# REGIOSELECTIVE PROTECTION OF 11-HYDROXY GROUP AND INVERSION OF CONFIGURATION AT C-15 IN *m*-PHENYLENE $PGI_2$ DERIVATIVES

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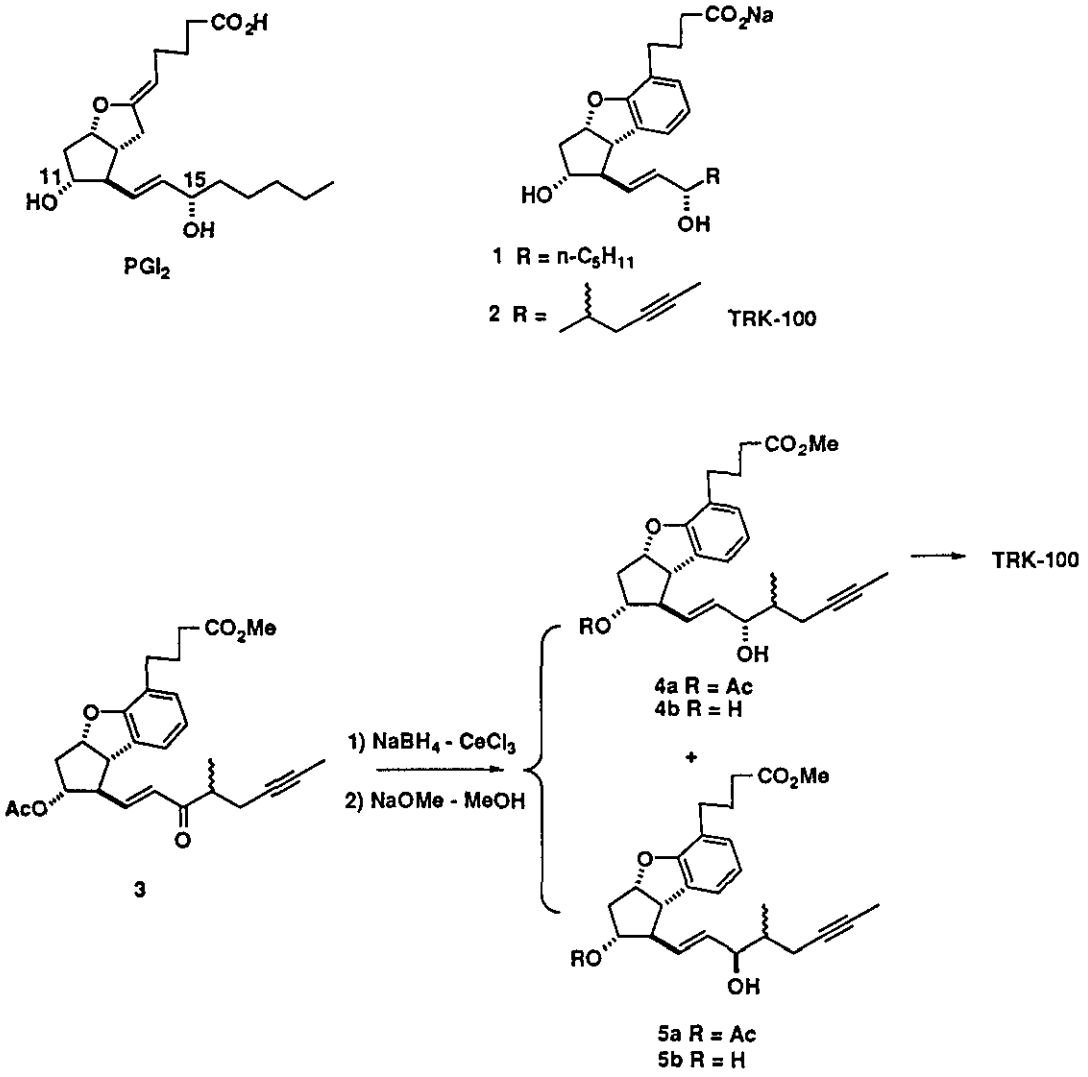
**Abstract**-The 15 $\beta$-hydroxy isomer of a *m*-phenylene $PGI_2$ derivative was converted to its 15 $\alpha$-hydroxy isomer by regioselective protection of 11-hydroxyl group by acylation using 3,5-dinitrobenzoyl chloride followed by inversion of configuration at C-15. A possibility of the presence of $\pi$-$\pi$ interaction between the benzene ring (electron donor) in *m*-phenylene $PGI_2$ derivative and that (electron acceptor) in the acid chloride is discussed.

We have disclosed *m*-phenylene $PGI_2$ derivatives (**1**) and (**2**) as stable analogs of natural $PGI_2$ (Scheme I).[1-3] One of the most difficult problems in the area of prostaglandin synthesis has been the establishment of synthetic approaches to obtain selectively a 15 $\alpha$-hydroxy isomer from the corresponding 15-keto derivative. We also faced on the same problem in the stereoselective syntheses of *m*-phenylene $PGI_2$ derivative. The reduction of 15-ketone (**3**) with $NaBH_4$-$CeCl_3$ afforded 1:1 mixture of 15 $\beta$- and 15- $\alpha$ hydroxy isomers. Two methods are considered to solve the problem: (1)stereoselective reduction of 15-keto group;[4] (2)inversion of configuration at C-15 in a $\beta$-hydroxy isomer (side-product in the reduction of 15-ketone (**3**)).[5] Although a number of study have been tried toward the former method, much less work has been carried out on the latter one in the prostaglandin area. In the synthesis of a *m*-phenylene $PGI_2$ derivative, particularly anti-platelet drug TRK-100 (**2**), we attempted the stereoselective reduction of ketone (**3**). However our reductive approach by using many bulky

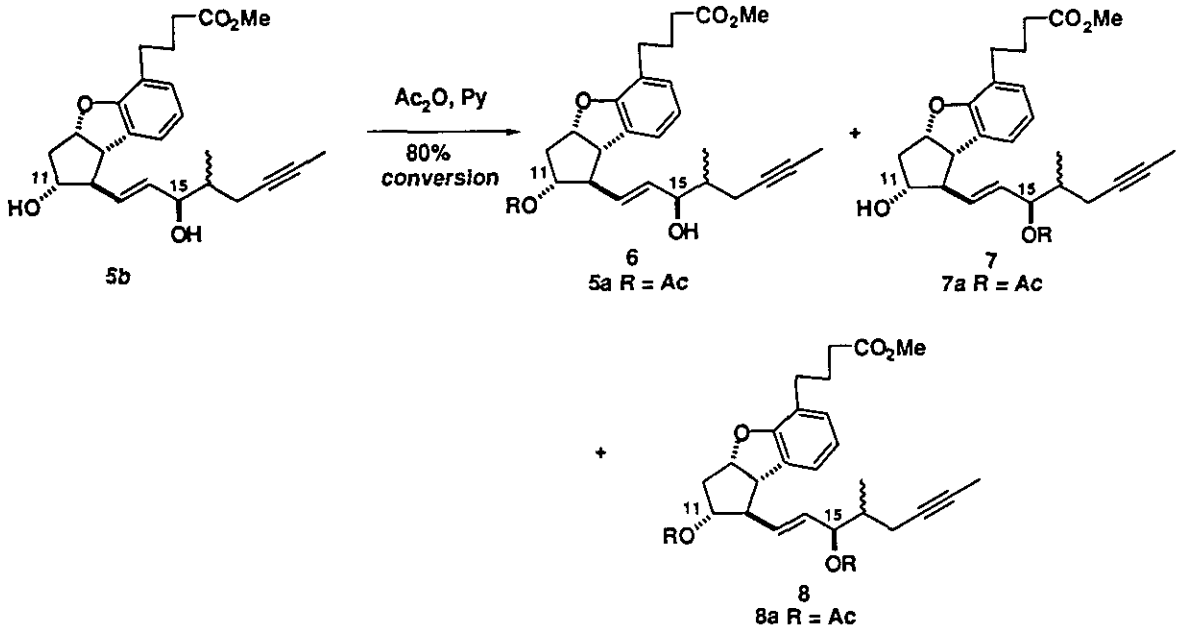
reducing agents could not give sufficient stereoselectivity. Therefore we investigated the inversion method, which gave us another difficult problem: the regioselective protection of 11-hydroxyl group in the presence of 15-hydroxyl one.[6,7] In the area of prostaglandin synthesis, the regioselective protection of 11-hydroxyl group in 11,15-dihydroxy derivative has never been reported so far. We wish to report the regioselective protective reaction by utilizing the structural character of *m*-phenylene $PGI_2$ derivatives and the effective inversion of the configuration at C-15.




Scheme I. *m*-Phenylene $PGI_2$ derivatives and the reduction of 15-keto group

## Results and Discussions

Treatment of **5 b** with acetic anhydride gave a mixture of 11-acetate (**5 a**), 15-acetate (**7 a**), and 11,15-diacetate (**8 a**) in a ratio of 44:16:40 (Scheme II).[8]



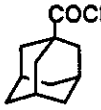
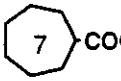
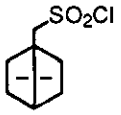

Scheme II. Acetylation of 15$\beta$-hydroxy-*m*-phenylene $PGI_2$ derivative (**5 b**)

As the moderate regioselectivity was considered to arise from the difference of steric factor at 11- and 15-positions, the first examination of hydroxy protection was mainly attempted by use of the reagent having bulky substituents (Table I). The protective reaction with the bulky reagent, however, gave desired 11-protected 15$\beta$-hydroxy isomer (**6**) in lower regioselectivity (entries 2-4, 8-11) than regioselectivity of the acetylation with acetic anhydride (entry 1). No reaction took place by using diphenylacetyl chloride or trityl chloride (entries 6,7). Interestingly only the reaction with benzoyl chloride gave desired 11-protected isomer (**6**) in rather high regioselectivity (entry 5).

The result prompted us to try a number of protective reaction with benzoyl chloride derivatives (Table II). Among them protective reaction by *p*-*t*-butyl or *p*-methylbenzoyl chloride gave high regioselectivity with long reaction time (entries 11, 13). On the other hand protection by *m*-nitrobenzoyl chloride showed both high regioselectivity and high reactivity (entry 14).

Therefore a variety of benzoyl chlorides having electron-withdrawing group such as nitro or chloro group were tried for the regioselective protection (Table III). During this investigation we found that protection by 3,5-dichlorobenzoyl chloride showed the best regioselectivity without detection of 15-protected isomer (**7**) (entry 3). The protection by highly reactive 3,5-dinitrobenzoyl chloride also gave the desired 11-protected isomer (**6**) without detection of 15-protected isomer (**7**) (11:15:11,15 = 60:0:40, entry 1). In this reaction, the diprotected isomer (**8**) was clearly formed *via* not 15-protected isomer but 11-protected isomer by TLC analysis. Thus we considered that the regioselectivity should be higher at shorter reaction time. On the

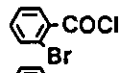
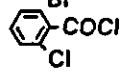
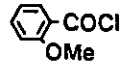
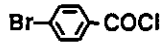
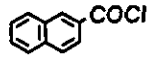
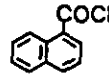
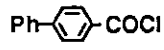
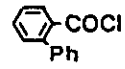
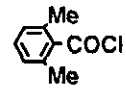
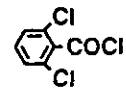
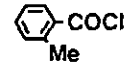
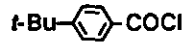
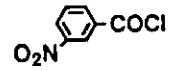
Table I. Protective reaction of 15 $\beta$-hydroxy isomer of *m*-phenylene $PGI_2$ methyl ester (**5b**) [a]

| entry | Protective Reagent | Time (h) | Temp. (°C) | Conv.[c] (%) | Ratio [c] (11:15:11,15) |
|---|---|---|---|---|---|
| 1 | $Ac_2O$[b] | 3.5 | 20 | 80 | 44:16:40 |
| 2 | *t*-BuCOCl | 16 | 20 | 80 | 36:28:36 |
| 3 |  | 100 | 70 | 75 | 32:29:38 |
| 4 |  | 80 | 50 | 80 | 32:30:38 |
| 5 | BzCl | 50 | 20 | 100 | **66: 2:32** |
| 6 | $Ph_2CHCOCl$ | 100 | 70 | 0 | - |
| 7 | $Ph_3CCl$ | 100 | 80 | 0 | - |
| 8 | *t*-$BuMe_2SiCl$ | 2 | 20 | 100 | 32:32:34 |
| 9 | $PhMe_2SiCl$ | 3 | 20 | 100 | 35:30:35 |
| 10 | $Ph_3SiCl$ | 6 | 20 | 100 | 36:29:35 |
| 11 |  | 0.5 | 20 | 100 | 30:10:60 |

a) Unless otherwise stated, all reaction were carried out by use of DME as a solvent, excess of $Et_3N$, 3 equiv. of acid chloride or silyl chloride derivatives. b) Pyridine as a solvent and 2.2 equiv. of acetic anhydride were used. c) Conversion and ratio were determined by column chromatography or HPLC.

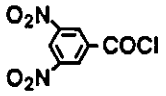
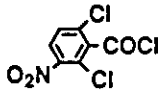
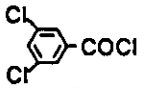
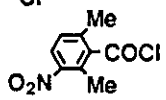
basis of the results shown in Table III, the reaction conditions (solvent, equivalent of acid chloride, and substrate conversion) with 3,5-dinitrobenzoyl chloride or 3,5-dichlorobenzoyl chloride were optimized (Table IV) and the results were summarized as follows :

Table II. Protective reaction of 15 $\beta$-hydroxy isomer of *m*-phenylene $PGI_2$ methyl ester (**5b**) [a]

| entry | Protective Reagent | Time (h) | Temp. (℃) | Conv.[b] (%) | Ratio [b] (11:15:11,15) |
|---|---|---|---|---|---|
| 1 |  | 20 | 20 | 95 | 62: 5:33 |
| 2 |  | 20 | 20 | 95 | 62: 5:33 |
| 3 |  | 100 | 65 | 5 | - |
| 4 |  | 20 | 20 | 100 | 62: 5:33 |
| 5 |  | 90 | 65 | 90 | 60:15:25 |
| 6 |  | 90 | 65 | 90 | 60:15:25 |
| 7 |  | 30 | 60 | 60 | 60:15:25 |
| 8 |  | 100 | 70 | 0 | - |
| 9 |  | 100 | 80 | 0 | - |
| 10 |  | 100 | 80 | 0 | - |
| 11 |  | **21** | **100** | **83** | **72: 5:23** |
| 12 |  | 21 | 100 | 93 | 43:17:40 |
| 13 |  | **42** | **60** | **95** | **65: 2:33** |
| 14 |  | **9** | **20** | **100** | **68: 0:32** |

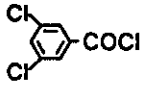
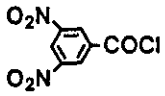
a)*All reaction were carried out by use of* DME as a solvent, excess of $Et_3N$, and 3 equiv. of acid chloride. b) Conversion and ratio were determined by column chromatography or HPLC.

Table III. Protective reaction of 15 $\beta$-hydroxy isomer of *m*-phenylene $PGI_2$ methyl ester (**5b**) [a]

| entry | Protective Reagent | Time (h) | Temp. (℃) | Conv.[b] (%) | Ratio [b] (11:15:11,15) |
|---|---|---|---|---|---|
| 1 |  | **0.5** | 20 | **100** | **60: 0:40** |
| 2 |  | 6 | 20 | 5 | 60:40:0 |
| 3 |  | 9 | 20 | **100** | **72: 0:28** |
| 4 |  | 6 | 20 | 10 | 34:38:28 |

a)All reaction were carried out by use of DME as a solvent, excess of $Et_3N$, and 3 equiv. of acid chloride. b) Conversion and ratio were determined by HPLC.

Table IV. Protective reaction of 15 $\beta$-hydroxy isomer of *m*-phenylene $PGI_2$ methyl ester (**5b**) [a]

| entry | Protective Reagent | eq. of acid chloride | Solvent | Time (h) | Temp. (℃) | Conv.[b] (%) | Ratio [b] (11:15:11,15) |
|---|---|---|---|---|---|---|---|
| 1 |  | 3 | DME | 1 | 20 | 90 | 80: 0:20 |
| 2 | | 3 | THF | 1 | 20 | 80 | 82.5: 2.5: 15 |
| 3 | | 10 | THF | 10 | -78 | 88 | 84: 1:15 |
| 4 |  | 2 | THF | 0.3 | 20 | 93 | 85: 1:14 |
| 5 | | 3 | THF | 0.5 | -78 | 93 | **94: 0: 6** |

a)All reaction were carried out by use of excess of $Et_3N$. b) Conversion and ratio were determined by HPLC.

(1) The large difference of regioselectivity between DME and THF as solvent was not seen (entry 1 vs 2). The reactivity was also almost the same.

(2) The protection by dinitrobenzoyl chloride gave higher regioselectivity at -78 ℃ than at 20 ℃ (entry 4 vs 5). In the case of dichlorobenzoyl chloride the regioselectivity was almost the same(entry 2 vs 3 ).

(3) Dinitrobenzoyl chloride gave higher regioselectivity than dichlorobenzoyl chloride at -78 ℃ (entry 3 vs 5).

Finally the highest regioselectivity, 11:15:11,15 = 94:0:6 was attained with 3 equiv. of 3,5-dinitrobenzoyl chloride at -78 ℃ in THF under 93% conversion. On the high regioselectivity of 3,5-dinitrobenzoyl chloride, we assumed the presence of the efficient interaction between the benzene ring (electron donor) in **5b** and benzene ring (electron acceptor) in the acyl chloride as shown in Figure II. Such an interaction is exemplified by the complex formed by tetramethyl-*p*-phenylenediamine with chloranil (Figure III).[9] As the compound (**5b**) has the electron rich benzene ring with electron-donating oxygen atom and alkyl substituents, it is considered that the strong electron-withdrawing nitro group on the benzene ring of the acyl chloride enhances the $\pi$ - $\pi$ interaction with the aromatic ring in **5b**.[10] In addition, the nitro groups at *meta* positions would not sterically affect the $\pi$ - $\pi$ interaction.

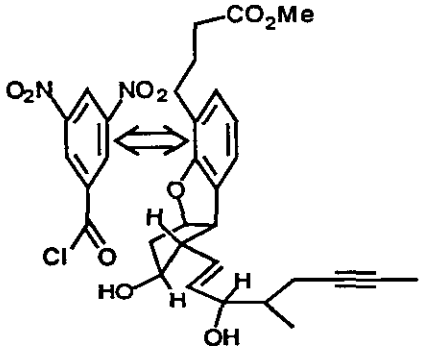



Figure II. The interaction between *m*-phenylene $PGI_2$ derivative and 3,5-dinitrobenzoyl chloride

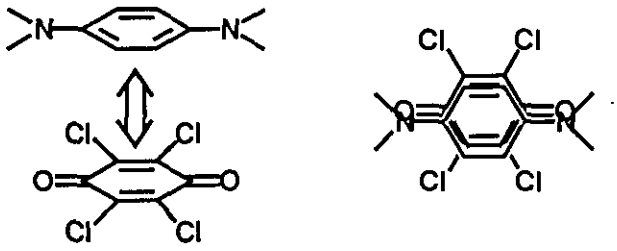
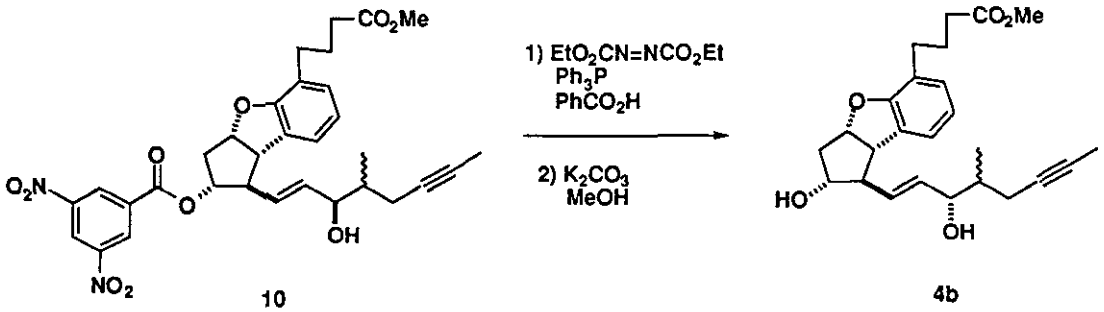



Figure III. $\pi$ Doner - $\pi$ acceptor complex

The Mitsunobu reaction[11] of the obtained **10** ( = **6** (R = 3,5-dinitrobenzoyl)) gave 15 $\alpha$ -hydroxy isomer (**4b**) by following sequence: (1) treatment with diethyl azodicarboxylate,

triphenylphosphine, and benzoic acid ; (2) methanolysis with MeOH in the presence of $K_2CO_3$ (2 steps, 85% yield, Scheme IV).[12]

In summary the 15 $\beta$-hydroxy isomer of a *m*-phenylene $PGI_2$ derivative was converted to its 15 $\alpha$-hydroxy isomer by regioselective protection of 11-hydroxy group using 3,5-dinitrobenzoyl chloride and subsequent Mitsunobu reaction.




Scheme IV. The Mitsunobu reaction in the 11-protected *m*-phenylene $PGI_2$ derivative

## EXPERIMENTAL

IR spectra were obtained on a JUSCO FT/IR-5000. NMR spectra were recorded at ambient temperature on a JEOL JNM-GSX400 using $CDCl_3$ as solvent and $Me_4Si$ as internal standard. MS spectra were obtained on a JEOL JMS D300 mass spectrometer or a VG ZAB-HF mass spectrometer. Melting point was determined on a Yanaco MP500D melting point apparatus and are uncorrected. THF was obtained by distillation from sodium benzophenone ketyl immediately prior to use. DME and triethylamine were obtained by distillation from $P_2O_5$ and NaOH, respectively. Diethyl azodicarboxylate was purified by distillation. Triphenylphosphine, benzoic acid, and 3,5-dinitrobenzoyl chloride were recrystallized from n-hexane, benzene, and $CCl_4$, respectively. Other reagents and solvents were reagent grade and used without subsequent purification. All reactions were carried out under argon atmosphere. The extract was evaporated under reduced pressure with a rotary evaporator and the residue was chromatographed on a silica gel column (Merck Co. Lobar Column, type B) using an EtOAc-cyclohexane mixture as the eluent. HPLC analyses were performed with a Shimadzu LC-4A or LC-6A equipped with a column of A-012 (6 x 150 mm, 5 $\mu$m, 120Å, YMC).

**Acetylation of methyl (1*R**,2*R**,3a*S**,8b*S**)-2,3,3a,8b-tetrahydro-2-hydroxy-1-[(*E*)-(3*R**,4*RS*)-3-hydroxy-4-methyl-1-octen-6-ynyl]-1*H*-cyclopenta[*b*]-benzofuran-5-butylate (5b)**

To a solution of **5b**[1] (100 mg, 0.242 mmol) in pyridine (0.5 mL) was added acetic anhydride (50 mL, 0.534 mmol). After the solution was stirred at 20 ℃ for 3.5 h, EtOAc (4 mL) and 1N HCl (10 mL) were added into the solution. The mixture was extracted with EtOAc (20 mL x 2). Each organic layer was washed with 1N HCl (10 mL) followed by brine. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue (116.9 mg) was purified by column chromatography (EtOAc:cyclohexane = 1:4-1:1) to yield 11-acetoxy isomer (**5a**) (41.3 mg, 37.5%), 15-acetoxy isomer (**7a**) (15.4 mg, 14.0%), 11,15-diacetoxy isomer (**8a**) (42.4 mg, 35.3%), and recovered starting material (**5b**) (20.3 mg, 20.3%).

Compound (**5a**) (colorless oil): IR (neat) 3486, 1738, 1243, 1031 $cm^{-1}$; $^1H$ NMR $\delta$ 0.96, 0.99 (3H, d, $J$ = 6.8 Hz), 1.70-1.84 (7H, m), 1.84-1.98 (3H, m), 2.03-2.14 (1.7H, m), 2.19-2.29 (1.3H, m), 2.35 (2H, t, $J$ = 7.6 Hz), 2.52-2.67 (3H, m), 2.78-2.85 (1H, m), 3.62 (1H, dd, $J$ = 8.5, 6.1 Hz), 3.66 (3H, s), 4.02-4.08 (0.3H, m), 4.17-4.25 (0.7H, br s), 4.92 (1H, q, $J$ = 5.9 Hz), 5.17-5.26 (1H, m), 5.62 (1H, dd, $J$ = 15.6, 4.9 Hz), 5.69 (1H, dd, $J$ = 15.6, 6.8 Hz), 6.76 (1H, t, $J$ = 7.3 Hz), 6.94 (1H, d, $J$ = 7.3 Hz), 6.98 (1H, d, $J$ = 7.3 Hz); LRMS (EI) m/z 454 ($M^+$); HRMS (EI) Calcd for $C_{27}H_{34}O_6$: 454.2355. Found : 454.2363.

Compound (**7a**) (colorless oil): IR (neat) 3588, 1734, 1241, 1025 $cm^{-1}$; $^1H$ NMR $\delta$ 1.00, 1.04 (3H, d, $J$ = 6.8 Hz), 1.78 (3H, t, $J$ = 2.4 Hz), 1.70-2.14 (9H, m), 2.15-2.28 (1H, m), 2.32 (2H, t, $J$ = 7.3 Hz), 2.44-2.53 (1H, m), 2.53-2.66 (3H, m), 3.44-3.54 (1H, m), 3.65 (3H, s), 3.90-4.00 (1H, m), 5.07-5.17 (1H, m), 5.20 (0.35H, t, $J$ = 6.6 Hz), 5.25 (0.65H, t, $J$ = 6.4 Hz), 5.46-5.58 (1H, m), 5.64-5.78 (1H, m), 6.76 (1H, t, $J$ = 7.3 Hz), 6.94 (2H, d, $J$ = 7.3 Hz); LRMS (EI) m/z 454 ($M^+$); HRMS (EI) Calcd for $C_{27}H_{34}O_6$: 454.2355. Found : 454.2355.

Compound (**8a**) (colorless oil): IR (neat) 1734, 1228, 1025 $cm^{-1}$; $^1H$ NMR $\delta$ 0.97(1.1H, d, $J$ = 6.8 Hz), 1.02 (1.9H, d, $J$ = 6.4 Hz), 1.73-1.82 (6H, m), 1.82-2.12 (8H, m), 2.14-2.27 (1H, m), 2.35 (2H, t, $J$ = 7.6 Hz), 2.52-2.65 (3H, m), 2.73-2.81 (1H, m), 3.55-3.65 (1H, m), 3.66 (3H, s), 4.87-4.95 (1H, m), 5.10-5.25 (2H, m), 5.43-5.53 (1H, m), 5.63-5.76 (1H, m), 6.75 (1H, t, $J$ = 7.6 Hz), 6.94 (2H, d, $J$ = 7.6 Hz); LRMS (EI) m/z 496 ($M^+$); HRMS (EI) Calcd for $C_{29}H_{36}O_7$:

496.2461. Found : 496.2455.

**Study of protective reaction of 15$\beta$-hydroxy isomer (5b) of *m*-phenylene $PGI_2$ methyl ester**

To a solution of **5b** (100 mg, 0.242 mmol) in dry DME (5 mL) was added 3 equivalents of acyl chloride or silyl chloride derivative (0.726 mmol). To the solution was added $Et_3N$ (1 mL, 7.18 mmol). The solution was stirred at rt or in a heating bath under monitoring substrate conversion on TLC analysis. On the time when maximum amount of 11-protected compound was produced on TLC monitoring, 1N HCl (10 mL) was added into the solution. The mixture was extracted with EtOAc (20 mL x 2). Each organic layer was washed with 1N HCl (10 mL) followed by brine. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was analyzed by HPLC (a mixture of EtOAc and cyclohexane as a eluent) detected by refractive index to determine substrate conversion and the ratio of products.

**Optimization of reaction parameter using 3,5-dinitrobenzoyl chloride or 3,5-dichlorobenzoyl chloride**

Both of 11-protected and 11,15-diprotected compounds were obtained by the similar procedure as described above and purified by column chromatography. The sample obtained was analyzed by HPLC (a mixture of EtOAc and cyclohexane as a eluent) detected UV (280 nm) and the correction factor for each peak was calculated. The correction factor of 11-protected compound was substituted for that of 15-protected compound because a very slight amount of the 15-protected compound produced in a study of optimization of reaction parameter and monoprotected compound was presumed to have almost the same correction factor. The ratio of products determined by UV detection was almost the same as that determined by refractive index detection described above.

11-protected compound by 3,5-dinitrobenzoyl group (yellow oil): IR (neat) 1734, 1547, 1348 $cm^{-1}$; $^1H$ NMR $\delta$ 0.94, 0.97 (3H, d, $J$ = 6.8 Hz), 1.55-1.73 (6H, m), 1.92-2.48 (5H, m), 2.67-2.74 (1H, m), 3.24-3.29 (1H, m), 3.54 (3H, s), 3.96-4.15 (3H, m), 5.29-5.32 (1H, m), 5.43-5.47 (1H, m), 5.74-5.86 (2H, m), 6.76 (1H, t, $J$ = 7.3 Hz), 6.84 (1H, d, $J$ = 7.3 Hz), 7.13 (1H, d, $J$ = 7.3 Hz), 8.53-8.56 (2H, m), 9.06-9.08 (1H, m); LRMS (EI) m/z 606 ($M^+$); HRMS (EI) Calcd for $C_{32}H_{34}N_2O_{10}$: 606.2214. Found : 606.2207.

11,15-diprotected compound by 3,5-dinitrobenzoyl group (pale yellow crystal): mp 41.0-48.0 ℃; IR (KBr) 3858, 1731, 1549, 1344, 1276, 1168 $cm^{-1}$; $^1H$ NMR $\delta$ 1.08, 1.15 (3H, d, $J$ = 6.6 Hz), 1.60-1.80 (5H, m), 2.05-2.35 (5H, m), 2.35-2.65 (4H, m), 3.15-3.25 (1H, m), 3.61 (3H, s), 3.87 (1H, dd, $J$ = 8.3, 3.4 Hz), 5.25-5.43 (2H, m), 5.50-5.62 (1H, m), 5.70-5.82 (1H, m), 5.88-6.02 (1H, m), 6.68-6.75 (1H, m), 6.86 (1H, d, $J$ = 7.3 Hz), 6.97 (1H, d, $J$ = 7.8 Hz), 8.55-8.66 (2H, m), 9.13 (1H, t, $J$ = 2.3 Hz), 9.17 (2H, d, $J$ = 2.3 Hz), 9.20-9.30 (1H, m); LRMS (EI) m/z 800 ($M^+$); HRMS (EI) Calcd for $C_{39}H_{36}N_4O_{15}$: 800.2177. Found : .

11-protected compound by 3,5-dichlorobenzoyl group (colorless oil): IR (neat) 3450, 2958, 2924, 1717, 1572, 1458, 1270 $cm^{-1}$; $^1H$ NMR $\delta$ 0.93-1.03 (3H, m), 1.73-1.93 (7H, m), 2.07-2.17 (1H, m), 2.17-2.30 (3H, m), 2.30-2.38 (1H, m), 2.45-2.63 (3H, m), 3.13 (1H, br s), 3.63 (3H, s), 3.86-3.93 (1H, m), 4.04-4.27 (1H, m), 5.23-5.28 (1H, m), 5.38 (1H, t, $J$ = 7.1 Hz), 5.65-5.77 (2H, m), 6.81 (1H, t, $J$ = 7.3 Hz), 7.00 (1H, d, $J$ = 7.8 Hz), 7.03 (1H, d, $J$ = 7.3 Hz), 7.24 (2H, d, $J$ = 2.0 Hz), 7.43 (1H, t, $J$ = 2.0 Hz); LRMS (EI) m/z 584 ($M^+$); HRMS (EI) Calcd for $C_{32}H_{34}O_6Cl_2$: 584.1732. Found : 584.1721.

11,15-diprotected compound by 3,5-dichlorobenzoyl group (colorless oil): IR (neat) 2930, 1717, 1572, 1458, 1435, 1259, 1149 $cm^{-1}$; $^1H$ NMR $\delta$ 1.04, 1.10 (3H, d, $J$ = 6.8 Hz), 1.75-1.88 (5H, m), 1.98-2.38 (6H, m), 2.45-2.62 (3H, m), 3.05-3.13 (1H, m), 3.63 (3H, s), 3.82-3.89 (1H, m), 5.22-5.28 (1H, m), 5.32-5.38 (1H, m), 5.38-5.51 (1H, m), 5.60-5.71 (1H, m), 5.78-5.90 (1H, m), 6.77 (1H, td, $J$ = 7.6, 3.9 Hz), 6.98 (2H, d, $J$ = 7.6 Hz), 7.21-7.33 (2H, m), 7.43-7.47 (1H, m), 7.55-7.59 (1H, m), 7.91 (2H, d, $J$ = 2.0 Hz); LRMS (EI) m/z 756 ($M^+$); HRMS (EI) Calcd for $C_{39}H_{36}O_7Cl_4$: 756.1215. Found : 756.1189.

To a solution of **5b** (80 mg, 0.194 mmol) in dry THF (4 mL) was added 3,5-dinitrobenzoyl chloride (134 mg, 0.582 mmol). To the stirring solution was added $Et_3N$ (0.27 mL, 1.94 mmol) at -78 ℃. The reaction mixture was sampled and analyzed by HPLC detected UV (280 nm). The peak ratio was corrected using the corresponding correction factor to calculate the ratio of the products.

The same procedure was conducted when DME as a solvent or dichlorobenzoyl chloride as acid chloride was used or the reaction was carried out at rt.

**Methyl (1*R**,2*R**,3a*S**,8b*S**)-2,3,3a,8b-tetrahydro-2-hydroxy-1-[(*E*)-(3*S**,4*RS*)-**

**3-hydroxy-4-methyl-1-octen-6-ynyl]-1*H*-cyclopenta[*b*]benzofuran-5-butylate (4b)**

Triphenylphosphine (333 mg, 1.27 mmol) and benzoic acid (158 mg, 1.29 mmol) were added to a stirred solution of **10** (328 mg, 0.619 mmol) in THF (3 mL). The solution was cooled in an ice bath and a solution of diethyl azodicarboxylate (284 mg, 1.29 mmol) in THF (6 mL) was slowly added to the solution. After the solution was stirred for 2 h, saturated $NaHCO_3$ aq. and EtOAc were added. The organic layer was separated and concentrated. The obtained residue was dissolved in MeOH (10 mL) and treated with $K_2CO_3$ (1 g). The reaction mixture was stirred for 16 h, and then concentrated and a mixture of EtOAc and $H_2O$ was added into the residue. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography (EtOAc:cyclohexane = 1:2) to yield **4b** (216 mg, 85%) as a colorless oil; IR (neat) 3370, 1720 $cm^{-1}$; $^1H$ NMR $\delta$ 1.01 (3H, two d, $J$ = 7.1 Hz), 1.75-1.87 (5H, m), 1.87-2.06 (4H, m), 2.10-2.35 (4H, m), 2.50-2.68 (4H, m), 3.48-3.54 (1H, m), 3.65 (3H, s), 3.92-4.02 (1H, m), 4.07-4.13 (0.5H, m), 4.22-4.28 (0.5H, m), 5.10-5.18 (1H, m), 5.63-5.78 (2H, m), 6.77 (1H, td, $J$ = 7.3, 1.0 Hz), 6.95 (1H, d, $J$ = 7.3 Hz), 7.00 (1H, d, $J$ = 7.3 Hz); LRMS (EI) m/z 412 ($M^+$); HRMS (EI) Calcd for $C_{25}H_{32}O_5$: 412.2250. Found : 412.2213.

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6. Reduction products (**4 a** and **5 a**) of **3** could not be separated from each other. Separation of 15-hydroxy isomer was practically performed on **4 b** and **5b** which were obtained by methanolysis of a mixture of **4 a** and **5 a**.
7. The Mitsunobu reaction in the unprotected 15 $\beta$-hydroxy isomer (**5 b**) gave poor result because of the concomitance of inversion product at C-11.
8. Acetylation of **5 b** with acetyl chloride and triethylamine gave a complex mixture and desired compound (**5 a**) was not obtained predominantly.
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10. The same reaction in illoprost 15 $\beta$-hydroxy methyl ester (no benzene ring) afforded only lower regioselectivity under our condition (11:15:11,15 = 58:1:41).
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12. The diastereomer ratio at C-16 was not affected in the protective reaction followed by inversion of configuration at C-15.

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