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Total synthesis of $PGF_{2\alpha}$ and 6,15-diketo-$PGF_{1\alpha}$ and formal synthesis of 6-keto-$PGF_{1\alpha}$ via three-component coupling

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ABSTRACT

The asymmetric total synthesis of $PGF_{2\alpha}$ and 6,15-diketo-$PGF_{1\alpha}$ and formal synthesis of 6-keto-$PGF_{1\alpha}$ from a common key intermediate are described. The key intermediate, which has a chiral cyclopentane backbone possessing suitable functional groups with required stereochemistry for both side chains, was prepared from (*R*)-4-silyloxy-2-cyclopentenone through a three-component coupling reaction. The Wittig reaction, Nozaki-Hiyama-Kishi (NHK) coupling and cross metathesis completed the synthesis of $PGF_{2\alpha}$, 6,15-diketo-$PGF_{1\alpha}$ and 6-keto-$PGF_{1\alpha}$.

1. Introduction

Prostaglandins (PGs) are a group of naturally occurring lipid compounds. They exist in animals and human-beings and mediate various physiological functions [1]. PGs contain 20 carbon atoms including a five-membered carbon ring and have several types of analogues which vary in carbon ring and upper and lower side chain structures. Due to their wide array of bioactivities [2], PGs have attracted considerable attention from synthetic chemists and numerous synthetic explorations have been implemented over several decades [3]. Since the pioneering work by Corey and co-workers [4], utilization of the key intermediate Corey lactone has been one of the most successful strategies to synthesize the entire family of PGs for nearly 50 years [3(b)]. Meanwhile, three-component coupling reactions which involve Michael addition of the lower side chain to cyclopentenone using an organometallic reagent, followed by an electrophilic trapping to install the upper side chain have become another mainstream synthetic method for PGs [5]. Recently, a concise asymmetric total synthesis for $PGF_{2\alpha}$ (**1**) (Scheme 1) and therapeutic prostaglandin analogues [(6a)] by Aggarwal and co-workers was developed through the aldol cascade reaction with proline as the organocatalyst [((6b–d))]. In 2017, based on the promising potential of cross metathesis, Hoveyda's group reported the synthesis of $PGF_{2\alpha}$ (**1**) via three-component coupling following cross metathesis [7].

Another bicyclic prostaglandin which has excellent ability to inhibit platelet aggregation and vasodilation is prostacyclin (PGI_2) [2]. Because PGI_2 is unstable in aqueous conditions and rapidly decomposed to its metabolites [8]; for instance, 6,15-diketo-$PGF_{1\alpha}$ (**2**) [9] and 6-keto-$PGF_{1\alpha}$ (**3**) [10] are known metabolites of prostacyclin. Compared with $PGF_{2\alpha}$ (**1**), synthetic studies on PGI_2 and its stable metabolites, 6,15-diketo-$PGF_{1\alpha}$ (**2**) and 6-keto-$PGF_{1\alpha}$ (**3**) have rarely been reported [(3b)]. To the best of our knowledge, there is no synthetic example for 6,15-diketo-$PGF_{1\alpha}$ (**2**) and only one example of total synthesis of 6-keto-$PGF_{1\alpha}$ (**3**) from simple starting material was reported [(10e)] in spite of their many biochemical and analytical studies [9,10].

Considering the same core structures of **1**, **2** and **3**, we envisioned that three target compounds would be synthesized from common intermediate **4**, because appropriate functional groups can be easily introduced for the installation of both side chains. Herein, we reported an efficient synthetic route to $PGF_{2\alpha}$, 6,15-diketo-$PGF_{1\alpha}$ and 6-keto-$PGF_{1\alpha}$ with high levels of stereoselectivity from a common synthetic intermediate **4**.

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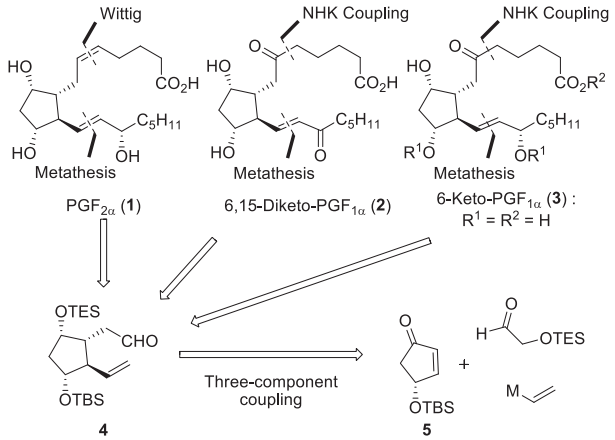


Scheme 1. Retrosynthetic analysis of $PGF_{2\alpha}$ (**1**), 6,15-diketo-$PGF_{1\alpha}$ (**2**) and 6-keto-$PGF_{1\alpha}$ (**3**).

2. Results and discussion

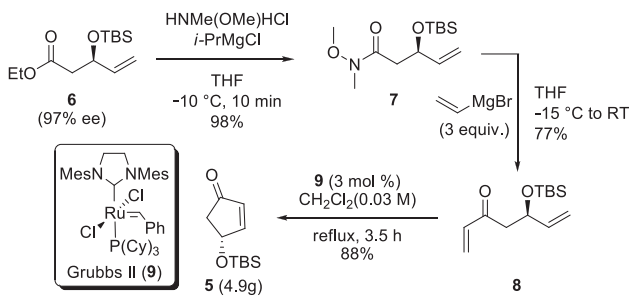
The retrosynthetic analysis of $PGF_{2\alpha}$ (**1**), 6,15-diketo-$PGF_{1\alpha}$ (**2**) and 6-keto-$PGF_{1\alpha}$ (**3**) is illustrated in Scheme 1. The key intermediate **4** possessing a chiral cyclopentane skeleton with the required stereochemistry could serve as a common precursor for the facile synthesis of $PGF_{2\alpha}$ (**1**), 6,15-diketo-$PGF_{1\alpha}$ (**2**) and 6-keto-$PGF_{1\alpha}$ (**3**) via cross metathesis and the Wittig reaction or Nozaki-Hiyama-Kishi (NHK) coupling. Access to **4** could be achieved through a stereoselective three-component coupling reaction of (*R*)-4-*t*-butyldimethylsilyloxy-2-cyclopentenone (**5**).

Based on this plan, the synthesis of key intermediate **4** was initiated with the preparation of chiral cyclopentenone **5** (Scheme 2). Although there are several studies on the synthesis of compound **5** and its derivatives due to their synthetic utilities [11,12], we designed a facile and scalable synthetic route to produce chiral 4-silyloxy-2-cyclopentenone **5** by employing easily accessible chemicals. The ethyl ester moiety of **6** which was prepared from ethyl acetate and acrolein in three steps with 97% ee [13] was directly converted to Weinreb amide **7** in 98% yield [14]. Dropwise addition of vinylmagnesium bromide solution to **7** at −15 °C furnished hepta-1,6-diene **8**. Overalkylation was not observed in this reaction. Ring closing metathesis of diene **8** with a second-generation Grubbs catalyst (**9**, 3 mol %) in dichloromethane resulted in (*R*)-4-*t*-butyldimethylsilyloxy-2-cyclopentenone (**5**) in 88% yield [(11c)]. It is notable that preparation of 4.9 g of **5** was achieved through this scalable procedure.

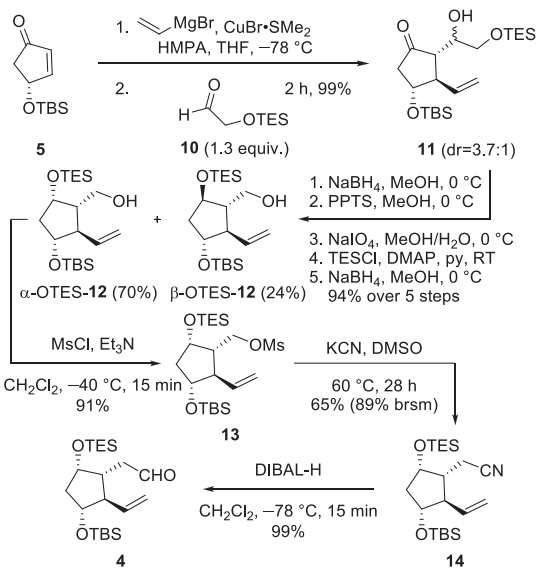
After successful establishment of a multigram scale synthetic procedure of **5**, we commenced our work by constructing the chiral cyclopentane framework through a three-component coupling reaction (Scheme 3). The vinyl group was introduced at the β-position via the Michael addition reaction of vinylmagnesium bromide in the presence of copper bromide. The resulting enolate was then exposed to various electrophiles in the same pot to introduce the upper side chain. Unfortunately, our attempts to introduce the α-side chain with alkyl halides or epoxy alkane gave unsatisfactory results [15]. However, after extensive screening of electrophiles, we found that α-silyloxy aldehyde **10** [16] was a good aldol acceptor and β-hydroxy cyclopentanone **11** was obtained in 99% yield as a mixture of diastereomers at the newly generated β-stereogenic center (3.7:1). By modification of Noyori's three-component coupling method [(10e)], the yield was greatly improved with commercially available cheap reagents. Additionally, introduced versatile vinyl group which makes it easy to install diverse (*E*)-lower side chain double bond would allow a flexible and direct synthesis of many prostaglandin type derivatives through a powerful cross metathesis tool [17].

Continuing the synthesis, cyclopentylmethanols **12** were synthesized from cyclopentanone **11** via highly efficient five-sequential chemical transformations. In detail, stereoselective carbonyl reduction of cyclopentanone **11** with $NaBH_4$ afforded a mixture of cyclopentanol diastereoisomers (α:β = 3:1) [18]. Removal of the terminal TES protecting group with PPTS in methanol and successive cleavage of vicinal diol in the α-side chain with $NaIO_4$ produced cyclopentyl aldehyde. After protection of cyclopentyl alcohol with a TES group, reduction of aldehyde with $NaBH_4$ furnished a mixture of α-OTES-**12** and β-OTES-**12** in 94% combined yield over five steps. Chiral cyclopentane α-OTES-**12** was isolated in 70% yield. The use of commercially available and inexpensive reagents, and simple workup procedures between each step followed by single silica gel chromatography as the last step was noteworthy. Then, one carbon homologation of α-OTES-**12** was accomplished by mesylation and subsequent nucleophilic substitution with KCN to give compound **14** [19]. Treatment of **14** with DIBAL-H produced the key intermediate **4** in 99% yield. The versatile aldehyde moiety of **4** enables to introduce the (*Z*)-alkene upper side chain through Wittig reaction and the 6-hydroxy or 6-keto upper side chain through NHK coupling.

With the key intermediate **4** in hand, we focused our attention on the synthesis of $PGF_{2\alpha}$ (**1**) (Scheme 4). Initially, cross metathesis was performed for the installation of *E*-alkene at the lower side



Scheme 2. Synthesis of (*R*)-4-*t*-butyldimethylsilyloxy-2-cyclopentenone (**5**).



Scheme 3. Synthesis of the key intermediate **4**.

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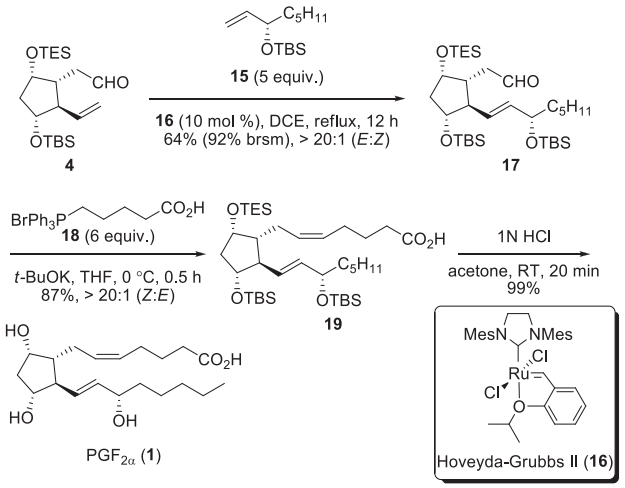
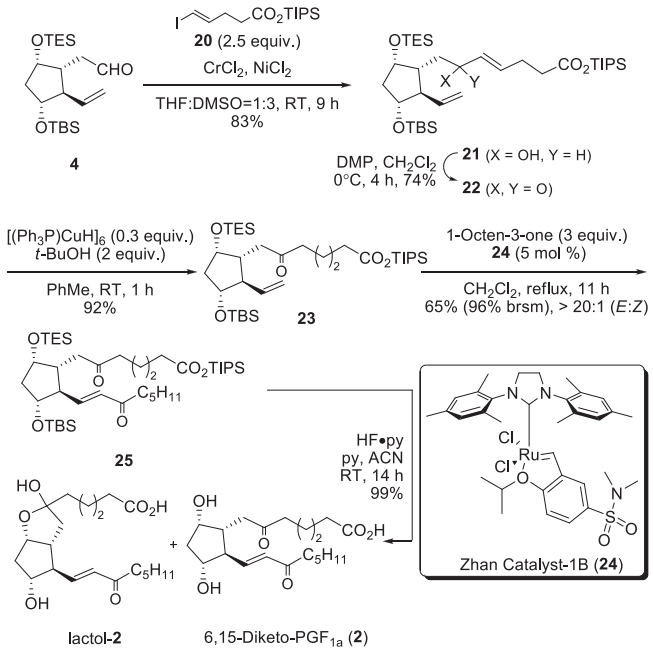


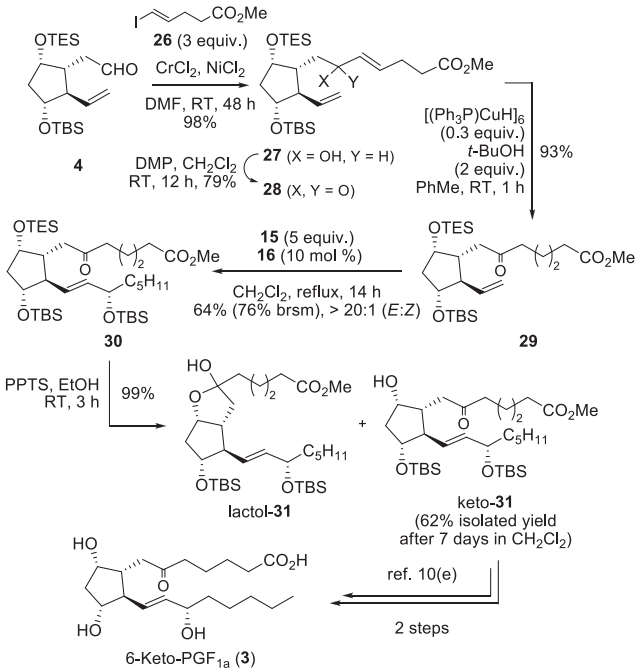
Scheme 4. Total synthesis of $PGF_{2\alpha}$ (**1**).

chain. The best result was obtained with second-generation Hoveyda-Grubbs catalyst **16** (10 mol %) in 1,2-dichloroethane with chiral octenol **15** and the desired product **17** was formed in 64% yield (92% brsm) [17]. Chiral octenol **15** was easily prepared from commercially available 1-octen-3-ol over 3 steps with 96% ee [20]. Treatment of **17** with the commercially available Wittig salt **18** in the presence of potassium *tert*-butoxide enabled the formation of *Z*-alkene at the upper side chain providing **19** in high yield [((6b–d))]. Finally, deprotection of all silyl groups of **19** under acidic conditions completed the total synthesis of $PGF_{2\alpha}$ (**1**). The identity of the synthetic $PGF_{2\alpha}$ has been fully established through comparison of the ^1H and ^{13}C NMR spectra and specific rotation, $[\alpha]_D^{25} = +24.7$ ($c = 0.5$, THF) [lit. $[\alpha]_D^{20} = +23.7$ ($c = 0.5$, THF)] [21].

Our next goal was to synthesize the prostacyclin metabolites, 6,15-diketo-$PGF_{1\alpha}$ (**2**) and 6-keto-$PGF_{1\alpha}$ (**3**) from the key intermediate **4** (Schemes 5 and 6). We considered the Nozaki-Hiyama-Kishi



Scheme 5. Total synthesis of 6,15-diketo-$PGF_{1\alpha}$ (**2**).



Scheme 6. Completion of 6-keto-$PGF_{1\alpha}$ (**3**) synthesis.

(NHK) coupling reaction between vinyl iodides and the key intermediate **4** for the installation of the upper side chain of **2** and **3**. To the best of our knowledge, there is no example that applies this reaction to the synthesis of prostaglandin derivatives. The NHK coupling reaction of **4** with vinyl iodide **20** [22] under THF:DMSO = 1:3 gave allylic alcohol **21** in 83% isolated yield [23]. Two epimers of allylic alcohol **21** were transformed to enone **22** using Dess-Martin periodinane. Selective conjugated reduction of α,β-enone was performed with Stryker's reagent and gave ketone **23** in 92% isolated yield [24]. Then, cross metathesis with Zhan Catalyst-1B (**24**) produced the precursor of target molecule, **25** in excellent *E*/*Z* selectivity [17]. Finally, deprotection of all silyl groups under HF·py conditions gave a 1:1 mixture of cyclized lactol-**2** and 6,15-diketo-$PGF_{1\alpha}$ (**2**) which was determined by ^1H NMR analysis of the crude mixture. Unfortunately, lactol-**2** and 6,15-diketo-$PGF_{1\alpha}$ (**2**) were inseparable and isolation of pure **2** was unsuccessful. Deprotection of silyl group with HCl conditions gave 5:1 mixture of lactol-**2** and 6,15-diketo-$PGF_{1\alpha}$ (**2**).

Continuing the synthesis for another prostacyclin metabolite 6-keto-$PGF_{1\alpha}$ (**3**), the NHK coupling reaction of **4** with vinyl iodide **26** [25] in degassed DMF furnished allylic alcohol **27** in 98% isolated yield (Scheme 5) [23]. A diastereomeric mixture of allylic alcohols **27** was subjected to Dess-Martin oxidation to give enone **28** in 79% yield. Chemoselective conjugate reduction of **28** with Stryker's reagent furnished the desired ketone **29** in 93% yield [26]. Then, cross metathesis with second-generation Hoveyda-Grubbs catalyst (**16**) in dichloromethane produced *E*-alkene **30** in 64% yield (76% brsm) [17]. Selective TES group deprotection with PPTS and ethanol [27] gave a 12:1 mixture of lactol-**31** and keto-**31** which was determined by ^1H NMR analysis of the crude mixture. Interestingly, we observed lactol-**31** was slowly converted to keto-**31** at room temperature. As a result, a 1:2 mixture of lactol-**31** and keto-**31** was obtained after 7 days in dichloromethane and keto-**31** was isolated in 62% yield. Another single cycle of ring opening of the remaining mixture furnished the desired product keto-**31** in 86% total yield. The spectroscopic data and specific rotation of the synthetic keto-**31** were in full agreement with those reported in the literature,

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$[\alpha]_D^{25} = -12.3$ ($c = 1.0$, MeOH) [lit. $[\alpha]_D^{22} = -14$ ($c = 2.3$, MeOH)] [(10e)]. Keto-**31** can be readily converted to 6-keto-$PGF_{1\alpha}$ (**3**) in two steps according to procedures in the literature [(10e)].

3. Conclusion

In summary, asymmetric total synthesis of $PGF_{2\alpha}$ and 6,15-diketo-$PGF_{1\alpha}$ and formal synthesis of 6-keto-$PGF_{1\alpha}$ were achieved from (*R*)-4-*t*-butyldimethylsilyloxy-2-cyclopentenone (**5**). The key step is a three-component coupling of chiral cyclopentenone **5** with vinyl copper reagent and α-silyloxy aldehyde, which quantitatively provided the key intermediate **4** having suitable functionality for the required side chains. A cross metathesis approach with vinyl group of **4** enables to introduce the fully functionalized many types of (*E*)-lower side chain double bonds. Additionally, with the aldehyde moiety of common key intermediate **4**, the (*Z*)-alkene or the 6-hydroxy upper side chain could be installed through Wittig reaction or NHK coupling, respectively. The Wittig reaction and cross metathesis of **4** have been successfully applied for the complete synthesis of $PGF_{2\alpha}$ (**1**). Moreover, the NHK coupling reaction and cross metathesis of **4** enabled the first synthesis of 6,15-diketo-$PGF_{1\alpha}$ (**2**) and formal synthesis of 6-keto-$PGF_{1\alpha}$ (**3**).

4. Experimental section

4.1. General description

Unless stated otherwise, reactions were performed in vacuum-flame dried glassware under a positive pressure of dry argon atmosphere using freshly distilled solvents. Dry reagents were prepared by distillation over adequate drying reagents under nitrogen atmosphere. All reactions including reagents sensitive to air and moisture were held under nitrogen atmosphere (glove box and/or Schlenk techniques). Reactions were monitored by TLC using Merck silica gel 60 F_{254} plates. Flash column chromatography was performed using E. Merck silica gel (40–60 μm particle size). ^{1}H and ^{13}C NMR spectra were recorded on an AVS 400 instrument (Bruker) at 500 and 125 MHz. Deuterated chloroform was used as solvent and spectra were calibrated against the residual solvent peak (7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C). Deuterated methanol was used as solvent and spectra were calibrated against the residual solvent peak (4.84 ppm for ^{1}H and 49.1 ppm for ^{13}C). IR spectra were recorded on a Bruker Vertex 70. HRMS were recorded on LTQ Orbitrap XL mass spectrometer (ThermoFisher Scientific). LRMS data were obtained by Bruker Impact HD quadrupole time of flight and Agilent (1100). Analytic HPLC was performed on YL 9100 HPLC system using the denoted chiral column (4.6 mm × 25 cm). Analytic GC was performed on YL 6500 GC system using the denoted chiral column (30 m × 0.25 mm x 0.12 μm). Optical rotations were recorded on a Perkin-Elmer polarimeter Model 343 plus at 589 nm.

4.2. (R)-3-(tert-butyldimethylsilyloxy)-N-Methoxy-N-methylpent-4-enamide (7)

To a stirred solution of **6** (7.25 g, 28 mmol, 1.0 equiv) in THF (50 mL) at −20 °C was added N,O-dimethylhydroxylamine hydrochloride (4.33 g, 43.5 mmol, 1.55 equiv). After 20 min isopropyl magnesium chloride (42 mL, 84 mmol, 3.0 equiv, 2.0 M solution in THF) was added dropwise to the reaction mixture for 15 min at −10 °C. The reaction mixture was stirred for 10 min and quenched with saturated NH_4Cl solution (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (Diethyl ether:*n*-Hexane = 1:3) on silica gel to obtain the product **7** (7.94 g, 98% yield) as yellow oil: TLC $R_f = 0.22$ (silica gel, Diethyl ether:*n*-Hexane = 1:3); $[\alpha]_D^{25} = +11.4$ ($c = 1.0$, $CHCl_3$); IR (neat) υ_{max} 2957, 2931, 2896, 2858, 1665, 1472, 1421, 1385, 1253, 1179, 1132, 1081, 1028, 1004, 952, 835, 778, 672 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (ddd, $J_{AB} = 16.8$ Hz, $J_{AC} = 10.8$ Hz, $J_{AD} = 5.4$ Hz, 1H), 5.26 (dt, $J_{AB} = 16.8$ Hz, $J_{AC} = 1.2$ Hz, 1H), 5.07 (dt, $J_{AB} = 10.8$ Hz, $J_{AC} = 1.2$ Hz, 1H), 4.68–4.72 (m,1H), 3.70 (s, 3H), 3.18 (s, 3H), 2.82 (dd, $J_{AB} = 13.8$ Hz, $J_{AC} = 7.8$ Hz, 1H), 2.42 (dd, $J_{AB} = 14.4$ Hz, $J_{AC} = 4.8$ Hz, 1H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 141.0, 114.3, 70.9, 61.5, 40.6, 32.1, 26.0, 18.3, −4.4, −4.9; LRMS (ESI): Calcd. for $C_{13}H_{27}NNaO_3Si$ ($[M+Na]^+$): 296.17, found: $m/z = 296.17$; HRMS (ESI): Calcd. for $C_{13}H_{27}NNaO_3Si$ ($[M+Na]^+$): m/z 296.1652, found: $m/z = 296.1651$.

4.3. (R)-5-(tert-Butyldimethylsilyloxy)hepta-1,6-dien-3-one (8)

To a stirred solution of **7** (4.5 g, 15.58 mmol, 1.0 equiv) in THF (100 mL) at −15 °C was added dropwise vinylmagnesium bromide (46.7 mL, 46.74 mmol, 3.0 equiv, 1.0 M in THF). The reaction mixture was allowed to gradually warm to room temperature and quenched with saturated NH_4Cl solution (100 mL) at 0 °C after completion of reaction. The aqueous layer was extracted with ethyl acetate (3 × 50 mL) and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (Diethyl ether:*n*-Hexane = 1:10) on silica gel to obtain the product **8** (2.9 g, 77% yield) as yellow oil: TLC $R_f = 0.71$ (silica gel, Diethyl ether:*n*-Hexane = 1:3); $[\alpha]_D^{25} = +20$ ($c = 1.0$, $CHCl_3$); IR (neat) υ_{max} 2957, 2930, 2858, 1684, 1616, 1473, 1403, 1362, 1254, 1084, 1028, 925, 836, 778, 674 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.37 (dd, $J_{AB} = 18.0$ Hz, $J_{AC} = 10.8$ Hz, 1H), 6.22 (dd, $J_{AB} = 18.0$ Hz, $J_{AC} = 0.6$ Hz, 1H), 5.83–5.88 (m,2H), 5.23 (dt, $J_{AB} = 17.4$ Hz, $J_{AC} = 1.2$ Hz, 1H), 5.06 (dt, $J_{AB} = 10.8$ Hz, $J_{AC} = 1.2$ Hz, 1H), 4.65–4.68 (m, 1H), 2.91 (dd, $J_{AB} = 15.0$ Hz, $J_{AC} = 7.8$ Hz, 1H), 2.59 (dd, $J_{AB} = 15.0$ Hz, $J_{AC} = 4.8$ Hz, 1H), 0.86 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.2, 140.7, 137.6, 128.9, 114.4, 70.8, 47.8, 26.0, 18.3, −4.3, −4.4; LRMS (ESI): Calcd. for $C_{13}H_{24}NaO_2Si$ ($[M+Na]^+$): 263.14, found: $m/z = 263.14$; HRMS (ESI): Calcd. for $C_{13}H_{24}NaO_2Si$ ($[M+Na]^+$): m/z 263.1438, found: $m/z = 263.1437$.

4.4. (R)-4-(tert-Butyldimethylsilyloxy)cyclopent-2-enone (5)

To a stirred solution of **8** (6.3 g, 26.2 mmol, 1.0 equiv) in CH_2Cl_2 (30 mL) at room temperature was added a second-generation Grubbs catalyst (667 mg, 0.78 mmol, 0.03 equiv). The reaction mixture was refluxed for 3.5 h and cooled to room temperature. The reaction mixture was concentrated *in vacuo*. The residue was purified by column chromatography (Diethyl ether:*n*-Hexane = 1:10) on silica gel to obtain the product **5** (4.9 g, 88% yield) as brown oil. The ^{1}H and ^{13}C NMR data of compound **5** were in full agreement with those reported in the literature [28]: TLC $R_f = 0.26$ (silica gel, Diethyl ether:*n*-Hexane = 1:3); $[\alpha]_D^{25} = +51.5$ ($c = 1.0$, $CHCl_3$), Lit.: $[\alpha]_D^{20} = +51.0$ ($c = 1.02$, $CHCl_3$, 98% ee) [28]; IR (neat) υ_{max} 2956, 2931, 2858, 1724, 1472, 1356, 1254, 1184, 1109, 1072, 900, 836, 778, 670 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (dd, $J = 5.7$, 2.3 Hz, 1H), 6.18 (dd, $J = 5.7$, 1.3 Hz, 1H), 4.98 (dtd, $J = 5.9$, 2.2, 1.4 Hz, 1H), 2.70 (dd, $J = 18.2$, 6.0 Hz, 1H), 2.24 (dd, $J = 18.2$, 2.2 Hz, 1H), 0.90 (s, $J = 2.9$ Hz, 9H), 0.13 (s, $J = 2.4$ Hz, 3H), 0.12 (s, $J = 3.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.5, 163.8, 134.4, 70.8, 44.9, 25.7, 18.1, −4.7, −4.8; LRMS (ESI): Calcd. for $C_{11}H_{20}NaO_2Si$ ($[M+Na]^+$): 235.11, found: $m/z = 235.11$.

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*4.5. (2S,3R,4R)-4-(tert-Butyldimethylsilyloxy)-2-(1-hydroxy-2-(triethylsilyloxy)ethyl)-3-vinylcyclopentanone (**11**)*

To a stirred solution of copper bromide dimethyl sulfide complex (1.71 g, 8.24 mmol, 0.3 equiv) in THF (200 mL) at −78 °C were added vinylmagnesium bromide (55 mL, 54.96 mmol, 2.0 equiv, 1.0 M in THF) and HMPA (2.4 mL, 13.74 mmol, 0.5 equiv). The reaction mixture was stirred for 15 min. Compound **5** (5.84 g, 27.48 mmol, 1.0 equiv) in THF (20 mL) was added dropwise to the reaction mixture for 15 min and aldehyde **10** (7.15 mL, 35.7 mmol, 1.3 equiv) was added to the reaction mixture. After 2 h, the reaction mixture was quenched with saturated NH_4Cl solution (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (Ethyl acetate:*n*-Hexane = 1:50) on silica gel to obtain the product **11** (11.3 g, 99% yield, 3.7:1 ratio) as yellow oil: TLC $R_f = 0.55$ (silica gel, Ethyl acetate:*n*-Hexane = 1:7); IR (neat) υ_{max} 3460, 2956, 2878, 1745, 1463, 1413, 1376, 1252, 1109, 1006, 917, 880, 837, 778, 743, 672 cm^{-1}; LRMS (ESI): Calcd. for $C_{21}H_{42}NaO_4Si_2$ ($[M+Na]^+$): 437.25, found: $m/z = 437.25$; HRMS (ESI): Calcd. for $C_{21}H_{42}NaO_4Si_2$ ($[M+Na]^+$): m/z 437.2514, found: $m/z = 437.2514$.

*4.6. ((1S,2R,3R,5S)-3-(tert-Butyldimethylsilyloxy)-5-(triethylsilyloxy)-2-vinylcyclopentyl)methanol (α-OTES-**12**)*

To a stirred solution of **11** (2.3 g, 5.56 mmol, 1.0 equiv) in methyl alcohol (50 mL) at 0 °C was added sodium borohydride (1.05 g, 27.8 mmol, 5.0 equiv). After 30 min, the reaction mixture was quenched with saturated NH_4Cl solution (10 mL) at 0 °C. The aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Without any purification, pyridinium p-toluenesulfonate (419 mg, 1.67 mmol, 0.3 equiv) was added to crude mixture in methyl alcohol (50 mL) at 0 °C. After 70 min, the reaction mixture was quenched with saturated NH_4Cl solution (10 mL) at 0 °C. The aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Without any purification, sodium periodate (2.38 g, 11.12 mmol, 2.0 equiv) was added to crude mixture in methyl alcohol (25 mL) and water (25 mL) at 0 °C. After 30 min, water (10 mL) was added to the reaction mixture. The aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Without any purification, chlorotriethylsilane (1.87 mL, 11.12 mmol, 2.0 equiv) and 4-dimethylaminopyridine (34 mg, 0.278 mmol, 0.05 equiv) were added to crude mixture in pyridine (25 mL) at room temperature. After 20 min, water (10 mL) was added to the reaction mixture. The aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Without any purification, sodium borohydride (819 mg, 21.6 mmol, 3.9 equiv) was added to crude mixture in methyl alcohol (50 mL) at 0 °C. After 30 min, the reaction mixture was quenched with saturated NH_4Cl solution (10 mL) at 0 °C. The aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (Ethyl acetate:*n*-Hexane = 1:30) on silica gel to obtain the product α-OTES-**12** (1.5 g, 70% isolated yield) as colorless oil and its diastereomer 24% isolated yield: TLC $R_f = 0.39$ (α-OTES-**12**), 0.3 (β-OTES-**12**, silica gel, Ethyl acetate:*n*-Hexane = 1:9); $[\alpha]_D^{25} = +18.6$ ($c = 1.0$, $CHCl_3$); IR(neat) υ_{max} 2956, 2930, 2878, 1471, 1362, 1251, 1131, 1073, 1006, 894, 836, 776, 744, 670 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.60 (ddd, $J_{AB} = 16.8$ Hz, $J_{AC} = 10.2$ Hz, $J_{AD} = 8.4$ Hz, 1H), 5.51 (ddd, $J_{AB} = 16.8$ Hz, $J_{AC} = 1.8$ Hz, $J_{AD} = 0.6$ Hz, 1H), 5.07 (ddd, $J_{AB} = 10.2$ Hz, $J_{AC} = 1.8$ Hz, $J_{AD} = 0.6$ Hz, 1H), 4.34 (q, $J = 6.6$ Hz, 1H), 3.80 (ddd, $J_{AB} = 11.4$ Hz, $J_{AC} = 3.6$ Hz, $J_{AD} = 3.0$ Hz, 1H), 3.75 (dt, $J_{AB} = 7.2$ Hz, $J_{AC} = 8.4$ Hz, 1H), 3.64−3.68 (m, 1H), 2.88 (dd, $J_{AB} = 9.0$ Hz, $J_{AC} = 4.2$ Hz, 1H), 2.60−2.65 (m, 1H), 2.29 (dt, $J_{AB} = 13.2$ Hz, $J_{AC} = 6.6$ Hz, 1H), 1.73−1.77 (m, 1H), 1.63 (ddd, $J_{AB} = 13.2$ Hz, $J_{AC} = 9.0$ Hz, $J_{AD} = 6.0$ Hz, 1H), 0.97 (t, $J = 8.4$ Hz, 9H), 0.86 (s,9H), 0.62 (q, $J = 7.8$ Hz, 6H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.5, 117.0, 75.8, 73.0, 61.6, 51.9, 48.2, 45.3, 26.0, 18.2, 6.9, 4.9, −4.3, −4.4; LRMS (ESI): Calcd. for $C_{20}H_{42}NaO_3Si_2$ ($[M+Na]^+$): 409.26, found: $m/z = 409.26$; HRMS (ESI): Calcd. for $C_{20}H_{42}NaO_3Si_2$ ($[M+Na]^+$): m/z 409.2565, found: m/z (%) = 409.2565.

*4.7. ((1S,2R,3R,5S)-3-(tert-Butyldimethylsilyloxy)-5-(triethylsilyloxy)-2-vinylcyclopentyl)methyl methanesulfonate (**13**)*

To a stirred solution of α-OTES-**12** (2.4 g, 6.23 mmol, 1.0 equiv) in CH_2Cl_2 (48 mL) at −40 °C were added triethylamine (2.17 mL, 15.6 mmol, 2.5 equiv) and methanesulfonyl chloride (0.97 mL, 12.46 mmol, 2.0 equiv). After 15 min, the reaction mixture was quenched with saturated $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (Ethyl acetate:*n*-Hexane = 1:20) on silica gel to obtain the product **13** (2.64 g, 91% yield) as colorless oil: TLC $R_f = 0.31$ (silica gel, Ethyl acetate:*n*-Hexane = 1:9); $[\alpha]_D^{25} = +24.1$ ($c = 1.0$, $CHCl_3$); IR(neat) υ_{max} 2956, 2931, 2879, 1361, 1251, 1177, 1109, 1076, 1005, 954, 893, 836, 777, 746 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.59−5.65 (m, 1H), 5.11−5.12 (m, 1H), 5.09−5.10, (m,1H), 4.39 (t, $J = 9.0$ Hz, 1H), 4.26 (td, $J_{AB} = 5.4$ Hz, $J_{AC} = 2.4$ Hz, 1H), 4.20 (dd, $J_{AB} = 9.6$ Hz, $J_{AC} = 4.8$ Hz, 1H), 3.85−3.89 (m,1H), 2.96 (s, 3H), 2.42 (td, $J_{AB} = 12.0$ Hz, $J_{AC} = 8.4$ Hz, 1H), 2.30 (ddd, $J_{AB} = 14.4$ Hz, $J_{AC} = 6.0$ Hz, $J_{AD} = 8.4$ Hz, 1H), 1.94−1.99 (m, 1H), 1.61 (ddd, $J_{AB} = 14.4$ Hz, $J_{AC} = 6.0$ Hz, $J_{AD} = 2.4$ Hz, 1H), 0.97 (t, $J = 7.8$ Hz, 9H), 0.86 (s,9H), 0.61 (q, $J = 7.8$ Hz, 6H), 0.003 (s, 3H), −0.004 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 117.6, 77.1, 70.3, 68.8, 53.2, 47.9, 44.8, 37.3, 25.9, 18.2, 7.0, 5.0, −4.4, −4.5; LRMS (ESI): Calcd. for $C_{21}H_{44}NaO_5SSi_2$ ($[M+Na]^+$): 487.23, found: $m/z = 487.23$.

*4.8. 2-((1R,2R,3R,5S)-3-(tert-Butyldimethylsilyloxy)-5-(triethylsilyloxy)-2-vinylcyclopentyl)acetonitrile (**14**)*

To a stirred solution of **13** (11.5 mg, 0.024 mmol, 1.0 equiv) in DMSO (1 mL) at room temperature was added potassium cyanide (5.6 mg, 0.086 mmol, 3.5 equiv). The reaction mixture was allowed to 60 °C. After 28 h, the reaction mixture was quenched with water (1 mL) and brine (1 mL) was added to the reaction mixture. The aqueous layer was extracted with ethyl acetate (3 × 1 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (Ethyl acetate:*n*-Hexane = 1:20) on silica gel to obtain the product **14** (5.5 mg, 65% yield, the starting was recovered, 89% brsm) as colorless oil: TLC $R_f = 0.57$ (silica gel, Diethyl ether:*n*-Hexane = 1:5); $[\alpha]_D^{25} = +14.5$ ($c = 1.0$, $CHCl_3$); IR(neat) υ_{max} 2955, 2928, 2878, 2349, 1741, 1462, 1434, 1250, 1134, 1089, 1016, 836, 777, 743, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.56 (ddd, $J_{AB} = 16.8$ Hz, $J_{AC} = 10.2$ Hz, $J_{AD} = 9.0$ Hz, 1H), 5.14−5.15 (m, 1H), 5.11−5.13 (m, 1H), 4.26 (td, $J_{AB} = 5.4$ Hz, $J_{AC} = 2.4$ Hz, 1H), 3.84−3.88 (m, 1H), 2.49 (dd, $J_{AB} = 16.8$ Hz, $J_{AC} = 10.2$ Hz, 1H), 2.31−2.40 (m, 2H), 2.28 (dd, $J_{AB} = 16.8$ Hz, $J_{AC} = 4.8$ Hz, 1H), 1.79−1.84 (m, 1H), 1.62 (ddd, $J_{AB} = 14.4$ Hz, $J_{AC} = 6.0$ Hz, $J_{AD} = 3.0$ Hz, 1H), 0.98 (t, $J = 8.4$ Hz, 9H), 0.86 (s,9H), 0.64 (q, $J = 7.8$ Hz, 6H), 0.003 (s, 3H), −0.005 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 119.8, 118.4, 76.8, 71.1, 55.9, 45.4,

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44.6, 25.9, 18.2, 15.7, 7.0, 5.0, −4.42, −4.5; LRMS (ESI): Calcd. for $C_{21}H_{41}NNaO_2Si_2$ ([M+Na]$^+$): 418.26, found: $m/z = 418.25$.

4.9. 2-((1R,2R,3R,5S)-3-(tert-Butyldimethylsilyloxy)-5-(triethylsilyloxy)-2-vinylcyclopentyl)acetaldehyde (**4**)

To a stirred solution of **14** (536 mg, 1.35 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) at −78 °C was added dropwise diisobutylaluminium hydride (1.76 mL, 1.76 mmol, 1.3 equiv, 1 M in cyclohexane). After 15 min, the reaction mixture was quenched with saturated Rochelle salt solution (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (Ethyl acetate:*n*-Hexane = 1:30) on silica gel to obtain the product **4** (536 mg, 99% yield) as yellow oil: TLC $R_f = 0.61$ (silica gel, Ethyl acetate:*n*-Hexane = 1:9); $[\alpha]_D^{25} = +40.4$ ($c = 1.0$, $CHCl_3$); IR υ_{max} 2955, 2934, 2878, 2857, 2712, 1726, 1462, 1415, 1366, 1250, 1142, 1109, 1075, 1006, 939, 892, 836, 776, 742, 654 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.80 (s, 1H), 5.50−5.56 (m, 1H), 5.08−5.10 (m, 1H), 5.07 (br s, 1H), 4.21 (td, $J_{AB} = 6.0$ Hz, $J_{AC} = 3.0$ Hz, 1H), 3.80−3.84 (m, 1H), 2.74 (ddd, $J_{AB} = 18.0$ Hz, $J_{AC} = 9.0$ Hz, $J_{AD} = 1.2$ Hz, 1H), 2.31−2.38 (m, 3H), 2.03−2.08 (m, 1H), 1.57 (ddd, $J_{AB} = 13.8$ Hz, $J_{AC} = 6.6$ Hz, $J_{AD} = 3.0$ Hz, 1H), 0.93 (t, $J = 8.4$ Hz, 9H), 0.86 (s,9H), 0.50−0.59 (m, 6H), 0.003 (s, 3H), −0.003 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.7, 139.4, 117.6, 76.7, 71.1, 55.9, 45.1, 42.6, 42.2, 36.0, 18.2, 7.0, 5.0, −4.4, −4.4; LRMS (ESI): Calcd. for $C_{21}H_{42}NaO_3Si_2$ ([M+Na]$^+$): 421.26, found: $m/z = 421.25$; HRMS (ESI): Calcd. for $C_{21}H_{42}NaO_3Si_2$ ([M+Na]$^+$): m/z 421.2565, found: $m/z = 421.2563$.

4.10. 2-((1R,2R,3R,5S)-3-(tert-Butyldimethylsilyloxy)-2-((S,E)-3-(tert-butyldimethylsilyloxy)oct-1-enyl)-5-(triethylsilyloxy)cyclopentyl)acetaldehyde (**17**)

To a stirred solution of **4** (15.7 mg, 0.039 mmol, 1.0 equiv) and **15** (58.6 μl, 0.197 mmol, 5.0 equiv) in dichloroethane (1 mL) at room temperature was added second-generation Hoveyda-Grubbs catalyst (2.4 mg, 0.0039 mmol, 0.1 equiv). The reaction mixture was refluxed for 12 h. After 12 h, the reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was purified by column chromatography (Diethyl ether:*n*-Hexane = 1:99) on silica gel to obtain the product **17** (15.2 mg, 64% isolated yield, 92% brsm, Only *E*-form was observed.) as colorless oil: TLC $R_f = 0.51$ (silica gel, Ethyl acetate:*n*-Hexane = 1:10); $[\alpha]_D^{25} = +13.0$ ($c = 1.0$, $CHCl_3$); IR(neat) υ_{max} 2956, 2929, 2857, 1727, 1472, 1361, 1256, 1086, 1005, 972, 894, 836, 774, 746, 684 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.78 (s, 1H), 5.52 (dd, $J = 15.4$, 5.4 Hz, 1H), 5.34 (dd, $J = 15.3$, 8.8 Hz, 1H), 4.21 (dd, $J = 8.8$, 5.8 Hz, 1H), 4.06 (dd, $J = 11.4$, 5.7 Hz, 1H), 3.83 (dd, $J = 14.6$, 7.8 Hz, 1H), 2.74 (dd, $J = 18.0$, 9.6 Hz, 1H), 2.39−2.28 (m, 3H), 2.04−1.97 (m, 1H), 1.56 (ddd, $J = 13.8$, 6.3, 3.2 Hz, 1H), 1.51−1.34 (m, 3H), 1.33−1.19 (m, 8H), 0.93 (t, $J = 7.9$ Hz, 9H), 0.88 (s, 9H), 0.86 (s, 9H), 0.59−0.49 (m, 6H), 0.03 (s, $J = 5.2$ Hz, 3H), 0.02 to −0.01 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.4, 136.5, 129.6, 76.9, 72.7, 71.0, 53.8, 45.0, 42.9, 42.0, 38.6, 31.8, 25.9, 25.8, 25.1, 22.6, 18.2, 18.0, 14.0, 6.8, 4.8, −4.3, −4.5, −4.6, −4.8; HRMS (ESI): Calcd. for $C_{33}H_{68}NaO_4Si_3$ ([M+Na]$^+$): m/z 635.4318, found: $m/z = 635.4318$.

4.11. (Z)-7-((1R,2R,3R,5S)-3-(tert-Butyldimethylsilyloxy)-2-((S,E)-3-(tert-butyldimethylsilyloxy)oct-1-enyl)-5-(triethylsilyloxy)cyclopentyl)hept-5-enoic acid (**19**)

To a stirred solution of (4-carboxybutyl)triphenylphosphonium bromide (**18**, 67.3 mg, 0.15 mmol, 6.0 equiv) in tetrahydrofuran (0.5 mL) was added potassium *tert*-butoxide (34 mg, 0.3 mmol, 12.0 equiv) in tetrahydrofuran (0.3 mL, 1 M) at 0 °C. After 40 min, compound **17** (15.2 mg, 0.025 mmol, 1.0 equiv) in tetrahydrofuran (0.5 mL) was added to the reaction mixture at 0 °C. After 30 min, the reaction mixture was quenched with water (1 mL) and acidified by 1 N HCl to pH 1 at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (Ethyl acetate:*n*-Hexane = 1:30) on silica gel to obtain the product **19** (15.0 mg, 87% yield, Only *Z*-form was observed.) as colorless oil: TLC $R_f = 0.22$ (silica gel, Ethyl acetate:*n*-Hexane = 1:3); $[\alpha]_D^{25} = +11.5$ ($c = 1.0$, $CHCl_3$); IR(neat) υ_{max} 2955, 2929, 2856, 1711, 1463, 1250, 1129, 1006, 970, 893, 836, 774, 673 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.54−5.43 (m, 2H), 5.39 (dd, $J = 15.4$, 8.4 Hz, 1H), 5.30 (dt, $J = 10.8$, 7.3 Hz, 1H), 4.12 (dd, $J = 7.8$, 5.3 Hz, 1H), 4.08 (dd, $J = 11.9$, 5.9 Hz, 1H), 3.82 (dt, $J = 13.5$, 6.9 Hz, 1H), 2.35 (dt, $J = 15.1$, 7.8 Hz, 3H), 2.21 (ddd, $J = 14.1$, 8.4, 5.9 Hz, 1H), 2.17−2.11 (m, 1H), 2.11−2.00 (m, 3H), 1.68 (dt, $J = 14.2$, 7.2 Hz, 2H), 1.58 (ddd, $J = 14.0$, 5.4, 2.8 Hz, 1H), 1.52−1.42 (m, 2H), 1.40−1.22 (m, 10H), 0.96 (t, $J = 7.9$ Hz, 9H), 0.89 (s, $J = 5.1$ Hz, 9H), 0.86 (s, 9H), 0.58 (ddd, $J = 9.9$, 7.8, 1.6 Hz, 6H), 0.06 (s, $J = 4.7$ Hz, 3H), 0.04 (s, $J = 5.1$ Hz, 3H), 0.00 (d, $J = 1.8$ Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.0, 134.9, 131.0, 130.2, 128.4, 77.4, 73.2, 71.5, 54.2, 49.4, 44.8, 38.4, 33.2, 31.9, 26.6, 25.9, 25.9, 25.2, 24.9, 24.6, 22.6, 18.3, 18.0, 14.0, 6.9, 5.0, −4.3, −4.5, −4.5, −4.7; HRMS (ESI): Calcd. for $C_{38}H_{76}NaO_5Si_3$ ([M+Na]$^+$): m/z 719.4893, found: $m/z = 719.4892$.

4.12. (Z)-7-((1R,2R,3R,5S)-3,5-Dihydroxy-2-((S,E)-3-hydroxyoct-1-enyl)cyclopentyl)hept-5-enoic acid ($PGF_{2\alpha}$, **1**)

To a stirred solution of **19** (13.8 mg, 0.02 mmol, 1.0 equiv) in acetone (1 mL) was added 1 N HCl (0.26 mL, 0.26 mmol, 13.0 equiv) at room temperature. After 20 min, water (1 mL) and brine (1 mL) were added to the reaction mixture. The aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (Acetic acid:Ethyl acetate = 1:30) on silica gel to obtain the product **1** (6.9 mg, 99% yield) as colorless oil: TLC $R_f = 0.21$ (silica gel, Acetic acid:Ethyl acetate = 1:30); $[\alpha]_D^{25} = +24.7$ ($c = 0.5$, THF), Lit.: $[\alpha]_D^{20} = +23.7$ ($c = 0.5$, THF) [20]; IR(neat) υ_{max} 3406, 2959, 2929, 2879, 2858, 1729, 1560, 1458, 1410, 1254, 1188, 1116, 1068, 1035 cm^{-1}; ^{1}H NMR (500 MHz, MeOD) δ 5.52−5.41 (m, 3H), 5.33 (dt, $J = 10.4$, 7.3 Hz, 1H), 4.07 (td, $J = 5.6$, 2.1 Hz, 1H), 3.98 (q, $J = 6.4$ Hz, 1H), 3.80 (dt, $J = 7.9$, 5.7 Hz, 1H), 2.32 (ddd, $J = 14.4$, 8.4, 6.0 Hz, 1H), 2.29−2.15 (m, 4H), 2.13−2.01 (m, 3H), 1.63 (dd, $J = 14.6$, 7.3 Hz, 2H), 1.59−1.52 (m, 2H), 1.44 (td, $J = 9.7$, 5.7 Hz, 2H), 1.36−1.28 (m, 6H), 0.88 (t, $J = 6.7$ Hz, 3H); ^{13}C NMR (125 MHz, MeOD) δ 136.6, 134.3, 130.7, 130.3, 78.0, 74.1, 72.3, 56.2, 51.0, 44.4, 38.5, 35.3, 33.1, 28.1, 27.0, 26.5, 26.3, 23.8, 14.5; HRMS (ESI): Calcd. for $C_{20}H_{34}NaO_5$ ([M+Na]$^+$): m/z 377.2298, found: $m/z = 377.2299$.

4.13. (E)-Triisopropylsilyl 7-((1R,2R,3R,5S)-3-(tert-butyldimethylsilyloxy)-5-(triethylsilyloxy)-2-vinylcyclopentyl)-6-hydroxyhept-4-enoate (**21**)

To chromium(II) chloride (44.7 mg, 0.36 mmol, 4.1 equiv) and nickel(II) chloride (4.6 mg, 0.036 mmol, 0.4 equiv) was added DMSO (3 mL) and THF (1 mL) at room temperature. The reaction mixture was stirred for 5 min and **4** (35.4 mg, 0.089 mmol, 1.0 equiv) and vinyl iodide **20** (0.68 mL, 0.22 mmol, 2.5 equiv) were added to the reaction mixture and the reaction mixture was stirred for 9 h at room temperature. The reaction mixture was quenched with saturated NH_4Cl solution (2 mL) at 0 °C. The aqueous layer was extracted with diethyl ether (3 × 5 mL). The combined organic

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layers were washed with brine and dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (Ethyl acetate:*n*-Hexane = 1:10) on silica gel to obtain the product **21** (48 mg, 83% yield) as yellow oil: TLC $R_f = 0.12$ (silica gel, Ethyl acetate:*n*-Hexane = 1:9); IR(neat) υ_{max} 3357, 2928, 2866, 1712, 1464, 1383, 1252, 1065, 882, 836, 777, 678 cm^{-1}; HRMS (ESI): Calcd. for $C_{35}H_{70}NaO_5Si_3$ ($[M+Na]^+$): *m*/*z* 677.4423, found: *m*/*z* = 677.4424.

4.14. (E)-Triisopropylsilyl 7-((1R,2R,3R,5S)-3-(tert-butyldimethylsilyloxy)-5-(triethylsilyloxy)-2-vinylcyclopentyl)-6-oxohept-4-enoate (**22**)

To a stirred solution of **21** (72 mg, 0.11 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) at 0 °C was added Dess–Martin periodinane (1.26 mL, 0.35 M in CH_2Cl_2, 4.0 equiv). The reaction mixture was stirred for 4 h. The reaction mixture was quenched with saturated $NaHCO_3$ solution (2 mL), saturated $Na_2S_2O_3$ solution (2 mL) and water (2 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (Ethyl acetate:*n*-Hexane = 1:30) on silica gel to obtain the product **22** (53.3 mg, 74% yield) as colorless oil: TLC $R_f = 0.43$ (silica gel, Ethyl acetate:*n*-Hexane = 1:10); $[\alpha]_D^{25} = +24.4$ ($c = 0.5$, $CHCl_3$); IR(neat) υ_{max} 2951, 2871, 1721, 1464, 1369, 1258, 1071, 1005, 885, 836, 748, 670, 512 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ δ 6.78–6.83 (m, 1H), 6.09 (d, $J = 15.6$ Hz, 1H), 5.51 (ddd, $J_{AB} = 16.8$ Hz, $J_{AC} = 10.2$ Hz, $J_{AD} = 9.6$ Hz, 1H), 5.04–5.07 (m, 2H), 4.21 (td, $J_{AB} = 6.0$ Hz, $J_{AC} = 3.0$ Hz, 1H), 3.82 (td, $J_{AB} = 8.4$ Hz, $J_{AC} = 6.6$ Hz, 1H), 2.89 (dd, $J_{AB} = 18.0$ Hz, $J_{AC} = 10.2$ Hz, 1H), 2.51 (br s, 3H), 2.28–2.38 (m, 3H), 2.04–2.09 (m, 1H), 1.53 (ddd, $J_{AB} = 13.8$ Hz, $J_{AC} = 6.0$ Hz, $J_{AD} = 3.0$ Hz, 1H), 1.30 (sept, $J = 7.2$ Hz, 3H), 1.25 (br s, 1H), 1.07 (d, $J = 7.2$ Hz, 18H), 0.90 (t, $J = 7.8$ Hz, 9H), 0.85 (s,9H), 0.45–0.55 (m, 6H), −0.002 (s, 3H), −0.007 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.13, 172.46, 144.20, 139.88, 131.44, 117.25, 71.07, 55.78, 45.19, 43.02, 37.59, 34.26, 27.92, 25.98, 18.27, 17.91, 12.03, 7.03, 4.99, 0.15, −4.36, −4.43; HRMS (ESI): Calcd. for $C_{35}H_{68}NaO_5Si_3$ ($[M+Na]^+$): 675.4267, found: *m*/*z* = 675.4268.

4.15. Triisopropylsilyl 7-((1R,2R,3R,5S)-3-(tert-butyldimethylsilyloxy)-5-(triethylsilyloxy)-2-vinylcyclopentyl)-6-oxoheptanoate (**23**)

To a stirred solution of **22** (246.6 mg, 0.38 mmol, 1.0 equiv) in toluene (3 mL) at room temperature were added *t*-butyl alcohol (72 μl, 0.76 mmol, 2.0 equiv) and Stryker's reagent (227 mg, 0.12 mmol, 0.3 equiv) in toluene (10 mL). After 1 h, the reaction mixture was quenched with saturated NH_4Cl solution (12 mL). The aqueous layer was extracted with ethyl acetate (3 × 12 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (Diethyl ether:*n*-Hexane = 1:30) on silica gel to obtain the product **23** (226.7 mg, 92% yield) as colorless oil: TLC $R_f = 0.47$(silica gel, Ethyl acetate:*n*-Hexane = 1:10); $[\alpha]_D^{25} = +16.4$ ($c = 0.5$, $CHCl_3$); IR(neat) υ_{max} 3007, 2989, 1718, 1464, 1276, 1261, 751 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.50 (ddd, $J_{AB} = 16.8$ Hz, $J_{AC} = 10.2$ Hz, $J_{AD} = 9.0$ Hz, 1H), 5.03–5.09 (m, 2H), 4.20 (td, $J_{AB} = 6.0$ Hz, $J_{AC} = 3.0$ Hz, 1H), 3.80 (td, $J_{AB} = 8.4$ Hz, $J_{AC} = 6.6$ Hz, 1H), 2.70 (dd, $J_{AB} = 18.0$ Hz, $J_{AC} = 9.6$ Hz, 1H), 2.24–2.44 (m, 7H), 1.99–2.04 (m, 1H), 1.56–1.63 (m, 3H), 1.52 (ddd, $J_{AB} = 13.8$ Hz, $J_{AC} = 6.0$ Hz, $J_{AD} = 3.0$ Hz, 1H), 1.29 (sept, $J = 7.8$ Hz, 3H), 1.25 (br s, 1H), 1.06 (d, $J = 7.8$ Hz, 18H), 0.92 (t, $J = 8.4$ Hz, 9H), 0.85 (s,9H), 0.47–0.57 (m, 6H), −0.006 (s, 3H), −0.012 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.44, 173.67, 139.89, 117.20, 76.81, 71.20, 55.90, 45.16, 42.99, 42.88, 40.43, 35.81, 25.98, 24.95, 23.36, 17.93, 12.05, 7.03, 5.05, 0.15, −4.36, −4.42; HRMS (ESI): Calcd. for $C_{35}H_{70}NaO_5Si_3$ ($[M+Na]^+$): 677.4423, found: *m*/*z* (%) = 677.4424.

4.16. Triisopropylsilyl 7-((1R,2R,3R,5S)-3-(tert-butyldimethylsilyloxy)-2-((E)-3-oxooct-1-enyl)-5-(triethylsilyloxy)cyclopentyl)-6-oxoheptanoate (**25**)

To a stirred solution of **23** (226.7 mg, 0.346 mmol, 1.0 equiv) and 1-octen-3-one (157 μl, 1.04 mmol, 3.0 equiv) in CH_2Cl_2 (7 mL) at room temperature was added Zhan Catalyst-1B (13 mg, 0.017 mmol, 0.05 equiv). The reaction mixture was allowed to reflux and stirred for 11 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was purified by column chromatography (Diethyl ether:*n*-Hexane = 1:20) on silica gel to obtain the product **25** (170.3 mg, 65% yield, 96% brsm, Only *E*-form was observed.) as colorless oil: TLC $R_f = 0.3$ (silica gel, Ethyl acetate:*n*-Hexane = 1:10); $[\alpha]_D^{25} = +17.2$ ($c = 0.5$, $CHCl_3$); IR(neat) υ_{max} 2953, 2871, 1717, 1464, 1370, 1253, 1006, 980, 884, 837, 747, 520 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.54 (dd, $J_{AB} = 15.6$ Hz, $J_{AC} = 9.6$ Hz, 1H), 6.12 (dd, $J_{AB} = 16.2$ Hz, $J_{AC} = 0.6$ Hz, 1H), 4.24 (td, $J_{AB} = 6.0$ Hz, $J_{AC} = 2.4$ Hz, 1H), 3.91 (td, $J_{AB} = 8.4$ Hz, $J_{AC} = 6.0$ Hz, 1H), 2.74 (dd, $J_{AB} = 18.0$ Hz, $J_{AC} = 9.6$ Hz, 1H), 2.50 (t, $J = 7.8$ Hz, 2H), 2.44–2.48 (m, 1H), 2.33–2.41 (m, 5H), 2.20 (dd, $J_{AB} = 18.0$ Hz, $J_{AC} = 3.6$ Hz, 1H), 2.13–2.18 (m, 1H), 1.55–1.63 (m, 7H), 1.25–1.35 (m, 7H), 1.06 (t, $J = 7.8$ Hz, 18H), 0.92 (t, $J = 8.4$ Hz, 9H), 0.89 (t, $J = 7.2$ Hz, 3H), 0.84 (s,9H), 0.48–0.58 (m, 6H), −0.02 (s, 3H), −0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.62, 200.48, 173.60, 147.76, 132.39, 76.68, 71.31, 54.68, 45.32, 43.ㅋ31, 42.79, 40.33, 40.28, 35.75, 31.64, 25.87, 24.90, 24.13, 23.25, 22.63, 18.15, 17.92, 14.08, 12.03, 6.99, 5.01, −4.45, −4.52; HRMS (ESI): Calcd. for $C_{41}H_{80}NaO_6Si_3$ ($[M+Na]^+$): *m*/*z* 775.5155, found: *m*/*z* = 775.5155.

4.17. 7-((1R,2R,3R,5S)-3,5-dihydroxy-2-((E)-3-oxooct-1-enyl)cyclopentyl)-6-oxoheptanoic acid (6,15-diketo-$PGF_{1\alpha}$, **2**)

To a stirred solution of **25** (32 mg, 0.026 mmol, 1.0 equiv) in acetonitrile (2 mL) at room temperature was added pyridine (0.03 mL) and hydrogen fluoride-pyridine (0.09 mL). The reaction mixture was stirred for 14 h. The reaction mixture was quenched with water (2 mL) and brine (2 mL). The aqueous layer was extracted with diethyl ether (3 × 2 mL) and concentrated *in vacuo* at 0 °C to obtain the product lactol-**2** and 6,15-diketo-$PGF_{1\alpha}$ (**2**) mixture (15.5 mg, 99% yield) as yellow oil. The ratio of lactol-**2** and 6,15-diketo-$PGF_{1\alpha}$ (1:1) was determined by ^1H NMR analysis of crude mixture: TLC $R_f = 0.52$ (lactol-**2**), 0.27 (6,15-diketo-$PGF_{1\alpha}$, silica gel, Acetic acid:Ethyl acetate = 1:100); IR(neat) υ_{max} 3440, 2955, 2924, 2854, 1711, 1627, 1461, 1378, 1250, 1065, 984, 880, 732, 593, 555, 527 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, mixture) δ 6.72–6.60 (m, 1H, lactol-**2**), 6.53 (dd, $J = 16.0$, 6.1 Hz, 1H, **2**), 6.20 (dd, $J = 20.3$, 9.8 Hz, 1H, lactol-**2**), 6.08 (dd, $J = 16.0$, 1.6 Hz, 1H, **2**), 4.81 (t, $J = 5.1$ Hz, 1H, **2**), 4.46 (d, $J = 1.4$ Hz, 1H, **2**), 4.06 (ddd, $J = 18.6$, 13.1, 6.7 Hz, 1H, lactol-**2**), 3.03–2.91 (m, 2H, **2**), 2.80–2.61 (m, 1H, lactol-**2**), 2.57–2.44 (m, 5H), 2.42–2.28 (m, 5H), 2.23–2.03 (m, 3H), 1.98–1.83 (m, 3H), 1.78–1.53 (m, 12H), 1.53–1.34 (m, 5H), 1.34–0.95 (m, 13H), 0.93–0.85 (m, 6H); HRMS (ESI): Calcd. for $C_{20}H_{32}NaO_6$ ($[M+Na]^+$): *m*/*z* 391.2091, found: *m*/*z* = 391.2093.

4.18. (E)-Methyl 7-((1R,2R,3R,5S)-3-(tert-butyldimethylsilyloxy)-5-(triethylsilyloxy)-2-vinylcyclopentyl)-6-hydroxyhept-4-enoate (**27**)

To chromium(II) chloride (280 mg, 2.28 mmol, 10.0 equiv) and nickel(II) chloride (295.5 mg, 2.28 mmol, 10.0 equiv) was added DMF (1.5 mL) at room temperature (chromium(II) chloride and nickel(II) chloride were handled in a glove box and DMF was degassed by argon gas for 10 min). The reaction mixture was stirred

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for 30 min and **4** (91 mg, 0.23 mmol, 1.0 equiv) in DMF (1 mL) was added to the reaction mixture. Vinyl iodide **26** (0.1 mL, 0.68 mmol, 3.0 equiv) was added dropwise to the reaction mixture and the reaction mixture was stirred for 48 h at room temperature. The reaction mixture was quenched with saturated NH_4Cl solution (2 mL) at 0 °C. The aqueous layer was extracted with diethyl ether (3 × 5 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (Ethyl acetate:*n*-Hexane = 1:8) on silica gel to obtain the product **27** (114 mg, 98% yield, 1 : 1 ratio) as yellow oil: TLC R_f = 0.09 (silica gel, Ethyl acetate:*n*-Hexane = 1:10); IR(neat) υ_{max} 2955, 2935, 2879, 1742, 1462, 1438, 1414, 1374, 1249, 1067, 1006, 894, 836, 776, 743, 726, 670 cm^{-1}; LRMS (ESI): Calcd. for $C_{27}H_{52}NaO_5Si_2$ ($[M+Na]^+$): 535.32, found: *m*/*z* = 535.32; HRMS (ESI): Calcd. for $C_{27}H_{52}NaO_5Si_2$ ($[M+Na]^+$): *m*/*z* 535.3246, found: *m*/*z* = 535.3246.

4.19. (E)-Methyl 7-((1R,2R,3R,5S)-3-(tert-butyldimethylsilyloxy)-5-(triethylsilyloxy)-2-vinylcyclopentyl)-6-oxohept-4-enoate (**28**)

To a stirred solution of **27** (8.4 mg, 0.016 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) at 0 °C was added Dess–Martin periodinane (18 mg, 0.04 mmol, 2.5 equiv). The reaction mixture was allowed to warm to room temperature and stirred for 12 h. The reaction mixture was quenched with saturated $NaHCO_3$ solution (2 mL), saturated $Na_2S_2O_3$ solution (2 mL) and water (2 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (Ethyl acetate:*n*-Hexane = 1:8) on silica gel to obtain the product **28** (6.5 mg, 79% yield) as colorless oil: TLC R_f = 0.43 (silica gel, Ethyl acetate:*n*-Hexane = 1:10); $[\alpha]_D^{25}$ = +38.0 (*c* = 1.0, $CHCl_3$); IR(neat) υ_{max} 2955, 2935, 2878, 2857, 1742, 1699, 1677, 1637, 1462, 1438, 1372, 1248, 1111, 1070, 1007, 895, 837, 777, 742, 669 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.77 (dt, *J* = 15.9, 6.4 Hz, 1H), 6.07 (dt, *J* = 15.7, 1.3 Hz, 1H), 5.51 (ddd, *J* = 17.0, 10.1, 9.1 Hz, 1H), 5.09–5.00 (m, 2H), 4.19 (td, *J* = 5.8, 2.7 Hz, 1H), 3.80 (td, *J* = 8.2, 6.4 Hz, 1H), 3.67 (s, 3H), 2.89 (dd, *J* = 18.1, 10.1 Hz, 1H), 2.55–2.42 (m, 4H), 2.38–2.26 (m, 3H), 2.12–2.04 (m, 1H), 1.51 (ddd, *J* = 14.0, 6.4, 2.7 Hz, 1H), 0.88 (t, *J* = 7.9 Hz, 9H), 0.84 (s, 9H), 0.53–0.44 (m, 6H), −0.02 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.0, 172.7, 143.7, 139.7, 131.4, 117.1, 70.9, 55.6, 51.8, 45.0, 42.8, 37.5, 32.3, 27.4, 25.8, 18.1, 6.9, 6.8, 4.8, −4.5, −4.6; LRMS (ESI): Calcd. for $C_{27}H_{50}NaO_5Si_2$ ($[M+Na]^+$): 533.31, found: *m*/*z* = 533.30.

4.20. Methyl 7-((1R,2R,3R,5S)-3-(tert-butyldimethylsilyloxy)-5-(triethylsilyloxy)-2-vinylcyclopentyl)-6-oxoheptanoate (**29**)

To a stirred solution of **28** (30.5 mg, 0.06 mmol, 1.0 equiv) in toluene (1 mL) at room temperature were added *t*-butyl alcohol (11.4 μL, 0.12 mmol, 2.0 equiv) and Stryker's reagent (39 mg, 0.018 mmol, 0.3 equiv) in toluene (2 mL). After 1 h, the reaction mixture was quenched with saturated NH_4Cl solution (2 mL). The aqueous layer was extracted with ethyl acetate (3 × 2 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (Ethyl acetate:*n*-Hexane = 1:10) on silica gel to obtain the product **29** (28.5 mg, 93% yield) as colorless oil: TLC R_f = 0.71(silica gel, Ethyl acetate:*n*-Hexane = 1:5); $[\alpha]_D^{25}$ = +25.9 (*c* = 1.0, $CHCl_3$); IR(neat) υ_{max} 2954, 2933, 2878, 2857, 1742, 1715, 1462, 1413, 1371, 1250, 1100, 1073, 1007, 895, 837, 776, 742, 728, 670 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.49 (ddd, *J* = 16.9, 10.3, 9.1 Hz, 1H), 5.07–5.01 (m, 2H), 4.18 (td, *J* = 5.9, 2.8 Hz, 1H), 3.79 (td, *J* = 8.2, 6.4 Hz, 1H), 3.65 (s, 3H), 2.70 (dd, *J* = 18.1, 9.7 Hz, 1H), 2.40–2.23 (m, 7H), 2.03–1.97 (m, 1H), 1.61–1.49 (m, 5H), 0.91 (t, *J* = 7.9 Hz, 9H), 0.84 (s, *J* = 2.9 Hz, 9H), 0.55–0.48 (m, 6H), −0.02 (s, *J* = 2.1 Hz, 3H), −0.02 (s, *J* = 3.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.2, 173.8, 139.7, 117.0, 76.6, 71.0, 55.7, 51.4, 45.0, 42.8, 42.6, 40.3, 33.8, 25.8, 24.5, 23.1, 18.0, 6.8, 4.9, −4.6, −4.6; LRMS (ESI): Calcd. for $C_{27}H_{52}NaO_5Si_2$ ($[M+Na]^+$): 535.32, found: *m*/*z* (%) = 535.32.

4.21. Methyl 7-((1R,2R,3R,5S)-3-(tert-butyldimethylsilyloxy)-2-((S,E)-3-(tert-butyldimethylsilyloxy)oct-1-enyl)-5-(triethylsilyloxy)cyclopentyl)-6-oxoheptanoate (**30**)

To a stirred solution of **29** (3.9 mg, 0.008 mmol, 1.0 equiv) and **15** (11.3 μl, 0.038 mmol, 5.0 equiv) in CH_2Cl_2 (1 mL) at room temperature was added second-generation Hoveyda-Grubbs catalyst (0.56 mg, 0.0008 mmol, 0.1 equiv). The reaction mixture was allowed to reflux and stirred for 14 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was purified by column chromatography (Diethyl ether:*n*-Hexane = 1:10) on silica gel to obtain the product **30** (3.5 mg, 64% yield, 76% brsm, Only *E*-form was observed.) as colorless oil: TLC R_f = 0.46 (silica gel, Ethyl acetate:*n*-Hexane = 1:10); $[\alpha]_D^{25}$ = +19.2 (*c* = 0.5, $CHCl_3$); IR(neat) υ_{max} 2955, 2930, 2858, 1743, 1416, 1462, 1372, 1252, 1069, 1007, 973, 837, 775, 735, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.49 (dd, *J* = 15.4, 5.5 Hz, 1H), 5.31 (ddd, *J* = 15.4, 8.8, 1.0 Hz, 1H), 4.19 (td, *J* = 5.8, 2.8 Hz, 1H), 4.05 (q, *J* = 5.6 Hz, 1H), 3.81 (td, *J* = 8.1, 6.3 Hz, 1H), 3.66 (s, 3H), 2.72 (dd, *J* = 18.3, 10.3 Hz, 1H), 2.38–2.21 (m, 7H), 2.00–1.93 (m, 1H), 1.63–1.48 (m, 6H), 1.44–1.38 (m, 2H), 1.32–1.22 (m, 8H), 0.91 (t, *J* = 7.9 Hz, 9H), 0.87 (s, 9H), 0.85 (s, *J* = 3.1 Hz, 9H), 0.55–0.46 (m, 6H), 0.03 (s, 3H), 0.00 (s, 3H), −0.00 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.1, 173.8, 136.2, 130.1, 72.8, 71.0, 53.7, 51.5, 45.0, 43.1, 42.5, 40.1, 38.7, 33.9, 31.9, 30.3, 25.9, 25.9, 25.1, 24.6, 23.2, 22.7, 18.2, 18.1, 14.1, 6.9, 4.9, −4.2, −4.5, −4.5, −4.8; LRMS (ESI): Calcd. for $C_{39}H_{78}NaO_6Si_3$ ($[M+Na]^+$): 749.50, found: *m*/*z* = 749.50; HRMS (ESI): Calcd. for $C_{39}H_{78}NaO_6Si_3$ ($[M+Na]^+$): *m*/*z* 749.4998, found: *m*/*z* = 749.4999.

4.22. Methyl 7-((1R,2R,3R,5S)-3-(tert-butyldimethylsilyloxy)-2-((S,E)-3-(tert-butyldimethylsilyloxy)oct-1-enyl)-5-hydroxycyclopentyl)-6-oxoheptanoate (keto-**31**)

To a stirred solution of **30** (32.4 mg, 0.04 mmol, 1.0 equiv) in ethyl alcohol (2 mL) at room temperature was added pyridinium *p*-toluenesulfonate (1 mg, 0.004 mmol, 0.1 equiv). After 3 h, the reaction mixture was quenched with saturated $NaHCO_3$ solution (2 mL) and stirred for 1 h. The aqueous layer was extracted with diethyl ether (3 × 5 mL) and the organic layer was washed with saturated $NaHCO_3$ solution (1 mL), water (1 mL), and brine (1 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The ratio of lactol-**31** and keto-**31** (12:1) was determined by ^1H NMR analysis of crude mixture in $CDCl_3$. The residue was purified by column chromatography (Diethyl ether:*n*-Hexane = 1:10) on silica gel to obtain the mixture of lactol-**31** and keto-**31** as colorless oil. Then, CH_2Cl_2 (1 mL) was added to the mixture of lactol-**31** and keto-**31**. The reaction mixture was stirred for 7 d at room temperature and concentrated *in vacuo*. The ratio of lactol-**31** and keto-**31** (1:2) was determined by ^1H NMR analysis of crude mixture. The residue was purified by column chromatography (Diethyl ether:*n*-Hexane = 1:10) on silica gel to obtain the product keto-**31** (15.2 mg, 62% isolated yield) as colorless oil. The remaining lactol-**31** was completely recovered and after one cycle of ring opening attempt, total 21.1 mg of keto-**31** (86% total yield) was obtained. Because tautomer of the product keto-**31** was observed by NMR, it was taken at 50 °C and assigned for major peaks: TLC R_f = 0.64 (lactol-**31**), 0.20 (keto-**31**, silica gel, Ethyl acetate:*n*-Hexane = 1:5); $[\alpha]_D^{25}$ = −12.3 (*c* = 1.0, MeOH), Lit.: $[\alpha]_D^{22}$ = −14 (*c* = 2.3, MeOH) [10(e)]; IR(neat) υ_{max} 3675, 2959, 2929,

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2901, 1742, 1471, 1393, 1251, 1066, 1056, 973, 836, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.49–5.34 (m, 2H), 4.63–3.91 (m, 3H), 3.66 (s, 3H), 2.80–1.30 (m, 23H), 0.93–0.87 (m, 21H), 0.03 to −0.06 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.7, 173.7, 135.4, 130.0, 78.9, 73.2, 73.1, 55.9, 51.4, 45.9, 43.4, 42.8, 41.3, 38.6, 33.8, 31.9, 25.9, 25.8, 25.0, 24.5, 23.3, 22.6, 18.2, 17.9, 13.9, −4.2, −4.6, −4.7, −4.7; LRMS (ESI): Calcd. for $C_{33}H_{64}NaO_6Si_2$ ($[M+Na]^+$): 635.41, found: $m/z = 635.41$; HRMS (ESI): Calcd. for $C_{33}H_{64}NaO_6Si_2$ ($[M+Na]^+$): m/z 635.4134, found: $m/z = 635.4134$.

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Appendix A. Supplementary data

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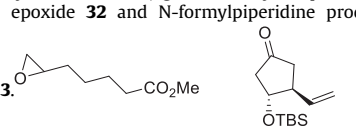

32 **33**

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