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PROSTAGLANDIN CHEMISTRY—VIII

SYNTHESIS OF OPTICALLY ACTIVE 7-OXOPROSTAGLANDINS

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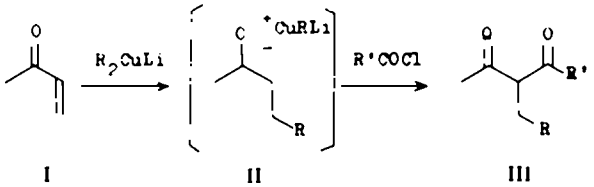
Abstract—Regiospecific α-acylation of β-alkenylated enolates generated by conjugate addition of lithium organocuprates to α,β-unsaturated ketones is described. Several new 7-oxoprostaglandin analogues, 7-oxoprostaglandin E_1 (**18**), 11-deoxy-7-oxoprostaglandin E_1 (**23**), and their 15-*epi* enantiomers **17** and **22**, were synthesized by conjugate addition-acylation method. From optically active 4(*R*) - t - butyldimethylsiloxycyclopent - 2 - en - 1 - one (*R*-**11**), 7-oxoprostaglandin E_1 (**18**) was synthesized. Determination of the absolute configuration of 11-deoxy-7-oxoprostaglandin E_1 (**23**) and its 15-*epi* enantiomer (**22**) on the basis of CD study is described. Successful acylation of β-alkenylated lithium copper enolates with reactive acylating agents such as thiol esters and N-acyl imidazole as well as acyl halides is described.

The prostaglandins, showing highly biological activities in various systems, are cyclic, oxygenated C_{20} fatty acids possessing four (E type) or five (F type) chiral centers. The prostaglandins have become the synthetic targets of many groups[1] because of their limited accessibility from natural sources and their necessity for biological and clinical tests. A variety of synthetic efforts[1] have been focused on how to introduce these chiral centers into the prostaglandin skeleton. Optically active Corey's lactone[2] has been important as a prostaglandin synthon with four chiral centers. Sih's group has achieved the asymmetric synthesis of naturally occurring prostaglandins from protected 2 - substituted - 4(*R*) - hydroxycyclopent - 2 - en - 1 - ones through microbial transformation.[3] Recently, it has been reported that β-alkylated organocopper enolates generated by conjugate addition of organocuprates to various α,β-unsaturated ketones react with a variety of electrophiles, such as α-silylated vinyl ketones,[4] alkyl halides,[5-9] aldehydes,[8,9,12,13] and methyl chloroformate,[14] to afford corresponding α,β-disubstituted ketones. These methods provided a possibile short and highly efficient synthetic method of prostanoids.[10,11,15,16] However, a difficulty arose in the synthesis of naturally occurring prostaglandin $F_{2\alpha}$($PGF_{2\alpha}$) by this methodology presumably due to the steric hindrance of 3- and/or 4-substituents on the cyclopentanone ring.[17] Stork's group successfully overcame this difficulty to trap the resultant γ-substituted β-alkylated enolate with formaldehyde and achieved the total synthesis of F-type prostaglandins.[17] While studies on the synthesis of naturally occurring prostaglandins[18] have been made, new types of prostaglandin analogues[19] which have more specific biological activity are now intensively studied to provide therapeutic agents. In the previous communication,[20] it was reported that enolates (II) generated by conjugate addition of organocuprates to α,β-unsaturated ketones (I) reacted regiospecifically with various acyl chlorides to afford α-acylated-β-alkylated ketones (III) (Scheme 1). This method provided a new synthesis of (*dl*)-7-oxoprostaglandin E_1 and (*dl*)-11-deoxy-7-oxoprostaglandin E_1. In this paper, the synthesis of optically active 7-oxoprostaglandin E_1 started from optically active 4(*R*) - t - butyldimethyl - siloxycyclopent - 2 - en - 1 - one (*R*-**11**),[21,22] as well as optically active 11 - deoxy - 7 - oxoprostaglandins E_1 (**22** and **23**), and the later developments of this acylation reaction are described.

Synthesis of α-acylated ketones. Regiospecific C-acylation of ketones is a useful procedure in organic synthesis. While considerable studies[23-25] have been made to control C- or O-acylation of metal enolates, it is often difficult to achieve regiospecific C-acylation of metal enolates. Recently, β-alkylated magnesium enolates in the presence of cuprous salt were directly trapped with acyl chlorides to give a mixture of C- and O-acylated products in various ratios depending on solvents and/or acylating agents used.[9] We found that β-alkylated organocupper enolates generated by conjugate addition of lithium organocuprates to various α,β-unsaturated ketones were regiospecifically acylated with a variety of acyl chlorides to give predominantly C-acylated products. Results of the preparation of various β-diketones by this method are summarized in Table 1.

As shown in the entry 1 of Table 1, acetylation of resultant 3-n-butylcyclohexanone enolate (**2**) with acetyl chloride gave mainly C-acetylated product (**3a**; 97%) with a small amount of O-acetylated product (**4a**; 3%). On the



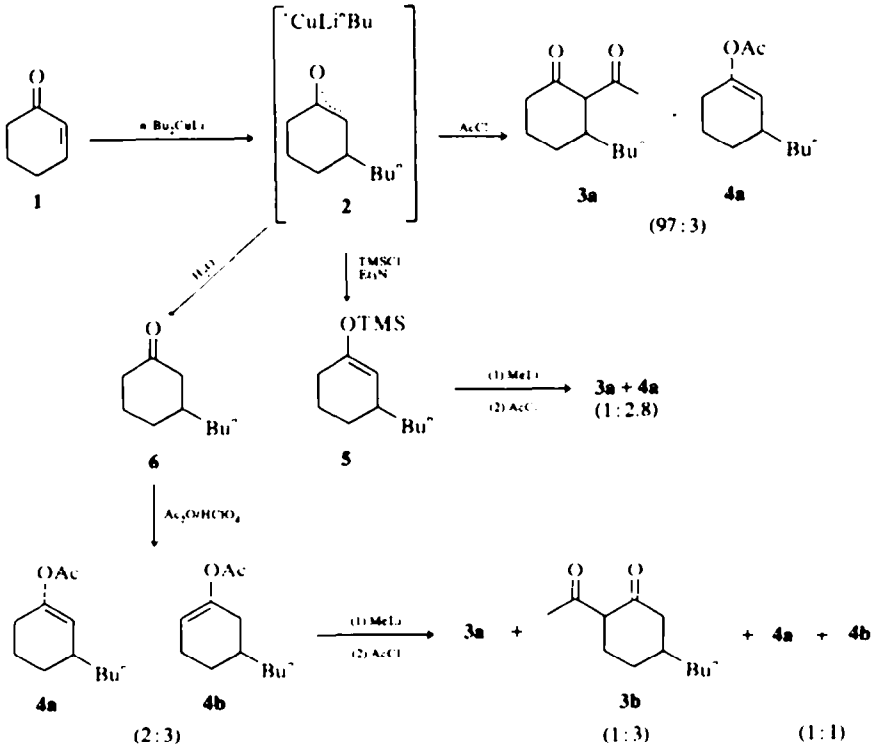
Scheme 1.

Table 1. Acylation of β-alkylated organocopper enolates

Entry	Organocopper Reagent	α,β-Unsaturated Ketone	Acylating Agent	Solvent System	β-Diketone[a] (%)
1	n-Bu_2CuLi[b]	2-cyclohexenone	CH_3COCl	ether-HMPA	92
2	n-Bu_2CuLi[b]	2-cyclohexenone	CH_3COCl	ether	56[d]
3	n-Bu_2CuLi	2-cyclohexenone	$(CH_3CO)_2O$	ether-HMPA	9(39[c])[d]
4	n-Bu_2CuLi[b]	2-cyclopentenone	CH_3COCl	ether-HMPA	38(59[c])[d]
5	n-Bu_2CuLi[b]	methyl vinyl ketone	PhCOCl	ether-HMPA	52[d]
6	Et_2CuLi	2-cyclohexenone	CH_3COCl	THF-HMPA	72[d]
7	Me_2CuLi	2-cyclohexenone	CH_3COCl	ether-HMPA	0

a) Isolation yields were not optimized.
b) Tri-n-butylphosphine was used as a ligand.
c) Including further O-acylated products of the β-diketone.
d) The rest of the products was the β-alkylated product.

other hand, acetylation with acetic anhydride gave O-acetylated product **4a** in 56% yield, as well as C-acetylated products (39%). In the reaction of 2-cyclopentenone (**10**; entry 4), further O-acetylated products (21%) of the resulting C-acetylated β-diketone (**7**) were also obtained. In these experiments, hexamethylphosphoric triamide (HMPA) was found to be effective for the C-acylation. It is known, however, that acetylation of the enolates derived from conjugate addition of lithium dimethylcuprate[1,26,27] or of methylmagnesium iodide[28] with cuprous salt gives mainly O-acetylated products, i.e. enol acetates (entry 7). On the contrary, acetylation of organocopper enolates derived from lithium diethyl-(entry 6) or di-n-butylcuprate (entry 1) with acetyl chloride led predominantly to C-acetylation. These results were presumably due to the difference of the reactivity of each formed enolate toward acyl chlorides. Regiospecificity of this reaction was confirmed by the following experiments. Organocopper enolate **2** prepared by conjugate addition of lithium di-n-butylcuprate to 2-cyclohexenone **1** was trapped with trimethylchlorosilane[10,29] to afford silyl enol ether (**5**). The enol ether **5** was treated with methyllithium and then acetyl chloride[24] to give a mixture of C-acetylated product **3a** and O-acetylated product **4a** in a ratio of 1:2.8 (Scheme 2). These products **3a** and **4a** coincided with the two products obtained by direct acetylation of β-alkylated enolate **2** with acetyl chloride. Furthermore, when enol acetates (**4a** and **4b** in a ratio of 2:3) prepared from 3-n-butylcyclohexanone (**6**) and acetic anhydride were treated with methyllithium and then acetyl chloride, two C-acetylated products (**3a** and **3b** in a ratio of 1:3) and two



Scheme 2.

O-acetylated products (**4a** and **4b** in a ratio of 1:1) were obtained in a ratio of 5:1, respectively (Scheme 2). These resultant positional isomers **3a** through **4b** were separated by gas chromatography and identified. These observations to the conclusion that the β-alkylated lithium organocopper enolate was regiospecifically acylated with acyl chlorides to give α-acylated-β-alkylated products.

Synthesis of 7-oxoprostaglandins. In the previous paper,[20] the application of this acylation reaction was demonstrated by the synthesis of new prostaglandin analogues, i.e. (*dl*)-7-oxoprostaglandin E_1 from (*dl*) - 4 - t - butyldimethylsiloxycyclopent - 2 - en - 1 - one (*dl*-**11**) and (*dl*) - 11 - deoxy - 7 - oxoprostaglandin E_1 from 2-cyclopentenone (**10**). A chiral prostaglandin synthon, 4(*R*) - t - butyldimethylsiloxycyclopent - 2 - en - 1 - one *R*-**11** was synthesized from 3(*R*) - acetoxy - 5(*R*) - hydroxycyclopent - 1 - ene obtained by microbiological hydrolysis[21-30] of (*dl*) - 3,5 - diacetoxycyclopent - 1 - ene.[31] Thus, we next tried to synthesize optically active 7-oxoprostaglandin E_1 (**18**) from this optically active synthon *R*-**11**. The chiral enone *R*-**11** ($[\alpha]_D^{20}$ +51°, 86% *R* e.e.)[22] was allowed to react with chiral mixed cuprate reagent (**12**),[32] prepared from 3(*S*) - t - butyldimethylsiloxy - 1 - lithio - *trans* - 1 - octene[29] and n-propylethynylcopper,[29,33] followed by treatment with 6-methoxycarbonylcaproyl chloride (**13a**)[34] to give protected 7-oxoprostaglandin E_1 methyl ester (**14a**; 35%). Desilylation[32] of **14a** by exposure to acetic acid-water-tetrahydrofuran (3:1:1) afforded 7-oxoprostaglandin E_1 methyl ester (**16a**; 70%) accompanied by a small amount of 7 - oxo - 15 - *epi* - *ent* - prostaglandin E_1 methyl ester (**15a**; 1%).[34] Reaction of (*dl*) - 4 - t - butyldimethylsiloxycyclopent - 2 - en - 1 - one (*dl*)-**11** with chiral cuprate **12** and acyl chloride **13a** gave a mixture of two diastereomeric methyl esters **15a** and **16a** in equal amounts after desilylation. Enzymatic hydrolysis[29] of methyl esters **15a** and **16a** by partially purified hog pancreas lipase gave 7-oxoprostaglandin E_1 **18** (60%) and 7 - oxo - 15 - *epi* - *ent* - prostaglandin E_1 **17** (42%), respectively.

Similarly, reaction of 2-cyclopentenone **10** with chiral mixed cuprate reagent **12**, followed by addition of acyl chloride **13a** gave protected 11 - deoxy - 7 - oxoprostaglandin E_1 methyl ester (**19a**; 38%), which was deprotected to afford a diastereomeric mixture of 11 - deoxy - 7 - oxoprostaglandin E_1 methyl ester (**21a**) and 11 - deoxy - 7 - oxo - 15 - *epi* - *ent* - prostaglandin E_1 methyl ester (**20a**) in almost equal amounts (82% based on **19a**). These methyl esters, **20a** and **21a**, were isolated by preparative thin layer chromatography. More polar methyl ester exhibited the following Cotton effects ($[\theta]_{241}$ + 1.03 × 10⁴, $[\theta]_{288}$ +3.32 × 10³, and $[\theta]_{319}$ −1.52 × 10³), while less polar methyl ester showed the opposite Cotton effects ($[\theta]_{241}$ −1.03 × 10⁴, $[\theta]_{288}$ − 3.32 × 10³, and $[\theta]_{319}$ + 1.52 × 10³) (Fig. 1). Methyl ester of 7-oxoprostaglandin E_1 **16a**, which was synthesized from chiral

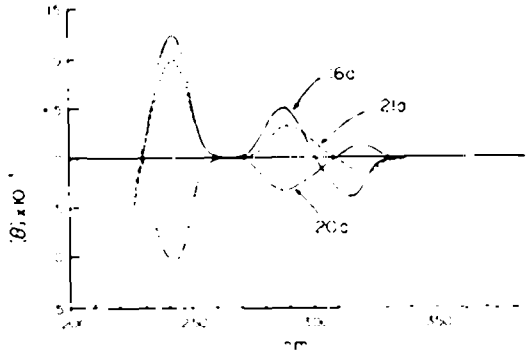
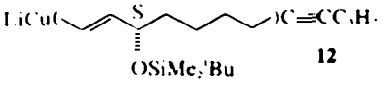


Fig. 1. Circular dichroism spectra of 7-oxo-PGE$_1$ Me ester **16a** (——), 11 - deoxy - 7 - oxo - 15 - *epi* - *ent* - PGE$_1$ Me ester **20a** (– – – –), and 11 - deoxy - 7 - oxo - PGE$_1$ Me ester **21a** (— — —).



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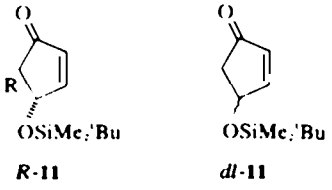
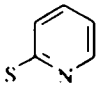


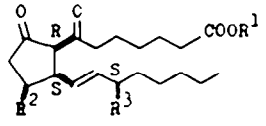
***R*-11** ***dl*-11**

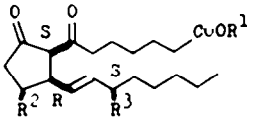
$R'OCO(CH_2)_4COX$

13a: R' = CH_3, X = Cl
13b: R' = C_2H_5, X = Cl
24: R' = CH_3, X = SPh

25: R' = CH_3, X = 

26: R' = CH_3, X = 





14a; R' = CH_3, R^2 = R' = $OSiMe_2{}^tBu$
14b; R' = C_2H_5, R^2 = R' = $OSiMe_2{}^tBu$
15a; R' = CH_3, R^2 = R' = OH
15b; R' = C_2H_5, R^2 = R' = OH
17; R' = H, R^2 = R' = OH
19a; R' = CH_3, R^2 = H, R' = $OSiMe_2{}^tBu$
19b; R' = C_2H_5, R^2 = H, R' = $OSiMe_2{}^tBu$
20a; R' = CH_3, R^2 = H, R' = OH
20b; R' = C_2H_5, R^2 = H, R' = OH
22; R' = R^2 = H, R' = OH

14a; R' = CH_3, R^2 = R' = $OSiMe_2{}^tBu$
14b; R' = C_2H_5, R^2 = R' = $OSiMe_2{}^tBu$
16a; R' = CH_3, R^2 = R' = OH
16b; R' = C_2H_5, R^2 = R' = OH
18; R' = H, R^2 = R' = OH
19a; R' = CH_3, R^2 = H, R' = $OSiMe_2{}^tBu$
19b; R' = C_2H_5, R^2 = H, R' = $OSiMe_2{}^tBu$
21a; R' = CH_3, R^2 = H, R' = OH
21b; R' = C_2H_5, R^2 = H, R' = OH
23; R' = R^2 = H, R' = OH

synthon *R*-**11** with natural configuration as mentioned above, exhibited Cotton effects ($[\theta]_{241}$ $+1.27\times10^4$, $[\theta]_{288}$ $+5.20\times10^3$, and $[\theta]_{316}$ -4.04×10^3) similar to those of the more polar component. Thus, the more polar compound was assigned to be 11 - deoxy - 7 - oxoprostaglandin E_1 methyl ester **21a** and the less polar compound was assigned to be 11 - deoxy - 7 - oxo - 15 - *epi* - *ent* - prostaglandin E_1 methyl ester **20a** as illustrated. Each of the ester **20a** and **21a** was converted into 11 - deoxy - 7 - oxo - 15 - *epi* - *ent* - prostaglandin E_1 (**22**) and 11 - deoxy - 7 - oxoprostaglandin E_1 (**23**; 60 ~ 72%), respectively, by hydrolysis with aqueous sodium hydroxide.

Thus, we succeeded in the synthesis of new prostaglandin analogues by one-pot reaction of reactive acyl chlorides to copper enolates, which were difficult to be alkylated by less reactive alkyl halides. Since acyl imidazoles[36] or thiol esters[37] were known as effective acylating agents, it is of further interest to apply them to our reaction. In addition, since the S atom has a strong affinity for the Cu atom, thiol esters such as thiophenol esters were expected to be a powerful acylating agent for organocopper enolates. Indeed, it was found that three acyl derivatives, **24**, **25** and **26**, were effective to acylate β-alkenylated organocopper enolates and gave protected 11 - deoxy - 7 - oxoprostaglandin E_1 methyl ester **19a** (Table 2). Acylation of β-alkenylated organocopper enolates with the acyl chloride **13a** was thought to proceed regiospecifically as mentioned above. Regiospecificity of new acylation reactions with acyl derivatives, **24**, **25**, or **26**, was also confirmed by the fact that these desilylated products were identical with products obtained with acyl chloride **13a** by thin layer chromatographic and spectroscopic analyses.

Table 2. Acylation of β-alkylated enolate with various acylating agents

Acylating Agent			Condition		Acylated Product	Yield (%)
	R	X	Temp.(°C),	Time(min)		
13a	CH_3	Cl	-25°	15	19a	38
13b	C_2H_5	Cl	r.t.	30	19b	26
24	CH_3	SPh	-25°	240	19a	46
25	CH_3		-40°	120	19a	40
26	CH_3		-40°	120	19a	25

According to a preliminary biological assay, 7-oxoprostaglandin E_1 showed inhibitory activities of platelet aggregation and gastric secretion. The detailed biological evaluation of these prostaglandin analogues will be published elsewhere. We are interested in the relationship between biological activities of these new 7-oxoprostaglandins and those of 6-oxoprostaglandin $F_{1\alpha}$[38] obtained from arachidonic acid with a homogenate of the rat stomack fundus.

EXPERIMENTAL

All m.ps and b.ps are uncorrected. M.ps were observed with a Yanaco micro melting point apparatus. IR spectra were recorded on a Hitachi EPI-S10 spectrometer. NMR spectra were determined on a Varian EM 360 (60 MHz), a Jeol JNM-MH-100 (100 MHz), and a Jeol JNM-PS-100 (100 MHz) spectrometer. Mass spectra were taken at 70 or 11 eV on a GLC-linked LKB 9000 mass spectrometer equipped with a Simazu GC-MSPAC 300 computer; only the major ions and their relative intensities are listed. Exact mass analyses were carried out with a tolerance of 30.0 ppm for a measured mass. Optical rotations were measured in MeOH on a JASCO Model DIP-SL automatic polarimeter. CD spectra were recorded on a JASCO J-20 automatic recording spectropolarimeter. GLC was carried out with a Hitachi 073 gas chromatograph (for analysis) equipped with a column (2 m × 3 mm i.d.) packed with 20% carbowax 20M on chromosorb W (NAW) (oven temp. 180°, injection temp. 250°, N_2, 35 ml/min) with Takeda Riken TR-2215A digital integrator. Layer chromatography was performed using Merck silica gel (Kieselgel 60 F_{254}) analytical and preparative plates. Column chromatography was carried out on Wako gel C-200 (silica gel). All reactions were carried out under nitrogen. Magnetic stirring devices were used in all cases. Solvents for reactions were purified if necessary before use by distillation from suitable drying agents. Solvents for extraction were GR grades. Organic extracts were always dried over Na_2SO_4 or $MgSO_4$. As the esterase for enzymatic hydrolysis was used hog pancreas lipase purchased from Sigma Chemical Co.

Conjugate addition of di-n-butylcuprate to 2-cyclohexenone **1** *and acetylation of enolate with acetyl chloride or acetic anhydride*

To a stirred soln of tri-n-butylphosphine (n-Bu_3P)-copper (I) iodide complex (n-Bu_3P–CuI)[39] (3.9 g, 10 mmol) in ether (30 ml) at 78° was added a 1.31 M hexane soln of n-BuLi (15.3 ml, 20 mmol). After stirring for 30 min, **1** (960 mg, 10 mmol) in ether (5 ml) was added at -78°. After stirring for further 30 min, acetyl chloride (4 ml, 56 mmol) in ether (10 ml) and hexamethylphosphoric triamide (HMPA; 5 ml) was rapidly added, and the mixture was allowed to warm up to room temp. After stirring at room temp. for 4 hr, the mixture was treated with $NaHCO_3$ aq. then ammoniacal NH_4Cl aq for 30 min. The organic layer was separated and the aqueous layer was extracted with ether (3 × 50 ml). The combined organic layers were washed with sat NH_4Cl, dried (Na_2SO_4), and concentrated under vacuum to give 5.48 g of a crude product, whose GLC analysis (2 m × 3 mm i.d., 20% Carbowax 20M on chromosorb W (NAW), 180°) indicated two products, **3a** (13.6 min) and **4a** (5.3 min) in a ratio of 97:3 by comparing retention times with those of authentic samples as described later. Distillation of the crude product afforded 1.81 g (9.2 mmol, 92%) of **3a** (b.p.: 64–66°/0.06 mmHg) with 60 mg (0.3 mmol, 3%) of **4a**. **3a**; IR (liquid film): 3350, 1720, 1700, 1600, 980 and 745 cm^{-1}; NMR (60 MHz, CCl_4): 0.90 (3H, CH_3), 2.10 (3H, s, $COCH_3$); 1.1–2.4 (13H, CH_2) and 16.13 (1H, enol H); MS (70 eV; *m/e*, %): 196 (6, M^+), 178 (3), 153 (3), 140 (10), 139 (100), 121 (10), 111 (13), 100 (20), 97 (82), 85 (12), 55 (23), 43 (64) and 41 (17). Calc. for $C_{12}H_{20}O_2$: 196.1464. Found: 196.1473 ± 0.0059. The product **3a** showed a positive result in $FeCl_3$ test indicating a characteristic property of 1,3-dicarbonyl system.

Acetylation of enolate generated from 3 - r butyl - 1 - trimethylsiloxycyclohexene **5** *with acetyl chloride*

To a stirred soln of **2** (10 mmol) generated as described was added at -78° trimethylchlorosirane (6 ml) and triethylamine (8 ml) in THF (20 ml).[10,26] After stirring at room temp for 2 hr, the mixture was poured into a mixture of hexane (599 ml) and ice-water (300 ml). The organic layer was separated, dried

(Na_2SO_4), and concentrated *in vacuo* to afford 5.47 g of a residue. To the residue in THF (20 ml) was added at 0° a 3.0 M ether soln of MeLi (3.3 ml, 10 mmol). After stirring at room temp. for 20 min, acetyl chloride (4 ml) in ether (10 ml) was added, and the mixture was stirred at room temp. for 2 hr, treated with sat NaHCO, (50 ml) for 30 min. The mixture was extracted with ether (3 × 50 ml), and the combined organic solns were washed with brine, dried (Na_2SO_4), and evaporated *in vacuo* to leave 5.05 g of an oily residue, which was distillated to give 1.79 g of a volatile product (up to 74°/0.5 mmHg). The GLC of the product indicated three products, 3-n-butylcyclohexanone **6** (1.36 g, 8.8 mmol, 88%), **4a** (13 mg, 0.06 mmol, 0.6%), and **3a** (46 mg, 0.2 mmol, 2%). These yields were estimated by GLC peak intensities. The ratio of **6**, **4a**, and **3a** was 61 : 2.8 : 1 by GLC before distillation.

Acetylation of enolate generated from 1 - *acetoxy* - 3 - *n* - *butylcyclohexene* **4a** *and* 1 - *acetoxy* - 5 - *n* - *butylcyclohexene* **4b** *with acetyl chloride*

A soln of **6** (13.4 g, 87 mmol), prepared from **1** by conjugate addition of lithium di-n-butylcuprate, and Ac_2O (40.8 g, 0.4 mol) in CCl_4 (100 ml) with a catalytic amount of 70% $HClO_4$ aq was stirred at room temp. for 20 hr.[40] The usual work-up gave 8.98 g (b.p.: 61–69°/0.05 mmHg, 46 mmol, 53%) of the isomeric enol acetates **4a** (5.3 min) and **4b** (5.9 min) in a ratio of 2 : 3 by GLC. The retention time of the minor enol acetate **4a** was identical with that of the O-acetylated product of organocopper or lithium enolates with acetyl chloride as described above. Therefore, the other major enol acetate **4b** was assigned 1 - acetoxy - 5 - n - butylcyclohexene. **4a**: IR (film): 1750, 1680, 1360, 1215, and 1130 cm $^{-1}$; NMR (60 MHz, CCl_4): 0.91 (3H, CH_3), 1.2–1.8 (12H, CH_2), 2.00 (3H, $COCH_3$), 5.21 (1H, olefinic H); MS (70 eV; *m/e*, %): 196 (12, M$^+$), 154 (7), 97 (100), and 43 (10). Calc. for $C_{12}H_{20}O_2$: 196.1464. Found: 196.1419 ± 0.0059. **4b**: IR (film): 1750, 1680, 1360, 1215 and 1130 cm $^{-1}$; NMR (60 MHz, CCl_4): 0.91 (3H, CH_3), 1.2–1.8 (12H, CH_2), 2.00 (3H, $COCH_3$) and 5.21 (1H, olefinic H); MS (70 eV; *m/e*, %): 196 (23, M$^+$), 154 (8), 137 (8), 97 (100), and 43 (10). Calc. for $C_{12}H_{20}O_2$: 196.1464. Found: 196.1464 ± 0.0059.

To a stirred soln of this isomeric enol acetates **4a** and **4b** in a ratio of 2 : 3 (3.92 g, 20 mmol) in dimethoxyethane (20 ml) was added at 0° a 3.0 M ether soln of MeLi (13.3 ml, 40 mmol). After the mixture was stirred at 0°, acetyl chloride (8 ml) in ether (20 ml) was added.[25] After stirring at 0° for 3 hr, the mixture was treated with $NaHCO_3$ aq, and extracted with ether (3 × 50 ml). The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated to afford 5.42 g of a crude product, which was distillated to give 2.90 g of a volatile product (up to 115°/0.1 mmHg). The GLC analysis of the product indicated five components and yields were estimated by peak intensities of GLC. These products were identified by the retention times of GLC. The five products were **6** (4.4 min, 670 mg, 4.3 mmol, 22%), **4a** and **4b** in a ratio of 1 : 1 (5.3 and 5.9 min, 160 mg, 0.8 mmol, 4%), **3a** (13.6 min, 390 mg, 2.0 mmol, 10%), and **3b** (17.2 min, 1.18 g, 6.0 mmol, 30%). **3b**: IR (film): 3400, 1720, 1700, 1600, 980, and 750 cm $^{-1}$; NMR (60 MHz, CCl_4): 0.90 (3H, CH_3), 2.10 (3H, s, $COCH_3$), 1.1–2.4 (13H, CH_2), and 16.10 (1H, enol H); MS (70 eV; *m/e*, %): 196 (38, M$^+$), 181 (46), 178 (16), 139 (77), 111 (32), 97 (66), 84 (18), 71 (18), 69 (21), 55 (30), and 43 (100). Calc. for $C_{12}H_{20}O_2$: 196.1464. Found: 196.1453 ± 0.0059.

Conjugate addition of di-n-butylcuprate to 2-*cyclopentenone* **10** *and acetylation of enolate with acetyl chloride*

To a stirred soln of n-Bu_3P–CuI (3.9 g, 10 mmol) in ether (20 ml) at −78° was added a 1.56 M hexane soln of n-BuLi (12.8 ml, 20 mmol). After stirring for 30 min, **10** (820 mg, 10 mmol) in ether (5 ml) was added at −78°. After stirring for 30 min, acetyl chloride (3.93 g, 50 mmol) in ether (20 ml) and HMPA (5 ml) was gradually added at −78°, and the mixture was allowed to warm up to room temp. After stirring at room temp. for 1 hr, the usual work-up gave 10.78 g of a residue, which was distillated to afford the following products; 3-n-butylcyclopentanone (460 mg, 3.3 mmol, 33%) identified with an authentic one; MS (70 eV; *m/e*, %): 140 (22, M$^+$), 111 (28), 96 (17), 83 (100), 70 (18), 69 (19), 56 (65), 55 (79), 43 (25), and 41 (50). 2 - acetyl - 3 - n - butylcyclopentanone **7** (700 mg, 3.8 mmol, 38%); b.p.: 82–83°/3 mmHg; IR (film) 1740, 1710 and 1650 cm $^{-1}$; NMR (60 MHz, CCl_4): 0.93 (3H, CH_3), 1.1–1.7 (11H, CH_2), and 2.00 (3H, s, $COCH_3$); MS (70 eV; *m/e*, %): 182 (10, M$^+$), 164 (2), 139 (8), 127 (23), 125 (100), 107 (15), 83 (85), 71 (50), 55 (20) and 43 (90); Calc. for $C_{11}H_{18}O_2$: 182.1308. Found: 182.1306 ± 0.0055; and further O-acetylated product of **7** (470 mg, 2.1 mmol, 21%) detected by the GLC–MS method; MS (70 eV; *m/e*, %): 224 (0.1, M$^+$), 209 (12), 194 (4), 180 (2), 164 (16), 152 (100), 123 (6), 122 (5), 110 (22), 109 (17), 108 (8), 96 (7) and 43 (12).

Conjugate addition of di-n-butylcuprate to methyl vinyl ketone and acetylation of enolate with benzoyl chloride

To a stirred soln of n-Bu_3P–CuI (3.9 g, 10 mmol) in ether (20 ml) at −78° was added a 1.56 M hexane soln of n-BuLi (12.8 ml, 20 mmol). After stirring for 30 min, methyl vinyl ketone (700 mg, 10 mmol) in ether (10 ml) was added at −78°. After stirring for further 1 hr, benzoyl chloride (3.53 g, 25 mmol) in ether (20 ml) and HMPA (5 ml) was added at −78°, and the mixture was allowed to warm up to room temp. After stirring at room temp. for 1 hr, the usual work-up gave 12.33 g of a crude product, which was purified by silica gel column chromatography with benzene to afford 1.20 g of 3-benzoyl-2-octanone (5.2 mmol, 52%); IR (film): 3050, 1720, 1680, 1600, 1580, 1270, 710, and 690 cm $^{-1}$; NMR (60 MHz, CCl_4): 0.90 (3H, CH_3), 1.1–1.9 (8H, CH_2), 2.02 (3H, s, $COCH_3$); and 7.2–7.5 and 7.7–8.1 (3H and 2H, Ph); MS (70 eV; *m/e*, %): 232 (1, M$^+$), 189 (5), 162 (17), 161 (5), 123 (15), 105 (100), 82 (15), 77 (32), 55 (12) and 43 (18).

Conjugate addition of diethylcuprate to 2-*cyclohexenone* **1** *and acetylation of enolate with acetyl chloride*

To a stirred suspension of cuprous iodide (950 mg, 5 mmol) at −78° was added a 0.58 M ether soln of EtLi (17 ml, 10 mmol). After stirring for 30 min, **1** (480 mg, 5 mmol) in ether (1 ml) was added at −78°. After stirring for 30 min, acetyl chloride (2.2 g, 28 mmol) in THF (10 ml) and HMPA (2 ml) was added, and the mixture was stirred for 1 hr. The usual work-up gave 1.26 g of a crude product, which was purified by preparative TLC (ether, R_f 0.65) to afford 605 mg of **9** (3.6 mmol, 72%); $FeCl_3$ test, positive; IR (film): 3400, 1720, 1690, 1600, 1230 and 1040 cm $^{-1}$; NMR (60 MHz, CCl_4): 0.93 (3H, CH_3), 1.3–2.5 (9H, CH_2), 2.07 (3H, s, $COCH_3$), and 16.10 (1H, enol H); MS (70 eV; *m/e*, %): 168 (18, M$^+$), 139 (100), 121 (11), 111 (13), 100 (13), 97 (83), 55 (18) and 43 (46). Calc. for $C_{10}H_{16}O_2$: 168.1151. Found: 168.1135 ± 0.0067. The two minor products were detected by the GLC–MS analysis. One of them was 1-acetoxy-3-ethylcyclohexene (25 mg, 0.15 mmol, 3%); MS (70 eV; *m/e*, %): 168 (25, M$^+$), 139 (8), 132 (10), 131 (8), 126 (12), 97 (100) and 43 (10). Calc. for $C_{10}H_{16}O_2$: 168.1151; Found: 168.1103 ± 0.0067. The other was further O-acetylated product of the C-acetylated product **9** (60 mg, 0.30 mmol, 6%); MS (70 eV; *m/e*, %): 210 (8), 168 (10), 139 (100), 121 (8), 97 (10), and 43 (25). Calc. for $C_{12}H_{18}O_3$: 210.1257. Found: 210.1238 ± 0.0063.

7-Oxo-15-epi-ent-*PGE$_1$ methyl ester* **15a** *and 7-oxo-PGE$_1$ methyl ester* **16a**

(a) A 1.4 M pentane soln of t-BuLi[31] (1.6 ml, 2.2 mmol) was added at −78° to a stirred soln of 3(*S*) - t - butyldimethylsiloxy - 1 - iodo - *trans* - 1 - octene (405 mg, 1.1 mmol, $[\alpha]_D^{20}$ −28.9° (*c*, 39.1, CCl_4) prepared by silylation[31] of 3(*S*) - hydroxy - 1 - iodo - *trans* - 1 - octene[28] ($[\alpha]_D^{20}$ +9.3° (*c*, 28.7, MeOH)) in ether (5 ml), and the resulting mixture was stirred at −78° for 2 hr. To the mixture was added at −78° a stirred soln of n-propylethynylcopper[32] (144 mg, 1.1 mmol) and n-Bu_3P (444 mg, 2.2 mmol) in ether (1 ml) at room temp. for 20 min. After stirring for 1 hr, (*dl*) - 4 - t - butyldimethylsiloxycyclopent - 2 - en - 1 - one[33] (*dl*)-**11** (212 mg, 1.0 mmol) in ether (4 ml) was added at −78°, and the mixture was stirred at −78° for 15 min, then at −40° for 30 min. A soln of 6-methoxycarbonycaproyl chloride **13a** (b.p.: 89–91°/1.5 mmHg, 210 mg, 1.1 mmol), which was prepared from pimelic acid mono methyl ester (b.p.: 103–117°/0.03 mmHg) and thionyl chloride in 98% yield by a partially modified method of the cited procedure,[34] in THF (4 ml) and HMPA (0.5 ml) was added at −40°, and the mixture was stirred at −40° for 1 hr. The mixture was treated with ammoniacal NH_4Cl aq (40 ml), and extracted with ether (3 × 50 ml). The combined organic layers, after washing with brine and drying (Na_2SO_4), were concentrated *in vacuo* to afford 1.28 g of a

crude product, which was purified by preparative TLC (hexane–EtOAc, 4:1, R_f 0.53) to give 208 mg of diastereomeric **14a** (0.34 mmol, 34%); IR (film): 1740, 1720, 1650, 1610, 1460, 1360, 1255, 1070, 830 and 770 cm $^{-1}$; NMR (60 MHz, CCl_4): 0.05 (6H, s, $SiCH_3$), 0.88 (21H, t-Bu and CH_3), 1.1–1.6 (14H, CH_2), 1.8–2.4 (7H, CH_2 and CH), 3.23 (1H, COCHCO), 3.59 (3H, s, OCH_3), 4.02 (2H, CHOSi) and 5.43 (2H, olefinic H); MS (70 eV; *m/e*, %): 553 (1, M-Bu), 466 (0.5), 464 (0.5), 421 (1), 409 (1), 189 (43), 157 (41), 153 (54), 125 (39), 120 (41), 92 (100), 78 (63), 75 (48), 69 (43), 57 (48), 55 (52) and 41 (40). Calc. for $C_{29}H_{53}O_4Si_2$ (M-^{t}Bu): 553.3384. Found: 553.3403 ± 0.0166.

The ester **14a** (208 mg, 0.34 mmol) obtained above was dissolved in a mixture of AcOH (12 ml), water (4 ml), and THF (4 ml).[31] After standing at room temp. for 87 hr, toluene (50 ml) was added and the mixture was azeotropically evaporated to leave 308 mg of a crude product, which was purified twice by preparative TLC (hexane–EtOAc, 1:4) to give two β-dicarbonyl products (R_f 0.27 and 0.22). The less polar component was **15a** (53 mg, 0.12 mmol, 35% based on **14a**) as described later; $[\alpha]_D^{20}$ 0° (*c*, 7.6, MeOH); IR (film): 3450, 1740, 1720, 1650, 1610, 1180, 1030 and 980 cm $^{-1}$; NMR (100 MHz, $CDCl_3$): 0.89 (3H, CH_3), 1.2–1.8 (14H, CH_2), 2.0–2.5 (7H, CH_2 and CH), 3.38 (1H, COCHCO), 3.66 (3H, s, OCH_3), 3.7–4.4 (4H, CHOH), and 5.64 (2H, olefinic H); MS (12 eV; *m/e*, %): 382 (0.1, M$^+$), 364 (60, M-H_2O), 358 (66), 346 (100), 264 (19) and 208 (27). Calc. for $C_{21}H_{30}O_4$ (M-2H_2O): 346.2146. Found: 346.1880 ± 0.0277. The more polar product was **16a** (56 mg, 0.12 mmol, 35% based on **14a**) as described later; $[\alpha]_D^{20}$ +12.5° (*c*, 7.1, MeOH); CD (MeOH): $[\theta]_{241}$ $+1.27 \times 10^4$, $[\theta]_{288}$ $+5.20 \times 10^3$, $[\theta]_{315}$ -4.04×10^3 (*c*, 8.65×10^{-4} M); IR (film): 3450, 1740, 1720, 1650, 1610, 1180, 1030 and 980 cm $^{-1}$; NMR (100 MHz, $CDCl_3$): 0.89 (3H, CH_3), 1.1–1.8 (14H, CH_2), 2.1–2.5 (7H, CH_2 and CH), 3.24–3.53 (3H, OH and COCHCO), 3.65 (3H, s, OCH_3), 4.16 (2H, CHOH), and 5.62 (2H, olefinic H); MS (12 eV; *m/e*, %): 382 (0.1, M$^+$), 364 (80, M-H_2O), 358 (94), 346 (100), 293 (14), 264 (16), 250 (11), 208 (33), 190 (14), 157 (20) and 43 (16). Calc. for $C_{21}H_{30}O_4$ (M-2H_2O): 346.2146. Found: 346.1880 ± 0.0277.

(b) A soln of (*R*)-**11**[22] (212 mg, 1.0 mmol, $[\alpha]_D^{20}$ +51° (*c*, 7.9, MeOH), 86% R e.e.) was added at −78° to the soln of chiral mixed cuprate **12** (1.1 mmol) prepared in the same way as in (a). Similarly, **13a** (210 mg, 1.1 mmol) in THF (4 ml) and HMPA (0.5 ml) was added at −40°, and the mixture was stirred at −40° for 1 hr. The same work-up and purification gave 214 mg of **14a** (0.35 mmol, 35%), which was identical (TLC, IR, NMR and MS) with **14a** obtained in (a). Desilylation of **14a** (141 mg, 0.23 mmol) gave **16a** (94 mg, 0.24 mmol, 70%), which was identical (TLC, IR, NMR and MS) with the more polar component obtained in (a), accompanied by a small amount of **15a** (1.3 mg, 0.004 mmol, 1%).

7-Oxo-PGE$_1$ **18** *and 7-oxo-15-epi-ent-PGE*$_1$ **17**

A soln of **16a** (3 mg, 0.0079 mmol) in acetone (0.1 ml) was added to the lipase soln (5 ml) partially purified from crude hog pancreas lipase (Sigma) in the same way as described.[26] The mixture was sonicated at 0° for 25 min, and poured into acetone (50 ml). After filtering through Celite, the resulting soln was concentrated *in vacuo* and the residue was extracted with EtOAc (3 × 50 ml). The combined organic layers, after washing with brine and drying ($MgSO_4$), were concentrated to give 5.4 mg of a crude product, which was purified by preparative TLC (EtOAc–cyclohexane–acetic acid, 40:60:2, R_f 0.35) to afford 1.6 mg of **18** (0.0045 mmol, 60%). Hydrolysis of **15a** by the same procedure gave **17** (42%). 7-Oxo-PGE$_1$ **18**: IR (film): 3100, 1740, 1710 and 1650 cm $^{-1}$; NMR (100 MHz, $CDCl_3$): 0.88 (3H, CH_3), 1.2–1.8 (14H, CH_2), 2.0–2.5 (7H, CH_2 and CH), 3.2–3.5 (3H, OH and COOH), 4.14 (3H, CHOH and COCHCO) and 5.52–5.75 (2H, olefinic H); MS (11 eV; *m/e*, %): 368 (0.2, M$^+$), 350 (60, M-H_2O), 332 (50), 314 (30), 264 (10), 251 (60), 250 (100), 249 (50), 247 (60), 237 (38), 233 (42), 190 (40) and 151 (31). Calc. for $C_{20}H_{30}O_5$ (M-H_2O): 350.2095. Found: 350.1990 ±0.0105. 7-Oxo-15-*epi-ent*-PGE$_1$ **17**: IR (film): 3100, 1740, 1710 and 1650 cm $^{-1}$; NMR (100 MHz, $CDCl_3$): 0.90 (3H, CH_3), 1.1–1.9 (14H, CH_2), 2.1–3.0 (7H, CH_2 and CH), 3.2–3.7 (3H, OH and COOH), 4.15 (3H, CHOH and COCHCO) and 5.5–5.8 (2H, olefinic H); MS (11 eV; *m/e*, %): 368 (0.1, M$^+$), 350 (30, M-H_2O), 332 (20), 314 (20), 264 (8), 251 (40), 250 (100), 249 (60), 247 (70), 237 (45), 233 (47), 190 (15) and 151 (30). Calc. for $C_{20}H_{30}O_5$ (M-H_2O): 350.2095. Found: 350.2003 ± 0.0105.

(dl)-*7-Oxo-PGE*$_1$ *ethyl ester* **14b**

Similarly, reaction of (*dl*)-**11** (212 mg, 1.0 mmol) with achiral mixed cuprate (*dl*)-**12** (1.2 mmol), followed by addition of **13b** (b.p.: 85–86°/1.0 mmHg, 1.03 g, 5 mmol), which was prepared from pimelic acid monoethyl ester (b.p.: 159–163°/5.0 mmHg) in 94% yield, gave (*dl*)-**14b** (143 mg, 0.23 mmol, 23%) after purification by preparative TLC (ether, R_f 0.54); IR (film): 1730, 1635, 1250, 1180, 1075, 840 and 775 cm $^{-1}$; NMR (60 MHz, CCl_4): 0.08 (12H, s, $SiCH_3$), 0.93 (21H, t-Bu and CH_3), 1.29 (3H, CH_3 of ethyl ester), 1.3–1.8 (14H, CH_2), 2.1–2.6 (7H, CH_2 and CH), 3.60 (1H, COCHCO), 3.8–4.3 (4H, CHOSi and CH_2 of ethyl ester) and 5.4–5.7 (2H, olefinic H); MS (11 eV; *m/e*, %): 624 (0.5, M$^+$), 609 (0.5), 567 (100), 549 (10), 492 (18), 435 (17), 417 (10), 397 (14) and 322 (40).

A similar desilylation of (*dl*)-**14b** (125 mg, 0.20 mmol) gave (*dl*)-**15b** and -**16b** (56 mg, 0.14 mmol, 70%) after TLC purification (EtOAc, R_f 0.34). These diastereomeric esters showed two spots on TLC (ether, R_f 0.20 and 0.14, 4 irrigations); IR (film): 3400, 1730, 1715, 1635, 1180, 1030 and 975 cm $^{-1}$; NMR (60 MHz, $CDCl_3$): 0.90 (3H, CH_3), 1.24 (3H, CH_3 of ethyl ester), 1.2–1.8 (14H, CH_2), 2.1–2.7 (7H, CH_2 and CH), 2.60 (2H, OH), 3.58 (1H, COCHCO), 4.07 (4H, CHOH and CH_2 of ethyl ester), and 5.4–5.7 (2H, olefinic H); MS (11 eV; *m/e*, %): 396 (0.1, M$^+$), 378 (56), 368 (30), 360 (63), 332 (10), 314 (18), 307 (22), 250 (5), 208 (14), 190 (7), 164 (10), 124 (11), 112 (11), 108 (26), 99 (26), 94 (18) and 92 (100). Calc. for $C_{22}H_{36}O_5$ (M-H_2O): 378.2408. Found: 378.2497 ± 0.0113.

11-*Deoxy*-7-*oxo*-*PGE*$_1$ *methyl ester* **21a** *and* 11-*deoxy*-7-*oxo*-15-epi-ent-*PGE*$_1$ *methyl ester* **20a**

(a) *Using 6-methoxycarbonylcaproyl chloride* **13a**. A soln of **10** (82 mg, 1.0 mmol) in ether (4 ml) was added at −60° to the soln of chiral mixed cuprate **12** (1.1 mmol) which was prepared from 3(S)-t-butyldimethylsiloxy-1-iodo-*trans*-1-octene (405 mg, 1.1 mmol) and n-propylethynylcopper (144 mg, 1.1 mmol) with n-Bu_3P (444 mg, 2.2 mmol) in a similar way to the preparation of 7-oxo-PGE$_1$. After stirring at −60° for 15 min and then at −25° for 30 min, **13a** (210 mg, 1.1 mmol) in THF (4 ml) and HMPA (0.5 ml) was added at −25°. The resulting mixture was stirred at 25° for 1 hr. The similar work-up gave 1.11 g of a crude product, which was purified by preparative TLC (hexane–EtOAc, 4:1, R_f 0.26) to afford 181 mg of a diastereomeric mixture of **19a** (0.38 mmol, 38%); IR (film): 1740, 1700, 1640, 1170, 1030, 840, 780 and 670 cm $^{-1}$; NMR (60 MHz, CCl_4): 0.08 (6H, s, $SiCH_3$), 0.93 (12H, t-Bu and CH_3), 1.2–1.8 (16H, CH_2), 2.1–2.6 (7H, CH_2 and CH), 3.60 (4H, OCH_3 and COCHCO), 4.00 (1H, CHOSi), and 5.4–5.7 (2H, olefinic H); MS (70 eV; *m/e*, %): 480 (0.1, M$^+$), 465 (1), 449 (1), 447 (1), 423 (43), 405 (32), 391 (21), 373 (14), 299 (12), 239 (12), 225 (15), 219 (15), 217 (12), 193 (16), 157 (77), 153 (100), 125 (80), 111 (37), 97 (43), 83 (53), 75 (72), 73 (57), 69 (86), 57 (57), 55 (72), 43 (49) and 41 (60). Calc. for $C_{27}H_{52}O_5Si$ (M-^{t}Bu): 423.2569. Found: 423.2460 ± 0.0127.

The ester **19a** (87 mg, 0.181 mmol) obtained above was dissolved in a mixture of AcOH (3 ml), water (1 ml), and THF (1 ml). After standing at room temp. for 80 hr, toluene (50 ml) was added and the mixture was evaporated azeotropically under vacuum to afford 79 mg of a crude product, TLC analysis of which showed two spots stained by ferric chloride (cyclohexane–EtOAc, 3:2, R_f 0.38 and 0.36). The crude product was purified by preparative TLC to give two products corresponding to the above two spots. The less polar (higher R_f) product was **20a** (29 mg, 0.079 mmol, 44%); CD (MeOH): $[\theta]_{241}$ -1.03×10^4, $[\theta]_{288}$ -3.32×10^3, $[\theta]_{319}$ $+1.52 \times 10^3$ (*c*, 1.80×10^{-4} M); IR (film): 3450, 1740, 1715, 1640, 1610, 1225 and 980 cm $^{-1}$; NMR (100 MHz, CCl_4): 0.92 (3H, CH_3), 1.2–1.8 (16H, CH_2), 2.1–2.5 (7H, CH_2 and CH), 3.44 (1H, COCHCO), 3.64 (3H, s, OCH_3), 4.00 (2H, CHOH), and 5.52 (2H, olefinic H); MS (70 eV; *m/e*, %): 366 (1, M$^+$), 348 (35), 335 (4), 318 (8), 278 (19), 214 (25), 209 (71), 192 (87), 161 (30), 157 (70), 147 (31), 135 (40), 125 (88), 121 (56), 109 (52), 99 (40), 97 (50), 79 (38), 69 (88), 55 (100), 43 (82) and 41 (64). Calc. for $C_{21}H_{34}O_4$ (M-H_2O): 348.2302; Found: 348.2258 ± 0.0104. The more polar (lower R_f) product was 11-deoxy-7-oxo-PGE$_1$ methyl ester **21a** (25 mg, 0.068 mmol, 38%);

CD (MeOH): $[\theta]_{241}$ +1.03 × 10⁴, $[\theta]_{228}$ +3.32 × 10⁴, $[\theta]_{215}$ −1.52 × 10⁴ (c, 1.80 × 10⁻⁴M); IR (film): 3450, 1740, 1715, 1640, 1610, 1225 and 980 cm⁻¹; NMR (100 MHz, CCl_4): 0.88 (3H, CH_3), 1.2–1.8 (16H, CH_2), 2.1–2.4 (7H, CH_2 and CH), 3.40 (1H, COCHCO), 3.60 (3H, s, OCH_3), 3.96 (2H, CHOH) and 5.53 (2H, olefinic H); MS (70 eV; *m/e*, %): 366 (1, M⁺), 348 (34), 335 (3), 318 (7), 278 (16), 214 (24), 209 (57), 192 (80), 161 (31), 157 (67), 147 (30), 135 (39), 125 (84), 121 (51), 109 (53), 99 (33), 97 (49), 79 (36), 69 (88), 55 (100), 43 (84) and 41 (66). Calc. for $C_{21}H_{32}O_4$ (M-H_2O): 348.2302. Found: 348.2262 ± 0.0104.

(b) *Using methyl S-phenyl monothiopimelate* **24**. **24** was prepared from **13a** and thiophenol in quantitative yield. The ester **24** (300 mg, 1.1 mmol) in ether (2 ml) was added at −25° to the soln of the β-alkylated organocopper enolate generated from **10** (82 mg, 1.0 mmol) and **12** (1.1 mmol) complexed with n-Bu_3P in the same way as in (a), and the mixture was stirred at −25° for 30 min. After filtration of the formed a ppt insoluble in water and ether, the usual work-up of the filtrate gave 1.24 g of a crude product, which was purified by preparative TLC to yield 214 mg of **19a** (0.45 mmol, 45%). Ester **19a** and each of the two desilylated products of **19a** (**20a** and **21a**) were completely identical (TLC, IR, NMR and MS) with authentic samples obtained above. When hexamethylphosphorous triamide was used as a ligand of the chiral mixed cuprate reagent **12** instead of n-Bu_3P, the product **19a** was also yielded in 46%.

(c) *Using N-(6-methoxycarbonylcaproyl)imidazole* **25**. **25** (250 mg, 1.1 mmol, m.p.: 49–50° recrystallized from ether) in ether (2 ml) was added at −40° to the soln of the β-alkylated organocopper enolate generated from **10** (82 mg, 1.0 mmol) and the chiral **12** (1.1 mmol) complexed with hexamethylphosphorous triamide (360 mg, 2.2 mmol) in a similar way to (a), and the mixture was stirred at −40° for 2 hr. A white ppt deposited at once, and the desired **19a** was detected in the mixture by TLC. Usual work-up gave 367 mg of a crude product, which was purified by preparative TLC to afford 190 mg of **19a** (0.40 mmol, 40%). The ester **19a** and each of the two desilylated products of **19a** (**20a** and **21a**) were identical (TLC, IR, NMR and MS) with authentic samples obtained above.

(d) *Using methyl S-2-pyridyl monothiopimelate* **26**. **26** was prepared from pimelic acid monomethyl ester and 2,2'-dipyridyl disulfide in the presence of triphenylphosphine in 88% yield by the cited method.[7a,7b] The ester **26** (400 mg, 1.5 mmol) was allowed to react with the same organocopper enolate as described in (c) at −40° for 2 hr. After filtering off the formed yellow solid, usual work-up and purification by preparative TLC yielded 120 mg of **19a** (0.25 mmol, 25%). The product **19a** and each of the two desilylated products of **19a** (**20a** and **21a**) were also identical with authentic samples.

11-Deoxy-7-oxo-PGF$_1$, **23** *and 11-deoxy-7-oxo-epi-ent-PGE*$_1$, **22**

To a soln of the less polar **20a** (13 mg, 0.036 mmol) in THF (0.6 mmol) and water (0.2 ml) was added at room temp. 0.1 ml of 1.0 N NaOH. After stirring at room temp. for 3 hr, the mixture was acidified (pH 3) with 5% HCl, extracted with ether (3 × 20 ml). The combined organic layers, after washing with brine and drying ($MgSO_4$), were concentrated to give 12 mg of a crude product, which was purified by preparative TLC (cyclohexane–EtOAc, 2:3, R_f 0.35) to yield 9 mg of **22** (0.026 mmol, 72%); IR (film): 3350, 1735 and 1710 cm⁻¹; NMR (100 MHz, $CDCl_3$): 0.88 (3H, CH_3), 1.2–1.8 (16H, CH_2), 2.0–2.7 (7H, CH_2 and CH), 3.50 (1H, COCHCO), 4.10 (3H, CHOH and COOH), and 5.56 (2H, olefinic H); MS (12 eV; *m/e*, %): 352 (3, M⁺), 335 (23), 334 (100), 316 (7), 299 (6), 281 (20), 263 (16), 252 (10), 238 (13), 234 (15), 209 (31), 200 (12), 193 (16), 192 (93) and 121 (13). Calc. for $C_{20}H_{32}O_4$ (M-H_2O): 334.2146. Found: 334.2117 ± 0.0100.

Similar hydrolysis of the more polar **21a** (19 mg, 0.052 mmol) with NaOH aq yielded 21 mg of a crude product, which was purified by preparative TLC (cyclohexane–EtOAc, 2:3, R_f 0.28) to give 11 mg of **23** (0.031 mmol, 60%); IR (film): 3350, 1735 and 1710 cm⁻¹; NMR (100 MHz, $CDCl_3$): 0.88 (3H, CH_3), 1.2–1.8 (16H, CH_2), 2.1–2.6 (7H, CH_2 and CH), 3.50 (1H, COCHCO), 4.10 (3H, CHOH and COOH) and 5.56 (2H, olefinic H); MS (12 eV; *m/e*, %): 352 (4, M⁺), 335 (26), 334 (100), 316 (8), 298 (8), 281 (16), 263 (18), 252 (11), 238 (15), 234 (15), 226 (11), 225 (12), 209 (37), 200 (15), 193 (16), 192 (94), 182 (12) and 121 (13). Calc. for $C_{20}H_{30}O_4$ (M-H_2O): 334.2146. Found: 334.2103 ± 0.0100.

(dl)-11-Deoxy-7-oxo-PGE, ethyl ester **20b** *and* **21b**

Similarly, reaction of **10** (164 mg, 2.0 mmol) with achiral mixed cuprate reagent (*dl*)-**12** (2.0 mmol), followed by addition of **13b** (1.24 g, 6.0 mmol) gave (*dl*)-**19b** (260 mg, 0.53 mmol, 26%) after preparative TLC purification (ether–hexane, 2:1, R_f 0.43); IR (film): 1730, 1720, 1630, 1170, 1030, 830 and 770 cm⁻¹; NMR (60 MHz, CCl_4): 0.08 (6H, s, $SiCH_3$), 0.93 (12H, *t*-Bu and CH_3), 1.29 (3H, CH_3 of ethyl ester), 1.3–1.8 (16H, CH_2), 2.1–2.6 (7H, CH_2 and CH), 3.60 (1H, COCHCO), 4.16 (3H, CHOSi and CH_2 of ethyl ester), and 5.4–5.7 (2H, olefinic H); MS (70 eV; *m/e*, %): 494 (0.2, M⁺), 479 (2), 461 (1), 449 (3), 437 (96), 419 (100), 391 (34), 373 (28), 299 (26), 219 (24), 217 (22), 171 (28), 155 (32), 125 (64), 121 (31), 75 (94), 73 (79), 69 (36) and 55 (34). Calc. for $C_{24}H_{41}O_4Si$ (M-^{t}Bu): 437.2726. Found: 437.2669 ± 0.0131.

A similar desilylation of (*dl*)-**19b** (29 mg, 0.06 mmol) afforded (*dl*)-**20b** and -**21b** (10 mg, 0.03 mmol, 50%) after TLC purification (ether, R_f 0.38); IR (film): 3450, 1730, 1710, 1635, 1170, 1030 and 975 cm⁻¹; NMR (60 MHz, $CDCl_3$): 0.89 (3H, CH_3), 1.2–1.8 (16H, CH_2) 2.1–2.7 (7H, CH_2 and CH), 1.24 (3H, CH_3 of ethyl ester), 3.4–3.8 (2H, OH and COCHCO), 4.13 (3H, CHOH and CH_2 of ethyl ester), and 5.4–5.7 (2H, olefinic H); MS (11 eV; *m/e*, %): 380 (0.4, M⁺), 362 (100), 316 (12), 298 (17), 291 (38), 253 (18), 228 (20), 209 (31), 192 (84), 171 (46), 125 (18) and 121 (13). Calc. for $C_{22}H_{36}O_4$ (M-H_2O): 362.2456. Found: 362.2381 ± 0.0109.

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