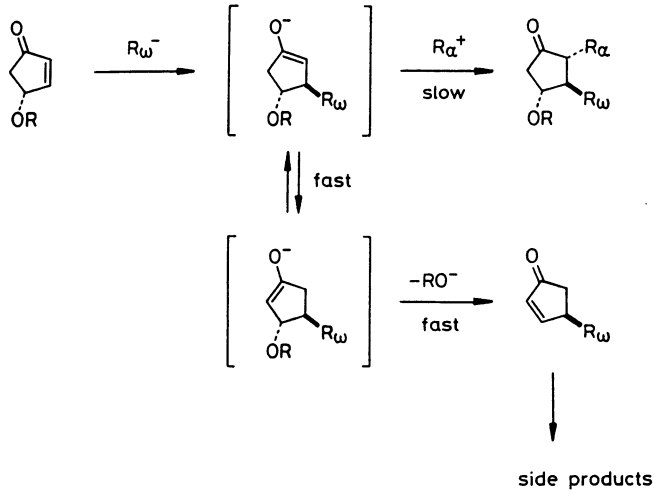
  Bull. Chem. Soc. Jpn., 61, 1299—1312 (1988)

Three-Component Coupling Synthesis of Prostaglandins: The Aldol Route[1)]

Masaaki SUZUKI, Toshio KAWAGISHI, Akira YANAGISAWA, Takehiko SUZUKI, Noriaki OKAMURA,[2)] and Ryoji NOYORI*
Department of Chemistry, Nagoya University, Chikusa, Nagoya 464
(Received November 13, 1987)

A one-pot, high yield construction of the whole prostaglandin (PG) skeleton is accomplishable by combination of the copper-mediated conjugate addition of an ω side-chain unit to a 4*R*-oxygenated 2-cyclopentenone derivative and aldol condensation of the in situ generated enolate with an α side-chain aldehyde. Subsequent removal of the 7-hydroxyl group from the adducts and deblocking of the protective groups give PGs of E series. PGE_1 has been prepared in 56% overall yield through the five-step sequence. Selective transformation of the PGE to PGD structure can be realized simply by appropriate selection of the hydroxyl protective groups in the five-membered ring and ω side-chain units. The vicinal carba-condensation using methyl 6-formyl-5-hexynoate as the α side-chain aldehyde unit followed by deoxygenation from the aldol products gives the 5,6-didehydro-PGE_2 derivatives which serve as key intermediates in the general synthesis of various natural PGs. An efficient method for resolution of 4-hydroxy-2-cyclopentenone is also described.

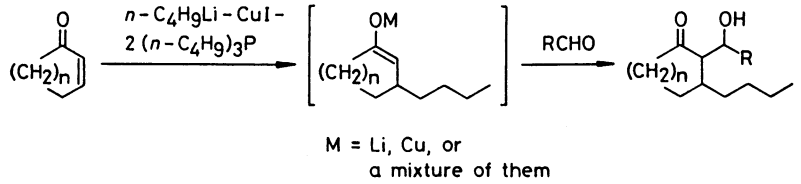
The prostaglandin (PG) skeleton is constituted by the oxygenated cyclopentanone ring and the seven-and eight-carbon (α and ω, respectively) side-chains. Obviously, the three-component coupling process, viz., consecutive nucleophilic/electrophilic introduction of the two side-chain units to (*R*)-4-hydroxy-2-cyclopentenone derivatives, is regarded as the simplest converging synthesis (Scheme 1).[3)] One may anticipate that well-known organocuprate conjugate addition of the ω side-chain unit to the enone followed by reaction with alkyl halides completes the desired vicinal carba-condensation.[4,5)] However, extensive studies along this line have revealed that such direct vicinal carba-condensation is not easy to achieve.[5p,6,7)] The difficulty is presumably attributable to the complex nature of the reaction system which causes a facile double-bond migration of the initially formed enolate,[3,5p)] causing concomitant dehydration to give the cyclopentenone products. The slow alkylation reaction cannot compete with such side sequences.[8)] However, use of highly reactive electrophiles is capable of suppressing the undesired reaction and the successful trapping has indeed been achieved with acyl chlorides[5n,o,9)] and ketene bis(methylthio)acetal monoxide, a strong Michael acceptor.[5p)] The aldol route is even more attractive.[5l,m,q-v,10)] Stork and Isobe thus employed very reactive formaldehyde as a trapping agent to introduce hydroxymethyl group at C-2 regiospecifically,[5k)] and constructed the full prostanoic acid skeleton by supplementing a six-carbon unit forming the full α side chain and the rectification of the oxidation state of the functional groups. They synthesized natural $PGF_{2\alpha}$ in 9% overall yield from a racemic 4-cumyloxy-2-cyclopentenone.[5k)] We intended to realize a one-pot construction of the full PG skeleton by the aldol strategy.[11)]



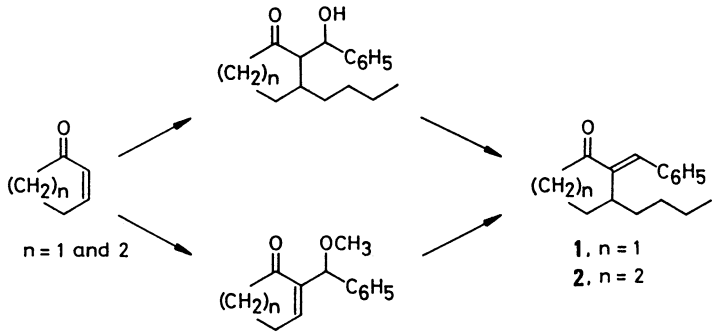
Scheme 1.

Results and Discussion

A. Vicinal Carba-Condensation of α,β-Unsaturated Ketones via the Tandem Organocopper Conjugate Addition/Aldol Reaction. We recently found a new recipe for the organocopper conjugate addition to α,β-unsaturated ketones using an organolithium (RLi), copper(I) iodide, and tributylphosphine in 1:2—3 mole ratio.[12)] The organocopper reagents undergo the conjugate addition to enones smoothly by employing 1:1 R/enone ratio and, in addition, the regio-defined enolate intermediates can be trapped effectively with equimolar amounts of aldehydes (Scheme 2). This stoichiometry-controlled, high-yield combination of the organometallic reagents and enone substrates, unlike under ordinary reaction conditions using excess organometallics, generates enolate species as only strong nucleophile present in the reaction system and, therefore, the latter reacts cleanly with one equivalent of the aldehyde trap, giving the aldol products. The results of the reaction of 2-cyclopentenone or -hexenone, the butylcopper reagent, and aldehydes are summarized in Table 1. The three-component joining effected with 1:1:1 molar ratio was general for a wide range of aldehydes including formaldehyde, simple alkanals, and α,β-unsaturated or aromatic aldehydes.



Scheme 2.



Scheme 3.

Table 1. Vicinal Carba-Condensation with α,β-Unsaturated Ketones via the Organocopper/Aldehyde Joining Process[a]

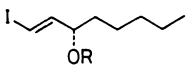
Entry	Enone	Aldehyde trapping	Aldol product Yield/%[b]
1	2-Cyclopentenone	Formaldehyde[c]	66[d]
2	2-Cyclopentenone	Butanal	98[e]
3	2-Cyclopentenone	2-Methylpropanal	93[e]
4	2-Cyclopentenone	2,2-Dimethylpropanal	71[e]
5	2-Cyclopentenone	Benzaldehyde	91[f]
6	2-Cyclopentenone	(*E*)-Cinnamaldehyde	94[f]
7	2-Cyclopentenone	2-Hexynal	72[f]
8	2-Cyclohexenone	Formaldehyde[c]	60[e]
9	2-Cyclohexenone	Acetaldehyde	91[f]
10	2-Cyclohexenone	Butanal	88[e]
11	2-Cyclohexenone	2-Methylpropanal	94[e]
12	2-Cyclohexenone	Benzaldehyde	96[f,g], 89
13	2-Cyclohexenone	(*E*)-Cinnamaldehyde	92[f]

a) The butylcopper phosphine complex was prepared in situ by mixing coppe(I) iodide, butyllithium, and tributylphosphine in 1:1:2 mole ratio at −78 °C in ether. The conjugate addition was conducted at −40 to −78 °C. Enolate trapping was carried out at −78 °C for 5—60 min. b) Yield after silica-gel column chromatography. c) Introduced with an argon stream after cracking of paraformaldehyde. d) A 59:1 stereomixture. e) A single isomer. f) A mixture of stereoisomers. g) Yield determined by ^{1}H NMR analysis.

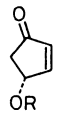
Alkanals as the trapping agent tend to produce single coupling adducts, whereas acetaldehyde and aromatic or other α,β-unsaturated aldehydes give rise to a mixture of stereoisomers.

The two side chains are incorporated in the vicinal positions in a regiospecific manner via kinetically defined, nonequilibrating enolates. This is confirmed, for examples, by comparison of the samples of 2-benzylidene-3-butylcycloalkanones, **1** and **2**, derived from the corresponding aldols by dehydration and those prepared by an unambiguous method consisting of the combination reaction of α-alkoxyalkylation[13] and organocopper conjugate addition (Scheme 3). No α′,β-condensation products associated with possible enolate equilibration were detected in the reaction mixture.

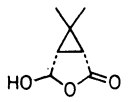
B. Chiral Building Blocks. The optically active building blocks requisite for convergent PG synthesis are accessible in various ways.[3a] The ω side-chain alcohol having S configuration, **3**, is available by optical resolution,[14a] kinetic resolution by asymmetric epoxidation,[14b] or asymmetric reduction of the corresponding enone by chemical,[14c] or enzymatic[14d] method. The R cyclopentenone derivative, **6**, is obtainable by chemical[15a,b] or chromatographic resolution,[15c] transformation from D-tartaric acid ((2*S*,3*S*)-(−)-tartaric acid),[15d] chemical kinetic resolution of racemic 4-hydroxy-2-cyclopentenone,[15e] enzymatic kinetic resolution of the acetate,[15f] and asymmetric reduction of 2-cyclopentene-1,3-dione,[14c] etc. We now found that **6** was obtainable by efficient optical resolution of the racemate[16] using the resolving agent **9** derived from chrysanthemic acid.[17] Thus condensation of (±)-**6** with **9** in the presence of pyridinium *p*-toluenesulfonate gave the two diastereomeric mixture **10** in 99% yield based on **9**. The diastereomers separated by silica-gel column chromatography were subjected to hydrolysis in aqueous dioxane at 70 °C to give desired (*R*)-4-hydroxy-2-cyclopentenone (**6**) and its antipode in 88% and 82% of theory, respectively. No racemization was observed under these conditions. The resolving reagent **9** was recovered in >75% yield and could be recycled for the resolution precedure. The hydroxyl group of **6** was protected by a silyl or tetrahydropyranyl group by conventional methods[18]



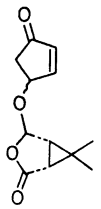
3, R = H
4, R = $Si(CH_3)_2$-*t*-C_4H_9
5, R = THP



6, R = H
7, R = $Si(CH_3)_2$-*t*-C_4H_9
8, R = THP



9

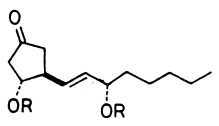


10

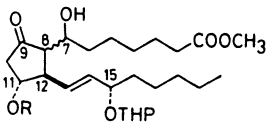
for the purpose of the organometallic operation.

C. A Short Synthesis of PGE_1 and PGD_1. When organocopper reagent formed from **4** was coupled with (*R*)-siloxy enone **7**, a single adduct **11** was obtained after aqueous work-up.[3a] The C-3/C-4 trans relationship was established simply by nonbonded interaction between the siloxy moiety and the entering organometallic. Encouraged by the clean trans stereochemistry induced in the conjugate addition step, we then moved to the aldehyde trapping of the enolate intermediate. The conjugate addition using the enone **8** and the organocopper reagent formed from the alkenyl iodide **5** was followed by aldol trapping of the enolate with one equivalent of methyl 6-formylhexanoate. As expected, the desired aldol **12** (a threo/erythro[19] mixture) possessing the whole PG framework was obtained in 83% yield.[20] The undesired β-elimination leading to the PGA type structure could not be observed. Removal of the C-7 hydroxyl group from **12** was accomplished via the enone **14** formed by dehydration with methanesulfonyl chloride and 4-(dimethylamino)pyridine (92% yield). Exposure of **14** to excess zinc dust in a 95:5 2-propanol-acetic acid mixture gave the saturated PGE_1 derivative **16** in 84% yield. Heating of **14** with tributyltin hydride in the presence of a catalytic amount of di-*t*-butyl peroxide increased the product yield up to 90%. Deblocking the tetrahydropyranyl protective groups gave PGE_1 methyl ester (**18**) in 92% yield. The spectroscopic and chromatographic behavior was identical with that of authentic PGE_1 methyl ester. Hydrolysis of the ester function by porcine liver esterase (86% yield)[22] completes the synthesis of natural PGE_1. Thus PGE_1 was synthesized in 56% overall yield through the five-step sequence from the starting enone **8**. PGE_1 possesses four asymmetric carbons. Here the absolute configuration at C-11 and C-15 is inherently determined at the stage of the starting enone and ω side-chain components, and the mutual trans relationship of the three ring substituents at C-11, C-12, and C-8 is established automatically through the vicinal carba-condensation and the following functional group manipulation.

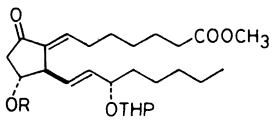
PGD_1 was also accessible by fundamentally the same strategy. PGD_1, like PGE_1, has the β-hydroxycyclopentanone structure but bears a hydroxyl group at C-9 and a keto function at C-11. The choice of proper hydroxyl protective groups in the starting five-membered ring and ω side-chain units allows ready arrangement of such functional groups. Trialkylsilyl protection of 4-hydroxy-2-cyclopentenone and tetrahydropyranyl blocking of the ω side-chain alcohol were the best choice in view of their different profiles of the removal conditions. Thus the vicinal carba-condensation of the enone **7** under our standard conditions by using **5** and methyl 6-formylhexanoate as side-chain components gave the aldol **13** (a threo/erythro[19] mixture) in 70% yield. Treatment of **13** with methanesulfonyl chloride and 4-(dimethylamino)pyridine gave the dehydration product **15** in 75% yield, which upon exposure to excess tributyltin hydride and di-*t*-butyl peroxide catalyst afforded **17** in 88% yield. The oxidation states of the C-9 and C-11 positions was easily rectified as follows. Requisite stereoselective reduction of the 9-keto group was accomplished with L-Selectride (lithium tri-*s*-butylborohydride) in THF to



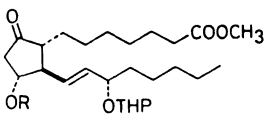
11, R = $Si(CH_3)_2$-*t*-C_4H_9



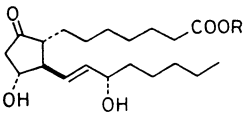
12, R = THP
13, R = $Si(CH_3)_2$-*t*-C_4H_9



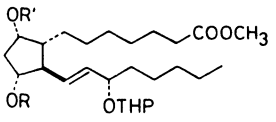
14, R = THP
15, R = $Si(CH_3)_2$-*t*-C_4H_9



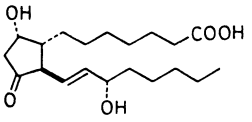
16, R = THP
17, R = $Si(CH_3)_2$-*t*-C_4H_9



18, R = CH_3
19, R = H



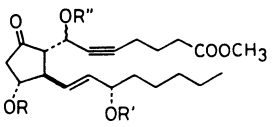
20, R = $Si(CH_3)_2$-*t*-C_4H_9; R' = H
21, R = $Si(CH_3)_2$-*t*-C_4H_9; R' = THP
22, R = H; R' = THP



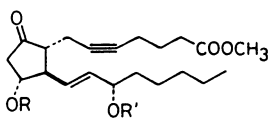
23

give the 9α alcohol **20** exclusively in 92% yield. After tetrahydropyranylation of 9-hydroxyl in **20** under standard conditions leading to **21** (94%), removal of the silyl protective group with tetrabutylammonium fluoride gave **22** in 84% yield. Alkaline hydrolysis of the methyl ester, Jones oxidation of the C-11 hydroxyl function, and final deblocking of the tetrahydropyranyl protective groups completed the synthesis of PGD_1 (**23**) as crystals in 61% overall yield from **22**. These three operations were conducted successively without purification of the intermediates. The ester hydrolysis at the stage of 9,15-*O*-bis(tetrahydropyranyl)-$PGF_{1\alpha}$, rather than the final step, turned out to be more appropriate in view of the instability of PGD_1 causing dehydration.

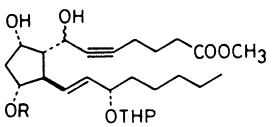
D. Synthesis of 5,6-Didehydro-PGE_2 Derivatives. Introduction of the unsaturation at the C-5 and C-6 positions (PG numbering) using methyl 6-formyl-5-hexynoate, an acetylenic aldehyde, as the α side-chain unit leads to a promising, general way to PGs. The tandem conjugate addition/aldol reaction was conducted by using the enone **7**, an (*E*)-alkenylcopper reagent derived from **4**, and methyl 6-formyl-5-hexynoate in ether to give the aldol adduct **24** (a 1 : 1 mixture of the C-7 epimers[23]) in 50% yield. This yield has been improved up to 83% by conducting the conjugate addition in THF, followed by addition of one equivalent of boron trifluoride etherate prior to the treatment with the aldehyde. Although attempts to remove the C-7 hydroxyl function in **24** by the above described dehydration/reduction procedure failed, the Barton deoxygenation[26] of secondary alcohols proved useful for this purpose. Thus treatment of the aldol **24** with thiobenzoyl chloride and 4-(dimethylamino)-pyridine afforded the thiobenzoate **26** in 71% yield, which upon heating at 50 °C with tributyltin hydride with a catalytic amount of di-*t*-butyl peroxide gave a single deoxygenated compound **28**[27] in 98% yield. The successful removal of the thiobenzoate moiety relies heavily on the presence of the 5,6-triple bond which effects propargylic resonance stabilization to the radical intermediate.[28] The acetylenic compound **28** acts as a key intermediate for synthesis of various naturally occuring PGs including prostacyclin.[3a]



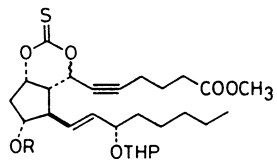
24, R = R′ = $Si(CH_3)_2$-*t*-C_4H_9; R″ = H
25, R = $Si(CH_3)_2$-*t*-C_4H_9; R′ = THP; R″ = H
26, R = R′ = $Si(CH_3)_2$-*t*-C_4H_9; R″ = C(=S)C_6H_5
27, R = $Si(CH_3)_2$-*t*-C_4H_9; R′ = THP; R″ = C(=S)C_6H_5



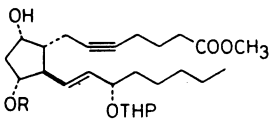
28, R = R′ = $Si(CH_3)_2$-*t*-C_4H_9
29, R = $Si(CH_3)_2$-*t*-C_4H_9; R′ = THP



30, R = $Si(CH_3)_2$-*t*-C_4H_9



31, R = $Si(CH_3)_2$-*t*-C_4H_9



32, R = $Si(CH_3)_2$-*t*-C_4H_9

This method also allows the preparation of PGD intermediates. The aldol **25** (a mixture of the C-7 epimers) was available by the vicinal carba-condensation of the silylated hydroxycyclopentenone **7** with equimolar amounts of the tetrahydropyranylated ω side-chain unit **5** and methyl 6-formyl-5-hexynoate in 65% yield. Application of the Barton deoxygenation procedure[26] to this aldol product gave **29** in 66% yield via the corresponding thiobenzoate **27**. Removal of the C-7 hydroxyl function in **25** was also realized via the cyclic thiocarbonate intermediate.[31] Thus reduction of the more polar isomer of **25** with sodium borohydride gave the diol **30** stereoselectively in 77% yield (9α : 9β=97.5 : 2.5). Treatment of **30** with 1,1′-thiocarbonyldiimidazole and 4-(dimethylamino)pyridine afforded the cyclic thiocarbonate **31** in 92% yield. Then exposure of **31** to tributyltin hydride and di-*t*-butyl peroxide followed by alkaline treatment gave the C-7 deoxygenated compound **32** in 77% yield. The same compound was also derived in 35% overall yield from the less polar isomer of **30** via the corresponding thiocarbonate intermediate. It should be added that reduction of the less polar isomer of **30** with sodium borohydride gave a mixture of the 9α and 9β alcohols in 54 and 14% yield, respectively.

This expeditious tandem conjugate addition/aldol reaction sequence is synthetically flexible enough to apply to the synthesis of a variety of natural and unnatural PG derivatives. A range of artificial PGs can be prepared by using the 7-hydroxyl group as trigger functionality. The aldol product **24** is an important synthetic intermediate of stable PGI_2 analogues, (7*R*)- and (7*S*)-fluoro-PGI_2.[3a,32] It should be added that **12**, **13**, and the 11,15-*O*-bis-silylated analogue serve as synthetic precursors of Δ^7-PGA_1, an artificial strong antineoplastic prostaglandin.[33]

Experimental

General. (a) Spectrometers: IR spectra were obtained with a JASCO IRA-1 spectrometer. NMR spectra were determined on a JEOL PMX-60, FX-90Q, Varian HA-100, or NEVA NV-21 spectrometer. Chemical shifts are reported as δ vaules in parts per million relative to tetramethylsilane (δ=0). Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet, and br means a broad

signal. Mass spectra (MS) were obtained with a JEOL D-10 mass spectrometer under an ionization potential of 75 eV. High-resolution mass spectra (HRMS) were recorded with a JEOL TMS-DX 300 spectrometer. Optical rotation was measured on a JASCO DIP-4 or DIP-181polarimeter. (b) Chromatography: R_f values on TLC were recorded on E. Merck precoated (0.25 mm) Silica Gel 60 F_{254} plates. The plates were sprayed with a solution of 2% *p*-anisaldehyde in 5% ethanolic sulfuric acid and then heated until the spots became clearly visible. Column chromatography was conducted under Florisil (Nakarai, M7P4145), silica gel (E. Merck, 7734, 70—230 mesh, or Fuji Devison, BW-80, 80—200 mesh), or deactivated silica gel (E. Merck) by mixing with water (6—9 wt%). Column chromatography at low temperature (0 °C) was conducted using a glass column equipped with a cold jacket. High-performance liquid chromatography (HPLC) was conducted on Waters 6000A instrument using a column packed with Develosil 100-5 (3.8 mmϕ×250 mm). (c) Solvents: Dry ether, THF, toluene, and benzene were prepared by distillation over Na-benzophenone ketyl under argon. Dry dichloromethane was prepared by distillation over P_4O_{10}. Dry hexamethylphosphoric triamide (HMPA), *N,N*-dimethylformamide (DMF), acetonitrile, *t*-C_4H_9OH, and dimethyl sulfoxide (DMSO) were prepared by distillation from CaH_2. The solution obtained after extraction was dried over anhydrous Na_2SO_4 or $MgSO_4$ and evaporated by a rotary evaporator under aspirator pressure. (d) Reagents and materials: Copper(I) iodide (CuI) (Nakarai) was continuously extracted with THF in a Soxhlet extractor overnight and dried in vacuo at room temperature for several hours. Tributylphosphine (Nakarai) was purified by distillation before use. *n*-C_4H_9Li (Mitsuwa or Nakarai), *t*-C_4H_9Li (Aldrich), and a THF solution of L-Selectride (Aldrich) were used directly from the bottles. Molarity of alkyllithiums were determined by titration[34] and stored at 4 °C. Zn powder was used after treatment with 2% HCl aqueous solution followed by drying in vacuo. Formaldehyde was generated from paraformaldehyde (excess) by flash heating with a heat gun and introduced into a enolate system with a stream of agron. Jones reagent was prepared by mixing CrO_3 (26.72 g) and concd sulfuric acid (23 mL) in water (50 mL). Methyl 6-formylhexanoate was prepared by ozonolysis of 1-methoxycycloheptene[35] or cycloheptene.[36] Ozonolysis of 1-methoxycycloheptene: Ozone was introduced into a mixture of 1-methoxycycloheptene (24 g, 0.19 mol) and methanol (150 mL) at −78 °C for 3 h. Remaining ozone dissolved in the solution was excluded by introducing argon into the mixture for 10 min at this temperature. To this was added dimethyl sulfide (20 mL) at −78 °C and then the mixture was slowly warmed up to room temperature over a period of 2 h. After stirring for 2 days at room temperature, the mixture was concentrated under reduced pressure and the residual oil was dissolved in a 1 : 1 mixture of ether and petroleum ether (100 mL) and the mixture was washed with water (50 mL) and dried. After evaporation of the solvent using a rotary evaporator, the residual oil was distilled under reduced pressure to give methyl 6-formylhexanoate (20.5 g, bp 82—86 °C/5 mmHg,† 68% yield) as colorless oil: ^{1}H NMR (CCl_4) δ=1.3—1.9 (m, 6H, 3 CH_2), 2.2—2.6 (m, 4H, 2 CH_2CO), 3.60 (s, 3H, OCH_3), 9.68 (br s, 1H, CHO). Methyl 6-formyl-5-hexynoate was prepared by the Swern oxidation[37] of the corresponding propargylic alcohol:[38] In a 100-mL two-necked round-bottomed flask were placed CH_2Cl_2 (20 mL) and DMSO (3.0 mL, 42 mmol) and the atmosphere was replaced with argon. After cooling to −78 °C, to this was added trifluoroacetic anhydride (4.5 mL, 32 mmol) over a period of 10 min and the mixture was stirred at this temperature for 20 min. To this mixture was added a solution of methyl 7-hydroxy-5-heptynoate (3.30 g, 21.1 mmol) in CH_2Cl_2 (5 mL) at −78 °C over a period of 15 min and the mixture was stirred for 30 min at this temperature, followed by the addition of triethylamine (9.1 mL, 65 mmol) over a period of 10 min. The mixture was stirred for 10 min at the same temperature and the cold bath was removed. After stirring for 1 h, the mixture was poured into satd $NaHCO_3$ aqueous solution (50 mL) and the resulting mixture was extracted three times with CH_2Cl_2 (30 mL each). The combined extracts were dried and evaporated. The residual material was subjected to column chromatography on silica gel (100 g) using a 5 : 1 mixture of hexane and ethyl acetate as eluant to give methyl 6-formyl-5-hexynoate (2.31 g, 71%) as colorless oil: IR (neat) 2280, 2200, 1740, 1670 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.7—2.7 (m, 6H, 3 CH_2), 3.70 (s, 3H, OCH_3), 9.20 (s, 1H, CHO). HRMS Found: *m/z* 153.0522. Calcd for $C_8H_{13}O_3$: M−H, 153.0552. (*S,E*)-3-Hydroxy-1-iodo-1-octene (**3**) was prepared by optical resolution of the racemate[14a] or asymmetric reduction[14c] of the corresponding enone followed by the purification through the crystalline salt of the corresponding hydrogen phthalate and (−)-α-methylbenzylamine.[14a] Silylated **4**, $[\alpha]_D^{23}$ −37.5° (*c* 0.97, CH_3OH) and tetrahydropyranylated **5**, $[\alpha]_D^{22}$ −65.9° (*c* 1.05, CH_3OH), were used in the reaction. These optically pure compounds were supplied from Teijin Co. Racemic 4-hydroxy-2-cyclopentenone was prepared by our previous procedure,[16a] acid-catalyzed rearrangement of furfuryl alcohol,[39] or oxidative dimethoxylation of 2-methylfuran[40] followed by phosphate-buffer treatment.[41] (*R*)-4-Hydroxy-2-cyclopentenone (**6**) was obtained by optical resolution using the lactol **9**.

Optical Resolution of 4-Hydroxy-2-cyclopentenone. In a 1-L one-necked round-bottomed flask equipped with a Dean-Stark water separator were placed (1*R*,2*S*)-cis-2-formyl-3,3-dimethylcyclopropane-1-carboxylic acid (**9**)[17] (a cyclic hemiacylal form) (71 g, 0.50 mol, mp 116 °C, $[\alpha]_D^{20}$−102° (*c* 0.5, C_2H_5OH), >97% ee), racemic 4-hydroxy-2-cyclopentenone (69 g, 0.70 mol), pyridinium *p*-toluenesulfonate (63 g, 0.25 mol), and dry benzene (500 mL). When the mixture was heated at reflux under stirring for ca. 5 h, the theoretical amount of water (9 mL) was collected in the separatory condenser. After removal of benzene on a rotary evaporator, the residual material was dissolved in ethyl acetate (500 mL) and washed twice with water, once with satd $NaHCO_3$ aqueous solution (200 mL),[42] and three times with water. The organic solution was dried and concentrated on a rotary evaporator to give a crude mixture of the condensation product **10** (110 g, 99% yield based on **9**).[43] Chromatography of this material on silica-gel column using a 1 : 1 mixture of hexane and ethyl acetate as eluant afforded the less polar material (41 g, 37% yield based on **9**) and more polar one (44 g, 40% yield based on **9**). The less polar material: mp 89.0—90.5 °C; $[\alpha]_D^{23}$−45° (*c* 0.36, CH_3OH); IR (KBr) 1775, 1760, 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.16 (s, 3H, CH_3), 1.18 (s, 3H, CH_3), 2.04 (s, 2H, 2 CH), 2.27 (dd, 1H, *J*=18 and 2.5 Hz, a proton of CH_2), 2.72 (dd, 1H, *J*=18 and 5.5 Hz, a proton of CH_2), 4.9—5.0 (m, 1H, CHO), 5.27 (s, 1H, OCHO),

†1 mmHg≈133.322 Pa.

6.21 (dd, 1H, J=6 and 1.5 Hz, CH=CHCO), 7.58 (dd, 1H, J=6 and 2 Hz, CH=CHO). The more polar material: mp 97.5—98 °C; $[\alpha]_D^{22.6}$ −222° (c 0.71, CH_3OH), IR (KBr) 1776 (shoulder), 1760, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.15 (s, 3H, CH_3), 1.17 (s, 3H, CH_3), 2.03 (s, 2H, 2 CH), 2.37 (dd, 1H, J=19 and 3 Hz, a proton of CH_2), 2.82 (dd, 1H, J=19 and 5.5 Hz, a proton of CH_2), 4.8—5.1 (m, 1H, CHO), 5.30 (s, 1H, OCHO), 6.25 (dd, 1H, J=6 and 1 Hz, CH=CHCO), 7.55 (dd, 1H, J=6 and 2.5 Hz, CH=CHCO).

A mixture of the less polar material (41 g, 0.18 mol) obtained above, dioxane (50 mL), and water (100 mL) was placed in a 500-mL one-necked round-bottomed flask and heated at 80 °C for 1 h under stirring. After cooling, the mixture was mixed with toluene (100 mL) and concentrated on a rotary evaporator. To the aqueous residue was added satd $NaHCO_3$ aqueous solution (100 mL) and then $NaHCO_3$ powder until the system became basic. The aqueous mixture was extracted five times with ethyl acetate (200 mL each). The combined extracts were dried and evaporated to afford (*R*)-4-hydroxy-2-cyclopentenone (**6**) (16 g, 88% yield, $[\alpha]_D^{22}$ +90.1° (c 0.43, CH_3OH), >97% ee) as a colorless oil. The optical purity was assayed by ^1H NMR analysis of the corresponding α-methoxy-α-(trifluoromethyl)phenylacetate.[44] Recovery of the resolving agent **9**: After acidification of the $NaHCO_3$ solution with 4 mol dm^{-3} HCl, the mixture was extracted with ethyl acetate (500 mL). The organic solution was washed twice with water, dried and evaporated, giving a crude hemiacylal resolving agent which was recrystallized from ether to afford pure hemiacylal **9** in 75% yield. Hydrolysis of the polar material (44 g, 0.20 mol) under similar conditions gave (*S*)-4-hydroxy-2-cyclopentenone (16 g, 82% yield). (4*R*)-4-(Tetrahydropyran-2-yloxy)-2-cyclopentenone (**8**), $[\alpha]_D^{22}$ +90.3° (c 1.02, CH_3OH), and (*R*)-4-(*t*-butyldimethylsiloxy)-2-cyclopentenone (**7**), $[\alpha]_D^{22}$ +67.4° (c 0.4, CH_3OH), were used for the synthesis of PGs. These optically pure materials were supplied from Teijin Co.

Standard Procedure for Vicinal Carba-Condensation via Organocopper Conjugate Addition/Aldol Condensation. Prior to introduction of solvents and materials, the reaction vessel was evacuated and dried by heating in vacuo with a heat gun and then, after cooling, the system was replaced with argon. Addition or transfer of the materials in the reaction was conducted under argon atmosphere. The typical procedure is illustrated in the synthesis of 3-butyl-2-(1-hydroxy-2-methylpropyl)cyclopentanone (Entry 3 in Table 1): In a 150-mL ampule was placed CuI (390 mg, 2.05 mmol) under argon atmosphere. To this was added successively dry ether (20 mL) and tributylphosphine (1.02 mL, 4.10 mmol) under stirring. The suspension was further stirred at room temperature until giving a clear solution (ca. 10 min). After cooling to −78 °C, to this was added a solution of butyllithium (1.64 mol dm^{-3}, 1.25 mL, 2.05 mmol) in hexane by using a glass syringe under stirring. After 5 min at −78 °C, a solution of 2-cyclopentenone (164 mg, 2.0 mmol) in dry ether (5 mL) was added over a period of 5 min at this temperature under stirring. After 10 min at −78 °C, a solution of 2-methylpropanal (148 mg, 2.05 mmol) in dry ether (5 mL) was added at −78 °C. After stirring for 10 min at this temperature, the mixture was quenched with satd aqueous NH_4Cl solution (50 mL) at −78 °C under vigorous shaking. The organic layer was separated and the aqueous layer was extracted with ether (10 mL). The combined ethereal extracts were dried and evaporated. The residue was subjected to column chromatography on silica gel (50 g), eluted with a 4 : 1 mixture of hexane and ethyl acetate, to give the aldol (396 mg, 93% yield) as a colorless oil: R_f 0.42 (5 : 1 benzene/ethyl acetate); IR (neat) 3450, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.8—1.1 (m, 6H, 2 CH_3), 1.2—2.0 (m, 13H, 6 CH_2 and CH), 2.2—2.4 (m, 3H, CH_2CO and CHCO), 2.68 (br, 1H, OH), 3.73 (dt, 1H, J=7.2 and 4.4 Hz, CHO). Found: C, 73.36; H, 11.49%. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39%.

Unless otherwise stated, the reaction indicated in Table 1 was conducted by a similar procedure.

3-Butyl-2-(hydroxymethyl)cyclopentanone (Entry 1). A 59 : 1 stereomixture. Liquid chromatography (LC): SiO_2, 2 : 1 petroleum ether/ethyl acetate as eluant. IR (neat) 3440, 3738 cm^{-1}; ^1H NMR (CCl_4) δ=0.8—2.5 (m, 15H, 5 CH_2, 2 CH, and CH_3), 2.78 (m, 1H, OH), 3.3—4.0 (m, 2H, CH_2O); ^{13}C NMR ($CDCl_3$) (major stereoisomer) δ=14.1, 22.9, 27.3, 29.5, 34.4, 38.4 (2C), 57.3, 59.7, 221.2. Found: C, 70.35; H, 10.69%. Calcd for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66%.

3-Butyl-2-(1-hydroxybutyl)cyclopentanone (Entry 2). LC: SiO_2, 10 : 1 benzene/ethyl acetate as eluant. TLC R_f 0.42 (5 : 1 benzene/ethyl acetate); IR (neat) 3450, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.8—1.1 (m, 6H, 2 CH_3), 1.2—2.0 (m, 13H, 6 CH_2 and CH), 2.2—2.4 (m, 3H, CH_2CO and CHCO), 2.68 (br, 1H, OH), 3.73 (dt, 1H, J=7.2 and 4.4 Hz, CHO). Found: C, 73.36; H, 11.49%. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39%.

3-Butyl-2-(2,2-dimethyl-1-hydroxypropyl)cyclopentanone (Entry 4). LC: SiO_2, 6 : 1 hexane/ethyl acetate as eluant. TLC R_f 0.35 (4 : 1 hexane/ethyl acetate); IR (neat) 3450, 1729 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.8—1.1 (m, 12H, 4 CH_3), 1.1—2.4 (m, 13H, 5 CH_2, 2 CH, and OH), 3.31 (s, 1H, CHO). Found: C, 74.21; H, 11.66%. Calcd for $C_{14}H_{26}O_2$: C, 74.29; H, 11.58%.

3-Butyl-2-(hydroxyphenylmethyl)cyclopentanone (Entry 5). LC: SiO_2, 5 : 1 petroleum ether/ether as eluant. TLC R_f 0.41 (1 : 1 petroleum ether/ether); IR (neat) 3440, 1730, 694 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.7—2.5 (m, 15H, 5 CH_2, 2 CH, and CH_3), 3.39 (d, 0.36H, J=6.2 Hz, OH), 4.28 (d, 0.64H, J=1.5 Hz, OH), 4.75 (dd, 0.63H, J=7.8 and 1.5 Hz, CHO), 5.20 (dd, 0.37H, J=6.2 and 3.0 Hz, CHO), 7.32 (m, 5H, phenyl). HRMS Found: m/z 246.1594. Calcd for $C_{16}H_{22}O_2$: M, 246.1619.

3-Butyl-2-(1-hydroxy-3-phenyl-2-propenyl)cyclopentanone (Entry 6). LC: SiO_2, 4 : 1 hexane/ethyl acetate as eluant. TLC R_f 0.41 and 0.36 (2 : 1 hexane/ethyl acetate); IR (neat) 3480, 1723, 962 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.90 (m, 3H, CH_3) 1.1—1.9 (m, 8H, 4 CH_2), 1.9—2.6 (m, 4H, CH_2CO and 2 CH), 3.35 (d, 0.33H, J=8.0 Hz, OH), 3.45 (d, 0.67H, J=3.0 Hz, OH), 4.48 (m, 0.67H, CHO), 4.63 (m, 0.33H, CHO), 6.19 (dd, 0.33H, J=16.0 and 6.6 Hz, vinyl), 6.32 (dd, 0.67H, J=16.0 and 6.8 Hz, vinyl), 6.60 (d, 1H, J=16.0 Hz vinyl), 7.32 (m, 5H, phenyl). HRMS Found: m/z 272.1755. Calcd for $C_{18}H_{24}O_2$: M, 272.1776.

3-Butyl-2-(1-hydroxy-2-heptynyl)cyclopentanone (Entry 7). LC: SiO_2, 3 : 1 hexane/ether as eluant. TLC R_f 0.31 (1 : 1 hexane/ether); IR (neat) 3450, 2230, 1739 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.8—1.0 (m, 6H, 2 CH_3), 1.2—1.8 (m, 12H, 6 CH_2), 1.8—2.5 (m, 7H, 2 CH_2, 2 CH, and OH), 4.63 (m, 1H, CHO). Found: C, 76.75; H, 10.50%. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47%.

3-Butyl-2-(hydroxymethyl)cyclohexanone (Entry 8). LC: SiO_2, 2 : 1 petroleum ether/ether as eluant. TLC R_f 0.23 (1 : 1 petroleum ether/ether); IR (neat) 3400, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.93 (t, 3H, CH_3), 1.1—2.5 (m, 14H, 6 CH_2 and 2 CH), 2.6 (br, 1H, OH), 3.5—4.1 (m, 2H, CH_2O); ^{13}C NMR

($CDCl_3$) δ=14.0, 22.9, 25.7, 28.2, 30.3, 33.2, 40.1, 41.9, 56.9, 59.5, 214.8. Found: C, 71.63; H, 10.99%. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94%.

3-Butyl-2-(1-hydroxyethyl)cyclohexanone (Entry 9). LC: SiO_2, 10:1 benzene/ethyl acetate as eluant. TLC R_f 0.43 and 0.40 (2:1 benzene/ethyl acetate); IR (neat) 3430, 1709 cm^{-1}; ^1H NMR (CCl_4) δ=0.90 (t, 3H, CH_3), 1.1—2.5 (m, 17H, 6 CH_2, 2 CH, and CH_3), 2.78 (br, 1H, OH), 4.0 (br, 1H, CHO). Found: C, 72.77; H, 11.09%. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18%.

3-Butyl-2-(1-hydroxybutyl)cyclohexanone (Entry 10). LC: SiO_2, 3:1 petroleum ether/ether as eluant. TLC R_f 0.31 (1:1 petroleum ether/ether); IR (neat) 3400, 1698 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.93 (m, 6H, 2 CH_3), 1.1—3.0 (m, 19H, 8 CH_2, 2 CH, and OH), 3.8 (m, 1H, CHO). Found: C, 74.19; H, 11.63%. Calcd for $C_{14}H_{26}O_2$: C, 74.28; H, 11.58%.

3-Butyl-2-(1-hydroxy-2-methylpropyl)cyclohexanone (Entry 11). LC: SiO_2, 8:1 to 6:1 hexane/ethyl acetate as eluant. TLC R_f 0.31 (1:1 ether/petroleum ether); IR (neat) 3480, 1697 cm^{-1}; ^1H NMR (CCl_4) δ=0.8—1.0 (m, 9H, 3 CH_3), 1.1—2.2 (m, 12H, 5 CH_2 and 2 CH), 2.2—2.4 (m, 3H, CH_2CO and CHCO), 3.16 (dd, 1H, J=8.4 and 3.2 Hz, CHO). Found: C, 74.05; H, 11.72%. Calcd for $C_{14}H_{26}O_2$: C, 74.29; H, 11.58%.

3-Butyl-2-(hydroxyphenylmethyl)cyclohexanone (Entry 12). LC: SiO_2, 4:1 hexane/ethyl acetate as eluant. The less polar isomer: 18% yield; TLC R_f 0.48 (2:1 hexane/ethyl acetate); IR ($CHCl_3$) 3600, 3490, 1701 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.8—2.6 (m, 17H, CH_3, 6 CH_2, CH, and OH), 2.64 (dd, 1H, J=5.7 and 5.7 Hz, CHCO), 5.13 (d, 1H, J=5.5 Hz, CHO), 7.33 (m, 5H, phenyl). The more polar isomer: 71% yield; TLC R_f 0.32 (2:1 hexane/ethyl acetate); IR ($CHCl_3$) 3595, 3530, 1697 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.85 (t, 3H, CH_3), 1.0—2.1 (m, 11H, 5 CH_2 and CH), 2.3—2.5 (m, 2H, CH_2CO), 2.63 (dd, 1H, J=5.9 and 5.9 Hz, CHCO), 3.05 (br, 1H, OH), 4.96 (d, 1H, J=5.9 Hz, CHO), 7.35 (m, 5H, phenyl). Found: C, 78.38; H, 9.30%. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29%.

3-Butyl-2-(1-hydroxy-3-phenyl-2-propenyl)cyclohexanone (Entry 13). LC: SiO_2, 8:1 hexane/ethyl acetate as eluant. TLC R_f 0.16 and 0.10 (4:1 hexane/ethyl acetate); IR (neat) 3400, 1704, 964, 740, 685 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.91 (m, 3H, CH_3), 1.2—2.2 (m, 11H, 5 CH_2 and CH), 2.2—2.7 (m, 3H, CH_2CO and CHCO), 3.01 (br, 0.7H, OH), 3.56 (br, 0.3H, OH), 4.50 (br, 1H, CHO), 6.37 (dd, 1H, J=15.8 and 6.2 Hz, vinyl), 6.59 (dd, 1H, J=15.8 and 2.0 Hz, vinyl), 7.1—7.6 (m, 5H, phenyl). Found: M, 286.1938; M−H_2O, 268.1844. Calcd for $C_{19}H_{26}O_2$: M, 286.1933; M−H_2O, 268.1844.

***(E)*-2-Benzylidene-3-butylcyclopentanone (1).** To a solution of 3-butyl-2-(hydroxyphenylmethyl)cyclopentanone (49.2 mg, 0.20 mmol) in CH_2Cl_2 (2 mL) was added 4-(dimethylamino)pyridine (73 mg, 0.60 mmol) and the mixture was cooled to 0 °C. To this was added methanesulfonyl chloride (23 μL, 0.30 mmol) at 0 °C and the mixture was stirred for 2 h at 25 °C. Additional 4-(dimethylamino)-pyridine (146 mg, 1.20 mmol) and methanesulfonyl chloride (46 μL, 0.60 mmol) were added to the mixture and the mixture was further stirred for 10 h. The resulting mixture was poured into satd $NaHCO_3$ aqueous solution and extracted twice with CH_2Cl_2 (15 mL each). The combined extracts were washed successively with dil HCl and satd brine and dried. After evaporation of the solvent, the residual material was subjected to column chromatography on silica gel (5 g) using a 4:1 mixture of hexane and ether as eluant to give the enone **1** (33 mg, 77% yield): TLC R_f 0.55 (1:1 hexane/ether); IR (neat) 1717, 1618, 751, 687 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.91 (t, 3H, CH_3), 1.1—1.7 (m, 6H, 3 CH_2), 1.8—2.1 (m, 2H, CH_2), 2.1—2.5 (m, 2H, CH_2CO), 3.17 (br, 1H, CH), 7.2—7.6 (m, 6H, vinyl and phenyl); MS m/z: 228 (M^+). Found: C, 84.18; H, 9.11%. Cacld for $C_{16}H_{20}O$: C, 84.16; H, 8.83%. The compound **1** prepared here was identical in all respects with the product derived from the regio-controlled authentic synthesis[14] starting from 2-cyclopentenone as follows: To a solution of phenyl trimethylsilyl selenide (1.70 g, 7.42 mmol) in CH_2Cl_2 (15 mL) was added successively a solution of trimethylsilyl trifluoromethanesulfonate (0.097 mol dm^{-3}, 1.55 mL, 0.15 mmol) in CH_2Cl_2 and a solution of 2-cyclopentenone (609 mg, 7.42 mmol) in CH_2Cl_2 (5 mL) at −78 °C with stirring under argon atmosphere. After stirring at this temperature for 1 h, to this was added a solution of benzaldehyde dimethyl acetal (1.16 g, 7.62 mmol) in CH_2Cl_2 (5 mL) at −78 °C. The mixture was stirred −78 °C for 1 h and then −27 °C for 17 h. After successive addition of pyridine (0.5 mL) and 30% H_2O_2 (4.5 mL, 40 mmol), the mixture was stirred at −20 to 0 °C for 20 min and then quenched with water. The organic extract was evaporated and the residual material was subjected to column chromatography on silica gel (50 g) using a 10:1 mixture of benzene and ethyl acetate as eluant to afford 2-methoxyphenylmethyl-2-cyclopentenone (301 mg, 20% yield). IR (neat) 1703 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.3—2.5 (m, 2H, CH_2), 2.5—2.7 (m, 2H, CH_2) 3.33 (s, 3H, OCH_3), 5.02 (dd, 1H, J=2 Hz, CHO), 7.33 (br, 5H, phenyl), 7.51 (dt, 1H, J=3.0 and 1.5 Hz, vinyl). MS m/z: 202 (M^+). The butylcopper phosphine complex was prepared by the standard procedure[12b] using CuI (200 mg, 1.05 mmol), tributylphosphine (0.52 mL, 2.10 mmol), butyllithium (1.55 mol dm^{-3}, 0.68 mL, 1.05 mmol), and dry ether (15 ml) under argon atmosphere. To this solution was added a solution of 2-methoxyphenylmethyl-2-cyclopentenone (202 mg, 1.00 mmol) in ether (3.5 mL) at −78 °C over a period of 5 min. After stirring at −78 °C for 10 min and −40 °C for 10 min, the mixture was quenched with satd NH_4Cl aqueous solution (15 mL) with vigorous shaking. The organic layer was separated and the aqueous layer was extracted twice with ether (10 mL each). The combined ethereal extracts were dried and evaporated. Column chromatography on silica gel (20 g) using a 6:1 mixture of hexane and ether as eluant gave a mixture of **1** and 3-butyl-2-(methoxyphenylmethyl)-cyclopentanone (90.4 mg). This mixture was further treated with 1.8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.29 mL, 1.91 mmol) in benzene (4.5 mL) under reflux for 44 h. After being diluted with benzene (20 mL), the mixture was washed with dil HCl (36 mL×2) and then satd brine (36 mL). The solution was dried over magnesium sulfate and evaporated. Column chromatography on silica gel (18 g) using a 8:1 mixture of petroleum ether and ether gave a pure **1** (63.5 mg) as colorless oil.

***(E)*-2-Benzylidene-3-butylcyclohexanone (2).** To a solution of the more polar stereoisomer (R_f 0.32) of 3-butyl-2-(hydroxyphenylmethyl)cyclohexanone (313 mg, 1.20 mmol) and triethylamine (1.67 mL, 12 mmol) in CH_2Cl_2 (10 mL) was added methanesulfonyl chloride (0.46 mL, 6.0 mmol) at 0 °C. After being stirred at 0 °C for 30 min and 25 °C for 3 h, the mixture was diluted with ether (10 mL) and then washed twice with 1 mol dm^{-3} HCl (10 mL each). The ethereal layer was dried and evaporated. The residual material was dissolved in benzene (20 mL) and the mixture was heated with DBU (0.36 mL, 2.40 mmol) under reflux for 2 h. The mix-

ture was dissolved in benzene (20 mL) and washed with 1 mol dm^{-3} HCl (15 mL). The organic layer was dried over magnesium sulfate and evaporated. Column chromatography on silica gel (15 g) using a 4:1 mixture of hexane and ethyl acetate as eluant afforded **2** (187 mg, 64% yield) as colorless oil: TLC R_f 0.61 (2:1 hexane/ethyl acetate); IR (neat) 1689, 1599, 757, 691 cm^{-1}; ^1H NMR (CCl_4) δ=0.85 (m, 3H, CH_3), 1.0—2.0 (m, 10H, 5 CH_2), 2.1—2.6 (m, 2H, CH_2CO), 3.23 (br, 1H, CH), 7.08 (s, 1H, vinyl), 7.29 (m, 5H, phenyl); MS *m/z*: 242 (M^+). Found: C, 84.45; H, 9.22%. Calcd for $C_{17}H_{22}O$: C, 84.25; H, 9.15%. The compound prepared here was identical in all respects with the product derived from 2-cyclohexenone by the regio-controlled synthesis.[14]

7-Hydroxy-11,15-bis-*O*-(tetrahydropyran-2-yl)PGE$_1$ Methyl Ester (12). In a 20-mL test tube equipped with a septum rubber was placed (*E*,3*S*)-3-(tetrahydropyran-2-yloxy)-1-iodo-1-octene (**5**), (744 mg, 2.20 mmol) and the atmosphere was replaced with argon. Dry ether (10 mL) was added and the mixture was cooled to −95 °C. A solution of *t*-butyllithium (3.19 mL, 4.40 mmol) in pentane was added to this mixture at this temperature and then the resulting mixture was stirred at −78 °C for 3 h, giving the white suspension containing (*E*,3*S*)-3-(tetrahydropyran-2-yloxy)-1-octenyllithium. In a separated 150-mL ampule equipped with a septum rubber was placed CuI (419 mg, 2.20 mmol) and the system was evacuated under heating in vacuo. After cooling, the system was replaced with argon. To this was added dry ether (40 mL) and tributylphosphine (1.43 mL, 5.72 mmol) and the mixture was stirred until the suspension became a clear solution. The solution was cooled to −78 °C and to this was added the ethereal suspension containing (*E*,3*S*)-3-(tetrahydropyran-2-yloxy)-1-octenyllithium prepared above at −78 °C through a stainless steel cannula under argon atmosphere. The test tube was rinsed with an additional dry ether (10 mL) and this ethereal solution was added to the reaction mixture. After stirring the mixture for 10 min at this temperature, a solution of 4-(tetrahydropyran-2-yloxy)-2-cyclopentenone (**8**) (364 mg, 2.00 mmol) in dry ether (20 mL) was slowly added along the cooled (−78 °C) wall of the reaction vessel over a period of 35 min under stirring. After stirring the mixture for 15 min, a solution of methyl 6-formylhexanoate (348 mg, 2.20 mmol) in dry ether (5 mL) was added at −78 °C under stirring. The mixture was stirred at this temperature for 15 min and quenched with satd NH_4Cl aqueous solution (40 mL) and shaken vigorously. The organic layer was separated and the aqueous layer was extracted twice with ether (25 mL each). The combined organic extracts were dried and evaporated. The residual material was subjected to column chromatography on deactivated silica gel (30 g) using a 3:1 to 1:1 mixture of hexane and ethyl acetate as eluant to give the aldol product **12** (919 mg, 83% yield, a mixture of two stereoisomers) as a colorless oil: TLC R_f 0.17 (2:1 hexane/ethyl acetate); IR (neat) 3480, 1746, 974 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.89 (t, 3H, CH_3), 1.0—1.9 (m, 29H, 14 CH_2 and OH), 2.2—2.5 (m, 5H, 2 CH_2 and CH), 2.78 (dd, 1H, *J*=18.0 and 7.4 Hz, CH), 3.68 (s, 3H, OCH_3), 3.2—4.3 (m, 7H, 2 CH_2O and 3 CHO), 4.68 (br, 2H, 2 OCHO), 5.4—5.8 (m, 2H, vinyls); $[\alpha]_D^{22}$ −52.3° (*c* 1.02, CH_3OH). HRMS Found: *m/z* 384.2488. Calcd for $C_{21}H_{36}O_6$: M−$C_{10}H_{16}O_2$, 384.2512.

(7*E*)-7,8-Didehydro-11,15-bis-*O*-(tetrahydropyran-2-yl)-PGE$_1$ Methyl Ester (14). To a solution of the 7-hydroxy derivative **12** (480 mg, 0.87 mmol) in dry CH_2Cl_2 (5 mL) was added 4-(dimethylamino)pyridine (531 mg, 4.35 mmol) and the atmosphere was replaced with argon. To this was added methanesulfonyl chloride (0.17 mL, 2.17 mmol) at 18 °C and then stirred at 18 °C for 15 min and at 40 °C for 20 min. The mixture was diluted with CH_2Cl_2 (20 mL) and washed with satd $NaHCO_3$ aqueous solution (15 mL), 1 mol dm^{-3} HCl (15 mL), and satd brine (15 mL). After the mixture was dried and evaporated, the residual material was subjected to column chromatography on deactivated silica gel (10 g) using a 4:1 mixture of hexane and ethyl acetate as eluant to give the dehydrated product **14** (429 mg, 92% yield) as colorless oil: TLC R_f 0.40 (2:1 hexane/ethyl acetate); IR (neat) 1736, 1728, 1646, 974 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.88 (t, 3H, CH_3), 1.0—2.0 (m, 26H, 13 CH_2), 2.0—2.6 (m, 6H, 2 CH_2CO and CH_2C=), 3.68 (s, 3H, OCH_3), 3.3—4.3 (m, 7H, 2 CHO, 2 CH_2O, and CHC=), 4.5—4.8 (br, 2H, OCHO), 5.29 (d, 1H, *J*=14.0 and 7.9 Hz, vinyl), 5.63 (ddd, 1H, *J*=14.0, 6.3, and 3.2 Hz, vinyl), 6.75 (dt, 1H, *J*=9.7 and 1.9 Hz, vinyl); $[\alpha]_D^{22}$ +29.5° (*c* 1.01, CH_3OH). HRMS Found: *m/z* 330.2194. Calcd for $C_{21}H_{30}O_3$: M−$C_{10}H_{20}O_4$, 330.2195.

11,15-Bis-*O*-(tetrahydropyran-2-yl)PGE$_1$ Methyl Ester (16). Method A: The mixture of the enone **14** (12.0 mg, 0.022 mmol), (n-C_4H_9)$_3$SnH (0.5 mL), and di-*t*-butyl peroxide (4 mg, 0.027 mmol) was stirred at 110 °C for 25 min under argon. After cooling to room temperature, the mixture was directly chromatographed on a column of silica gel (3 g) by using a 12:2:1 mixture of hexane, benzene, and ethyl acetate as eluant to give **16** (10.8 mg, 90% yield) as colorless oil. Method B: To a solution of **14** (161 mg, 0.30 mmol) in a 95:5 mixture of 2-propanol and CH_3COOH (4 mL) was added zinc powder (1.46 g, 22.3 mmol) in several portions over a period of 2 h. The mixture was filtered through Celite 545 and the Celite was washed successively with ethyl acetate (10 mL) and ether (15 mL). The combined filtrates were washed with satd $NaHCO_3$ aqueous solution (15 mL) and then satd brine (15 mL), dried, and evaporated. Column chromatography on deactivated silica gel (6 g) using a 4:1 mixture of hexane and ethyl acetate as eluant gave **16** (126 mg, 78% yield) as a colorless oil: TLC R_f 0.41 (2:1 hexane/ethyl acetate); IR (neat) 1750, 974 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.89 (t, 3H, CH_3), 1.0—2.0 (m, 30H, 15 CH_2), 2.0—2.6 (m, 5H, 2 CH_2CO and CHCO), 2.76 (dd, 1H, *J*=18.0 and 7.2 Hz, CHC=), 3.68 (s, 3H, OCH_3), 3.3—4.4 (m, 6H, 2 CHO and 2 CH_2O), 4.70 (br, 2H, 2 OCHO), 5.4—5.8 (m, 2H, vinyls); $[\alpha]_D^{22}$ −85.4° (*c* 0.99, CH_3OH); HRMS Found: *m/z* 434.3029. Calcd for $C_{26}H_{42}O_5$: M−$C_5H_{10}O_2$, 434.3033.

PGE$_1$ Methyl Ester (18). The mixture of the tetrahydropyranylated derivative **16** (17.2 mg, 0.032 mmol) and a 3:1:1 mixture of acetic acid, water, and THF (2 mL) was stirred at 19 °C for 18 h. Then the mixture was placed in vacuo to evaporate the volatile materials. The resulting residual material was further co-evaporated three times with toluene under reduced pressure and then subjected to column chromatography on silica gel (1.7 g) using a 1:3 mixture of hexane and ethyl acetate as eluant to give PGE$_1$ methyl ester (**18**) (10.9 mg, 92% yield): TLC R_f 0.22 (1:3 hexane/ethyl acetate); IR (neat) 3390, 1748, 970 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.89 (t, 3H, CH_3), 1.1—1.8 (m, 18H, 9 CH_2), 1.8—2.6 (m, 7H, 2 CH_2CO, CHCO, and 2 OH), 2.73 (dd, 1H, *J*=18.0 and 7.6 Hz, CHC=), 3.68 (s, 3H, OCH_3), 3.9—4.3 (m, 2H, 2 CHO), 5.63 (m, 2H, vinyls); ^{13}C NMR ($CDCl_3$) δ=14.0 (C-20), 22.6, 24.8, 25.1, 26.6, 27.8, 28.8, 29.3, 31.7, 34.0, 37.4, 45.9 (C-10), 51.4 (OCH_3), 54.5 (C-12), 54.8 (C-8), 72.0 (C-11), 73.0 (C-15),

131.8 (C-13), 136.9 (C-14), 174.2 (C-1), 214.4 (C-9); $[\alpha]_D^{22}$ −53.8° (*c* 1.04, CH_3OH).

Reaction of commercial PGE_1 with diazomethane followed by HPLC (Develosil, hexane:ethyl acetate: CH_3OH= 1 : 9 :0.05 as eluant) afforded a sample indicating $[\alpha]_D^{23}$−54.0° (*c* 1.08, CH_3OH). The spectral data (IR, ^1H and ^{13}C NMR) and chromatographic behavior of **18** were identical with those of this authentic material.

11-*O*-(*t*-Butyldimethylsilyl)-7-hydroxy-15-*O*-(tetrahydropyran-2-yl)PGE_1 Methyl Ester (13). This compound was synthesized by the similar reaction procedure to the synthesis of **12**. (*E*,3*S*)-3-(tetrahydropyran-2-yloxy)-1-octenyllithium was prepared by adding a solution of *t*-butyllithium (3.21 mL, 4.40 mmol) in pentane to a solution of (*E*,3*S*)-3-(tetrahydropyran-2-yloxy)-1-iodo-1-octene (**5**) (744 mg, 2.20 mmol) in dry ether (10 mL) at −95 °C and then by stirring the mixture at −78 °C for 1.5 h. The organocopper complex was prepared by adding the organolithium compound prepared above to a solution of CuI (491 mg, 2.20 mmol) and tributylphosphine (1.43 mL, 5.72 mmol) in ether (50 mL) at −78 °C. The conjugate addition reaction was conducted by slow addition of a solution of (*R*)-4-(*t*-butyldimethylsiloxy)-2-cyclopentenone (**7**) (425 mg, 2.00 mmol) in dry ether (20 mL) to the organocopper complex prepared above at −78 °C over a period of 40 min. The aldehyde trapping of the enolate were conducted by addition of a solution of methyl 6-formylhexanoate (348 mg, 2.20 mmol) in dry ether (15 mL) at −78 °C. The reaction mixture was quenched with satd ammonium acetate aqueous solution (40 mL) with vigorous shaking at −78 °C. The organic layer was separated and aqueous layer was extracted twice with ether (20 mL each). The combined organic extracts were washed with a 20 : 5 : 1 mixture of water, benzene, and DMSO (52 mL) and then with satd brine (40 mL). After the solvent was dried and evaporated, the residual material was chromatographed at 0 °C on a two-layer column filled with Florisil (10 g, upper portion) and deactivated silica gel (100 g, lower portion) by using a 6 : 1 : 1 mixture of hexane, ethyl acetate, and benzene as eluant to give the aldol **13** (811 mg, 70%, four stereoisomers) as a pale yellow oil: TLC R_f 0.44 (2 : 1 hexane/ethyl acetate); IR ($CHCl_3$) 3600—3300, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.06 (s, 6H, 2 $SiCH_3$), 0.7—1.1 (m, 12H, $SiC(CH_3)_3$ and CH_3), 1.1—2.9 (m, 29H, 13 CH_2, 2 CH, and OH), 3.1—4.2 (m, 8H, OCH_3, 3 CHO, and CH_2O), 4.63 (m, 1H, OCHO), 5.4—5.7 (m, 2H, vinyls); $[\alpha]_D^{20}$ +14.3° (*c* 1.74, CH_3OH). HRMS Found: *m*/*z* 480.3283. Calcd for $C_{27}H_{48}O_5Si$: M−$C_5H_{10}O_2$, 480.3271.

(7*E*)-11-*O*-(*t*-Butyldimethylsilyl)-7,8-didehydro-15-*O*-(tetrahydropyran-2-yl)PGE_1 Methyl Ester (15). To a solution of **13** (348 mg, 0.60 mmol) in dry CH_2Cl_2 (20 mL) was added 4-(dimethylamino)pyridine (728 mg, 6.96 mmol) at 0 °C and the atmosphere was replaced with argon. To this was added methanesulfonyl chloride (0.23 mL, 2.97 mmol) at 0 °C and the mixture was stirred at 24 °C for 29 h. The reaction mixture was washed with satd $NaHCO_3$ aqueous solution (15 mL) and then satd brine (15 mL). After the organic layer was dried and evaporated, the residual oil was chromatographed on a column of deactivated silica gel (35 g) by using a 12:1 mixture of hexane and ethyl acetate as eluant to give **15** (255 mg, 75%) and its 7*Z*-isomer (9.2 mg, 2.7%). 7*E*-isomer **15**: TLC R_f 0.37 (4 : 1 hexane/ethyl acetate); IR (neat) 1742, 1642 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.05 (s, 6H, 2 $SiCH_3$), 0.7—1.0 (m, 12H, $SiC(CH_3)_3$ and CH_3), 1.0—2.7 (m, 26H, 13 CH_2), 3.3—4.3 (m, 8H, OCH_3, 2 CHO, CH_2O, and CH), 4.60 (m, 1H, OCHO), 5.0—5.8 (m, 2H, vinyls); 6.73 (dt, 1H, *J*=6.7 and 2.0 Hz, vinyl); $[\alpha]_D^{20}$ +16.0° (*c* 0.80, CH_3OH). HRMS Found: *m*/*z* 507.3141. Calcd for $C_{28}H_{47}O_6Si$: M−C_4H_9, 507.3142.

11-*O*-(*t*-Butyldimethylsilyl)-15-*O*-(tetrahydropyran-2-yl)-PGE_1 Methyl Ester (17). The mixture of the enone **15** (169.3 mg, 0.30 mmol), (n-C_4H_9)$_3$SnH (1.0 mL, 3.72 mmol), and di-*t*-butyl peroxide (5 mg, 0.034 mmol) was heated at 110 °C for 15 min under argon. After cooling to room temperature, the reaction mixture was directly chromatographed on a column of deactivated silica gel (20 g) by using a 15 : 2 : 1 mixture of hexane, benzene, and ethyl acetate as eluant to give **17** (149 mg, 88%) as a colorless oil: TLC R_f 0.48 (4 : 1 hexane/ethyl acetate); IR ($CHCl_3$) 1740, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.05 (s, 6H, 2 $SiCH_3$), 0.7—1.0 (m, 12H, $Si(CH_3)_3$ and CH_3), 1.0—2.8 (m, 30H, 14 CH_2 and 2 CH), 3.3—4.2 (m, 7H, OCH_3, 2CHO, and CH_2O), 4.68 (m, 1H, OCHO), 5.4—5.6 (m, 2H, vinyls); $[\alpha]_D^{23}$ −66.2° (*c* 0.60, CH_3OH). MRMS Found: *m*/*z* 566.4015. Calcd for $C_{32}H_{58}O_6Si$: M, 566.4003.

11-*O*-(*t*-Butyldimethylsilyl)-15-*O*-(tetrahydropyran-2-yl)-$PGF_{1\alpha}$ Methyl Ester (20). In a 10-mL Schlenk tube was placed **17** (38.5 mg, 0.0679 mmol) and dissolved in dry THF (3 mL). After cooling to −78 °C, a solution of L-Selectride in THF (0.081 mL, 0.0815 mmol) was added at this temperature. After stirring at −78 °C for 20 min, 3% aqueous H_2O_2 solution (2mL) was added to the mixture at −78 °C with vigorous shaking and then diluted with ether (4 mL). The organic layer was separated and the aqueous layer was extracted with ether (4 mL). After the combined organic extracts were dried and evaporated, the residual oil was chromatographed on a column of silica gel (4 g) by using a 1 : 5 mixture of ethyl acetate and hexane as eluant to give **20** (35.4 mg, 92%) as a colorless oil: TLC R_f 0.25 (1 : 4 ethyl acetate/hexane); IR ($CHCl_3$) 3600—3320, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.04 (s, 6H, 2 $SiCH_3$), 0.7—1.1 (m, 12H, $SiC(CH_3)_3$ and CH_3), 1.1—2.7 (m, 31H, 14 CH_2, 2 CH, and OH), 3.3—4.3 (m, 8H, OCH_3, 3 CHO, and CH_2O), 4.67 (m, 1H, OCHO), 5.2—5.6 (m, 2H, vinyls); $[\alpha]_D^{20}$ −13.8° (*c* 0.62, CH_3OH). HRMS Found: *m*/*z* 511.3423. Calcd for $C_{28}H_{51}O_6Si$: M−C_4H_9, 511.3455.

11-*O*-(*t*-Butyldimethylsilyl)-9,15-bis-*O*-(tetrahydropyran-2-yl)-$PGF_{1\alpha}$ Methyl Ester (21). In a 10-mL test tube was placed **20** (102.8 mg, 0.181 mmol) and the atmosphere was replaced with argon. Dry CH_2Cl_2 (1 mL) was added and the mixture was cooled to 0 °C. To this were added 3,4-dihydro-2*H*-pyran (33.4 mg, 0.398 mmol) and then pyridinium *p*-toluenesulfonate (13.5 mg, 0.0543 mmol) at 0 °C. After being stirred for 10 min at 0 °C and then 5 h at 30 °C, the mixture was diluted with CH_2Cl_2 (5 mL), followed by the addition of satd brine (10 mL). After shaking, the organic layer was separated and the aqueous layer was extracted twice with CH_2Cl_2 (10 mL each). After the combined organic extracts were dried and evaporated, the residual material was chromatographed on a column of silica gel (12 g) by using a 1 : 10 mixture of ethyl acetate and hexane as eluant to give **21** (110.8 mg, 94%) as a colorless oil: TLC R_f 0.54 (1 : 4 ethyl acatate/hexane); IR ($CHCl_3$) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.01 (s, 6H, 2 $SiCH_3$), 0.7—1.0 (m, 12H, $SiC(CH_3)_3$ and CH_3), 1.1—2.5 (m, 36H, 17 CH_2 and 2 CH), 3.3—4.2 (m, 10H, OCH_3, 3 CHO, and 2 CH_2O), 4.5—4.8 (m, 2H, 2 OCHO), 5.40 (m, 2H, vinyls); $[\alpha]_D^{25}$ +15.9° (*c* 0.37, CH_3OH). HRMS Found: *m*/*z* 550.4028. Calcd for $C_{32}H_{58}O_5Si$: M−$C_5H_{10}O_2$,

550.4054.

9,15-Bis-*O*-(tetrahydropyran-2-yl)PGF$_{1\alpha}$ Methyl Ester (22). In a 10-mL round-bottomed flask was placed **21** (103.5 mg, 0.158 mmol) and dissolved with THF (1 mL). To this was added a solution of tetrabutylammonium fluoride (1 mol dm^{-3}, 1.58 mL, 1.58 mmol) in THF at 23 °C and the mixture was stirred for 5 h at this temperature. THF (5 mL) and satd brine (5 mL) were added and the mixture was shaken vigorously. The organic layer was separated and the aqueous layer was extracted twice with ethyl acetate (5 mL each). After the combined extracts were dried and evaporated, the residual material was chromatographed on a column of silica gel (10 g) by using a 1 : 4 to 1 : 1 mixture of ethyl acetate and hexane as eluant to give **22** (71.7 mg, 84%) as a colorless oil: TLC R_f 0.17 (1 : 4 ethyl acetate/hexane); IR ($CHCl_3$) 3620—3280, 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.88 (t, 3H, J=4.5 Hz, CH_3), 1.1—2.5 (m, 37H, 17 CH_2, 2 CH, and OH), 3.3—4.3 (m, 10H, OCH_3, 3 CHO, and 2 CH_2O), 4.5—4.8 (m, 2H, 2 OCHO), 5.45 (m, 2H, vinyls); $[\alpha]_D^{25}$ +0.65° (*c* 0.59, CH_3OH). HRMS Found: *m*/*z* 436.3165. Calcd for $C_{26}H_{44}O_5$: M−$C_5H_{10}O_2$, 436.3189.

PGD$_1$ (23). In a 10-mL test tube was placed **22** (15.6 mg, 0.0290 mmol) and dissolved in CH_3OH (1 mL). After cooling to 0 °C, 20% NaOH aqueous solution (1 mL) was added. The mixture was stirred for 3.7 h at 25 °C and acidified by 1 mol dm^{-3} aqueous oxalic acid solution (5 mL). The resulting mixture was extracted three times with ethyl acetate (10 mL each) and the organic extracts were washed with satd brine (10 mL), dried, and evaporated. The residual oil was placed in a 10-mL test tube and dissolved in acetone (0.8 mL). After cooling to −30 °C, Jones reagent (2.4 mol dm^{-3}, 18.1×10^{-3} mL, 0.0434 mmol) was added slowly to the mixture. The mixture was stirred for 40 min at this temperature and then ethyl acetate (10 mL) and satd $NaHCO_3$ aqueous solution (10 mL) were added. The mixture was neutralized by 1 mol dm^{-3} aqueous oxalic acid (10 mL) and the organic layer was separated. The aqueous layer was extracted twice with ethyl acetate (10 mL each). After the combined extracts were dried and evaporated, the residual oil was dissolved in a 3 : 1 : 1 mixture of acetic acid, water, and THF (2 mL) and the mixture was stirred at 25 °C for 23 h. The mixture was concentrated by exposing in vacuo and the residual material was dissolved in toluene. The toluene solution was evaporated under reduced pressure and this azeotropic operation was repeated three times. The residual oil was subjected to column chromatography on silica gel (1.5 g) using a 4 : 2 1 mixture of cyclohexane, ethyl acetate, and acetone and then pure acetone as eluant to give (+)-PGD$_1$ (**23**) (6.3 mg, 61%) as a white crystal: mp 64.5—65 °C; TLC R_f 0.14 (4 : 1 ethyl acetate/hexane); IR ($CHCl_3$) 3720—2300, 1740, 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.88 (t, 3H, J=6.0 Hz, CH_3), 1.1—2.1 (m, 19H, 9 CH_2 and CH), 2.35 (t, 2H, J=6.4 Hz, CH_2C=O), 2.44 (d, 2H, J=2.6 Hz, CH_2C=O), 2.1—3.4 (br m, 4H, CHC=O, 2 OH, and CO_2H), 4.12 (br q, 1H, J=6.0 Hz, CHO), 4.51 (m, 1H, CHO), 5.53 (m, 2H, vinyls); $[\alpha]_D^{26}$ +9.8° (*c* 0.17, THF).

11,15-Bis-*O*-(*t*-butyldimethylsilyl)-5,6-didehydro-7-hydroxy-PGE$_2$ Methyl Ester (24). In a 150-mL ampule equipped with a spiral tube was placed (*E*,3*S*)-3-(*t*-butyldimethylsiloxy)-1-iodo-1-octene (**4**) (1.41 g, 3.83 mmol) and the atomsphere was replaced with argon. Dry ether (15 mL) was added and the mixture was cooled to −95 °C. To this was added a solution of *t*-butyllithium (4.41 mL, 7.80 mmol) in pentane at this temperature and the resulting mixture was further stirred at −78 °C for 3 h, giving the white suspension containing (*E*,3*S*)-3-(*t*-butyldimethylsiloxy)-1-octenyllithium. In a separaed 50-mL test tube equipped with a septum rubber was placed CuI (729 mg, 3.83 mmol) and the atmosphere was replaced with argon. To this was added dry ether (15 mL) and tributylphosphine (2.48 mL, 9.95 mmol) and the mixture was stirred until the suspension became a clear solution. After cooling to −78 °C, to this was added the suspension containing (*E*,3*S*)-3-(*t*-butyldimethylsiloxy)-1-octenyllithium prepared above through a stainless steel cannula under argon atmosphere. The test tube was rinsed with dry ether (15 mL) and the ethereal solution was added to the reaction mixture. After stirring the mixture at −78 °C for 5 min, a solution of 4-(*t*-butyldimethylsiloxy)-2-cyclopentenone (**7**) (796 mg, 3.75 mmol) in dry THF (30 mL) was slowly added at −78 °C along the cooled (−78 °C) wall of the reaction vessel over a period of 30 min under stirring. After stirring the mixture for 1 h, boron trifluoride etherate (0.461 mL, 3.75 mmol) was added at −78 °C and the mixture was stirred at −78 °C for 3 h. The mixture was cooled to −95 °C and then a solution of methyl 6-formyl-5-hexynoate (637 mg, 4.13 mmol) in dry ether (15 mL) was added at this temperature. The mixture was stirred at −78 °C for 1 h and quenched with satd NH_4Cl aqueous solution (30 mL) under vigorous shaking. The organic layer was separated and the aqueous layer was extracted twice with ether (20 mL each). The combined ethereal extracts were washed with a 1 : 5 : 20 mixture of DMSO, benzene, and water (52 mL) and then satd brine (20 mL). After the organic layer was dried and evaporated, the residual oil was chromatographed at 0 °C on a two-layered column filled with Florisil (10 g, upper layer) and deactivated silica gel (70 g, lower layer) by using a 1 : 10 : 2 mixture of ethyl acetate, hexane, and benzene and then a 1 : 5 mixture of ethyl acetate and hexane as eluants to give the aldol product **24** (1.90 g, 83%, a mixture of two stereoisomers) as a slightly yellow oil: The less polar material: TLC R_f 0.44 (3 : 1 hexane/ethyl acetate); IR (neat) 3630—3180, 1743 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.02, 0.03, 0.06 and 0.07 (s each, 12H, 4 $SiCH_3$), 0.89 (s, 18H, 2 $SiC(CH_3)_3$), 0.8—0.9 (hidden in this region, 3H, CH_3), 1.2—3.0 (m, 18H, 8 CH_2 and 2 CH), 3.68 (s, 3H, OCH_3), 3.86 (d, 1H, J=10 Hz, OH), 4.10 (m, 2H, 2 CHO), 4.46 (m, 1H, CHO), 5.59 (m, 2H, vinyls); ^{13}C NMR ($CDCl_3$) δ=−4.5 (3C), −4.1, 13.9, 18.1, 18.4 (2C), 22.6, 24.2 25.0, 25.9 (3C), 26.0 (3C), 32.0, 33.0, 38.7, 48.3, 50.9, 51.4, 59.1, 62.1, 73.0, 73.6, 80.2, 85.9, 128.2, 136.9, 173.2, 214.8; $[\alpha]_D^{19}$ −34.3° (*c* 0.91, CH_3OH). HRMS Found: *m*/*z* 608.3931. Calcd for $C_{33}H_{60}O_6Si_2$: M, 608.3929. The more polar material: TLC R_f 0.40 (3 : 1 hexane/ethyl acetate); IR (neat) 3620—3200, 1745 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.02, 0.04, 0.06 and 0.07 (s each, 12H, 4 $SiCH_3$), 0.87 and 0.88 (s each, 18H, 2 $SiC(CH_3)_3$), 0.8—0.9 (hidden in this region, 3H, CH_3), 1.2—3.0 (m, 19H, 8 CH_2, 2 CH, and OH), 3.68 (s, 3H, OCH_3), 4.10 (m, 2H, 2 CHO), 4.66 (m, 1H, CHO), 5.63 (m, 2H, vinyls); ^{13}C NMR ($CDCl_3$) δ=−4.5 (3C), −4.1, 14.0, 18.1, 18.4 (2C), 22.6, 24.1, 25.0, 25.9 (3C), 26.1 (3C), 32.0, 33.0, 38.7, 48.0, 51.4 (2C), 59.4, 62.9, 73.0, 73.6, 80.1, 85.9, 129.3, 136.7, 173.2, 213.7; $[\alpha]_D^{19}$ −15.1° (*c* 1.03, CH_3OH).

The two isomers of **24** were converted independently to the corresponding 7-benzoyloxy-PGE$_2$ derivative by the catalytic hydrogenation using Lindlar catalyst followed by benzoylation with benzoyl chloride in the presence of pyridine.[45] The benzoate derivative from the less polar isomer of **24**: CD

(cyclohexane) λ_{ext} 226 nm ($\Delta\varepsilon$+10.5°). The benzoate from the more polar isomer of **24**: CD (cyclohexane) λ_{ext} 226 nm ($\Delta\varepsilon$ −7.37°). These results indicate that the benzoyl derivative from the less polar isomer of **24** has 7*R* configuration and the other possesses 7*S* configuration. Turning back to the starting hydroxy derivatives, the less polar and the more polar isomers of **24** proved to have 7*S* and 7*R* configurations, respectively. This assignment was confirmed chemically by transformation to 7-hydroxy PGI_2 derivatives.[25]

11,15-Bis-*O*-(*t*-butyldimethylsilyl)-5,6-didehydro-7-thiobenzoyloxy-PGE$_2$ Methyl Ester (26). To a solution of the aldol **24** (126 mg, 0.21 mmol) in dry CH_2Cl_2 (2.5 mL) was added 4-(dimethylamino)pyridine (55 mg, 0.45 mmol) and then a solution of thiobenzoyl chloride (65 mg, 0.41 mmol) in CH_2Cl_2 (0.5 mL) at 21 °C under stirring. After stirring at this temperature for 70 min, the mixture was diluted with CH_2Cl_2 (20 mL) and washed successively with satd $NaHCO_3$ aqueous solution (20 mL), dil HCl (20 mL), and satd brine (20 mL) and then dried over magnesium sulfate. After evaporation of the solvent, the residual material was chromatographed on a column of silica gel (15 g) by using a 10 : 1 mixture of hexane and ethyl acetate as eluant to give the thiobenzoate **26** (108 mg, 71% yield, two stereoisomers at C-7) as yellow-brown oil: TLC R_f 0.29 (5 : 1 hexane/ethyl acetate); IR (neat) 2230, 1743, 1596, 1210 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ= −0.09, −0.04, 0.07, and 0.08 (s, each, 12H, 4 $SiCH_3$), 0.8—1.0 (m, 21H, 7 CCH_3), 1.1—3.2 (m, 18H, 8 CH_2 and 2 CH), 3.65 and 3.66 (s each, 3H, OCH_3), 3.9—4.3 (m, 2H, 2 CHO), 5.4—5.9 (m, 2H, vinyls), 6.28 and 6.60 (br, 0.5H each, CHOC(=S)), 7.3—7.7 (m, 3H, aromatic), 8.1—8.4 (m, 2H, aromatic); $[\alpha]_D^{22}$+2.64° (*c* 1.21, CH_3OH). Found: C, 65.83; H, 8.78%. Calcd for $C_{40}H_{64}O_6SSi$: C, 65.88; H, 8.85%.

11,15-Bis-*O*-(*t*-butyldimethylsilyl)-5,6-didehydro-PGE$_2$ Methyl Ester (28). A mixture of the thiobenzoate **26** (93 mg, 0.13 mmol), (n-C_4H_9)$_3$SnH (0.7 mL, 2.65 mmol), and di-*t*-butyl peroxide (4 mg) was heated at 50 °C under argon atmosphere for 30 min. The mixture was directly subjected to column chromatography on a column of silica gel (5 g) using a 1 : 20 : 5 mixture of ethyl acetate, hexane, and benzene as eluant to give **28** (74.2 mg, 98% yield) as colorless oil: TLC R_f 0.50 (5 : 1 hexane/ethyl acetate); IR (neat) 1746, 1246, 827, 767 cm^{-1}; ^{1}H NMR ($CDCl_3$-CCl_4) δ=0.04 and 0.06 (s each, 12H, 4 $SiCH_3$), 0.89 (s, 18H, 2 $SiC(CH_3)_3$), 0.92 (t, 3H, J=6.5 Hz, CH_3), 1.1—1.5 (m, 8H, 4 CH_2), 1.7—2.9 (m, 12H, 2 CH_2CO, 2 CH_2C=, 2 CH, and CH_2), 3.65 (s, 3H, OCH_3), 4.05 (m, 2H, 2 CHO), 5.4—5.7 (m, 2H, vinyls); ^{13}C NMR ($CDCl_3$) δ=−4.7, −4.5 (2C), −4.2, 13.6, 14.0, 16.9, 18.0, 18.2, 22.6, 24.2, 25.0, 25.8 (3C), 25.9 (3C), 31.9, 32.7, 38.6, 47.7, 51.4, 51.9, 52.9, 72.7, 73.1, 77.3, 80.8, 128.2, 136.8, 173.4, 213.4; $[\alpha]_D^{21}$−13.9° (*c* 1.59, CH_3OH); HRMS Found: *m*/*z* 592.3956. Calcd for $C_{33}H_{60}O_5Si_2$: M, 592.3979. Spectral data (IR and ^{1}H NMR) of **28** were identical with those of the authentic sample gifted from Dr. C. H. Lin of Upjohn Co.

11-*O*-(*t*-Butyldimethylsilyl)-5,6-didehydro-7-hydroxy-15-*O*-(tetrahydropyran-2-yl)PGE$_2$ Methyl Ester (25). This compound was synthesized by similar reaction and work-up procedures to those of the synthesis of **13**. (*E*,3*S*)-3-(tetrahydropyran-2-yloxy)-1-octenyllithium was prepared by adding a *t*-butyllithium pentane solution (2.87 mL, 3.93 mmol) to a solution of (*E*,3*S*)-3-(tetrahydropyran-2-yloxy)-1-iodo-1-octene (**5**) (664 mg, 1.96 mmol) in ether (10 mL) at −95 °C and then stirring the mixture −78 °C for 1.5 h. The organocopper complex was prepared by adding the lithium compound prepared above to a solution of CuI (374 mg, 1.96 mmol) and tributylphosphine (1.27 mL, 5.10 mmol) in ether (40 mL) at −78 °C. The conjugate addition was conducted by slow addition of a solution of (*R*)-4-(*t*-butyldimethylsiloxy)-2-cyclopentenone (**7**) (379 mg, 1.78 mmol) in ether (20 mL) to the organocopper reagent prepared above and at −78 °C. The aldehyde trapping of the enolate was conducted by addition of a solution of methyl 6-formyl-5-hexynoate (303 mg, 1.96 mmol) in ether (15 mL) at −78 °C. After work-up, column chromatography was performed at 0 °C on a two-layer column filled with Florisil (10 g, upper layer) and deactivated silica gel (100 g, lower layer) by using a 6 : 1 : 1 mixture of hexane, ethyl acetate, and benzene and then a 3 : 1 mixture of hexane and ethyl acetate as eluants to give **25** (670.2 mg, 65%, two stereoisomers) as a pale yellow oil. The less polar material: TLC R_f 0.45 (1 : 2 ethyl acetate/hexane); IR ($CHCl_3$) 3720—3000, 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.0—0.1 (m, 6H, 2 $SiCH_3$), 0.7—1.1 (m, 12H, $SiC(CH_3)_3$ and CH_3), 1.1—3.2 (m, 25H, 11 CH_2, 2 CH, and OH), 3.3—4.8 (m, 9H, OCH_3, CH_2O, 3 CHO, and OCHO), 5.51 (m, 2H, vinyls); $[\alpha]_D^{26}$ −80.2° (*c* 0.5, CH_3OH). HRMS Found: *m*/*z* 521.2950. Calcd for $C_{28}H_{45}O_7Si$: M−C_4H_9, 521.2935. The more polar material: TLC R_f 0.41 (1 : 2 ethyl acetate/hexane); IR ($CHCl_3$) 3700—3000, 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.0—0.1 (m, 6H, 2 $SiCH_3$), 0.7—1.1 (m, 12H, $SiC(CH_3)_3$ and CH_3), 1.1—3.1 (m, 25H, 11 CH_2, 2 CH, and OH), 3.4—4.2 (m, 8H, OCH_3, CH_2O, and 3 CHO), 4.68 (m, 1H, OCHO), 5.57 (m, 2H, vinyls); $[\alpha]_D^{26}$ −26.2° (*c* 0.19, CH_3OH).

11-*O*-(*t*-Butyldimethylsilyl)-5,6-didehydro-15-*O*-(tetrahydropyran-2-yl)-7-thiobenzoyloxy-PGE$_2$ Methyl Ester (27). To a solution of **25** (100 mg, 0.173 mmol) in dry CH_3CN (10 mL) was added 4-(dimethylamino)pyridine (69.8 mg, 0.571 mmol) and then a solution of thiobenzoyl chloride (81.3 mg, 0.519 mmol) in CH_3CN (4 mL) at −40 °C under stirring. After stirring at −30 °C for 18 h, the mixture was diluted with CH_2Cl_2 (20 mL) and washed with satd $NaHCO_3$ aqueous solution (10 mzL), dil HCl (10 mL), and then satd brine (10 mL). After the mixture was dried and evaporated, the residual material was chromatographed on a column of silica gel (10 g) by using a 10 : 1 mixture of hexane and ethyl acetate as eluant to give **27** (93.2 mg, 77%) as brown oil: TLC R_f 0.62 and 0.57 (2 : 1 hexane/ethyl acetate); IR ($CHCl_3$) 1730, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=−0.1—0.2 (m, 6H, 2 $SiCH_3$), 0.7—1.1 (m, 12H, $SiC(CH_3)_3$ and CH_3), 1.1—3.2 (m, 24H, 11 CH_2 and 2 CH), 3.2—4.3 (m, 7H, OCH_3, 2 CHO, and CH_2O), 4.5—4.8 (m, 1H, OCHO), 5.1—5.8 (m, 2H, vinyls), 6.3—7.2 (m, 1H, CHOC(=S)), 7.2—8.3 (m, 5H, phenyl). HRMS Found: *m*/*z* 596.2962. Calcd for $C_{34}H_{48}O_5SSi$: M−$C_5H_{10}O_2$, 596.2992.

11-*O*-(*t*-Butyldimethylsilyl)-5,6-didehydro-15-*O*-(tetrahydropyran-2-yl)PGE$_2$ Methyl Ester (29). A mixture of thiobenzoate **27** (34.3 mg, 0.0491 mmol), (n-C_4H_9)$_3$SnH (0.5 mL, 1.86 mmol), and di-*t*-butyl peroxide (4 mg) was heated at 50 °C for 7.5 h under argon atmosphere. The reaction mixture was directly chromatographed on a column of silica gel (3 g) by using a 1 : 15 : 2 mixture of ethyl acetate, hexane, and benzene as eluant to give **29** (23.4 mg, 85%) as colorless oil: TLC R_f 0.31 (4 : 1 hexane/ethyl acetate); IR (neat) 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.0—0.1 (two s, 6H, 2 $SiCH_3$), 0.7—1.0 (m, 12H, $SiC(CH_3)_3$ and CH_3), 1.0—3.0 (m, 26H, 2 CH_2CO, 10 CH_2, and 2 CH), 3.3—4.3 (m, 7H, OCH_3, 2 CHO, and CH_2O), 4.69 (m, 1H, OCHO), 5.4—5.7 (m, 2H, vinyls); $[\alpha]_D^{26}$−46.1° (*c* 0.38, CH_3OH). HRMS Found: *m*/*z* 505.2967.

Calcd for $C_{28}H_{45}O_6Si$: M−C_4H_9, 505.2986.

11-*O*-(*t*-Butyldimethylsilyl)-5,6-didehydro-7-hydroxy-15-*O*-(tetrahydropyran-2-yl)-PGF$_{2\alpha}$ Methyl Ester (30). To a solution of the more polar isomer of **25** (R_f 0.41, 1:2 ethyl acetate/hexane) (226.1 mg, 0.39 mmol) in CH_3OH (15 mL) was added $NaBH_4$ (147.8 mg, 3.9 mmol) at 0 °C under stirring. After 5 min at this temperature, the mixture was poured into satd NH_4Cl aqueous solution (15 mL) at 0 °C under stirring. After the evolution of H_2 gas ceased, the mixture was extracted three times with ethyl acetate (20 mL each). After the combined organic extracts were dried and evaporated, the residual material was chromatographed on a column of silica gel (20 g) by using a 1:3 mixture of ethyl acetate and hexane as eluant to give the diol **30** (174.2 mg, 77%) as colorless oil: TLC R_f 0.62 (1:1 hexane/ethyl acetate); IR ($CHCl_3$) 3720—3300, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.0—0.1 (m, 6H, 2 $SiCH_3$), 0.7—1.1 (m, 12H, $SiC(CH_3)_3$ and CH_3), 1.1—3.0 (m, 26H, CH_2CO, 10 CH_2, 2 CH, and 2 OH), 3.3—4.2 (m, 7H, OCH_3, 2 CHO, and CH_2O), 4.3—4.7 (m, 3H, 2 CHO and OCHO), 5.3—5.6 (m, 2H, vinyls); $[\alpha]_D^{26}$−38.4° (*c* 0.50, CH_3OH). HRMS Found: *m/z* 523.3063. Calcd for $C_{28}H_{47}O_7Si$: M−C_4H_9, 523.3091.

11-*O*-(*t*-Butyldimethylsilyl)-5,6-didehydro-7-hydroxy-7,9-*O*-thiocarbonyl-15-*O*-(tetrahydropyran-2-yl)PGF$_{2\alpha}$ Methyl Ester (31). To a solution of the diol **30** (57.6 mg, 0.0992 mmol) in dry CH_3CN (3 mL) were added 1,1′-thiocarbonyldiimidazole (26.5 mg, 0.149 mmol) and 4-(dimethylamino)-pyridine (36.4 mg, 0.298 mmol) at 0 °C under stirring. After stirring at 25 °C for 12 h, the mixture was diluted with CH_2Cl_2 (7 mL) followed by the addition of satd NH_4Cl aqueous solution (10 mL). The organic layer was separated and the aqueous layer was extracted twice with CH_2Cl_2 (10 mL each). The combined extracts were washed with satd brine (10 mL), dried, and evaporated. The residual material was chromatographed on a column of silica gel (5 g) by using a 1:5:1 mixture of ethyl acetate, hexane, and benzene as eluant to give the thiocarbonate **31** (56.7 mg, 92%) as yellow oil: TLC R_f 0.49 (2:1 hexane/ethyl acetate); IR ($CHCl_3$) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.04 (two s, 6H, 2 $SiCH_3$), 0.7—1.1 (m, 12H, $SiC(CH_3)_3$ and CH_3), 1.1—2.8 (m,, 24H, CH_2CO, 10 CH_2, and 2 CH), 3.3—4.2 (m, 7H, OCH_3, 2 CHO, and CH_2O), 4.63 (m, 1H, OCHO), 4.9—5.1 (m, 2H, 2 CHO), 5.4—5.6 (m, 2H, vinyls); $[\alpha]_D^{27}$−7.66° (*c* 0.32, CH_3OH). HRMS Found: *m/z* 565.2643. Calcd for $C_{29}H_{45}O_7SiS$: M−C_4H_9, 565.2656.

11-*O*-(*t*-Butyldimethylsilyl)-5,6-didehydro-15-*O*-(tetrahydropyran-2-yl)PGF$_{2\alpha}$ Methyl Ester (32). A mixture of the thiocarbonate **31** (41.5 mg, 0.0666 mmol), (n-C_4H_9)$_3$SnH (0.4 mL, 1.49 mmol), and di-*t*-butyl peroxide (4 mg) was heated at 50 °C for 1.5 h under argon atmosphere. To this mixture was added a 1 mol dm^{-3} solution of CH_3ONa in CH_3OH (1 mL) and dry THF (1 mL) and the mixture was stirred at 20 °C for 14.5 h. To this were added THF (10 mL) and then satd NH_4Cl aqueous solution (10 mL). The organic layer was separated and the aqueous layer was extracted twice with ethyl acetate (10 mL). After the combined organic extracts were dried and evaporated, the residual oil was chromatographed on a column of silica gel (2.5 g) by using a 1:6 mixture of ethyl acetate and hexane as eluant to give **32** (29.0 mg, 77%) as colorless oil: TLC R_f 0,53 (2:1 hexane/ethyl acetate); IR ($CHCl_3$) 3720—3300, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.03 (two s, 6H, 2 $SiCH_3$), 0.6—1.1 (m, 12H, $SiC(CH_3)$ and CH_3), 1.1—2.7 (m, 27H, CH_2CO, 11 CH_2, 2 CH, and OH), 3.3—4.4 (m, 8H, OCH_3, 3 CHO, and CH_2O), 4.66 (m, 1H, OCHO), 5.2—5.6 (m, 2H, vinyls); $[\alpha]_D^{26}$−28.8° (*c* 1.30, CH_3OH). HRMS Found: *m/z* 564.3828. Calcd for $C_{32}H_{56}O_6Si$: M, 564.3846.

A generous gift of chrysanthemic acid from Sumitomo Chemical Co. for the preparation of **9** is acknowledged. We deeply appreciate Ono Pharmaceutical Co. for the supply of precious samples of PGE_1, PGD_1 and for the identification of PGD_1 by 200-MHz ^1H NMR measurement. We also thank Dr. C. H. Lin of Upjohn Co. for sending us IR and ^1H NMR spectra of **28**. We also indebted to Teijin Co. for generous supply of the homochiral 4-hydroxy-2-cyclopentenone and side-chain units.

References

1) Prostaglandin Synthesis 17. Part 16: M. Suzuki, A. Yanagisawa, and R. Noyori, *J. Am. Chem. Soc.* in press.

2) Institute for Bio-Medical Research, Teijin Ltd., Tokyo.

3) a) R. Noyori and M. Suzuki, *Angew. Chem., Int. Ed. Engl.*, **23**, 847 (1984), and references cited therein; b) R. J. K. Taylor, *Synthesis*, **1985**, 364.

4) This term was suggested by Professor B. M. Trost (July, 1980). Since the entering groups are not limited to simple and functionalized alkyls, this term is more groups are not limited to simple and functionalized alkyls, this term is more appropriate than the conventionally used "vicinal alkylation".

5) Nucleophilic reactions of enolates generated from enones and lithium homocuprates: [alkyl halides] a) R. K. Boeckman, Jr., *J. Org. Chem.*, **38**, 4450 (1973); b) G. H. Posner, C. E. Whitten, and J. J. Sterling, *J. Am. Chem. Soc.*, **95**, 7788 (1973); c) R. M. Coates and L. O. Sandefur, *J. Org. Chem.*, **39**, 275 (1974); d) G. H. Posner, J. J. Sterling, C. E. Whitten, C. M. Lentz, and D. J. Brunelle, *J. Am. Chem. Soc.*, **97**, 107 (1975); e) G. H. Posner and C. M. Lentz, *Tetrahedron Lett.*, **1977**, 3215; f) G. H. Posner C. E. Whitten, J. J. Sterling, D. J. Brunelle, C. M. Lentz, A. W. Runquist, and A. Alexakis, *Ann. N. Y. Acad. Sci.*, **295**, 249 (1977); g) G. H. Posner and C. M. Lentz, *J. Am. Chem. Soc.*, **101**, 934 (1979); h) G. H. Posner, M. J. Chapdelaine, and C. M. Lentz, *J. Org. Chem.*, **44**, 3661 (1979); i) G. H. Posner, J. P. Mallamo, and K. Miura, *J. Am. Chem. Soc.*, **103**, 2886 (1981); j) G. H. Posner, J. P. Mallamo, M. Hulce, and L. L. Frye, *ibid.*, **104**, 4180 (1982); [aldehydes] k) G. Stork and M. Isobe, *J. Am. Chem. Soc.*, **97**, 6260 (1975); l) K. K. Heng and R. A. J. Smith, *Tetrahedron*, **35**, 425 (1979); m) K. K. Heng, J. Simpson, R. A. J. Smith, and W. T. Robinson, *J. Org. Chem.*, **46**, 2932 (1981); [acyl chlorides] n) T. Tanaka, S. Kurozumi, T. Toru, M. Kobayashi, S. Miura, and S. Ishimoto, *Tetrahedron Lett.*, **1975**, 1535; o) *idem*, *Tetrahedron*, **33**, 1105 (1977); [ketene bis(methylthio)acetal monoxide] p) R. Davis and K. G. Untch, *J. Org. Chem.*, **44**, 3755 (1979), and other nucleophilic reactions are also cited in this literature. Trapping with aldehydes of enolates generated from enone and Grignard reagents in the presence of catalytic amounts of copper salts; q) G. Stork and J. d'Angelo, *J. Am. Chem. Soc.*, **96**, 7114 (1974); r) F. Näf and R. Decorzant, *Helv. Chim. Acta*, **57**, 1317 (1974); s) F. Näf, R. Decorzant, and W.

Thommen, *ibid.*, **58**, 1808 (1975); for the excellent review, see t) J. d'Angelo, *Tetrahedron*, **32**, 2979 (1976); for some similar aldol reactions of enolates generated by the conjugate reaction of other organometallics and enones, see u) A. Hosomi, H. Hashimoto, H. Kobayashi, and H. Sakurai, *Chem. Lett.*, **1979**, 245; v) J. Schwartz, M. J. Loots, and H. Kosugi, *J. Am. Chem. Soc.* **102**, 1333 (1980).

6) J. W. Patterson, Jr., and J. H. Fried, *J. Org. Chem.*, **39**, 2506 (1974).

7) For such reason, they first trapped the enolate with the trimethylsilyl chloride and then alkylated the lithium enolate which was regenerated from the resulting enol silyl ether with lithium amide in liquid ammonia.

8) For a direct solution to this problem: M. Suzuki, A. Yanagisawa, and R. Noyori, *J. Am. Chem. Soc.*, **107**, 3348 (1985).

9) 7-Oxo-PGE_1 was synthesized via the one-pot combination of diorganocuprate conjugate addition of the enone and the acyl chloride trapping by a Teijin research group. See Ref. 5n and 5o.

10) a) G. Stork, *Pure Appl. Chem.*, **17**, 383 (1968); b) G. Stork, G. A. Kraus, and G. A. Garcia, *J. Org. Chem.*, **39**, 3459 (1974); c) G. Stork and G. A. Kraus, *J. Am. Chem. Soc.*, **98**, 6747 (1976).

11) Preliminary reports of this paper: a) M. Suzuki, T. Kawagishi, T. Suzuki, and R. Noyori, *Tetrahedron Lett.*, **23**, 4057 (1982); b) M. Suzuki, T. Kawagishi, and R. Noyori, *ibid.*, **23**, 5563 (1982); c) M. Suzuki, A. Yanagisawa, and R. Noyori, *ibid.*, **25**, 1383 (1984); See also Ref. 3a.

12) a) M. Suzuki, T. Suzuki, T. Lawagishi, and R. Noyori, *Tetrahedron Lett.*, **21**, 1247 (1980); b) M. Suzuki, T. Kawagishi, T. Suzuki. Y. Morita, and R. Noyori, *Isr. J. Chem.*, **24**, 118 (1984).

13) M. Suzuki, T. Kawagishi, and R. Noyori, *Tetrahedron Lett.*, **22**, 1809 (1981).

14) a) A. F. Kluge, K. G. Untch, and J. H. Fried, *J. Am. Chem. Soc.*, **94**, 7827 (1972); J. Fried, C. Lin, M. Mehra, W. Kao, and P. Dalven, *Ann. N.Y. Acad. Sci.*, **180**, 38 (1971); R. Pappo, P. Collins, and C. Jung, *ibid.*, **180**, 64 (1971); C. J. Sih, R. G. Salomon, P. Price, R. Sood, and G. Peruzzotti, *J. Am. Chem. Soc.*, **97**, 857 (1975); b) S. Okamoto, T. Shimazaki, Y. Kobayashi, and F. Sato, *Tetrahedron Lett.*, **28**, 2033 (1987); Y. Kitano, T. Matsumoto, S. Okamoto, T. Shimazaki, Y. Kobayashi, and F. Sato, *Chem. Lett.*, **1987**, 1523; c) R. Noyori, I. Tomino, and M. Nishizawa, *J. Am. Chem. Soc.*, **101**, 5843 (1979); R. Noyori, I. Tomino, M. Yamada, and M. Nishizawa, *ibid.*, **106**, 6717 (1984); See also M. M. Midland, D. C. McDowell, R. L. Hatch, and A. Tramontano, *ibid.*, **102**, 867 (1980); J. P. Vigneron and V. Bloy, *Tetrahedron Lett.*, **21**, 1735 (1980); T. Mukaiyama and K. Suzuki, *Chem. Lett.*, **1980**, 255; d) C. J. Sih, J. B. Heather, R. Sood, P. Price, G. Peruzzotti, L. F. H. Lee, and S. S. Lee, *J. Am. Chem. Soc.*, **97**, 865 (1975).

15) a) M. Gill and R. W. Rickards, *J. Chem. Soc., Chem. Commun.*, **1979**, 121; b) M. Gill and R. W. Rickards, *Tetrahedron Lett.*, **1979**, 1539; c) Y. Okamoto, R. Aburatani, M. Kawashima, K. Hatada, and N. Okamura, *Chem. Lett.*, **1986**, 1767; d) K. Ogura, M. Yamashita, and G. Tsuchihashi, *Tetrahedron Lett.*, **1976**, 759; e) M. Kitamura, K. Manabe, R. Noyori, and H. Takaya, *Tetrahedron Lett.*, **28**, 4719 (1987); f) I. Dohgane, H. Yamachika, and M. Minai, *Yuki Gousei Kagaku*, **41**, 896 (1983); see also T. Tanaka, S. Kurozumi, T. Toru, S. Miura, M. Kobayashi, and S. Ishimoto, *Tetrahedron*, **32**, 1713 (1976); Y.-F. Wang, C.-S. Chen, G. Girdaukas, and C. J. Sih, *J. Am. Chem. Soc.*, **106**, 3695 (1984); K. Laumen and M. Schneider, *Tetrahedron Lett.*, **25**, 5875 (1984); D. R. Deardoff, A. J. Matthews, D. S. McMeekin, and C. L. Craney, *ibid.*, **27**, 1255 (1986).

16) a) M. Suzuki, Y. Oda, and R. Noyori, *J. Am. Chem. Soc.*, **101**, 1623 (1979); b) *idem, Tetrahedron Lett.*, **22**, 4413 (1981), and references cited in Ref. 3a.

17) J. Martel, Japanese Patent 46-24694; Japan Kokai 54-130556, 54-130557; French Patent 159066.

18) Reviews: T. W. Greene, "Protective Groups in Organic Synthesis," John Wiley & Sons, New York (1981); J. F. W. McOmie, "Protective Groups in Organic Chemistry," Plenum Press (1973).

19) For the reasonable threo/erythro nomenclature, see R. Noyori, I. Nishida, and J. Sakata, *J. Am. Chem. Soc.*, **103**, 2106 (1981); **105**, 1598 (1983).

20) Now the aldol product is obtainable in 70—80% yield also by using one equivalent of the lithium (*E*)-alkenyl-1-pentynylcuprate (a mixed cuprate)[21] under certain optimized reaction conditions.

21) E. J. Corey and D. J. Beames, *J. Am. Chem. Soc.*, **94**, 7210 (1972).

22) A. Hazato, T. Tanaka, T. Toru, N. Okamura, K. Bannai, S. Sugiura, K. Manabe, and S. Kurozumi, *Nippon Kagaku Kaishi*, **1983**, 1390.

23) The stereochemistry of the C-7 hydroxyl group of these stereoisomers was determined by the exciton chirality method[24] after converting to the 7-benzoyloxy-PGE_2 derivatives.[25]

24) N. C. Gonnella, K. Nakanishi, V. S. Martin, and K. B. Sharpless, *J. Am. Chem. Soc.*, **104**, 3775 (1982).

25) S. Sugiura, T. Toru, T. Tanaka, N. Okamura, A. Hazato, K. Bannai, K. Manabe, and S. Kurozumi, *Chem. Pharm. Bull.*, **32**, 1248 (1984).

26) D. H. R. Barton and S. W. McCombie, *J. Chem. Soc., Perkin Trans. 1*, **1975**, 1574.

27) C. H. Lin, S. J. Stein, and J. E. Pike, *Prostaglandins*, **11**, 377 (1976).

28) It is well-known that simple β-oxoalkyl radicals undergo facile skeletal rearrangement via the tautomeric cyclopropyloxyl radicals.[29] Actually we have observed such skeletal rearrangement in the reaction of xanthate[30] of 3-butyl-2-(1-hydroxybutyl)cyclopentanone with tributyltin hydride (1.2 equiv) and azobisisobutyronitrile (0.2 equiv) at 70 °C for 2 h in toluene leading to 4-butyl-2-propylcyclohexanone (51% yield) and 3-butyl-2-butylcyclopentanone (17% yield).

29) B. Giese and H. Horler, *Tetrahedron Lett.*, **24**, 3221 (1983); B. Giese, *Angew. Chem., Int. Ed. Engl.*, **24**, 553 (1985); D. A. Lindsay, J. Lusztyk and K. U. Ingold, *J. Am. Chem. Soc.*, **106**, 7087 (1984); P. Dowd and S.-C. Choi, *ibid.*, **109**, 3493 (1987).

30) Review: W. Hartwig, *Tetrahedron*, **39**, 2609 (1983).

31) D. H. R. Barton and R. Subramanian, *J. Chem. Soc., Perkin Trans. 1*, **1977**, 1718.

32) (7*S*)-Fluoro-PGI_2: see Ref. 25 and T. Toru, S. Sugiura, and S. Kurozumi, Japan Kokai 59-10577 (1984); K. Bannai, T. Toru, T. Ōba, T. Tanaka, N. Okamura, K. Watanabe, A. Hazato, and S. Kurozumi, *Tetrahedron*, **39**, 3807 (1983); G. W. Holland and H. Maag, Ger. Offen DE3208880 (1982). (7*R*)-Fluoro-PGI_2: A. Yasuda, T. Arai, M. Kato, K. Uchida, and M. Yamabe, Kyoto Conference on Prostaglandins;

Kyoto, 1984; Abstracts, pp. 4—5. Japanese Patent Janan Kokai 59-227888.

33) a) S. Sugiura, T. Toru, T. Tanaka, A. Hazato, N. Okamura, K. Bannai, K. Manabe, S. Kurozumi, and R. Noyori, *Chem. Pharm. Bull.*, **32**, 4658 (1984); b) T. Kato, M. Fukushima, S. Kurozumi, and R. Noyori, *Cancer Research*, **46**, 3538 (1986).

34) W. G. Kofron and L. M. Baclawski, *J. Org. Chem.*, **41**, 1879 (1976); M. F. Lipton, C. M. Sorensen, A. C. Sadler, and R. H. Shapiro, *J. Organomet. Chem.*, **186**, 155 (1980).

35) R. A. Wohl, *Synthesis*, **1974**, 38.

36) S. L. Schreiber, R. E. Claus, and J. Reagan, *Tetrahedron Lett.*, **23**, 3867 (1982).

37) K. Omura, A. K. Sharma, and D. Swern, *J. Org. Chem.*, **41**, 957 (1976).

38) J. Martel, Japanese Patent 45-28153; Japan Kokai 46-5625.

39) M. Minai, Japanese Patent, 55-138502; Japan Kokai, 57-62236.

40) Review: N. Elming, "Adv. Org. Chem.," ed by R. A. Raphael, E. C. Taylor, and H. Wynberg, Interscience Publishers, Inc., New York (1960), Vol. 2, pp. 67—115.

41) T. Tanaka, Japanese Patent, 54-163510; Japan Kokai, 56-86128.

42) An unreacted hemiacylal was removed by this operation. This solution was combined with the sodium hydrogencarbonate solution obtained after hydrolysis of **10** for recovery of the resolving agent **9**.

43) For the stereochemistry, see J. J. Martel, J. P. Demonte, A. P. Tèche, and J. R. Tissier, *Pestic. Sci.*, **11**, 188 (1980).

44) J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **34**, 2543 (1969).

45) Contribution of Mr. S. Sugiura of Teijin Co. is greately appreciated.