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SYNTHETIC STUDIES OF YESSOTOXIN: STEREOSELECTIVE ANNULATION OF THE CD AND JK RING FRAGMENTS BY USING Pd(II)-CATALYZED CYCLIZATION

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Abstract – Yessotoxin is the polycyclic ether implicated in diarrheic shellfish poisoning. This toxin has A-K ring system involving 6-, 7-, 8-membered ether rings. We have been studying high stereoselective Pd(II)-catalyzed cyclization. Herein we describe the CD and JK ring fragments of yessotoxin by our annulation based on Pd(II)-catalyzed cyclization. The efforts to understand these high stereoselectivities are also disclosed. This annulation method could be applicable to other polyethers and related natural products.

Yessotoxin is the polycyclic ether implicated in diarrheic shellfish poisoning (Figure 1). Its unique structure involves 6-, 7-, 8-membered ether rings and the *trans* fused junctures.[1,2] Four groups reported the synthesis of A-F ring system (Suzuki and Nakata (2002), Mori and Noyori (2003), Kadota and Yamamoto (2003), Rainier (2016)).[3] In 2008, Oishi's group reported the convergent synthesis of A-J ring system.[3m] Many synthetic efforts attracted our interest of synthesis towards yessotoxin. We have been studying the novel methods to synthetic studies of natural products by using Pd(II)-catalyzed cyclization.[4] One of our trials to develop the new annulation methods was the Pd(II)-catalyzed cyclization methods to ether.[5] Herein we describe the way to CD and JK ring fragments of yessotoxin by Pd(II)-catalyzed cyclization.[6]

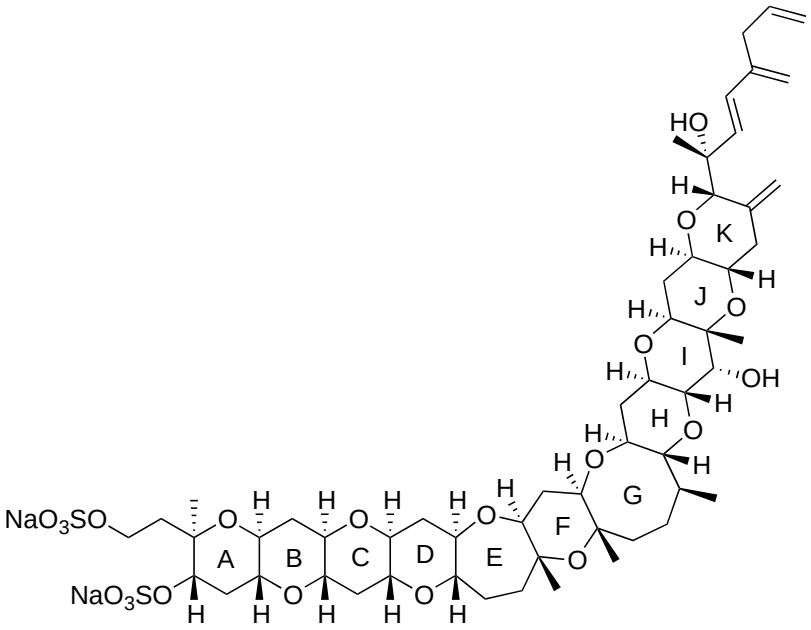


Figure 1. Yessotoxin-natural polyether

The strategy of our method is almost iterative method (Figure 2). In general, iterative method is longer than convergent method, but it is just simple, automation-fitted and compatible method. The beginning of this annulation is homo-allylic alcohol (**1**). The protection of hydroxyl moiety and transformation of alkene to formyl moiety afford the aldehyde (**2**). The allylic alcohol part is introduced by coupling the aldehyde (**2**) and nucleophilic carbon unit. The Pd(II)-catalyzed cyclization of resulting allyl alcohol (**3**) gives homo-allylic alcohol (**4**) as same as starting material (**1**). Our iterative method has been executed since.[5] Thus we see the method could be applicable to other polyethers and related natural products.

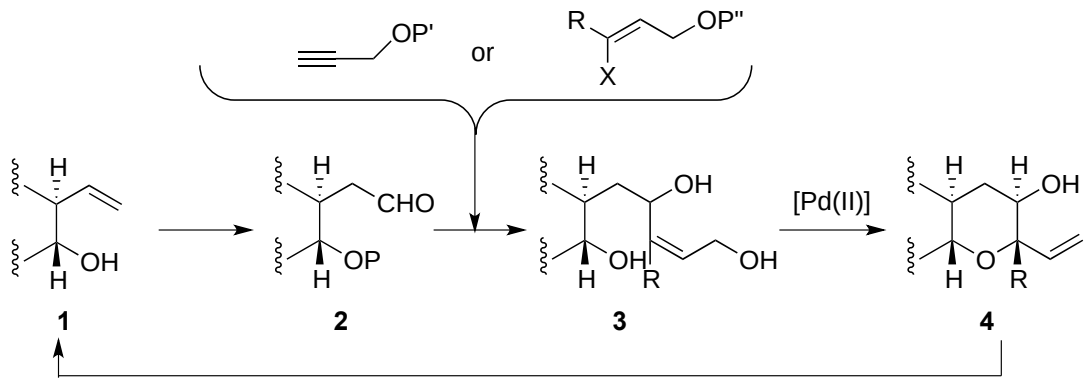
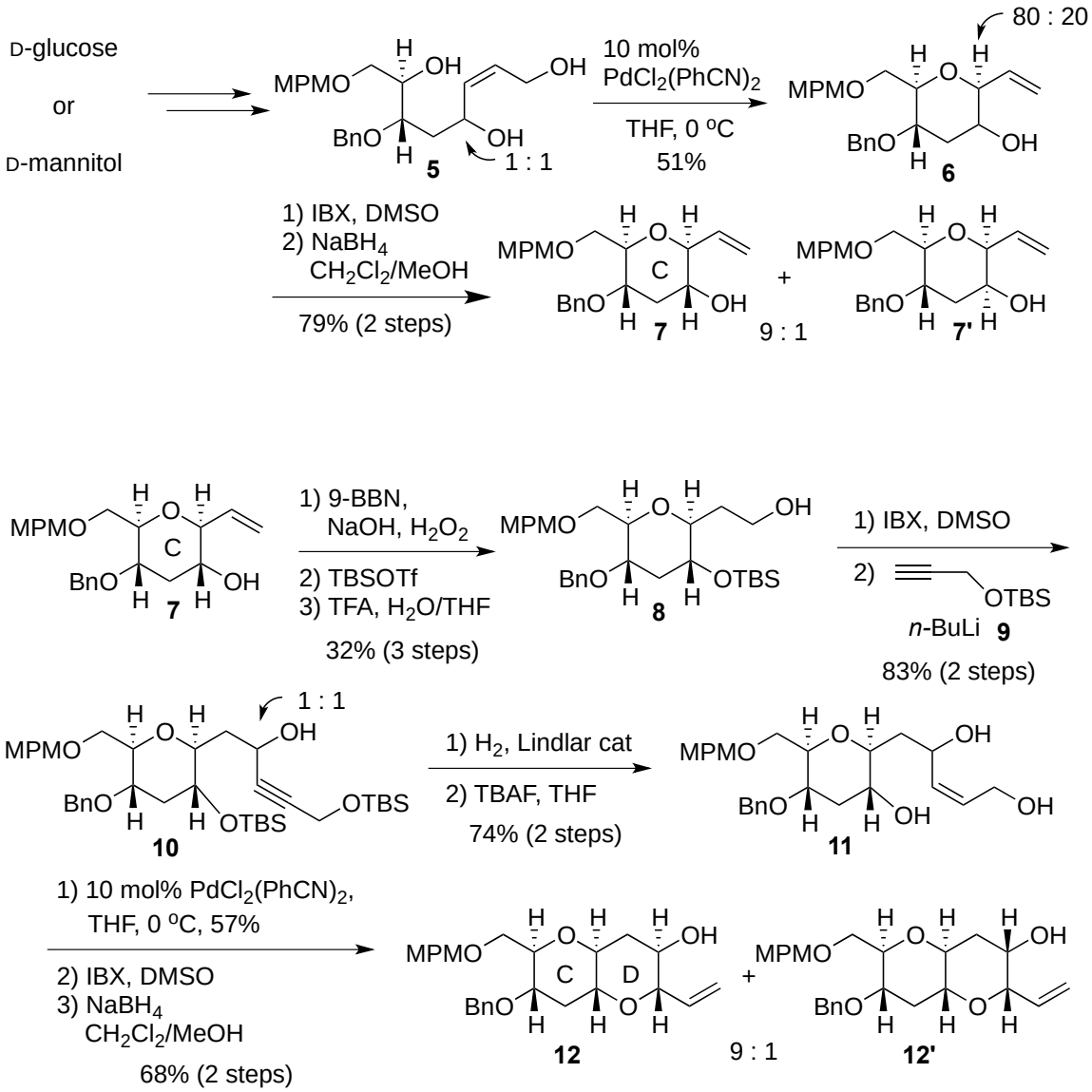


Figure 2. Our annulation strategy

At first, we prepared the triol (**5**) by our methods.[7] Our methods involved two approaches. One was the approach by using D-mannitol as starting material. Another was the approach from D-glucose. The triol

(**5**) was treated with $PdCl_2(PhCN)_2$ in THF at 0 ºC to give the cyclic adduct (**6**) in 51% yield as 80 : 20 ratio (Scheme 1). After oxidation and reduction, the C ring (**7**) was separated in 79% yield. The hydroboration of the C ring (**7**), protection and selective deprotection gave the alcohol (**8**), followed by oxidation and the coupling with propargylic derivative (**9**) to afford the alcohol (**10**) (dr 1 : 1). After Lindlar hydrogenation, the resulting alcohol was treated with TBAF to give the triol (**11**) in 74% yield from the coupled adduct (**10**). The triol (**11**) was treated with $PdCl_2(PhCN)_2$ in THF at 0 ºC in 57% yield,[8] followed with oxidation and reduction to give the CD ring fragment (**12**) and (**12'**) in 68% yield (dr 9 : 1). The structure and stereochemistry of this CD ring fragment (**12**) was determined by X-ray crystallography, shown in Figure 3.[9]



Scheme 1. Synthesis of CD ring fragment (**12**)

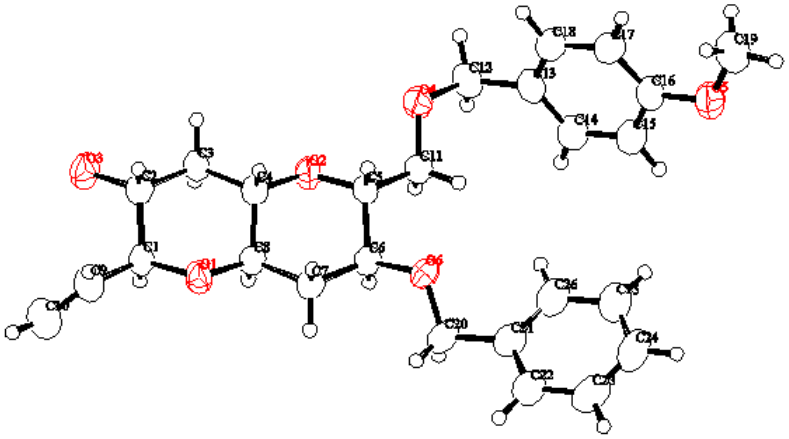
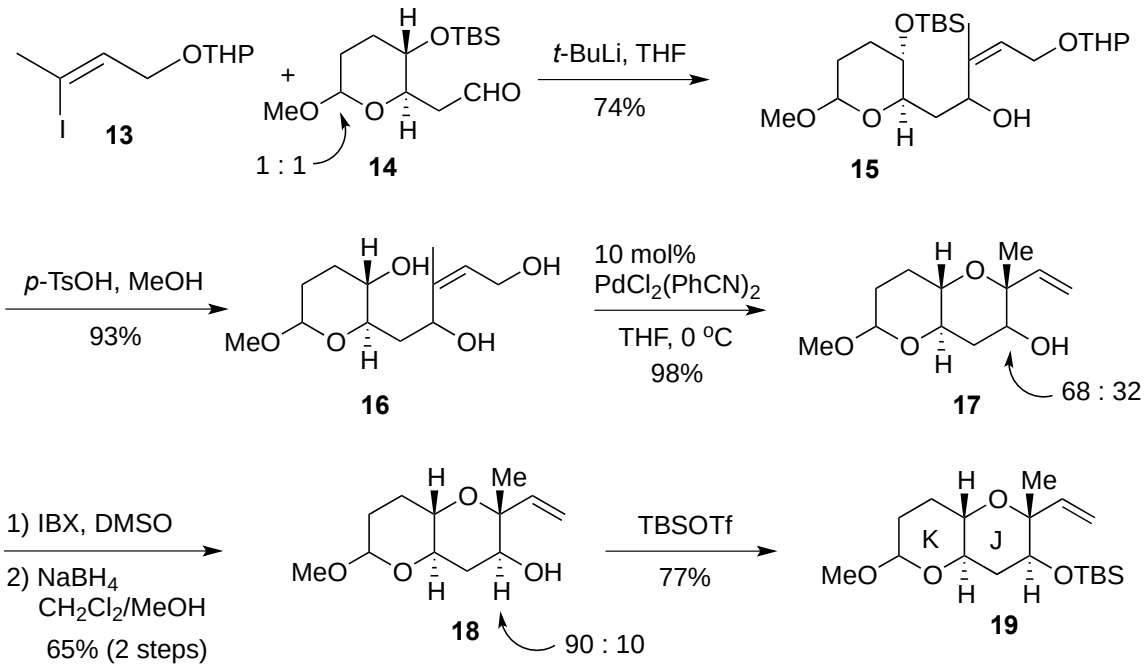


Figure 3. Crystal structure of CD ring fragment (**12**)

Next, we examined the synthesis of the JK ring fragment (Scheme 2).[6] The aldehyde (**14**) was prepared from tri-*O*-acetyl glucal by 9 steps.[7] According to reported method, we intended the preparation of the *Z*-allyl alcohol (**13**).[10] The vinyl iodide (**13**) and the aldehyde (**14**) were coupled, after halogen-lithium exchange, by the addition reaction, followed with the acid treatment to afford the triol (**16**) in 69% yield. The triol (**16**) was treated with $PdCl_2(PhCN)_2$ in THF at 0 ºC to give the bicyclic adduct (**17**).[11] The oxidation of this compound (**17**) and reduction gave the JK ring fragment (**18**) in 65% yield. The stereochemistry of the JK ring fragment (**18**) was determined by analysis of ^{1}H NMR of **19** in relative of the reported data after the protection.[12]



Scheme 2. Synthesis of JK ring fragment (**18**)

In these schemes, Pd(II)-catalyzed cyclizations seem to be highly stereoselective.[5,6,13] First cyclization of triol (**5**) was occurred through cyclic transition states with just only steric control (Figure 4). Second cyclization of conformational restricted triol (**11**) was proceeded in similar manner on the chair-chair conformation. The last cyclization of trisubstituted allylic alcohol (**16**) was stereoselective as we expected, because of also conformational restricted substance. The favored transition state should be influenced by steric control.

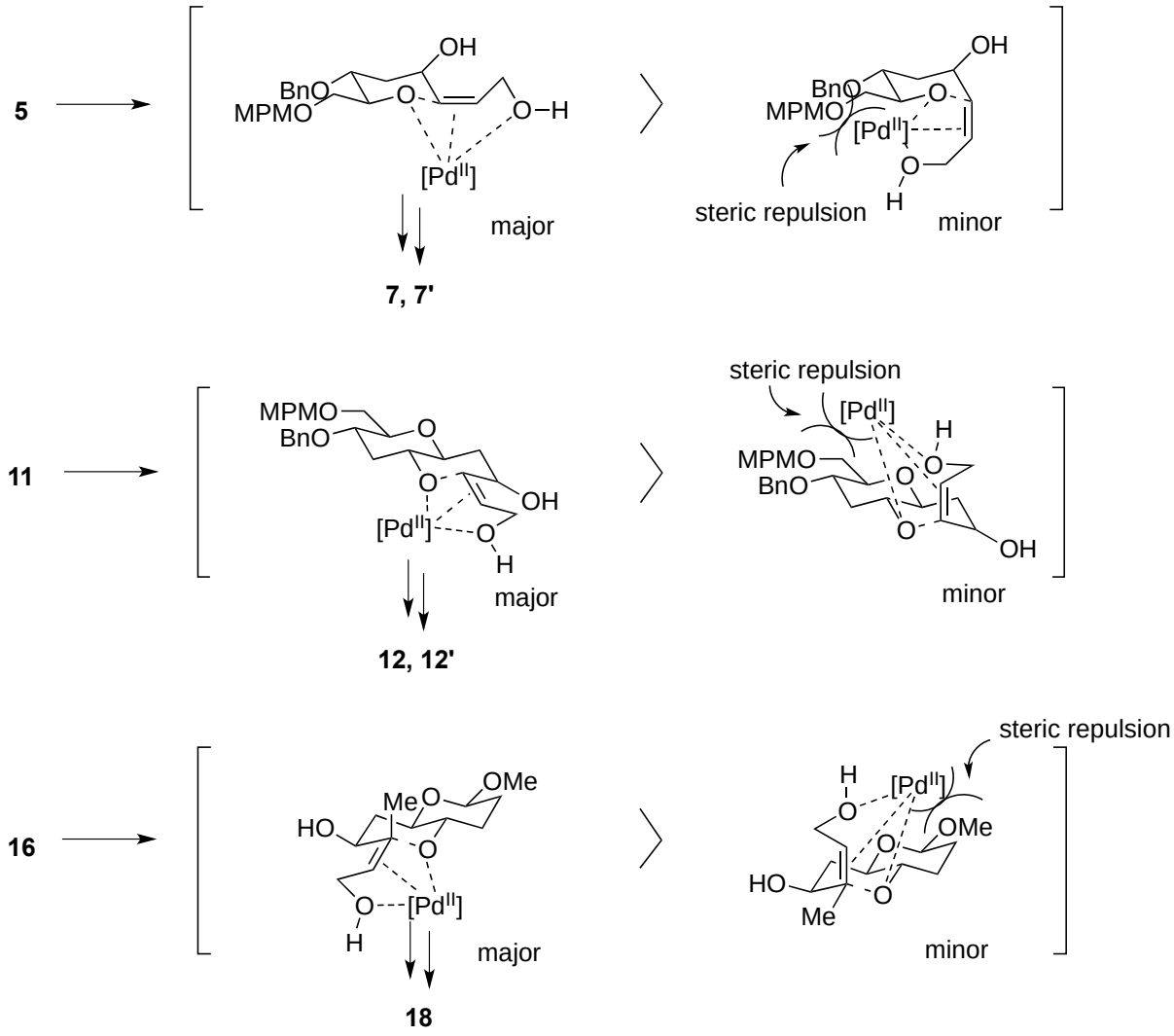


Figure 4. Proposed transition states of Pd(II)-catalyzed cyclization

In summary, we attained the synthesis of the CD and JK ring fragments of yessotoxin by Pd(II)-catalyzed cyclization. We are going on the further synthesis of yessotoxin. We believe these annulation method could be applicable to other polyethers and related natural products.

EXPERIMENTAL

General

^{1}H NMR spectra and ^{13}C NMR spectra were measured with JEOL JNM-ECX 300/TRH (300 MHz/75 MHz) and JEOL JNM-ECP 600 (600 MHz/150 MHz) spectrophotometers. Chemical shifts (^{1}H, ^{13}C) were relative to tetramethylsilane or chloroform (7.26 ppm, 77.0 ppm) as an internal standard. Infrared spectra (IR) were recorded on JASCO Model FT/IR-7300 spectrophotometer. Mass spectra (MS-EI) were obtained on JEOL JMS-700 spectrometer. Analytical thin layer chromatography (TLC) was performed by using Merck precoated TLC plate 60F254 (silica gel) with indicator. All solvents were dried over drying agents and distilled.

5-Benzyloxy-6-(4-methoxybenzyloxymethyl)-2-vinyltetrahydropyran-3-ol (6)

To a stirred solution of the triol (**5**) (1.82 g, 4.52 mmol) in THF (45 mL) was added 10 mol% bis(benzonitrile)palladium dichloride (0.17 g, 0.45 mmol) at 0 ^{o}C under an argon atmosphere. After being stirred for 1 h, the reaction mixture was filtered through silica gel and the filtrate was concentrated *in vacuo*. This crude product was purified by column chromatography on silica gel using AcOEt / hexane mixture as eluent to afford the alcohol (**6**) (0.88 g, 51%, 80 : 20) as a colorless oil.

5-Benzyloxy-6-(4-methoxybenzyloxymethyl)-2-vinyltetrahydropyran-3-ol (7)

To a stirred solution of the alcohol (**6**) (0.42 g, 1.10 mmol) in DMSO (11 mL) was added *o*-iodoxybenzoic acid (IBX) (0.92 g, 3.30 mmol) and the mixture was stirred at room temperature for 2 h under an argon atmosphere. The reaction mixture was quenched by an addition of saturated aqueous $NaHCO_3$ and $Na_2S_2O_3$ solution. The aqueous phase was extracted with Et_2O (3 times). The organic phases were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was used in the next step subsequently without further purification. To a stirred solution of the crude ketone in CH_2Cl_2 (11 mL) and MeOH (11 mL) at -78 ^{o}C was added $NaBH_4$ (0.10 g, 2.75 mmol) and the reaction mixture was stirred at -78 ^{o}C for 30 min. The reaction mixture was concentrated *in vacuo* and diluted with AcOEt. The extracts were washed with HCl aq., $NaHCO_3$ aq. and brine, dried over $MgSO_4$. Concentration and chromatography gave the alcohol (**7**) (0.33 g, 79% in 2 steps) and (**7'**) as colorless oil ((**7**) : (**7'**) = 9 : 1).

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.32-7.20 (m, 7H), 6.87-6.84 (m, 2H), 5.87 (ddd, *J* = 7.4, 10.5, 17.6 Hz, 1H), 5.42 (ddd, *J* = 0.8, 1.5, 17.6 Hz, 1H), 5.34 (ddd, *J* = 0.8, 1.5, 10.5 Hz, 1H), 4.58 (d, *J* = 11.8 Hz, 1H), 4.57 (d, *J* = 11.8 Hz, 1H), 4.47 (d, *J* = 11.6 Hz, 1H), 4.41 (d, *J* = 11.6 Hz, 1H), 3.78 (s, 3H), 3.72 (dd, *J* = 2.2, 10.7 Hz, 1H), 3.67 (dd, *J* = 4.6, 10.7 Hz, 1H), 3.56 (ddd, *J* = 4.4, 9.4, 11.4 Hz, 1H), 3.55 (dd, *J* = 7.4, 9.0 Hz, 1H), 3.42 (ddd, *J* = 2.2, 4.6, 9.4 Hz, 1H), 3.40-3.35 (m, 1H), 2.61 (ddd, *J* = 4.4, 4.4, 11.4 Hz, 1H), 1.49 (ddd, *J* = 11.4, 11.4, 11.4 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 159.2, 137.4, 131.2, 130.0, 129.3, 128.4, 128.4, 127.8, 127.7, 118.2, 113.8, 113.7, 82.3, 79.1, 74.3, 73.2, 70.7, 69.7, 55.2, 40.8. IR (neat)

cm^{-1}; 3741-3135. EIMS *m/z* 384 (M^+). HREIMS *m/z* calcd. for $C_{23}H_{28}O_5$ (M^+) 384.1937, found 384.1919.

5-Benzyloxy-2-(2-hydroxyethyl)-6-(4-methoxybenzyloxymethyl)tetrahydropyran-3-ol

To a stirred solution of the alcohol (**7**) (0.28 g, 0.73 mmol) in THF was added 9-BBN (4.4 mL, 2.2 mmol, 0.50 M THF solution) at 0 °C under an argon atmosphere. The mixture was warmed to room temperature. After 12 h, the reaction mixture was cooled to 0 °C and added 3 N aqueous NaOH (3.7 mL, 11.0 mmol) solution and 30% aqueous solution of H_2O_2 (2.4 mL, 19.0 mmol). The reaction mixture was stirred for 12 h at room temperature. The reaction mixture was quenched by an addition of aqueous $Na_2S_2O_3$ solution and the aqueous phase was extracted with AcOEt (3 times). The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give a crude diol. The crude diol was used in the next step subsequently without further purification.

3-Benzyloxy-5-(*tert*-butyldimethylsilyloxy)-6-[2-(*tert*-butyldimethylsilyloxy)ethyl]-2-(4-methoxybenzyloxymethyl)tetrahydropyran

To a solution of crude diol (0.73 mmol) and 2,6-lutidine (0.43 mL, 3.65 mmol) in CH_2Cl_2 (7.3 mL) was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.5 mL, 2.2 mmol) at 0 °C under an argon atmosphere. The reaction mixture was warmed to room temperature. After 1 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and the resulting mixture was extracted with CH_2Cl_2 (3 times). The organic phase was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel using AcOEt / hexane mixture as an eluent to afford the ether (0.35 g, 76% in 2 steps) as a colorless oil.

2-[5-Benzyloxy-3-(*tert*-butyldimethylsilyloxy)-6-(4-methoxybenzyloxymethyl)tetrahydropyran-2-yl]-ethanol (8)

A catalytic amount of trifluoroacetic acid was added dropwise to a solution of the ether (0.35 g, 0.56 mmol) in THF (5.6 mL) and H_2O (5.6 mL) at 0 °C. After 90 min, saturated aqueous $NaHCO_3$ was carefully added and followed by an addition of AcOEt. The organic layer was separated and washed with H_2O and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel using AcOEt / hexane mixture as an eluent to afford the alcohol (**8**) (0.12 g, 42%) as colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.33-7.21 (m, 7H), 6.87-6.84 (m, 2H), 4.55 (d, *J* = 11.7 Hz, 1H), 4.50 (d, *J* = 11.7 Hz, 1H), 4.43 (d, *J* = 11.7 Hz, 1H), 4.41 (d, *J* = 11.7 Hz, 1H), 3.81 (q, *J* = 5.1 Hz, 2H), 3.78 (s, 3H), 3.69 (dd, *J* = 1.1, 10.5 Hz, 1H), 3.53 (dd, *J* = 5.1, 10.5 Hz, 1H), 3.42-3.40 (m, 2H), 3.37 (ddd, *J* = 4.3, 10.0, 10.0 Hz, 1H), 3.31 (ddd, *J* = 2.6, 9.2, 9.2 Hz, 1H), 2.36 (ddd, *J* = 4.3, 4.3, 12.1 Hz, 1H), 2.03-1.99 (m, 1H), 1.70-1.55 (m, 1H), 1.50-1.40 (m, 1H), 0.86 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 159.2, 138.1, 130.2, 130.1 129.5, 129.4, 128.4, 127.7, 113.7, 83.4, 79.7, 73.1, 72.5, 71.2, 69.9, 69.2, 62.0, 55.3, 39.3, 33.6, 25.7, 17.9, -4.70. IR (neat) cm^{-1}; 3731-3147, 776. EIMS *m/z* 425 (M^+-Bn).

HREIMS *m/z* calcd. for $C_{22}H_{37}O_6Si$ (M^+-Bn) 425.2359, found 425.2362.

[5-Benzyloxy-3-(*tert*-butyldimethylsilyloxy)-6-(4-methoxybenzyloxymethyl)tetrahydropyran-2-yl]-acetaldehyde

To a stirred solution of the alcohol (**8**) (0.29 g, 0.56 mmol) in DMSO (8 mL) was added *o*-iodoxybenzoic acid (IBX) (0.47 g, 1.68 mmol) and the reaction mixture was stirred at room temperature for 4 h under a nitrogen atmosphere. The reaction mixture was quenched by an addition of saturated aqueous $NaHCO_3$ and $Na_2S_2O_3$ solution. The aqueous phase was extracted with Et_2O (3 times). The organic phase was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give the aldehyde. The crude aldehyde was used in the next step subsequently without further purification.

1-[5-Benzyloxy-3-(*tert*-butyldimethylsilyloxy)-6-(4-methoxybenzyloxymethyl)tetrahydropyran-2-yl]-5-(*tert*-butyldimethylsilyloxy)pent-3-yn-2-ol (10)

To a stirred suspension of lithium *tert*-butyldimethylsilylacetylene (**9**) (prepared from *tert*-butyldimethylsilylacetylene (0.52 g, 3.08 mmol) and *n*-BuLi (1.8 mL, 2.91 mmol, 1.6 M hexane solution) in THF (5 mL)) was added the solution of the aldehyde (0.56 mmol) in THF (5 mL) at -78 °C and the resulting mixture was stirred at -78 °C for an additional 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and filtered through celite. The filtrate was extracted with AcOEt (3 times). The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. This crude product was purified by column chromatography using AcOEt / hexane mixture as eluent to afford the alcohol (**10**) (0.32 g, 83% in 2 steps, 1 : 1) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.33-7.23 (m, 7H), 6.86-6.85 (m, 2H), 4.71-4.69 (m, 1H), 4.66-4.33 (m, 4H), 3.79 (s, 1.5H), 3.78 (s, 1.5H), 3.68-3.33 (m, 8H), 2.41-2.34 (m, 1H), 2.21-2.17 (m, 1H), 1.86-1.76 (m, 1H), 1.49-1.41 (m, 1H), 0.90 (s, 9H), 0.87 (s, 9H), 0.11 (s, 6H), 0.04 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 159.18, 159.16, 138.05, 138.03, 130.08, 129.49, 129.44, 129.38, 128.36, 128.34, 127.77, 127.74, 127.72, 127.68, 127.63, 113.79, 113.76, 113.71, 85.27, 83.27, 82.81, 82.22, 80.19, 79.74, 73.11, 73.07, 72.91, 72.45, 72.26, 71.38, 71.23, 70.92, 69.99, 68.99, 68.87, 62.32, 61.90, 60.91, 55.21, 55.19, 51.79, 51.72, 39.48, 39.23, 25.81, 25.74, 18.26, 17.96, -5.04, -5.13. IR (neat) cm^{-1}; 3697-3152, 777. EIMS *m/z* 666 (M^+-H_2O). HREIMS *m/z* calcd. for $C_{34}H_{49}O_6Si_2$ (M^+-H_2O-Bu) 609.3068, found 609.3095.

1-[5-Benzyloxy-3-(*tert*-butyldimethylsilyloxy)-6-(4-methoxybenzyloxymethyl)tetrahydropyran-2-yl]-5-(*tert*-butyldimethylsilyloxy)pent-3-en-2-ol

A suspension containing Lindlar catalyst ($Pd/CaCO_3$, poisoned by lead) (5.0+7.0 mg, 20 wt%) and the alcohol (**10**) (25.0+35.4 mg, 0.088 mmol) in AcOEt (1.5+2.6 mL) was placed at room temperature under H_2 atmosphere. After being stirred for 120 min, the reaction mixture was filtered through silica gel and the filtrate was concentrated *in vacuo* to give the silyl ether. The silyl ether was used in the next step subsequently without further purification.

5-[5-Benzyloxy-3-hydroxy-6-(4-methoxybenzyloxymethly)tetrahydropyran-2-yl]pent-2-ene-1,4-diol (11)

To a solution of the silyl ether (0.088 mmol) in THF (1.0+1.6 mL) was added tetrabutylammonium fluoride (0.144+0.21 mL, 0.354 mmol) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred for 2 h. The reaction mixture was quenched with H_2O and the mixture was extracted with AcOEt (3 times). The extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography using AcOEt / hexane mixture as eluent to afford the triol (**11**) (0.03 g, 74% in 2 steps) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.35-7.22 (m, 7H), 6.90-6.85 (m, 2H), 5.76-5.69 (m, 1H), 5.66-5.54 (m, 1H), 4.80-4.71 (m, 1H), 4.67-4.38 (m, 4H), 4.26-4.05 (m, 2H), 3.79 (s, 1.5H), 3.78 (s, 1.5H), 3.59-3.28 (m, 6H), 2.59-2.54 (m, 1H), 2.29-2.17 (m, 1H), 2.03-1.93 (m, 1H), 1.50-1.39 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 159.30, 159.25, 130.89, 129.87, 129.59, 129.54, 129.47, 129.40, 128.81, 128.54, 128.41, 127.96, 127.83, 127.81, 127.77, 113.94, 113.91, 113.84, 113.81, 86.37, 86.07, 79.89, 79.85, 73.10, 72.45, 72.42, 71.03, 69.24, 69.10, 69.08, 69.02, 68.97, 68.18, 65.61, 60.30, 58.54, 55.27, 50.89, 39.79, 38.90, 38.61, 38.34, 23.75, 10.97. IR (neat) cm^{-1}; 3636-3100. EIMS *m/z* 440 (M^+-H_2O).

7-Benzyloxy-6-(4-methoxybenzyloxymethyl)-2-vinyloctahydropyrano[3,2,*b*]pyran-3-ol

To a stirred solution of the triol (**11**) (1.4 g, 3.05 mmol) in THF (40 mL) was added 10 mol% bis(benzonitrile)palladium dichloride (115 mg, 0.03 mmol) at 0 °C under an argon atmosphere. After being stirred for 1 h, the reaction mixture was filtered through silica gel and the filtrate was concentrated *in vacuo*. The crude product was purified by column chromatography using AcOEt / hexane mixture as eluent to afford the alcohol (0.77 g, 57%) as colorless oil.

7-Benzyloxy-6-(4-methoxybenzyloxymethyl)-2-vinyloctahydropyrano[3,2,*b*]pyran-3-ol (12)

To a stirred solution of the alcohol (770 mg, 1.75 mmol) in DMSO (20 mL) was added *o*-iodoxybenzoic acid (IBX) (1.47 g, 5.25 mmol) and the mixture was stirred at room temperature for 1 h under an argon atmosphere. The reaction mixture was quenched by an addition of saturated aqueous $NaHCO_3$ and $Na_2S_2O_3$ solution. The aqueous phase was extracted with Et_2O. The organic phase was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give the ketone. The crude ketone was used in the next step subsequently without further purification. To a stirred solution of the crude ketone in CH_2Cl_2 (20 mL) and MeOH (20 mL) at -78 °C was added $NaBH_4$ (165 mg, 4.38 mmol) and the reaction mixture was stirred at -78 °C for 1 h. The reaction mixture was poured into water and the mixture was extracted with AcOEt (3 times). The extract was washed with water and brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel using AcOEt / hexane mixture as eluent to afford the alcohol (**12**) (520 mg, 68% in 2 steps) and (**12'**) as colorless oil (dr 9 : 1).

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.31-7.19 (m, 7H), 6.88-6.85 (m, 2H), 5.84 (ddd, *J* = 7.4, 10.4, 17.3 Hz, 1H), 5.43 (ddd, *J* = 1.1, 1.5, 17.3 Hz, 1H), 5.36 (ddd, *J* = 0.7, 1.5, 10.4 Hz, 1H), 4.56 (d, *J* = 11.7 Hz, 1H), 4.55 (d, *J* = 11.4 Hz, 1H), 4.48 (d, *J* = 11.7 Hz, 1H), 4.37 (d, *J* = 11.4 Hz, 1H), 3.78 (s, 3H), 3.73 (dd, *J* = 1.8, 10.6 Hz, 1H), 3.63 (dd, *J* = 5.1, 10.6 Hz, 1H), 3.55 (ddd, *J* = 4.4, 9.1, 11.3 Hz, 1H), 3.55 (dd, *J* = 7.4, 9.1 Hz, 1H), 3.43 (ddd, *J* = 1.8, 5.1, 9.4 Hz, 1H), 3.44-3.40 (m, 1H), 3.11 (ddd, *J* = 4.4, 9.0, 11.2 Hz, 1H), 3.07 (ddd, *J* = 4.4, 9.0, 11.2 Hz, 1H), 2.57 (ddd, *J* = 4.4, 4.4, 11.2 Hz, 1H), 2.49 (ddd, *J* = 4.4, 4.4, 11.2 Hz, 1H), 1.47 (ddd, *J* = 11.2, 11.2, 11.2 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 159.2, 137.9, 135.4, 130.9 129.6, 128.8, 128.4, 127.8, 127.7, 119.9, 113.7, 83.7, 80.4, 76.2, 75.6, 73.1, 72.4, 71.1, 68.7, 68.2, 55.3, 38.7, 37.4. IR (neat) cm^{-1}; 3787-3128. EIMS *m/z* 440 (M^+). HREIMS *m/z* calcd. for $C_{26}H_{32}O_6$ (M^+) 440.2199, found 440.2172.

(*Z*)-1-[(2*R*,3*S*)-3-(*tert*-Butyldimethylsilyloxy)-6-methoxy-3,4,5,6-tetrahydro-2*H*-pyran-2-yl]-3-methyl-5-(2-tetrahydropyranyloxy)-3-penten-2-ol (15)

To a solution of (*Z*)-3-iodo-1-(2-tetrahydropyranyloxy)-2-butene (**13**)[10] (116.3 mg, 0.412 mmol) in THF (4.5 mL) was added *t*-BuLi (0.55 mL, 0.97 mmol, 1.77 M *n*-pentane solution) at -78 °C and the mixture was stirred at -78 °C for 10 min. Then, a solution of [(2*R*,3*S*)-3-(*tert*-butyldimethylsilyloxy)-6-methoxy-3,4,5,6-tetrahydro-2*H*-pyran-2-yl]acetaldehyde (**14**) (81.2 mg, 0.281 mmol) in THF (2.5 mL) was added and the reaction mixture was allowed to room temperature. After 5 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with Et_2O. The organic phase was washed with brine and then dried over $MgSO_4$. Concentration and column chromatography (*n*-hexane : AcOEt = 9 : 1 to 3 : 2) afforded the alcohol (**15**) (92.4 mg, 74%) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.50-5.37 (m, 1H), 4.85-4.68 (m, 1H), 4.67-4.60 (m, 1H), 3.90-3.79 (m, 2H), 3.52-3.45 (m, 1H), 3.38-3.31 (m, 4H), 1.85-1.45 (m, 12H), 0.88 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 143.4, 142.4, 141.1, 123.3, 122.9, 122.9, 122.3, 97.3, 97.1, 96.9, 96.3, 74.3, 74.0, 71.1, 71.0, 69.9, 69.4, 63.0, 63.0, 62.1, 62.0, 62.0, 61.8, 61.6, 54.7, 54.7, 54.3, 54.3, 37.2, 37.0, 36.9, 30.6, 30.5, 30.3, 29.3, 29.0, 28.2, 27.7, 25.7, 25.7, 25.4, 25.3, 19.4, 19.3, 19.0, 18.4, 18.3, 18.2, 17.9, 17.8, -4.0, -4.1, -4.1, -4.7, -4.8, -4.8. IR (neat) cm^{-1}: 3449, 2952, 2857, 1463, 1441, 1375, 1257, 1129, 1099, 1056, 1023, 838, 776.

(*Z*)-5-[(2*R*,3*S*)-3-Hydroxy-6-methoxy-3,4,5,6-tetrahydro-2*H*-pyran-2-yl]-3-methyl-2-pentene-1,4-diol (16)

To a solution of the alcohol (**15**) (41.4 mg, 0.093 mmol) in MeOH (1.4 mL) was added *p*-TsOH·H_2O (1.8 mg, 0.009 mmol) at 0 °C. After stirring for 24 h at room temperature, the reaction mixture was quenched with Et_3N and concentration *in vacuo*. The residue was purified by column chromatography (*n*-hexane : AcOEt = 1 : 3 to AcOEt to AcOEt : MeOH = 4 : 1) to afford the triol (**16**) (21.4 mg, 93%) as a slightly

yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.55-5.49 (m, 1H), 4.86-4.66 (m, 1H), 4.24-4.06 (m, 2H), 3.50-3.30 (m, 6H), 2.14-1.66 (m, 8H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 142.7, 141.6, 125.8, 125.7, 125.5, 124.9, 124.8, 123.0, 103.0, 102.9, 97.5, 97.4, 97.2, 81.1, 79.2, 78.1, 74.0, 73.7, 73.0, 71.7, 70.0, 69.8, 69.7, 69.4, 69.2, 67.8, 67.6, 66.8, 66.7, 57.7, 57.6, 57.5, 56.5, 56.3, 54.8, 54.7, 54.6, 38.9, 38.7, 37.2, 37.1, 37.1, 32.3, 32.1, 30.8, 30.6, 30.4, 30.3, 29.2, 29.1, 27.2, 27.1, 25.5, 25.3, 18.8, 18.5, 18.3. IR (neat) cm^{-1}: 3369, 2931, 1440, 1377, 1207, 1128, 1055, 946.

(2*R*,4a*R*,8a*S*)-3-Hydroxy-2-methyl-6-methoxy-2-vinyl-1,5-dioxadecalin (17)

10 mol% $PdCl_2(PhCN)_2$ (6.2 mg, 0.016 mmol) was added to a solution of the triol (**16**) (38.5 mg, 0.156 mmol) in THF (1.6 mL) at 0 ºC. After stirring at room temperature for 19 h, the reaction mixture was diluted with *n*-hexane and purified by column chromatography (*n*-hexane : AcOEt = 3 : 2) to afford the alcohol (**17**) (35.0 mg, 98%, dr 68 : 32) as colorless oil.

(2*R*,3*S*,4a*R*,8a*S*)-3-Hydroxy-2-methyl-6-methoxy-2-vinyl-1,5-dioxadecalin (18)

To a solution of the alcohol (**17**) (5.4 mg, 0.024 mmol) in DMSO (0.25 mL) was added IBX (22.3 mg, 0.129 mmol) at room temperature. After stirring for 1.5 d, the reaction mixture was quenched with aqueous $Na_2S_2O_3$ and diluted with Et_2O. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentration *in vacuo* to give the ketone. The crude ketone was used in subsequent reaction without further purification. $NaBH_4$ (2.2 mg, 0.058 mmol) was added to a solution of the crude ketone in a mixture of CH_2Cl_2 (0.05 mL) and MeOH (0.05 mL) at -78 ºC. After stirring for 30 min at room temperature, the reaction mixture was quenched with water and the aqueous phase was extracted with AcOEt. The combined organic phases were washed with brine, and dried over $MgSO_4$. Concentration and column chromatography (*n*-hexane : AcOEt = 3 : 1 to 3 : 2) afforded the alcohol (**18**) (3.5 mg, 65% in 2 steps, dr 9 : 1) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.93 (dd, J = 17.3, 11.0 Hz, 1H), 5.34 (d, J = 17.6 Hz, 1H), 5.22 (d, J = 11.0 Hz, 1H), 4.65 (d, J = 2.2 Hz, 1H), 3.59 (dd, J = 11.8, 4.6 Hz, 1H), 3.50-3.44 (m, 2H), 3.35 (s, 3H), 1.82-1.36 (m, 6H), 1.33 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 142.9, 142.8, 114.9, 103.0, 97.7, 77.8, 77.7, 74.5, 71.6, 71.3, 70.2, 69.8, 68.1, 56.5, 54.6, 33.5, 33.4, 30.7, 29.7, 29.6, 28.0, 24.7, 13.79, 13.75. IR (neat) cm^{-1}: 3449, 2946, 1461, 1376, 1222, 1159, 1128, 1093, 1024, 925.

(2*R*,3*S*,4a*R*,8a*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-methyl-6-methoxy-2-vinyl-1,5-dioxadecalin (19)

To a solution of the alcohol (**18**) (16.9 mg, 0.074 mmol) in CH_2Cl_2 (0.38 mL) were added 2,6-lutidine (0.065 mL, 0.56 mmol) and TBSOTf (0.065 mL, 0.28 mmol) at 0 ºC. After stirring for 24 h at room temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with AcOEt. The organic phase was washed with brine and dried over $MgSO_4$. Concentration and column

chromatography (*n*-hexane : AcOEt = 19 : 1) afforded the protected alcohol (**19**) (19.6 mg, 77%) as a colorless oil. The stereochemistry of (**19**) was determined by analysis of ^{1}H NMR in relative of the reported data.[10]

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