Diisobutylaluminum 2,6-Di-*t*-butyl-4-methylphenoxide. Novel Stereoselective Reducing Agent for Prostaglandin Synthesis[1)]

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In an effort to explore the selective reducing agents suitable for prostaglandin synthesis, diisobutylaluminum 2,6-di-*t*-butyl-4-methylphenoxide (**1**) is found to be among the best. Reduction of the C-15 ketone with **1** in toluene at −78 °C produced the desired 15*S*-alcohol in 95% yield with 92% stereoselectivity. The present procedure is suitable for the synthesis of prostaglandin derivatives and related polyfunctional natural products as shown in the conversion of PGE_2 methyl ester to $PGF_{2\alpha}$ methyl ester in 95% yield and 100% selectivity.

One major problem encountered in the synthesis of prostaglandins[2)] is stereoselective construction of the functional groups present in these molecules. Three of the four chiral centers of prostaglandin E_2, those at position 8, 11, and 12, are mutually *trans* and are relatively easily established. Stereochemical control of the fourth center at C-15, however, placed in a conformationally mobile side chain, and at a considerable distance from influence of the ring, poses a much more difficult problem. For example, introduction of the lower side-chain and establishment of the *trans*-C-13-ene unit are readily accomplished by simple Wadsworth-Emmons' reaction. The successive zinc borohydride or Meerwein-Ponndorf-Verley reduction of the resulting α,β-unsaturated ketone produced a 1 : 1 mixture of 15*S* and 15*R* allylic alcohols.

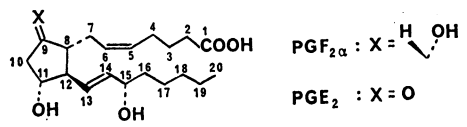

Fig. 1.

So far tremendous efforts have been devoted to solve this problem, and 15*S*/15*R* ratio of 92% was recorded in the reduction of the enone having a *p*-phenylphenylcarbamoyl protecting group at C-11 using a bulky trialkylhydroborate reagent at −130 °C.[3)] This result was explained on the basis that at low temperature the molecule is frozen into a conformation wherein the *p*-phenylphenylcarbamoyl group is lined up with the enone side-chain, effectively screening one side of the molecule. The hydride then attacks from the opposite side of the molecule, but can give rise to the desired 15*S* alcohol only if the enone is in a *S-cis* conformation.

Very recently an interesting asymmetric reduction of this enone with special binaphthol modified aluminum hydride reagent was reported.[4)] With this optically active reagent at −100 °C, 99.5% stereoisomeric purity was achieved.

Our interest has been focused on the stereoselective approach to the reduction of the C-9 and C-15 ketones in prostaglandins[5)] using the more practical reagent under mild reaction conditions. Diisobutylaluminum 2,6-di-*t*-butyl-4-methylphenoxide (**1**)[6)] has solved this problem practically, and has been found to be among the best selective reducing agent for the control of the stereochemistry at C-15.

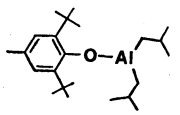

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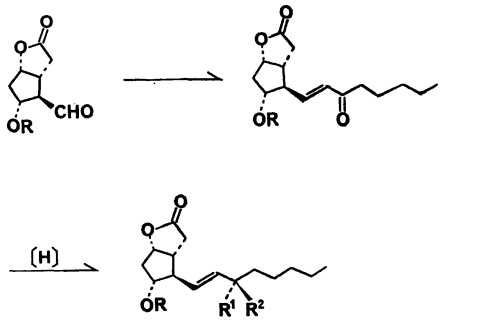
Fig. 2.

Results and Discussion

A solution of diisobutylaluminum 2,6-di-*t*-butyl-4-methylphenoxide (**1**) can be prepared from diisobutylaluminum hydride (DIBAH) in toluene and 2,6-di-*t*-butyl-4-methylphenol (molar ratio 1 : 1 to 1 : 2)[7)] in toluene at 0 °C for 1 h. Reduction of the C-11 hydroxy enone **2a** with the reagent **1** (10 equiv.) in toluene was

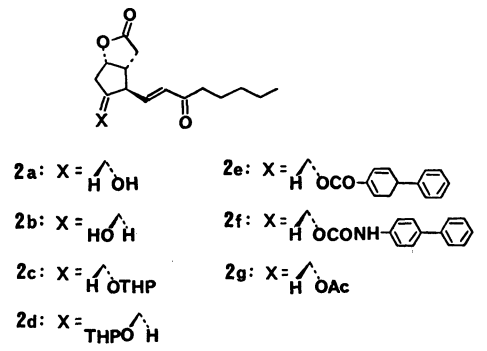


15*S*: R^1=OH, R^2=H
15*R*: R^1=H, R^2=OH

Scheme 1.

complete at −78 °C for 2 h, then at −40 °C for 1 h. The reaction mixture was then poured onto diluted hydrochloric acid and extracted with ethyl acetate. Short-path chromatographic separation to remove the recovered phenol gave allylic alcohol **3a** in 95% yield. The ratio of 15*S* to 15*R* isomers in several runs was 92/8 by high pressure liquid chromatographic analysis. When the aluminum reagent **1** was decreased to 3 equiv, the reaction proceeded slowly under the reaction conditions described above to give **3a** in 85% yield with the similar stereoselectivity (15*S*/15*R*=92/8).

The enone unit exists in both the *S-cis* and *S-trans* conformations, and the hydride attack can occur from either direction to give the 15*S* or 15*R* configuration. Therefore, reduction of the enone with sodium borohydride or zinc borohydride produced a 1 : 1 mixture



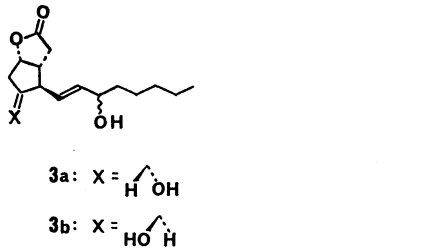
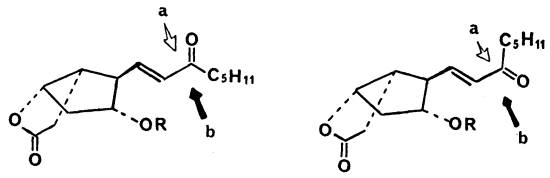


Fig. 3.



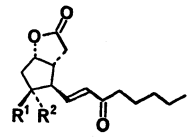
S-cis enone form *S-trans* enone form

Fig. 4.

of epimeric 15*S* and 15*R* alcohols. As previously reported, the examination of Corey-Pauling-Koltun models showed that van der Waals contact of the *p*-biphenylyl group in **2f** and the enone unit is indeed most favored when the enone is in the *S-cis* conformation. Clearly, the *p*-biphenylyl group must not only block approach from axis b but also stabilize the *S-cis* enone conformation in order to direct the formation of 15*S* alcohol. The present high stereoselectivity shown especially in **2a** can be attributed to the significant frontal steric bulk of the reagent **1** and at the same time to the substantial screening effect of *S-cis* enone chain to inhibit the α-approach of the reagent. Thus, the excess aluminum reagent, which is strongly coordinated at the C-11 hydroxyl function appears to play an important role as an exogeneous directing group to block the approach from axis b as well as to maintain *S-cis* enone conformation.

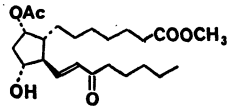
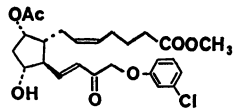
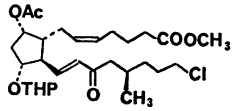
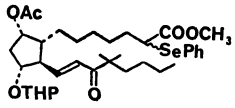
On the basis of this hypothesis, we examined the reduction of the THP ethers **2c** and **2d** using the reagent **1** under the standard conditions. It was thought that moderate selectivity for formation of 15*S* alcohol should be observed in these cases, since the aluminum reagent may be coordinated with ethers rather weakly.[6,8] The substrates and the observed 15*S*/15*R* ratios are shown in Table 1. In contrast to the high stereoselectivity in the

Table 1. Reduction of the enones containing the lactone function with diisobutylaluminum 2,6-di-*t*-butyl-4-methylphenoxide in toluene

	15*S*/15*R*	%Total yield	Conditions
R^1=H, R^2=OH	92/8[a]	95	d) or e)
R^1=OH, R^1=H	85/15[a]	94	d)
R^1=H, R^2=OTHP	66/34[a]	98	d) or e)
R^1=OTHP, R^2=H	79/21[b]	92	d) or e)
R^1=H, R^2=OAc	50/50[a]	91	d) or e)
R^1=H, R^2=OCO-C_6H_4-C_6H_5-*p*	50/50[c]	90	e)

a) The ratio of 15*S* to 15*R* isomers was determined by high pressure liquid chromatography using a silica-gel column with a refractive index detector. b) After the removal of the THP group, the ratio was determined by high pressure liquid chromatography. c) The ratio was determined by high pressure liquid chromatography with UV (254 nm) index detector. d) The reaction conditions were −78 °C for 2 h, and then −40 °C for 1 h. e) The enone was added to the aluminum reagent at −78 °C and the temperature was raised gradually to −20 °C over 2 h.

Table 2. Reduction of the enones containing α-chain with diisobutylaluminum 2,6-di-*t*-butyl-4-methylphenoxide in toluene

Enones	15α-OH/ 15β-OH	%Total yield	Conditions
	82/18[a]	95	c)
	86/14[b]	83	c)
	82/18[a]	95	c)
	87/13[b]	92	d)

a) The ratio was determined by the isolation of each isomer using the usual silica-gel column chromatography. b) The ratio was determined by high pressure liquid chromatography. c) To a solution of the aluminum reagent in toluene cooled at −78 °C was added a solution of the enone in toluene and then the temperature was raised gradually to −20 °C over 2 h. d) The reaction conditions were −78 °C for 2 h, and then −40 °C for 1 h.

reduction of hydroxy ketones, the *p*-phenylbenzoyl ester **2e**[9] and the acetate **2g** afforded the corresponding alcohols without any stereoselectivity (15*S*/15*R*=1/1).

Although the reduction of the hydroxy enone **2a** with the lactone unit using the reagent **1** was complete within 2 h at −78 °C, the reduction of hydroxy enones

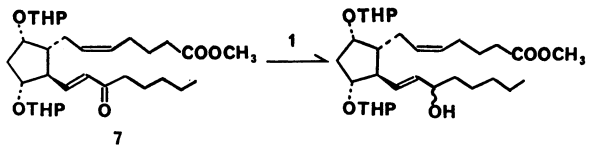
having α-chains proceeded considerably slowly at −78 °C to afford a trace of the product in 4 h. Therefore, the reaction mixture was warmed gradually to −20 °C over 2 h to produce 15α-allylic alcohols with moderate stereoselectivity as shown in Table 2. Presumably, in the reduction of the C-11 hydroxy enones with α-chains the *S-cis* enone conformation would be maintained at −78 °C by van der Waals contact of O-Al-OPh group and the enone moiety. However due to the steric hindrance of α-chains, the hydride attack along axis a would be unfavorable. At −20 °C, the stereoselectivity for formation of 15α-allylic alcohols is somewhat lost, since the *S-cis* enone conformation would not be stabilized at this temperature.

The stereoselectivity in the reduction of **7** was significantly influenced by the equivalent of the aluminum reagent **1**, as listed in Table 3. The best result was obtained using more than 10 equiv. of the aluminum reagent **1**. Surprisingly, with 2 equiv. of **1**, the 15*R* alcohol was produced predominantly. These results might be attributed to the relatively weak coordination of the reagent **1** to C-11 THP ether and then the direct attack of the coordinated aluminum reagent **1** to the substrate from the front side of the molecule (axis b). This is in sharp contrast with the reduction of **2a**, in which the stereoselectivity is essentially independent of the equivalent of **1** as described previously.

The substituent effect of the aryl group in the aluminum reagents upon the stereoselectivity of allylic alcohols was investigated using the enone **2c** and various diisobutylaluminum phenoxides in toluene. Under the similar reaction conditions, the use of 2,6-di-*t*-butylphenoxides gave higher stereoselectivity compared to other phenoxides in shorter reaction time (Table 5).

The significance of the frontal steric effect by the use of the aluminum reagent **1** was further demonstrated. Reduction of prostaglandin E with sodium borohydride or zinc borohydride proceeds in a nonstereoselective manner to give a mixture of C-9α and C-9β hydroxy compounds[10] with somewhat higher yield of the C-9β hydroxy isomer. Owing to the lack of the stereochemical control in this transformation, the design of chemical synthesis of these substances was extremely limited: the protected prostaglandin F_α derivative (*e.g.* **4**) may be prepared first, and oxidized to prostaglandin E derivative. Recently, some bulky trialkylhydroborate reagents[5] have been employed successfully for the reduction of prostaglandin E to prostaglandin F_α. Our aluminum reagent **1** can be also effective for the preparation of prostaglandin F_α with excellent stereoselectivity. Thus, reaction of prostaglandin E_2 methyl ester (**5a**) with **1** in toluene at −78 °C for 2 h produced prostaglandin

Table 3. Reduction of C_{11}-OTHP enone **7** with various equiv. of diisobutylaluminum 2,6-di-*t*-butyl-4-methylphenoxide (**1**)



7

Equiv. of **1**	15*S*/15*R*[a]	%Total yield	Conditions
2	35/65	85	−78 °C→ 10 °C (2 h)
5	59/41	85	−78 °C→ 0 °C (2 h)
10	74/26	89	−78 °C→−20 °C (2 h)
20	68/32	85	−78 °C→−20 °C (2 h)

a) The ratio was determined by high pressure liquid chromatography.

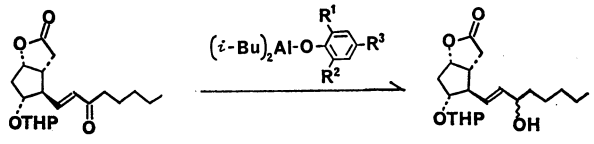
Table 4. Reduction of C_{11}-hydroxy enone **2a** with diisobutylaluminum 2,6-di-*t*-butyl-4-methylphenoxide (**1**)

2a **3a**

Equiv. of **1**	15*S*/15*R*[a]	%Total yield	Coditions
3	92/8	85	−78 °C(2 h)→−40 °C(1 h)
10	92/8	95	−78 °C(2 h)→−40 °C(1 h)

a) The ratio was determined by high pressure liquid chromatography.

Table 5. Reduction of C_{11}-OTHP enone **2c** with various diisobutylaluminum phenoxides



2c **11**

Phenoxide	15*S*/15*R*[a]	%Total yield	Conditions
$R^1=R^2=t$-Bu R^1=H or Me	66/34	(95)	−78 °C→−10 °C(3 h)
$R^1=R^2=R^3=t$-Bu	59/41	(95)	−78 °C→−40 °C(2 h)
$R^1=t$-Bu, R^2=H, R^3=H or Me	61/39	(94)	−78 °C→−10 °C(3 h)
$R^1=R^3=t$-Bu, R^2=H	54/46	(92)	−78 °C→−10 °C(3 h), 25 °C(1 h)
$R^1=R^2=i$-Bu, R^3=H	62/38	(90)	−78 °C→−40 °C(1 h), 25 °C(17 h)
$R^1=R^2$=Me, R^3=H	54/46	(95)	−78 °C (30 min), 0 °C (1 h)
$R^1=R^2=R^3$=H	63/37	(95)	−78 °C (30 min), 25 °C (12 h)

a) The ratio was determined by high pressure liquid chromatography.

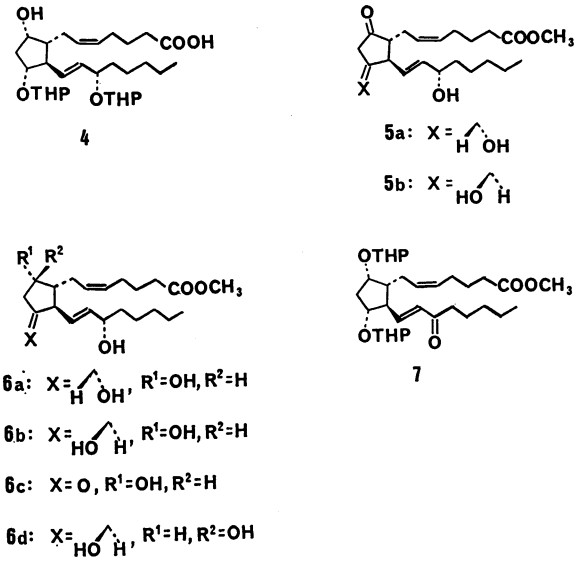
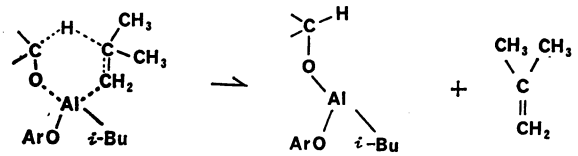


Fig. 5.

$F_{2\alpha}$ methyl ester (**6a**) cleanly in 95% yield with 100% selectivity. Furthermore, treatment of the C-11 epimeric prostaglandin E_2 methyl ester (**5b**) or prostaglandin D_2 methyl ester (**6c**) using **1** afforded the C-11 epimeric prostaglandin $F_{2\alpha}$ methyl ester (**6b**) with 76% or 98% selectivity.[11,12]

The generality of the new reagent **1** was examined using a simple hydroxy ketone and cyclic ketones with alkyl chains on the ring. Thus, treatment of 4-hydroxy-3-methyl-2-butanone with **1** at −78 °C gave a mixture of *erythro*- and *threo*-2-methyl-1,3-butanediols (ratio, 2 : 1) in 96% yield. Moreover, reduction of 4-*t*-butylcyclohexanone or 2-methylcyclohexanone with **1** at −78 °C furnished 4-*t*-butylcyclohexanol (84% yield; *cis*/*trans* ratio, 28 : 72) or 2-methylcyclohexanol (85% yield; *cis*/*trans* ratio, 75 : 25), respectively. The results of this investigation clearly reveal that unlike in the reduction of prostaglandin derivatives, the aluminum reagent **1** showed no remarkable stereoselectivity in the case of the simple unhindered hydroxy ketone. Therefore, the conformation of substrates also appears to be highly important to achieve the favorable frontal steric effect. It is also evident from the results that the reactivity of **1** is totally different from that of the usual bulky metal hydrides (*e.g.* Selectrides), which gave the less stable (*cis*) isomer predominantly in the reduction of cyclic ketones with an alkyl chain.[13]

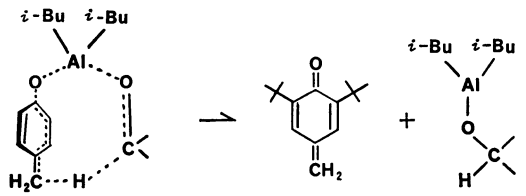
A plausible mechanism for the reduction of ketones with **1** involves an initial coordination of the trivalent aluminum reagent to the carbonyl group, followed by an intramolecular hydride transfer from the β-carbon of the isobutyl group as shown in Scheme 2. Such a mechanism seems to be analogous to those in reductions



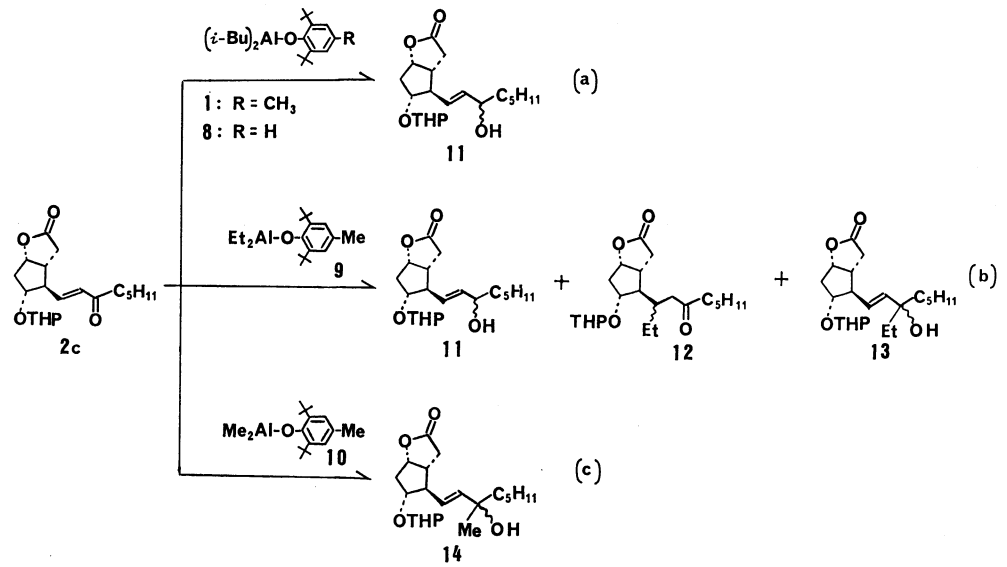
Scheme 2.

with Grignard reagents,[14,15] dialkylmagnesium compounds,[15] and triisobutylaluminum.[16] Therefore, in the reduction of α,β-unsaturated ketones only 1,2-reduction products can be obtained *via* the six-membered transition state. This is in sharp contrast with the reduction of enones using the bulky aluminum hydride reagents,[17] which afforded conjugate addition products predominantly.

Another mechanism may be considered for the



Scheme 3.



Scheme 4.

reduction with **1**, in which the actual hydride source of the reagent **1** is derived from the methyl group of phenoxide. This possibility was ruled out by the following experimental results. Scheme 4 represents the results obtained for the reduction of **2c** with several aluminum phenoxides. Since the reduction with diisobutylaluminum 2,6-di-*t*-butylphenoxide (**8**) afforded the same result as obtained with **1**, the methyl group of the reagent **1** is not necessary for reduction (Eq. a). The use of diethylaluminum 2,6-di-*t*-butyl-4-methylphenoxide (**9**) (Eq. b) produced three kinds of products: **11** (reduction product), **12** (Michael adduct to the enone **2c**), and **13** (ethylation product). In the reaction with dimethylaluminum 2,6-di-*t*-butyl-4-methylphenoxide (**10**), only the methylation product **14** was formed (Eq. c). It is evident from these results (Eqs. b and c) that at least a β-hydrogen of alkyl group of dialkylaluminum phenoxides is indispensable for reduction. Based on the above consideration we conclude that the mechanism shown in Scheme 2 is a most plausible one.

The reduction process which is described herein should be extremely useful for complex or polyfunctional molecules. The new aluminum reagent **1** for the reduction of ketone group of prostaglandins is characterized by the following features. (a) Yields are high and selectivities are unique. (b) No side reaction occurs. (c) Diisobutylaluminum hydride and 2,6-di-*t*-butyl-4-methylphenol are commercially available and inexpensive. (d) This reagent is stable and can be stocked. (e) There is no neccessity for protecting the C-11 hydroxy group with the special hindered function. (f) The process is operationally simple and can be done on a large scale.

Experimental

^{1}H NMR spectra were taken on a JEOL PMX-60 or a Varian XL-100 spectrometer in $CDCl_3$. Chemical shifts are reported as parts per million relative to TMS as the internal standard. The infrared spectra were recorded on a Hitachi EPI-G2 model. The mass spectra were obtained on a JMS-OlSG double focussing mass spectrometer. Molecular ion peaks of some compounds were too weak to be detected because of their low volatility, and in these cases the molecular weights were determined by their dehydration peaks.

For TLC analysis throughout this work, Merck TLC plates (Kieselgel 60 F_{254}, pre-coated, layer thickness 0.2 mm) were used. Column chromatography was carried out on silica gel (Merck, particle size 0.063—0.20 mm) or using Lobar Prepacked Column (Merck, silica gel). The isomeric ratio of the products was determined by high pressure liquid chromatography using a JASCO TRI ROTAR instrument equipped with a Waters μ-Porasil and a refractive index detector or a UV index detector.

Unless otherwise specified, all reactions were carried out under an atmosphere of argon.

*Preparation of Diisobutylaluminum 2,6-Di-*t*-butyl-4-methylphenoxide (**1**).* Diisobutylaluminum hydride in toluene (1.76 M (1 M = 1 mol dm^{-3}), 21.7 ml, 38.2 mmol) was added slowly at 4 °C over 20 min to a solution of 2,6-di-*t*-butyl-4-methylphenol (16.81 g, 76.4 mmol) in toluene (180 ml) with the vigorous hydrogen gas evolution. During this operation, *ca.* 1 equiv. of hydrogen gas was collected. Strring was continued at 4 °C for 1 h. The reagent, thus prepared, was directly used for the following reduction, and is stable enough to be stored under argon at 0 °C for several weeks.

Reduction of Carbonyl Compounds. Method A: A solution of a carbonyl compound in toluene was added slowly below −60 °C to a solution of the aluminum reagent **1** (10 equiv.) in toluene. The mixture turned into orange. Further stirring was continued at −78 °C for 2 h, then at −40 °C for 1 h. The mixture was poured onto cold 1 M hydrochloric acid (*ca.* total volume of the reaction mixture), and extracted with ethyl acetate. The combined extracts were washed with aq sodium hydrogencarbonate, followed by brine, dried over magnesium sulfate, and concentrated by the evaporator. The residue was applied to column chromatography on silica gel with dichloromethane to separate 2,6-di-*t*-butyl-4-methylphenol, then with ethyl acetate to elute a mixture of 15*S* and 15*R* alcohols. The ratio of 15*S* and 15*R* isomers was determined Lobar Pre-packed Column (Merck) or high pressure liquid chromatographic analysis.

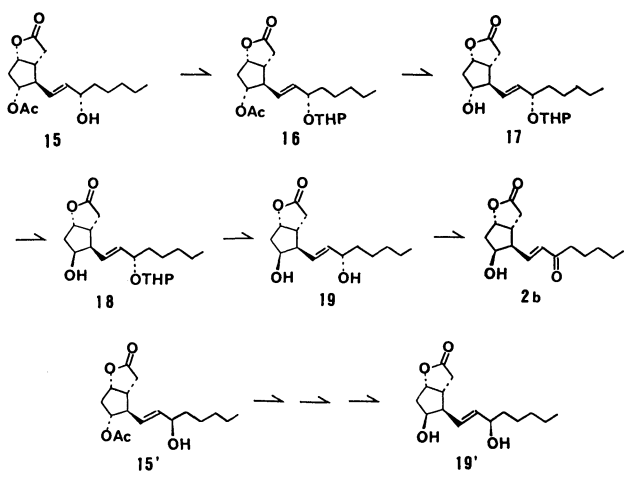
Method B: The reaction was carried out starting from −78 °C according to the method A. After addition of a carbonyl compound, the cooling bath was removed. The reaction mixture was allowed to warm to −10——20 °C over 2 h, stirred at this temperature for 30 min, and worked up as described above.

*Reduction of (1*S*, 5*R*, 6*R*, 7*R*)-7-Hydroxy-6-[(*E*)-3-oxo-1-octenyl]-2-oxabicyclo[3.3.0]octan-3-one (**2a**).* Reduction of **2a** (1.016 g, 3.82 mmol) with 2,6-di-*t*-butyl-4-methylphenol (16.81 g, 76.4 mmol) and DIBAH (25 g/100 ml in toluene; 21.7 ml, 38.2 mmol) was carried out using the method A to give a mixture of 15*S* and 15*R* isomers (0.964 g, 95% yield): TLC, R_f 0.229 for 15*S* isomer, 0.289 for 15*R* isomer (AcOEt–benzene, 2 : 1, 2 developments).[18] The ratio of 15*S* and 15*R* isomers was 92 : 8 by HPLC analysis (μ-Porasil, refractive index, AcOEt). Lobar Pre-packed Column chromatography on silica gel (Merck, size C, AcOEt–benzene, 4 : 1) separated the 15*S* isomer (833 mg) and the 15*R* isomer (72.3 mg): 15*S*: IR (film) 3400, 2950, 2850, 1770, 980 cm^{-1}; ^{1}H NMR δ 5.22—5.81 (2H, m, olefinic H), 4.55—5.02 (1H, m, C_1–H), 3.52—4.36 (2H, m, C<u>H</u>–OH), 0.87 (3H, t, CH_3); MS *m/e* 268 (M^+), 250 (M^+-H_2O), 232 (M^+-2H_2O); high resolution MS *m/e* 250.159 (dehydration peak, calcd for $C_{15}H_{22}O_3$, 250.157). The IR, ^{1}H NMR and MS spectra of the 15*R* isomer were identical with those of the 15*S* isomer: 15*R*: high resolution MS *m/e* 250.159 (dehydration peak, calcd for $C_{15}H_{22}O_3$, 250.157).

The reaction using the method B gave the similar results.

*Reduction of (1*S*, 5*R*, 6*R*, 7*S*)-7-Hydroxy-6-[(*E*)-3-oxo-1-octenyl]-2-oxabicyclo[3.3.0]octan-3-one (**2b**).* Reaction of the enone **2b** (50 mg, 0.188 mmol) and the aluminum reagent **1** in toluene (9 ml, 1.88 mmol) was carried out according to the method A to afford a mixture of 15*S* and 15*R* isomers (47 mg, 94% yield) after short column chromatography: IR (film) 3400, 2950, 2850, 1770, 980 cm^{-1}; ^{1}H NMR δ 5.66—5.89 (2H, m, olefinic H), 4.90—5.23 (1H, m, C_1–H), 4.20—4.42 (1H, m, C_3–H), 3.91—4.20 (1H, m, C_7–H), 0.89 (3H, t, CH_3); high resolution MS *m/e* 268.165 (calcd for $C_{15}H_{24}O_4$, 268.168). HPLC analysis showed the ratio of 15*S* and 15*R* isomers to be 85 : 15 : TLC, R_f, 0.420 for the 15*S* isomer, 0.374 for the 15*R* isomer (ether–EtOH, 100 : 1, 3 developments). These R_f values were identical with those by the $NaBH_4$ reduction of **2b**. The configuration of two isomers was determined by comparison with the authentic samples, which were prepared as shown in Scheme A.

*Synthesis of (1*S*, 5*R*, 6*R*, 7*S*)-7-Hydroxy-6-[(1*E*, 3*S*)-3-hydroxy-1-ocetenyl]-2-oxabicyclo[3.3.0]octan-3-one (**19**).* A mix-



Scheme A.

ture of **15** (10 g, 32.3 mmol),[18] 2,3-dihydropyran (5.9 ml 64.5 mmol), and *p*-toluenesulfonic acid (60 mg) in dichloromethane (100 ml) was stirred in a water bath for 20 min. The reaction was terminated by the addition of pyridine (20 drops). Dilution with ethyl acetate (500 ml), washing with aq sodium hydrogencarbonate, followed by brine, being dried over magnesium sulfate, and concentration of the extracts left the residue, which was dissolved in methanol (120 ml) and stirred at 25 °C for 15 min after addition of anhydrous potassium carbonate (5.348 g). The solution was then acidified to pH 4 by the addition of acetic acid, diluted with ethyl acetate (500 ml), and washed with aq sodium hydrogencarbonate, then brine. Being dried over magnesium sulfate, and purification of the concentrated product by column chromatography (silica gel, 360 g; AcOEt–benzene, 1 : 1) gave **17** (10.846 g, 96% yield): TLC, R_f 0.273 (benzene–AcOEt, 2 : 1, 2 developments); IR (film) 3450, 2950, 2850, 1780, 980 cm^{-1}; ^1H NMR δ 5.25—5.65 (2H, m, olefinic H), 4.70—5.15 (1H, m, C_1–H), 4.61 (1H, br s, OCHO), 3.00—4.20 (4H, m, C_7, $C_{3'}$–H, OCH_2), 0.90 (3H, t, CH_3); MS *m/e* 352 (M^+), 334 ($M^+ - H_2O$), 268 (M^+—DHP), 243 (M^+—OTHP—H_2O), 250 (M^+—HOTHP). The alcohol **17** (5.00 g, 14.2 mmol) in dry THF (70 ml) was treated with triphenylphosphine (7.443 g, 28.4 mmol) and benzoic acid (3.465 g, 28.4 mmol). Diethyl azodiformate (4.941 g, 28.4 mmol) in THF (10 ml) was then added slowly. The whole mixture was stirred at 25 °C for 30 min, and concentrated under reduced pressure. The residue, thus obtained, was dissolved in methanol (100 ml), treated with anhydrous potassium carbonate (3.919 g, 14.2 mmol) at 25 °C and stirred at 40—50 °C for 30 min. The mixture was cooled to 25 °C, acidified to pH 4 with acetic acid, diluted with ethyl acetate (500 ml), washed with aq sodium hydrogencarbonate followed by brine, dried over magnesium sulfate, and concentrated. Purification of the residue by column chromatography (silica gel, 150 g; cyclohexane–AcOEt, 2 : 1, then 1 : 1) gave **18** (4.689 g, 97% yield): TLC, R_f 0.357 (benzene–AcOEt, 2 : 1, 2 developments). The IR, ^1H NMR, and MS spectra of **18** were identical with those of **17**. The alcohol **18** (1.026 g) was dissolved in 65% acetic acid (30 ml) and THF (3 ml). The resulting mixture was stirred at 50 °C for 1 h, poured onto iced water (150 ml), and extracted with ethyl acetate. Concentration of the extracts left the residue, which was purified by column chromatography (silica gel, 30 g; AcOEt–cyclohexane, 2 : 1) to give **19** (664 mg, 85% yield): IR (film) 3600, 3450, 1760, 975 cm^{-1}; ^1H NMR δ 5.40—5.97 (2H, m, olefinic H), 4.98—5.25 (1H, m, C_1–H), 3.99—4.22 (2H, m, C_7, $C_{3'}$–H), 0.90 (3H, t, CH_3); MS *m/e* 268 (M^+), 250 ($M^+ - H_2O$), 232 ($M^+ - 2H_2O$), high resolution MS *m/e* 268.165 (calcd for $C_{15}H_{24}O_4$, 268.167).

Synthesis of (1S, 5R, 6R, 7S)-7-Hydroxy-6-[(E)-3-oxo-1-octenyl]-2-oxabicyclo[3.3.0]octan-3-one (19'). The title compound (275 mg) was prepared starting from **15'** (633 mg)[17] according to the procedure described above. The IR, ^1H NMR, and MS spectra of **19'** were similar to those of **19**: high resolution MS *m/e* 268.165 (calcd for $C_{15}H_{24}O_4$, 268.167).

Reduction of (1S, 5R, 6R, 7R)-7-(Tetrahydro-2-pyranyloxy)-6-[(E)-3-oxo-1-octenyl]-2-oxabicyclo[3.3.0]octan-3-one (2c). Reduction of the enone **2c** (500 mg, 1.43 mmol) with the aluminum reagent **1** (14.3 mmol) in toluene (48 ml) using the method B gave a mixture of 15*S* and 15*R* isomers (490 mg, 98% yield): TLC, R_f 0.418 for the major product, 0.345 for the minor product (ether, 2 developments). The R_f values of these isomers were identical with those of the reduction product of **2c** with sodium borohydride. Column chromatography (silica gel, 40 g; ether–hexane–AcOEt, 2 : 1 : 1) separated the more polar isomer (92 mg), the less polar isomer (97 mg), and these mixture (199 mg). The two isomers gave the similar spectral data: IR (film) 3450, 1770, 975 cm^{-1}; ^1H NMR δ 5.10—5.17 (2H, m, olefinic H), 4.77—5.11 (1H, m, C_1–H), 4.64 (1H, br s, OCHO), 3.64—4.25 (4H, m, C_7, $C_{3'}$–H, OCH_2), 0.91 (3H, t, CH_3); MS *m/e* 352 (M^+), 334 ($M^+ - H_2O$), 268 (M^+ —DHP); high resolution MS *m/e* 334.215 (dehydration peak, calcd for $C_{20}H_{30}O_4$, 334.214). The two isomers were separately converted by the hydrolysis of the THP group (aq 65% AcOH, 40—45 °C, 2 h) into the corresponding diols, which were compared with the authentic samples[18] by TLC. The less polar isomer (major component) was the 15*S* alcohol. The ratio of 15*S* to 15*R* was 66 : 34 by HPLC analysis (μ-Porasil, refractive index, AcOEt–CH_2Cl_2, 1 : 1).

Reduction of (1S, 5R, 6R, 7S)-7-(Tetrahydro-2-pyranyloxy)-6-[(E)-3-oxo-1-octenyl]-2-oxabicyclo[3.3.0]octan-3-one (2d). Reduction of **2d** (101 mg, 0.289 mmol) with the aluminum reagent **1** (2.89 mmol) in toluene (20 ml) by the method B furnished a mixture of 15*S* and 15*R* isomers (90 mg, 90% yield). Hydrolysis of the THP group in these isomers gave the diols, which was characterized as described in the reduction of **2b**. IR, ^1H NMR, and MS spectra of the diols were identical with those of the reduction products of **2b**. HPLC analysis showed the ratio of 15*S* to 15*R* isomers to be 79 : 21.

Reduction of (1S, 5R, 6R, 7R)-7-(p-Phenylbenzoyloxy)-6-[(E)-3-oxo-1-octenyl]-2-oxabicyclo[3.3.0]octan-3-one (2e). Reduction of **2e** (89 mg, 0.201 mmol) with the aluminum reagent **1** (2.01 mmol) in toluene (15 ml) using the method B afforded a mixture of 15*S* and 15*R* isomers (82 mg, 93% yield): TLC, R_f 0.546, 0.452 (2-butanone–benzene, 15 : 85). Column chromatography of the mixture (42 mg) on silica gel (2-butanone–benzene, 10 : 90) separated the less polar isomer (13 mg), the more polar isomer (11 mg), and a mixture of these isomers (17 mg). The two isomers gave the similar ^1H NMR spectra: δ 7.23—8.09 (9H, m, Phenyl H), 5.23—5.42 (1H, m, C_7–H), 4.89—5.10 (1H, m, C_1–H), 5.35—5.65 (2H, m, olefinic H), 3.80—4.20 (1H, m, $C_{3'}$–H), 0.90 (3H, t, CH_3). The products by hydrolysis of the *p*-phenylbenzoyl group (1 equiv. of K_2CO_3 in MeOH, 25 °C for 2 h) was identical with the reduction products of **2a** by TLC. HPLC analysis (μ-Porasil, UV index 254 nm, hexane–AcOEt, 1 : 1) indicated the ratio of 15*S*/15*R* isomers to be 1 : 1.

Reduction of (1S, 5R, 6R, 7R)-7-Acetoxy-6-[(E)-3-oxo-1-octenyl]-2-oxabicyclo[3.3.0]octan-3-one (2g). Reduction of **2g** (195 mg, 0.635 mmol) with the aluminum reagent **1** (6.35 mmol) in toluene (30 ml) according to the method A produced

a mixture of 15*S* and 15*R* isomers (177 mg, 91% yield): TLC, R_f 0.523, 0.424 (ether, 2 developments). Comparison of the R_f values with those of the authentic sample[18] showed the less polar isomer to be the 15*S* alcohol. The mixture (100 mg), obtained above, was applied to column chromatography (silica gel, 20 g; ether–AcOEt–cyclohexane, 2 : 1 : 1) to furnish the less polar isomer (33 mg), the more polar isomer (23 mg), and their mixture (35 mg). Both isomers had the similar spectroscopic properties (IR, ^{1}H NMR, and MS), which were identical with those of the authentic sample: IR (film) 3450, 2950, 2850, 1780, 1760, 1250, 975 cm^{-1}; ^{1}H NMR δ 5.55—5.77 (2H, m, olefinic H), 4.86—5.23 (2H, m, C_1, C_7–H), 3.90—4.21 (1H, m, C_3–H), 2.01 (3H, s, $CH_3C{=}O$), 0.90 (3H, t, CH_3); MS *m/e* 310 (M^+), 292 (M^+-H_2O), 250 (M^+-CH_3COOH); high resolution MS *m/e* 310.178 for the 15*S* isomer, 310.179 for the 15*R* isomer (calcd for $C_{17}H_{26}O_5$, 310.178). The ratio of 15*S*/15*R* isomers was 1 : 1 by HPLC analysis (μ-Porasil, refractive index, hexane–AcOEt, 1 : 1).

In the reduction products of enones with α-side chains using the aluminum reagent **1**, every less polar isomer correspond to the 15*R* alcohol. This was based on the transformation of both isomers into the end products, followed by the results of their biological activity. The 15*R* isomer had little activity.

Reduction of (5Z, 13E, 17R)-9α-Acetoxy-11α-(tetrahydro-2-pyranyloxy)-15-oxo-17-methyl-20-chloroprosta-5,13-dienoic Acid Methyl Ester. Reduction of the enone (1.8 g, 3.33 mmol) with the aluminum reagent **1** (33.3 mmol) in toluene (65 ml) using the method B produced a mixture of 15*R* and 15*S* isomers (1.71 g, 95% yield): TLC, R_f 0.42 for the 15*R* isomer, 0.31 for the 15*S* isomer (CH_2Cl_2–AcOEt, 4 : 1). Column chromatography (silica gel, 200 g; CH_2Cl_2–AcOEt, 5 : 1) separated the 15*R* isomer (295 mg) and the 15*S* isomer (1.346 g). Both isomers had the similar spectroscopic properties: IR (film) 3450, 2950, 2850, 1740, 980 cm^{-1}; ^{1}H NMR δ 4.80—5.93 (5H, m, olefinic H, and C_9–H), 4.52—4.55 (1H, m, OCHO), 3.63 (3H, s, $COOCH_3$), 3.50 (2H, t, CH_2Cl), 2.06 (3H, s, CH_3COO), 0.95 (3H, d, C_{17}–CH_3); MS *m/e* 524 (M^+-H_2O), 380 ($524-OCH_3-DHP$); high resolution MS *m/e* 524.290 for the 15*R* isomer, 524.291 for the 15*S* isomer (dehydration peak, calcd for $C_{29}H_{45}O_6Cl$, 524.290).

Reduction of (13E)-9α-Acetoxy-11α-hydroxy-15-oxoprost-13-enoic Acid Methyl Ester. Reduction of the enone (410 mg, 1.001 mmol) with the aluminum reagent **1** (10.01 mmol) in toluene (40 ml) using the method B afforded a mixture of 15*S* and 15*R* isomers (389 mg, 95% yield): TLC, R_f 0.46 for the 15*R* isomer, 0.26 for the 15*S* isomer (benzene–AcOEt, 1 : 2). Separation of the mixture (389 mg) by column chromatography (silica gel, 40 g; benzene–AcOEt, 1 : 1) gave the 15*R* isomer (299 mg) and the 15*S* isomer (65.8 mg). IR, ^{1}H NMR, and MS spectra of both isomers were identical: IR (film) 3450, 2950, 2850, 1740, 1250, 980 cm^{-1}; ^{1}H NMR δ 5.30—5.76 (2H, m, olefinic H), 4.92—5.30 (1H, m, C_9–H), 3.11 — 4.34(5H, m, C_{11}, C_{15}–H and $COOCH_3$), 2.31—2.82 [2H, br s, OH (disappearance in D_2O)], 2.05 (3H, s, CH_3COO), 0.90 (3H, t, C_{20}–H); MS *m/e* 394 (M^+-H_2O), 381 (M^+-OCH_3), 376 (M^+-2H_2O), 363 ($M^+-H_2O-OCH_3$), 334 ($M^+-H_2O-AcOH$); high resolution MS *m/e* 394.272 for both isomers (dehydration peak, calcd for $C_{23}H_{38}O_5$, 394.272). The 15*S* isomer was converted by treatment with potassium carbonate (1 equiv.) in MeOH at 45 °C for 2 h into the methyl ester of prostaglandin $F_{1\alpha}$ ($PGF_{1\alpha}$). The R_f value of this ester was in agreement with that of the authentic sample.

Reduction of (5Z, 13E)-9α-Acetoxy-11α-hydroxy-15-oxo-16-(3-chlorophenoxy)-17,18,19,20-tetranorprosta-5,13-dienoic Acid Methyl Ester. Reduction of the enone (388 mg, 0.812 mmol) with the aluminum reagent **1** (8.12 mmol) in toluene (20 ml) by the method B furnished a mixture of 15*R* and 15*S* isomers (329 mg): TLC, R_f 0.44 for the 15*R* isomer, 0.22 for the 15*S* isomer (benzene–AcOEt, 1 : 2). HPLC analysis (μ-Porasil, UV index 273 nm, CH_2Cl_2–AcOEt, 20 : 1) showed the ratio of 15*S*/15*R* to be 86 : 14. The mixture of 15*R* and 15*S* isomers: IR (film) 3450, 2950, 2850, 1740, 1600, 1450, 980, 780 cm^{-1}; ^{1}H NMR δ 6.70—7.22 (4H, m, phenyl H), 5.22—5.76 (4H, m, olefinic H), 5.05—5.23 (1H, m, C_9–H), 4.00—4.31 (1H, m, C_{15}–H), 3.55—4.00 (6H, m, C_{11}–H, CH_2OAr, and $COOCH_3$), 2.05 (3H, s, CH_3COO); MS *m/e* 462 (M^+-H_2O), 449 (M^+-OMe), 444 (M^+-2H_2O), 402 ($M^+-H_2O-AcOH$).

Reduction of (13E)-2-Phenylseleno-9α-acetoxy-11α-(tetrahydro-2-pyranyloxy)-15-oxo-16,16-dimethylprost-13-enoic Acid Methyl Ester. Reduction of the enone (448 mg, 0.644 mmol) with the aluminum reagent **1** (6.44 mmol) in toluene (20 ml) according to the method B afforded a mixture of 15*S* and 15*R* isomers (417 mg, 93% yield): TLC, homogeneous (CH_2Cl_2–AcOEt, 4 : 1). The ratio of 15*S*/15*R* was 87 : 13 by HPLC analysis (μ-Porasil, UV index 273 nm, CH_2Cl_2–AcOEt, 3 : 1). The mixture of 15*S* and 15*R* isomers: IR (film) 3400, 2950, 2850, 1740, 1580, 1440, 975, 790, 760 cm^{-1}; ^{1}H NMR δ 7.20—7.70 (5H, m, phenyl H), 5.50—5.72 (2H, m, olefinic H), 5.00—5.20 (1H, m, C_9–H), 4.50—4.70 (1H, m, OCHO), 3.62 (3H, s, $COOCH_3$), 2.05 (3H, s, CH_3COO), 0.80, 0.90, 0.91 (9H, s, s, t, CH_3); MS *m/e* 661 (M^+-H_2O), 648 (M^+-OMe), 619 (M^+-AcOH), 577 (M^+-H_2O-DHP).

Reduction of (5Z, 13E)-9α,11α-Bis(tetrahydro-2-pyranyloxy)-15-oxoprosta-5,13-dienoic Acid Methyl Ester (7). Reduction of the enone **7** (145 mg, 0.272 mmol) with aluminum reagent **1** (2.71 mmol) in toluene (5 ml) using the method B produced a mixture of 15*S* and 15*R* isomers (129 mg, 89% yield): TLC, R_f, 0.476 for the 15*R* isomer, 0.285 for the 15*S* isomer (benzene–AcOEt, 2 : 1). HPLC analysis (μ-Porasil, refractive index, CH_2Cl_2–AcOEt, 1 : 1) indicated the ratio of 15*R*/15*S* to be 74 : 26. Column chromatography (silica gel, 9 g; CH_2Cl_2–AcOEt, 7 : 1) separated the 15*S* isomer (96 mg) and 15*R* isomer (32 mg), which gave the similar spectral data: IR (film) 3450, 2950, 2850, 1740, 970 cm^{-1}; ^{1}H NMR δ 5.23—5.75 (4H, m, olefinic H), 4.50—4.83 (2H, m, OCHO), 3.30—4.20 (10H, m, s,$COOCH_3$, C_9 C_{11}, C_{15}–H, OCH_2), 0.90 (3H, t, CH_3); MS *m/e* 451 (M^+-THP), 434 ($M^+-HOTHP$), 332 ($M^+-2HOTHP$). Hydrolysis of the THP groups (65% aq AcOH, 40—45 °C for 2 h) in each isomer gave the corresponding triols. Their R_f values ($CHCl_3$–THF–AcOH, 10 : 2 : 1 or AcOEt) were identical with those of authentic samples ($PGF_{2\alpha}$ and its epimer).

Similarly, the enone **7** was reduced with 2, 5, and 20 equiv. of **1**, and their results are shown in Table 3.

Reduction of 2c with Various Diisobutylaluminum Phenoxides. The enone **2c** was reduced with various diisobutylaluminum phenoxides, which were prepared under the similar conditions as described for the synthesis of **1**. The reduction conditions are indicated in Table 5. The ratio of 15*S*/15*R* was determined by HPLC analysis (μ-Porasil, refractive index, CH_2Cl_2–AcOEt, 1 : 1).

Reduction of 2c with Diethylaluminum 2,6-Di-t-butyl-4-methylphenoxide (9). Triethylaluminum (2.71 mmol) in hexane was added dropwise at 0 °C to 2,6-di-*t*-butyl-4-methylphenol (715 mg, 3.25 mmol) in toluene (10 ml) under nitrogen. Stirring was continued at 0 °C for 30 min, then at 25 °C for 30 min. The solution was cooled to −78 °C, and the enone **2c** (210 mg, 0.600 mmol) in toluene (2 ml) was added dropwise at this temperature. Further stirring was carried out at −70 °C for 1 h, from −70 °C to 0 °C over 5 h, and at 25 °C for 1 h. The reaction was quenched by the addition of saturated

sodium hydrogentartarate. The crude product was extracted with ether, dried over $MgSO_4$, concentrated, and purified by column chromatography (silica gel, 5 g; CH_2Cl_2–cyclohexane, 1 : 1, then only AcOEt) to give a mixture of **11**, **12**, and **13**: TLC, R_f 0.727 for **2c**, 0.454 for **11**, and **13**, 0.808 for **12** (ether, 2 developments). Further purification by column chromatography (silica gel, 10 g; ether) afforded a mixture of **11** and **13** (105 mg), and **12** (32 mg): the mixture of **11** and **13**: IR (film) 3450, 1780, 1180, 980 cm^{-1}; ^1H NMR δ 5.30—5.55 (2H, m, olefinic H), 4.81—5.03 (1H, m, C_9–H), 4.61—4.70 (1H, m, OCHO), 3.02—4.05 (4H, m, C_{11},C_{15}–H, OCH_2), 0.90 (3H, t, CH_3); MS *m/e* 352 (M^+ of **11** $-H_2O$), 278 (M^+ of **13**—HOTHP), 250 (352—HOTHP): **12**: IR (film) 1780, 1720, 980 cm^{-1}; ^1H NMR δ 4.40—5.00 (2H,m, C_9–H, OCHO), 3.10—4.20 (3H, m, C_{11}–H, OCH_2), 0.90 (6H, t, CH_3); MS *m/e* 380 (M^+), 295 (M^+—THP).

Reduction of **2c** *with Dimethylaluminum 2,6-Di-t-butyl-4-methylphenoxide (***10***).* Trimethylaluminum (2.71 mmol) in hexane was added dropwise at 0 °C to a solution of 2,6-di-*t*-butyl-4-methylphenol (715 mg, 3.25 mmol) in toluene (10 ml) under nitrogen. Stirring was continued at 0 °C for 30 min, then at 25 °C for 30 min. The solution was cooled to −78 °C, and the enone **2c** (210 mg, 0.600 mmol) in toluene (2 ml) was added slowly over 5 min at this temperature. The whole mixture was stirred at −70 °C for 1 h, and warmed up to −5 °C over 2 h. The cooling bath was then removed and further stirring was carried out overnight. The reaction was terminated with saturated sodium hydrogentartarate. Extraction with ether, being dried over $MgSO_4$, concentration, and purification of the crude product by column chromatography (silica gel, 5 g; CH_2Cl_2–cyclohexane, 1 : 1, then only AcOEt) afforded the methylation product **14** with the recovery of **2c**: TLC, R_f 0.727 for **2c**, 0.461 for **14** (ether, 2 developments). Repurification by column chromatography (silica gel, 6 g; ether) furnished **2c** (50 mg) and **14** (100 mg): **14**: IR (film) 3450, 1770, 980 cm^{-1}; ^1H NMR δ 5.40—5.56 (2H, m, olefinic H), 4.75—5.00 (1H, m, C_9–H), 4.55—4.73 (1H, m, OCHO), 1.19 (3H, s, CH_3), 0.89 (3H, t, CH_3); MS *m/e* 366 (M^+), 348 (M^+ $-H_2O$), 264 (M^+ —HOTHP); high resolution MS *m/e* 366.242 (calcd for $C_{21}H_{34}O_5$, 366.241).

Reduction of Prostaglandin E_2 *Methyl Ester (***5a***).* A solution of the ester **5a** (104 mg, 0.284 mmol) in toluene (1 ml) was added slowly over 5 min to a solution of **1** (2.84 mmol) in toluene (15 ml) at −78 °C. The resulting mixture was stirred at −78 °C for 2 h, warmed up to −20 °C over 1 h, and again stirred at −20 °C for 30 min. The reaction mixture was poured onto cold 1 M hydrochloric acid (20 ml) and ethyl acetate (20 ml). The aqueous layer was extracted with ethyl acetate twice. The combined organic layers were washed successively with 1 M hydrochloric acid once, aq sodium hydrogencarbonate twice, then brine once, and dried over $MgSO_4$. Evaporation of the solvent, followed by purification of the residue by column chromatography (silica gel, 10 g; CH_2Cl_2, then AcOEt) gave $PGF_{2\alpha}$ methyl ester (**6a**) (99 mg, 95% yield): TLC, R_f 0.562 (homogeneous, AcOEt, 2 developments), which was in agreement with that of the authentic sample; boric acid impregnated TLC,[19] R_f 0.785 (homogeneous, AcOEt, 2 developments); IR (film) 3400, 2950, 2850, 1720, 1250, 975 cm^{-1}; ^1H NMR δ 5.22—5.65 (4H, m, olefinic H), 3.70—4.30 (3H, m, C_9, C_{11}, C_{15}–H), 3.66 (3H, s, $COOCH_3$), 0.90 (3H, t, CH_3); MS *m/e* 350 (M^+ $-H_2O$), 332 (M^+-2H_2O), 319 (M^+-H_2O-OMe), 314 (M^+-2H_2O), 301 (M^+ $-2H_2O-OMe$); high resolution MS *m/e* 350.244 (dehydration peak, calcd for $C_{21}H_{34}O_4$, 350.246). $PGF_{2\beta}$ methyl ester [TLC, R_f 0.424; boric acid impregnated TLC, R_f 0.462 (AcOEt, 2 developments)] was not detected in the reaction mixture.

Synthesis of 11-Epiprostaglandin E_2 *Methyl Ester (***5b***).* The ester **5b** was prepared starting from the diol **19** using the Corey method:[17] IR (film) 3400, 2950, 2850, 1740, 980 cm^{-1}; ^1H NMR δ 5.59—5.82 (2H, m, *trans* olefinic H), 5.26—5.45 (2H, m, *cis* olefinic H), 4.25—4.45 (1H, m, C_{11}–H), 3.92—4.15 (1H, m, C_{15}–H), 3.65 (3H, s, $COOCH_3$), 0.90 (3H, t, CH_3); MS *m/e* 348 (M^+-H_2O), 335 (M^+—OMe), 330 (M^+-2H_2O), 317 (M^+-H_2O-OMe); high resolution MS *m/e* 348.230 (dehydration peak, calcd for $C_{21}H_{32}O_4$, 348.230).

Reduction of **5b**. Reduction of the ester **5b** (200 mg, 0.546 mmol) with the aluminum reagent **1** (5.46 mmol) in toluene (30 ml) according to the method for reduction of **5a** afforded a mixture of 11-*epi*-$PGF_{2\alpha}$ methyl ester (**6b**) (major product) and 11-*epi*-$PGF_{2\beta}$ methyl ester (**6d**) (minor product) (188 mg, 94% yield): boric acid impregnated TLC, R_f 0.380 for **6b**, 0.565 for **6d** (AcOEt, 2 developments). These R_f values were in agreement with those of the reduction product from **5b** using $NaBH_4$.[20] Regular silica gel TLC plate showed a single spot with ethyl acetate (2 developments). The mixture of **6b** and **6d**: IR ($CHCl_3$) 3600, 3400, 1730, 980 cm^{-1}; ^1H NMR δ 5.48—5.72 (2H, m, *trans* olefinic H), 5.20—5.48 (2H, m, *cis* olefinic H), 3.82—4.43 (3H, m, C_9, C_{11}, C_{15}–H), 3.68 (3H, s, $COOCH_3$), 2.90—3.55 [3H, brs, OH disappearance in D_2O)], 0.89 (3H, t, CH_3): MS *m/e* 350 (M^+ $-H_2O$), 332 (M^+-2H_2O), 314 (M^+-3H_2O), 319 (M^+ $-H_2O-OMe$); high resolution MS *m/e* 350.243 (dehydration peak, calcd for $C_{21}H_{34}O_4$, 350.246). The ratio of **6b**/**6d** was determined by the conversion of **6b** and **6d** to the acids (2 M KOH–MeOH, 1 : 1, 25 °C for 2 h), then to the phenacyl esters (α,*p*-Dibromoacetophenone, Et_3N, CH_3CN, 25 °C for 3 min), followed by the HPLC analysis of these esters (μ-Porasil, UV index 264 nm, AcOEt–hexane, 4 : 1) to be 76 : 24.

Reduction of Prostaglandin D_2 *Methyl Ester (***6c***).* Reduction of **6c** (53 mg, 0.145 mmol) with the aluminum reagent **1** (1.61 mmol) in toluene (5 ml) using the method for the reduction of **5a** produced a mixture of 11-*epi*-$PGF_{2\alpha}$ methyl ester (**6b**) (major product) and $PGF_{2\beta}$ methyl ester (**6a**) (minor product) (49 mg, 92% yield): TLC, homogeneous; boric acid impregnated TLC, R_f 0.381 for **6b**, 0.501 for **6a** (AcOEt, 2 developments). The R_f values for **6b** and **6a** were completely identical with those for the reduction product of **5b**, and for the authentic $PGF_{2\alpha}$ methyl ester, respectively. The ratio of **6b**/**6a** (98/2) was determined, as described above, by the conversion of **6b** and **6a** into the corresponding phenacyl esters, followed by their HPLC analysis (μ-Porasil, UV index 264 nm, AcOEt–hexane, 4 : 1). The mixture of **6b** and **6a**: IR ($CHCl_3$) 3600, 3450, 1730, 980 cm^{-1}; ^1H NMR δ 5.50—5.69 (2H, m, *trans* olefinic H), 5.20—5.50 (2H, m, *cis* olefinic H), 3.96—4.46 (3H, C_9, C_{11}, C_{15}–H), 3.66 (3H, s, $COOCH_3$), 0.89 (3H, t, CH_3); MS *m/e* 350 (M^+-H_2O), 332 (M^+ $-2H_2O$), 319 (M^+-H_2O-OMe), 314 (M^+-3H_2O); high resolution MS *m/e* 350.246 (dehydration peak, calcd for $C_{21}H_{34}O_4$, 350.246).

Reduction of 4-Hydroxy-3-methyl-2-butanone. A solution of 4-hydroxy-3-methyl-2-butanone (500 mg, 4.90 mmol) in toluene (5 ml), which was cooled below −60 °C, was added dropwise to the aluminum reagent **1** (49 mmol) in toluene (100 ml) at −78 °C. The resulting mixture was stirred at −78 °C for 4 h, warmed up to −20 °C for 1 h, and again stirred at −20 °C for 30 min. The reaction mixture was poured onto 0.1 M hydrochloric acid (20 ml). Removal of the white solid by filtration, washing of the filtrate with brine, being dried over $MgSO_4$, and evaporation of the solvent left the crude oil, which was purified by column chromatography (silica gel, 150 g; CH_2Cl_2, then AcOEt) to furnish a

mixture of *erythro*- and *threo*-2-methyl-1,3-butanediol (480 mg, 96% yield): ^{1}H NMR (CD_3OD) δ 3.40—3.91 (3H, m, CH_2–O, CH–O), 1.41—1.70 (1H, m, CH_3–C<u>H</u>), 1.14, 1.16 (3H, two d, J=6.5 Hz, C_4–H), 0.87, 0.92 (3H, two d, J=7.0 Hz, C_2–CH_3); MS *m/e* 105 ($M^+ + 1$), 89 ($M^+ - CH_3$), 86 ($M^+ - H_2O$). The ratio of the peaks at δ 1.16 and 1.14 (or δ 0.92 and 0.87) was 2 : 1. The authentic *erythro* form[21] showed the peaks for 2 methyl groups at δ 1.16 (d, J=6.5 Hz) and 0.92 (d, J=7.0 Hz). Furthermore, the ^{1}H NMR analysis of the reduction product in the presence of the authentic *erythro* form showed the larger peaks at δ 1.16 and 0.92. Therefore, the ratio of *erythro* to *threo* form would be 2 : 1.

Reduction of 4-t-Butylcyclohexanone. A solution of 4-*t*-butylcyclohexanone (154 mg, 1 mmol) in toluene (2 ml) was added dropwise to the aluminum reagent **1** (10 mmol) in toluene (18 ml) at −78 °C. Stirring was continued at −78 °C for 4 h. Then the mixture was poured onto ice, and diluted with 1 M hydrochloric acid (75 ml). Extraction with ether, washing of the extracts with brine, being dried over $MgSO_4$, and concentration of the solvent left the crude oil, which was purified by column chromatography on silica gel (CH_2Cl_2, then CH_2Cl_2–AcOEt, 6 : 1) to afford the less polar isomer (37 mg, 24% yield) and the more polar isomer (94 mg, 60% yield) as white crystals: TLC, R_f 0.50 for the less polar isomer, 0.38 for the more polar isomer (AcOEt–CH_2Cl_2, 1 : 5). These R_f values were identical with those of the authentic samples (predominantly *cis*), which was prepared by the reduction of 4-*t*-butylcyclohexanone with L-Selectride in tetrahydrofuran at −78 °C.[22] The TLC analysis showed that the less polar isomer corresponded to the *cis* form, and therefore, the ratio of *cis*-/*trans*-4-*t*-butylcyclohexanol was 28 : 72. *cis*-4-*t*-Butyl-cyclohexanol: IR ($CHCl_3$) 3470, 1480, 1449, 1392, 1222, 1135, 1106, 949 cm^{-1}; ^{1}H NMR δ 3.93—4.18 (1H, m, CH–O), 1.14—2.04 (10H, m, aliphatic CH, OH), 0.87 (9H, s, *t*-Bu); MS *m/e* 156 (M^+), 141 ($M^+ - CH_3$), 138 ($M^+ - H_2O$), 123 ($M^+ - H_2O - CH_3$), 99 ($M^+ - t$-Bu); high resolution MS *m/e* 156.158 (calcd for $C_{10}H_{20}O$, 156.151). *trans*-4-*t*-Butylcyclohexanol: IR ($CHCl_3$) 3457, 1461, 1373, 1112, 1059, 978 cm^{-1}; ^{1}H NMR δ 3.29—3.80 (1H, m, CH–O), 0.80—2.23 (10H, m, aliphatic CH, OH), 0.83 (9H, s, *t*-Bu); MS *m/e* 138 ($M^+ - H_2O$), 123 ($M^+ - H_2O - CH_3$), 99 ($M^+ - t$-Bu), 81 ($M^+ - t$-Bu$- H_2O$).

Reduction of 2-Methylcyclohexanone. A solution of 2-methylcyclohexanone (112 mg, 1 mmol) in toluene (2 ml) was added dropwise to the aluminum reagent **1** (10 mmol) in toluene (18 ml) at −78 °C. Stirring was continued at −78 °C for 3.5 h, then at −20 °C for 3.5 h. The mixture was poured onto ice and diluted with 1 M hydrochloric acid (75 ml). Extraction with ether, washing of the extracts with brine, and purification of the concentrated crude product by column chromatography on silica gel (CH_2Cl_2, then ether) gave a mixture of *cis*- and *trans*-2-methylcyclohexanol (97 mg, 85% yield) as a colorless oil: IR ($CHCl_3$) 3490, 1452, 1378, 1220, 1123, 965 cm^{-1}; ^{1}H NMR δ 2.83—3.30, 3.63—3.97 (1H, m, CH–O), 1.10—2.12 (9H, m, aliphatic CH), 0.83—1.10 (3H, two d, CH_3); MS *m/e* 96 ($M^+ - H_2O$), 81 ($M^+ - H_2O - CH_3$). The ^{1}H NMR spectrum showed the ratio of the *cis* to *trans* isomers to be 75 : 25. This analysis was determined by an absorption due to the α-proton peak (C<u>H</u>–OH) of the hydroxyl group at δ 3.63—3.97 and 2.83—3.30.[23]

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