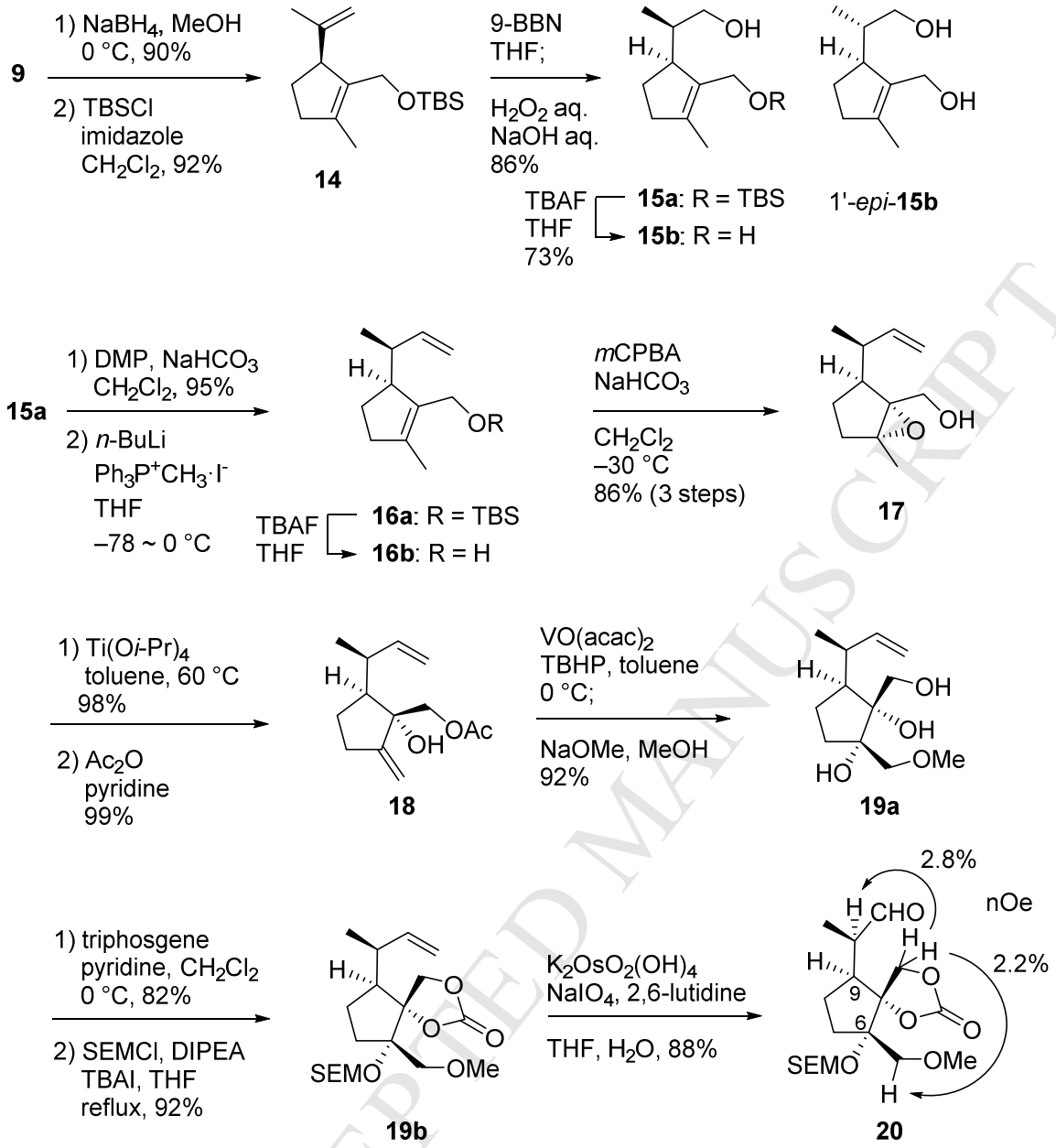
entry	Pd cat (mol%)	additive (mol%)	time (h)	ratio (**7**: **12**:**13**)[a]
1	$Pd_2(dba)_3$-$CHCl_3$ (5)	None	4	1:1:1
2	$Pd_2(dba)_3$-$CHCl_3$ (3)	Ph_3As (33)	3	5:1:3
3	$Pd_2(dba)_3$-$CHCl_3$ (7)	XPhos (15)	7	2:2:3
4	PEPPSI-IPr (5)	None	4	0:1:0

a: determined by ^{1}H NMR spectra. For details, see section 4.2.

Encouraged by these results, we next prepared **6**, for the use as the coupling partner of **7** (Scheme 2). First, aldehyde **9**[11] was reduced with sodium borohydride in methanol, and the resulting primary alcohol was protected as *tert*-butyldimethylsilyl (TBS) ether, forming **14** in 83% yield over two steps. The following hydroboration-oxidation sequence proceeded regio- and stereoselectively to give **15a** as a single diastereomer, as confirmed after transformation to **15b**. Comparison of the ^{1}H NMR spectrum with those of the diastereomers of **15b**[14] showed no contamination of the C-1' epimer (see Experimental, section 4.4). To avoid the interference of coordinating oxygen atoms, the unhindered $=CH_2$ group was chosen as a temporary protecting group for the terminal hydroxyl moiety, as in compound **16**.

Dess-Martin oxidation followed by one carbon homologation with a Wittig reagent yielded **16a**. Removal of the TBS group and subsequent epoxidation with *m*-chloroperoxybenzoic acid proceeded site- and stereoselectively to give **17** as a single product. The free hydroxy group in **16b** was beneficial to achieve high site-selectivity, improving the discrimination between internal and terminal olefins. Next, Lewis acid-mediated isomerization of the epoxide and acetylation of the resulting diol at the less hindered position afforded **18** in 97% yield over two steps. The

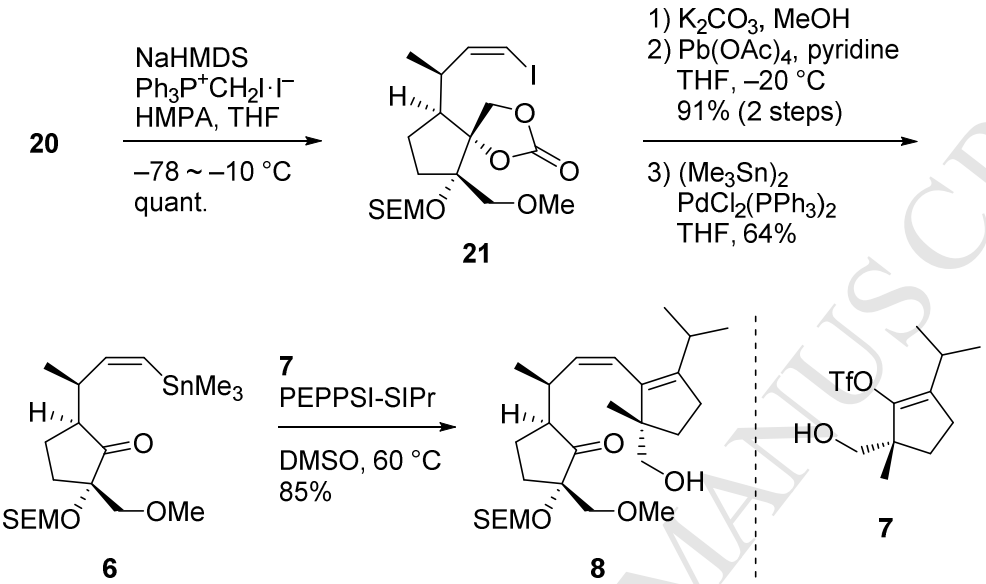
second stereoselective epoxidation-regioselective ring opening sequences were carried out with *tert*-butylhydroperoxide using vanadyl acetylacetonate as a catalyst, followed by the treatment with sodium methoxide in methanol to obtain methyl ether **19a** with a properly installed methoxy group in 92% yield. The three hydroxy groups were differentially protected; the less hindered glycol moiety reacted with triphosgene, and the remaining tertiary alcohol was protected by a 2-(trimethylsilyl)ethoxymethyl (SEM) group to give **19b** in 75% yield over two steps. In **20**, the correct stereochemistry with *cis* relationship between the side chains at C-6 and C-9 was confirmed by nuclear Overhauser effect (Scheme 2).



Scheme 2. Stereoselective synthesis of A ring segment intermediate **20** from **9**.

Treatment of **20** with (iodomethyl)triphenylphosphonium iodide[15] led to the successful introduction of a *cis*-iodovinyl group to form **21** (Scheme 3). Methanolysis of the cyclic carbonate protective group followed by the oxidative degradation of the unnecessary carbon atom under mild conditions furnished a cyclopentanone intermediate in 91% yield over two steps. Treatment of the alkenyl iodide with hexamethylditin in the presence of bis(triphenylphosphine)palladium dichloride

provided **6**, the desired A ring segment, as a single stereoisomer in 64% yield. The results summarized in Table 1 prompted us to examine PEPPSI-type catalysts, for the subsequent Stille coupling reaction, and PEPPSI-SIPr successfully gave the desired product **8** in 85% yield.



Scheme 3. Formation of Stille coupling precursor **6** and the successful construction of the 1,2-seco fusicoccane skeleton in **8**.

3. Conclusion

En route to the synthesis of highly functionalized 1,2-seco fusicoccane skeleton of **8**, the A ring segment **6** was prepared in 20.1% yield over 18 steps from (*S*)-**9**. The choice of functionalities and their size were important to achieve the correct stereochemical disposition of substituents on the congested cyclopentene ring, as shown in **16b**. The conditions for the Stille coupling reaction were optimized between triflate **7**, the C ring segment, and model alkenylstannane **11** were optimized, and PEPPSI-type catalysts were found to be most effective. The key cross-coupling reaction between **6** and **7** proceeded in 85% yield, and the desired **8** was obtained in 17.1% total

yield over 19 steps from (*S*)-**9**, which was easily accessible from commercially available (4*R*)-limonene oxide.

4. Experimental

4.1. General

IR spectra were measured as ATR on a Jeol FT-IR SPX60 spectrometer. ^{1}H NMR spectra were measured in $CDCl_3$ at 400 MHz on a VARIAN 400-MR spectrometer or at 500 MHz on a VARIAN 500-MR spectrometer and ^{13}C NMR spectra were measured in $CDCl_3$ at 100 MHz on a VARIAN 400-MR spectrometer or at 125 MHz on a VARIAN 500-MR spectrometer. Merck silica gel 60 N (spherical, neutral, 63-210 μm, 37565-84) from Kanto Chemical Co. was used for column chromatography, respectively. Optical rotation values were recorded on a Jasco P-1010 polarimeter.

4.2. (*S*)-3-Isopropyl-1-methyl-2-(2-phenylethenyl)cyclopent-2-enmethanol 12

To the mixture of Pd catalyst and additive were added the solutions of **7** (8 mg) in dimethyl sulfoxide (DMSO, 300 μL) and **11** (10 mg) in toluene/DMSO (2:1, 300 μL) successively and stirred at 60 °C. At the stage that the reaction no longer showed any progresss by TLC monitoring (hexane/EtOAc = 8:1, R_f = 0.22 for **7**, 0.26 for **12**, 0.36 for **13**, 0.69 for **11**), the reaction was quenched with H_2O and organic materials were extracted with EtOAc. The ratio of the components in crude mixture was estimated by ^{1}H NMR spectra by the comparison with authentic signals ($CDCl_3$): δ3.32 (d, 1H, J = 12.2 Hz, for **7**), 3.48 (d, 1H, J = 10.9 Hz, for **12**), and 7.09 (d, 2H, J = 16.9 Hz, for **13**).

4.3. (*S*)-3-Isopropenyl-2-*tert*-butyldimethylsiloxymethyl-1-methylcyclopentene 14

To a solution of **9** (4.30 g, 28.6 mmol) in MeOH (50 mL) was added $NaBH_4$ (875 mg, 23.1 mmol) and stirred at 0 °C for 1 h. The reaction was quenched with saturated NH_4Cl aq. solution and organic materials were extracted with EtOAc three times. The combined extract was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with hexane/EtOAc (2:1) to give an alcohol (3.92 g, 90%) as a colorless oil. ^{1}H NMR spectrum was identical with that reported previously.[10c] This was employed for the next step without further purification.

To a solution of the alcohol (7.13 mg, 7.42 mmol) in CH_2Cl_2 (20 mL) was added imidazole (1.04 g, 15.3 mmol) and TBSCl (1.66 g, 11.0 mmol) at 0 °C and stirred for 29 h at room temperature under argon atmosphere. The reaction was quenched with phosphate buffered solution (pH 7.0, 0.2 M) and organic materials were extracted with EtOAc twice. The combined extract was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with hexane/EtOAc (1:0–20:1) to furnish **14** (1.82 g, 92%) as a colorless oil. $[\alpha]_D^{20}$ +98.3 (*c* 1.14, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.03 (3H, s), 0.04 (3H, s), 0.86 (9H, s), 1.59–1.71 (4H, m), 1.72 (3H, s), 2.03 (1H, m), 2.23 (1H, ddd, *J* = 15.5, 9.0, 3.5 Hz), 2.33–2.39 (1H, m), 3.45 (1H, dd, *J* = 9.0, 0.0 Hz), 3.93 (1H, d, *J* = 11.5 Hz), 4.23 (1H, d, *J* = 11.5 Hz), 4.65–4.68 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ –5.4, –5.3, 14.1, 18.5, 19.3, 26.0 (3C), 28.0, 37.9, 54.0, 58.2, 110.2, 135.6, 136.7, 148.1; IR ν_{max} 2953, 2927, 2895, 2856, 1471, 1438, 1371 cm^{-1}.

4.4. (1'*S*,2*R*)-2-(2'-*tert*-Butyldimethylsiloxymethyl-3'-methylcyclopent-2'-enyl)-2-methylpropanol 15a

To a solution of **14** (1.82 g, 6.83 mmol) in tetrahydrofuran (THF, 27 mL) was added 9-BBN dimer (1.76 g, 14.4 mmol) at 0 °C and stirred at room temperature for 2 h under argon atmosphere. The reaction was treated with NaOH aq. solution (3 M, 30 mL) and H_2O_2 aq. solution (30%, 30 mL) and stirred for 1 h at room temperature. The organic materials were extracted with EtOAc three times and the combined extract was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with hexane/EtOAc (100:1–10:1) to furnish **15a** (1.68 g, 86%) as a colorless oil. $[\alpha]_D^{21}$ +20.4 (*c* 1.22, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.08 (3H, s), 0.10 (3H, s), 0.85 (3H, d, *J* = 7 Hz), 0.91 (9H, s), 1.61–1.66 (4H, m), 1.91 (1H, m), 2.11 (1H, m), 2.21 (1H, ddd, *J* = 14.5, 9.5, 4.5 Hz), 2.31–2.38 (1H, m), 2.97 (1H, m), 3.43 (1H, dd, *J* = 11.0, 6.0 Hz), 3.52 (1H, dd, *J* = 11.0, 8.0 Hz), 4.24 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ –5.5, –5.3, 14.1, 15.1, 18.3, 24.1, 25.9 (3C), 37.9, 38.5, 49.2, 56.4, 66.1, 135.2, 136.1; IR ν_{max} 3375, 2953, 2927, 2883, 2856, 1471, 1462, 1377, 1361, 1251 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{16}H_{32}NaO_2Si$: 307.2069, found: 307.2014.

To a solution of **15a** (40.4 mg, 0.142 mmol) in THF (1.0 mL) was added tetra-*n*-butylammonium fluoride (TBAF, 1 M solution in THF, 1 M, 300 μL) and stirred at room temperature for 2 h. The reaction was quenched with saturated NH_4Cl aq. solution and organic materials were extracted with EtOAc four times. The combined extract was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography with hexane/EtOAc (10:1–1:1) to afford

15b (17.7 mg, 73%). Diastereomeric ratio were estimated by ^{1}H NMR spectra with the comparison of authentic signals ($CDCl_3$): δ0.89 (d, 3H, *J* = 7 Hz, for **15b**), 0.67 (d, 3H, *J* = 7 Hz, for 1'-*epi*-**15b**).[14]

4.5. (1'*S*,3*S*)-3-(1'-methylprop-2'-enyl)-2-*tert*-butyldimethylsiloxymethyl-1-methylcyclopentene 16a

To a solution of alcohol **15a** (197 mg, 0.693 mmol) in CH_2Cl_2 (7.0 mL) was added $NaHCO_3$ (312 mg, 3.72 mmol) and Dess-Martin periodinate (517 mg, 1.22 mmol) at 0 °C and stirred at room temperature for 2 h. The reaction was quenched with a mixture of saturated $NaHCO_3$ aq. solution and saturated $Na_2S_2O_3$ aq. solution, and the organic materials were extracted with EtOAc three times. The combined extract was washed with brine and dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with hexane/EtOAc (1:0–50:1) to furnish an aldehyde (185 mg, 95%) as a colorless oil. $[\alpha]_D^{21}$ –65.1 (*c* 1.14, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.05 (3H, s), 0.06 (3H, s), 0.89 (9H, s), 1.03 (3H, d, *J* = 6.8 Hz), 1.54 (1H, m), 1.66 (3H, s), 1.96–2.16 (1H, m), 2.17–2.27 (2H, m), 2.75 (1H, dddd, *J* = 12.8, 6.8, 3.6, 1.2 Hz), 3.21 (1H, m), 4.15 (1H, d, *J* = 12.4 Hz), 4.28 (1H, d, *J* = 12.4 Hz), 9.71 (1H, d, *J* = 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ –5.4 (2C), 11.2, 14.0 18.3, 25.0, 25. 9 (3C), 37.5, 48.4, 48.6, 58.3, 134.3, 136.8, 206.8; IR ν_{max} 32953, 2030, 2895, 2885, 2857, 1722, 1471, 1462, 1251 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{16}H_{30}NaO_2Si$: 305.1913, found: 305.1866.

To a solution of $Ph_3P^+CH_3I^-$ (734 mg, 1.82 mmol) in THF (7 mL) was added *n*-BuLi solution in

hexane (1.56 M, 1.20 mL) at 0 °C and stirred for 30 min. The mixture was cooled to –78 °C, added a solution of the aldehyde (391 mg, 1.39 mmol) in THF (7 ml) and warmed to 0 °C in 1 h. The reaction was quenched with saturated NH_4Cl aq. solution and organic materials were extracted with EtOAc three times. The combined extract was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and the residue was filtered through a short pad of silica gel with hexane/EtOAc (100:1) to furnish a crude **16a**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.05 (3H, s), 0.07 (3H, s), 0.90 (9H, s), 1.01 (3H, d, *J* = 6.8), 1.56 (1H, dddd, *J* = 13.6, 7.6, 5.6, 5.2 Hz), 1.65 (3H, s), 1.72–1.82 (1H, m), 2.14–2.21 (2H, m), 2.56–2.62 (1H, m), 2.86–2.94 (1H, m), 4.11 (1H, d, *J* = 12.0 Hz), 4.29 (1H, d, *J* = 12.0 Hz), 4.92–4.97 (2H, m), 5.75 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ –5.4, –5.3, 14.0, 17.7, 18.4, 22.6, 25.8 (3C), 37.6, 37.9, 51.4, 58.3, 113.5, 135.5, 135.8, 141.1; IR ν_{max} 2956, 2927, 2885, 2856, 1471, 1462, 1371 cm^{-1}. This was employed for the next step without purification.

4.6. (1*R*,1'*S*,2*R*,5*S*)-1,2-epoxy-2-methyl-5-(1'-methylprop-2'-enyl)cyclopentanemethanol 17

To a solution of the above-mentioned crude **16a** in THF (3.5 mL) was added TBAF solution in THF (1 M, 2.50 mL) at 0 °C and stirred at room temperature for 2 days. The reaction was quenched with phosphate buffered solution (pH 7.0, 0.2 M) and organic materials were extracted with EtOAc four times. The combined extract was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and the residue was filtered through short pad silica gel hexane/EtOAc (5:1) to furnish crude **16b**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.03 (3H, d, *J* = 7.0 Hz), 1.58 (1H, dddd, *J* = 14.0, 9.0, 5.5, 5.5 Hz), 1.80–1.88 (1H, m), 2.20–2.24 (2H, m), 2.56–2.61 (1H, m), 2.92 (1H, m), 4.10 (1H, d, *J* = 12.0 Hz), 4.25 (1H, d, *J* = 12.0 Hz), 4.96–

5.10 (2H, m), 5.77 (1H, ddd, *J* = 17.0, 10.5, 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 17.5, 23.2, 37.7, 38.4, 51.5, 57.6, 114.0, 135.6, 138.4, 141.2; IR ν_{max} 3310, 2958, 2914, 2870, 2841, 1637, 1456, 1436, 1413, 1379, 1371 cm^{-1}.

To a solution of the above-mentioned crude **16b** in CH_2Cl_2 (12 mL) was added $NaHCO_3$ (230 mg, 2.74 mmol) and *m*CPBA (417 mg, 1.69 mmol) at –30 °C and stirred for 3 h. The reaction was quenched with saturated $Na_2S_2O_3$ aq. solution and organic materials were extracted with EtOAc twice. The combined extract was washed with 2 M NaOH aq. solution and brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography with hexane/EtOAc (20:1–4:1) to furnish **17** (217 mg, 86% over three steps) as a colorless solid. Mp 71.3–71.9 °C (colorless fine needles from hexane). $[\alpha]_D^{21}$ –29.1 (*c* 1.08, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.04 (3H, d, *J* = 6.5 Hz), 1.36 (3H, s), 1.44–1.47 (2H, m), 1.56–1.63 (1H, m), 1.85–1.89 (1H, m), 2.37–2.40 (1H, m), 2.53–2.61 (1H, m), 3.64 (1H, d, *J* = 12.0 Hz), 4.15 (1H, d, *J* = 12.0 Hz), 4.99–5.06 (2H, m), 5.64 (1H, ddd, *J* = 17.5, 10.5, 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.5, 18.7, 20.4, 33.6 37.2, 46.3, 60.4, 70.2, 72.8, 114.5, 140.1; IR ν_{max} 3296, 2958, 2939, 2927, 1639, 1460, 1425, 1379 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{11}H_{18}NaO_2$: 205.1205, found: 205.1147.

4.7. (1*S*,1'*S*,5*S*)-1-hydroxy-2-methylene-5-(1'-methylprop-2'-enyl)cyclopentanemethyl acetate 18

To a solution of **17** (409 mg, 2.24 mmol) in toluene (13 mL) was added Ti(O-*i*-Pr)$_4$ (670 μL, 2.26 mmol) at room temperature and stirred at 60 °C for 2 h under argon atmospher. The reaction was quenched with 1 M HCl aq. solution and organic materials were extracted with EtOAc five

times. The extract was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with hexane/EtOAc (6:1–2:1) to furnish a diol (402 mg, 98%) as a colorless oil. $[\alpha]_D^{21}$ –3.2 (*c* 1.08, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.18 (3H, d, *J* = 6.8 Hz), 1.30–1.36 (1H, m), 1.72 (1H, dd, *J* = 8.3, 4.4 Hz), 1.76–1.87 (2H, m), 2.23 (1H, s), 3.28 (1H, ddd, *J* = 15.4, 15.4, 6.9 Hz), 2.38–2.42 (2H, m), 3.45 (1H, dd, *J* = 11.2, 4.4 Hz), 3.73 (1H, dd, *J* = 11.2, 8.3 Hz), 4.90 (1H, dd, *J* = 10.2, 1.7 Hz), 4.99 (1H, dd, *J* = 16.2, 1.7 Hz), 5.04–5.09 (2H, m), 5.68 (1H, ddd, *J* = 16.2, 10.2, 8.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.9, 25.5 27.5, 38.7, 53.2, 63.4, 82.1, 108.0, 113.1, 143.6, 155.4; IR ν_{max} 3390, 3074, 2958, 2931, 2875, 1456, 1375 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{11}H_{18}NaO_2$: 205.1205, found: 205.1206.

To a solution of the diol (402 mg, 2.21 mmol) in pyridine (2.2 mL) was added Ac_2O (2.2 mL) and stirred for 1 h at room temperature. The reaction was quenched with water and organic materials were extracted with EtOAc four times. The combined extract was washed with 2 M HCl aq. solution and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with hexane/EtOAc (20:1–5:1) to furnish **18** (490 mg, 99%) as a colorless oil. $[\alpha]_D^{21}$ –25.8 (*c* 1.11, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): 1.20 (3H, d, *J* = 6.8 Hz), 1.36 (1H, dddd, *J* = 12.2, 12.2, 9.7, 9.7 Hz), 1.60–1.80 (1H, br–s), 1.74 (1H, ddd, *J* = 11.9, 9.7, 7.5 Hz), 1.80–1.87 (1H, m), 2.08 (3H, s), 2.22–2.28 (1H, m), 2.37–2.41 (2H, m), 4.11(1H, d, *J* = 12.3 Hz), 4.24 (1H, d, *J* = 12.3 Hz), 4.90 (1H, dd, *J* = 10.1, 2.0 Hz), 4.96–5.00 (2H, m), 5.08 (1H, dd, *J* = 2.5, 2.5 Hz), 5.65 (1H, ddd, *J* = 18.6 10.1, 8.6); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.8, 20.9, 25.8, 27.5, 39.1, 54.3, 65.5, 81.0, 108.1, 113.2, 143.3, 155.0, 171,2; IR ν_{max} 3479, 2970, 1732, 1373, 1224 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{13}H_{20}NaO_3$: 247.1310,

found: 247.1301.

4.8. (1*R*,1'*S*,2*S*)-1-hydroxymethyl-2-methoxymethyl-5-(1'-methylprop-2'-enyl)cyclopentane-1,2-diol 19a

To a solution of **18** (21.8 mg, 0.097 mmol) in toluene (1.5 mL) were added TBHP (solution in toluene, 2 M, 53 μL) and $VO(acac)_2$ (4.8 mg, 0.018 mmol) at 0 °C and stirred under argon atmosphere. After 2 h, to the reaction was added NaOMe solution in MeOH (0.5 M, 1.9 mL, 0.95 mmol) and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched with brine and organic materials were extracted with EtOAc eight times. The combined extract was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with hexane/EtOAc (5:1–2:1) to furnish **19a** (20.5 mg, 92%) as a colorless oil. $[\alpha]_D^{21}$ –26.7 (*c* 1.20, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.12 (3H, d, *J* = 6.3 Hz), 1.16–1.20 (1H, m), 1.63–1.69 (1H, m), 1.78–1.87 (2H, m), 2.08–2.22 (2H, m), 3.36 (1H, d, *J* = 10.0 Hz), 3.41 (3H, s), 3.46 (1H, d, *J* = 10.0 Hz), 3.64 (1H, d, *J* = 12.0 Hz), 3.71 (1H, d, *J* = 12.0 Hz), 4.86 (1H, dd, *J* = 10.0, 1.8 Hz), 4.96 (1H, ddd, *J* = 17.1, 1.8, 0.8 Hz), 5.62 (1H, ddd, *J* = 17.1, 10.0, 8.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.5, 24.4 29.7, 39.4, 48.5, 59.5, 61.1, 75.4, 81.1, 82.3, 112.8, 143.9; IR ν_{max} 3432, 2952, 2896, 1637, 1456, 1375, 1338 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{12}H_{22}NaO_4$: 253.1416, found: 253.1395.

4.9. (1'*S*,5*R*,6*S*,9S)-6-Methoxymethyl-9-(1'-methylprop-2'-enyl)-6-[(2"-trimethylsilylethoxy)methoxy]-1,3-dioxabicyclo[4.4]nonan-2-one 19b

To a solution of **19a** (33.1 mg, 0.144 mmol) in CH_2Cl_2 (1.0 mL) was added pyridine (115 μL,

1.42 mmol) and triphosgene (24.7 mg, 0.0832 mmol) at 0 °C and stirred for 1 h under argon atmosphere. The reaction was quenched with saturated NH_4Cl aq. solution and organic materials were extracted with EtOAc four times. The combined extract was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with hexane/EtOAc (10:1–3:1) to furnish a carbonate (30.2 mg, 82%) as a colorless oil. $[\alpha]_D^{22}$ –55.6 (*c* 1.14, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.09 (3H, d, *J* = 6.6 Hz), 1.10–1.16 (1H, m), 1.47 (1H, ddd, *J* = 14.9, 11.5, 4.9 Hz), 1.72 (1H, ddd, *J* = 14.9, 10.3, 5.9 Hz), 1.99 (1H, dddd, *J* = 10.3, 10.3, 5.1, 4.9 Hz), 2.13–2.19 (1H, m), 2.67 (1H, m), 3.15–3.20 (1H, br–s), 3.36 (3H, s), 3.44 (1H, d, *J* = 10.2 Hz), 3.53 (1H, d, *J* =10.2 Hz), 4.43 (1H, d, *J* = 9.5 Hz), 4.45 (1H, d, *J* = 9.5 Hz), 4.95 (1H, dd, *J* = 10.1, 1.5 Hz), 5.01 (1H, ddd, *J* = 16.9, 1.5, 0.8 Hz), 5.65 (1H, ddd, *J* = 16.9, 10.1, 8.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.2, 23.6, 28.4, 39.5, 45.0, 59.3, 66.0, 74.8, 80.4, 92.3, 114.2, 142.2, 154.3; IR ν_{max} 3500, 2969, 2933, 1877, 1793, 1735, 1637, 1456, 1375, 1241 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{13}H_{20}NaO_5$: 279.1208, found: 279.1173.

To the solution of carbonate (391 mg, 1.53 mmol) in THF (4.0 mL) was added *N*,*N*-diisopropylethylamine (1.40 mL, 8.02 mmol), SEMCl (800 μL, 4.56 mmol) and TBAI (178 mg, 0.477 mmol) and stirred for 14 h at 80 °C under argon atmosphere. The reaction was quenched with saturated $NaHCO_3$ aq. solution and organic materials were extracted with EtOAc three times. The combined extract was washed with 1 M HCl aq. solution, 1 M NaOH aq. solution and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with hexane/EtOAc (30:1–3:1) to furnish **19b** (543 mg, 92%) as a colorless solid. Mp 85.3–86.0 °C (colorless fine needles from hexane). $[\alpha]_D^{22}$ –29 (*c* 0.75, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.02 (9H, s), 0.87–0.97 (2H, m), 1.08 (3H, d, *J* = 6.8 Hz),

1.19–1.27 (1H, m), 1.55–1.62 (1H, m), 1.89–2.05 (2H, m), 2.21 (1H, ddq, *J* = 8.6, 8.6, 6.8 Hz), 2.58 (1H, ddd, *J* = 8.6, 8.6, 8.6 Hz), 3.33 (3H, s), 3.46 (1H, d, *J* = 11.2 Hz), 3.64 (1H, ddd, *J* =10.2, 10.2, 6.4 Hz), 3.67 (1H, d, *J* = 11.2 Hz), 3.73 (1H, ddd, *J* = 10.2, 10.2, 6.4 Hz), 4.38 (1H, d, *J* = 9.3 Hz), 4.47 (1H, d, *J* = 9.3 Hz), 4.83 (1H, d, *J* = 7.8 Hz), 4.95–5.04 (3H, m), 5.65 (1H, ddd, *J* = 18.6, 10.3, 8.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ –1.43 (3C), 18.3, 19.4, 23.4, 26.5, 39.2, 46.2, 59.2, 65.8, 65.9, 72.6, 85.5, 90.6, 92.6, 114.4, 141.8, 154.5; IR ν_{max} 2953, 2925, 2893, 1789, 1248, 1181 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{19}H_{34}NaO_6Si$: 409.2022, found: 409..2024.

4.10. (1'*R*,5*R*,6*S*,9*S*)-6-Methoxymethyl-9-(1'-methyl-1'-oxo-ethyl)-6-[((2"-trimethylsilyl)ethoxy)methoxy]-1,3-dioxabicyclo[4.4]nonan-2-one 20

To a solution of **19b** (297 mg, 0.767 mmol) in THF (1.4 mL) and H_2O (0.7 mL) was added $K_2OsO_2(OH)_4$ (17.6 mg, 0.0478 mmol), 2,6-lutidine (225 μL, 1.91 mmol) and $NaIO_4$ (420 mg, 1.96 mmol) and stirred for 3 h at room temperature. The reaction was quenched with saturated $Na_2S_2O_3$ aq. solution and organic materials were extracted with EtOAc three times. The combined extract was washed with brine and dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with hexane/EtOAc (20:1–3:2) to give **20** (261 mg, 88%) as a colorless solid. Mp 81.8–83.1 °C (colorless fine needles from hexane). $[\alpha]_D^{24}$ +1.12 (*c* 1.08, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.03 (9H, s), 0.92–0.96 (2H, m), 1.23 (3H, d, *J* = 7.1 Hz), 1.24–1.27 (1H, m), 1.64 (1H, ddd, *J* = 14.4, 10.5, 5.6 Hz), 2.50 (1H, ddd, *J* = 14.4, 9.7, 4.6 Hz), 2.10–2.18 (1H, m), 2.40–1.48 (1H, m), 2.95 (1H, ddd, *J* = 10.0, 9.8, 9.8 Hz), 3.34 (3H, s), 3.52 (1H, d, *J* =11.2 Hz), 3.65 (1H, ddd, *J* = 9.8, 9.8, 7.1 Hz), 3.72–3.77 (2H, m), 4.24 (1H, d, *J* = 9.5 Hz), 4.52 (1H, d, *J* = 9.5 Hz), 4.84 (1H, d, *J* = 8.1 Hz), 4.99 (1H,

d, *J* = 8.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ –1.4 (3C), 12.6, 18.3, 23.1, 26.7, 42.1, 47.4, 59.3, 65.9, 66.6, 72.5, 84.9, 90.6, 92.3, 154.1, 202.1; IR ν_{max} 2951, 2892, 1800, 1724, 1457, 1393, 1248, 1179 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{18}H_{32}NaO_7Si$: 411.1815, found: 411..1797.

4.11. (1'*R*,3*E*,5*R*,6*S*,9S)-6-Methoxymethyl-9-(3'-iodo-1'-methylprop-2'-enyl)-6-[((2"-trimethylsilyl)ethoxy)methoxy]-1,3-dioxabicyclo[4.4]nonan-2-one 21

To a suspension of $Ph_3PCH_2I\cdot I$ (206 mg, 0.388 mmol) in THF (1.5 mL) was added sodium bis(trimethylsilyl)amide (NaHMDS, solution in THF, 1.0 M, 385 μL) and stirred at room temperature under argon atmosphere. After 1 h, the red solution was cooled to –78 °C and added a solution of hexamethylphosphoric triamide (HMPA, 24 μL, 0.138 mmol) in THF (400 μL) and a solution of **20** (75.3 mg, 0.194 mmol) in THF (800 μL) successively. The reaction mixture was warmed to –10 °C over 2 h and quenched with saturated NH_4Cl aq. solution and organic materials were extracted with EtOAc three times. The combined extract was washed with brine and dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with hexane/EtOAc (30:1–4:1) to furnish **21** (104 mg, quant.) as a colorless oil. $[\alpha]_D^{22}$ –19.2 (*c* 1.53, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.02 (9H, s), 0.86–0.96 (2H, m), 1.21–1.30 (1H, m), 1.61 (1H, ddd, *J* = 14.4, 10.7, 5.4 Hz), 1.87–1.93 (1H, m), 1.98 (1H, ddd, *J* = 14.4, 9.5, 5.1 Hz), 2.65–2.76 (2H, m), 3.34 (3H, s), 3.49 (1H, d, *J* = 11.2 Hz), 3.64 (1H, ddd, *J* = 9.6, 9.6, 6.1 Hz), 3.69–3.74 (2H, m), 4.42 (1H, d, *J* = 9.5 Hz), 4.49 (1H, d, *J* = 9.5 Hz), 4.84 (1H, d, *J* = 7.9 Hz), 4.97 (1H, d, *J* = 7.9 Hz), 5.96 (1H, dd, *J* = 9.1, 7.4 Hz), 6.21 (1H, d, *J* = 7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ –1.4 (3C), 18.2, 18.3, 23.3, 26.7, 40.2, 45.9, 59.3, 65.7, 66.1, 72.8, 81.7, 85.4, 90.6, 92.4, 144.1, 154.3; IR ν_{max} 2953, 2888, 1806, 1246, 1075 cm^{-1}; HRMS

(ESI) $[M+Na]^+$ calculated for $C_{19}H_{33}NaO_6Si$: 535.0989, found: 535.0964.

4.12. (1'*R*,2*S*, 2'*E*,5*S*)-2-Methoxymethyl-5-[1'-methyl-3'-(trimethylstannyl)prop-2-enyl]-2-[((2"-trimethylsilyl)ethoxy)methoxy]cyclopentanone 6

To a solution of **20** (64.0 mg, 0.125 mmol) in MeOH (1.5 mL) was added K_2CO_3 (97.4 mg, 0.705 mmol) and stirred for 13 h at room temperature. The mixture was diluted with H_2O and organic materials were extracted with EtOAc three times. The combined extract was washed with brine and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude diol. This was employed for the next reaction without further purification.

To the solution of the above-mentioned crude diol in THF (1.5 mL) were added pyridine (100 μL, 1.24 mmol) and $Pb(OAc)_4$ (95.4 mg, 0.215 mmol) at –20 °C and stirred for 1 h. The reaction was quenched with a mixture of saturated $NaHCO_3$ aq. solution and saturated $Na_2S_2O_3$ aq. solution and organic materials were extracted with EtOAc twice. The combined extract was washed with brine and dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with hexane/EtOAc (20:1–6:1) to give a ketone (51.8 mg, 91% over 2 steps) as a colorless oil. $[\alpha]_D^{22}$ –1.07 (*c* 1.19, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.01 (9H, s), 0.77–0.88 (2H, m), 1.10 (3H, d, *J* = 6.8 Hz), 1.64–1.72 (1H, m,), 2.02–2.18 (2H, m), 2.23 (1H, ddd, *J* = 13.6, 7.5, 4.1 Hz), 2.42 (1H, ddd, *J* = 9.3, 7.1, 7.1 Hz), 2.76–2.82 (1H, m), 3.34 (3H, s), 3.43–3.47 (2H, m), 3.50 (1H, ddd, *J* =11.0, 9.5, 6.1 Hz), 3.61 (1H, ddd, *J* = 11.0, 9.5, 5.8 Hz), 4.65 (1H, d, *J* = 7.6 Hz), 4.87 (1H, d, *J* = 7.6 Hz), 6.14 (1H, dd, *J* = 9.1, 7.3 Hz), 6.19 (1H, d, *J* = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ –1.4 (3C),, 16.5 ,18.0, 22.7, 27.7, 39.6, 50.9, 59.6, 65.7, 74.3, 81.5, 82.0, 90.1, 144.1, 215.9; IR ν_{max} 2952, 2891, 1743, 1456, 1249, 1111 cm^{-1};

HRMS (ESI) $[M+Na]^+$ calculated for $C_{17}H_{31}INaO_4Si$: 477.0934, found: 477.0921.

To $PdCl_2(PPh_3)_2$ (23.8 mg, 0.0339 mmol) was added a solution of the above-mentioned ketone (317 mg, 0.697 mmol) and hexamethylditin (230 μL, 1.11 mmol) in THF (7 mL) and stirred 39 h at room temperature under argon atmosphere. The reaction mixture was concentrated under reduced pressure and the residue was purified by 10w/w% K_2CO_3 on silica gel column chromatography with hexane/EtOAc (1:0–40:1) to give a crude alkenyl stannane **7** and the crude **7** was further purified by silica gel column chromatography with hexane/EtOAc (1:0–40:1) to furnish **7** (220 mg, 64%). $[\alpha]_D^{23}$ –24.8 (*c* 1.32, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.01 (9H, s), 0.17 (9H, t, *J* = 26.4 Hz), 0.79–0.90 (2H, m), 1.12 (3H, d, *J* = 6.3 Hz), 1.60–1.67 (1H, m), 2.04–2.21 (3H, m), 2.28–2.32 (1H, m), 3.32 (3H, s), 3.38–3.40 (2H, m), 3.49 (1H, ddd, *J* = 10.9, 9.5, 6.1 Hz), 3.64 (1H, ddd, *J* = 10.9, 9.5, 5.9 Hz), 4.65 (1H, d, *J* = 7.8 Hz), 4.88 (1H, d, *J* = 7.8 Hz), 5.76 (1H, d, *J* = 12.5 Hz), 6.27 (1H, dd, *J* = 12.5, 9.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ –8.4 (3C), –1.4 (3C), 18.0, 19.4, 22.5, 27.3, 41.0, 52.0, 59.5, 65.7, 73.8, 82.0, 90.1, 128.8, 151.3, 215.9; IR ν_{max} 2954, 2893, 1743, 1598, 1250 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{20}H_{40}NaO_4SiSn$: 515.1616, found: 516.1613.

4.13. 1-Hydroxy-14-isoprpyl-3β-methoxymethyl-7β,11β -dimethyl-3α-[((2-trimethylsilyl)ethoxy)methoxy]-1,2-secofusicocca-8,10(14)-dien-2-one 8

To PEPPSI-SIPr (8.8 mg, 0.013 mmol) was added a solution of **7** (124 mg, 0.25 mmol) and **6** (114 mg, 0.376 mmol) in DMSO (5 mL) and stirred for 42 h at 60 °C under argon atmosphere. The reaction was quenched with H_2O and organic materials were extracted with EtOAc three times. The combined extract was washed with brine and dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with

hexane/EtOAc (40:1–3:1) to furnish **8** (103 mg, 85%) as a colorless oil. $[\alpha]_D^{23}$ –53.2 (*c* 1.17, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.01 (9H, s), 0.79–0.89 (2H, m), 0.94 (3H, d, *J* = 6.9 Hz), 0.96 (3H, s), 0.99 (3H, d, *J* = 6.8 Hz), 1.05 (3H, d, *J* = 6.6 Hz), 1.50–1.58 (1H, m), 1.64–1.73 (1H, m), 1.80–1.84 (1H, m), 1.97 (1H, ddd, *J* = 12.7, 8.8, 6.4 Hz), 2.02–2.09 (1H, m), 2.10–2.22 (2H, m), 2.26–2.34 (2H, m), 2.39 (1H, ddd, *J* = 10.8, 9.3, 5.4 Hz), 2.60–2.68 (2H, m), 3.28–3.33 (4H, m), 3.37 (1H, dd, *J* = 10.7, 4.6 Hz), 3.40–3.43 (2H, m), 3.49 (1H, ddd, *J* = 11.0, 9.8, 6.3 Hz), 3.62 (1H, ddd, *J* = 11.0, 9.5, 5.8 Hz), 4.65 (1H, d, *J* = 7.6 Hz), 4.87 (1H, d, *J* = 7.6 Hz), 5.58 (1H, ddd, *J* = 11.7, 2.5, 2.2 Hz), 5.64 (1H, dd, *J* = 11.7, 10.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ –1.5 (3C), 17.9, 18.0, 20.9, 21.0, 21.8, 22.1, 27.5, 27.8, 28.0, 32.7, 33.2, 52.6, 53.4, 59.6, 65.7, 69.3, 73.8, 82.3, 90.2, 122.5, 134.1, 135.8, 146.3, 216.6; IR ν_{max} 3460, 2953, 2893, 1740, 1455, 1249 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{27}H_{48}NaO_5Si$: 503.3169, found: 503.3170.

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