A Catalytic Asymmetric Synthesis of 11-Deoxy-PGF$_{1\alpha}$ Using ALB, a Heterobimetallic Multifunctional Asymmetric Complex

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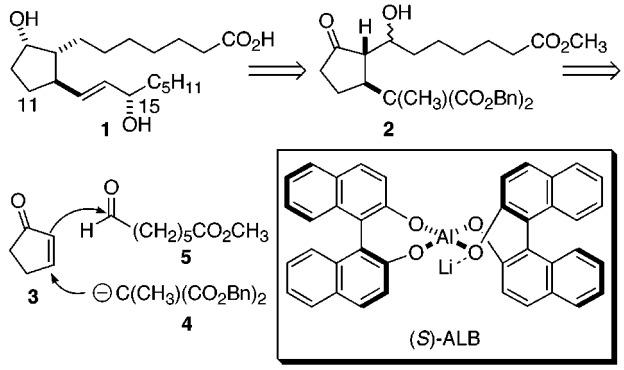
A catalytic asymmetric synthesis of 11-deoxy-PGF$_{1\alpha}$ has been achieved using a cascade Michael−aldol reaction as a key step. This cascade reaction was efficiently promoted by a catalytic use of AlLibis[(*S*)-binaphthoxide] complex (ALB) to give the three-component coupling product at room temperature in 92% ee and in 84% yield. The three-component coupling product was then converted to (+)-11-deoxy-PGF$_{1\alpha}$ through several steps, including an oxidative decarboxylation, an aldol reaction, and a Wharton reaction. Moreover, the racemic enone, **20** was transformed into **21**, the three-component coupling product, a potential intermediate for PGF$_{1\alpha}$, in 97% ee and in 75% yield through catalytic kinetic resolution.

We have developed a variety of heterobimetallic asymmetric complexes that efficiently promote many catalytic asymmetric reactions, such as nitro-aldol reactions,[1,2] Michael reactions,[1] hydrophosphonylations,[1] epoxide opening reactions with thiols,[3] epoxidations of α,β-unsaturated ketones,[4] and aldol reactions with unmodified ketones.[5] These heterobimetallic asymmetric complexes are multifunctional asymmetric catalysts, showing both Brønsted basicity and Lewis acidity to make a variety of useful catalytic asymmetric reactions possible. Among the many heterobimetallic complexes, AlLibis(binaphthoxide) complex (ALB) shows one of the most interesting chemical reactivities. That is, this catalyst enables a cascade Michael−aldol reaction,[6] which gives rise to the three-component coupling product in high enantiomeric excess even at room temperature. Other complexes, such as the $LaNa_3$tris(binaphthoxide) complex (LSB), the alkali metal-free lanthanum complex, or GaNabis(binaphthoxide), are also quite useful for catalytic asymmetric Michael reactions.[1] These complexes, however, do not promote cascade Michael−aldol reactions effectively and, thus, only give rise to highly optically active Michael adducts as major products. These results suggest that only intermediates of the aluminum enolate type, generated during the ALB-catalyzed Michael reactions, can react with aldehydes much faster than the competing protonation step can take place. We decided to demonstrate the usefulness of the above-mentioned cascade catalytic asymmetric Michael−aldol reactions by applying them to catalytic asymmetric syntheses of biologically significant compounds. As the first step of these planned synthetic projects, the development of a catalytic asymmetric synthesis of 11-deoxy-PGF$_{1\alpha}$ (**1**)[7] was undertaken. In this paper, we want to report a catalytic asymmetric synthesis of **1** using a cascade Michael−aldol reaction as a key step as well as an efficient synthesis of **21** through catalytic kinetic resolution.

Scheme 1



A retrosynthetic analysis for the catalytic asymmetric synthesis of 11-deoxy-PGF$_{1\alpha}$ (**1**) is described in Scheme 1. The rationale for adopting methyl-substituted dibenzyl malonate (**4**) as a Michael donor is as follows. Although a cascade catalytic asymmetric Michael−aldol reaction using dialkyl malonate proceeds, unfortunately, it results in only a modest chemical yield of the desired three-component coupling product. On the other hand, the use of methyl-substituted dialkyl malonate instead of dialkyl malonate gives rise, generally, to an excellent yield of the three-component coupling product. We thought that the three-component coupling product **2** could be converted to **1**.

According to the retrosynthetic analysis shown above, we first examined a cascade catalytic asymmetric

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(1) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236 and references cited therein.

(2) Takaoka, E.; Yoshikawa, N.; Yamada, Y. M. A.; Sasai, H.; Shibasaki, M. *Heterocycles* **1997**, *46*, 157.

(3) Iida, T.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1997**, *119*, 4783.

(4) Bougauchi, M.; Watanabe, S.; Arai, T.; Sasai, H.; Shibasaki, M. *Ibid*. **1997**, *119*, 2329.

(5) Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1871.

(6) Arai, T.; Sasai, H.; Aoe, K.; Okamura, K.; Date, T.; Shibasaki, M. *Ibid*. **1996**, *35*, 104.

(7) For previously reported total syntheses of (±)-11-deoxy-PGF$_{1\alpha}$, see; (a) Caton, M. P. L.; Coffee, E. C. J.; Watkins, G. L. *Tetrahedron Lett*. **1972**, 773. (b) Alvarez, F. S.; Wren, D.; Prince, A. *J. Am. Chem. Soc.* **1972**, *94*, 7823. (c) Alvarez, F. S.; Wren, D. *Tetrahedron Lett.* **1973**, *569*. (d) Burton, T. S.; Caton, M. P. L.; Coffee, E. C. J.; Parker, T.; Stuttle, K. A. J.; Watkins, G. L. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2550. For the only synthesis of optically pure (+)-11-deoxy-PGF$_{1\alpha}$ from natural PGs, see: (e) Lincoln, F. H.; Schneider, W. P.; Pike, J. E. *J. Org. Chem*. **1973**, *38*, 951.

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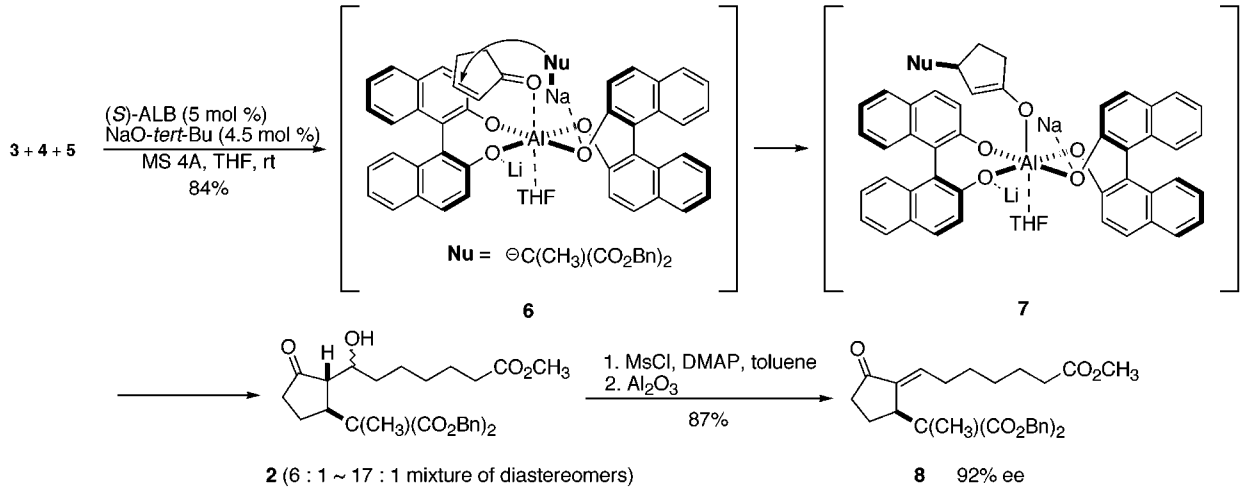
Scheme 2



Michael−aldol reaction. Prior to this research project, only benzaldehyde and hydrocinnamaldehyde had been utilized for the catalytic asymmetric three-component coupling reactions. So, the first challenging point in the present synthesis was to determine whether or not the aldehyde **5**[8] could be used for the catalytic asymmetric three-component coupling reaction. We were very pleased to find that AlLibis[(*S*)-binaphthoxide] (ALB) (10 mol %) can catalyze the tandem Michael−aldol reaction of cyclopentenone (**3**) with dibenzyl methylmalonate (**4**) (1.2 equiv)[9] and the aldehyde **5** (1.5 equiv) at room temperature to give the desired three-component coupling product **2** in 86% yield as a mixture of two diastereomers (6:1−17:1 by ^{1}H NMR). Barton deoxygenation of these diastereomers gave trans ketone **9** without a trace of cis ketone.[10] Thus, the relative stereochemistry of both side chains appeared to be perfectly controlled, and the stereochemistry of the secondary hydroxyl group was moderately controlled, giving a mixture of two diastereomers. The optical purity of **2** was determined to be 91% ee at the stage of the (*E*)-enone **8** (Scheme 2). The absolute configuration was unequivocally determined by converting **2** to 11-deoxy-PGF$_{1\alpha}$. It might be noteworthy that such a high enantioselectivity could be achieved even at room temperature. After several attempts, we succeeded in reducing the amount of ALB catalyst by using an improved, so-called second generation catalyst (ALB II)[1,11] and by simultaneously adding MS 4A. In the presence of MS 4A, ALB II (5 mol %), which was prepared from ALB (5 mol %) and sodium *tert*-butoxide (4.5 mol %), very efficiently catalyzed the tandem Michael−aldol reaction to give **2** in 84% yield and in 92% ee. The three-component coupling product **2** was then converted to **8** through mesylation followed by elimination[12] in 87% yield.[13] Recrystallization of **8** from ether−hexane (two times) afforded optically pure **8** in 57% yield. The intermediates **6** and **7**, shown in Scheme 2, are proposed for the highly efficient cascade reaction. The coordination of the enone to the aluminum should not only result in an activation of the enone but also fix the position of the enone so that high facial selectivity in the Michael addition could be achieved. The relatively large electronegativity of aluminum (1.5) would allow the intermediary aluminum enolate to react with the aldehyde faster than protonation of the enolate can take place.

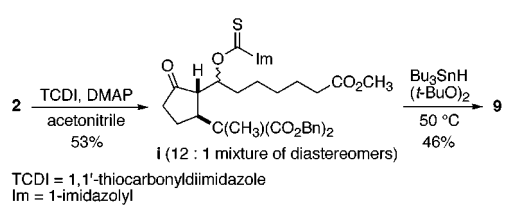
Hydrosilylation of optically pure **8** catalyzed by chlorotris(triphenylphosphine)rhodium at 80 °C[14] followed by treatment with aqueous hydrogen fluoride (46%) in acetonitrile at room temperature for 5 h gave the trans ketone **9** (Scheme 3). The *cis* isomer that was obtained as a mixture of diastereomers (cis:trans = 1:4) in a shorter reaction time (30 min) completely epimerized to *trans*-**9** in acidic conditions (catalytic CSA, 1,2-dichloroethane, reflux; or 46% aqueous hydrogen fluoride, acetonitrile, room temperature). The stereochemistry of *trans*-**9** was unequivocally determined by converting it to 11-deoxy-PGF$_{1\alpha}$. Reduction of the ketone **9** with L-Selectride in THF−CH_2Cl_2 at −78 °C furnished the α-alcohol **10** exclusively. The stereochemistry of **10** was determined by comparing the chemical shift of the carbinolic proton of **10** with that of the β-isomer.[15] The alcohol **10** then underwent a protection with *tert*-butyldimethylsilyl trifluoromethanesulfonate and 2,6-lutidine (CH_2Cl_2, −78 °C), giving **11** in 73% overall yield from **8**.

With the optically pure **11** in large quantities, the next synthetic task was an effective construction of the ω-chain. Toward this end, **11** was efficiently transformed

(8) Suzuki, M.; Kawagishi, T.; Yanagisawa, A.; Suzuki, T.; Okamura, N.; Noyori, R. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1299.

(9) As expected, the use of dibenzyl malonate instead of dibenzyl methylmalonate (**4**) as a Michael donor gave the three-component coupling products in only 9% yield.

(10) Acylation of **2** (ca. 17:1 mixture of diastereomers) with TCDI gave a mixture of diastereomers of **i** (ca. 12:1), whose reduction under radical conditions furnished **9** (as shown below). No cis isomer was detected by ^{1}H NMR.



(11) Arai, T.; Sasai, H.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 442.

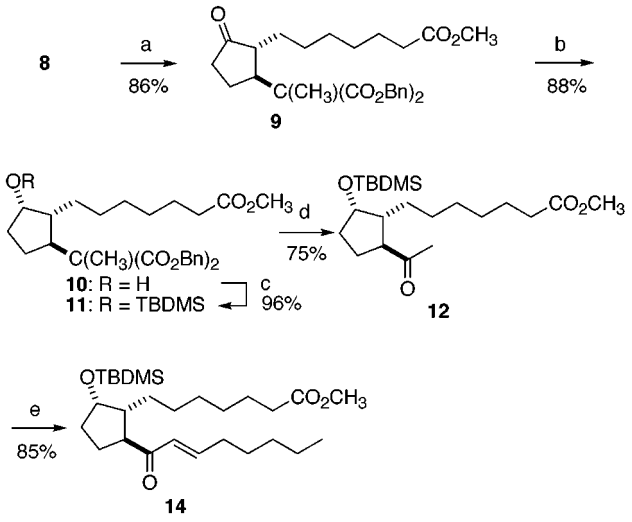
(12) Posner, G. H.; Gurria, G. M.; Babiak, K. A. *J. Org. Chem.* **1977**, *42*, 3173.

(13) The (*Z*)-isomer was also isolated as a minor product (<10%).

(14) Ojima, I.; Kogure, T. *Organometallics* **1982**, *1*, 1390.

(15) The chemical shift of the carbinolic proton of **10** was δ 4.2 and that of the epimer was δ 3.9. Carbinolic proton signals in α-alcohols in this type of substituted cyclopentanes appear consistently at lower field, relative to those in the β-alcohols (see ref 7c).

Scheme 3[a]

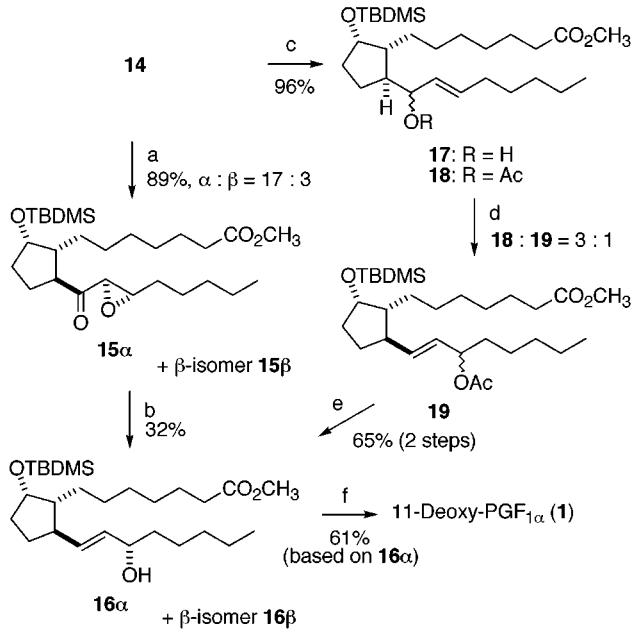


[a] Key: (a) (1) $(PH_3P)_3RhCl$, Et_3SiH; (2) aqueous HF, CH_3CN; (b) L-Selectride, THF−CH_2Cl_2; (c) TBDMSOTf, 2,6-lutidine, CH_2Cl_2; (d) (1) H_2 10% Pd−C, CH_3OH; (2) $Pb(OAc)_4$, pyridine, benzene; (3) K_2CO_3, CH_3OH; (e) (1) $TiCl_4$, *i*-$PrNEt_2$; hexanal (**13**), CH_2Cl_2; (2) MsCl, Et_3N; DBU, CH_2Cl_2.

into the methyl ketone **12**. Hydrogenolysis of **11** gave the dicarboxylic acid, which underwent oxidative decarboxylation[16] by treatment with lead tetraacetate in the presence of pyridine in benzene to furnish the diacetate. Reaction of the diacetate with potassium carbonate in methanol gave rise to the methyl ketone **12** in 75% overall yield. Aldol reaction of **12** with hexanal (**13**) through the lithium enolate generated by lithium hexamethyldisilazide, followed by elimination, furnished the enone **14** in 66% yield. This transformation was found to be improved using the titanium enolate,[17] giving the enone **14** in 85% overall yield.

Final conversion of **14** to 11-deoxy-$PGF_{1\alpha}$ (**1**) was achieved in two ways. As shown in Scheme 4, the first route to **1** utilized a Wharton reaction.[18] We first applied a catalytic asymmetric epoxidation[4] recently developed in our group to the enone **14**. Treatment with a catalyst, generated from La(O-*i*-Pr)$_3$[19] and (*S*)-3-(hydroxymethyl)-binaphthol, and *tert*-butyl hydroperoxide afforded the desired α-epoxide **15α** and the *β*-epoxide **15*β*** in a ratio of 17:3 (89%). Under standard epoxidation conditions with dimethyldioxirane, no stereoselectivity was observed, and **15α** and **15*β*** were produced in a ratio of 1:1. The mixture of the epoxides was then subjected to Wharton reaction conditions (hydrazine monohydrochloride and triethylamine in (dimethylamino)ethanol) to give the desired allylic alcohols **16α** and **16*β*** (ca. 17:3) as a mixture with some byproducts in 32% combined yield. In an attempt to improve the transformation of **14** to **16α**, we found another approach. That is, the second route to **1** involved the allylic acetate **18**. Thus, the enone **14** was reduced with sodium borohydride and cerium(III)

Scheme 4[a]



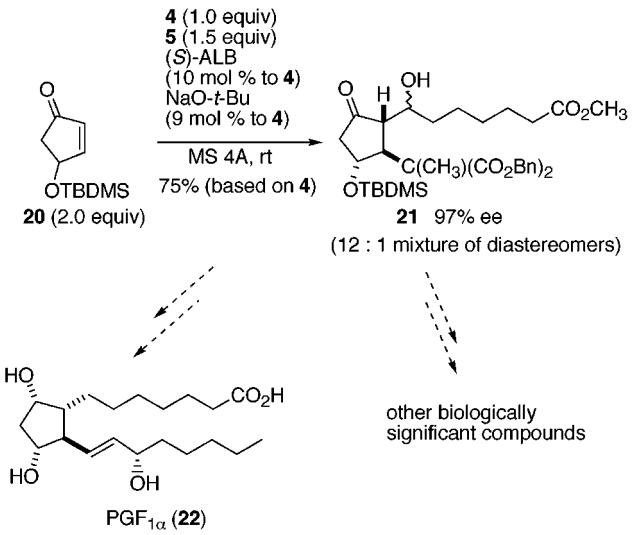
[a] KEY: (a) La-(*S*)-3-(hydroxymethyl)binaphthol complex, TBHP, MS4A, toluene; (b) N_2H_4·HCl, Et_3N, (dimethylamino)ethanol; (c) (1) $NaBH_4$, $CeCl_3$, CH_3OH; (2) Ac_2O, DMAP, pyridine; (d) $PdCl_2$-$(CH_3CN)_2$, THF; (e) K_2CO_3, CH_3OH; (f) (1) HF−pyridine, THF; (2) aq NaOH, THF.

chloride[20] in methanol at 0 °C, giving a mixture of diastereomers of the allylic alcohols **17**. The ratio of the allylic alcohols was determined to be 2 (α-alcohol):1(*β*-alcohol) by ^{1}H NMR analysis after converting the mixture of the allylic alcohols to the allylic acetates **18** (92% from **14**). The allylic acetates **18** were treated with a catalytic amount of bis(acetonitrile)dichloropalladium(II) (4 mol %) in THF at room temperature for 4.5 h.[21] Under these conditions, the desired product **19** was obtained as an equilibrium mixture with **18** in a ratio of 3 (**19**):1 (**18**). Deacetylation of the allylic acetates **19** and **18** gave the allylic alcohols **16** and **17** in 86% combined yield from **18**. Re-acetylation of recovered **17** gave **18** as a mixture of diastereomers in a ratio of 2:1 (α:*β*). Consequently, the ratio of diastereomers of **16** should be 2:1 (α:*β*). **16** was then transformed into 11-deoxy-PGF_α (**1**) by sequential deprotection (61% overall yield based on **16α**). The optical purity of **1** thus obtained as well as the absolute configuration were unequivocally confirmed by converting **16** to known optically pure 11-deoxy-PGE_1.[7e, 22]

Furthermore, we examined the possibility of synthesizing optically active $PGF_{1\alpha}$ (**22**) using a catalytic kinetic resolution as a key step. Thus, the racemic enone **20**[23] underwent a cascade catalytic asymmetric Michael−aldol reaction under the conditions shown in Scheme 5. The desired three-component coupling product **21**, a potential intermediate for $PGF_{1\alpha}$, was obtained in 75% yield (based on malonate **4**) and in 97% ee[24] as a mixture of two diastereomers (12:1 by ^{1}H NMR). Not only almost perfect

(16) Tufariello, J. J.; Kissel, W. J. *Tetrahedron Lett.* **1966**, 6145.
(17) (a) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047. (b) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *Ibid.* **1990**, *112*, 8215.
(18) (a) Castedo, L.; Mascañas, J. L.; Mouriño, A. *Tetrahedron Lett.* **1987**, *28*, 2099. (b) Wharton, P. S.; Bohlen, D. H. *J. Org. Chem.* **1961**, *26*, 3615.
(19) Purchased from Kojundo Chemical Co., Ltd., 5-1-28, Chiyoda, Sakato, Saitama 350-02, Japan (Fax: +81-492-84-1351).
(20) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.
(21) Grieco, P. A.; Takigawa, T.; Bongers, S. L.; Tanaka, H. *Ibid.* **1980**, *102*, 7588.
(22) (a) Abraham, N. A. *Tetrahedron Lett.* **1974**, 1393. (b) Sih, C. J.; Salomon, R. G.; Price, P.; Sood, R.; Peruzzotti, G. *J. Am. Chem. Soc.* **1975**, *97*, 857.
(23) (a) Krüger, G.; Harde, C.; Bohlmann, F. *Terahedron Lett.* **1985**, *26*, 6027. (b) Paquette, L. A.; Earle, M. J.; Smith, G. F. *Org. Synth.* **1996**, *73*, 36.

Scheme 5



kinetic resolution but also relatively high yield was achieved. This is the first example of a catalytic kinetic resolution using heterobimetallic multifunctional complexes. The three-component coupling product **21** should be a useful intermediate for synthesizing a variety of biologically significant compounds including PGF$_{1\alpha}$.

In conclusion, we have achieved a catalytic asymmetric synthesis of 11-deoxy-PGF$_{1\alpha}$ (**1**) using a cascade catalytic asymmetric Michael−aldol reaction as a key step and succeeded in demonstrating the usefulness of this cascade reaction.[25] Moreover, we have shown a new potential of heterobimetallic multifunctional catalysts to act as promoter in catalytic kinetic resolutions.

Experimental Section

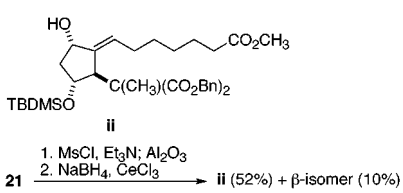
General Methods. ^{1}H NMR and ^{13}C NMR spectra were measured with $CDCl_3$ as a solvent. Chemical shifts are reported in ppm on the δ scale relative to residual $CHCl_3$ (δ = 7.26 for ^{1}H NMR and δ = 77.0 for ^{13}C NMR) as an internal reference. The THF solution of ALB was prepared according to the reported procedure.[6] MS 4A was dried at 180 °C under reduced pressure for 6 h prior to use. All solvents used in the reactions were dried prior to use. All reagents were purified by standard methods. All experiments were performed under an anhydrous argon atmosphere, unless otherwise mentioned, and monitored with analytical TLC (Merck Art. 5715, silica gel 60 F_{254} plates).

Methyl (*R*)-7-[(1*S*,2*S*)-2-[1,1-Bis(benzyloxycarbonyl)ethyl]-5-oxocyclopentyl]-7-hydroxyheptanoate (2α) and Methyl (*S*)-7-[(1*S*,2*S*)-2-[1,1-Bis(benzyloxycarbonyl)ethyl]-5-oxocyclopentyl]-7-hydroxyheptanoate (2b). To dried MS 4A (100 mg) was added a 0.1 M (*S*)-ALB THF solution (0.50 mL, 0.050 mmol), a THF solution of sodium *tert*-butoxide (0.49 M, 0.092 mL), 2-cyclopenten-1-one (**3**) (0.084 mL, 1.0 mmol), methyl 6-formylhexanoate (**5**) (0.24 mL, 1.5 mmol), and dibenzyl methylmalonate (**4**) (0.32 mL, 1.2 mmol) at room temperature. The reaction mixture was stirred for 90 h at the same temperature before filtration (Celite). The residual MS 4A was successively washed with EtOAc, and the filtrate was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine, then dried (Na_2SO_4) and concentrated. Purification of the resulting residue by flash column chromatography (SiO_2, 35% EtOAc−hexane) gave β-hydroxy ketones **2** (0.45 g, 84% based on enone **3**, a mixture of two diastereomers) as a pale yellow oil: IR (neat) ν 3513, 1732 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 3H), 1.21−1.75 (m, 9H), 2.32 (t, 2H, J = 7.3 Hz), 2.02−2.39 (m, 5H), 2.94 (m, 0.15H), 3.02 (dt, 0.85H, J = 8.0, 6.6 Hz), 3.66 (s, 3H), 3.60−3.66 (m, 1H), 5.00−5.16 (m, 4H), 7.22−7.33 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 18.5, 22.9, 24.8, 25.9, 28.9, 33.9, 34.2, 38.5, 43.4, 51.4, 55.4, 57.1, 67.3, 72.8, 128.2, 128.3, 128.4, 128.5, 128.6, 134.9, 135.0, 171.2, 171.3, 174.2, 218.6; FABMS: m/z 539 (M^+), 521 (M^+ − O); HRMS m/z calcd for $C_{31}H_{37}O_7$ (M^+ − OH) 521.2539, found 521.2515.

Methyl (*E*)-7-[(*S*)-2-[1,1-Bis(benzyloxycarbonyl)ethyl]-5-oxocyclopentylidene]heptanoate (8). To β-hydroxy ketone **2** (3.5 g, 6.5 mmol) in 70 mL of toluene was added triethylamine (4.5 mL, 30 mmol) and then methanesulfonyl chloride (1.3 mL, 17 mmol) at 0 °C. After the reaction mixture was warmed to room temperature and stirred for 25 min, activated alumina (38 g) was added in several portions. The reaction mixture was stirred for 26 h before filtration (Celite). The residual alumina was successively washed with EtOAc, and the filtrate was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated. Purification of the resulting residue by flash column chromatography (SiO_2, 15% EtOAc−hexane) gave enone **8** (2.9 g, 87%) in 91% ee as a white-to-yellow solid. Recrystallization of **8** from ether−hexane two times gave **8** (57%) in >99% ee: mp 78 °C; IR (KBr) ν 1725, 1647 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 3H), 1.24−1.63 (m, 6H), 2.27 (t, J = 7.5 Hz, 2H), 2.02−2.30 (m, 6H), 3.66 (s, 3H), 3.75 (d, J = 7.3 Hz, 1H), 5.04 (d, J = 12 Hz, 1H), 5.06 (s, 2H), 5.15 (d, J = 12 Hz, 1H), 6.60 (dd, J = 5.5, 9.5 Hz, 1H), 7.21−7.32 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 18.7, 23.7, 24.6, 28.3, 28.7, 29.7, 33.8, 35.3, 42.5, 51.4, 58.6, 67.2, 67.3, 127.9, 128.1, 128.3, 128.4, 128.5, 135.0, 137.7, 140.5, 170.8, 173.9, 206.9; MS m/z 521 (M^+ + 1), 520 (M^+); $[\alpha]^{28}_D$ +106 (c = 0.490, $CHCl_3$). Anal. Calcd for $C_{31}H_{36}O_7$: C, 71.52; H, 6.97. Found: C, 71.59; H, 7.10. The enantiomeric excess of **8** was determined by chiral stationary-phase HPLC analysis (DAICEL Chiralpak AD, 10% *i*-PrOH−hexane, flow rate: 1.0 mL/min, retention time: 23 min (*S*)-isomer and 29 min (*R*)-isomer, detection at 254 nm).

Methyl 7-[(1*R*,5*S*)-2-[1,1-Bis(benzyloxycarbonyl)ethyl]-5-oxocyclopentyl]heptanoate (9). To a mixture of enone **8** (1.6 g, 3.1 mmol) and chlorotris(triphenylphosphine)rhodium (I) (57 mg, 0.062 mmol) was added triethylsilane (2.5 mL, 15 mmol) slowly at 80 °C. After being stirred for 15 min at the same temperature, the reaction mixture was directly filtered (SiO_2, 10% EtOAc−hexane) to give a crude mixture (2.0 g). The mixture was dissolved in acetonitrile (29 mL), and 46% aqueous hydrogen fluoride (1.3 mL) was added to the solution. After being stirred for 6 h at room temperature, the reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$. The organic layer was separated and washed with brine, and the aqueous layer was extracted with EtOAc (50 mL × 2). The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography (SiO_2, 25% EtOAc−hexane) to give trans ketone **9** (1.4 g, 86%) as a colorless oil: IR (neat) ν 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 3H), 1.14−1.76 (m, 10H), 2.06−2.22 (m, 7H), 2.27 (t, 2H, J = 7.6 Hz), 2.76 (dt, 1H, J = 6.9, 6.9 Hz), 3.66 (s, 3H), 5.02−5.30 (m, 4H), 7.22−7.33 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 18.0, 22.6, 24.8, 25.9, 28.9, 29.4, 31.0, 34.0, 36.9, 45.0, 50.4, 51.4, 56.9, 67.1, 67.2, 128.1, 128.3, 128.5, 135.1, 170.9, 171.0, 174.1, 220.0; MS m/z 523 (M^+), 491 (M^+ − OMe); HRMS m/z

(24) The optical purity of **21** was determined after converting it to α-alcohol **ii**, shown below, by chiral stationary-phase HPLC analysis (DAICEL CHIRALPAK AD, 5% *i*-PrOH−hexane, flow rate: 1.0 mL/min, retention time: 25 min **ii** and 29 min its enantiomer, detection at 254 nm).



(25) For a very recent catalytic asymmetric Michael−aldol reaction, see: Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; de Vries, A. H. M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2620.

calcd for $C_{31}H_{38}O_7$ 522.2618, found 522.2623; $[\alpha]^{25}_D$ −3.8 (*c* = 0.588, $CHCl_3$).

Methyl 7-[(1*R*,2*S*,5*S*)-2-[1,1-Bis(benzyloxycarbonyl)ethyl]-5-hydroxycyclopentyl]heptanoate (10). To ketone **9** (31 mg, 0.060 mmol) in CH_2Cl_2 (3.0 mL) was added a THF solution of L-Selectride (1.0 M, 0.072 mL) at −78 °C. The reaction mixture was stirred for 40 min at the same temperature before THF solution of L-Selectride (1.0 M, 0.030 mL) was again added. After being stirred for 30 min at the same temperature, the reaction mixture was quenched by addition of 3% aqueous H_2O_2 and diluted with Et_2O. The organic layer was separated and washed with saturated aqueous $Na_2S_2O_4$ and brine, dried (Na_2SO_4), and concentrated. The resulting residue was purified by flash column chromatography (SiO_2, 20% EtOAc−hexane) to give α-alcohol **10** (28 mg, 88%) as a pale yellow oil: IR (neat) *ν* 3661, 1727 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 1.43 (s, 3H), 1.06−1.63 (m, 14H), 1.67−1.73 (m, 1H), 2.06 (ddt, 1H, *J* = 9.5, 14, 8.5 Hz), 2.28 (t, 2H, *J* = 7.5 Hz), 2.60 (dt, 1H, *J* = 5.8, 9.5 Hz), 3.66 (s, 3H), 4.19 (dt, 1H, *J* = 4.0, 3.7 Hz), 5.05 (d, 1H, *J* = 13 Hz), 5.09 (s, 2H), 5.10 (d, 1H, *J* = 13 Hz), 7.24−7.31 (m, 10H); ^{13}C NMR ($CDCl_3$) *δ* 17.3, 24.8, 26.5, 28.0, 28.8, 29.0, 29.5, 33.6, 34.0, 45.9, 46.1, 51.4, 56.7, 66.8, 66.9, 74.0, 128.0, 128.2, 128.4, 135.3, 135.4, 171.4, 171.7, 174.2; MS *m*/*z* 525 (M^+); $[\alpha]^{27}_D$ +21.6 (*c* = 0.614, $CHCl_3$). Anal. Calcd for $C_{31}H_{36}O_7$: C, 70.97; H, 7.68. Found: C, 70.68; H, 7.71.

Methyl 7-[(1*R*,2*S*,5*S*)-2-[1,1-Bis(benzyloxycarbonyl)ethyl]-5-(*tert*-butyldimethylsiloxy)cyclopentyl]heptanoate (11). To a mixture of alcohol **10** (3.5 g, 6.6 mmol) and 2,6-lutidine (1.5 mL, 13 mmol) in CH_2Cl_2 (6.6 mL) was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (2.3 mL, 9.9 mmol) at −78 °C. After being stirred for 30 min at the same temperature, the reaction mixture was quenched by addition of saturated aqueous NH_4Cl and diluted with Et_2O. The mixture was allowed to warm to room temperature, and the organic layer was separated. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, and then dried (Na_2SO_4) and concentrated. The resulting residue was purified by flash column chromatography (SiO_2, 5% EtOAc−hexane) to give TBDMS ether **11** (4.0 g, 96%) as a colorless oil: IR (neat) *ν* 1732 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 0.00 (s, 3H), 0.02 (s, 3H), 0.86 (s, 9H), 1.42 (s, 3H), 0.87−1.68 (m, 14H), 1.95−2.08 (m, 1H), 2.27 (t, 2H, *J* = 7.6 Hz), 2.54−2.63 (m, 1H), 3.66 (s, 3H), 4.13−4.16 (br, 1H), 5.01−5.14 (m, 4H), 7.22−7.32 (m, 10H); ^{13}C NMR ($CDCl_3$) *δ* −5.1, −4.3, 17.3, 18.0, 25.0, 25.8, 26.4, 28.2, 29.1, 29.3, 29.7, 34.0, 34.1, 46.4, 51.4, 56.9, 66.7, 66.8, 74.5, 128.0, 128.1, 128.4, 135.4, 135.5, 171.6, 171.9, 174.2; MS *m*/*z* 638 (M^+); HRMS *m*/*z* calcd for $C_{37}H_{54}O_7Si$ 638.3638, found 638.3662; $[\alpha]^{25}_D$ +29.2 (*c* = 0.646, $CHCl_3$).

Methyl 7-[(1*R*,2*S*,5*S*)-2-Acetyl-5-(*tert*-butyldimethylsiloxy)cyclopentyl]heptanoate (12). A mixture of dibenzyl ester **11** (0.41 g, 0.64 mmol) and 10% Pd−C (69 mg, 10 mol%) in methanol (6.4 mL) was stirred in a hydrogen atmosphere for 11 h at room temperature. The catalyst was removed by filtration (Celite) and washed successively with methanol. The filtrate was concentrated to give a crude residue (0.36 g), which was then dissolved in benzene (0.92 mL). To the solution were added pyridine (0.13 mL, 1.6 mmol) and lead tetraacetate (0.63 g, 13 mmol). The mixture was gently warmed until the evolution of carbon dioxide commenced. After the carbon dioxide evolution had ceased, the mixture was gently rewarmed. The rewarming was repeated three times before the reaction mixture was heated to reflux. After 12 h, the reaction mixture was diluted with Et_2O and cooled to room temperature. The reaction mixture was then filtered (Celite) to remove salt. The salt was successively washed with Et_2O. The filtrate was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine and then dried (Na_2SO_4) and concentrated to give a crude residue. The residue was dissolved in methanol (6.0 mL), and potassium carbonate (0.18 g, 1.3 mmol) was added to the solution. The mixture was stirred for 30 min at room temperature, and subsequently the pH value was adjusted to 7 with 1 N HCl and saturated aqueous $NaHCO_3$. Methanol was removed in vacuo, and the aqueous layer was extracted with EtOAc three times. The combined organic layers were dried (Na_2SO_4) and concentrated. The resulting residue was purified by flash column chromatography (SiO_2, 5% EtOAc−hexane) to give methyl ketone **12** (0.19 g, 75%) as a colorless oil: IR (neat) *ν* 1741, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 0.03 (s, s, 3H), 0.04 (s, 3H), 0.88 (s, 9H), 1.20−1.73 (m, 13H), 1.99−2.16 (m, 2H), 2.16 (s, 3H), 2.29 (t, 2H, *J* = 7.5 Hz), 2.77 (dt, 1H, *J* = 5.6, 9.1 Hz), 3.66 (s, 3H), 4.19 (br, 1H); ^{13}C NMR ($CDCl_3$) *δ* −5.1, −4.4, 18.0, 24.9, 25.7, 26.7, 28.1, 28.7, 29.1, 29.5, 29.6, 34.0, 34.5, 48.4, 51.3, 55.2, 74.8, 174.2, 211.9; MS *m*/*z* 385 (M^+), 369 ($M^+ - CH_3$), 353 ($M^+ - OCH_3$), 327 ($M^+ - CO_2CH_3$); HRMS *m*/*z* calcd for $C_{21}H_{40}O_4Si$ 384.2696, found 384.2688; $[\alpha]^{26}_D$ +69.8 (*c* = 0.634, $CHCl_3$).

Methyl (8*R*,9*S*,12*S*,*E*)-9-(*tert*-Butyldimethylsiloxy)-13-oxo-14-prosten-1-oate (14). A CH_2Cl_2 solution of $TiCl_4$ (1.0 M, 0.56 mL) was added dropwise to methyl ketone **12** (180 mg, 0.47 mmol) in CH_2Cl_2 (1.8 mL) at −78 °C. After 2 min, *N*,*N*-diisopropylethylamine (0.11 mL, 0.61 mmol) was added dropwise, and the solution was stirred at −78 °C for 1.5 h. After the dropwise addition of a solution of hexanal (55 mg, 0.55 mmol) in CH_2Cl_2 (2.3 mL), stirring was continued at −78 °C for 1.5 h. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl and warmed to room temperature. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The resulting residue was purified by flash column chromatography (SiO_2, 18% EtOAc−hexane) to give a mixture of products. The mixture was dissolved in CH_2Cl_2 (4.7 mL), and triethylamine (0.33 mL, 2.4 mmol) was added to the solution. Methanesulfonyl chloride (0.091 mL, 1.2 mmol) was added dropwise to the mixture, and the mixture was allowed to warm to room temperature. After 15 min, 1,8-diazabicyclo[5.4.0]undec-7-ene (0.35 mL, 2.4 mmol) was added, and the reaction mixture was stirred for 70 min at room temperature before being quenched with saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine and then dried (Na_2SO_4) and concentrated. The resulting residue was purified by flash column chromatography (SiO_2, 10% EtOAc−hexane) to give enone **14** (190 mg, 85%) as an oil: IR (neat) *ν* 1742, 1692, 1666, 1627 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 0.04 (s, 3H), 0.05 (s, 3H), 0.88−0.91 (m, 12H), 1.16−1.77 (m, 19H), 2.04−2.13 (m, 2H), 2.21 (ddt, 2H, *J* = 1.5, 7.0, 8.2 Hz), 2.28 (t, 2H, *J* = 7.6 Hz), 2.99 (dt, 1H, *J* = 6.1, 10.1 Hz), 3.65 (s, 3H), 4.20−4.23 (br, 1H), 6.14 (dt, 1H, *J* = 15.6, 1.5 Hz), 6.84 (dt, 1H, *J* = 15.6, 7.0 Hz); ^{13}C NMR ($CDCl_3$) *δ* −5.0, −4.4, 13.9, 18.0, 22.4, 24.9, 25.8, 27.6, 27.8, 28.2, 28.7, 29.1, 29.6, 31.3, 32.4, 34.0, 34.7, 48.8, 51.3, 51.8, 75.1, 130.3, 147.5, 174.2, 203.6; MS *m*/*z* 466 (M^+), 451 ($M^+ - CH_3$), 435 ($M^+ - OCH_3$), 410 (M^+ − *t*-Bu); HRMS *m*/*z* calcd for $C_{21}H_{40}O_4Si$ 466.3478, found 466.3478; $[\alpha]^{24}_D$ +62.9 (*c* = 0.476, $CHCl_3$).

Methyl (8*R*,9*S*,12*S*,14*R*,15*S*)-9-(*tert*-Butyldimethylsiloxy)-14,15-epoxy-13-oxo-1-prostanoate (15α) and Methyl (8*R*,9*S*,12*S*,14*S*,15*R*)-9-(*tert*-Butyldimethylsiloxy)-14,15-epoxy-13-oxo-1-prostanoate (15*β*). To dried MS 4A were added a solution of (*S*)-3-(hydroxymethyl)binaphthol (20 mg, 64 *μ*mol) in THF (0.64 mL) and a THF solution of lanthanum(III) isopropoxide (0.2 M , 0.23 mL). The suspension was stirred for 1 h at room temperature before THF was removed in vacuo. To the resulting residue was added a solution of the enone **14** (43 mg, 93 *μ*mol) in toluene (1.0 mL) and a toluene solution of *tert*-butyl hydroperoxide (4 M , 60 *μ*L) at 0 °C. After being stirred for 27 h at 0 °C, the reaction mixture was quenched by addition of saturated aqueous NH_4Cl. The insoluble material and aqueous layer were removed by filtration (Celite, Na_2SO_4) and successively washed with EtOAc. The filtrate and the washing were combined and concentrated. The resulting residue was purified by flash column chromatography (SiO_2, 5% EtOAc−hexane) to give epoxy ketones **15** (40 mg, 89%, α:*β* = 85:15 by ^1H NMR analysis): IR (neat) *ν* 1741, 1702, 1252 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 0.03 (s, 3H), 0.04 (s, 3H), 0.87−1.69 (m, 20H), 1.72−1.80 (m, 1H), 2.00−2.22 (m, 2H), 2.29 (t, 2H, *J* = 7.6 Hz), 2.76 (dt, 0.15H, *J* = 5.5, 10.7 Hz),

2.91 (dt, 0.85H, J = 5.8, 10.1 Hz), 2.99−3.04 (m, 1H), 3.26−3.27 (brd, 1H), 3.66 (s, 3H), 4.19−4.21 (br, 1H); ^{13}C NMR ($CDCl_3$) δ −5.0, −4.4, 13.9, 18.0, 22.5, 24.9, 25.4, 25.5, 25.8, 27.0, 27.4, 28.3, 28.7, 29.1, 29.5, 31.4, 31.8, 34.0, 34.5, 34.9, 47.3, 49.1, 49.5, 49.9, 51.4, 58.1, 58.5, 59.3, 74.8, 75.1, 174.2, 211.0; MS m/z 482 (M^+), 467 ($M^+ - CH_3$), 451 ($M^+ - OCH_3$), 425 ($M^+ - t$-Bu); HRMS m/z calcd for $C_{27}H_{50}O_5Si$ 482.3428, found 482.3432.

Methyl (8*R*,9*S*,12*S*,13*S*,*E*)-13-Acetoxy-9-(*tert*-butyldimethylsiloxy)-14-prosten-1-oate (18α) and Methyl (8*R*,9*S*,12*S*,13*R*,*E*)-13-Acetoxy-9-(*tert*-butyldimethylsiloxy)-14-prosten-1-oate (18*β*). To the enone **14** (99 mg, 0.21 mmol) and cerium(III) chloride heptahydrate (79 mg, 0.21 mmol) in methanol (0.53 mL) was added sodium borohydride (12 mg, 0.32 mmol) at 0 °C. The reaction mixture was stirred for 15 min at the same temperature and quenched by addition of saturated aqueous NH_4Cl. Methanol was removed in vacuo, and the aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated to give a mixture of α-alcohol **17α** and *β*-alcohol **17*β*** (95 mg, 96%) as a colorless oil.

The mixture of the alcohols **17** (95 mg, 0.20 mmol) was dissolved in pyridine (2.1 mL). To the solution were added acetic anhydride (0.20 mL, 2.1 mmol) and 4-(dimethylamino)-pyridine (3 mg, 0.02 mmol) at room temperature. The reaction mixture was stirred for 1.5 h at the same temperature, and water (10 mL) was added. The aqueous layer was extracted with EtOAc (5 mL × 3). The combined organic layers were washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography (SiO_2, 5% EtOAc−hexane) to give acetates **18** (99 mg, 96%, α:*β* = 2:1 by ^{1}H NMR analysis) as a colorless oil: IR (neat) ν 1741 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.02 (s, 3H), 0.03 (s, 3H), 0.86−0.89 (m, 12H), 1.14−1.65 (m, 19H), 2.03 (s, 3H), 1.8−2.05 (m, 4H), 2.30 (brt, 2H), 3.66 (s, 3H), 4.12−4.16 (br, 1H), 5.16 (dd, 0.34H, J = 7.0, 7.3 Hz), 5.23 (dd, 0.66H, J = 4.6, 7.0 Hz), 5.33−5.40 (m, 1H), 5.63−5.71 (m, 1H); ^{13}C NMR ($CDCl_3$) δ −5.1, −4.3, 14.0, 18.0, 21.3, 21.4, 22.4, 23.8, 24.5, 25.0, 25.8, 28.1, 28.2, 28.6, 29.2, 29.6, 29.7, 31.3, 32.2, 32.4, 34.0, 34.1, 34.3, 45.3, 46.0, 47.3, 48.2, 51.3, 74.5, 76.3, 78.1, 126.2, 127.6, 134.0, 135.6, 170.3, 170.4, 174.2; MS m/z 510 (M^+), 495 ($M^+ - CH_3$), 453 ($M^+ - t$-Bu); HRMS m/z calcd for $C_{29}H_{54}O_5Si$ 510.3740, found 510.3740.

9-*O*-(*tert*-Butyldimethylsilyl)-11-deoxy-PGF$_{1\alpha}$ Methyl Ester (16α) and 9-*O*-(*tert*-Butyldimethylsilyl)-15-*epi*-11-deoxy-PGF$_{1\alpha}$ Methyl Ester (16*β*). Method A. To a solution of the epoxy ketones **15** (16 mg, 34 μmol) and triethylamine (19 μL, 0.14 mmol) in (dimethylamino)ethanol (34 μL) was added hydrazine monohydrochloride (7 mg, 0.1 mmol) at 0 °C. After being stirred for 24 h at the same temperature, the reaction mixture was diluted with Et_2O, washed with 5% aqueous citric acid, saturated aqueous $NaHCO_3$, and brine, dried, and concentrated. The resulting residue was purified by flash column chromatography (SiO_2, 10% EtOAc−hexane) to give a mixture including mainly allylic alcohols **16** (5.1 mg, 32%).

Method B. The acetates **18** (98 mg, 0.19 mmol) were dissolved in THF (1.9 mL), and bis(acetonitrile)dichloropalladium(II) (2 mg, 4 mol %) was added to the solution. The reaction mixture was stirred for 4.5 h at room temperature, and water (5 mL) was added. The aqueous layer was extracted with EtOAc (5 mL × 3). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a crude mixture of acetates **19** and **18** (0.10 g, the ratio of **19** and **18** was determined to be 3:1 by ^{1}H NMR analysis) as a colorless oil.

The mixture of the acetates **19** and **18** (0.10 g) was dissolved in methanol (1.9 mL), and potassium carbonate (32 mg, 0.23 mmol) was added to the solution. The reaction mixture was stirred for 13 h at room temperature and neutralized by addition of 1 N HCl and saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography (SiO_2, 15% EtOAc−hexane) to give the desired allylic alcohols **16** (34 mg, 38%) as a more polar product, 13-hydroxy isomers **17** (4.1 mg, 4.5%) as a less polar product, and mixed products (40 mg, 44%). The mixed products were separated by flash column chromatography (SiO_2, 15% EtOAc−hexane) to give **16** (13 mg, 14%), **17** (6.4 mg, 7.1%), and mixed products (20 mg, 22%). The mixed products were separated again by flash column chromatography (SiO_2, 15% EtOAc−hexane) to give **16** (5.7 mg, 6.3%), **17** (5.1 mg, 5.6%), and mixed products (8.6 mg, 9.5%). **16**: IR (neat) ν 3372, 1743 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.02 (s, 3H), 0.03 (s, 3H), 0.86−0.90 (m, 12H), 1.14−1.64 (m, 21H), 1.72−1.80 (m, 1H), 1.92−2.00 (m, 1H), 2.26 (t, 2H, J = 7.6 Hz), 2.26−2.33 (m, 1H), 3.66 (s, 3H), 4.02−4.07 (m, 1H), 4.15−4.17 (br, 1H), 5.39−5.50 (m, 2H); ^{13}C NMR ($CDCl_3$) δ −5.1, −4.3, 14.0, 18.0, 22.6, 24.9, 25.1, 25.2, 25.8, 27.1, 27.2, 28.1, 28.2, 29.1, 29.2, 29.6, 29.7, 29.8, 29.9, 31.7, 31.8, 34.1, 34.3, 37.3, 45.6, 45.8, 51.4, 52.2, 73.0, 73.3, 74.2, 132.6, 136.1, 136.6, 174.3; MS m/z 468 (M^+), 450 ($M^+ - H_2O$), 437 ($M^+ - OCH_3$), 411 ($M^+ - t$-Bu); HRMS m/z calcd for $C_{27}H_{50}O_5Si$ 468.3635, found 468.3637.

(+)-11-Deoxy-PGF$_{1\alpha}$ (1). To a solution of allylic alcohols **16** (31 mg, 66 μmol) in THF (0.33 mL) was added HF−pyridine (66 mg) in THF (0.33 mL) at 0 °C. After being stirred for 46 h at room temperature, the reaction mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, saturated aqueous $CuSO_4$, water, and brine, dried (Na_2SO_4), and concentrated. The resulting residue was purified by preparative TLC (Si_2O, 40% EtOAc−hexane) and flash column chromatography (SiO_2, 35% EtOAc−hexane) to give less polar 15-*epi*-11-deoxy-PGF$_{1\alpha}$ methyl ester (7.5 mg, 34%) and more polar 11-deoxy-PGF$_{1\alpha}$ methyl ester (11 mg, 45%): IR (neat) ν 3394, 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H, J = 6.9 Hz), 1.25−1.67 (m, 21H), 1.90−2.05 (m, 2H), 2.30 (t, 2H, J = 7.5 Hz), 2.27−2.35 (m, 1H), 3.66 (s, 3H), 4.03−4.07 (m, 1H), 4.22−4.50 (br, 1H), 5.41−5.49 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.6, 24.8, 25.2, 27.0, 28.1, 29.0, 29.6, 30.0, 31.7, 33.8, 34.0, 37.4, 45.8, 51.5, 51.6, 73.2, 73.9, 133.1, 135.7, 174.3; MS m/z 354 (M^+), 336 ($M^+ - H_2O$), 318 ($M^+ - 2H_2O$); HRMS m/z calcd for $C_{21}H_{38}O_4$ 354.2770, found 354.2767; $[\alpha]^{24}_D$ +38 (c = 0.510, $CHCl_3$).

To a solution of more polar 11-deoxy-PGF$_{1\alpha}$ methyl ester (10.5 mg, 30 μmol) in wet THF (1.0 mL, containing 0.33 mL of water) was added 0.1 N NaOH (0.69 mL). After being stirred for 17 h at room temperature, the reaction mixture was quenched by addition of 0.1 N HCl (0.69 mL), and then THF was removed in vacuo. The residue was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The resulting residue was purified by preparative TLC (Si_2O, 1:15 $CH_3OH-CH_2Cl_2$) to give (+)-11-deoxy-PGF$_{1\alpha}$ (**1**) (9.1 mg, 90%): IR (neat) ν 3361, 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H, J = 6.9 Hz), 1.24−1.67 (m, 21H), 1.90−2.05 (m, 2H), 2.51−2.35 (m, 1H), 2.33 (t, 2H, J = 7.3 Hz), 4.07 (dt, 1H, J = 6.3, 6.3 Hz), 4.24 (br, 1H), 5.41−5.50 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.6, 24.5, 25.2, 26.5, 27.6, 28.5, 29.1, 29.9, 31.7, 33.7, 33.8, 37.3, 45.6, 51.4, 73.1, 73.9, 132.7, 135.6, 178.2; MS m/z 340 (M^+), 322 ($M^+ - H_2O$), 304 ($M^+ - 2H_2O$) ; HRMS m/z calcd for $C_{20}H_{36}O_4$ 340.2614, found 340.2614; $[\alpha]^{22}_D$ +38 (c = 0.46, $CHCl_3$).

Methyl (*R*)-7-[(1*R*,2*S*,3*R*)-2-[1,1-Bis(benzyloxycarbonyl)ethyl]-3-(*tert*-butyldimethylsiloxy)-5-oxocyclopentyl]-7-hydroxyheptanoate (21α) and Methyl (*S*)-7-[(1*R*,2*S*,3*R*)-2-[1,1-bis(benzyloxycarbonyl)ethyl]-3-(*tert*-butyldimethylsiloxy)-5-oxocyclopentyl]-7-hydroxyheptanoate (21*β*). To dried MS 4A (200 mg) were added a 0.1 M (*S*)-ALB THF solution (1.0 mL, 0.10 mmol), a THF solution of sodium *tert*-butoxide (0.44 M, 0.21 mL), (±)-4-(*tert*-butyldimethylsiloxy)-2-cyclopenten-1-one (**20**) (0.45 mL, 2.0 mmol), methyl 6-formylhexanoate (**5**) (0.24 mL, 1.5 mmol), and dibenzyl methylmalonate (**4**) (0.26 mL, 1.0 mmol) at room temperature. After being stirred for 40 h at the same temperature, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl. The insoluble material and aqueous layer were removed by filtration (Celite, Na_2SO_4) and successively washed with EtOAc. The filtrate and the washing were combined and then washed with water and brine. The organic layer was dried (Na_2SO_4) and concentrated.

The resulting residue was purified by flash column chromatography (SiO_2, 20% acetone−hexane) to give pure β-hydroxy ketones **21** (0.50 g, 75% based on malonate **4**, a mixture of two diastereomers): IR (neat) ν 3457, 1737 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (s, 3H), 0.11 (s, 3H), 0.87 (s, 9H), 1.44 (s, 3H), 1.19−1.67 (m, 8H), 2.15 (d, 1H, J = 21 Hz), 2.29 (t, 2H, J = 7.6 Hz), 2.32 (br, 1H), 2.45 (dd, 1H, J = 5.8, 10 Hz), 2.78 (br, 0.93H), 2.84 (br, 0.07H), 3.66 (s, 3H), 3.75 (s, 1H), 3.75−3.77 (br, 1H), 4.41 (d, 1H, J = 5.8 Hz), 5.01−5.16 (m, 4H), 7.20−7.33 (m, 10H); ^{13}C NMR ($CDCl_3$) δ −4.9, −4.8, 17.6, 19.3, 24.9, 25.6, 25.7, 29.0, 34.0, 49.4, 51.3, 55.8, 56.7, 57.1, 67.4, 67.5, 70.8, 74.9, 128.1, 128.2, 128.3, 128.5, 134.8, 170.4, 170.7, 174.1, 217.2; MS m/z 611 (M^+ − t-Bu), 593 (M^+ − t-Bu − H_2O), 519 (M^+ − TBDMSO − H_2O); HRMS m/z calcd for $C_{33}H_{43}O_9Si$ (M^+ − t-Bu) 611.2676, found 611.2657. Anal. Calcd for $C_{37}H_{52}O_9Si$: C, 66.44; H, 7.84. Found: C, 66.21; H, 7.85.

Supporting Information Available: ^{13}C NMR spectra of **1**, **2**, **9**, **11**, **12**, **14**−**16**, and **18** (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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