Total Synthesis of Prostaglandin $F_{2\alpha}$ Using Nickel-Catalyzed Stereoselective Cyclization of 1,3-Diene and Tethered Aldehyde *via* Transmetalation of Nickelacycle with Diisobutylaluminum Acetylacetonate

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Total synthesis of prostaglandin $F_{2\alpha}$ utilizing a nickel(0)-catalyzed cyclization of 1,3-diene and tethered aldehyde was achieved. The cyclization proceeded *via* a transmetalation of nickelacycle with diisobutylaluminum acetylacetonate ($^{i}Bu_2$–ALAC). Thus, the reaction of 19, having a side chain corresponding to the α-chain in $PGF_{2\alpha}$ with $Ni(cod)_2$ (10 mol %), PPh_3 (20 mol %), and 1,3-cyclohexadiene (25 mol %) in the presence of $^{i}Bu_2$–ALAC (1.5 eq) proceeded stereoselectively to give the cyclized product 26 in 54% yield. During the cyclization of 19, the *Z*-olefin at C-5 in the side chain completely retained its geometry, and the four contiguous chiral carbon centers in $PGF_{2\alpha}$ were stereoselectively constructed. Transformation of the key intermediate 19 into $PGF_{2\alpha}$ was successfully achieved.

Key words nickel; cyclization; nickelacycle; transmetalation; 1,3-diene; aldehyde

The nickel-promoted intramolecular oligomerization of 1,3-dienes and tethered multiple bonds is a useful methodology for the stereoselective construction of cyclic compounds.[1,2] In a recent study, we succeeded in developing a nickel-promoted cyclization of ω-formyl-1,3-dienes.[3] The reaction of ω-formyl-1,3-diene **1** using a stoichiometric amount of low-valent nickel complex **2**, generated by reduction of $Ni(acac)_2$ with DIBAL-H in the presence of PPh_3, afforded the cyclized products **3**-I and **3**-T in a stereoselective manner with respect to the stereochemistry of the substituents on the cycloalkane ring (Eq. 1, Chart 1).[3a] It was also found that the cyclized product **3**-T, having a terminal olefin in the side chain, was produced predominantly under the same reaction conditions in the presence of 1,3-cyclohexadiene (1,3-CHD) as an additive in the reaction mixture (Eq. 2).[3b,3g] The reaction course of this cyclization can be accounted for by two possible mechanisms. In one mechanism, a nickel hydride complex plays a key role and the cyclization proceeds *via* a π-allylnickel intermediate. In the other mechanism, a zerovalent nickel complex is the active species and the cyclization proceeds *via* nickelacycle intermediates.[3g] These mechanistic considerations led us to find two nickel(0)-catalyzed cyclizations of ω-formyl-1,3-dienes, which are depicted as the reactions of Type I and Type II in Chart 1. In the former reaction (Type I), a nickel(II) hydride complex is initially formed by the oxidative addition of trialkylsilane to a zero-valent nickel complex. The nickel(II) hydride complex reacts with substrate **1** to produce π-allylnickel intermediate **4**. The π-allyl moiety in **4** is reacted with tethered aldehyde to give the cyclized product **3′**-I, having an internal olefin in the side chain, through reductive elimination. On the other hand, a nickelacycle intermediate is initially generated by the reaction of a zero-valent nickel complex with substrate **1** in the latter reaction (Type II). Then the cyclized product **3**-T having a terminal olefin in the side chain is produced *via* transmetalation of a nickelacycle intermediate with diisobutylaluminum acetylacetonate ($^{i}Bu_2$–ALAC) such as intermediate **5**. These cyclizations are quite interesting and synthetically useful since they are complementary to each other for the regio-chemistry of olefin in the side chain to afford the cyclized product **3′**-I or **3**-T in a stereoselective manner using the same catalyst system, $Ni(cod)_2$–PPh_3, only depending upon the difference in the additive, Et_3SiH or $^{i}Bu_2$–ALAC. These unique properties encouraged us to apply these cyclizations to the synthesis of natural products.[3c,3d] Herein, we describe an application of the reaction of Type II to the synthesis of prostaglandin $F_{2\alpha}$.[4]

Results and Discussion

Plan for the Synthesis of Prostaglandin $F_{2\alpha}$ Using Nickel-Catalyzed Intramolecular Cyclization *via* Transmetalation of Nickelacycle with $^{i}Bu_2$–ALAC For several decades, prostaglandins (PGs) have attracted the interest of synthetic organic chemists as targets for total synthesis, and

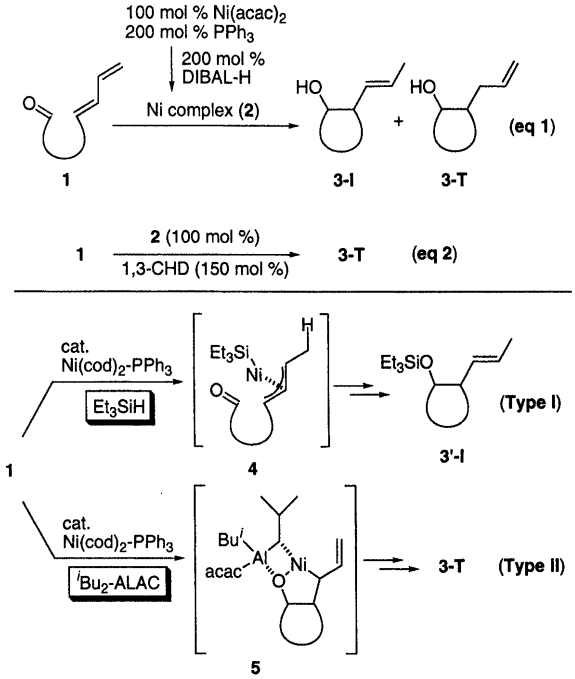

Chart 1

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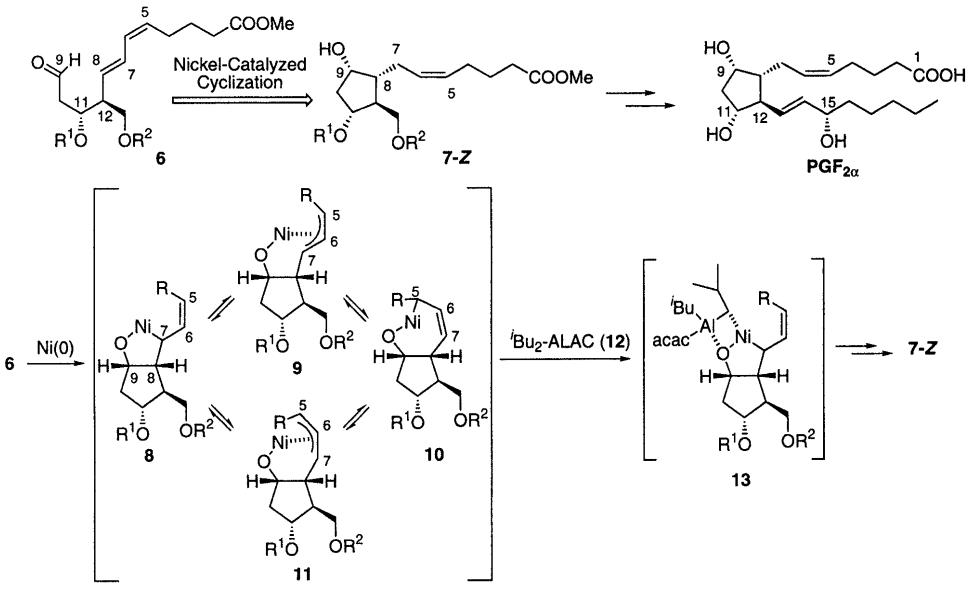


Chart 2

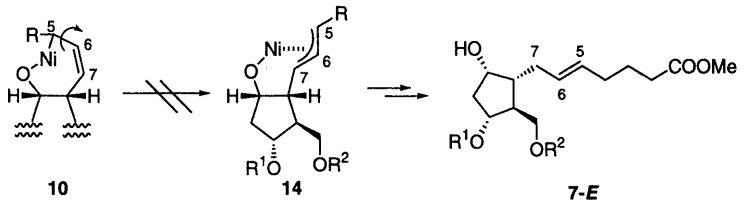
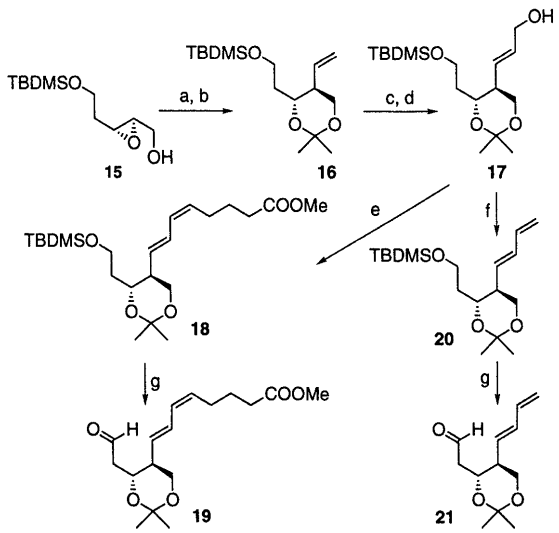


Fig. 1

various efficient methods for their syntheses have been reported.[5] We planned to apply the above-mentioned nickel(0)-catalyzed cyclization to the synthesis of $PGF_{2\alpha}$ as shown in Chart 2. According to the mechanism described above, the nickelacycle intermediates **8**—**11** would be generated by the reaction of the substrate **6** and a zero-valent nickel complex. Thus, regio- and stereoselective C–C bond formation would be expected to occur between C-8 and C-9 in **6**.[6] In general, a *syn*-π-allylmetal complex such as **14** (Fig. 1) should be more stable than an *anti*-complex such as **9** or **11**, and a rearrangement from an *anti*-π-allyl complex to a *syn*-π-allyl complex would occur *via* a σ-allylmetal complex in a linear π-allylmetal system.[7] In this cyclization, however, the π-σ-π rearrangement to **14** is restricted due to its cyclic form, as shown in Fig. 1. Thus, it was expected that the *Z*-olefin at C-5 in **6** would retain its geometry during the cyclization to give the cyclopentanoid **7**-*Z* in a stereoselective manner, and it was thought that the cyclized product **7**-*Z* would be readily transformed into $PGF_{2\alpha}$ (Chart 2).

Synthesis of Substrates for Cyclization The regiospecific ring-opening reaction of **15**[8] was accomplished by treatment with vinylmagnesium bromide (5 eq) in the presence of CuCN (0.5 eq)[9] to give the desired 1,3-diol in 70% yield,[10] and this was converted into acetonide **16**. Ozonolysis of **16** and successive reaction of the resulting crude aldehyde with (carbomethoxymethylene)triphenylphosphorane gave α,β-unsaturated ester, which was treated with DIBAL-H to produce allyl alcohol **17**. After oxidation of **17** with PCC reagent, the resulting aldehyde was reacted with the Wittig reagent generated from (4-carboxybutyl)triphenylphosphonium bromide and sodium methylsulfinylmethylide in DMSO,[11] and then treated with diazomethane to give the desired (5*Z*,7*E*)-dodecadienoic acid derivative **18** (66% from 17) along with the (5*E*,7*E*)-isomer (14%), which were easily separated by silica gel column chromatography. The substrate **19** for the cyclization was obtained in 80% yield (2 steps) by deprotection of the TBDMS group in **18** followed by oxidation with Dess–Martin reagent. The substrate **21** was also synthesized from allyl alcohol **17** for a model study of the cyclization. Thus, the aldehyde, derived from **17** by PCC oxidation, was condensed with the Wittig reagent generated from methyl triphenylphosphonium bromide and BuLi to give 1,3-diene **20**. The substrate **21** was obtained from **20** (84%, 2 steps) by procedures similar to those used for the synthesis of **19** from **18** (Chart 3).

Model Study of Cyclization Initially, the cyclization of **21** was investigated as a model study of cyclization. To a stirred solution of $Ni(cod)_2$ (5 mol %), PPh_3 (10 mol %), and $^iBu_2$–ALAC (**12**) (1.5 eq) in toluene was added a toluene solution of **21** at 0 °C, and the mixture was stirred at the same temperature for 2 h. We were very pleased to find that the cyclized product **22** was obtained in 91% yield as a single isomer (Chart 4). The stereochemistry of **22** was unambiguously determined by its NOESY spectrum, as shown in Fig. 2, which indicated that the four contiguous chiral carbon centers in **22** were stereoselectively produced with the same absolute configuration as those in $PGF_{2\alpha}$. Furthermore, conversion of **22** into the Corey lactone **24** or **25** was also achieved, as shown in Chart 5. Ozonolysis of **22** followed by reductive work-up gave the lactol **23**. Oxidation of **23** with PCC followed by treatment with DOWEX 50^W produced Corey lactone **24**, which was converted into **25**. The spectral data and



(a) CH_2=CHMgBr, CuCN, Et_2O-THF, -12 °C, 70%. (b) 2,2-dimethoxypropane, PPTS, r.t., 88%. (c) (1) O_3, CH_2Cl_2, -78 °C; (2) Ph_3P=$CHCO_2Me$, benzene, 65 °C, 93% (2 steps). (d) DIBAL-H, toluene, -78 °C, 95%. (e) (1) PCC, MS 4A, NaOAc, CH_2Cl_2, 0 °C; (2) $BrPh_3PC_4H_8COOH$, NaH, DMSO, r.t.; (3) CH_2N_2, MeOH-Et_2O, 66% (3 steps). (f) (1) PCC, MS 4A, CH_2Cl_2, 0 °C; (2) Ph_3PMeBr, BuLi, THF, -78 °C~0 °C, 84% (2 steps). (g) (1) TBAF, THF, r.t.; (2) Dess-Martin reagent, CH_2Cl_2, 0 °C, **19** from **18**: 80%, **21** from **20**: 84% (2 steps).

Chart 3

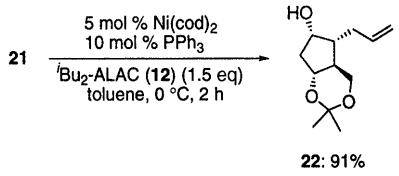


Chart 4

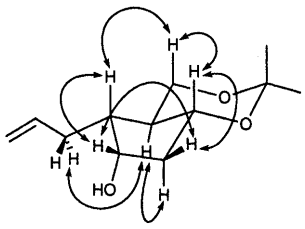
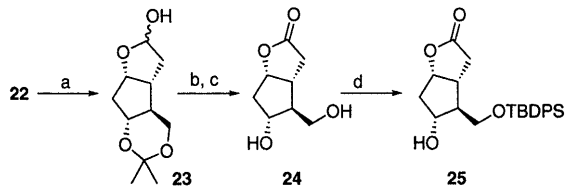


Fig. 2. NOESY Correlations of **22**



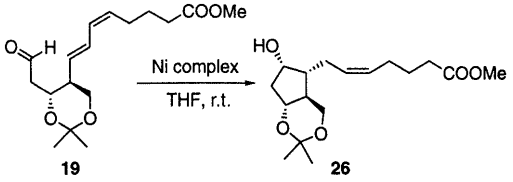
(a) (1) O_3, CH_2Cl_2, -78 °C; (2) PPh_3, -78 °C-rt, 78% (2 steps). (b) PCC, MS 4A, NaOAc, CH_2Cl_2, 0 °C, 80%. (c) DOWEX 50^W, THF-H_2O, r.t., 100%. (d) TBDPSCl, imidazole, DMF, 0 °C, 90%.

Chart 5

the $[\alpha]_D$ value of **24** and **25** were completely identical with those previously reported.[12]

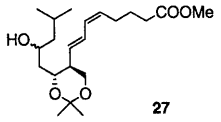
Study for the Cyclization of 19 The cyclization of the substrate **19**, having a side chain corresponding to the α-chain in $PGF_{2\alpha}$, was examined, and the results are summarized in Table 1. As mentioned above, we have already shown

Table 1. Cyclization of 19 Using $Ni(cod)_2$ and PPh_3 in the Presence of $^iBu_2$–ALAC (**12**)



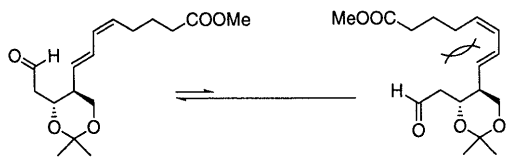
Run	Ni complex (mol %)	1,3-CHD (mol %)	$^iBu_2$–ALAC (eq)	Time (h)	Yield (%)
1	$Ni(cod)_2$ (100) PPh_3 (200)	150	2.2	15	51
2	$Ni(cod)_2$ (10) PPh_3 (20)	—	3.0	15	31
3[a]	$Ni(cod)_2$ (10) PPh_3 (20)	25	1.5	15	40
4[b]	$Ni(cod)_2$ (10) PPh_3 (20)	25	1.5	6	54

a) The by-product **27** was also obtained in 25% yield.



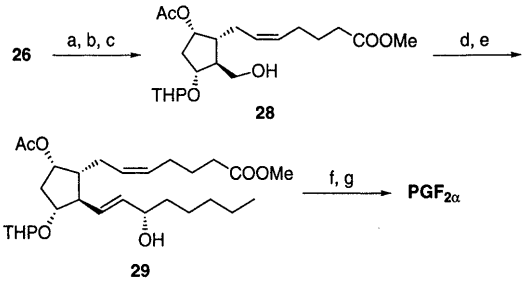
b) $^iBu_2$–ALAC was added slowly to the reaction mixture over a period of about 2 h.

that the addition of 1,3-cyclohexadiene (1,3-CHD) in nickel(0)-promoted cyclization of ω-formyl-1,3-dienes remarkably affected the regiochemistry of olefin on the side chain of the cyclized product.[3b,3g] Thus, the reaction of **19** was initially carried out using a stoichiometric amount of nickel(0) complex and $^iBu_2$–ALAC (**12**) in THF in the presence of 1,3-CHD (run 1). As a result, the cyclized product **26** was obtained in 51% yield as a single isomer. As expected, the ω-side chain of **26** had a *Z*-geometry, and the four contiguous chiral carbon centers in $PGF_{2\alpha}$ were stereoselectively constructed from **19**.[13] Next, we tried a catalytic reaction. In the catalytic cyclization, it was expected that the regio- and stereochemistry of the cyclized product would be controlled in the absence of 1,3-CHD because the coordination of the 1,3-diene moiety in the substrate would play the same role of additive 1,3-diene.[3g] However, cyclization using 10 mol% $Ni(cod)_2$, 20 mol% PPh_3, and 3.0 eq of **12** in the absence of 1,3-CHD gave the desired product **26** in only 31% yield along with some regio- and/or geometrical isomers with respect to the olefin at the side chain (run 2). Since a *s-cis* conformation of 1,3-diene moiety would be necessary for strong coordination to the central nickel metal,[3b,3g] it was thought that this result was caused by the structure of the 1,3-diene moiety in **19**. Thus, a *s-cis* conformation in **19** would be more unfavorable than a *s-trans* one due to the steric repulsion, which resulted in low stereoselectivity in the cyclization (Chart 6). A catalytic cyclization of **19** in the presence of 1,3-CHD was therefore examined, and the desired product **26** was obtained in 40% yield along with **27** in 25% yield (Table 1, run 3). We were pleased to find that the formation of **27** could be reduced by slow addition of **12** to the reaction mixture (over 2 h), and the yield of **26** was finally improved up to 54% (run 4). It is remarkable that compound **26**, having four chiral carbon centers and the α-chain in $PGF_{2\alpha}$, was stereoselectively produced from the linear diene **19** by the Ni(0)-catalyzed cyclization *via* a transmetalation process of nickelacy-



19 (*s-trans*) **19** (*s-cis*)

Chart 6



(a) Ac_2O, Pyridine, CH_2Cl_2, r.t., 95%. (b) (1) DOWEX 50^W, MeOH, 50 °C; (2) $^tBuPh_2SiCl$, Et_3N, CH_2Cl_2, 90% (2 steps). (c) (1) DHP,PPTS, CH_2Cl_2, r.t.; (2) TBAF, THF, r.t., 100% (2 steps). (d) (1) PCC, MS 4A, NaOAc, CH_2Cl_2, 0 °C; (2) $(MeO)_2POCH_2CO(CH_2)_4CH_3$, NaH, THF, r.t., 76% (2 steps). (e) (*S*)-binaphthol, $LiAlH_4$, EtOH, THF, -100 °C~-78 °C, 92%. (f) AcOH-H_2O-THF, 40 °C, 93%. (g) 1*N* NaOH, MeOH-THF, r.t., 95%.

Chart 7

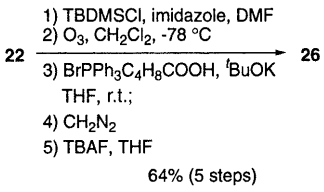


Chart 8

cle with $^tBu_2$–ALAC (**12**).

Total Synthesis of $PGF_{2\alpha}$ The cyclized product **26** was transformed into $PGF_{2\alpha}$ according to a procedure similar to that previously reported (Chart 7).[14] After manipulation of the protecting groups in **26**, introduction of a ω-chain followed by stereoselective reduction with (*S*)-BINAL-H[15] provided **29** in good yield. Finally, **29** was successfully converted into $PGF_{2\alpha}$ in the naturally occurring form.[16]

Conclusion

In summary, we have demonstrated that nickel(0)-catalyzed cyclization of 1,3-diene and tethered aldehyde *via* a transmetalation of nickelacycle with $^tBu_2$–ALAC (**12**) could be used to construct cyclopentanoids, and the total synthesis of $PGF_{2\alpha}$ was successfully achieved. A unique characteristic of the synthesis described herein is the regio- and stereoselective formation of the key intermediate **26** from the simple linear diene **19** in a one-pot reaction. The present results provide a basis for the development of new methods for the synthesis of cyclopentanoids.

Experimental

General All manipulations were performed under an argon atmosphere unless otherwise mentioned. All solvents and reagents were purified when necessary using standard procedures. Column chromatography was performed on silica gel 60 (Merck, 70—230 mesh), and flash chromatography was performed on silica gel 60 (Merck, 230—400 mesh) using the indicated solvent. Melting points are uncorrected. ^{1}H- and ^{13}C- NMR spectra were recorded at 270, 400, or 500 MHz and at 67.5, 100, 125 MHz, respectively. Infrared spectra were recorded on a Perkin-Elmer FTIR 1605 spectrometer. Mass spectra were measured on JEOL DX-303 and JEOL HX-110 mass spectrometer.

(2*R*,3*S*)-5-*tert*-Butyldimethylsilyloxy-2,3-epoxypentan-1-ol (15) To a stirred suspension of activated molecular sieves 4A (powdered, 1.84 g) in CH_2Cl_2 (50 ml) were added successively a solution of D-(−)-diethyl tartrate (352 mg, 1.70 mmol) in CH_2Cl_2 (5 ml), Ti(O-iso Pr)$_4$ (0.38 ml, 1.27 mmol), and *tert*-butyl hydroperoxide (5.0 M in decane, 8.5 ml, 43 mmol) at −20 °C, and the resulting mixture was stirred at the same temperature for 30 min. To the mixture was added a solution of 5-*tert*-butyldimethylsilyloxy-2-propen-1-ol (4.6 g, 21.2 mmol) in CH_2Cl_2 (30 ml) at −20 °C, and the mixture was stirred at the same temperature for 20 h. To the mixture was added 10% aqueous solution of citric acid monohydrate (15 ml), and the resulting mixture was stirred at 0 °C for 20 min. The mixture was filtered through Celite, and the filtrate was treated with 30% NaOH aq. (saturated with sodium chloride, 15 ml) at 0 °C for 1 h in order to hydrolyze the tartrate ester. The mixture was extracted with Et_2O, and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=2 : 1) to afford epoxide **15** (4.67 g, 94%, 91% ee) as a colorless oil. $[\alpha]_D^{22}$ +29.0° (*c*=1.26, $CHCl_3$). IR (neat) cm^{-1}: 3429, 2957, 2937, 2856, 1470, 1461. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.06 (6 H, s), 0.89 (9 H, s), 1.62 (1 H, dd, *J*=12.5, 7.4 Hz), 1.68—1.89 (2H, m), 2.98 (1H, m), 3.09 (1H, m), 3.63 (1H, ddd, *J*=12.5, 7.4, 4.4 Hz), 3.76 (2H, dd, *J*=6.7, 5.4 Hz), 3.93 (1H, ddd, *J*=12.5, 5.5, 2.6 Hz). MS *m/z*: 199 (M$^+$−MeOH-H), 189, 157, 145, 75. *Anal.* Calcd for $C_{11}H_{24}O_3Si$: C, 56.85; H, 10.41. Found: C, 56.77; H, 10.37. The enantiomeric purity of **15** was determined to be 91% ee on ^{1}H-NMR spectrum of the corresponding MTPA ester.

(2*S*,3*R*)-5-*tert*-Butyldimethylsilyloxy-2-ethenylpentan-1,3-diol To a suspension of CuCN (1.09 g, 12.2 mmol) in Et_2O (150 ml) was added vinylmagnesium bromide (1.1 M in THF, 109 ml, 122 mmol) at −78 °C, and the mixture was stirred at −30 °C for 1 h. To the resulting mixture was added a solution of **15** (5.68 g, 24.4 mmol) in Et_2O (35 ml), and the mixture was stirred at −12 °C for 8 h. The reaction mixture was poured into basic sat. NH_4Cl aq (that had been basified to pH 8 by addition of conc. NH_4OH), and the mixture was stirred until a clear aqueous phase was separated. The aqueous layer was extracted with ethyl acetate, and the combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=2 : 1) to afford the 1,3-diol (4.40 g, 70%) as an oil. $[\alpha]_D^{21}$ −3.7° (*c*=1.10, $CHCl_3$). IR (neat) cm^{-1}: 3405, 2960, 2927, 2855, 1743, 1728, 1476. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.03 (6H, s), 0.84 (9H, s), 1.54—1.78 (2H, m), 2.28 (1H, m), 3.23 (1H, dd, *J*=6.8, 4.6 Hz), 3.57—3.92 (5H, m), 4.18 (1H, d, *J*=2.4 Hz), 5.08 (1H, d, *J*=10.4 Hz), 5.09 (1H, d, *J*=17.1 Hz), 5.55 (1H, ddd, *J*=17.1, 10.4, 9.0 Hz). MS *m/z*: 261 (M$^+$+H), 203, 189, 185. *Anal.* Calcd for $C_{13}H_{28}O_3Si$: C, 59.95; H, 10.84. Found: C, 59.68; H, 10.46.

(4*R*,5*S*)-4-(2-*tert*-Butyldimethylsilyloxyethyl)-2,2-dimethyl-1,3-dioxa-5-ethenylcyclohexane (16) To a solution of the above 1,3-diol in $CHCl_3$ (50 ml) were added 2,2-dimethoxy propane (8.0 ml, 64.8 mmol) and pyridinium *p*-toluenesulfonate (100 mg, 0.39 mmol), and the mixture was stirred at room temperature for 12 h. To the mixture was added sat. $NaHCO_3$ aq., and the aqueous layer was extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=20 : 1) to afford **16** (3.43 g, 88%) as a colorless oil. $[\alpha]_D^{21}$ +32.0° (*c*=1.18, $CHCl_3$). IR (neat) cm^{-1}: 2994, 2953, 2928, 2856, 1638, 1471, 1463. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.04 (6H, s), 0.89 (9H, s), 1.38 (3H, s), 1.45 (3H, s), 1.48 (1 H, m), 1.85 (1H, m), 2.25 (1H, m), 3.60—3.74 (4H, m), 3.85 (1H, td, *J*=9.7, 2.5 Hz), 5.13 (1H, d, *J*=10.2 Hz), 5.15 (1H, d, *J*=17.4 Hz), 5.48 (1H, ddd, *J*=17.4, 10.2, 8.6 Hz). MS *m/z*: 285 (M$^+$−Me), 227, 213, 185, 75. *Anal.* Calcd for $C_{16}H_{32}O_3Si$: C, 63.95; H, 10.73. Found: C, 63.71; H, 10.66.

Methyl (2*E*)-2-[(1*S*,2*R*)-2-*tert*-Butyldimethylsilyloxyethyl-4,4-dimethyl-3,5-dioxacyclohexyl]-2-propenoate A solution of **16** (2.95 g, 9.81 mmol) in CH_2Cl_2 (50 ml) was cooled to −78 °C and treated with a stream of O_3/O_2 at −78 °C until the colorless solution had been converted to a blue one. The reaction mixture was treated with a stream of dry O_2 at −78 °C to remove an excess amount of O_3. To the reaction mixture was added a solution of PPh_3 (3.0 g, 11.8 mmol) in CH_2Cl_2 (5 ml) at −78 °C, and the mixture was allowed to stir at room temperature for 12 h. After removal of the solvent, the residue was filtered through a short column of silica gel (hexane/Et_2O=10 : 1) in order to remove triphenylphosphine oxide giving the crude aldehyde. To a solution of the crude aldehyde in benzene (47 ml) was added

Ph_3PCHCO_2Me (3.94 g, 11.7 mmol), and the mixture was stirred at 65 °C for 7 h. After removal of the solvent, the residue was purified by silica gel column chromatography (hexane/ethyl acetate=15/1) to afford the ester (3.27 g, 93% from **16**) as a colorless oil. $[\alpha]_D^{20}$ +27.3° (c=1.02, $CHCl_3$). IR (neat) cm^{-1}: 2994, 2953, 2391, 2958, 1728, 1656, 1472, 1463. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.04 (6H, s), 0.89 (9H, s), 1.39 (3H, s), 1.46 (3H, s), 1.50 (1H, m), 1.75 (1H, m), 2.45 (1H, m), 3.59—3.78 (4H, m), 3.74 (3H, s), 3.94 (1H, dd, J=9.6, 9.6, 2.4 Hz), 5.93 (1H, d, J=15.8 Hz), 6.68 (1H, dd, J=15.8, 9.3 Hz). MS m/z: 357 (M^+−H), 343, 301, 285, 243, 131. *Anal.* Calcd for $C_{18}H_{34}O_5Si$: C, 60.30; H, 9.56. Found: C, 60.34; H, 9.46.

(2*E*)-3-[(1*S*,2*R*)-2-(2-*tert*-Butyldimethylsilyloxyethyl)-4,4-dimethyl-3,5-dioxacyclohexyl]-2-propen-1-ol (17) To a solution of the above ester (3.27 g, 9.12 mmol) in toluene (46 ml) was added DIBAL-H (0.93 M in hexane, 23 ml, 21.4 mmol) at −78 °C, and the mixture was stirred at −78 °C for 1 h. To the mixture was added methanol (2 ml) followed by the addition of saturated aqueous solution of Rochell salt (45 ml), and the mixture was allowed to stir at room temperature. The mixture was extracted with Et_2O, and the organic layer was washed with sat. NH_4Cl aq. and brine, dried with Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=3 : 1) to afford **17** (2.86 g, 95%) as a colorless oil. $[\alpha]_D^{20}$ +29.6° (c=1.17, $CHCl_3$). IR (neat) cm^{-1}: 3426, 2993, 2954, 2930, 2850, 1472, 1461. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.04 (6H, s), 0.89 (9H, s), 1.33 (1 H, t, J=5.8 Hz), 1.38 (3H, s), 1.44 (3H, s), 1.49 (1H, m), 1.83 (1H, m), 2.28 (1H, m), 3.60—4.76 (4H, m), 3.84 (1H, ddd, J=9.9, 9.9, 2.3 Hz), 4.11 (2H, dd, J=5.8, 5.5 Hz), 5.39 (1H, dd, J=15.6, 8.8 Hz), 5.57 (1H, dt, J=15.6, 5.5 Hz). MS m/z: 315 (M^+−Me), 273 (M^+−*tert*-Bu), 215, 75. *Anal.* Calcd for $C_{17}H_{34}O_4Si$: C, 61.77; H, 10.37. Found: C, 61.58; H, 10.21.

Methyl (5*Z*,7*E*)-8-[(1*S*,2*R*)-2-(2-*tert*-Butyldimethylsilyloxyethyl)-4,4-dimethyl-3,5-dioxacyclohexyl]-5,7-octadienoate (18) To a solution of **17** (440 mg, 1.33 mmol) in CH_2Cl_2 (13 ml) were added sequentially molecular sieves 4A (2.0 g), anhydrous NaOAc (273 mg, 3.33 mmol), and PCC (574 mg, 3.29 mmol) at 0 °C. After being stirred at 0 °C for 1 h, the reaction mixture was diluted with Et_2O and filtered through a short column of Florisil. The filtrate was evaporated to provide the crude aldehyde (392 mg). A suspension of NaH (60% dispersion in mineral oil, 200 mg, 4.98 mmol) in DMSO (4 ml) was stirred at 75 °C for 1 h. To the resulting mixture was added a solution of 4-carboxybuthyltriphenylphosphonium bromide (1.08 g, 2.42 ml) in DMSO (4 ml) at room temperature, and the mixture was stirred for 15 min. To the resulting red solution was added a solution of the crude aldehyde in DMSO (4 ml) at room temperature, and the mixture was stirred for 1 h. The reaction mixture was poured into ice-water, and the solution was acidified to pH 3 by the addition of cooled 1 N HCl. The aqueous layer was extracted with Et_2O, and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was dissolved in methanol, and the mixture was treated with an ethereal solution of diazomethane at 0 °C. After an excess of diazomethane was decomposed by the addition of acetic acid, the mixture was diluted with Et_2O and washed with sat. $NaHCO_3$ aq. and brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (chloroform/hexane/ethyl acetate=50 : 50 : 2) to afford **18** (374 mg, 66%) as a colorless oil along with (5*E*,7*E*)-isomer (90 mg, 14%). $[\alpha]_D^{22}$ +7.7° (c=1.09, $CHCl_3$). IR (neat) cm^{-1}: 2994, 2953, 2929, 2857, 1740, 1654, 1459, 1437. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.04 (6H, s), 0.89 (9H, s), 1.45 (3H, s), 1.38 (3H, s), 1.50 (1H, m), 1.72 (2H, tt, J=7.5, 7.3 Hz), 1.82 (1H, m), 2.21 (2H, dt, J=7.8, 7.5 Hz), 2.27 (1H, m), 2.32 (2H, t, J=7.5 Hz), 3.59—3.77 (4H, m), 3.67 (3H, s), 3.84 (1H, ddd, J=11.9, 11.9, 2.4 Hz), 5.32 (1H, dd, J=15.1, 9.1 Hz), 5.34 (1H, dt, J=7.8 Hz), 5.95 (1H, dd, J=10.7, 10.7 Hz), 6.36 (1H, dd, J=15.1, 11.2 Hz). MS m/z: 411 (M^+−Me), 369 (M^+−*tert*-Bu), 351, 311 (M^+−*tert*-BuMe_2Si), 281, 219, 180. *Anal.* Calcd for $C_{23}H_{42}O_5Si$: C, 64.75; H, 9.92. Found: C, 64.58; H, 10.01.

Methyl (5*Z*,7*E*)-8-[(1*S*,2*R*)-4,4-Dimethyl-3,5-dioxa-2-(2-hydroxyethyl)-cyclohexyl]-5,7-octadienoate To a solution of **18** (280 mg, 0.66 mmol) in THF (6 ml) was added tetrabutylammonium fluoride (1.0 M in THF, 0.98 ml, 0.98 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 h. To the mixture was added sat. NH_4Cl aq., and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=2 : 1) to afford the alcohol (196 mg, 95%) as a colorless oil. $[\alpha]_D^{24}$ +27.8° (c=1.02, $CHCl_3$). IR (neat) cm^{-1}: 3472, 2995, 2947, 2865, 1738, 1655, 1460, 1437. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.41 (3 H, s), 1.49 (3 H, s), 1.58—1.75 (2 H, m), 1.72 (2 H, tt, J=7.3, 7.2 Hz), 1.86 (1H, m), 2.21 (2H, dt, J=7.7, 7.2 Hz), 2.33 (2H, t, J=7.4 Hz), 2.38 (1H, m), 2.53 (1H, br s), 3.67 (3H, s), 3.72 (1H, d, J=8.2 Hz), 3.70—3.80 (2H, m), 3.98 (1H, ddd, J=10.4, 8.8, 2.8 Hz), 5.29 (1H, dd, J=15.2, 9.1 Hz), 5.36 (1H, dt, J=10.7, 7.7 Hz), 5.94 (1H, dd, J=10.5, 9.1 Hz), 6.39 (1H, dd, J=15.2, 11.1 Hz). MS m/z: 311 (M^+−H), 297 (M^+−Me), 237, 180, 106. *Anal.* Calcd for $C_{17}H_{28}O_5$: C, 65.36; H, 9.03. Found: C, 65.45; H, 8.95.

Methyl (5*Z*,7*E*)-8-[(1*S*,2*R*)-4,4-Dimethyl-3,5-dioxa-2-(2-oxoethyl)cyclohexyl]-5,7-octadienoate (19) To a solution of the above alcohol (70 mg, 0.22 mmol) in CH_2Cl_2 (5 ml) was added Dess–Martin reagent (144 mg, 0.34 mmol) at 0 °C, and the mixture was stirred at the same temperature for 2 h. The reaction mixture was diluted with Et_2O, and filtered. To the filtrate was added a mixture of sat. $NaHCO_3$ aq. and 10% $Na_2S_2O_3$ aq. (1 : 1), and the mixture was stirred at 0 °C for 15 min. The resulting mixture was extracted with Et_2O, and the organic layer was washed with sat. $NaHCO_3$ aq. and brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=7 : 1) to afford **19** (59 mg, 84%) as a colorless oil. $[\alpha]_D^{27}$ +9.7° (c=1.12, $CHCl_3$). IR (neat) cm^{-1}: 2995, 2950, 2862, 2731, 1738, 1729, 1654, 1459, 1433. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.31 (3H, s), 1.43 (3H, s), 1.66 (2H, tt, J=7.5, 7.5 Hz), 2.14 (2H, dt, J=7.6, 7.5 Hz), 2.28 (1H, m), 2.26 (2H, t, J=7.5 Hz), 2.44 (1H, ddd, J=16.3, 7.8, 2.5 Hz), 2.52 (1H, ddd, J=16.3, 4.1, 1.7 Hz), 3.60 (3H, s), 3.68 (2H, d, J=8.2 Hz), 4.18 (1H, ddd, J=10.4, 7.8, 4.1 Hz), 5.21 (1H, dd, J=15.2, 9.3 Hz), 5.32 (1H, dt, J=10.3, 7.6 Hz), 5.87 (1H, dd, J=11.1, 10.3 Hz), 6.33 (1H, dd, J=15.2, 11.1 Hz), 9.69 (1H, dd, J=2.5, 1.7 Hz). MS m/z: 310 (M^+), 295 (M^+−Me), 252, 235, 180, 106. *Anal.* Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C 65.98, H, 8.21.

(4*R*,5*S*)-4-{5-[(1*E*)-1,3-Butadienyl]}-4-(2-*tert*-butyldimethylsilyloxyethyl)-2,2-dimethyl-1,3-dioxa]cyclohexane (20) To a solution of **17** (1.50 g, 4.5 mmol) in CH_2Cl_2 (50 ml) were added sequentially molecular sieves 4A (7.0 g), anhydrous NaOAc (744 mg, 9.1 mmol), and PCC (1.96 g, 9.1 mmol) at 0 °C, and the mixture was stirred at the same temperature for 1 h. The reaction mixture was diluted with Et_2O, and filtered through a pad of Florisil. The filtrate was evaporated to provide a crude aldehyde (1.36 g). To a suspension of methyltriphenylphosphonium bromide (1.93 mg, 5.4 mmol) in THF (18 ml) was added BuLi (1.64 M in hexane, 3.3 ml, 5.4 mmol) at 0 °C, and the mixture was stirred at 0 °C for 15 min. To the mixture was added a solution of the above crude aldehyde (1.36 g) in THF (10 ml) at −78 °C. The mixture was warmed to 0 °C over 2 h, and then stirred at the same temperature for 1 h. To the reaction mixture was added sat. NH_4Cl aq., and the aqueous layer was extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=35 : 1) to afford **20** (1.25 g, 84% from **17**) as a colorless oil. $[\alpha]_D^{20}$ +19.6° (c=1.10, $CHCl_3$). IR (neat) cm^{-1}: 2994, 2956, 2929, 2856, 1654, 1603, 1471, 1461. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.04 (6H, s), 0.89 (9H, s), 1.38 (3H, s), 1.45 (3H, s), 1.40—1.57 (1H, m), 1.77—1.90 (1H, m), 2.20—2.36 (1H, m), 3.60—3.75 (4 H, m), 3.80—3.90 (1H, m), 5.04 (1H, dd, J=10.2, 1.9 Hz), 5.16 (1H, dd, J=16.7, 1.9 Hz), 5.36 (1H, dd, J=15.0, 9.0 Hz), 6.15 (1H, dd, J=15.0, 10.4 Hz), 6.27 (1H, dd, J=16.7, 10.2, 10.2 Hz). MS m/z: 311(M^+−Me), 253, 211, 80. *Anal.* Calcd for $C_{18}H_{34}O_3Si$: C, 66.21; H, 10.49. Found: C, 66.08; H, 10.41.

2-{(1*R*,6*S*)-6-[(1*E*)-1,3-Butadienyl)]-3,3-dimethyl-2,4-dioxacyclohexyl}ethanol To a solution of **20** (365 mg, 1.11 mmol) in THF (6 ml) was added tetrabutylammonium fluoride (1.0 M in THF, 1.7 ml, 1.7 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 h. To the mixture was added sat. NH_4Cl aq., and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=2.5 : 1) to afford the alcohol (235 mg, 100%) as a colorless oil. $[\alpha]_D^{21}$ +47.7° (c=1.18, $CHCl_3$). IR (neat) cm^{-1}: 3434, 2994, 2942, 2864, 1659, 1603, 1455, 1418. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.40 (3H, s), 1.49 (3H, s), 1.59—1.75 (1H, m), 1.81—1.93 (1H, m), 2.31—2.47 (1H, m), 2.54 (1H, br s), 3.65—3.84 (4H, m), 3.92 (1H, ddd, J=9.7, 8.1, 2.6 Hz), 5.07 (1H, dd, J=10.2, 1.9 Hz), 5.18 (1H, dd, J=16.6, 1.9 Hz), 5.33 (1H, dd, J=14.7, 9.1 Hz), 6.16 (1H, ddd, J=14.7, 10.3, 1.8 Hz), 6.26 (1H, ddd, J=16.6, 10.2, 10.2 Hz). MS m/z: 212 (M^+), 197, 154, 137, 43. *Anal.* Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.64; H, 9.55.

2-{(1*R*,6*S*)-6-[(1*E*)-1,3-Butadienyl)]-3,3-dimethyl-2,4-dioxacyclohexyl}ethanal (21) To a solution of the above alcohol (230 mg, 1.08 mmol) in CH_2Cl_2 (11 ml) was added Dess–Martin reagent (690 mg, 1.62 mmol) at 0 °C, and the mixture was stirred at the same temperature for 1 h. The reaction mixture was diluted with Et_2O, and filtered. A mixture of sat. $NaHCO_3$ aq. and 10% $Na_2S_2O_3$ aq. (1 : 1) was added to the filtrate, and the mixture was stirred at 0 °C for 15 min. The mixture was extracted with Et_2O, and the organic layer was washed with sat. $NaHCO_3$ aq. and brine, dried

over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=7:1) to afford **21** (192 mg, 84%) as a colorless oil. $[\alpha]_D^{24}$ +30.7° (c=1.14, $CHCl_3$). IR (neat) cm^{-1}: 3089, 2993, 2939, 2860, 2727, 1726, 1602, 1460. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.38 (3H, s), 1.50 (3H, s), 2.35 (1H, m), 2.45—2.64 (2H, m), 3.75 (2H, d, J=4.7 Hz), 4.25 (1H, m), 5.09 (1H, d, J=10.4 Hz), 5.19 (1H, d, J=15.6 Hz), 5.32 (1 H, dd, J=14.7, 9.2 Hz), 6.17 (1H, dd, J=14.7, 10.4 Hz), 6.24 (1H, ddd, J=15.6, 10.4, 10.4 Hz), 9.76 (1H, t, J=2.4 Hz). MS m/z: 195 (M^+−Me), 167, 149, 122, 80. *Anal.* Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.42; H, 8.79.

(1*R*,6*S*,7*R*,8*S*)-3,3-Dimethyl-2,4-dioxa-7-(2-propenyl)bicyclo[4.3.0]-nonan-8-ol (22) (Cyclization of **21**). $Ni(cod)_2$ (3.5 mg, 0.013 mmol) and PPh_3 (6.6 mg, 0.026 mmol) were dissolved in degassed-toluene (0.33 ml), and the mixture was stirred at 0 °C for 20 min. To the mixture was added $^iBu_2$–ALAC (1.0 M in toluene, 0.38 ml, 0.38 mmol), and the mixture was stirred at room temperature for 15 min. To the mixture was added a solution of **21** (53 mg, 0.25 mmol) in degassed-toluene (6.3 ml) at 0 °C, and the mixture was stirred at 0 °C for 2 h. The reaction mixture was hydrolyzed with sat. NH_4Cl aqueous solution, and the aqueous layer was extracted with ether. After usual work-up, the residue was purified by silica gel column chromatography (hexane/AcOEt=2:1) to afford **22** (48 mg, 91%) as a colorless solid, which was recrystallized from hexane/ether (mp 64—69 °C). $[\alpha]_D^{20}$ +56.3° (c=1.16, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 3422, 3073, 2944, 2938, 2880, 1639, 1438. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.43 (3H, s), 1.45 (3H, s), 1.46—1.63 (2H, m), 1.65—1.80 (1H, m), 1.82 (1H, br.d, J=4.2 Hz), 2.12—2.26 (1H, m), 2.27—2.40 (1H, m), 2.53 (1H, ddd, J=13.0, 7.4, 7.4 Hz), 3.55 (1H, ddd, J=10.7, 7.4, 7.4 Hz), 3.71 (1H, dd, J=10.7, 10.7 Hz), 4.02 (1H, dd, J=10.4, 4.2 Hz), 4.24—4.34 (1H, m), 5.04 (1H, d, J=10.2 Hz), 5.14 (1H, d, J=17.2 Hz), 5.84 (1H, dddd, J=17.2, 10.2, 7.1, 6.3 Hz). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 19.5, 29.7, 31.6, 39.8, 42.4, 44.6, 65.9, 69.8, 72.7, 99.5, 115.9, 137.4. MS m/z: 213 (M^++H), 197, 171, 155, 137, 59. *Anal.* Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.65; H, 9.53.

Transformation of 22 into 25. (1*S*,2*S*,6*R*,8*S*)-10,10-Dimethyl-5,9,11-trioxatricyclo[6.4.0.0^{2,6}]dodecan-4-ol (23) A solution of **22** (140 mg, 0.66 mmol) in CH_2Cl_2 (10 ml) was cooled to −78 °C and treated with a stream of O_3/O_2 at −78 °C until the colorless solution had been converted to a blue one. The reaction mixture was treated with a stream of dry O_2 to remove an excess amount of O_3. To the reaction mixture was added a solution of PPh_3 (345 mg, 1.31 mmol), and the mixture was allowed to stir at ambient temperature for 15 h. After removal of the solvent, the residue was purified by silica gel column chromatography (hexane/AcOEt=1:1) to give **23** (110 mg, 78%). $[\alpha]_D^{24}$ +14.5° (c=1.07, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 3882, 2980, 2906, 2967. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.42 (3H, br s), 1.46 (3H, br s), 1.49—1.71 (1H, m), 1.77—2.07 (3H, m), 2.10—2.32 (1H, m), 2.36—2.52 (1H, m), 3.17—3.30 (1H, m), 3.44—3.80 (2H, m), 3.98—4.10 (1H, m), 4.55—4.70 (1H, m), 5.60—5.71 (1H, m). MS m/z: 215 (M^++H), 199, 59. *Anal.* Calcd for $C_{11}H_{18}O_4$: C, 61.67; H, 8.46. Found: C, 61.38; H, 8.32.

(1*S*,2*S*,6*R*,8*S*)-10,10-Dimethyl-5,9,11-trioxatricyclo[6.4.0.0^{2,6}]dodecan-4-one To the solution of **23** (90 mg, 0.42 mmol) in CH_2Cl_2 (5.0 ml) were added MS 4A (540 mg), AcONa (70 mg, 0.84 mmol), and PCC (181 mg, 0.84 mmol) at 0 °C, and the mixture was stirred at 0 °C for 2 h. The mixture was diluted with ether and filtered through a filtration paper. The filtrate was concentrated, and the residue was purified by silica gel column chromatography (hexane/AcOEt=1:1) to give the lactone (72 mg, 80%). $[\alpha]_D^{26}$ −2.6° (c=1.10, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 3002, 2947, 2887, 1786, 1447, 1430. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.43 (3H, s), 1.46 (3H, s), 1.65 (1H, ddd, J=11.0, 11.0, 4.6 Hz), 1.82 (1H, ddd, J=13.0, 11.0, 4.5 Hz), 2.30—2.47 (2H, m), 2.50—2.66 (1H, m), 2.69 (1H, dd, J=18.2, 9.2 Hz), 3.67 (1H, ddd, J=11.0, 11.0, 6.9 Hz), 3.79 (1H, dd, J=11.0, 4.5 Hz), 4.05 (1H, dd, J=11.0, 4.5 Hz), 4.90 (1H, ddd, J=7.2, 7.2, 4.6 Hz). MS m/z: 213 (M^++H), 197, 155, 54. *Anal.* Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.43; H, 7.51.

(3a*R*,4*S*,5*R*,6a*S*)-Hexahydro-5-hydroxy-4-(hydroxymethyl)-2*H*-cyclopenta-[*b*]furan-2-one (24) The above lactone (28 mg, 0.134 mmol) was dissolved in THF (2.0 ml) and H_2O (0.2 ml), and Dowex 50^{w}X8 (5 mg) was added to the mixture. The mixture was stirred at room temperature for 3 h. After the resin was removed by filtration, and the filtrate was concentrated. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH=10:1) to give **24** (23 mg, 100%), whose spectral data were completely identical with those previously reported.[12a]

(3a*R*,4*S*,5*R*,6a*S*)-Hexahydro-5-hydroxy-4-[(*tert*-butyldiphenylsilyl-oxy)methyl]-2*H*-cyclopenta[*b*]furan-2-one (25) To a solution of **24** (50 mg, 0.29 mmol) in DMF (2.0 ml) was added imidazole (30 mg, 0.44 mmol) and *tert*-butyldiphenylchlorosilane (0.09 ml, 0.35 mmol) at 0 °C, and the mixture was stirred at 0 °C for 2 h. After usual work-up, the residue was purified by silica gel column chromatography (hexane/AcOEt 3:2) to give **25** (107 mg, 90%), whose spectral data were completely identical with those previously reported.[12b]

Methyl (5*Z*)-7-{(1*R*,6*S*,7*R*,8*S*)-3,3-Dimethyl-2,4-dioxa-8-hydroxybicyclo[4.3.0]-nonan-7-yl}-5-heptenoate (26) (Cyclization of **19**). $Ni(cod)_2$ (4.8 mg, 0.017 mmol) and PPh_3 (9.1 mg, 0.034) were dissolved in degassed-THF (4.3 ml), and the mixture was stirred at 0 °C for 20 min. To the mixture were added 1,3-CHD (0.004 ml, 0.04 mmol) and a solution of **19** (54 mg, 0.173 mmol) in degassed-THF (4.3 ml) at 0 °C, and then $^iBu_2$–ALAC (0.25 M in toluene, 1.0 ml, 0.25 mmol) was slowly added to the mixture over a period of about 2 h at 25 °C. The mixture was stirred at 25 °C for 6 h. To the mixture was added sat. potassium sodium tartrate aqueous solution, and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, and dried over Na_2SO_4. After removal of the solvent, the residue was purified by silica gel column chromatography (hexane/AcOEt=2:1) to give **26** (30 mg, 54%). $[\alpha]_D^{27}$ +41.1° (c=1.07, $CHCl_3$). IR (neat) cm^{-1}: 3469, 2990, 2944, 2864, 1735, 1652. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.43 (3H, s), 1.45 (3H, s), 1.45—1.69 (2H, m), 1.66—1.77 (3H, m), 1.78 (1H, br.s), 2.07—2.18 (3H, m), 2.30 (1H, m), 2.32 (2H, t, J=7.3 Hz), 2.53 (1H, ddd, J=13.1, 7.5, 7.4 Hz), 3.54 (1H, ddd, J=10.5, 10.5, 7.5 Hz), 3.67 (3H, s), 3.72 (1H, dd, J=10.7, 10.7 Hz), 4.01 (1H, dd, J=10.7, 4.4 Hz), 4.25 (1H, ddd, J=6.8, 6.8, 4.4 Hz), 5.36—5.43 (2H, m). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 19.5, 24.6, 25.1, 26.6, 29.7, 33.3, 39.9, 43.3, 44.6, 51.4, 65.9, 69.7, 72.7, 99.4, 128.8, 129.9, 173.9. MS m/z: 312 (M^+), 297 (M^+−Me), 279, 187, 43. *Anal.* Calcd for $C_{17}H_{28}O_5$: C, 65.36; H, 9.03. Found: C, 65.59; H, 9.28.

Transformation of 22 into 26[13]. (1*R*,6*S*,7*R*,8*S*)-8-*tert*-Butyldimethylsilyloxy-3,3-dimethyl-2,4-dioxa-7-(2-propenyl)-bicyclo[4.3.0]nonane To a solution of **22** (71 mg, 0.334 mmol) in DMF (2.0 ml) were added imidazole (45 mg, 0.68 mmol) and *tert*-butyldimethylsilyl chloride (76 mg, 0.50 mmol) at room temperature, and the mixture was stirred for 7 h. After the usual workup, the residue was purified by silica gel column chromatography (hexane/ethyl acetate=20:1) to afford the silyl ether (95 mg, 87%) as a colorless oil. $[\alpha]_D^{31}$ +58.7° (c=1.29, $CHCl_3$). IR (neat) cm^{-1}: 2991, 2956, 2923, 2890, 2855, 1734, 1636, 1472, 1462. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.02 (3H, s), 0.03 (3H, s), 0.88 (9H, s), 1.42 (3H, s), 1.44 (3H, s), 1.42—1.58 (2H, m), 1.75 (1H, m), 2.09 (1H, m), 2.30 (1H, m), 2.41 (1H, ddd, J=12.6, 7.4, 7.1 Hz), 3.52 (1H, ddd, J=10.7, 10.5, 7.4 Hz), 3.68 (1H, dd, J=10.8, 10.8 Hz), 4.05 (1H, dd, J=10.8, 4.4 Hz), 4.20 (1H, ddd, J=7.1, 6.7, 4.3 Hz), 4.94 (1H, d, J=10.1 Hz), 5.03 (1H, d, J=17.4 Hz), 5.77 (1H, dddd, J=17.4, 10.1, 7.9, 5.9 Hz). MS m/z: 325 (M^+−H), 311 (M^+−Me), 269 (M^+−*tert*-Bu), 251, 211, 75. *Anal.* Calcd for $C_{18}H_{34}O_3Si$: C, 66.21; H, 10.49. Found: C, 66.14; H, 10.78.

Methyl (5*Z*)-7-{(1*R*,6*S*,7*R*,8*R*)-8-Acetoxy-3,3-dimethyl-2,4-dioxabicyclo[4.3.0]-nonan-7-yl}-5-heptenoate A solution of the above silyl ether (44 mg, 0.134 mmol) in CH_2Cl_2 (3 ml) was cooled to −78 °C and treated with a stream of O_3/O_2 at −78 °C until the colorless solution had been converted to a blue one. The reaction mixture was treated with a stream of dry O_2 to remove an excess amount of O_3. To the reaction mixture was added a solution of PPh_3 (42 mg, 0.160 mmol) in CH_2Cl_2 (2 ml), and the mixture was allowed to stir at ambient temperature for 12 h. After removal of the solvent, the residue was filtered through a short column of silica gel (hexane/Et_2O=10:1) in order to remove triphenylphosphine oxide giving the crude aldehyde. A suspension of potassium *tert*-butoxide (57 mg, 0.511 mmol) and 4-carboxybutyltriphenyl-phosphonium bromide (113 mg, 0.255 mmol) in THF (1.5 ml) was stirred at room temperature for 1 h. To the mixture was added a solution of the crude aldehyde (42 mg) in THF (1.5 ml), and the mixture was stirred for 15 min. After being cooled to 0 °C, the reaction mixture was diluted with Et_2O, and the solution was acidified (*ca.* pH 3) by the addition of cooled 1 N HCl aq., and the aqueous layer was extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was dissolved in methanol, and the mixture was treated with ethereal solution of diazomethane at 0 °C. After the usual workup, the residue was purified by silica gel column chromatography (hexane/ethyl acetate=12:1) to afford the methyl ester (45.6 mg, 80%, 3 steps) as a colorless oil. $[\alpha]_D^{24}$ +46.1° (c=1.00, $CHCl_3$). IR (neat) cm^{-1}: 2991, 2956, 2923, 2892, 2852, 1740, 1474, 1462, 1436. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.03 (6H, s), 0.88 (9H, s), 1.42 (3H, s), 1.42 (1H, m), 1.43 (3H, s), 1.52 (1H, ddd, J=12.5, 10.5, 4.4 Hz), 1.64—1.77 (3H, m), 2.03—2.10 (2H, m), 2.11—2.22 (2H, m), 2.31 (2H, t, J=7.5 Hz), 2.41 (1H, ddd, J=12.5, 7.5, 7.5 Hz), 3.50 (1H, ddd, J=10.5, 10.5, 7.4 Hz), 3.67 (3H, s), 3.68 (1H, dd, J=11.0, 10.7 Hz), 4.01 (1H, dd, J=10.7, 4.4 Hz), 4.19 (1H, ddd, J=6.7, 6.7, 4.2 Hz), 5.28—5.40 (2H, m). MS m/z: 426(M^+), 411 (M^+−Me), 395 (M^+−OMe),

369 (M^+-*tert*-Bu). *Anal.* Calcd for $C_{23}H_{42}O_5Si$: C, 64.75; H, 9.92. Found: C, 64.91; H, 9.61.

To a solution of the above methyl ester (40 mg, 0.093 mmol) in THF (1.5 ml) was added tetrabutylammonium fluoride (1.0 M in THF, 0.14 ml, 0.14 mmol) at 0 °C, and the mixture was stirred at room temperature for 3 h. After the usual workup, the residue was purified by silica gel column chromatography (hexane/ethyl acetate=2 : 1) to afford the corresponding alcohol (27 mg, 92%) as a colorless oil, whose spectral data were completely identical with those of **26** derived from **19**.

Synthesis of $PGF_{2\alpha}$ from 26. Methyl (5*Z*)-7-{(1*R*,6*S*,7*R*,8*R*)-8-acetoxy-3,3-dimethyl-2,4-dioxabicyclo[4.3.0]-nonan-7-yl}-5-heptenoate To a solution of **26** (115 mg, 0.368 mmol) in CH_2Cl_2 (3.5 ml) were added sequentially pyridine (0.25 ml, 2.21 mmol), DMAP (2 mg, 0.016 mmol), and acetic anhydride (0.11 ml, 1.10 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 h. To the mixture was added sat. $NaHCO_3$ aq., and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with sat. $NaHCO_3$ aq. and brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (hexane/AcOEt=4 : 1) to afford the acetate (124 mg, 95%) as a colorless oil. $[\alpha]_D^{28}$ +44.3° (*c*=1.04, $CHCl_3$). IR (neat) cm^{-1}: 2992, 2943, 2898, 2863, 1737, 1457, 1436. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.43 (3H, s), 1.45 (3H, s), 1.46—1.82 (6H, m), 2.01—2.19 (3H, m), 2.05 (3H, s), 2.31 (2H, t, *J*=7.4 Hz), 2.59 (1H, ddd, *J*=13.4, 7.7, 7.4 Hz), 3.59 (1H, ddd, *J*=10.3, 10.3, 7.7 Hz), 3.67 (3H, s), 3.73 (1H, dd, *J*=10.8, 10.8 Hz), 4.04 (1 H, dd, *J*=10.8, 4.1 Hz), 5.18 (1H, ddd, *J*=6.7, 6.7, 4.2 Hz), 5.23—5.42 (2H, m). MS *m/z*: 355 (M^++H), 339 (M^+-Me), 323 (M^+-OMe), 312 (M^+-Ac), 296, 279, 266, 43. *Anal.* Calcd for $C_{19}H_{30}O_6$: C, 64.39; H, 8.53. Found: C, 64.72; H, 8.90.

Methyl (5*Z*)-7-[(1*R*,2*S*,3*R*,5*R*)-5-Acetoxy-2-(*tert*-butyldiphenylsilyloxymethyl)-3-hydroxycyclopentyl]-5-heptenoate To a solution of the above acetate (124 mg, 0.349 mmol) in methanol (3.5 ml) was added Dowex 50^W×8 (6 mg), and the mixture was stirred at 50 °C for 30 min. After the mixture was cooled to room temperature, the resin was removed by filtration. The filtrate was evaporated to obtain the crude diol (108 mg), which was dissolved in CH_2Cl_2 (3.5 ml), and to the mixture were added sequentially Et_3N (0.11 ml, 1.06 mmol), DMAP (2 mg, 0.016 mmol), and *tert*-Butyldiphenylsilyl chloride (0.20 ml, 0.77 mmol) at room temperature. After the mixture was stirred at the same temperature for 36 h, sat. $NaHCO_3$ aq. was added to the solution, and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (hexane/AcOEt=2 : 1) to afford the TBDPS ether (173 mg, 90%, 2 steps) as a colorless oil. $[\alpha]_D^{27}$ +25.6° (*c*=1.08, $CHCl_3$). IR (neat) cm^{-1}: 3466, 3075, 3010, 2930, 2685, 1736, 1652, 1588, 1475, 1426. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.06 (9H, s), 1.62 (2H, tt, *J*=7.5, 7.4 Hz), 1.70—1.86 (2H, m), 1.87—2.18 (5H, m), 2.05 (3H, s), 2.19—2.40 (2H, m), 2.25 (2H, t, *J*=7.5 Hz), 3.59 (1H, dd, *J*=10.1, 6.9 Hz), 3.63 (3H, s), 3.89 (1H, d, *J*=10.1, 4.1 Hz), 4.21 (1H, m), 5.15 (1H, ddd, *J*=5.2, 5.2, 2.4 Hz), 5.18—5.34 (2H, m), 7.35—7.49 (6H, m), 7.62—7.69 (4H, m). MS *m/z*: 521 (M^+-OMe), 496, 435, 199. *Anal.* Calcd for $C_{32}H_{44}O_6Si$: C, 69.53; H, 8.02. Found: C, 69.76; H, 7.85.

Methyl (5*Z*)-7-[(1*R*,2*S*,3*R*,5*R*)-5-Acetoxy-2-(*tert*-butyldiphenylsilyloxymethyl)-3-(2-oxacyclohexyl)oxy-cyclopentyl]-5-heptenoate To a solution of the above TBDPS ether (155 mg, 0.280 mmol) in CH_2Cl_2 (1.5 ml) were added 2,3-dihydropyrane (0.10 ml, 1.12 mmol) and pyridinium *p*-toluenesulfonate (3.5 mg, 0.014 mmol) at room temperature, and the mixture was stirred for 12 h. To the solution was added sat. $NaHCO_3$ aq., and the aqueous layer was extracted with Et_2O, and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (hexane/AcOEt=5 : 1) to afford the THP ether (178 mg, 100%) as a colorless oil. $[\alpha]_D^{29}$ +13.9° (*c*=1.20, $CHCl_3$). IR (neat) cm^{-1}: 3063, 2939, 2856, 1737, 1557, 1472, 1428 cm. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.05 (9 H, s), 1.40—2.38 (16H, m), 2.03 (3H, s), 2.26 (2H, t, *J*=7.7 Hz), 3.39 (1H, m), 3.60—3.93 (3H, m), 3.65 (3H, s), 4.10 (1/2H, m), 4.30 (1/2H, m), 4.47 (1/2H, m), 4.54 (1/2H, m), 5.08 (1H, m), 5.25—5.40 (2H, m), 7.32—7.47 (6H, m), 7.61—7.70 (4H, m). MS *m/z*: 605 (M^+-OMe), 579 (M^+-*tert*-Bu), 552, 521, 495, 435, 85. *Anal.* Calcd for $C_{37}H_{52}O_7Si$: C, 69.78; H, 8.23. Found: C, 69.97; H, 8.14.

Methyl (5*Z*)-7-{(1*R*,2*S*,3*R*,5*S*)-5-Acetoxy-2-hydroxymethyl-3-[(2-oxacyclo-hexyl)oxy]cyclopentyl}-5-heptenoate (28) A solution of the above THP ether (175 mg, 0.274 mmol) in THF (3 ml) was treated with tetrabutylammonium fluoride (1.0 M in THF, 0.41 ml, 0.41 mmol) at 0 °C for 16 h. After the usual workup, the residue was purified by silica gel column chromatography (hexane/AcOEt 1 : 1) to afford **28** (110 mg, 100%) as a colorless oil. $[\alpha]_D^{28}$ +31.9° (*c*=1.05, $CHCl_3$). IR (neat) cm^{-1}: 3648, 2944, 2867, 1736, 1654, 1453, 1437. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.26—2.45 (17H, m), 2.06 (3H, s), 2.32 (2H, t, *J*=6.4 Hz), 3.44—3.69 (2H, m), 3.68 (3H, s), 3.74—4.18 (3H, m), 4.57 (1/2H, m), 4.72 (1/2H, m), 5.06 (1H, m), 5.31—5.46 (2H, m). MS *m/z*: 398 (M^+), 367 (M^+-OMe), 314, 283, 43. *Anal.* Calcd for $C_{21}H_{34}O_7$: C, 63.30; H, 8.60. Found: C, 63.19; H, 8.32.

Methyl (5*Z*)-7-{(1*R*,2*R*,3*R*,5*R*)-5-Acetoxy-3-(2-oxacyclohexyl)oxy-2-[(1*E*)-3-oxo-1-octenyl]cyclopentyl}-5-heptenoate To a solution of **28** (50 mg, 0.125 mmol) in CH_2Cl_2 (2.5 ml) were added sequentially MS 4A (280 mg), anhydrous NaOAc (31 mg, 0.38 mmol), and PCC (82 mg, 0.38 mmol) at 0 °C. After being stirred at 0 °C for 1 h, the reaction mixture was diluted with Et_2O, and filtered through a short column of Florisil. The filtrate was evaporated to afford the crude aldehyde. To a suspension of NaH (60% dispersion in mineral oil, 7.5 mg, 0.188 mmol) in THF (1.0 ml) was added a solution of dimethyl 2-oxoheptylphosphonate (42 mg, 0.188 mmol) in THF (1.0 ml) at room temperature. After the mixture was stirred for 5 min, a solution of the crude aldehyde in THF (1.0 ml) was added to the mixture, and the mixture was stirred for 1 h. To the reaction mixture was added sat. NH_4Cl aq., and the aqueous layer was extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (hexane/AcOEt=4 : 1) to afford the α,β-unsaturated ketone (47 mg, 76%) as a colorless oil. $[\alpha]_D^{28}$ +41.8° (*c*=1.00, $CHCl_3$). IR (neat) cm^{-1}: 2946, 2867, 1737, 1699, 1672, 1629, 1454, 1436. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.89 (3H, t, *J*=6.4 Hz), 1.23—1.40 (4H, m), 1.40—1.90 (12H, m), 1.90—2.30 (4H, m), 2.06 (3H, s), 2.28 (2H, t, *J*=7.5 Hz), 2.36—2.80 (2H, m), 2.54 (2H, t, *J*=9.0 Hz), 3.43 (1H, m), 3.66 (3H, s), 3.77 (1H, m), 4.02 (1.2H, m), 4.10 (1/2H, m), 4.55 (1H, m), 5.09 (1H, m), 5.23—5.42 (2H, m), 6.21 (1/2H, d, *J*=15.8 Hz), 6.25 (1/2H, d, *J*=15.8 Hz), 6.70 (1/2H, dd, *J*=15.8, 9.1 Hz), 6.73 (1/2H, dd, *J*=15.8, 8.8 Hz). MS *m/z*: 492 (M^+), 461 (M^+-OMe), 408, 348, 207. *Anal.* Calcd for $C_{28}H_{44}O_7$: C, 68.27; H, 9.00. Found: C, 68.16; H, 9.26

Methyl (5*Z*)-7-{(1*R*,2*R*,3*R*,5*S*)-5-Acetoxy-2-[(1*E*,3*S*)-3-hydroxy-1-octenyl]-3-[(2-oxacyclohexyl)oxy]cyclopentyl}-5-heptenoate (29) To a solution of $LiAlH_4$ (1.0 M in THF, 0.41 ml, 0.41 mmol) were added ethanol (1.0 M in THF, 0.41 ml, 0.41 mmol) and (*S*)-binaphthol (118 mg, 0.41 mmol) in THF (1.5 ml) at 0 °C. After the mixture was stirred at room temperature for 1 h, a solution of the above α,β-unsaturated ketone (58 mg, 0.118 mmol) in THF (1.5 ml) was added to the resulting solution of (*S*)-BINAL-H at −100 °C, and the mixture was stirred at the same temperature for 1 h. The solution was allowed to warm to −78 °C and stirred for 1 h. To the mixture were added successively methanol and sat. NH_4Cl aq., and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with sat. NH_4Cl aq. and brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (hexane/AcOEt=2 : 1) to afford **29** (54 mg, 92%) as a colorless oil. $[\alpha]_D^{29}$ +37.8° (*c*=1.05, $CHCl_3$). IR (neat) cm^{-1}: 3467, 2932, 2860, 1737, 1656, 1452, 1437. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.90 (3H, t, *J*=6.7 Hz), 1.20—1.90 (21H, m), 1.90—2.18 (5H, m), 2.06 (3H, s), 2.30 (2H, t, *J*=7.4 Hz), 2.33—2.60 (2H, m), 3.45 (1H, m), 3.78—4.06 (2H, m), 4.13 (1H, m), 4.60 (1/2H, m), 4.68 (1/2H, m), 5.08 (1H, m), 5.28—5.42 (2H, m), 5.49—5.74 (2H, m). MS *m/z*: 476 (M^+-H_2O), 463 (M^+-OMe), 410, 332, 191, 67. *Anal.* Calcd for $C_{28}H_{46}O_7$: C, 68.00; H, 9.37. Found: C, 68.22; H, 9.45.

Methyl (5*Z*)-7-{(1*R*,2*R*,3*R*,5*R*)-5-Acetoxy-3-hydroxy-2-[(1*E*,3*S*)-3-hydroxy-1-octenyl]cyclopentyl}-5-heptenoate A solution of **29** (54 mg, 0.109 mmol) in AcOH–H_2O–THF (19 : 11 : 3, 1.5 ml) was stirred at 40 °C for 2.5 h, and the solution was diluted with water, and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with sat. $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (chloroform/methanol=20 : 1) to afford the diol (42 mg, 93%) as colorless crystals. $[\alpha]_D^{25}$ +36.2° (*c*=1.00, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 3415, 3017, 2955, 2931, 2859, 1731, 1654, 1636, 1437. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J*=6.6 Hz), 1.17—1.72 (12H, m), 1.90—2.15 (5H, m), 2.05 (3H, s), 2.29 (2H, t, *J*=7.5 Hz), 2.32 (1H, m), 2.52 (1H, ddd, *J*=15.1, 8.8, 6.1 Hz), 2.68 (1H, br s), 3.67 (3H, s), 3.88 (1H, m), 4.08 (1H, m), 5.10 (1H, ddd, *J*=5.9, 5.9, 2.1 Hz), 5.25—5.41 (2H, m), 5.44 (1H, dd, *J*=15.3, 8.8 Hz), 5.61 (1H, dd, *J*=15.3, 7.1 Hz). MS *m/z*: 410 (M^+), 392, 368, 332, 43. *Anal.* Calcd for $C_{23}H_{38}O_6$: C, 67.29; H, 9.33. Found: C, 67.38; H, 9.43.

Prostaglandin $F_{2\alpha}$ To a solution of the above diol (42 mg, 0.085 mmol) in methanol (1.0 ml) and THF (0.5 ml) was added 1.0 M NaOH aq. (0.26 ml, 0.26 mmol) at room temperature, and the solution was stirred for 2 h. To the solution was added 1.0 M HCl aq. (0.3 ml, 0.3 mmol) at 0 °C, and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (chloroform/methanol/acetic acid=100 : 10 : 1) to afford $PGF_{2\alpha}$ (29 mg, 95%), whose spectral data were com-

pletely identical with those previously reported.[16] $[\alpha]_D^{29}$ +22.7° (c=1.59, THF). IR (neat) cm^{-1}: 3365, 959, 2930, 2860, 1729, 1705, 1577. ^{1}H-NMR (270 MHz, $CDCl_3/CD_3OD$=*ca.*10/1) δ: 0.88 (3H, t, J=6.6 Hz), 0.88 (3 H, t, J=6.6 Hz), 1.20—1.78 (12H, m), 1.88—2.37 (9H, m), 3.90 (1H, m), 4.02 (1H, m), 4.14 (1H, m), 5.29—5.50 (3H, m), 5.52 (1H, dd, J=15.2, 6.6 Hz). ^{13}C-NMR (67.5 MHz, $CDCl_3/CD_3OD$=*ca.*10/1) δ: 13.8, 22.4, 24.8, 25.0, 25.0, 26.3, 31.5, 33.8, 36.7, 42.2, 50.0, 55.0, 72.0, 72.8, 77.2, 128.9, 129.5, 132.7, 134.9, 178.3. MS *m/z*: 354 (M^+), 336 (M^+-H_2O), 318 (M^+-2H_2O), 300 (M^+-3H_2O), 264, 43.

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References and Notes

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16) The synthesized $PGF_{2\alpha}$ showed $[\alpha]_D^{29}$ +22.7° (c=1.59, THF), which agreed with the reported $[\alpha]_D^{25}$ +23.5° (c=1.00, THF),[17] and its ^{13}C-NMR spectrum was identical to those reported elsewhere.[18] The spectral data of $PGF_{2\alpha}$ methyl ester, obtained by treatment of synthetic $PGF_{2\alpha}$ with diazomethane, were also completely identical to those reported previously.[19]
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