Pergamon

Tetrahedron 55 (1999) 2449–2474

TETRAHEDRON

Synthesis of 5,6,7-Trinor-4,8-inter-*m*-phenylene PGI_2 and Beraprost

Hisanori Wakita,[a] Kazuhisa Matsumoto,[a] Hideo Yoshiwara,[a] Yutaka Hosono,[a] Ryoji Hayashi,[a] Hisao Nishiyama,[b] and Hiroshi Nagase*[a]

[a]Basic Research Laboratories, Toray Industries, Inc., 1111 Tebiro, Kamakura 248-8555, Japan

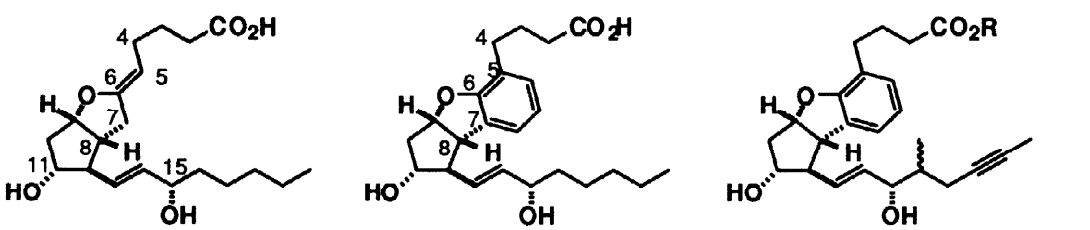
[b]School of Materials Science, Toyohashi University of Technology, Tempaku-cho, Toyohashi 441-8580, Japan

Received 9 November 1998; accepted 24 December 1998

Abstract: We have disclosed a new class of stable PGI_2 analogue, 5,6,7-trinor-4,8-inter-*m*-phenylene PGI_2 which has a phenyl ether moiety instead of enol-ether skeleton in PGI_2. The *m*-phenylene PGI_2 and its derivative (Beraprost) were synthesized *via* dihydrocyclopenta[*b*]benzofuran derivatives as key intermediates by *ortho*-selective metal-halogen exchange reaction with Grignard reagents and subsequent copper-catalyzed cyclization. The ω-side chains were introduced by stereoselective epoxide formation or Prins reaction.

INTRODUCTION

Since the discovery of prostacyclin (PGI_2), much attention has been paid to syntheses of its analogues to improve its chemical unstability and to separate its multiple biological activities.[1] Thus far several stable biomimics of PGI_2 have been reported.[2] As a reasonable approach we have adopted replacement of the unstable enol-ether linkage of PGI_2 with *m*-phenylene skeleton, which can maintain the *Z*-enol-ether skeleton of PGI_2 on the α-side chain.[3] We here report regio- and stereo-selective synthesis of new stable analogues, 5,6,7-trinor-4,8-inter-*m*-phenylene PGI_2 (**1**)[4] and its derivatives (Beraprost (**2**), Beraprost sodium (**3**)). Beraprost sodium (**3**) has been developed as an antiplatelet drug (Fig. 1).



PGI_2 — **1** 5,6,7-trinor-4,8-inter-*m*-phenylene PGI_2 — **2** R=H : Beraprost, **3** R=Na : Beraprost sodium

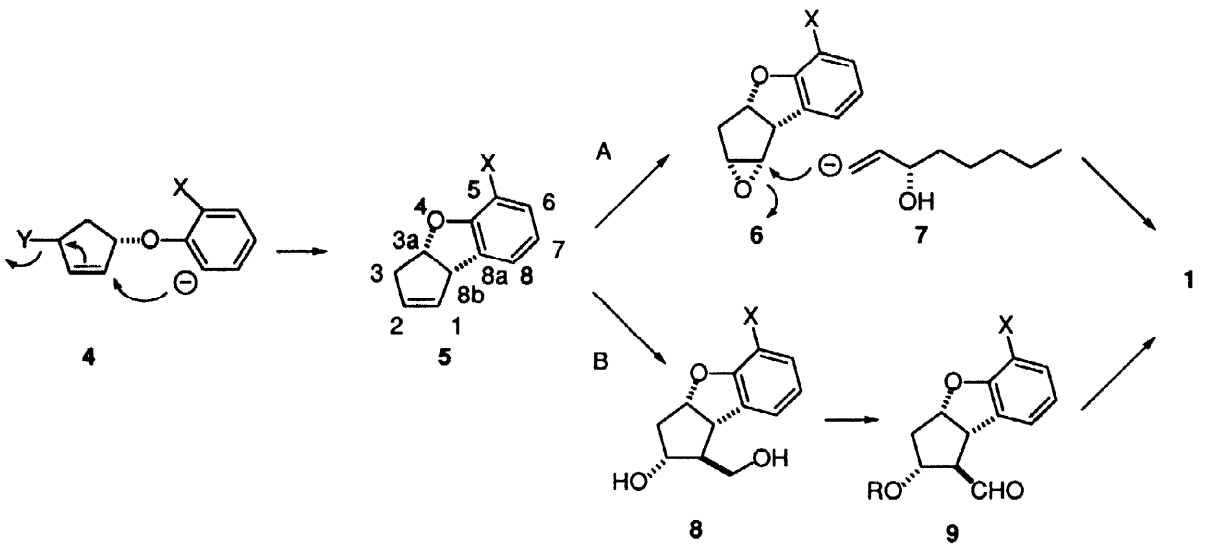
Fig.1. natural PGI_2 and stable PGI_2 analogues

RESULTS AND DISCUSSION

Synthesis of dihydro-3H-cyclopenta[b]benzofuran.

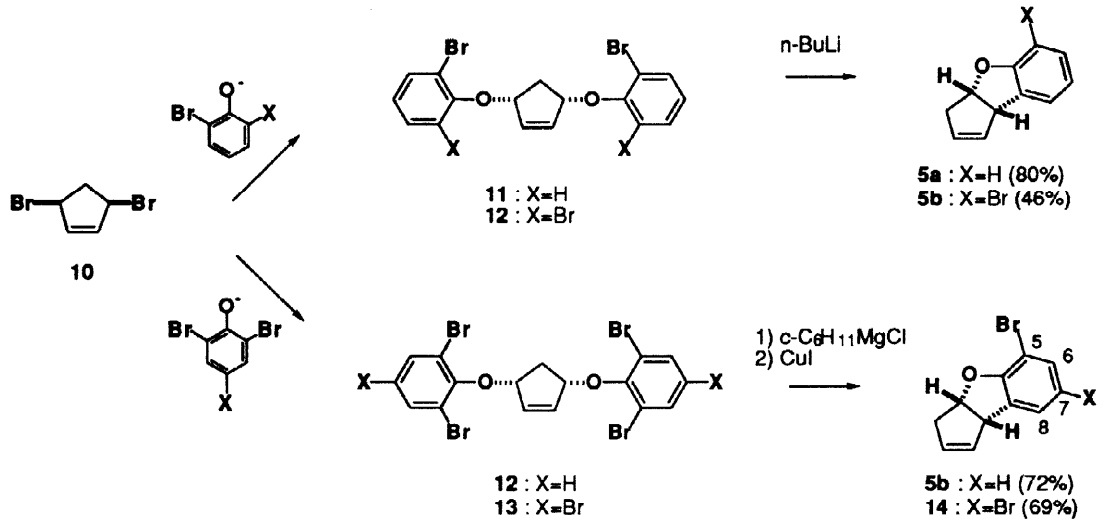
PII: S0040-4020(99)00020-4

At first total synthesis of 5,6,7-trinor-4,8-inter-*m*-phenylene PGI_2 (**1**) needed the basic skeleton, 5-substituted 3a,8b-*cis*-dihydro-3*H*-cyclopenta[*b*]benzofuran (**5**) (Scheme 1). The basic skeleton (**5**) was presumed to be synthesized by intramolecular S_N2' reaction of cyclopentene derivative (**4**). As the introduction of ω-side chain, two methods were considered: 1) stereoselective formation of cyclopenta[*b*]benzofuran-epoxide (**6**) and successive opening with ω-side chain equivalent (A route); 2) regio- and stereo-selective introduction of the 2-hydroxyl and 1-(hydroxymethyl) groups by Prins reaction, followed by oxidation of the 1-(hydroxymethyl) group and elongation of the ω-side chain (B route). In both of the two methods, the α-side chain may be introduced before or after the introduction of the ω-side chain.[5]



Scheme 1. Plan of total synthesis of 5,6,7-trinor-4,8-inter-*m*-phenylene PGI_2 (**1**)

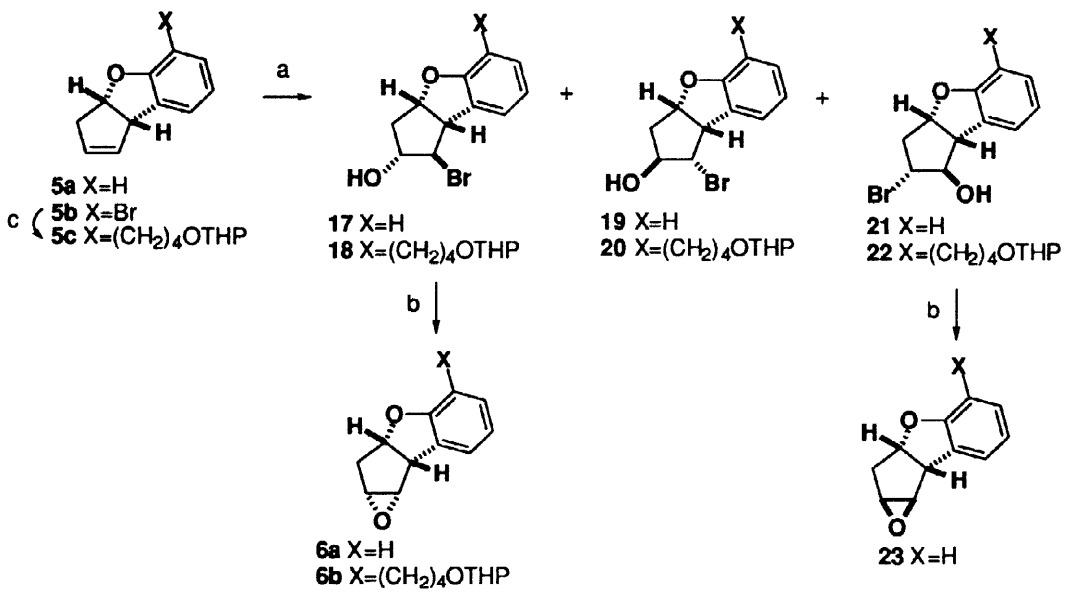
Substitution of easily available 3,5-*cis*-dibromo-1-cyclopentene (**10**)[6] with 2-bromophenoxide yielded phenylether (**11**) (Scheme 2). Treatment of **11** with n-BuLi generated the corresponding aryllithium species, which readily underwent an intramolecular S_N2' reaction to give the desired product (**5a**). In the case of the reaction with 2,6-dibromophenoxide, **12** was synthesized in the presence of catalytic amount of 18-crown-6.[7] However, similar treatment of **12** with n-BuLi and subsequent cyclization gave **5b** in low yield (46%) together with bromine-free compound (**5a**) (ca. 20%). It is apparent that the alkyllithium has too strong basicity to carry out the metal-halogen exchange effectively. Therefore, in an attempt to improve both the yield and the selectivity of the metal-halogen exchange, a Grignard reagent such as cyclohexylmagnesium chloride was employed. The subsequent cyclization was attained by addition of CuI. Thus, successive treatment of **12** with the Grignard reagent and CuI gave the desired cyclic product, the monobromide (**5b**) in high yield. A hexabromo compound (**13**) was similarly converted to benzofuran (**14**) in good yield.[8,9]



Scheme 2. Synthetic study of dihydro-3*H*-cyclopenta[*b*]benzofuran

Synthesis of m-phenylene PGI$_2$ via epoxide derivative.

Epoxidation of **5a** with NBS-DMSO-H_2O[10] gave a mixture of bromohydrin derivatives whose main product was **17** and minor products were **19** and **21** (Scheme 3). It was considered that in this reaction **5a** was attacked by bromonium cation stereoselectively from its less hindered side, followed by attack of H_2O regioselectively from less hindered C-2 side (Fig. 2). The obtained bromohydrins (**17** and **21**) were cyclized with K_2CO_3 to give *endo*-epoxide (**6a**) and *exo*-epoxide (**23**) respectively, while treatment of **5a** with MCPBA afforded an epoxide, which was identical with the *exo*-epoxide (**23**).



a: NBS, H_2O, DMSO; b: K_2CO_3, MeOH; c: n-BuLi, $I(CH_2)_4OTHP$

Scheme 3. Stereoselective synthesis of benzofuran epoxides (**6a** and **6b**)

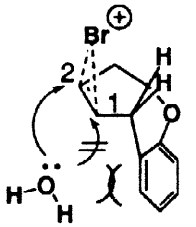
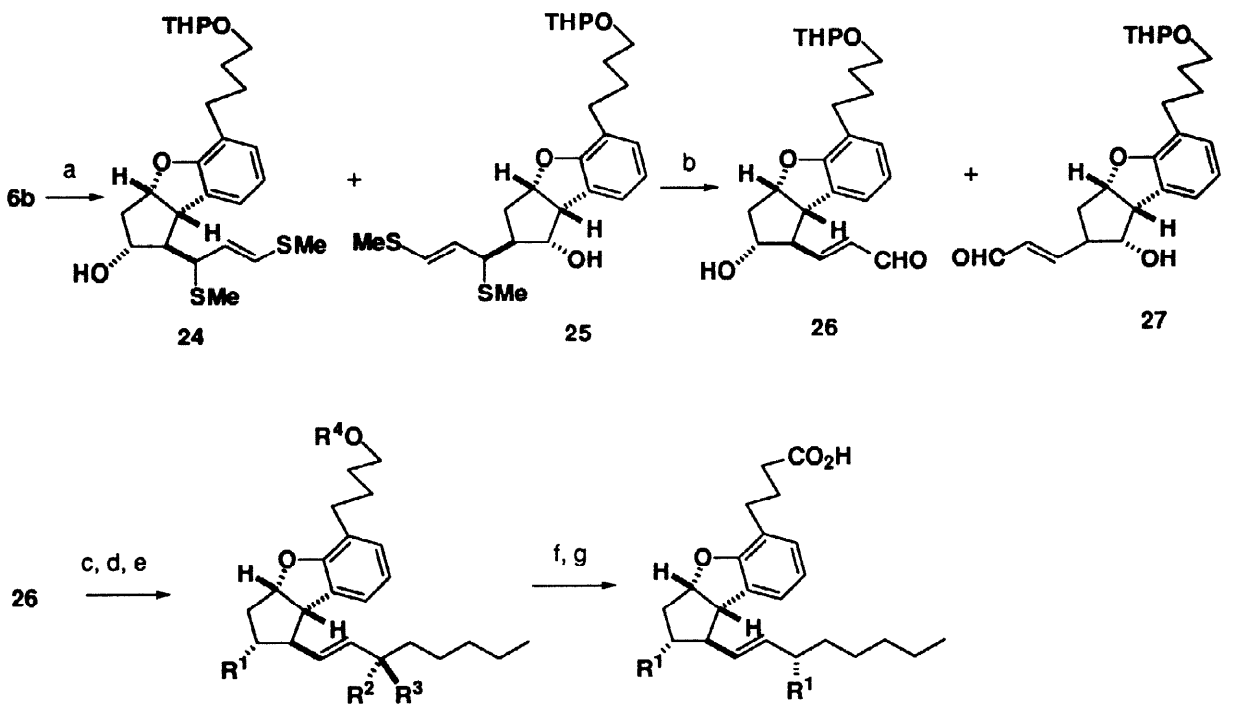


Fig.2. Stereoselectivity and regioselectivity of the reaction in benzofuran (**5a**)

Similarly, lithiation of the monobromide (**5b**) with n-BuLi and subsequent alkylation with $THPO(CH_2)_4I$ [11] gave alkylated benzofuran derivative (**5c**) (Scheme 3). Treatment of **5c** with NBS-DMSO-H_2O gave bromohydrin (**18**) regio- and stereo-selectively (**18**:**20**+**22** = ca. 5:1) in a manner similar to that described in the epoxidation of **5a**. The bromohydrin (**18**) was cyclized with K_2CO_3 to give *endo*-epoxide (**6b**).

1,3-Bis(methylthio)propenyl anion[12] was then added to the solution of the *endo*-epoxide (**6b**) to give a mixture of desired thioenolether (**24**) and its regioisomer (**25**) (Scheme 4). The crude mixture of the resultant thioenol ether was hydrolyzed, followed by separation of the regioisomers to yield α, β-unsaturated aldehyde (**26** and **27**).



28: R^1=OH, R^2=OH, R^3=H, R^4=THP
29: R^1=OH, R^2=H, R^3=OH, R^4=THP
30: R^1=R^2=OAc, R^3=H, R^4=THP
31: R^1=R^2=OAc, R^3=H, R^4=H

32:R^1=OAc
1:R^1=OH

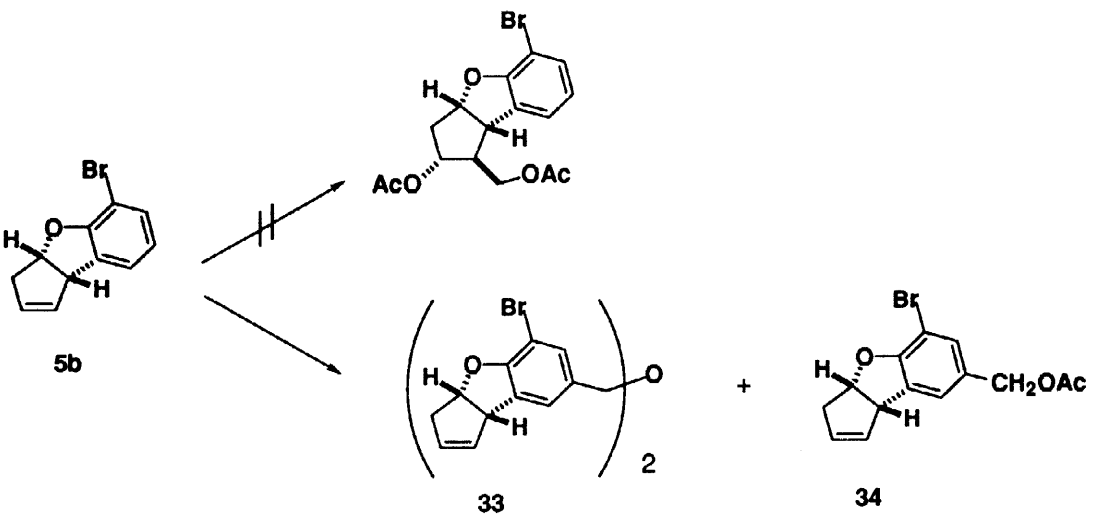
a: $MeSCH_2CH$=$CHSMe$, LDA; b: $HgCl_2$, $CaCO_3$; c: n-$C_5H_{11}Li$; d: Ac_2O, pyridine; e: HCl; f: PDC, DMF; g: NaOH

Scheme 4. Synthesis of *m*-phenylene PGI_2 (**1**) from epoxide (**6b**)

The target compound (**1**) was synthesized by alkylation of the aldehyde (**26**) and the following functionalizations. Addition of n-pentyllithium to the solution of the aldehyde and separation of stereoisomers gave **28** and **29**.[13] Acetylation of **28** gave diacetate (**30**). Then hydrolysis of THP ether, followed by oxidation[14] and successive deacetylation, produced the target compound (**1**) (26% overall from **26**).

Synthesis of m-phenylene PGI_2 via Prins reaction.

The route *via* the epoxide derivative as described above resulted in the low regioselectivity with regard to the epoxide cleavage. Alternatively, regio- and stereo-selective construction of both 2-hydroxyl and 1-hydroxymethyl groups in the benzofuran (**5**) was presumed to be accomplished by attack of protonated formaldehyde (Fig. 3). In fact, Prins reaction has been already applied to Corey lactone synthesis.[15] However, treatment of the monobromide (**5b**) with paraformaldehyde and sulfuric acid in acetic acid gave only a mixture of dimer (**33**) and acetate (**34**) as shown in Scheme 5. The formation of these products was attributed to high nucleophilicity of the aromatic ring of **5b** due to mesomeric effect at the *para* position to the oxygen atom.



Scheme 5. Prins reaction of dihydrocyclopenta[*b*]benzofuran (**5b**)

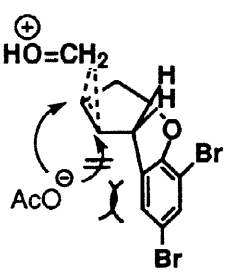
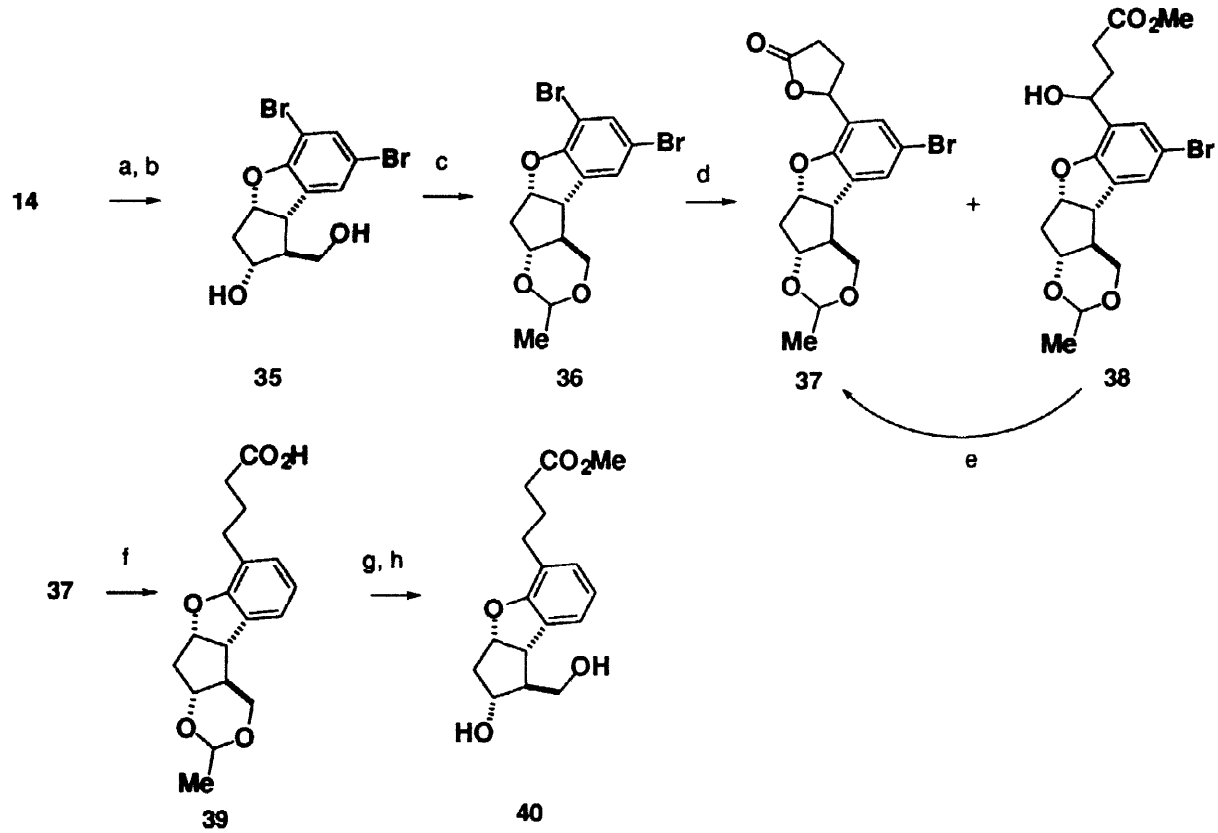


Fig.3. Stereoselectivity and regioselectivity of the Prins reaction in benzofuran (**14**)

Consequently, the dibromo compound (**14**), whose bromine atom at C-7 prohibited the hydroxymethylation at the benzene ring, was used for Prins reaction. Treatment of **14** by the method similar to the Prins reaction of the monobromo compound (**5b**) provided a mixture of diol (**35**), its mono- and di-acetates, which was successively converted to the pure diol (**35**) by alkaline hydrolysis (Scheme 6).

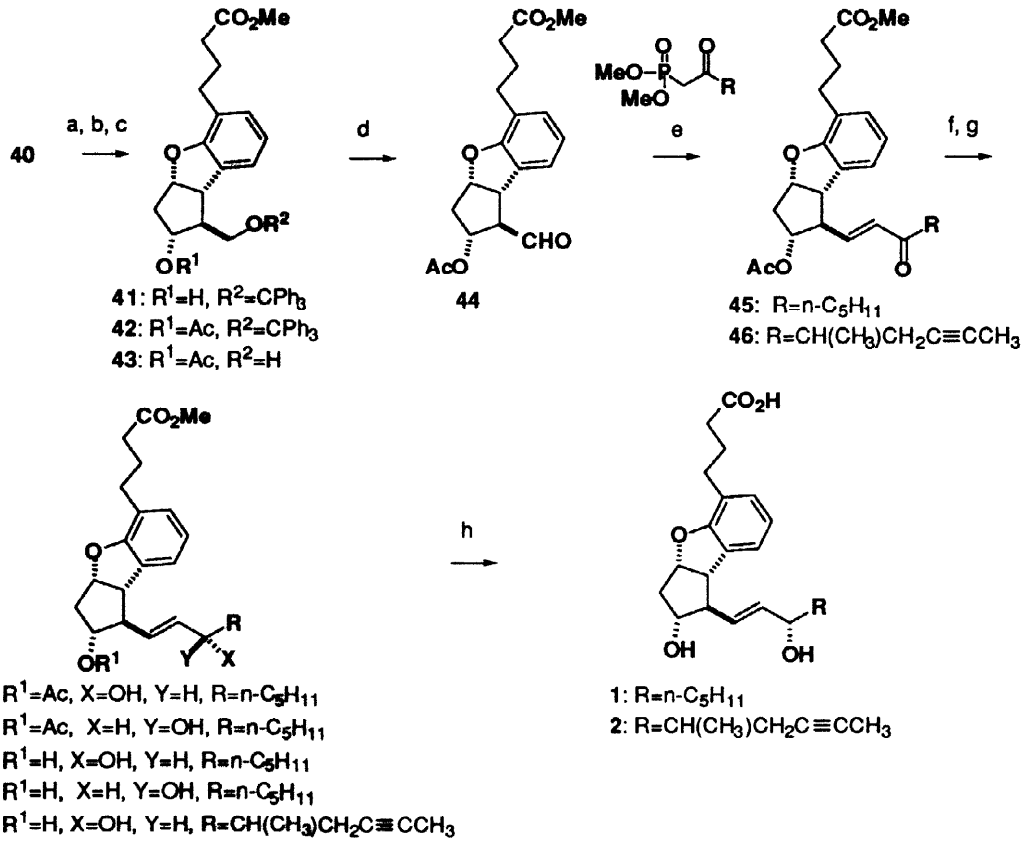


Scheme 6. Prins reaction and α -side chain elongation of benzofuran (**14**)

Protection of the hydroxyl groups in diol (**38**), followed by regioselective metalation of **36** and subsequent coupling with methyl 3-formylpropionate, gave a mixture of lactone (**37**) and hydroxy ester (**38**)(Scheme 6). After the mixture was converted to the lactone (**37**), hydrogenation of **37**, followed by esterification and successive treatment of HCl, produced the dihydroxy ester (**40**).

Conversion of the dihydroxy ester (**40**) into 2-acetyl-1-hydroxymethyl ester (**43**) was effected by the following sequence: (a) transformation of **40** into the monotrityl derivative, (b) acetylation, and (c) hydrolysis (Scheme 7). Oxidation of **43** with DCC and DMSO[16] provided aldehyde (**44**), which was immediately condensed with dimethyl 2-oxohepylphosphonate to give enone (**45**).[17] Reduction of **45** with $NaBH_4$ and $CeCl_3 \cdot 7H_2O$ yielded a mixture of isomeric alcohols (**47** and **48**).[18] Methanolysis of the mixture and separation

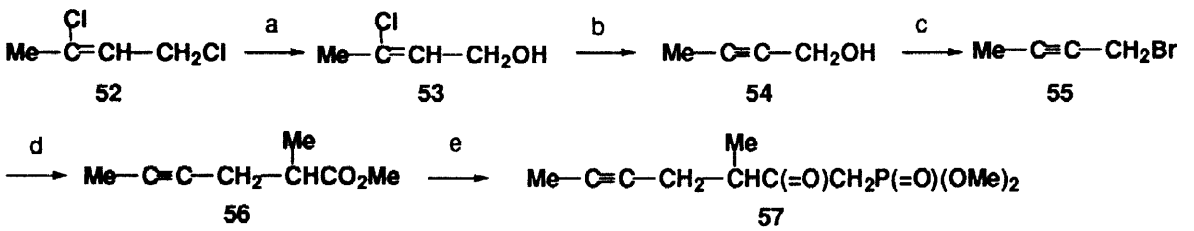
of stereoisomer gave 15 α -hydroxy isomer (4 9). Hydrolysis of 4 9 yielded the target molecule (1). Similar treatment as described above by using dimethyl 3-methyl-2-oxo-5-heptynylphosphonate instead of dimethyl 2-oxoheptylphosphonate afforded Beraprost (2).[19]



a: Ph_3CCl, Et_3N; b: Ac_2O, Py; c: HCl, MeOH; d: DMSO, DCC, TFA, pyridine; e: NaH; f: $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH; g: MeONa, MeOH; h: NaOHaq, MeOH

Scheme 7. Synthesis of *m*-phenylene PGI_2

Synthesis of Wadsworth reagent (5 7) of Beraprost was effected by the following sequence: (a) hydrolysis of allylchloride (5 2) and elimination of HCl in 5 3, (b) bromination to give allylbromide (5 5), (c) alkylation to give ester (5 6), and (d) transformation of ester (5 6) to 5 7 (Scheme 8).



a: Na_2CO_3, H_2O; b: Na, liq. NH_3; c: PBr_3, Py; d: 1) LDA, $EtCO_2H$, 2) CH_2N_2; e: $(MeO)_2P(=O)CH_2Li$

Scheme 8. Synthesis of Wadsworth reagent of Beraprost

Thus obtained PGI_2 analogues were assayed for inhibitory activities toward human platelet aggregation induced by ADP. IC_{50} values for compounds (**1**) and (**2**) were 16 and 0.9 ng/mL, respectively.[3a, 20]

CONCLUSION

In summary, 5,6,7-trinor-4,8-inter-*m*-phenylene PGI_2 derivatives, a new class of stable PGI_2 analogues, were synthesized by *ortho*-selective metal-halogen exchange reaction by Grignard reagent, copper-catalyzed S_N2' cyclization, and regio- and stereo-selective introduction of 11-hydroxyl group and ω-side chain by Prins reaction.

EXPERIMENTAL

General. ^1H NMR spectra of $CDCl_3$ solution were recorded with JEOL JNM-FX100 spectrometer or Varian XL-100 spectrometer at 100 MHz. ^{13}C NMR spectra were recorded with JEOL JNM-FX100 spectrometer at 25.2 MHz or JEOL GX-270 spectrometer at 67.9 MHz. Infrared spectra were recorded with JASCO A-3 spectrometer. MS spectra were recorded with Hitachi RML 7-M or JEOL JMS D-300 spectrometer. Melting points were determined on a Yanaco MP-500D melting point apparatus and are uncorrected. Elemental analysis was determined with a Heraeus CHN-O RAPID for carbon and hydrogen and a Kyoto Electronics AT-118 (potentiometric automatic titrator) for bromine. Analytical TLC was performed with Merck precoated (0.25mm) silica gel plates. Column chromatography was performed with Merck silica gel Art 7734. THF was distilled from $LiAlH_4$ or sodium benzophenone ketyl immediately prior to use. All synthesized compounds were racemic.

3,5-*cis*-Bis(2-bromophenoxy)-1-cyclopentene (11).

To a suspension of NaH (2.78 g, 0.058 mol) and DME (20 mL) at 0℃ was slowly added 2-bromophenol (6.67 mL, 0.058 mol). After the evolution of H_2 had ceased, a solution of 3,5-*cis*-dibromocyclopentene[6] (6.24 g, 0.0276 mol) in DME (25 mL) was added. The mixture was stirred at rt for 1 day. The mixture was concentrated and treated with EtOAc (300mL). The organic layer was washed with brine (20 mL × 2) and 1 N NaOH aqueous solution (20 mL). The organic layer was dried over Na_2SO_4, warmed at 50-60℃ with activated charcoal, and filtered. The filtrate was concentrated to give a white solid. The solid was filtered and washed with cyclohexane to give pure **11** (6.0 g, 0.0146 mol, 53%): mp 138.0-138.5℃; ^1H NMR δ 2.21 (1H, dt, J = 14.0, 5.0 Hz), 3.08 (1H, dd, J = 14.0, 7.0 Hz), 5.20 (2H, dd, J = 7.0, 5.0 Hz), 6.30 (2H, s), 6.8-7.6 (8H, m); IR (KBr) 3060, 2900, 1585, 1570, 1472, 1440, 1380, 1272, 1236, 1165, 1130, 1090,

1050, 1030, 992, 790, 760, 750 cm^{-1}; MS m/e 239, 237, 174, 172, 171, 158. Anal. calcd for $C_{17}H_{15}Br_2O_2$: C, 49.79; H, 3.44; Br, 38.97. Found: C, 49.69; H, 3.49; Br, 38.92.

3a,8b-*cis*-Dihydro-3*H*-cyclopenta[*b*]benzofuran (5a).

To a solution of **11** (6.0 g, 14.6 mmol) in THF (80 mL) at -50℃ was slowly added ca. 2 M n-BuLi solution in n-hexane (11 mL, 22 mmol). The solution was stirred at -50℃ for 1 hr and at -5℃ for 3 hr. To the solution was added brine (5 mL) and the resulting mixture was concentrated. To the residue was added ether (300 mL) and the organic layer was washed with brine (30 mL), dried over Na_2SO_4, and concentrated. Thus obtained residue was purified by column chromatography (cyclohexane : EtOAc = 19:1) to give **5a** (1.84 g, 11.7 mmol, 79.8 %) as an oily material: ^1H NMR δ 2.80 (1H, dd, J = 2.2, 0.5 Hz), 2.82 (1H, dd, J = 5.2, 0.5 Hz), 4.35 (1H, d, J = 7.8 Hz), 5.43 (1H, ddd, J = 7.8, 5.2, 2.2 Hz), 5.71 (2H, s), 6.7-7.2 (4H, m); IR (neat) 3050, 2920, 2830, 1602, 1590, 1472, 1457, 1420, 1340, 1315, 1290, 1262, 1220, 1160, 1095, 1000, 940, 900, 860, 827, 790, 750, 700 cm^{-1}; LRMS m/e 158 (M^+), 131, 115; HRMS (EI) Calcd for $C_{11}H_{10}O$: 158.0732. Found: 158.0730.

3,5-*cis*-Bis(2,6-dibromophenoxy)-1-cyclopentene (12).

To a suspension of NaH (5.6 g, 0.117 mol) and DME (100 mL) at 0℃ was slowly added a solution of 2,6-dibromophenol (29.4 g, 0.117 mol) in DME (159 mL). After the evolution of H_2 had ceased, 18-crown-6 (280 mg, 1.06 mmol) and 3,5-*cis*-dibromocyclopentene (12.0 g, 0.053 mol) were added. The mixture was warmed to rt and stirred for 3 days. The white precipitate that formed was collected by filtration and washed with DME (20 mL × 3). Then it was dissolved in $CHCl_3$. The solution was dried over $MgSO_4$. Concentration gave almost pure **12** (22.6 g, 0.040 mol, 75%): mp 205-206℃; ^1H NMR δ 2.90 (1H, dt, J = 16.0, 8.0 Hz), 3.12 (1H, dt, J = 8.0, 7.0 Hz), 5.10 (1H, dd, J = 8.0, 7.0 Hz), 6.31 (2H, s), 6.83 (1H, t, J = 8.0 Hz), 7.52 (2H, d, J = 8.0 Hz); IR (KBr) 1550, 1430, 1375, 1235, 1068, 1015, 988, 960, 935, 895, 820, 760, 740, 715 cm^{-1}; MS m/e 572, 571, 570, 569, 568, 567, 566, 565, 564 (M^+), 319, 317, 315.

3a,8b-*cis*-Dihydro-3*H*-5-bromocyclopenta[*b*]benzofuran (5b).

To a suspension of the tetrabromide (**12**) (87.1 g, 0.115 mol) in THF (300 mL) at 40℃ was added cyclohexylmagnesium chloride (140 mL of 2.18 M solution in THF, 0.305 mol). The mixture was stirred for 20 min, and then CuI (0.58 g, 3.0 mmol) was added at rt. The mixture was stirred for 30 min and then was filtered. The filtrate was concentrated. The residue was dissolved in cyclohexane. The solution was washed with 5% aqueous NaOH, dried, and concentrated to give ca. 60 g of an oily material. This was distilled under reduced pressure (60-62℃/10^{-3} mmHg) to afford **5b** (26.0 g, 0.11 mol, 72%) as pure crystals: mp 38-39℃; ^1H NMR δ 2.90 (2H, m), 4.80 (1H, d, J = 8.0 Hz), 5.54 (1H, dt, J = 8.0, 4.0 Hz), 5.66 (2H, m), 6.70

(1H, t, J = 8.0 Hz), 7.20 (2H, m); ^{13}C (67.9 MHz) 40.61, 55.12, 87.05, 102.45, 121.69, 123.18, 129.57, 130.29, 130.55, 131.16, 156.84; IR (neat) 3060, 2950, 1600, 1585, 1480, 1220, 1162, 1130, 1050, 945, 860, 832, 770, 750, 740, 710 cm^{-1}; MS m/e 238, 236 (M^+), 209, 211, 128. Anal. calcd for $C_{11}H_9BrO$: C, 55.72; H, 3.83; Br, 33.80. Found: C, 55.46; H, 3.82; Br, 34.10.

3,5-*cis*-Bis(2,4,6-tribromophenoxy)-1-cyclopentene (13).

In a manner similar to that used to prepare **12**, **13** (131 g, 0.133 mol, 51%) was prepared from 2,4,6-tribromophenol (193 g, 0.509 mol) and 3,5-*cis*-dibromocyclopentene (59 g, 0.26 mol). **13**: mp 253-254℃; ^{1}H NMR δ 2.73 (1H, m), 3.06 (1H, m), 5.05 (2H, m), 6.24 (2H, s), 7.68 (4H, s); IR (KBr) 1600, 1570, 1470, 805, 780 cm^{-1}; MS m/e 393 (M^+ - 327), 327. Anal. calcd for $C_{17}H_{10}Br_6O_2$: C, 28.14; H, 1.39; Br, 66.07. Found: C, 28.09; H, 1.37; Br, 65.78.

3a,8b-*cis*-Dihydro-3*H*-5,7-dibromocyclopenta[*b*]benzofuran (14).

In a manner similar to that (Grignard exchange reaction) used to prepare **5b**, crude product (**14**) (20 g) was obtained after the work-up of the reaction mixture using the hexabromide (**13**) (50 g, 0.069 mol). Recrystallization (EtOAc/cyclohexane) gave pure **14** (15 g, 0.0457 mol, 69%): mp 110-112℃; ^{1}H NMR δ 2.90 (2H, m), 4.48 (1H, m), 5.60 (1H, m), 5.80 (2H, m), 7.25 (1H, d, J = 2.0 Hz), 7.40 (1H, d, J = 2.0 Hz); ^{13}C (67.9 MHz) 40.59, 55.06, 87.74, 103.06, 112.10, 126.32, 130.00, 130.12, 132.02, 133.20, 156.38; IR (KBr) 3070, 2980, 2920, 1585, 1570, 865, 830, 740, 718 cm^{-1}; MS m/e 318 (M^+ for $C_{11}H_8O^{81}Br_2$), 316 (M^+ for $C_{11}H_8O^{81}Br^{79}Br$), 314 (M^+ for $C_{11}H_8O^{79}Br_2$); Anal. calcd for $C_{11}H_8Br_2O$: C, 41.81; H, 2.55; Br, 50.58. Found: C,41.67; H, 2.53; Br, 50.60.

1,2-*trans*-2,3a,8b-*cis*-2,3,3a,8b-Tetrahydro-1-bromo-2-hydroxy-1*H*-cyclopenta[*b*]-benzofuran (17).

The benzofuran derivative (**5a**) (439 mg, 2.78 mmol) was added to a mixture of DMSO and H_2O (18:1, 7 mL). To the mixture was added NBS (741 mg, 4.17 mmol). The resulting mixture was stirred at 0-5℃ for 1 hr. To the solution were added $NaHCO_3$ (100 mg) and H_2O (1 mL). The mixture was extracted with a mixture of cyclohexane and EtOAc (cyclohexane : EtOAc = 3:1, 10 mL × 15). The organic layer was separated, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (cyclohexane:EtOAc = 3:1) to give bromohydrin (**17**) (537 mg, 2.11 mmol, 75.9 %) and regioisomer (**21**) (93.8 mg, 0.368 mmol, 13.2%), and stereoisomer (**19**) (41.9 mg, 0.164 mmol, 5.9%).

17: mp 92.0-93.0℃; ^{1}H NMR δ 2.17 (1H, dt, J = 14.2, 4.5 Hz), 2.73 (1H, dt, J = 14.2, 6.2 Hz), 2.9 (1H, s), 4.16 (2H, m), 4.22 (1H, dd, J = 8, 4.4 Hz), 5.33 (1H, m), 6.6-7.4 (4H, m); IR (KBr) 3600-3300, 3030, 2960, 2920, 1590, 1473, 1407, 1240, 1220, 1165, 1100, 1060, 1020, 958, 920, 860, 812, 747, 690

cm^{-1}; LRMS m/e 256 (M^+ for $C_{11}H_{11}O_2{}^{81}Br$), 254 (M^+ for $C_{11}H_{11}O_2{}^{79}Br$), 175, 158, 131; HRMS (EI) Calcd for $C_{11}H_{11}O_2Br$: 254.0142. Found: 253.9916.

3a,8b-*cis*-Dihydro-3*H*-1,2-*syn*-epoxycyclopenta[*b*]benzofuran (6a).

The obtained bromohydrin (**17**) (347 mg, 1.36 mmol) was dissolved in MeOH (5 mL), and K_2CO_3 (376 mg, 2.7 mmol) was added to the solution. The mixture was stirred at rt for 1 hr and treated with ether (10 mL). The resulting mixture was filtered and the filtrate was concentrated. The residue was purified by column chromatography (cyclohexane : EtOAc = 3:1) to give *syn*-epoxide (**6a**) (198.7 mg, 1.14 mmol, 84%): mp 96.0-97.0℃; ^1H NMR δ 2.23 (1H, dd, J = 16.0, 8.0 Hz), 2.56 (1H, d, J = 16.0 Hz), 3.68 (2H, s), 3.77 (1H, d, J = 8 Hz), 5.32 (1H, t, J = 8.0 Hz), 6.6-7.4 (4H, m); IR (KBr) 3020, 2960, 2920, 1592, 1478, 1223, 1019, 962, 932, 840, 750 cm^{-1}; MS m/e 174 (M^+), 145, 131, 118.

3a,8b-*cis*-Dihydro-3*H*-1,2-*anti*-epoxycyclopenta[*b*]benzofuran (23).

To the solution of benzofuran derivative (**5a**) (100 mg, 0.633 mmol) in CH_2Cl_2 (2 mL) was added MCPBA (164 mg, ca. 0.8 mmol) at 0℃. The mixture was stirred at 0℃ for 2.5 hr and treated with saturated $NaHCO_3$ aqueous solution (3 mL). The resulting mixture was extracted with ether (10mL × 2). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (cyclohexane : EtOAc = 10:1) to give *anti*-epoxide (**23**) (85 mg, 0.49 mmol, 77%): mp 58.5-59.2℃; ^1H NMR δ 2.0 (1H, dt, J = 15.6, 4.0 Hz), 2.66 (1H, dd, J = 15.6, 7.5 Hz), 3.52 (1H, t, J = 4.0 Hz), 3.68 (1H, d, J = 4.0 Hz), 4.12 (1H, d, J = 7.5 Hz), 5.01 (1H, dt, J = 7.5, 4.0 Hz), 6.7-7.3 (4H, m); IR (KBr) 3060, 3020, 2950, 2920, 1605, 1590, 1475, 1452, 1292, 1222, 1165, 1040, 1015, 980, 935, 915, 838, 750, 693 cm^{-1}; LRMS m/e 174 (M^+), 145, 131, 118; HRMS (EI) Calcd for $C_{11}H_{10}O_2$: 174.0681. Found: 174.0655.

4-(Tetrahydropyranyloxy)butyl iodide.

To THF (50 mL) was added $NaBH_4$ (0.56 g, 15 mmol) under N_2. After cooling, I_2 (7.62 g, 30 mmol) solution in THF (20 mL) was added to the mixture. The solution was stirred for 1 hr and cooled in an ice bath. To the solution was added H_2O (30 mL). The resulting mixture was concentrated and extracted with ether. The organic layer was dried over $MgSO_4$ and concentrated to afford crude 4-iodo-1-butanol (6.82 g, 34.1 mmol, 75.8%).[11]

The resultant crude 4-iodo-1-butanol (6.7 g, ca. 33.5 mmol) was dissolved in CH_2Cl_2 (30 mL). After cooling in an ice bath, *p*-toluenesulfonic acid (57 mg in THF 0.5 mL) and dihydropyrane (4.5 g, 53 mmol) were added to the solution. The solution was stirred for 40 min, treated with pyridine (1 drop) and saturated $NaHCO_3$ aqueous solution (3 mL), and filtered. The filtrate was concentrated to give crude product (9.5 g).

The residue was purified by column chromatography (silica gel 200 g, cyclohexane : EtOAc = 97:3) to afford 4-(tetrahydropyranyloxy)butyl iodide (8 g, 28 mmol, 84%): ^{1}H NMR δ 2.4-3.0 (10H, m), 3.1-4.0 (6H, m), 4.56 (1H, m); IR (neat) 2930, 2850, 1435, 1345, 1255, 1220, 1165, 1130, 1110, 1070, 1025, 980, 898, 865, 810 cm^{-1}.

3a,8b-*cis*-Dihydro-3*H*-5-(4-tetrahydropyranyloxybutyl)cyclopenta[*b*]benzofuran (5c).

The benzofuran derivative (**5b**) (150 mg, 0.632 mmol) was dissolved in THF (7 mL) and treated with n-BuLi (ca. 2 M, 0.32 mL, 0.64 mmol) at -78℃. After stirring for 15 min, 4-(tetrahydropyranyloxy)butyl iodide (216 mg, 0.758 mmol) was added to the solution. The solution was stirred at -78℃ for 2 hr and at -72℃ for 2 hr. To the solution was added brine, and the resulting mixture was extracted with ether (20 mL × 2). The organic layers were combined, dried over Na_2SO_4, and concentrated to give an oily product (230 mg). The residue was purified by HPLC (cyclohexane : acetone = 95:5) to afford **5c** as a colorless oil (171 mg, 0.545 mmol, 86.2%): ^{1}H NMR δ 1.3-2.0 (10H, m), 2.58 (2H, t, J = 7.0 Hz), 2.84 (2H, m), 3.4 (2H, m), 3.8 (2H, m), 4.37 (1H, d, J = 8 Hz), 4.56 (1H, m), 5.44 (1H, m), 5.74 (2H, s), 6.7-7.1 (3H, m); IR (neat) 3040, 2920, 2850, 1590, 1440, 1340, 1330, 1310, 1065, 1010, 855, 810, 748 cm^{-1}; MS m/e 314 (M^+), 230, 214, 171.

3a,8b-*cis*-Dihydro-3*H*-5-[4-(tetrahydropyranyloxy)butyl]-1,2-*syn*-epoxycyclopenta[*b*]-benzofuran (6b).

The benzofuran derivative (**5c**) (720 mg, 2.3 mmol) was added to a mixture of DMSO and H_2O (18:1, 20 mL). To the mixture were added THF (3 mL) and NBS (575 mg, 3.22 mmol). The resulting mixture was stirred at 0-5℃ for 1.5 hr. To the solution were added saturated $NaHCO_3$ aqueous solution (5 mL) and brine (3 mL). The mixture was extracted with ether (200 mL). The organic layer was separated, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography (cyclohexane : EtOAc = 1:1) to give pure bromohydrin (**18**) (459 mg, 1.12 mmol, 50%). A mixture of regioisomer (**22**) and stereoisomer (**20**) was isolated in 10% yield.

The obtained bromohydrin (**18**) (450 mg, 1.09 mmol) was dissolved in MeOH (5 mL) and K_2CO_3 (322 mg, 2.3 mmol) was added to the solution. The mixture was stirred at 0℃ for 1.5 hr and concentrated. To the residue were added ether (20 mL), NH_4Cl aqueous solution (5 mL), and brine (5 mL). The organic layer was separated and the aqueous layer was extracted with ether (20 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography to give *syn*-epoxide (**6b**) (320 mg, 0.97 mmol, 89%): ^{1}H NMR δ 1.4-1.8 (10H, m), 2.2 (1H, dd, J = 16, 6.6 Hz), 2.5 (3H, m), 3.5(2H, m), 3.64 (2H, m), 3.7 (2H, m), 3.84 (1H, m), 4.56 (1H, br s), 5.3 (1H, t, J = 8.0 Hz), 6.7-7.3 (3H,

m); IR (neat) 3030, 2920, 2850, 1590, 1470, 1445, 1220, 1180, 1130, 1110, 1065, 1025, 965, 840, 745 cm^{-1}; LRMS m/e 330 (M^+), 246, 227, 200, 197; HRMS (EI) Calcd for $C_{20}H_{26}O_4$: 330.1831. Found: 330.1830.

1,2-*trans*-2,3a,8b-*cis*-2,3,3a,8b-Tetrahydro-1*H*-5-(4-tetrahydropyranyloxybutyl)-1-(2-formylethenyl)-2-hydroxycylopenta[*b*]benzofuran (26).

Under Ar were dissolved 1,3-bis(methylthio)-2-methoxypropane[12] (825 mg, 5 mmol) and diisopropylamine (1.04 g, 10.3 mmol) in THF (20 mL). To the solution was dropped n-BuLi (2 M, 5 mL, ca. 10 mmol) and the resulting solution was allowed to stand at -15℃ for 70 hr in a freezer to give a deep purple solution of 1,3-bis(methylthio)allyllithium (ca. 0.19 M in THF).

The benzofuran derivative (**6b**) (315 mg, 0.95 mmol) was dissolved in THF (2 mL). The solution was added to 1,3-bis(methylthio)allyl anion (2.4 mmol) in THF solution (10 mL) at -78℃ and the resulting mixture was stirred for 2 hr. To the solution were added MeOH (1 mL) and saturated NH_4Cl aqueous solution (3 mL). The mixture was extracted with ether (100 mL). The organic layer was separated, dried over Na_2SO_4, and concentrated.

To the residue were added $HgCl_2$ (2.7 g, 10 mmol), $CaCO_3$ (1.6 g, 1.6 mmol), MeCN (12 mL), H_2O (3 mL), and THF (2 mL). The mixture was heated at 40℃ overnight under Ar and filtered. The insoluble solid was washed with ether (50 mL). The filtrate was washed with brine (10 mL), dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography to give desired product (**26**) (151 mg, 40.9%) and regioisomer (**27**) (187 mg, 50.8%).

26: ^1H NMR δ 1.5-1.8 (10H, m), 2.1 (1H, m), 2.5 (1H, m), 2.6 (2H, t, J = 7.0 Hz), 2.83 (1H, q, J = 7.4 Hz), 3.4 (2H, m), 3.62 (1H, dd, J = 8, 7 Hz), 3.8 (2H, m), 4.1 (1H, m), 4.56 (1H, br s), 5.2 (1H, m), 6.24 (1H, dd, J = 16, 7.5 Hz), 6.7-7.1 (4H, m), 9.6 (1H, d, J = 7.5 Hz); IR (neat) 3600-3300, 2930, 2850, 1687, 1635, 1590, 1475, 1445, 1255, 1230, 1190, 1135, 1115, 1070, 1025, 970, 860, 750 cm^{-1}; MS m/e 386 (M^+), 302 (M^+-84), 284 (M^+-84-18).

27: ^1H NMR δ 1.4-2.0 (10H, m), 2.2-2.7 (4H, m), 3.45 (2H, m), 3.8 (2H, m), 4.1 (3H, m), 4.56 (1H, br s), 5.22 (1H, m), 6.18 (1H, dd, J = 15, 7.0 Hz), 6.7-7.2 (4H, m), 9.5 (1H, d, J = 7.4 Hz); IR (neat) 3600-3300, 2940, 2850, 1690, 1630, 1590, 1475, 1446, 1130, 860, 752 cm^{-1}; MS m/e 386 (M^+), 302 (M^+-84), 284 (M^+-84-18).

2-Decarboxy-2-[(tetrahydropyranyloxy)methyl]-5,6,7-trinor-4,8-inter-*m*-phenylene-PGI_2 (28).

A solution of the aldehyde (**26**) (150 mg, 0.388 mmol) in THF (4 mL) was treated with n-pentyllithium (ca. 1.08 M, 1.1 mL, 1.17 mmol) at -78℃. To the solution were added MeOH (0.5 mL) and NH_4Cl aqueous

solution (0.5 mL) and the resulting mixture was extracted with ether (30 mL). The organic layer was separated, dried over $MgSO_4$, and concentrated to give the residue (200 mg). The residue was purified by column chromatography to afford 15 α isomer (**28**) (78.8 mg, 0.172 mmol, 44.3%) and 15 β isomer (**29**) (53 mg, 0.116 mmol, 30.0%).

28: ^{1}H NMR δ 0.90 (3H, t, J = 6.0 Hz), 1.2-2.1 (22H, m), 2.4-2.7 (4H, m), 3.42 (2H, t, J = 8.0 Hz), 3.8 (2H, m), 3.85 (1H, m), 4.1 (1H, m), 4.57 (1H, br s), 5.1 (1H, m), 5.62 (2H, m), 6.7-7.2 (3H, m); IR (neat) 3600-3300, 2920, 2850, 1590, 1450, 1070, 1020, 965, 865, 750 cm^{-1}; MS m/e 458 (M^+), 440 (M^+-18), 422, 396, 374, 356, 338, 302, 286, 240.

29: ^{1}H NMR δ 0.90 (3H, t, J = 6.0 Hz), 1.2-1.8 (19H, m), 2.3 (2H, br s), 2.4-2.8 (4H, m), 3.42 (2H, m), 3.8 (2H, m), 3.85 (1H, m), 4.1 (1H, m), 4.56 (1H, br s), 5.1 (1H, m), 5.65 (2H, m), 6.7-7.2 (3H, m); IR (neat) 3600-3300, 2920, 2850, 1590, 1445, 1065, 1020, 965, 860, 745 cm^{-1}; MS m/e 458 (M^+), 440 (M^+-18), 396, 385, 374, 356, 338, 312, 302, 284.

2-Decarboxy-11,15-diacetyl-2-[(tetrahydropyranyloxy)methyl]-5,6,7-trinor-4,8-inter-*m*-phenylene-PGI$_2$ (30).

A solution of the 15 α isomer (**28**) (75 mg, 0.163 mmol) in pyridine (1.2 mL) was treated with Ac_2O (1.6 mL, 16.9 mmol) at rt and stirred for 3 hr. The solution was concentrated and the resulting residue was dissolved in ether (50 mL). The organic layer was washed with saturated $NaHCO_3$ aqueous solution (3 mL), saturated $CuSO_4$ aqueous solution (5 mL), and brine (3 mL). The organic layer was separated, dried over $MgSO_4$, and concentrated to give diacetate (**30**) (82.7 mg, 0.152 mmol, 93.3%): ^{1}H NMR δ 0.90 (3H, t, J = 7.0 Hz), 2.2-2.8 (18H, m), 1.73 (3H, s), 2.06 (3H, s), 2.1 (1H, m), 2.6 (3H, m), 2.8 (1H, m), 3.4-3.9 (5H, m), 4.56 (1H, br s), 4.92 (1H, m), 5.2 (2H, m), 5.6 (2H, m), 6.7-7.1 (3H, m); IR (neat) 2930, 2840, 1735, 1590, 1250, 1020, 965, 800 cm^{-1}.

2-Decarboxy-11,15-diacetyl-2-hydroxymethyl-5,6,7-trinor-4,8-inter-*m*-phenylene-PGI$_2$ (31).

A solution of the diacetate (**30**) (82 mg, 0.151 mmol) in a mixture of MeCN (5 mL) and THF (3mL) was treated with 0.1 N HCl (3 mL) and stirred at rt for 7 hr. To the solution was added triethylamine (50 mg), saturated $NaHCO_3$ aqueous solution (3 mL), and brine (3 mL). The mixture was extracted with ether (30 mL). The organic layer was separated and concentrated. The residue was purified by column chromatography to give alcohol (**31**) (51.1 mg, 0.112 mmol, 73.9%): ^{1}H NMR δ 0.9 (3H, t, J = 6.0 Hz), 1.2-1.9 (12H, m), 1.73 (3H, s), 2.04 (3H, s), 2.1 (1H, m), 2.6 (3H, m), 2.8 (1H, m), 3.6 (1H, m), 3.64 (2H, t, J = 6.0 Hz), 4.9 (1H, m), 5.2 (2H, m), 5.6 (2H, m), 6.7-7.0 (3H, m); IR (neat) 3600-3300, 2920, 2850, 1730, 1590, 1445,

1370, 1230, 1020, 960, 800, 740 cm^{-1}; MS m/e 458 (M^+), 398 (M^+-60), 338 (M^+-60 × 2), 267, 150.

11,15-Diacetyl-5,6,7-trinor-4,8-inter-*m*-phenylene-PGI_2 (32).

A solution of the alcohol (**31**) (51 mg, 0.112 mmol) in DMF (1 mL) was treated with PDC (336 mg, 0.9 mmol) and stirred at rt overnight. After addition of H_2O (3 mL), the resulting mixture was extracted with ether (100 mL). The organic layer was separated, washed with brine (5 mL), and dried over $MgSO_4$. Concentration gave acid (**32**) (46.2 mg, 0.0979 mmol, 87.9%): ^1H NMR δ 0.9 (3H, t, J = 6.0 Hz), 1.2-2.1 (1H, m), 1.64 (3H, s), 2.06 (3H, s), 2.38 (2H, t, J = 7.0 Hz), 2.62 (2H, t, J = 7.0 Hz), 2.8 (2H, m), 3.66 (1H, dd, J = 8, 6 Hz), 4.92 (1H, q, J = 5.6 Hz), 5.2 (2H, m), 5.6 (2H, m), 6.7-7.1 (3H, m); IR (neat) 3600-2500, 2920, 2850, 1700, 1590, 1440, 1370, 1240, 1020, 965, 800, 750 cm^{-1}; MS m/e 472 (M^+), 352, 281, 225, 211, 197, 183, 169, 155, 141.

5,6,7-Trinor-4,8-inter-*m*-phenylene-PGI_2 (1).

To a solution of the acid (**32**) (46 mg, 0.0974 mmol) in MeOH (3 mL) was added 1 N NaOH aqueous solution (1 mL, 1 mmol) and the solution was stirred at rt overnight. After removal of MeOH *in vavuo*, the resulting aqueous layer was washed with cyclohexane-ether (2:1, 5 mL). The aqueous layer was adjusted to pH 2 by slow addition of 1 N HCl (1 mL) at 0℃ and extracted with EtOAc (8 mL × 4). The organic layers were combined, dried over $MgSO_4$, and concentrated to give **1** (36.7 mg, 0.0946 mmol, 97%): mp 90-92℃; ^1H NMR δ 0.90 (3H, t, J = 6.0 Hz), 1.2-1.6 (18H, m), 1.8-2.1 (3H, m), 2.35 (2H, t, J = 7.0 Hz), 2.5 (2H, m), 2.63 (2H, t, J = 6.8 Hz), 3.40 (1H, t, J = 8 Hz), 3.9 (1H, m), 4.1 (1H, m), 4.8 (3H, br s), 5.1 (1H, m), 5.6 (2H, m), 6.7-7.0 (3H, m); ^{13}C (25.2 MHz) 14.0343, 22.6594, 24.6087, 25.2433, 29.0918, 31.7233, 33.1852, 37.0838, 41.2259, 50.2411, 58.6714, 73.1932, 76.1640, 84.3037, 120.4618, 121.8263, 123.1401, 128.8906, 129.6702, 131.7129, 136.1493, 157.1540, 178.2526; IR (neat) 3600-2500, 2920, 2850, 1700, 1590, 1440, 1250, 1180, 1020, 965, 860, 740 cm^{-1}; MS m/e 388 (M^+), 370, 352, 326, 308, 219, 204, 158, 144, 131; HRMS (EI) Calcd for $C_{23}H_{32}O_5$: 388.2250. Found: 388.2276.

Prins reaction of monobromide (5b).

To the solution of **5b** (236 mg, 0.995 mmol) and paraformaldehyde (50 mg) in acetic acid (3 mL) was added concentrated sulfuric acid (0.026 mL) at 60℃. After stirring at 70℃ for 2 hr, the solution was cooled and treated with ether. The organic layer was washed with H_2O and saturated $NaHCO_3$ aqueous solution, dried, and evaporated to give an oily product (400 mg). The oil was purified by column chromatography cyclohexane : EtOAc = 4:1) to give a mixture of **33** (160 mg, 0.310 mmol, 62%) and **34** (16 mg, 0.052 mmol, 5%).

33: ^1H NMR δ 2.08 (3H, s), 2.90 (2H, m), 4.50 (1H, m), 5.00 (2H, s), 5.60 (2H, s), 5.68 (2H, m),

7.16 (1H, d, J = 1.2 Hz), 7.30 (1H, d, J = 1.2 Hz).

34: ^{1}H NMR δ 2.85 (4H, m), 3.76 (2H, s), 4.42 (2H, d, J = 7.0 Hz), 5.50 (2H, m), 5.75 (4H, m), 6.92 (1H, d, J = 1.0 Hz), 7.08 (1H, d, J = 1.0 Hz).

1,2-*trans*-2,3a,8b-*cis*-2,3,3a,8b-Tetrahydro-5,7-dibromo-2-hydroxy-1-hydroxymethyl-1*H*-cyclopenta[*b*]benzofuran (35).

The dibromide (**14**) (33 g, 0.10 mol) and trioxane (66 g, 0.73 mol) were dissolved in AcOH (400 mL) and concentrated sulfuric acid (30 mL) was added to the solution at 80℃. The mixture was stirred at 80℃ for 15 hr, cooled, and concentrated. To the residue was added EtOAc (1 L) and the organic layer was washed with H_2O (500 mL), saturated $NaHCO_3$ aqueous solution (500 mL × 5). Each aqueous layer was extracted with EtOAc (500 mL) and the combined organic layers were dried and concentrated to give an oily product (46 g). This residue was dissolved in MeOH (400 mL) and treated with 3 N NaOH aqueous solution (160 mL). The solution was stirred at rt for 30 min, concentrated, and treated with 6 N HCl (50 mL). The mixture was extracted with EtOAc (300 mL, 100 mL × 2). The combined organic layers were washed with H_2O (200 mL, 100 mL) and brine (100 mL), dried, and concentrated to afford an oily material (30 g). This residue was recrystallized from a mixture of n-hexane (50 mL) and EtOAc (25 mL) to give diol (**35**) as a colorless crystal (16 g, 0.044 mol, 42%). The mother liquor was concentrated and the resultant residue was purified by column chromatography (from cyclohexane : EtOAc = 2:1 to EtOAc) to give the diol (**35**) (8.1 g, 0.022 mol, 21%): mp 126-128℃; ^{1}H NMR δ 2.05 (2H, m), 2.54 (1H, m), 3.68 (3H, s), 4.04 (3H, m), 5.24 (1H, ddd, J = 9.5, 7.2, 5.0 Hz), 7.22 (1H, d, J = 2.0 Hz), 7.39 (1H, d, J = 2.0 Hz); IR (KBr) 3300, 2970, 2925, 2870, 1600, 1575, 750, 730 cm^{-1}; MS m/e 366 (M^++4), 364 (M^++2), 362 (M^+). Anal. calcd for $C_{12}H_{12}O_3Br_2$: C, 39.59; H, 3.32; Br, 43.90. Found: C, 39.64; H, 3.32; Br, 43.87.

4a,5a,10b-*cis*-4a,10c-*trans*-3-Methyl-7,9-dibromo-1,4a,5,5a,10b,10c-hexahydrodioxino[5,4-a]cyclopenta[*b*]benzofuran (36).

To a solution of the diol (**35**) (180 mg, 0.494 mmol) in THF (5 mL) was added 1,1-diethoxyethane (2 mL, 14 mmol). Then a part (0.3 mL) of THF solution (10 mL) of *p*-toluenesulfonic acid (200 mg) was added to the solution. The solution was stirred at 60℃ for 6 hr and at 80℃ for 1.5 hr. To the solution were added H_2O (3 mL) and $NaHCO_3$ (280 mg). The organic solvent was removed *in vacuo* and the resulting mixture was extracted with EtOAc (30 mL × 1, 20 mL × 2). The combined organic layers were washed with water and brine, dried, and concentrated. To the residue (200 mg) were added EtOAc (8 mL) and n-hexane (10 mL) and desired acetal (**36**) was recrystallized as a colorless crystal (47mg, 0.12 mmol, 24%). The mother liquor was concentrated to yield an oily material (195 mg). The residue was purified by column chromatography

(cyclohexane : EtOAc = 2:1) to give the acetal (**36**) (75 mg, 0.19 mmol, 39%): m.p. >200℃ (sublimation); ^{1}H NMR δ 1.36 (3H, d, J = 5.0 Hz), 1.7-2.2 (2H, m), 2.77 (1H, m), 3.15-3.6 (2H, m), 3.70 (1H, t, J = 10.5 Hz), 4.40 (1H, dd, J = 10.5, 4.0 Hz), 4.72 (1H, q, J = 5.0 Hz), 5.24 (1H, m), 7.24 (1H, d, J = 2.0 Hz), 7.47(1H, d, J = 2.0 Hz); IR (KBr) 2850, 1600, 1575, 1160, 750, 730 cm^{-1}; LRMS m/e 392 (M^++4), 390 (M^++2), 388 (M^+); HRMS (EI) Calcd for $C_{14}H_{14}O_3Br_2$: 387.9710. Found: 387.9292.

4-(4a,5a,10b-*cis*-4a,10c-*trans*-3-Methyl-9-bromo-1,4a,5,5a,10b,10c-hexahydrodioxino[5,4-a]cyclopenta[*b*]benzofuran-7-yl)butanolide (37).

To a solution of the acetal (**36**) (58 mg, 0.15 mmol) in THF was added a THF solution (0.85 M, 0.44 mL, 0.37 mmol) of cyclohexylmagnesium chloride under argon atmosphere. The solution was stirred at 40℃ for 2 hr. A solution of methyl 3-formylpropionate (69 mg, 0.59 mmol) in THF (0.5 mL) was cooled at -20℃ and treated with the Grignard solution described above. The mixture was stirred for 30 min, treated with a mixture of H_2O (2 mL) and 0.1 N HCl (0.1 mL), and extracted with EtOAc (2 mL × 5). The combined organic layers were washed with water, dried, and concentrated. The residue (90 mg) was purified by column chromatography (cyclohexane : EtOAc = 2:1) to give a mixture (58 mg) of desired butanolide (**37**) and hydroxyester (**38**). The mixture was dissolved in toluene (1 mL) and treated with *p*-toluenesulfonic acid (2 mg). The solution was stirred at rt for 1 hr and concentrated. To the residue were added $NaHCO_3$ (50 mg) and ether (20 mL). The mixture was stirred vigorously and filtered. The filtrate was concentrated to give almost pure butanolide (**37**) (54.5 mg, 0.138 mmol, 92%); ^{1}H NMR δ 1.35 (3H, d, J = 4.9 Hz), 1.72-2.01 (2H, m), 2.08-2.34 (1H, m), 2.44-2.80 (4H, m), 3.16 (1H, t, J = 10.7 Hz), 3.38-3.48 (1H, m), 3.71 (1H, t, J = 10.7 Hz), 4.35-4.42 (1H, m), 4.72 (1H, q, J = 4.9 Hz), 5.12-5.24 (1H, m), 5.48-5.60 (1H, m), 7.16-7.18 (1H, m), 7.30 (1H, dd, J = 5.2, 2.2 Hz); IR (KBr) 2930, 2870, 1780, 1600, 735 cm^{-1}; LRMS m/e 398 (M^++4), 396 (M^++2), 394 (M^+); HRMS (EI) Calcd for $C_{18}H_{19}O_5Br$: 394.0616. Found: 394.0411.

4-(4a,5a,10b-*cis*-4a,10c-*trans*-3-Methyl-1,4a,5,5a,10b,10c-hexahydrodioxino[5,4-a]cyclopenta[*b*]benzofuran-7-yl)butanoic acid (39).

To a solution of the butanolide (**37**) (30 mg, 0.076 mmol) in EtOAc were added 10% Pd-C (8 mg) and AcONa (8 mg). The mixture was stirred vigorously under hydrogen atmosphere at 1 atm for 16 hr and filtered. The filtrate was concentrated to give an oily product (34.5 mg). The residue was dissolved in toluene (5 mL) and the resulting solution was washed with saturated aqueous solution of $NaHCO_3$ three times. The combined aqueous layers were adjusted to pH 4 by addition of 1 N HCl and extracted with EtOAc 4 times. The combined organic layers were dried and concentrated to give acid (**39**) (22 mg, 0.069 mmol, 90%): ^{1}H NMR δ 1.36 (3H, d, J = 5.0 Hz), 1.7-2.9 (9H, m), 3.14 (1H, m), 3.41 (1H, m), 3.72 (1H, t, J = 10.5 Hz), 4.40 (1H, dd,

J = 10.5, 4.4 Hz), 4.73 (1H, q, J = 5.0 Hz), 5.08 (1H, m), 6.7-7.0 (3H, m); IR (neat) 3450 (3600-2300), 1710, 1600, 750 cm^{-1}; LRMS m/e 318 (M^+); HRMS (EI) Calcd for $C_{18}H_{22}O_5$: 318.1467. Found: 318.1462.

Methyl 4-(2,3a,8b-*cis*-1,2-*trans*-2-hydroxy-1-hydroxymethyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-5-yl)butanoate (40).

A solution of the acid (**39**) (390 mg, 1.23 mmol) in EtOAc (5 mL) was treated with excess of CH_2N_2 ether solution at 0℃ for 5 min and the solution was concentrated. The residue was dissolved in MeOH (3 mL) and treated with 1 N HCl (1 mL) at rt for 3 h. The mixture was concentrated and H_2O (1 mL) was added to the obtained residue. The mixture was extracted with EtOAc (5 mL × 3). The combined organic layers were washed with H_2O and brine, dried, and concentrated to give crude crystal (380 mg). The crude product was recrystallized from a mixture of EtOAc and n-hexane to give pure diol (**40**) (304 mg, 0.992 mmol, 80.7%): mp 69-70.5℃; ^1H NMR δ 1.7-2.7 (11H, m), 3.40 (1H, dd, J = 8.0, 7.0 Hz), 3.64 (3H, s), 3.7-4.2 (3H, m), 5.10 (1H, m), 6.76 (1H, t, J = 7.5 Hz), 6.98 (2H, m); IR (KBr) 3350 (3600-3000), 1735, 1600, 755 cm^{-1}; MS m/e 306 (M^+). Anal. calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.44; H, 7.23.

Methyl 4-(2,3a,8b-*cis*-1,2-*trans*-2-acetoxy-1-hydroxymethyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-5-yl)butanoate (43).

To a solution of the diol (**40**) (5 g, 0.016 mol) in THF (50 mL) were added triethylamine (7.5 mL, 54 mmol) and trityl chloride (7 g, 25 mmol). The solution was stirred at rt for 24 hr. In order to complete the reaction, additional amounts of triethylamine (2 mL, 14 mmol) and trityl chloride (2 g, 7 mmol) and additional stirring for 14 hr were necessary. The reaction mixture was treated with Ac_2O (13.8 mL, 0.146 mol) and pyridine (10.6 mL, 0.131 mol) and stirred at rt for 14 hr. The mixture was cooled in an ice bath, adjusted to pH 1 with 3.7 N HCl-MeOH (55 mL), and stirred at rt for 4 hr. The reaction mixture was cooled in an ice bath and adjusted to pH 6 by slow addition of $NaHCO_3$ (23.2 g). The mixture was evaporated and the resulting residue was treated with EtOAc. The mixture was filtered and the insoluble solid was washed with EtOAc. The filtrate was washed with H_2O and the aqueous layer was washed with EtOAc 3 times. The combined organic layers were washed with H_2O and brine, dried, and concentrated to give an oily product (15.8 g). The residue was purified by column chromatography to give acetate (**43**) (4.4 g, 0.0126 mol, 78%): ^1H NMR δ 1.82 (3H, s), 1.82-2.80 (10H, m), 3.66 (3H, s), 3.70 (3H, m), 5.00-5.35 (2H, m), 6.80 (3H, t, J = 7.0 Hz), 6.95 (2H, m); IR (neat) 3450, 1740, 1595, 1240, 745 cm^{-1}; LRMS m/e 348 (M^+); HRMS (EI) Calcd for $C_{19}H_{24}O_6$: 348.1573. Found: 348.1570.

11,15-Didehydroxy-11-acetoxy-15-oxo-5,6,7-trinor-4,8-inter-*m*-phenylene PGI_2 methyl ester (45).

To a solution of the acetate (**43**) (200 mg, 0.574 mmol) in dry benzene (10 mL) were added dry DMSO (10 mL, 0.14 mol), dry pyridine (0.3 mL, 3.7 mmol), trifluoroacetic acid (0.18 mL, 2.4 mmol), and DCC (453 mg, 2.20 mmol). The mixture was stirred at rt for 14 hr and filtered. The filtrate was concentrated to give the crude aldehyde (300 mg). A DME solution (10 mL) of dimethyl 2-oxoheptylphosphonate (918 mg, 4.13 mmol) was added to a DME suspension (10 mL) of NaH (55% dispersion in mineral oil, 157 mg, 3.6 mmol) and the mixture was stirred at rt for 30 min. To the mixture was added a DME solution (5 mL) of the aldehyde (300 mg) described above and the resulting mixture was stirred at rt for 30 min. The mixture was adjusted to pH 7 by addition of AcOH and concentrated. The residue was suspended in a mixture (10 mL) of pentane and ether (1:1) and the insoluble solid was filtered out. The filtrate was concentrated to give an oily material (800 mg). The residue was purified by column chromatography (cyclohexane : EtOAc = 3:1) to give enone (**45**) (150 mg, 0.339 mmol, 59.1%): ^{1}H NMR δ 0.93 (3H, t, J = 6.0 Hz), 1.78 (3H, s), 2.90 (1H, m), 3.65 (3H, s), 3.75 (1H, m), 5.00 (1H, q, J = 6.0 Hz), 5.25 (1H, m), 6.20 (1H, d, J = 17.0 Hz), 6.80 (4H, m); IR (neat) 1742, 1705, 1680, 1632, 1595, 1240, 835, 750 cm^{-1}; LRMS m/e 442 (M^+); HRMS (EI) Calcd for $C_{26}H_{34}O_6$: 442.2355. Found: 442.2353.

5,6,7-Trinor-4,8-inter-*m*-phenylene PGI$_2$ methyl ester (49)

To a solution of the enone (**45**) (2.09 g, 4.73 mmol) and $CeCl_3 \cdot 7H_2O$ (1.76 g, 4.73 mmol) in MeOH (20 mL) was added $NaBH_4$ (89.5 mg, 2.37 mmol) at 0℃ and the solution was stirred for 10 min. To the solution were added saturated $NaHCO_3$ aqueous solution (10 mL), H_2O (10 mL), and EtOAc (50 mL). The insoluble solid was filtered off and washed with EtOAc. The aqueous layer in the filtrate was separated and extracted with EtOAc (50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to give an oily product. The residue was dried with azeotropic distillation of toluene (5 mL × 2) and vacuum pump to yield a crude mixture of **47** and **48** (2.44g).

To a solution of the mixture in dry MeOH (5 mL) was added NaOMe (0.26 g, 4.73 mmol) in dry MeOH solution (15 mL). The reaction solution was stirred at rt for 7.5 hr. The solution was adjusted to pH 7 by addition of AcOH. The reaction mixture was treated with H_2O (20 mL) and extracted with EtOAc (50 mL × 2). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to give an oily product. The residue was purified by column chromatography (cyclohexane : EtOAc = 3:2-1:2) to give diol (**49**) (0.64 g, 1.6 mmol, 34%) and isomer (**50**) (0.81 g, 2.0 mmol, 43%).

49 (colorless oil): ^{1}H NMR δ 0.80-1.10 (3H, m), 1.10-1.75 (10H, m), 1.75-2.20 (3H, m), 2.32 (2H, t, J = 7.2 Hz), 2.48-2.80 (4H, m), 3.40 (1H, t, J = 8.0 Hz), 3.64 (3H, s), 3.74-4.30 (2H, m), 4.95-5.22 (1H, m), 5.50-5.70 (2H, m), 6.60-6.84 (1H, m), 6.93 (2H, d, J = 6.6 Hz); IR (neat) 3370, 1740, 1695,

1255, 970, 865, 745 cm^{-1}; LRMS m/e 402 (M^+); HRMS (EI) Calcd for $C_{24}H_{34}O_5$: 402.2406. Found: 402.2430.

50 (pale yellow crystal): mp 76.0-77.5℃; ^1H NMR δ 0.90 (3H, t, J = 6.8 Hz), 1.23-1.45 (4H, m), 1.45-1.85 (6H, m), 1.88-2.12 (3H, m), 2.33 (2H, t, J = 7.6 Hz), 2.46-2.70 (4H, m), 3.51 (1H, t, J = 8.3 Hz), 3.65 (3H, s), 3.97 (1H, q, J = 7.6 Hz), 4.10-4.22 (1H, m), 5.08-5.20 (1H, m), 5.60-5.77 (2H, m), 6.77 (1H, t, J = 7.4 Hz), 6.95 (1H, d, J = 7.4 Hz), 6.99 (1H, d, J = 7.4 Hz); IR (neat) 3478, 2929, 1717, 1455, 1355, 1288, 1189, 1089, 1023, 978, 741 cm^{-1}; HRMS (EI) Calcd for $C_{24}H_{34}O_5$: 402.2406. Found: 402.2385.

5,6,7-Trinor-4,8-inter-*m*-phenylene PGI_2 (1).

To a solution of the diol (**49**) (50 mg, 0.124 mmol) in MeOH (5 mL) was added 1 N NaOH aqueous solution (1 mL, 1 mmol) and the solution was stirred at rt for 14 hr. The solution was concentrated and adjusted to pH 4 by addition of 1 N HCl in an ice bath. The mixture was extracted with EtOAc (5 mL × 3). The combined organic layers were washed with H_2O (2 mL) and brine (2 mL), dried, and concentrated to give a solid. The solid was recrystallized from a mixture of EtOAc and n-hexane to give acid (**1**) (30 mg, 0.077 mmol, 62.5%).

2-Butyn-1-ol (54).

A mixture of 1,3-dichloro-2-butene (**52**) (250 g, 2 mol) and 10% Na_2CO_3 aqueous solution (1.25 L) was refluxed for 3 hr. After cooling, the mixture was extracted with ether three times and the combined organic layers were carefully concentrated. The obtained residue was distilled to afford 3-chloro-2-buten-1-ol (**53**) (134 g, 63%): bp 58-60℃/8 mmHg; IR (neat) 3300, 2920, 1670, 1120, 1090, 1020 cm^{-1}.

To a flask equipped with a condenser were added liquid NH_3 (3 L) and $Fe(NO_3)_3$ (1.5 g). To the mixture was gradually added Na (65 g, 2.8 mol). The obtained **53** was added to the mixture over 30 min and the resulting mixture was stirred for 14 h. The mixture was treated with NH_4Cl (148 g), stirred for 30 min, and concentrated. The residue was extracted with ether 5 times and the combined organic layers were carefully concentrated. The residue was distilled under reduced pressure to give 2-butyn-1-ol (**54**) (66 g, 47%): 55℃/8 mmHg; ^1H NMR δ 1.84 (3H, t, J = 3.0 Hz), 2.89 (1H, br s), 4.22 (2H, br s); IR (neat) 3350, 2230, 1145, 1050 cm^{-1}; GCMS m/e 70 (M^+).

1-Bromo-2-butyne (55).

To a solution of 2-butyn-1-ol (**54**) (63 g, 0.90 mol) in dry ether (250 mL) was added pyridine (5 mL) and the solution was cooled at -30℃. To the solution was added PBr_3 (86 g, 0.32 mol) and the mixture was stirred at -30℃ for 2 hr. The temperature was raised to 20℃ during a period of 3 hr. Then the mixture was stirred at

40℃ for 30 min. After the mixture was poured into brine (500 mL), the organic layer was separated and the aqueous layer was extracted with ether. The combined organic layers were dried and concentrated with Widmer column (40 cm). The residue was distilled under reduced pressure to give 1-bromo-2-butyne (**55**) (95 g, 0.71 mol, 79%): bp 60℃/80 mmHg; ^{1}H NMR δ 1.85 (3H, t, J = 3.0 Hz), 3.90 (2H, m); IR (neat) 2240, 1220, 1210 cm^{-1}.

Dimethyl 3-methyl-2-oxo-5-heptynylphosphonate (57).

To a solution of diisopropylamine (30 g, 0.30 mol) in dry THF (186 mL) was added 1.51 M n-BuLi solution (182.3 mL, 0.275 mol) at -20℃ and the solution was stirred for 20 min. Then propionic acid (12 g, 0.16 mol) was slowly added to the solution. After addition of dry HMPA (25 mL), the reaction mixture was allowed to stand at rt and stirred for 40 min. The solution was cooled in an ice bath and treated with 1-bromo-2-butyne (**55**) (16.7 g, 0.126 mol). After stirring at rt for 2 hr, the mixture was treated with 10% HCl (130 mL) and extracted with ether-pentane (1/1) three times. The combined organic layers were washed with H_2O, dried, and concentrated. The residue was treated with excess of CH_2N_2 ether solution. The resulting solution was concentrated and distilled under reduced pressure to give methyl 2-methyl-4-hexynate (**56**) (10.4 g, 0.0742 mol, 58.9%): bp 60-70℃/11 mmHg.

To a solution of dimethyl methylphosphonate (18 g, 0.145 mol) in dry THF (294 mL) was added 1.5 M n-BuLi solution (86 mL, 0.129 mol) at -78℃. The solution was stirred at -78℃ for 20 min and treated with a solution of **56** (10.4 g, 0.0742 mol) in THF (20 mL). The solution was stirred at -78℃ for 15 min and at rt for 1 hr. The solution was treated with saturated aqueous solution of oxalic acid (150 mL) and ether (300 mL). The organic layer was separated, washed with H_2O (150 mL) and brine (50 mL), and concentrated. The residue was distilled to give dimethyl 3-methyl-2-oxo-5-heptynylphosphonate (**57**) (14.7 g, 0.0633 mol, 43.7%): bp 138-142℃/0.62 mmHg; ^{1}H NMR δ 1.15 (3H, d, J = 3.0 Hz), 1.75 (3H, t, J = 3.0 Hz), 2.35 (2H, m), 2.90 (1H, m), 3.20 (2H, d, J = 18.8 Hz), 3.75 (3H, s), 3.80 (3H, s); IR (neat) 3450, 1715, 1255, 1030 cm^{-1}; MS m/e 232 (M^+).

11,15-Didehydroxy-11-acetoxy-16-methyl-15-oxo-18,19-tetradehydro-5,6,7-trinor-4,8-inter-*m*-phenylene PGI_2 methyl ester (46).

To a solution of the acetate (**43**) (250 mg, 0.721 mmol) in dry THF (2.5 mL) were added dry DMSO (2.5 mL, 35.2 mmol), dry pyridine (0.057 mL, 0.70 mmol), trifluoroacetic acid (0.042 mL, 0.55 mmol), and DCC (221 mg, 1.07 mmol). The mixture was stirred at rt for 14 hr and cooled in an ice bath. The mixture was treated with $CaCO_3$ (357 mg, 3.57 mmol) and stirred at 0℃ for 30 min.

A DME solution (1.8 mL) of dimethyl 3-methyl-2-oxo-5-heptynylphosphonate (250 mg, 1.08 mmol) was

added to a DME suspension (2 mL) of NaH (55% dispersion in mineral oil, 43 mg, 3.0 mmol) and the mixture was stirred at rt for 30 min. To the mixture was added the supernant solution of the aldehyde described above and the resulting mixture was stirred at rt for 30 min. The mixture was adjusted to pH 7 by addition of AcOH and concentrated. To the residue was added H_2O (3 mL) and EtOAc (10 mL). The insoluble solid was filtered out and washed with EtOAc (3 mL × 2). The aqueous layer in the filtrate was separated and extracted with EtOAc (3 mL × 2). The combined organic layers were washed with H_2O (2 mL) and brine (3 mL), dried over Na_2SO_4, and concentrated to give an oily material (567 mg). The residue was purified by column chromatography (cyclohexane : EtOAc = 2:1) to give enone (**46**) (240 mg, 0.530 mmol, 73.5%): ^{1}H NMR δ 1.20 (3H, d, J = 6.3 Hz), 1.78 (3H, t, J = 3.1 Hz), 1.60-2.60 (12H, m), 3.67 (3H, s), 3.68 (2H, m), 5.00 (1H, q, J = 6.3 Hz), 5.40 (1H, m), 6.25 (1H, d, J = 16.0 Hz), 6.60-7.10 (4H, m); IR (neat) 1740, 1700, 1670, 1630, 1595 cm^{-1}; LRMS m/e 452 (M^+); HRMS (EI) Calcd for $C_{27}H_{32}O_6$: 452.2199. Found: 452.2215.

16-Methyl-18,19-tetradehydro-5,6,7-trinor-4,8-inter-*m*-phenylene PGI$_2$ methyl ester (51).

To a solution of the enone (**46**) (122 mg, 0.270 mmol) and $CeCl_3 \cdot 7H_2O$ (150 mg, 0.403 mmol) in MeOH (10 mL) was added $NaBH_4$ (15 mg, 0.40 mmol) at 0℃ and the solution was stirred for 10 min. To the solution was added saturated $NaHCO_3$ aqueous solution and the mixture was stirred at 0℃ for 10 min. The mixture was concentrated and the obtained residue was treated with EtOAc (5 mL), filtrated, and washed with EtOAc (2 mL × 2). The combined filtrate was washed with H_2O and brine, dried, and evaporated to give an oily product (130 mg). The residue was purified by column chromatography (cyclohexane : EtOAc = 2:1) to give a mixture of hydroxyacetate derivative of **51** and its stereoisomer (54 mg, 0.119 mmol, 44.0%): IR (neat) 3475, 1740, 1595, 970 cm^{-1}; MS m/e 454 (M^+).

The obtained hydroxyacetate (54 mg, 0.119 mmol) in MeOH (4.5 mL) was added 4.8 N NaOMe solution (0.001 mL, 0.005 mmol). The reaction solution was stirred at rt for 1.5 hr. The solution was adjusted to pH 7 by addition of AcOH and concentrated. The residue was dissolved in EtOAc (20 mL) and the solution was washed with saturated $NaHCO_3$ aqueous solution, H_2O, and brine. The organic layer was dried and evaporated to give an oily product (55 mg). The residue was purified by column chromatography (cyclohexane : EtOAc = 1:3) to give diol (**51**) (48 mg, 0.116 mmol, 97.5%): mp 67.0-72.0℃; ^{1}H NMR δ 1.00 (3H, d, J = 6.3 Hz), 1.80 (3H, t, J = 3.1 Hz), 1.80-2.80 (14H, m), 3.45 (1H, t, J = 7.8 Hz), 3.65 (3H, s), 4.00 (2H, m), 5.10 (1H, m), 5.65 (2H, m), 6.60-7.00 (3H, m); IR (neat) 3370, 1740, 1595, 970, 745 cm^{-1}; MS m/e 412 (M^+); Anal. calcd for $C_{25}H_{32}O_5$: C, 72.79; H, 7.82. Found: C, 72.57; H, 7.81.

16-Methyl-18,19-tetradehydro-5,6,7-trinor-4,8-inter-*m*-phenylene PGI$_2$ (2).

To a solution of the diol (**51**) (41 mg, 0.099 mmol) in MeOH (4.3 mL) was added 1 N NaOH aqueous solution (1 mL, 1 mmol) and the solution was stirred at 30℃ for 17 hr. The solution was concentrated, treated with H_2O, and adjusted to pH 4 by addition of 1 N HCl in an ice bath. The mixture was extracted with EtOAc (5 mL × 3). The combined organic layers were washed with H_2O (5 mL) and brine (5 mL), dried, and concentrated to give the acid (**2**) (39 mg, 0.098 mmol, 99.0%): mp 120.0-123.0℃; ^{1}H NMR δ 1.00 (3H, m), 1.79 (3H, s), 1.50-3.00 (12H, m), 3.35 (1H, t, J = 9.1 Hz), 4.00 (2H, m), 5.20 (4H, m), 5.60 (2H, m), 6.80 (1H, m), 6.90 (2H, m); IR (neat) 3700-2200, 1710, 1595, 743 cm^{-1}; MS m/e 398 (M^+). Anal. calcd for $C_{24}H_{30}O_5$: C, 72.34; H, 7.59. Found: C, 72.01; H, 7.52.

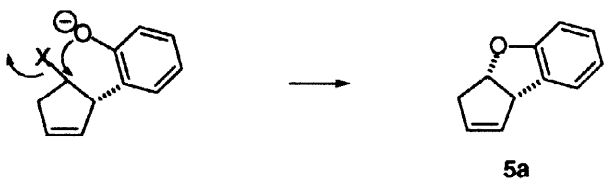
ACKNOWLEDGEMENT

We gratefully acknowledge the late Dr. K. Ohno for his leadership and passion.

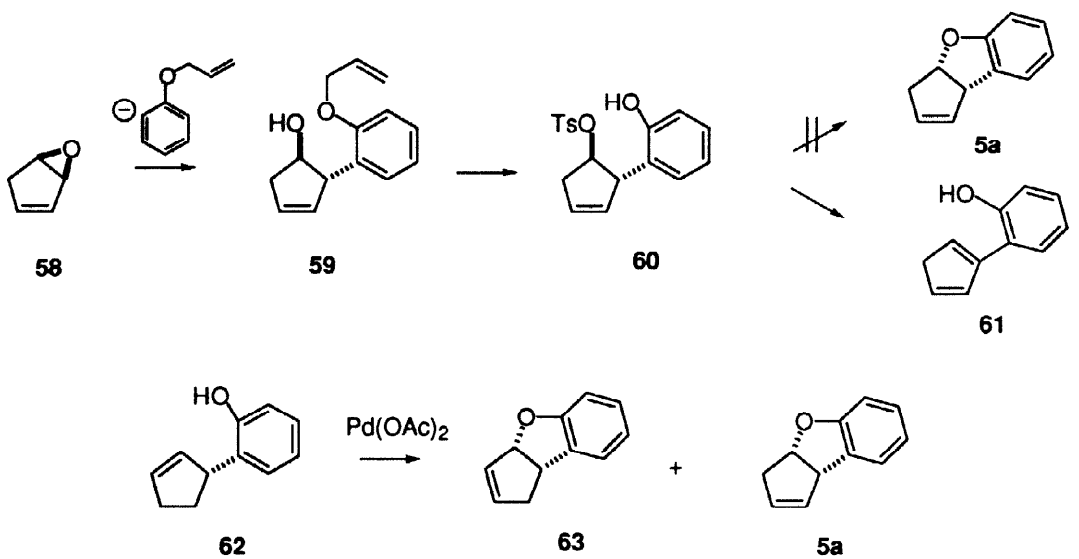
REFERENCES AND NOTES

1. Moncada, S.; Gryglewski, R.; Bunting, S.; Vane, J. R. *Nature* **1976**, *263*, 663-665.
2. (a) Bartmann, W.; Beck, G. *Angew. Chem., Int. Ed. Engl.*, **1982**, *21*, 751-764. (b) Nickolson, R. C.; Town, M. H.; Vorbruggen, H. *Med. Res. Rev.* **1985**, *5*, 1-53. (c) Collins, P. W.; Djuric, S. W. *Chem. Rev.* **1993**, *93*, 1533-1564. (d) Ohno, K; Nishiyama, H. *Tetrahedron Lett.* **1979**, 3003-3004. (e) Nishiyama, H.; Ohno, K. *Ibid.* **1979**, 3481-3484.
3. (a) Ohno, K.; Nagase, H.; Matsumoto, K.; Nishiyama, H.; Nishio, S. In *Advances in Prostaglandin, Thromboxane, and Leukotriene Research* ; vol. 15 eds. Hayashi, O; Yamamoto, S., Eds.; Ravan Press: New York, 1985; pp. 279-281. (b) Ohno, K.; Nishiyama, H.; Nagase, H.; Matsumoto, K.; Ishikawa, M. *Tetrahedron Lett.* **1990**, *31*, 4489-4492. (c) Nagase, H.; Matsumoto, K.; Yoshiwara, H.; Tajima, A; Ohno, K. *Ibid.* **1990**, *31*, 4493-4494. (d) Nagase, H.; Matsumoto, K.; Nishiyama, H. *Yuki Gosei Kagaku Kyokaishi (J. Synth. Org. Chem. Jpn.)* **1996**, *54*, 1055-1066.
4. Numbering of carbon in *m*-phenylene PGI_2 follows the literatures: (a) Nelson, N. A. *J. Med. Chem.* **1974**, *17*, 911-918. (b)Johnson, R. A.; Morton, D. R.; Nelson, N. A. *Prostaglandins*, **1978**, *15*, 737-750.
5. Retrosynthetic analysis of basic skeleton, dihydro-3*H*-cyclopenta[*b*]benzofuran derivative (**5a**) afforded another route, S_N2 reaction of phenoxide anion (Scheme 9). In fact cyclopentenol derivative (**59**) was synthesized from cyclopentadiene *via* cyclopentadienemonoxide (**58**)(Scheme 10). Tosylation and

successive base-promoted cyclization failed because of preferential elimination. Years later transformation of derivative of **60** into cyclopenta[*b*]benzofuran skeleton was effected by intramolecular Mitsunobu reaction (Yoshida, Y.; Sato, Y.; Okamoto, S.; Sato, F. *Chem. Commun.* **1995**, 811-812). As a related route the cyclization of cyclopentenylphenol (**62**) with $Pd(OAc)_2$ gave the desired benzofuran derivative (**5a**) as minor product and the isomer (**63**) as major product (Hosokawa, T.; Miyagi, S.; Murahashi, S.; Sonoda, A. *J. Org. Chem.* **1978**, *43*, 2752-2757).



Scheme 9. another route of cyclopenta[*b*]benzofuran (**5a**)



Scheme 10. Another plan of dihydro-3*H*-cyclopenta[*b*]benzofuran derivative (**5a**)

6. (a) Heasly, G.E.; Heasly, V. L.; Manatt, S. L.; Day, H. A.; Hodges, R. V.; Kroon, P. A.; Redfield, D. A.; Rold, T. L.; Williamson, D. E. *J. Org. Chem.* **1973**, *38*, 4109-4117. (b) Young, W. G.; Hall, H. K.; Winstein, Jr. S. *J. Am. Chem. Soc.* **1956**, *78*, 4338-4344.

7. The reaction of 3,5-*cis*-dibromo-1-cyclopentene with 2,6-diboromophenoxide was very slow without 18-crown-6 and the yield of 3,5-*cis*-bis(2,6-diboromophenoxy)-1-cyclopentene (**12**) was below 20% even if the reaction was performed for 1 week.

8. Nishiyama, H.; Isaka, K.; Itoh, K.; Ohno, K.; Nagase, H.; Matsumoto, K.; Yoshiwara, H. *J. Org. Chem.* **1992**, *57*, 407-410.

9. The syntheses of cyclopenta[*b*]benzofuran derivatives by using Pd(0) or radical cyclization have recently been reported, see: (a) Larock, R. C.; Lee, N. H., *US patent*, US 5169959, 1992 (*Chem. Abstr.*, 1993, **118**, 233757x). (b) Larock, R. C.; Lee, N. H., *US patent*, US 5233059, 1993 (*Chem. Abstr.*, 1994, **120**, 30609u). (c) Larock, R. C.; Lee, N. H. *J. Org. Chem.* **1991**, *56*, 6253-6254.

10. (a) Dalton, D. R.; Hendrickson, J. B.; Jones, D. G. *Chem. Commun.* **1966**, 591-592. (b) Dalton, D. R.; Jones, D. G. *Tetrahedron Lett.* **1967**, 2875-2877.

11. Long, L. H.; Freeguard, G. F. *Nature*, **1965**, *207*, 403.

12. (a) Corey, E. J.; Noyori, R. *Tetrahedron Lett.* 1970, 311-313. (b) Corey, E. J.; Erickson, B. W.; Noyori, R. *J. Am. Chem. Soc.* **1971**, *93*, 1724-1729. (c) Newton, R. F.; Howard, C. C.; Reynolds, D. P.; Wadsworth, A. H.; Crossland, N. M.; Roberts, S. M. *Chem. Commun.* **1978**, 662-664.

13. The stereochemistry at C-15 was presumed from the general knowledge in prostaglandin area that less polar compound is 15 β isomer and polar compoud is 15 α isomer: Corey, E. J.; Vlattas, I.; Anderson, N. H.; Harding, K. *J. Am. Chem. Soc.* **1968**, *90*, 3247-3248. In fact 15 β isomer of Beraprost derivative, whose stereochemistry was determined by X ray, was less polar (see reference 19).

14. Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399-402.

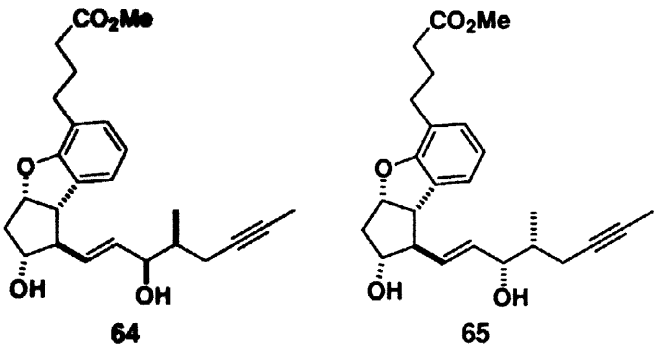
15. (a)Arundale, E.; Mikeska, L. A. *Chem. Rev.* **1952**, 505-555. (b)Adams, D. R.; Bhatnager, S. P. *Synthesis*, **1977**, 661-672. (c)Tomoskozi, I.; Gruber, L.; Kovacs, G.; Szekely, I.; Simonidesz, V. *Tetrahedron Lett.* **1976**, 4639-4642.

16. (a) Moffatt, J. G. *Organic Synthesis*, Coll. Vol. 5 eds. Baumgarten, H. E., Eds.; John Wiley and Sons. Inc.: New York, 1973; pp. 242-245. (b) Pfitzner, K. E.; Moffatt, J. G. *J. Am. Chem. Soc.* **1965**, *87*, 5661-5670. (c) Pfitzner, K. E.; Moffatt, J. G. *J. Am. Chem. Soc.* **1965**, *87*, 5670-5678.

17. Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675-5677.

18. Gemal, A. L.; Luche, J-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454-5459.

19. Absolute configuration of Beraprost (**2**) was determined by X ray analysis of **64** and **65**. The stereoselective syntheses of **64** and **65** will be reported in due course.



Scheme 11. Beraprost derivatives, whose absolute configurations were determined

20. The authors thank Dr. Shintaro Nishio at Basic Research Laboratories for pharmacological assays of the synthesized compounds (Nishio, S.; Matsuura, H.; Kanai, N.; Fukatsu, Y.; Hirano, T.; Nishikawa, N.; Kameoka, K.; Umetsu, T. *Jpn. J. Pharmacol.* **1988**, *47*, 1-10).