[Chem. Pharm. Bull.
31(8)2607—2615(1983)]

Novel Reactivities on *tert*-Butyldimethylsilyl and *tert*-Butyldiphenylsilyl Ethers; Application to the Synthesis of 11-*epi*-$PGF_{2\alpha}$

YASUHIRO TORISAWA, MASAKATSU SHIBASAKI, and SHIRO IKEGAMI*

Faculty of Pharmaceutical Sciences, Teikyo University, Sagamiko, Kanagawa 199-01, Japan

(Received January 10, 1983)

A facile 1,5-migration of *tert*-butyldimethylsilyl and *tert*-butyldiphenylsilyl groups in the Wittig reaction and under other basic conditions was observed during synthetic studies on prostaglandins. A new method for the cleavage of these two silyl protecting groups to the parent alcohol was developed by the combined use of potassium superoxide and crown ether in dimethyl sulfoxide. Utilizing these new reactivities, an efficient synthesis of 11-*epi*-$PGF_{2\alpha}$ from the well-known Corey lactone was successfully achieved.

Keywords——*tert*-butyldimethylsilyl ether; *tert*-butyldiphenylsilyl ether; Wittig reaction; thermodynamically equilibrated mixture; base-induced migration; cleavage of silyl ether; potassium superoxide; 18-crown-6; 11-*epi*-$PGF_{2\alpha}$

In synthetic studies of prostaglandin and other hydroxy-containing natural products, the selection of a suitable protective group is one of the most important problems.[1] Among many useful protecting groups for the hydroxy functionality, *tert*-butyldimethylsilyl (TBDMS) ether had found most favor because of its wide applicability. In their pioneering report, Corey and Venkateswarlu demonstrated that this protective group is quite stable under Wittig reaction conditions in dimethyl sulfoxide (DMSO), and they successfully applied it to some transformations of prostaglandin intermediates.[2]

During our research,[3] however, we have observed undesirable scrambling of this TBDMS group in some prostaglandin intermediates.[4] Other examples of the scrambling were also reported in molecules which contain a suitably disposed hydroxy functionality, such as nucleosides,[5] carbohydrates,[6] and others.[7]

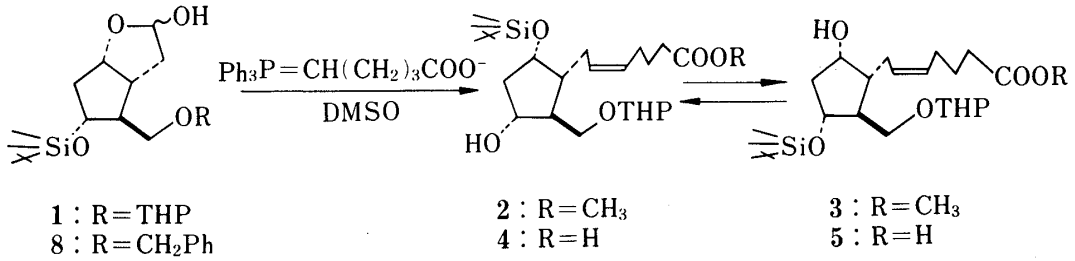
In order to circumvent these limitations as well as the susceptibility to acid of TBDMS ethers, the more stable *tert*-butyldiphenylsilyl (TBDPS) group has recently been introduced by Hanessian.[8] Owing to its superior stability to acid and other conditions, TBDPS ether has been used in some natural product syntheses.[9] Even in the case of TBDPS ether, however, we have found a facile 1,5-migration of this group in the Wittig reaction as well as under other basic conditions. We report herein the full details of these investigations, including the development of a convenient method for the cleavage of these silyl ethers to the parent alcohol. By utilizing these new reactivities, an efficient synthesis of 11-*epi*-$PGF_{2\alpha}$ was achieved.

Migration of the TBDMS Group

Reaction of the lactol (**1**) with the Wittig ylid (5 eq), prepared from (4-carboxybutyl(triphenylphosphonium bromide and sodium methylsulfinylmethanide in dimethyl sulfoxide (DMSO), at 25 °C for 1 h yielded a mixture of two methyl esters after treatment with diazomethane. The more polar product, obtained in 37% yield, was proved surprisingly to be the migrated silyl ether (**2**), whereas the less polar component (33% yield) was identified as the 'normal' silyl ether (**3**). The structures of the products (**2**) and (**3**) were

determined from their spectral data (see "Experimental") and the following transformations.

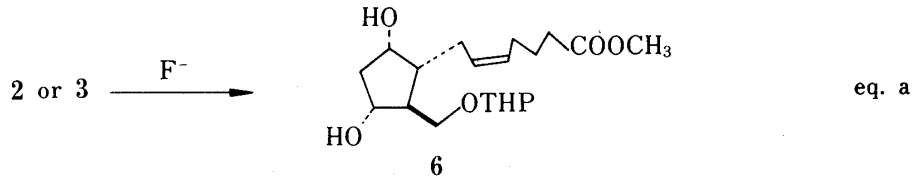
Treatment of **2** and/or **3** with tetra-*n*-butylammonium fluoride (*n*-$Bn_4N^+F^-$) in tetrahydrofuran (THF) gave the same diol (**6**) (eq. a). Reaction of the less polar isomer (**3**) with *N*-bromosuccinimide (NBS, 2 eq) in methylene chloride at room temperature resulted in the formation of the bromo-cyclic ether (**7**) in good yield, while none of the cyclic ethers could be obtained in the case of the more polar isomer (**2**), (eq. b).



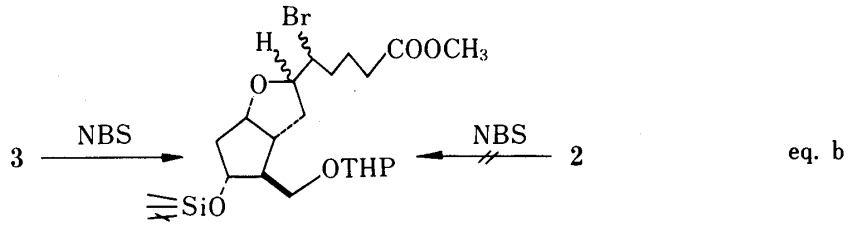
1 : R=THP
8 : R=CH_2Ph

2 : R=CH_3
4 : R=H

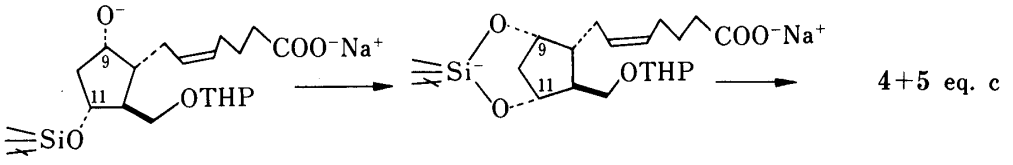
3 : R=CH_3
5 : R=H



6 eq. a



7 eq. b



9 10

Chart 1

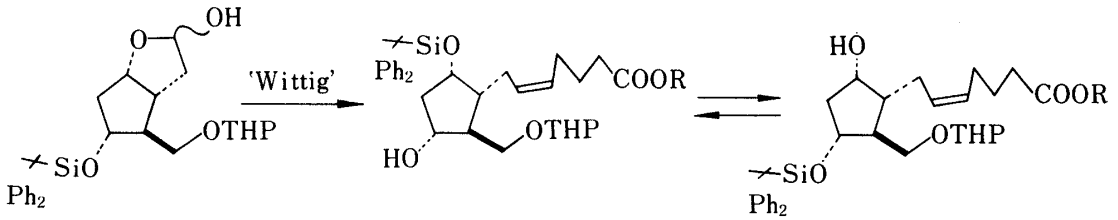
In view of the report by Corey and Venkateswarlu[2] that the TBDMS group in the case of the benzyl derivative (**8**) remained intact under the same Wittig conditions, the migration of the silyl group observed in our Wittig reaction is noteworthy.

In regard to the formation of the migrated product (**2**), a plausible mechanism is shown in eq. c. Reaction of the lactol with the Wittig ylid initially produces the alkoxide anion (**9**), which passes through a 6-membered bicyclic transition state (**10**) involving a pentacovalent silicon atom to afford a thermodynamically equilibrated mixture of **4** and **5**. This mechanism was supported by the results of the following studies. With longer reaction times (2 h, 5 h), the ratio of the Wittig products remained almost unchanged. Furthermore, treatment of the 11α-silyl ether (**5**)[10] with two molar equivalents of sodium hydride (NaH) in DMSO or

N,N-dimethylformamide (DMF) at 25 °C for 2 h afforded a mixture of **4** and **5** in a ratio of 1 : 1. Similarly, the 9α-silyl ether (**4**) gave the same product ratio. In addition, this base-induced migration was found to be strongly dependent on the solvent used; that is, the use of different solvents such as THF and dimethoxyethane (DME) resulted in recovery of the starting silyl ether (NaH or *n*-butyllithium was employed as a base).

Migration of the TBDPS Group

As previously mentioned, TBDPS ethers are known to be more stable than TBDMS ethers under both alkaline and acidic conditions.[8] To our knowledge, no report has appeared concerning the scrambling of the TBDPS group in basic media. Accordingly, we became interested in the migratory behavior of this stable silyl group under the Wittig conditions and other basic conditions. When the lactol (**11**) was subjected to the same Wittig reaction as described above, migration again occurred to produce two methyl esters after treatment with CH_2N_2. In this case the more polar migrated product (**12**) was obtained in 41% yield, while the normal product (**13**) was obtained in 36% yield, nearly the same product ratio as was observed in the case of the TBDMS group.



11 12 : R=CH_3 14 : R=H 13 : R=CH_3 15 : R=H

Chart 2

Furthermore, treatment of the acid (**14**) or (**15**) with two molar equivalents of NaH in DMSO at room temperature caused migration of the TBDPS group, affording a mixture of **14** and **15** in a ratio of *ca.* 1 : 1. Thus, even in the case of more stable TBDPS ethers, scrambling was found to occur under Wittig reaction and other basic conditions.

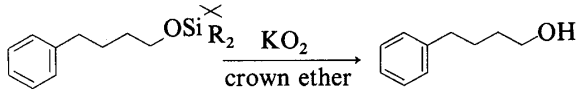
These observations are of value in relation to the selection of a desirable protecting group and reaction conditions in the synthesis of complex molecules such as prostaglandins and macrolides.

Cleavage of TBDMS and TBDPS Ethers by the Use of KO_2

TBDMS and TBDPS ethers are smoothly cleaved by fluoride anion, usually employed in the form of *n*-$Bu_4N^+F^-$.[2,8] From the results obtained above, it was anticipated that a strong oxygen nucleophile would also cleave these silyl ethers cleanly to the parent alcohol in dipolar solvents such as DMSO. Therefore we examined the reaction of potassium superoxide (KO_2),[11] a strong oxygen nucleophile, with these silyl ethers. Typically, simple silyl ethers (**16**) or (**17**) were added to a stirred solution of KO_2 and 18-crown-6 in DMSO or other solvents at room temperature. Stirring was continued until the starting material was completely consumed. These results are summarized in Table I, showing the effectiveness of this method. When DMSO was replaced by some other non polar solvent such as benzene, very slow reaction was observed and a large excess of reagents was required.

Thus, the use of KO_2 in DMSO in the presence of crown ether was proved to be a quite effective method to cleave such silyl ethers. Compared with conventional conditions (F^-), we believe, these new conditions are of general utility for the deprotection of TBDMS and TBDPS ethers, because the reagents are easily available and the reaction is simple and fast.

TABLE I. Reaction of Silyl Ethers with KO_2 and 18-Crown-6 at 25°C



16: R=Me, **17**: R=Ph

Entry	Substrate	Solvent	KO_2 : 18-Crown-6 (eq)	Reaction time	Yield[a] (%)
1	**16**	DMSO	3:3	10 min	85
2	**16**	DMSO	3:1	30 min	85
3	**16**	DMSO	3:0.1	1 h	85
4	**16**	DME	3:3	15 h	85
5	**17**	DMSO	3:1	1 h	83

a) Isolated yield.

A Total Synthesis of 11-*epi*-$PGF_{2\alpha}$

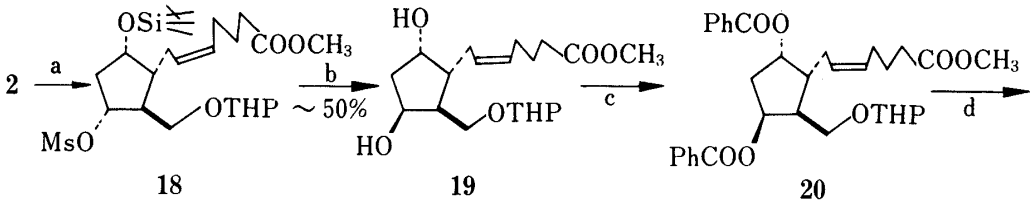
The migrated silyl ether (**2**) can be obtained rather efficiently by utilizing two types of migration conditions (Wittig reaction and NaH treatment), and is an attractive synthetic intermediate for the manipulation of the PG 11-position. So, as an application of the new reactivities of silyl ethers described above to PG synthesis, **2** was further converted to (+)-11-*epi*-$PGF_{2\alpha}$ (**27**), which is a biologically interesting and hitherto rather inaccessible substance.[12)]

First, for the inversion of the 11α-alcohol, optically pure alcohol (**2**) was converted to the corresponding mesylate (**18**) by the standard method. When **18** was reacted with excess KO_2 (15 eq) and 18-crown-6 (3 eq) in DMSO–DME (2 : 1) at 25 °C for 7 h, inversion of the alcohol with concominant deprotection of the TBDMS group was observed to afford the diol (**19**) in *ca.* 50% yield after treatment with ethereal diazomethane. By means of the same reaction sequence, the TBDPS ether (**12**) was similarly converted to the diol (**19**).

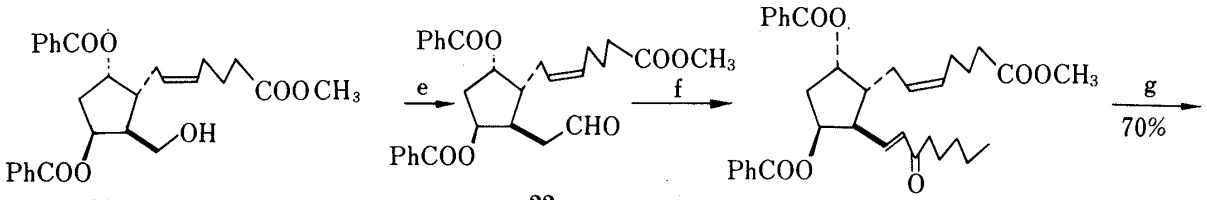
Thus, our new cleavage method was effective for accomplishing two transformations (inversion and deprotection) in a single step. The diol (**19**) was further converted to the benzoate (**20**) in the usual manner, followed by deprotection of the tetrahydropyranyl ether to give the alcohol (**21**) in 52% yield from the diol (**19**).

Elongation of the lower chain was accomplished in a conventional way. The alcohol (**21**) was oxidized with excess Collins reagent (10 eq) in methylene chloride at 0 °C, or more conveniently with sulfur trioxide pyridine complex (5 eq) in DMSO at room temperature, to yield the aldehyde (**22**). The crude aldehyde was immediately treated with the sodium salt of dimethyl (2-oxoheptyl)phosphonate in DME at room temperature to give the desired enone (**23**) in 61% yield from the alcohol (**21**). This enone (**23**) was then carefully reduced with zinc borohydride in DME at 0—25 °C to afford the diasteromeric alcohols (**24**) and (**25**) in a ratio of 5 : 2 in *ca.* 75% yield. Fortunately, the major alcohol was proved to have 15α-configuration from the results of further transformation. The alcohol with natural configuration (**24**) was treated with potassium carbonate in dry methanol to afford 11-*epi*-$PGF_{2\alpha}$ methyl ester (**26**) in 72% yield. This material was spectroscopically and chromatographically identical with an authentic sample prepared from 11-*epi*-PGE_2 methyl ester.[13)]

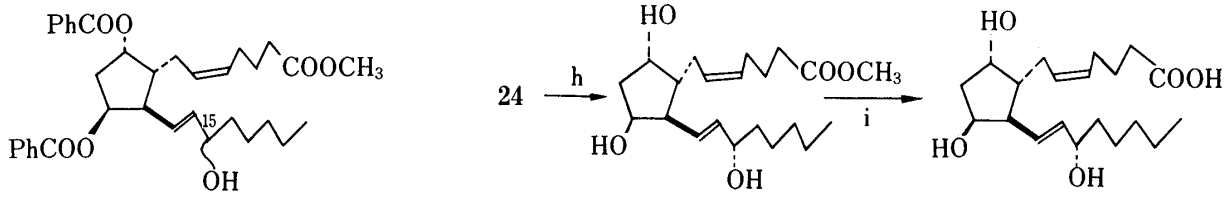
Finally the ester (**26**) was hydrolyzed in a usual way to give (+)-11-*epi*-$PGF_{2\alpha}$ (**27**) [mp 120—122 °C, recrystallized from ethyl acetate–*n*-hexane, lit. 117—119 °C,[12)] $[\alpha]_D$ +83.3° (*c*= 0.24, MeOH)]. Thus, we have succeeded in developing an efficient synthesis of 11-*epi*-$PGF_{2\alpha}$ by utilizing the new reactivities of TBDMS and TBDPS ethers.



18 19 20



21, 52% from 19 22 23, 61% from 21



24 : 15α-OH
25 : 15β-OH

26 27

a: MsCl, Et_3N, CH_2Cl_2; −25°C
b: KO_2, 18-crown-6, DMSO–DME, r.t.
c: PhCOCl, Pyridine, CH_2Cl_2
d: AcOH–H_2O–THF (3:1:1), r.t.
e: $CrO_3 \cdot 2py$, CH_2Cl_2
f: $(MeO)_2PO-\overset{-}{C}H-COC_5H_{11}$, $^{-}Na^{+}$, DME
g: $Zn(BH_4)_2$, DME, r.t.
h: K_2CO_3, MeOH
i: KOH, MeOH, H_2O, r.t.

Chart 3

Experimental

Melting points were measured on a Yanagimoto micro melting point apparatus and are corrected. Infrared (IR) spectra were measured on a Hitachi 215 grating infrared spectrometer. ^1H nuclear magnetic resonance (^1H-NMR) spectra were recorded with a Varian EM360A NMR spectrometer or a Varian XL-100-12 NMR spectrometer in $CDCl_3$ solution with tetramethylsilane as an internal standard. Low-resolution mass spectra were obtained with a JEOL JMS-D300 mass spectrometer and high-resolution mass spectra with a JEOL JMS-OISG-2 mass spectrometer. Thin-layer chromatography (TLC) was carried out on a silica gel plate (Merk Art 5715) and all *Rf* values refer to a silica gel plate. In general, reactions were carried out under an argon atmosphere unless otherwise mentioned.

Methyl (*Z*)-[1*R*,2*R*,3*R*,5*S*)-5-*tert*-Butyldimethylsilyloxy-2-[(tetrahydro-2-pyranyloxy)methyl]-3-hydroxycyclopentyl]-5-heptenoate (2) and Methyl (*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3-*tert*-Butyldimethylsilyloxy-2-[(tetrahydro-2-pyranyloxy)methyl]-5-hydroxycyclopentyl]-5-heptenoate (3)——The lactol (**1**) was prepared from the corresponding lactone[14] by reduction with DIBAL (4 eq) in toluene at −78 °C for 2 h. Nearly pure (**1**) (IR ν_{max} (film): 3400, 2925, 1460, 1250, 830 cm^{-1}) thus obtained was directly subjected to the Wittig reaction.

A 2 M solution of sodium methylsulfinylmethanide (dimsyl sodium) in DMSO was prepared from NaH (20 mmol) and DMSO (10 ml) under stirring at 75±2 °C for *ca.* 1 h. A suitable amount of this solution (2.1 ml, 4.2 mmol) was added at room temperature to a stirred solution of (4-carboxybutyl)triphenylphosphonium bromide (935 mg, 2.1 mmol) in dry DMSO (2 ml) to yield a deep red ylid. A solution of the above lactol (**1**) (157 mg, 0.42 mmol) in DMSO (1.5 ml) was then added to this ylid solution at room temperature and the whole was kept stirring at room temperature for 1 h. This mixture was then diluted with ether (20 ml) and AcOH (0.25 ml), followed by the careful addition of brine (5 ml). The aqueous layer was further extracted with ether (50 ml × 2), and the combined ether layer was washed with brine (5 ml × 2) and dried over $MgSO_4$. The ether was evaporated off to afford

crude acids, which were immediately treated with excess CH_2N_2 in ether at 0 °C. The crude esters thus obtained were purified by silica gel column chromatography (ether–petr. ether, 2 : 1). The silyl ether (**3**) (98 mg, 32.6%) was obtained from the first eluate as a pale yellow oil: *Rf* 0.51 (ether–petr. ether, 2 : 1); IR ν_{max} (film): 3525, 2925, 2850, 1740, 840 cm^{-1}; ^{1}H-NMR δ(ppm): 5.40 (m, 2H), 4.54 (m, 1H), 3.62 (s, 3H), 0.80 (s, 9H); MS *m/e*: 470 (M^+), 439, 421, 413; *m/e* 470.3058 (calcd for $C_{25}H_{46}O_6Si$, 470.3063, parent peak). The second fraction gave the migrated silyl ether (**2**) (116 mg, 38.6%) as a pale yellow oil: *Rf* (0.24, same system as above), IR ν_{max} (film): 3450, 2925, 2850, 1740, 840 cm^{-1}; δ (ppm), 5.37 (m, 2H), 4.66 (m, 1H), 3.65 (s, 3H), 0.92 (s, 9H); MS *m/e*: 470 (M^+), 439, 421, 413; *m/e*, 470.3058 (calcd for $C_{25}H_{46}O_6Si$, 470.3063, parent peak).

Methyl (*Z*)-7-[(1*R*, 2*R*, 3*R*, 5*S*)-2-[(Tetrahydro-2-pyranyloxy)methyl]-3,5-dihydroxycyclopentyl]-5-heptenoate (6)——A solution of excess tetra-*n*-butylammonium fluride (400 mg, 1.5 mmol) in THF (2 ml) was added to a stirred solution of the silyl ether (**2**) (200 mg, 0.425 mmol) in dry THF (3 ml) at room temperature. After the reaction was complete, the mixture was diluted with ether (50 ml) and saturated NH_4Cl aq. (5 ml). The ether layer was further washed with brine (5 ml × 3) and dried over $MgSO_4$. Evaporation of the ether gave a crude residue (160 mg), which was purified by preparative TLC (silica gel, ether–petr. ether, 4 : 1) to afford a yellow oil (**6**) (116 mg, 76.8%): *Rf* 0.14 (ether–petr. ether, 4 : 1); IR ν_{max} (film): 3425, 2950, 1735, 1030 cm^{-1}; ^{1}H-NMR δ (ppm): 5.40 (m, 2H), 4.55 (m, 1H), 4.15 (m, 2H), 3.65 (s, 3H); MS *m/e*: 356 (M^+), 318, 307; *m/e*, 356.2183 (calcd for $C_{19}H_{32}O_6$, 356.2190 parent peak).

When the silyl ether (**3**) was subjected to the same reaction, the same diol (**6**) was obtained in 75% yield.

Methyl (*R)-5-Bromo-5-[(1*S*, 3*R**, 5*R*, 7*R*)-7-*tert*-butyldimethylsilyloxy-6-[(tetrahydro-2-pyranyloxy)methyl]-2-oxabicyclo[3,3,0]octan-3-yl]pentanoate (7)**——NBS (40 mg, 0.22 mmol) was added to a stirred solution of the silyl ether (**3**) (52 mg, 0.11 mmol) in dry CH_2Cl_2 (2 ml) at room temperature. The mixture was kept stirring for 1 h under these conditions, while TLC (ether–petr. ether, 1 : 1) showed the formation of the less polar product. The mixture was then diluted with ether and saturated Na_2SO_3 aq, followed by extraction with ether. The ether layer was washed with H_2O and saturated NaCl aq, the dried over $MgSO_4$. Evaporation of the ether gave a crude product, which was further purified by preparative TLC (silica, ether–petr. ether, 1 : 1) to afford the bromocyclic ether (**7**) (40 mg, 66.6%) as a pale yellow oil; *Rf* 0.39 (silica, ether–petr. ether, 1 : 1); IR ν_{max} (film): 2925, 2850, 1730 cm^{-1}; ^{1}H-NMR δ (ppm): 4.50 (s, 1H), 3.55 (s, 3H), 0.85 (s, 9H); MS *m/e*: 493, 491 ($M-C_4H_9$), 435, 433, 409, 407; *m/e*, 491.1446 (calcd for $C_{21}H_{36}BrO_6Si$, 491.1454, parent peak-C_4H_9). When the silyl ether (**2**) was subjected to the same reaction, no less-polar product was detected on TLC, and after work-up, **2** was recovered in high yield.[15]

Base-Induced Migration of (4) or (5)——A DMSO (1.5 ml) solution of the carboxylic acid (**5**)[16] (200 mg, 0.439 mmol) was added to a stirred suspension of NaH (2 mg, 1.08 mmol) in dry DMSO (2 ml) at room temperature. The reaction mixture was kept stirring at room temperature for 2.5 h. The reaction was then quenched with AcOH (0.2 ml), diluted with AcOEt (50 ml), and washed with brine (5 ml × 2). The organic layer was dried over $MgSO_4$ and concentrated to afford a dark yellow oil, which was treated with CH_2N_2 in ether at 0 °C. The crude ester (159 mg) thus obtained was further purified by column chromatography (silica, ether–petr. ether, 2 : 1) to give **2** (60 mg, 30%) and **3** (62 mg, 30%). When DMF was used as a solvent in place of DMSO, nearly the same result was obtained. The silyl ether (**4**)[16] was also subjected to these conditions, providing the same isomeric mixture (**2** and **3** in yields of 31% and 33% respectively).

Methyl (*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-5-*tert*-Butyldiphenylsilyloxy-2-[(tetrahydro-2-pyranyloxy)methyl]-3-hydroxycyclopentyl]-5-heptenoate (12) and Methyl (*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3-*tert*-Butyldiphenylsilyloxy-2-[(tetrahydro-2-pyranyloxy)methyl]-5-hydroxycyclopentyl]-5-heptenoate (13)——The lactol (**11**) was prepared from the corresponding lactone[14] by reduction with DIBAH in toluene at −78 °C for 1.5 h. Nearly pure (**11**) (IR ν_{max} film: 3400, 3050, 2925, 1105, 1020, 700 cm^{-1}) thus obtained was directly subjected to the Wittig reaction.

A 2 M solution of sodium methylsulfinylmethanide in DMSO (6 ml, 12 mmol) was added at room temperature to a stirred solution of (4-carboxylbutyl)triphenylphosphonium bromide (2.70 g, 6 mmol) in dry DMSO (4 ml) to yield a red ylid. To this was added at room temperature a solution of the lactol (**11**) (840 mg, 1.70 mmol) in DMSO (5 ml), and the whole was kept stirring under these conditions for 1 h. TLC (ether–petr. ether, 2 : 1) showed almost no starting material and two polar products. The mixture was then diluted with ether (30 ml) and AcOH (0.7 ml), followed by the careful addition of brine (10 ml). The aqueous layer was further extracted with ether (100 ml × 2), and the combined ether layer was washed with brine (10 ml × 2) then dried over $MgSO_4$. The ether was removed to afford crude acids, which were immediately treated with excess CH_2N_2 in ether at 0 °C. The crude esters thus obtained were purified by silica gel column chromatography (ether–petr. ether, 2 : 1).

The first eluate gave the silyl ether (**13**) (360 mg, 35.6%) as a yellow oil; *Rf*, 0.64 (ether–petr. ether, 4 : 1); IR ν_{max} (film): 3530, 3060, 2975, 2850, 1740, 1590 cm^{-1}; ^{1}H-NMR δ (ppm): 7.85—7.35 (m, 10H), 5.45 (m, 2H), 4.30 (m, 2H), 3.67 (s, 3H), 1.10 (s, 9H) MS *m/e*: 594; *m/e*, 594.3396 (calcd for $C_{35}H_{50}O_6Si$, 594.3376, parent peak). The migrated silyl ether (**12**) (410 mg, 40.6%) was obtained from the second fraction as a yellow oil; *Rf* 0.40 (ether–petr. ether, 4 : 1); IR ν_{max} (film): 3475, 3060, 2925, 2850, 1740, 1590 cm^{-1}; ^{1}H-NMR δ (ppm): 7.85—7.20 (m, 10H), 5.25 (m, 2H), 4.55 (m, 1H), 3.65 (s, 3H), 1.10 (s, 9H); MS *m/e*: 594; *m/e*, 594.3396 (calcd for $C_{35}H_{50}O_6Si$, 594.3376, parent peak).

Base-Induced Migration of 14 or 15——A DMSO solution (4 ml) of the carboxylic acid (**15**)[16] (580 mg, 1.10 mmol) was added to a stirred suspension of NaH (60 mg, 2.5 mmol) in dry DMSO (5 ml) at room temperature. The resulting mixture was kept stirring at room temperature for 3 h then quenched with AcOH (0.3 ml), diluted with

AcOEt (—70 ml) and washed with brine (5 ml × 2). The organic layer was dried over $MgSO_4$ and concentrated to afford a dark yellow oil, which was then treated with CH_2N_2 in ether at 0 °C.

The crude ester thus obtained was further purified by column chromatography (silica, ether–petr. ether, 1 : 1) to afford **12** (175 mg, 30%) and **13** (160 mg, 27%).

The isomeric carboxylic acid (**14**)[16] was also subjected to these conditions, affording the same mixture (**12** and **13** in yields of 29% and 25% respectively).

Cleavage of TBDMS and TBDPS Ethers by KO_2 (Typical Procedure)——A solution of the silyl ether (**16**)[17] (500 mg, 1.89 mmol) or (**17**)[17] in DMSO (2 ml) was added at room temperature to a stirred solution of KO_2 (400 mg, 5.6 mmol) and 18-crown-6 (500 mg, 1.9 mmol) in DMSO (3 ml). The resulting orange mixture was kept stirring for 1 h under these conditions. After a TLC check, the reaction was quenched by the addition of AcOH (0.3 ml). Then AcOEt (50 ml) and brine (5 ml) were added and the organic layer was washed further with brine then dried over $MgSO_4$. The solvent was removed to give a crude product, which was purified by column chromatography (silica, ether–petr. ether, 1 : 1) to give 4-phenylbutanol (235 mg, 82.8%) as a colorless oil.

Methyl (*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-5-*tert*-Butyldimethylsilyloxy-2-[(tetrahydro-2-pyranyloxy)methyl]-3-methylsulfonyloxycyclopentyl]-5-heptenoate (18)——Triethylamine (133 μl, 0.96 mmol) and methanesulfonyl chloride (74 μl, 0.96 mmol) were added to a stirred solution of the alcohol (**2**) at −25 °C. The resulting mixture was stirred at this temperature for 0.5 h, when TLC (ether–petr. ether, 2 : 1) showed no starting material. The mixture was diluted with ether (*ca.* 30 ml) and H_2O (5 ml), and the ether layer was further washed with cold 5% HCl (5 ml), saturated $NaHCO_3$ aq and brine, then dried over $MgSO_4$. The ether was evaporated off to give the crude mesylate (**18**) (195 mg, quantitative) as a yellow oil; IR ν_{max} (film): 1735, 1360, 1170 cm^{-1} *Rf* 0.36, (ether–petr. ether, 2 : 1); ^{1}H-NMR δ (ppm): 5.40 (m, 2H), 5.05 (m, 1H), 4.55 (m, 1H), 4.15 (m, 1H), 3.60 (s, 3H), 2.95 (s, 3H), 0.85 (s, 9H).

This mesylate was directly subjected to the next reaction without purification.

Methyl (*Z*)-7-[(1*R*,2*R*,3*S*,5*S*)-2-[(Tetrahydro-2-pyranyloxy)methyl]-3,5-dihydroxycyclopentyl]-5-heptenoate (19)——A solution of the crude mesylate (**18**) (160 mg, 0.29 mmol) in DME (2 ml) was added to a yellow suspension of KO_2 (350 mg, 4.91 mmol) and 18-crown-6 (400 mg, 1.52 mmol) in DMSO (2 ml) at room temperature. The resulting orange solution was stirred under these conditions for 7 h, then the mixture was quenched by the addition of AcOH (1 ml, pH 4), and concentrated *in vacuo*. The crude residue thus obtained was diluted with a large amount of AcOEt (70 ml), and the AcOEt layer was washed with small portions of brine (4 ml × 3). The collected aqueous layer was further extracted with AcOEt (20 ml × 2). The combined AcOEt layer was dried over $MgSO_4$, followed by evaporation to give a crude yellow oil (containing a small amount of DMSO). This oil was subsequently esterified by the use of ethereal diazomethane at 0 °C. The crude ester thus obtained was purified by silica gel preparative TLC (ether–MeOH, 95 : 5) to yield the pure diol (**19**) (50 mg, 48%) *Rf* 0.34 (ether–MeOH, 95 : 5), or 0.27 (isopropyl ether–isopropyl alcohol, 10 : 1, in this system the *Rf* value for **6** was 0.32); IR ν_{max} (film): 3450, 2930, 1740, 1030 cm^{-1}; ^{1}H-NMR δ (ppm): 5.40 (m, 2H), 4.50 (m, 1H), 3.67 (s, 3H); MS *m/e*: 356 (M^+), 338, 307; *m/e*, 356.2182 (calcd for $C_{19}H_{32}O_6$, 356.2190, parent peak).

Methyl (*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-Dibenzoyloxy-2-[(tetrahydro-2-pyranyloxy)methyl]cyclopentyl]-5-heptenoate (20)——Pyridine (0.4 ml, 4.94 mmol) and benzoyl chloride (0.05 ml, 0.43 mmol, 3.5 eq) were added to a stirred solution of the diol (**19**) (45 mg, 0.12 mmol) in CH_2Cl_2 (0.5 ml) under ice-cooling. The mixture was kept stirring at room temperature for 2 h, when TLC (ether–petr. ether, 2 : 1) showed no starting material. Then the reaction was quenched by adding a few drops of H_2O with stirring. The mixture was diluted with ether (30 ml), and ether layer was washed with saturated $NaHCO_3$ aq, saturated $CuSO_4$ aq, and brine, then dried over $MgSO_4$. Filtration and evaporation gave the crude bisbenzoate (**20**) (100 mg, quant) as a yellow oil, which was directly subjected to the next step. *Rf* 0.57 (ether–petr. ether, 2 : 1).

Methyl (*Z*)-7-[(1*R*,2*R*,3*S*,5*S*)-3,5-Dibenzoyloxy-2-hydroxymethylcyclopentyl]-5-heptenoate (21)——The crude benzoate obtained above (100 mg) was dissolved in AcOH–H_2O–THF (3 : 1 : 1, 2 ml) at room temperature and this mixture was warmed at 45 °C for 12 h. The solvent was removed *in vacuo* and the residue was diluted with ether (30 ml). The ether layer was washed with saturated $NaHCO_3$ aq and brine, then dried over $MgSO_4$. Evaporation of the ether gave a yellow oil, which was further purified by preparative TLC (silica gel, ether–petr. ether, 2 : 1) to yield pure (**21**) (31 mg, 51.7% from **19**), *Rf* 0.25 (ether–petr. ether, 2 : 1); IR ν_{max} (film): 3350, 3075, 3000, 2950, 1720, 1600, 1580, 1270, 1110, 710 cm^{-1}; ^{1}H-NMR δ (ppm): 8.15—7.20 (m, 10H), 5.65 (m, 2H), 5.35 (m, 2H), 3.70 (s, 3H); MS *m/e*: 480 (M^+), 462, 449, 358, 340; *m/e*, 480.2169 (calcd for $C_{28}H_{32}O_7$, 480.2139, parent peak).

15-Deoxy-15-oxo-11-*epi*-PGF$_{2\alpha}$ Methyl Ester 9,11-Dibenzoate (23)——A solution of the alcohol (**21**) (47 mg, 0.09 mmol) in CH_2Cl_2 (0.2 ml) was added to a stirred suspension of Collins reagent (CrO_3. 2pyridine, 200 mg, 0.774 mmol) and celite-545 (200 mg) in CH_2Cl_2 (5 ml) under ice-cooling. The mixture was kept stirring for 1 h under these conditions. The reaction was then quenched with $NaHSO_4$. H_2O (600 mg) under cooling and the mixture was diluted with CH_2Cl_2 (20 ml) under stirring. The dark mixture was filtered through a pad of $MgSO_4$ and the residue was washed well with CH_2Cl_2. This CH_2Cl_2 layer was carefully evaporated (below 10 °C) to give a pale red oil (**22**). The unstable aldehyde thus obtained was immediately added to a fleecy suspension of phosphonate [prepared from NaH (0.2 mmol) and dimethyl 2-oxoheptylphosphonate (50 mg, 0.22 mmol) in DME (2 ml)] at room temperature. Stirring was continued for 2 h at room temperature, followed by quenching with AcOH (12 μl) and the mixture was

worked up as usual. Purification by preparative TLC (silica, ether–petr. ether, 1 : 1) gave the pure enone (**23**) as a colorless oil (33 mg, 59% from **18**) *Rf* 0.50 (ether–petr. ether, 1 : 1 × 2); IR ν_{max} (film): 2925, 1730, 1660, 1450, 1265, 1105, 710 cm^{-1}; ^{1}H-NMR δ (ppm): 8.20—7.20 (m, 10H), 6.85 (dd, J = 16, 9 Hz, 7H), 6.25 (d, J = 16 Hz, 1H) 5.67 (m, 2H), 5.40 (m, 2H), 3.65 (s, 3H), 0.85 (m, 3H); MS *m/e*: 574 (M^+), 543, 518, 503; *m/e*, 575.3003 (calcd for $C_{35}H_{42}O_7$, 574.2919, parent peak).

11-*epi*-PGF$_{2\alpha}$-Methyl Ester 9,11-Dibenzoate (24)——An ethereal solution of zinc borohydride (excess) was added under ice-cooling to a stirred solution of the none (**23**) (50 mg, 0.087 mmol) in DME (5 ml) and the resulting mixture was kept stirring under these conditions (finally at room temperature) overnight. Then the reaction was quenched with 10% HCl (pH 2—3) and most of the solvent was removed under reduced pressure. The residue was diluted with ether (70 ml), washed with saturated $NaHCO_3$ aq, and brine, then dried over $MgSO_4$. The crude product obtained after evaporation of the ether was purified by preparative TLC (silica, AcOEt–*n*-hexane, 2 : 1) to afford the 15α-alcohol (**24**) as a major product (26 mg, 51.8%); IR ν_{max}: 4370, 2925, 2850, 1735, 1710, 1600, 1450, 1265, 1105, 710 cm^{-1}; ^{1}H-NMR δ (ppm): 8.20—7.20 (m, 10H), 5.65 (m, 4H), 5.40 (m, 2H), 4.07 (m, 1H), 3.60 (s, 3H), 0.85 (m, 3H); MS *m/e*: 558, 545, 505, 454, 437; *m/e*, 558.2984 (calcd for $C_{25}H_{42}O_6$, 558.2970, M–H_2O).

11-*epi*-PGF$_{2\alpha}$ Methyl Ester (26)——Excess K_2CO_3 powder was added to a stirred solution of the benzoate (**24**) (10 mg, 0.017 mmol) in dry MeOH (1 ml) at room temperature. The mixture was diluted with ether (10 ml) and adjusted with 10% HCl (1 ml) to pH 3—4. AcOEt (—50 ml) was further added and the organic layer was washed with saturated $NaHCO_3$ aq and brine, then dried over $MgSO_4$. The solvent was removed to afford a crude product, which was purified by preparative TLC (silica, CH_2CL_2–MeOH, 9 : 1 × 2) to afford pure 11-*epi*-PGF$_{2\alpha}$ methyl ester (**26**) (4.6 mg, 73%) *Rf* 0.36 (CH_2Cl_2–MeOH, 9 : 1 × 2); IR ν_{max} ($CHCl_3$): 3620, 3470, 3000, 2970, 2870, 1730, 1470, 1205 cm^{-1}; ^{1}H-NMR δ (ppm): 5.67 (m, 2H), 5.45 (m, 2H) 4.35 (m, 2H), 3.60 (s, 3H), 0.87 (bs, 3H); MS *m/e*: 368 (M^+), 350, 332, 301, 278; *m/e*, 350.2427 (calcd for $C_{21}H_{34}O_4$, 350.2488 P–H_2O).

This material was chromatographically and spectroscopically identical with an authentic sample prepared from 11-*epi*-PGE_2 methyl ester.[13]

11-*epi*-PGF$_{2\alpha}$ (27)——KOH pellets (excess) were added at room temperature to a stirred solution of 11-*epi*-PGF$_{2\alpha}$ methyl ester (**26**) (9 mg, 0.024 mmol) in MeOH–H_2O (3 : 1, 2 ml). The resulting mixture was kept stirring until TLC showed no starting material. Then most of the solvent was removed and the resulting mixture was diluted with AcOEt (20 ml), followed by acidification with 1 N HCl (pH 2—3). The organic layer was separated, washed with brine (2 ml), and dried over $MgSO_4$. The solvent was removed to give a crude product (pale yellow oil), which was purified on a silica gel short column (ether–MeOH, 95 : 5). Pure (**27**), initially obtained as a colorless oil (6 mg, 70%), solidified on standing, and was further purified by recrystallization from AcOEt–*n*-hexane. Thus, crystalline (**27**) was obtained; mp 120—122 °C; IR ν_{max} (film): 3350, 2925, 2850, 1700, 1425 cm^{-1}; ^{1}H-NMR δ (ppm): 5.80—5.25 (m, 4H), 4.40—3.80 (m, 4H), 0.90 (bs, 3H); MS *m/e*: 336, 318, 300, 274, 264; *m/e*, 336.2275 (calcd for $C_{20}H_{32}O_4$, 336.2292, P–H_2O); *Anal.* Calcd for $C_{20}H_{34}O_5$: C, 67.77; H, 9.65. Found: C, 67.76; H, 9.57 $[\alpha]_D$ +83.3° (c = 0.24, MeOH).

Acknowledgements We thank Mr. Hiroshi Sakata, Miss Keiko Takahashi and Mr. Tsuneyuki Sakai for their technical assistance. We also thank Mrs. Kazuko Uchida for mass spectrometric measurements. Financial support of this research by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture is gratefully acknowledged.

References and Notes

1) Reviews; T. W. Greene, "Protective Groups in Organic Synthesis," John Wiley & Sons, Inc., New York, 1981, pp. 10—86.
2) E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, **94**, 6160 (1972).
3) *a*) M. Shibasaki and S. Ikegami, *Tetrahedron Lett.*, **1978**, 559; *b*) J. Ueda, T. Yanagisawa, M. Shibasaki, and S. Ikegami, *ibid.*, **1978**, 2511; *c*) M. Shibasaki, J. Ueda, and S. Ikegami, *ibid.*, **1979**, 433; *d*) M. Shibasaki, *Yakugaku Zassi*, **101**, 1073 (1981).
4) Y. Torisawa, M. Shibasaki, and S. Ikegami, *Tetrahedron Lett.*, **1979**, 1865. See also D. P. Reynolds, R. F. Newton, and S. M. Roberts, *J. Chem. Soc., Chem. Commun.*, **1979**, 1150.
5) S. S. Jones and C. B. Reese, *J. Chem. Soc., Perkin Trans. 1*, **1979**, 2762 and references cited therein.
6) F. Franke and R. D. Guthrie, *Aust. J. Chem.*, **31**, 1285 (1978).
7) M. Shibasaki, A. Nishida, and S. Ikegami, *Tetrahedron Lett.*, **1980**, 3061.
8) S. Hanessian and P. Lavallee, *Can. J. Chem.*, **53**, 2975 (1975).
9) See for example, K. C. Nicolaou, D. A. Claremon, and W. E. Bernette, *J. Am. Chem. Soc.*, **102**, 6611 (1980).
10) In this report, positions of substituents are indicated according to PG numbering.
11) *a*) R. A. Johnson and E. G. Nidy, *J. Org. Chem.*, **40**, 1680 (1975); *b*) J. San Filippo, Jr., C. I. Chern, and J. S. Valentine, *ibid.*, **40**, 1678 (1975); *c*) E. J. Corey, K. C. Nicolaou, M. Shibasaki, Y. Machida, and C. S. Shiner, *Tetrahedron Lett.*, **1975**, 3183; *d*) E. J. Corey, K. C. Nicolaou, and M. Shibasaki, *J. Chem. Soc., Chem. Commun.*,

1975, 658.
12) *a*) D. M. Floyd, G. A. Crosby, and N. M. Weinshenker, *Tetrahedron Lett.*, **1972**, 3269; *b*) E. J. Corey, K. C. Nicolaou, and M. Shibasaki, *J. Chem. Soc., Chem. Commun.*, **1975**, 658.
13) W. P. Schneider, G. L. Bundy, F. H. Lincoln, E. G. Daniels, and J. E. Pike, *J. Am. Chem. Soc.*, **99**, 1222 (1977).
14) This lactone was prepared from commercially available, optically active (1*S*, 5*R*, 6*R*, 7*R*)-7-benzoyloxy-6-hydroxymethyl-2-oxa-bicyclo[3.3.0]octane-3-one in the usual manner.
15) J. C. Sih and D. R. Graber, *J. Org. Chem.*, **47**, 4919 (1982).
16) These carboxylic acids were prepared from the corresponding methyl esters in the usual manner (KOH–MeOH–H_2O).
17) These silyl ethers were prepared from commercially available 4-phenylbutanol by the standard method (TBDMS chloride or TBDPS chloride–imidazole–DMF).