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A Facile Route for Synthesis of (±)-Dinoprost, (±)-Carboprost and Its Analogs

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A general synthetic approach was developed for (±)-dinoprost (**1**), (±)-carboprost (**2**) and their analogs (**3-5**) through a key intermediate (**6**). Compound **6** can be converted into the target compounds in two or three steps. Diastereomeric separation was accomplished easily for obtaining (±) dinoprost. Separation of diastereomers was difficult for (±) carboprost and their analogs. Key intermediate **6** was obtained, in turn, from (±)-corey lactone.

Key Words: Corey lactone, Dinoprost, Carboprost, $PGF_{2\alpha}$ analogs.

INTRODUCTION

Prostaglandins are a family of 20-carbon fatty acids found in virtually all mammalian cells[1,2]. These are highly biologically active and have been implicated in the mediation of many physiological responses[3,4]. Natural prostaglandins possess an allylic, secondary alcohol group at C-15 position. This alcohol group can be oxidized into a ketone in the presence of 15-hydroxyprostaglandin dehydrogenase and this process is very rapid *in vivo* in animals and man[5-7]. The oxidation to 15-keto-prostaglandins leads to the inactivation of prostaglandin *in vivo*. Thus a number of prostaglandins with different substituent's at C-15 were synthesized in order to prevent easy oxidation and maintain biological activity[8,9]. Several $PGF_{2\alpha}$ analogs are available in the clinic for various therapeutic applications (Fig. 1)[10].

Dinoprost (**1**) has been used to induce labor and as an abortifacient. Carboprost (**2**) which is the first $PGF_{2\alpha}$ analog (15(S)-15-methyl-prostaglandin $F_{2\alpha}$) of this type was developed by Upjohn chemists as tromethamine salt which is used for post partum haemorrhage indication[11,12].

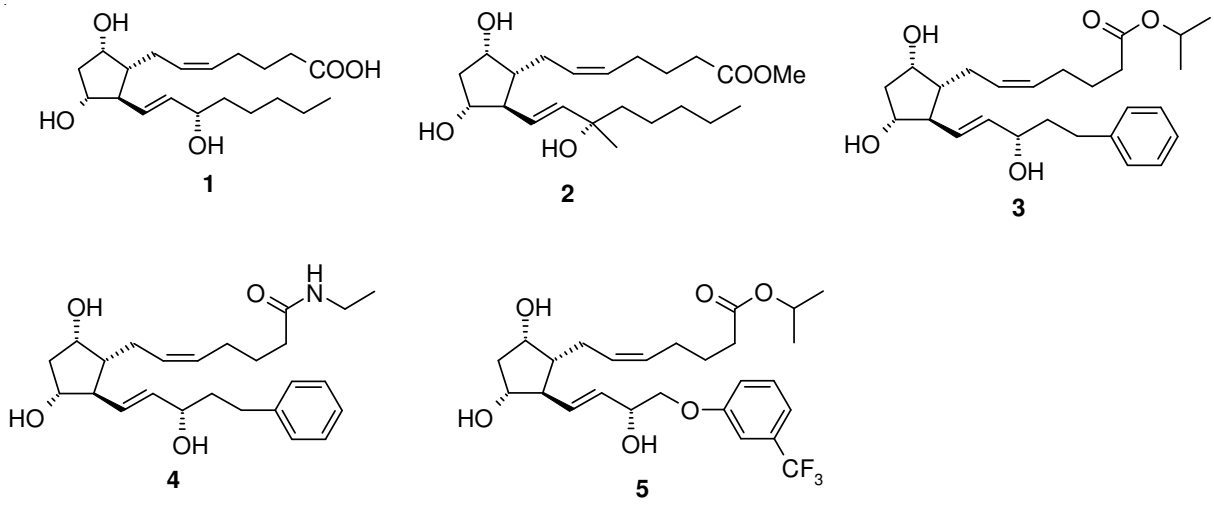


Fig. 1. $PGF_{2\alpha}$ analogs

Recently attention has been focussed on Prostaglandin $F_{2\alpha}$ esters [latanoprost (**3**), bimatoprost (**4**) and travoprost (**5**)] for the treatment of glaucoma[13-16] we have reported, recently, the general synthetic approach for synthesis of **3**, **4** and **5** using common intermediate **7**[17-19].

Literature methods for preparation of $PGF_{2\alpha}$ analogs from corey lactone (**9**) involves several steps through introduction of phosphonate ester (**8**) first at ω-side chain (lower) followed by α-side chain (upper) to get desired products[20,21]. The main variations in all $PGF_{2\alpha}$ analogs are at at ω-side chain only, so if we have to prepare a variety of analogs, the literature strategies proceeds through multiple steps even from the advance intermediate[22,23].

In this paper, our focus is to develop common key intermediate (**6**) which can be elaborated in to dinoprost (**1**), carboprost (**2**) and their analogs in two or three steps (Fig. 2). Advantage of this method over literature reported methods is that variety of analogs can be prepared from key intermediate (**6**) by reacting with different alkyl and aryl Grignard's at C-15 position to get several $PGF_{2\alpha}$ analogs in a rapid and efficient manner (Fig. 3).

EXPERIMENTAL

General: All the reactions were performed either under an argon or nitrogen atmosphere, unless otherwise mentioned. THF was distilled from sodium benzophenone ketyl, methylene dichloride (stabilized with amylene) from calcium hydride and all solvents were degassed immediately prior to use. The progress of the reactions was monitored by thin layer chromatography (TLC) over silica gel 60F (E. Merck) thin water layer (0.25 mm). The chromatograms were visualized by irradiation with UV light or by heat staining with poly phosphoric acid and *p*-anisaldehyde in ethanol/sulphuric acid. Column chromatography was performed on silica gel 60 (Merck, 70-230 mesh) and flash chromatography was performed on silica gel 60 (Merck, 230-400 mesh) using the indicated solvent. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 300 MHz NMR unit using $CDCl_3$ as solvent. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane for spectra. Infrared spectra were recorded on a Perkin-Elmer FTIR 1605 spectrometer. Mass spectra were measured on Waters Quatro Micro API.

Preparation of methyl hexanoate (10): A solution of hexanoic acid (25 g, 215.22 mmol), (1 mL) of dimethyl formamide in (125 mL) of dichloromethane were cooled to 10-15 ºC in an ice bath and thionyl chloride (51.2 g, 430.6 mmol) was added drop wise. The resulting mass slowly warmed to ambient temperature and stirred for 2 h at same temperature. Resulting mixture was cooled to 5-10 ºC and (50 mL) of MeOH was added drop wise and stirred for 1 h at room temperature which TLC indicates complete conversion of the reaction. Added (250 mL) of water and extracted with EtOAc (2 × 250 mL). The combined extracts were washed with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give compound **10** as a light yellow colour liquid. Yield: 25.7 g (92 %). FTIR (KBr, ν_{max}, cm^{-1}): 2957, 2934, 1743, 1459, 1437, 1172. ^{1}H NMR (300 MHz) ($CDCl_3$) δ (ppm): 0.86 (t, *J* = 7.0 Hz, 3H, CH_3-$(CH_2)_4$), 1.23-1.31 (m, 4H, CH_3-CH_2-$(CH_2)_2$-CH_2-C=O), 1.55-1.65 (m, 2H, CH_3-CH_2-$(CH_2)_3$-C=O), 2.28 (t, *J* = 7.5 Hz, 2H, CH_3-$(CH_2)_3$-CH_2-C=O), 3.64 (s, 3H, O-CH_3). MS (ES): m/z 131 [M+H$^+$].

Preparation of dimethyl 2-oxoheptylphosphonate (8): A solution of dimethyl methane phosphonate **11** (22.8 g, 183.75 mmol) in (100 mL) of THF were cooled to -75 to -78 ºC under nitrogen atmosphere. *n*-Butyl lithium (1.6 M in hexanes, (120 mL, 192 mmol) was added drop wise to the reaction mass at -78 ºC and stirred for 0.5 h at -75 to -78 ºC and methyl hexanoate (**10**) (10 g, 76.81 mmol) in (50 mL) of THF was added slowly into the reaction mass at -78 ºC. Resulting mixture was stirred for 0.5 h at -75 to -78 ºC and at room temperature for 0.5 h. The progress of the reaction was monitored by TLC.

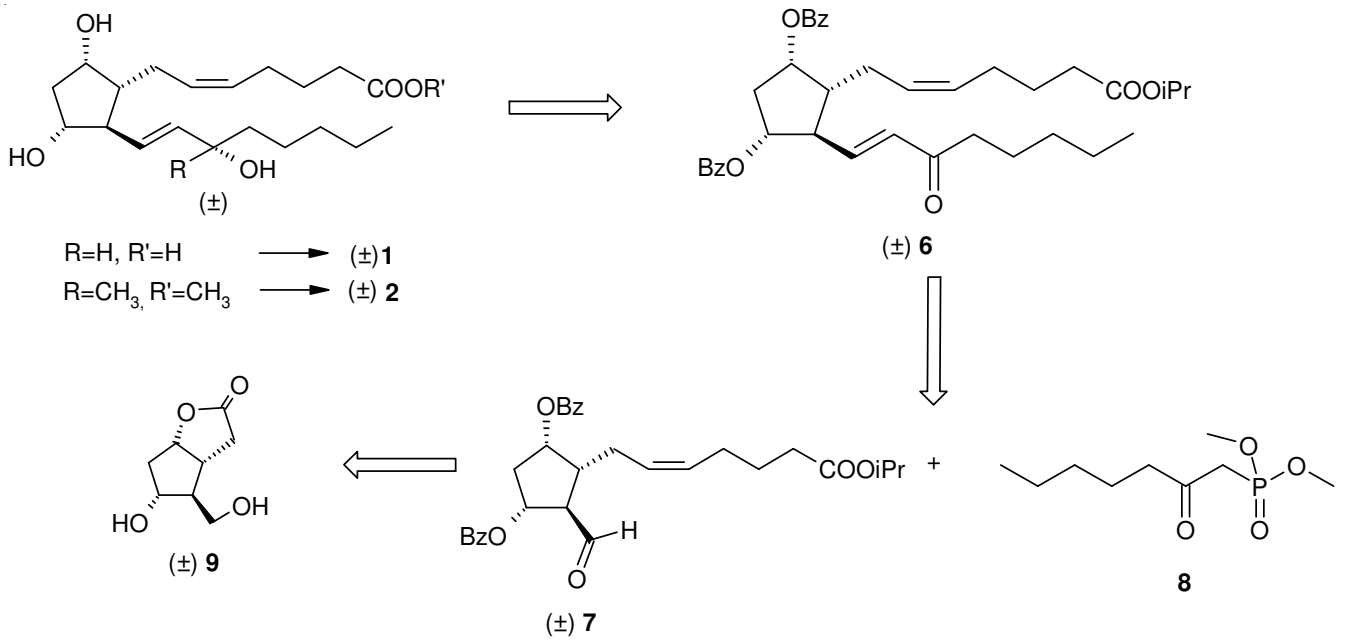


Fig. 2. Retrosythetic scheme for $PGF_{2\alpha}$ analogs

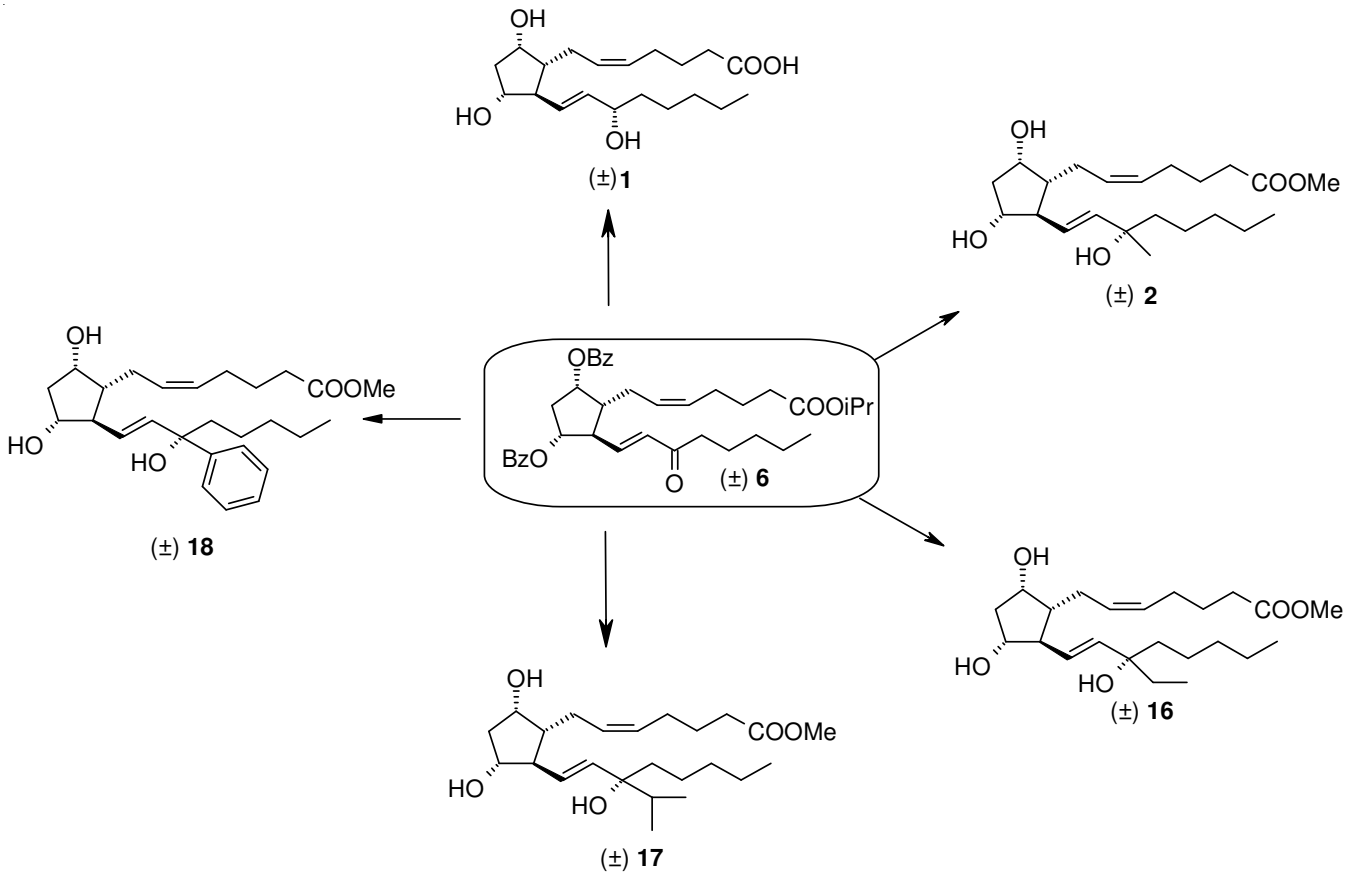


Fig. 3. Synthesis of $PGF_{2\alpha}$ analogs from key intermediate (**6**) (Overview of present work)

After completion of the reaction, (50 mL) water was added and stirred for 10 min. To the resulting mass, acetic acid (5 mL) was added and stirred for 10 min and extracted with EtOAc (2 × 250 mL). The combined extracts were washed with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (230-400 mesh) with ethyl acetate-hexane (2:8) as eluent to give compound **8** as a light yellow colour liquid. Yield: 11.9 g (70 %). IR (KBr, ν_{max}, cm^{-1}): 2957, 2934, 2861, 1716, 1460, 1251, 1185, 1032. ^1H NMR (300 MHz) ($CDCl_3$) δ (ppm): 0.87 (t, *J* = 6.9 Hz, 3H, CH_3-$(CH_2)_4$-C=O), 1.24-1.29 (m, 4H, CH_3-CH_2-$(CH_2)_2$-CH_2-C=O), 1.50-1.59 (m, 2H, CH_3-CH_2-$(CH_2)_3$-C=O), 2.59 (t, *J* = 7.2 Hz, 2H, CH_3-$(CH_2)_3$-CH_2-C=O), 3.09 (d, *J* = 22.8 Hz, 2H, P-CH_2-C=O), 3.78 (d, *J* = 11.4 Hz, 6H, P-$(O\text{-}CH_3)_2$). MS (ES): m/z 223 [M+H^+].

Preparation of 4-((*Z*)-7-isopropoxy-7-oxohept-2-enyl)-5-((*E*)-3-oxooct-1-enyl) cyclopentane-1, 3-diyl dibenzoate (6): A suspension of 60 % sodium hydride (0.59 g, 14.822 mmol) in (21 mL) of dimethoxyethane was cooled to 0 to -5 ºC under nitrogen atmosphere. Resulting mixture was cooled to -5 to 0 ºC, dimethyl 2-oxoheptylphosphonate (**8**) (3.3 g, 14.82 mmol) in (12 mL) of dimethoxyethane was added drop wise at -5 to 0 ºC and stirred for 15 min at 0 ºC. Resulting mass temperature was raised to ambient temperature and stirred for 1 h at same temperature. Resulting mass temperature was further cooled to 0 to -5 ºC and (*Z*)-4-formyl-5-(7-isopropoxy-7-oxohept-2-enyl)cyclopentane-1,3-diyl dibenzoate (**7**) (3 g, 5.9288 mmol) in dimethoxyethane (12 mL) was added slowly over a period of 0.5 h at -5 to 0 ºC. Reaction mixture temperature was raised to room temperature and stirred for 1.5 h at ambient temperature. The reaction mixture was cooled to 10 ºC and added saturated ammonium chloride solution (30 mL) then stirred for 10 min and concentrated under vacuum at below 40 ºC. Obtained residue was dissolved in EtOAc (30 mL) and separated aqueous layer was extracted with EtOAc (2 × 50 mL). Combined organic layers were washed with brine (25 mL) and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure at below 40 ºC. Crude was purified by flash column chromatography on silica gel (230-400 mesh) with ethyl acetate-hexane (3:7) as eluent to give compound **6** as a yellow colour liquid. Yield: 2.3 g (65 %). IR (KBr, ν_{max}, cm^{-1}): 3063, 2955, 2932, 1721, 1683, 1452, 1374, 1273, 1111, 1070. ^1H NMR (300 MHz) ($CDCl_3$) δ (ppm): 0.88 (t, *J* = 7.2 Hz, CH_3-$(CH_2)_4$-C=O), 1.18 (d, *J* = 6.3 Hz, 6H, HC-$(CH_3)_2$), 1.32 (m, 5H, $2CH_2$, CHa), 1.48-1.67 (m, 5H, $2CH_2$, CHb), 1.87-1.90 (m, 2H, CH_2), 2.04 (t, *J* = 7.5 Hz, 2H, CH_2), 2.20-2.24 (m, CH), 2.32-2.37 (m, CH), 2.57 (t, *J* = 7.5 Hz, 2H, CH_3-$(CH_2)_3$-CH_2-C=O), 2.64-2.72 (m, 1H, CHa), 2.99-3.03 (m, 1H, CHb), 4.94 (m, 1H, CH, $CH(CH_3)_2$), 5.30-5.38 (m, 3H, HC=CH(*cis*), OBz-CH), 5.47 (t, *J* = 4.5 Hz, 1H, OBz-CH), 6.26 (d, *J* = 15.9 Hz, 1H, O=C-CH (*trans*)), 6.86 (dd, *J* = 15.9, 8.7 Hz, 1H, HC-CH (*trans*)), 7.32 (t, *J* = 7.8 Hz, 2H, H_{Ar}), 7.45 (t, *J* = 7.5 Hz, 2H, H_{Ar}), 7.50 (t, *J* = 7.5 Hz, 1H, H_{Ar}), 7.59 (t, *J* = 7.5 Hz, 1H, H_{Ar}), 7.91 (dd, *J* = 8.1, 1.5 Hz, 2H, H_{Ar}), 8.07 (dd, *J* = 8.1, 1.5 Hz, 2H, H_{Ar}). MS (ES): m/z 603 [M+H^+].

Preparation of 4-((*E*)-3-hydroxyoct-1-enyl)-5-((*Z*)-7-isopropoxy-7-oxohept-2-enyl)cyclo-pentane-1,3-diyl

dibenzoate (12): Compound **6** (0.7 g,1.1614 mmol) in 7 mL of methanol was cooled to 0 ºC and sodium borohydride (0.08 g, 2.322 mmol) was added at 0 ºC and stirred for 10 min. The resulting mixture temperature was raised to ambient temperature and stirred for 0.5 h at which TLC indicates complete conversion of the reaction. Solvent was concentrated under vacuum at below 40 ºC. Saturated ammonium chloride solution (7 mL) was added to the residue and stirred for 10 min. Aqueous layer was extracted with EtOAc (2 × 25 mL). Combined ethyl acetate layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure at below 40 ºC to obtain residue. Crude product was purified by flash column chromatography on silica gel (230-400 mesh) with ethyl acetate-hexane (3:7) as eluent. The pure fractions were combined and the distilled under vacuum at 40 ºC to give compound **12** as a yellow colour liquid. Yield: 0.60 g (85 %). ^{1}H NMR (300 MHz) ($CDCl_3$) δ (ppm): 0.84 (t, *J* = 7.2 Hz, 3H, CH_3-$(CH_2)_4$-HC-OH), 1.22 (d, *J* = 6.3 Hz, 6H, HC-$(CH_3)_2$), 1.25 (m, 6H, $3CH_2$), 1.46-1.53 (m, 4H, CH_2, CHa, CH), 1.61-1.85 (m, 4H, $2CH_2$), 2.08-2.18 (m, 2H, CHb, CH), 2.25 (t, *J* = 7.2 Hz, 2H, CH_2), 2.59-2.77 (m, 2H, CH_2), 4.06-4.12 (m, 1H, HO-CH), 4.95-5.02 (m, 1H, OBz-CH), 5.12-5.18 (m, 1H, OBz-CH), 5.35-5.67 (m, 4H, HC=CH(*cis*), HC=CH(*trans*)), 7.41 (t, *J* = 7.2 Hz, 2H, H_{Ar}), 7.54 (t, *J* = 7.2 Hz, 2H, H_{Ar}), 8.00 (m, 1H, H_{Ar}). MS (ES): m/z 622 [M+NH_3^+].

Preparation of (*Z*)-methyl 7-(3, 5-dihydroxy-2-((*E*)-3-hydroxyoct-1-enyl)cyclopentyl)hept-5-enoate (13): Compound **12** (0.4 g, 0.661 mmol), potassium carbonate (0.36 g, 2.64 mmol) and 4 mL of MeOH were stirred at ambient temperature for 6 h. The progress of the reaction was monitored by TLC. After complete conversion of the reaction, 4 mL of water was added and pH adjusted to 2 with 10 % citric acid (4 mL) and aqueous layer was extracted with EtOAc (3 × 10 mL). Combined ethyl acetate layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure at 40 ºC to obtain crude product. Crude product contains two diastereomers and desired isomer was separated by flash column chromatography on silica gel (230-400 mesh) with ethyl acetate-hexane (6:4) as eluent. The pure fractions were combined and concentrated under vacuum at 40 ºC to give compound **13**. Yield: 0.12 g (50 %). IR (KBr, ν_{max}, cm^{-1}): 3379, 3006, 2929, 2857, 1739, 1723, 1455, 1436, 1315, 1173, 1026. ^{1}H NMR (300 MHz) ($CDCl_3$) δ (ppm): 0.87 (t, *J* = 7.2 Hz, 3H, CH_3-$(CH_2)_4$-HC-OH), 1.26 (m, 4H, $2CH_2$), 1.46-1.53 (m, 5H, $2CH_2$, CH), 1.68 (t, *J* = 7.2 Hz, 2H, CH_2), 1.72 (m, 2H, CH_2), 2.05-2.24 (m, 5H, $2CH_2$, CH), 2.31 (t, *J* = 7.2 Hz, 2H, CH_2), 3.66 (s, 3H, O-CH_3), 3.95 (br, 1H, HO-CH), 4.06 (q, *J* = 6.3 Hz, 1H, HO-CH-HC=CH(*trans*)), 4.18 (br, 1H, HO-CH), 5.37-5.43 (m, 2H, HC=CH(*cis*)), 5.48-5.55 (m, 2H, HC=CH(*trans*)). ^{13}C NMR (75 MHz) ($CDCl_3$) δ (ppm): 13.90, 22.50, 24.68, 25.09, 26.49, 31.61, 33.29, 37.11, 42.70, 50.30, 51.47, 55.66, 72.77, 72.94, 77.33, 128.98, 129.52, 132.50, 135.10, 174.24. MS (ES): m/z 391 [M+Na^+].

Preparation of (*Z*)-7-(3,5-dihydroxy-2-((*E*)-3-hydroxy-oct-1-enyl)cyclopentyl)hept-5-enoic acid (1): To a solution of compound **13** (0.3 g, 0.815 mmol) in 3 mL of THF was added lithium hydroxide monohydrate (0.13 g, 3.2608 mmol) and stirred for 2 h at ambient temperature at which TLC indicates complete conversion of the reaction. Water (3 mL) was added to the reaction mixture and pH adjusted to 2 with 10 % citric acid (3 mL) and aqueous layer was extracted with EtOAc (3 × 10 mL). Combined ethyl acetate layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure at 40 ºC to obtain crude. Crude product was purified by column chromatography on silica gel (230-400 mesh) using EtOAc/hexane gradient system (9:1) as eluent. The pure fractions were combined and the solvent was removed in vacuum at 40 ºC to give compound **1** as a light yellow colour viscous liquid. Yield: 0.24 g (85 %). IR (KBr, ν_{max}, cm^{-1}): 3368, 3009, 2958, 2929, 2859, 1720, 1458, 1276, 1218. ^{1}H NMR (300 MHz) ($CDCl_3$) δ (ppm): 0.88 (t, *J* = 7.2 Hz, 3H, CH_3-(CH_2)4-C-OH), 1.23-1.68 (m, 13H, $6CH_2$, CH), 2.08-2.35 (m, 9H, $4CH_2$, CH), 3.96-4.23 (m, 3H, (HO-$CH)_3$), 5.34-5.62 (m, 4H, HC=CH(*cis*), HC=CH(*trans*)). ^{13}C NMR (75 MHz) ($CDCl_3$) δ (ppm): 13.94, 22.51, 24.2, 24.45, 25.04, 25.13, 31.65, 33.09, 36.90, 42.79, 50.64, 55.16, 72.37, 73.13, 77.60, 129.38, 130.78, 132.82, 135.04, 177.52. MS (ES): m/z 377 [M+Na^+]. HRMS (ESI): Calcd. for $C_{20}H_{34}O_5$ Na [M+ Na]$^+$ 377.2304; found 377.2307.

Preparation of 15: (General procedure for Grignard reaction) 15a-d: Compound **6** (1.2 g, 1.991 mmol) and anhydrous THF (12 mL) were cooled to -75 to -80 ºC, phenyl magnesium chloride (**14a-d**) (previously prepared by magnesium turnings (0.1 g, 4.34 mmol) and catalytic amount of iodine and dibromoethane in anhydrous THF (1.2 mL) were heated to 75-85 ºC under nitrogen atmosphere and phenyl bromide (0.5 g, 3.205 mmol) was diluted with 1.2 mL of anhydrous THF slowly added over a period of 15 min at 75-85 ºC and stirred for 2 h at 75-85 ºC) was added to reaction mass at -75 to -80 ºC under nitrogen atmosphere and stirred for 2 h at -75 to -80 ºC. After complete conversion indicates by TLC 10 % citric acid solution was added and stirred for 10 min at room temperature. Aqueous layer extracted with ethyl acetate (3 × 15 mL) and combined organic layers were dried over anhydrous sodium sulphate and concentrated under reduced pressure and purified by flash column chromatography on silica gel (230-400 mesh) with ethyl acetate-hexane (3:7) as eluent. The pure fractions were combined and the solvent was removed under reduced pressure at below 40 ºC to give compound (**15a-d**).

4-[(*E*)-3-Hydroxy-3-methyloct-1-enyl]-5-[(*Z*)-7-isopropoxy-7-oxohept-2-enyl]cyclopentane-1,3-diyl-dibenzoate (15a): IR (KBr, ν_{max}, cm^{-1}): 3525, 3063, 2956, 2930, 2857, 1721, 1452, 1374, 1271, 1176, 1111, 1070. ^{1}H NMR (300 MHz) ($CDCl_3$) δ (ppm): 0.84 (t, *J* = 6.9 Hz, 3H, CH_3-$(CH_2)_4$), 1.18 (s, 3H, CH_3-C-OH), 1.27 (d, 6H, *J* = 6.9 Hz, HC-$(CH_3)_2$), 1.25-1.53 (m, 8H, $3CH_2$, CHa, CH), 1.87-2.09 (m, 8H, $3CH_2$, CHb, CH), 2.28 (t, 2H, *J* = 7.5 Hz, CH_2), 2.68-2.72 (m, 1H, CHa), 2.84-2.87 (m, 1H, CHb), 4.91-4.99 (m, 1H, $CH(CH_3)_2$), 5.20-5.27 (m, 1H, OBz-CH), 5.30-5.46 (m, 3H, OBz-CH, HC=CH(*cis*)), 5.60-5.76 (m, 2H, HC=CH(*trans*)), 7.33 (t, 2H, *J* = 7.5 Hz, H_{Ar}), 7.44 (t, 2H, *J* = 7.5 Hz, H_{Ar}), 7.48 (t, 1H, *J* = 7.8 Hz, H_{Ar}), 7.56 (t, 1H, *J* = 7.5 Hz, H_{Ar}), 7.93 (dd, 2H, *J* = 7.5, 1.2 Hz, H_{Ar}), 8.07 (dd, 2H, *J* = 7.5, 1.2 Hz, H_{Ar}). MS (ES): m/z 636 and 641 [M+NH_3^+] and [M+Na^+].

4-[(*E*)-3-Ethyl-3-hydroxyoct-1-enyl]-5-((*Z*)-7-isopropoxy-7-oxohept-2-enyl)cyclopentane-1,3-diyl-dibenzoate (15b): IR (KBr, ν_{max}, cm^{-1}): 3427, 3063, 2958, 2933, 2872, 1720, 1602, 1452, 1374, 1271, 1176, 1111, 1070. ^{1}H NMR

(300 MHz) ($CDCl_3$) δ (ppm): 0.79 (t, 3H, *J* = 7.2 Hz, CH_3-$(CH_2)_4$), 0.87 (t, 3H, *J* = 7.5 Hz, CH_3-CH_2-C-OH), 1.19 (d, 6H, *J* = 6.3 Hz, HC-$(CH_3)_2$), 1.20-1.25 (m, 4H, $2CH_2$), 1.51-1.56 (m, 4H, $2CH_2$), 1.87-2.02 (m, 6H, $3CH_2$), 2.06 (t, 2H, *J* = 7.2 Hz, CH_2), 2.29 (t, 2H, *J* = 6.9 Hz, CH_2), 2.69-2.74 (m, 1H, CH), 2.86-2.89 (m, 1H, CH), 4.07 (q, 2H, *J* = 7.2 Hz, CH_3-CH_2-C-OH), 4.91-4.99 (m, 1H, HC-$(CH_3)_2$), 5.20-5.50 (m, 4H, HC=CH(*cis*), (OBz-$CH)_2$), 5.62 (d, 2H, *J* = 3.9 Hz, HC=CH(*trans*)), 7.33 (t, 2H, *J* = 7.5 Hz, H_{Ar}), 7.47 (t, 2H, *J* = 7.5 Hz, H_{Ar}), 7.50 (t, 1H, *J* = 7.2 Hz, H_{Ar}), 7.58 (t, 1H, *J* = 7.5 Hz, H_{Ar}), 7.93 (dd, 2H, *J* = 8.1, 1.5 Hz, H_{Ar}), 8.07 (dd, 2H, *J* = 8.1, 1.5 Hz, H_{Ar}). MS (ES): m/z 655 [M+Na^+].

4-((*E*)-3-Hydroxy-3-isopropyloct-1-enyl)-5-((*Z*)-7-isopropoxy-7-oxohept-2-enyl)cyclopentane-1,3-diyl dibenzoate (15c): IR (KBr, ν_{max}, cm^{-1}): 3525, 3063, 2957, 2930, 1721, 1452, 1374, 1271, 1176, 1111, 1070. ^{1}H NMR (300 MHz) ($CDCl_3$) δ (ppm): 0.85 (t, 3H, *J* = 7.2 Hz, CH_3-$(CH_2)_4$), 0.90 (d, 6H, *J* = 6.3 Hz, HC-$(CH_3)_2$), 1.19 (d, 6H, *J* = 6.3 Hz, O-CH-$(CH_3)_2$), 1.20-1.31 (m, 8H, $4CH_2$), 1.45-1.72 (m, 3H, CH_2, CH), 1.89-2.01 (m, 3H, CH_2, CH), 2.06 (t, 2H, *J* = 7.5 Hz, CH_2), 2.29 (t, 2H, *J* = 7.2 Hz, CH_2), 2.70-2.78 (m, 1H, CH), 2.87-2.91 (m, 1H, CH), 4.91-4.99 (m, 1H, HC-$(CH_3)_2$), 5.22-5.26 (m, 1H, O-CH-$(CH_3)_2$), 5.29-5.46 (m, 4H, HC=CH(*cis*), (OBz-$CH)_2$), 5.60-5.63 (m, 2H, HC=CH(*trans*)), 7.30-7.36 (m, 2H, H_{Ar}), 7.43 (t, 2H, *J* = 8.1 Hz, H_{Ar}), 7.48 (t, 1H, *J* = 7.5 Hz, H_{Ar}), 7.59 (t, 1H, *J* = 7.5 Hz, H_{Ar}), 7.92-7.95 (m, 2H, H_{Ar}), 8.06-8.09 (m, 2H, H_{Ar}). MS (ES): m/z 669 [M+Na^+].

4-((*E*)-3-Hydroxy-3-phenyloct-1-enyl)-5-((*Z*)-7-isopropoxy-7-oxohept-2-enyl)cyclopentane-1,3-diyl-dibenzoate (15d): IR (KBr, ν_{max}, cm^{-1}): 3502, 3061, 2935, 2870, 1721, 1602, 1492, 1451, 1374, 1273, 1111, 1027. ^{1}H NMR (300 MHz) ($CDCl_3$) δ (ppm): 0.82 (t, 3H, *J* = 7.5 Hz, CH_3-$(CH_2)_4$), 1.10-1.19 (m, 4H, $2CH_2$), 1.21 (d, 6H, *J* = 6.3 Hz, CH-$(CH_3)_2$), 1.22-1.25 (m, 4H, $2CH_2$), 1.56-1.67 (m, 2H, CH_2), 1.76-1.84 (m, 2H, CH_2), 2.16-2.27 (m, 6H, $3CH_2$), 2.62-2.79 (m, 2H, 2CH), 4.92-5.03 (m, 1H, CH-$(CH_3)_2$), 5.12-5.15 (m, 1H, OBz-CH), 5.17 (t, 1H, *J* = 4.5 Hz, OBz-CH), 5.31-5.39 (m, 2H, HC=CH(*cis*)), 5.66 (ddd, 1H, *J* = 15.6, 9.0, 4.2 Hz, HC=CH-C-OH(*trans*)), 5.98 (dd, 1H, *J* = 15.6, 4.2 Hz, HC=CH(*trans*)), 7.18-7.24 (m, 4H, H_{Ar}), 7.36-7.45 (m, 5H, H_{Ar}), 7.55-7.56 (m, 2H, H_{Ar}), 7.95-8.02 (m, 4H, H_{Ar}). MS (ES): m/z 703 [M+Na^+].

Preparation of (*Z*)-methyl 7-(3, 5-dihydroxy-2-((*E*)-3-hydroxy-3-methyloct-1-enyl)cyclopentyl)hept-5-enoate (2): Compound **15** (0.4 g, 0.647 mmol), potassium carbonate (0.316 g, 2.29 mmol) and (4 mL) of MeOH were stirred at ambient temperature for 20 h. The progress of the reaction was monitored by TLC. After complete conversion of the reaction, (4 mL) of water was added and pH adjusted to 2 with 10 % citric acid (4 mL) and aqueous layer was extracted with EtOAc (3 × 10 mL). Combined ethyl acetate layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure at 40 ºC to obtain crude product which was purified by flash column chromatography using eluent as ethyl acetate/hexane. The pure fractions were combined and concentrated under vacuum at 40 ºC to give compound **2**. Yield 0.12 g (50 %). IR (KBr, ν_{max}, cm^{-1}): 3395, 2958, 2928, 2858, 1720, 1454, 1372, 1278, 1178, 1072. ^{1}H NMR (300 MHz) ($CDCl_3$) δ (ppm): 0.86 (t, 3H, *J* = 7.2 Hz, CH_3-$(CH_2)_4$), 1.26-1.28 (m, 8H, $4CH_2$), 1.27 (s, 3H, CH_3-C-OH), 1.48-1.52 (m, 4H, $2CH_2$), 1.63-1.82 (m, 3H, CH_2, CH), 2.09-2.18 (m, 3H, CH_2, CH), 2.32 (t, 2H, *J* = 7.2 Hz, CH_3-$(CH_2)_3$-CH_2-C-OH), 3.66 (s, 3H, O-CH_3), 3.93-3.98 (m, 1H, HO-CH), 4.19 (t, 1H, *J* = 4.2 Hz, HO-CH), 5.35-5.51 (m, 3H, HC=CH(*cis*), HC=CH(*trans*)), 5.62 (d, 1H, *J* = 15.3 Hz, HC=CH(*trans*)). ^{13}C NMR (75 MHz) ($CDCl_3$) δ (ppm): 13.91, 22.50, 23.63, 24.68, 25.58, 26.48, 28.17, 32.13, 33.26, 42.65, 42.80, 50.90, 51.50, 56.04, 72.69, 73.19, 78.45, 128.40, 129.06, 129.53, 138.91, 174.19. MS (ES): m/z 405 [M+Na^+]. HRMS (ESI): Calcd. for $C_{22}H_{38}O_5$ Na [M+Na]$^+$ 405.2794; found 405.2785.

(*Z*)-Methyl 7-(2-((*E*)-3-ethyl-3-hydroxyoct-1-enyl)-3,5-dihydroxycyclopentyl)hept-5-enoate (16): IR (KBr, ν_{max}, cm^{-1}): 3401, 2956, 2932, 2860, 1726, 1458, 1438, 1376, 1275, 1170, 1075. ^{1}H NMR (300 MHz) ($CDCl_3$) δ (ppm): 0.86 (t, 3H, *J* = 7.2 Hz, CH_3-$(CH_2)_4$), 0.87 (t, 3H, *J* = 7.5 Hz, CH_3-CH_2-C-OH), 1.21-1.31 (m, 8H, $4CH_2$), 1.49-1.71 (m, 8H, $4CH_2$), 2.09-2.13 (m, 3H, CH_2, CH), 2.29 (m, 1H, CH), 2.32 (t, 2H, *J* = 7.2 Hz, CH_3-CH_2-C-OH), 3.67 (s, 3H, O-CH_3), 3.95-3.97 (m, 1H, HO-CH), 4.20-4.23 (m, 1H, HO-CH), 5.39-5.49 (m, 4H, HC=CH(*cis*), HC=CH(*trans*)). ^{13}C NMR (75 MHz) ($CDCl_3$) δ (ppm): 7.79, 13.90, 22.50, 23.12, 24.68, 25.54, 26.45, 28.12, 32.20, 33.35, 40.53, 42.73, 50.70, 51.44, 55.91, 72.95, 75.03, 78.33, 128.67, 129.34, 130.74, 137.32, 174.21. MS (ES): m/z 419 [M+Na^+]. HRMS (ESI): Calcd. for $C_{23}H_{40}O_5$ Na [M+Na]$^+$ 419.2781; found 419.2773.

(*Z*)-Methyl 7-(3,5-dihydroxy-2-((*E*)-3-hydroxy-3-isopropyloct-1-enyl)cyclopentyl)hept-5-enoate (17): IR (KBr, ν_{max}, cm^{-1}): 3403, 3005, 2956, 2934, 2872, 1725, 1457, 1438, 1316, 1218, 1171, 1027. ^{1}H NMR (300 MHz) ($CDCl_3$) δ (ppm): 0.87 (t, 3H, *J* = 7.2 Hz, CH_3-$(CH_2)_4$), 0.88 (d, 6H, *J* = 6.3 Hz, HC-$(CH_3)_2$), 1.23-1.29 (m, 8H, $3CH_2$, CHa, CH), 1.50-1.72 (m, 4H, $2CH_2$), 2.04-2.16 (m, 6H, $2CH_2$, CHb, CH), 2.31 (t, 2H, *J* = 7.2 Hz, CH_2), 2.41 (m, 1H, CH), 3.66 (s, 3H, O-CH_3), 3.95-3.97 (m, 1H, HO-CH), 4.20 (t, 1H, *J* = 3.9 Hz, HO-CH), 5.39-5.49 (m, 4H, HC=CH(*cis*), HC=CH(*trans*)). ^{13}C NMR (75 MHz) ($CDCl_3$) δ (ppm): 13.92, 16.49, 17.53, 22.53, 22.94, 24.68, 25.66, 26.47, 32.26, 33.27, 38.47, 38.66, 42.76, 50.77, 51.45, 56.12, 73.09, 77.14, 78.52, 129.10, 129.38, 129.92, 135.61, 174.19. MS (ES): m/z 433 [M+Na^+]. HRMS (ESI): Calcd. for $C_{24}H_{42}O_5$ Na [M+Na]$^+$ 433.2936; found 433.2930.

(*Z*)-Methyl-7-(3,5-dihydroxy-2-((*E*)-3-hydroxy-3-phenyloct-1-enyl)cyclopentyl)hept-5-enoate (18): IR (KBr, ν_{max}, cm^{-1}): 3395, 3058, 2952, 2933, 1737, 1493, 1446, 1374, 1172, 1117, 1026. ^{1}H NMR (300 MHz) ($CDCl_3$) δ (ppm): 0.83 (t, 3H, *J* = 7.2 Hz, CH_3-$(CH_2)_4$), 1.20-1.26 (m, 8H, $4CH_2$), 1.50-1.91 (m, 4H, $2CH_2$), 2.01-2.37 (m, 8H, $4CH_2$), 3.64 (s, 1.8H, O-CH_3), 3.67 (s, 1.2H, O-CH_3), 3.95-3.98 (m, 1H, HO-CH), 4.18 (br, 1H, HO-CH), 5.30-5.59 (m, 3H, HC=CH(*cis*), HC=CH(*trans*)), 5.93 (dd, 1H, *J* = 15.3, 3.0 Hz, HC=CH (*trans*)), 7.22 (t, 1H, *J* = 7.2 Hz, H_{Ar}), 7.32 (t, 2H, *J* = 7.2 Hz, H_{Ar}), 7.42 (d, 2H, *J* = 7.2Hz, H_{Ar}). ^{13}C NMR (75 MHz) ($CDCl_3$) δ (ppm): 14.28, 22.80, 23.51, 24.99, 25.03, 25.79, 26.72, 32.42, 33.59, 33.63, 42.74, 43.12, 50.81, 51.83, 56.01, 72.99, 76.84, 78.10, 125.96, 126.75, 129.60, 130.73, 138.94, 146.54, 174.63. MS (ES): m/z 467 and 483 [M+Na^+] and [M+K^+]. HRMS (ESI): Calcd. for $C_{27}H_{40}O_5$ Na [M+Na]$^+$ 467.2788; found 467.2773.

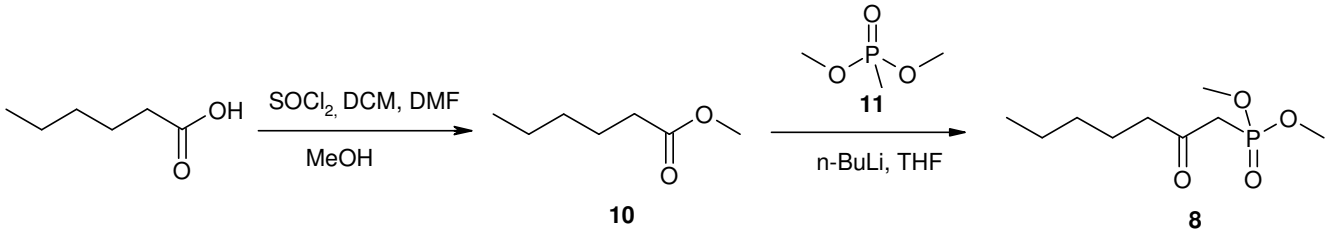
RESULTS AND DISCUSSION

Synthesis for dimethyl 2-oxoheptylphosphonate (8) (Scheme-I): Esterification of hexanoic acid was carried out through acid chloride preparation with thionyl chloride in dichloromethane using catalytic amount of DMF at 10-15 ºC followed by addition of methanol at 5-10 ºC for 1 h which gave **10** with 92 % yield[24,25]. Reaction of **10** with dimethyl methane phosphonate (**11**) in THF using *n*-BuLi (1.6 M in hexane) at -75 to -78 ºC for 0.5 h gave crude product which was purified by flash column chromatography to get compound **8** in 70 % yield[26,27]. During preparation of phosphonate ester (**8**), we have tried reactions at various temperatures such as at -40 ºC and at 0 ºC but we observed more impurities by TLC and led to lower yields after column purification. The reaction should be carried out at between -75 and -78 ºC.

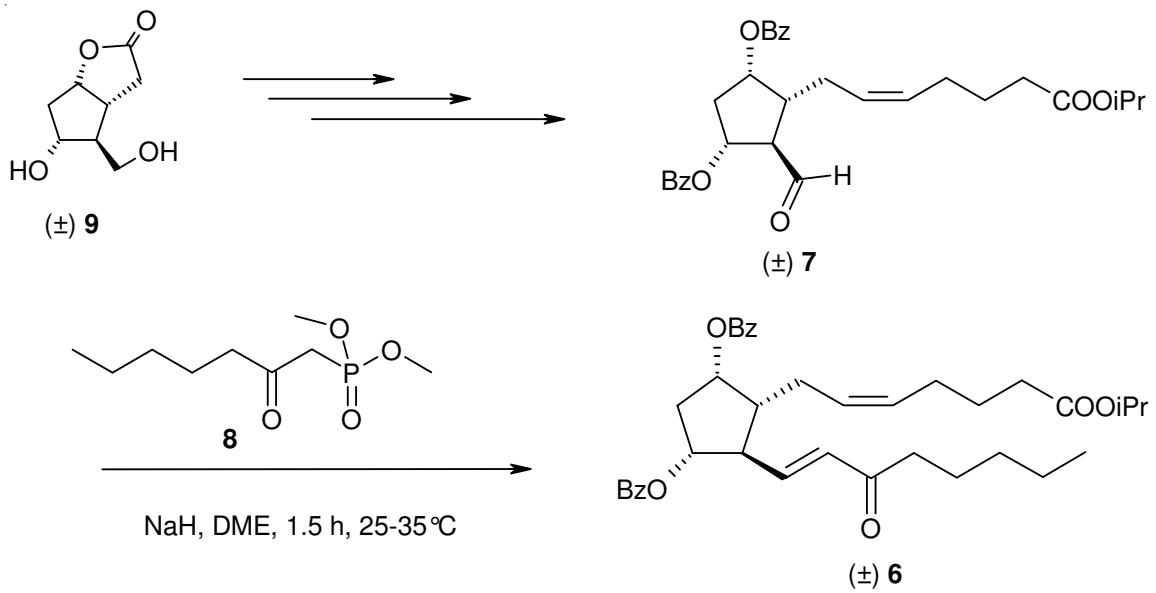
Synthesis of key intermediate (6) (Scheme-II): Synthesis of intermediate **7** was developed earlier by us in seven linear steps from racemic corey lactone (**9**)[17]. Horner-Wadsworth-Emmons reaction of **7** with phosphonate ester reagent, **8** in the presence of 60 % sodium hydride in dimethoxyethane (DME) for 0.5 h at 0-5 ºC and for 1.5 h at ambient temperature afforded key intermediate (B)[28,29] in 65 % yield which is the key intermediate for several $PGF_{2\alpha}$ analogs.

Synthesis of dinoprost (1) (Scheme-III): Key intermediate **6** was reduced with sodium borohydride in methanol at 25 ºC for 0.5 h to give 12 in 85 % yield. During reduction of carbonyl group to alcohol with sodium borohydride, we observed diasteromeric mixture in the ratio of 3:2 by TLC and one of the benzoyl ester group also get hydrolyzed to get free secondary hydroxyl group. Separations of diasteromers at this stage were very difficult and hence, we have taken to further step without separation. Deprotection of another benzoyl group on **12** with K_2CO_3 in methanol for 6 h at room temperature followed by separation of mixtures of diastereomers by column chromatography using EtOAc/hexane as eluent gave compound **13** in about 50 % yield. Transesterification was observed from isopropyl ester to methyl ester during deprotection of **12** to **13** in methanol/K_2CO_3 conditions. Ester hydrolysis of **13** with $LiOH{\cdot}H_2O$ in THF/water for 2 h at ambient temperature yielded **1** in 85 % yield (**Scheme-III**). Spectral data was well compared for **1** with literature for dinoprost (**1**)[30-34].

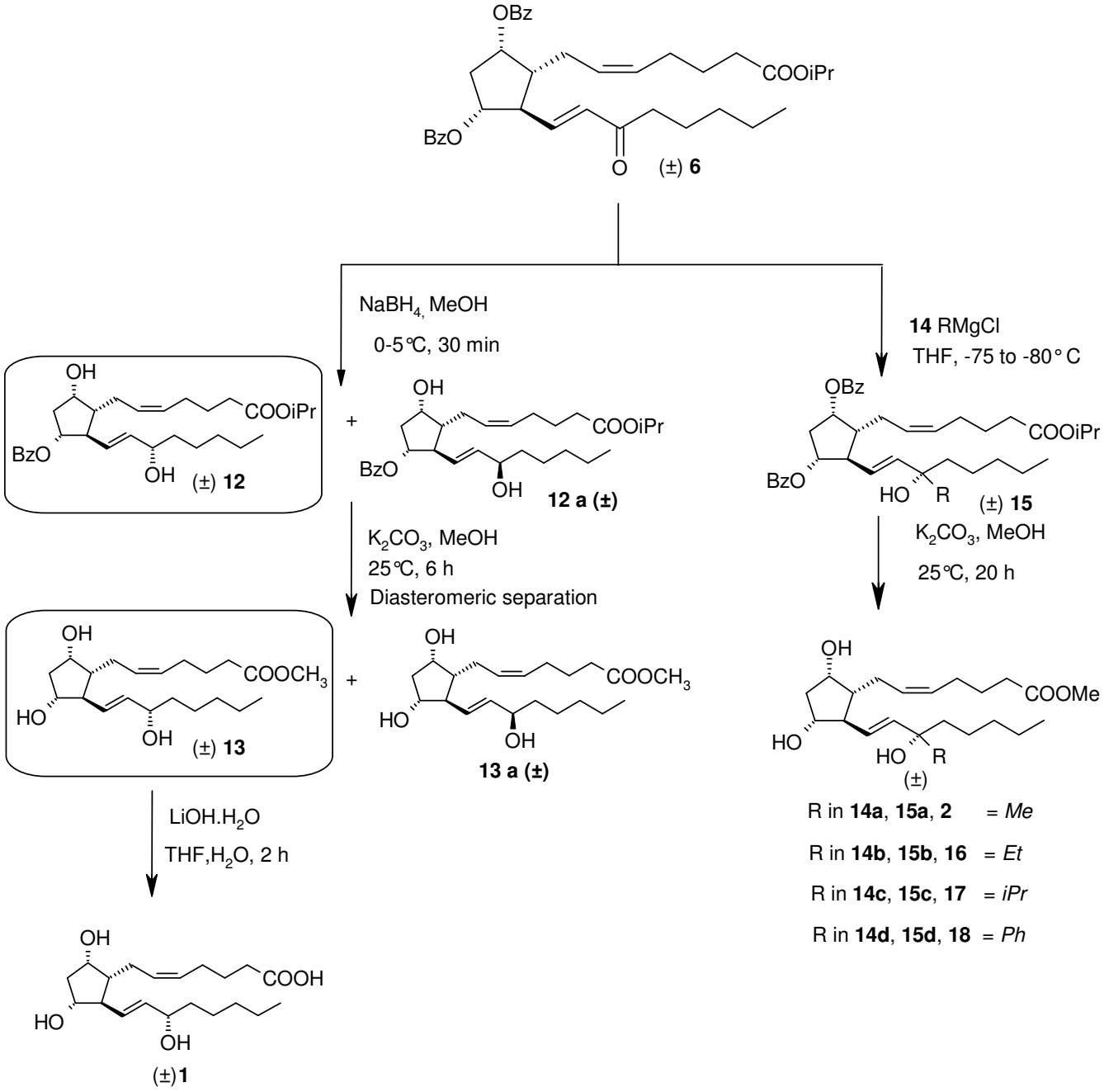
Synthesis of carboprost (2) and its analogs (16-18) (Scheme-III): Grignard reaction of **6** with various Grignard reagents such as methyl, ethyl, isopropyl and phenyl magnesium chlorides in THF at -75 ºC using dry ice/acetone bath for 2 h afforded **15a-d**[35] in good yields after column purifications. When we have tried reactions at higher temperatures between -20 to 10 ºC, observed more impurities by TLC and optimum temperature for preparation of **15a-d** is -75 to 80 ºC. Based on observations, rate of reaction decreases when we increase is bulky nature of Grignard reagent during preparation of **15a-d**. Reaction time and yields were reported in Table-1. No thin layer chromatographic solvent system was found to distinguish the expected diastereomeric mixture at C-15 position during preparation of **15a-d**. We proceeded further deprotection both benzoyl groups of **15a-d** with K_2CO_3 in methanol for 16-24 h



Scheme-I: Synthesis of phosphonate ester derivative



Scheme-II: Synthesis of Key intermediate



Scheme-III: Synthesis of (±) dinoprost (**1**), (±) carboprost (**2**) and its analogs (**16-18**) from key intermediate (**6**)

TABLE-1
SYNTHESIS OF CARBOPROST (**2**) AND ITS ANALOGS (**16-18**)

Compound	Conditions	Yields[a] (%)	Compound	Condition	Yields[b] (%)
15a	MeMgCl (3.0 M in THF), THF,-75 to -80°C, 0.5 h	90	**2**	K_2CO_3, MeOH, 20 h, Room temp.	65
15b	EtMgCl (3.0 M in THF), THF, -75 to -80°C, 1.0 h	82	**16**[39,40]	K_2CO_3, MeOH, 24 h, Room temp.	60
15c	^{i}PrMgCl (3.0 M in THF), THF, -75 to -80°C, 1 h	78	**17**	K_2CO_3, MeOH, 24 h, Room temp.	58
15d	PhMgCl (3.0 M in THF), THF, -75 to -80°C, 2 h	70	**18**	K_2CO_3, MeOH, 16 h, Room temp.	50

[a]Isolated by silica gel column chromatography and based on compound **6;** [b]Isolated by silica gel column chromatography and based on compound **15.**

at room temperature followed by flash column chromatography using silica gel by elution with ethyl acetate/hexane (70/30, 80/20) gradient mobile phase, which afforded (±)**2**[36-38], **16**[39,40], **17** and **18** (**Scheme-III**). Transesterification was observed from isopropyl ester to methyl ester during both benzoyl deprotections of **15a-d**. We did not observe expected diastereomeric mixture separation at C-15 position after deprotection of benzoyl groups by thin layer chromatography using different solvent combinations. Based on ^{13}C NMR analysis, we found diastereomeric mixture and this can be separated by preparative HPLC method to get (±) **2** and (±) **16, 17** and **18**. Reaction yields were reported for (±) **2**, **16**[39,40], **17** and **18** in Table-1.

Conclusion

A general synthetic approach was developed for (±)-dinoprost, (±)-carboprost and its analogs from the advanced key intermediate (**6**). By the use of optically pure Corey lactone and key intermediate (**6**) in the reported approach, optically pure dinoprost, carboprost and their analogs can be synthesized.

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REFERENCES

1. S. Bergstrom, *Science*, **157**, 382 (1967).
2. Prostaglandins in Proceedings of the Second Nobel Symposium, Stockholm, June, (1966), S. Bergstrom and B. Samuelsson, Almquist and Wiksell, Gebers Forlag AB, Stockholm (1967).
3. J.R. Weeks, *Ann. Rev. Pharmacol.*, **12**, 317 (1972).
4. J.W. Hinman, *Ann. Rev. Biochem.*, **41**, 161 (1972).
5. B. Samuelsson, K. Granstrom, GrCen, M. Hamberg, *Ann. N.Y. Acad. Sci.*, **180**, 138 (1971).
6. B. Samuelsson, *Aduan. Biosci.*, **9**, 7 (1973).
7. E. AnggHrd and B. Samuelsson, *Ark. Kemi*, **25**, 293 (1966).
8. M. Harikrishna, H. Rama Mohan, P.K. Dubey, M. Shankar and G.V. Subbaraju, *Asian J. Chem.*, **23**, 3121 (2011).
9. W. Lippmann, *Ann. N. Y. Acad. Sci.*, **180**, 332 (1971).
10. P.W. Collins and S.W Djuric, *Chem. Rev.*, **93**, 1533 (1993).
11. V. Hingorani and A. Dua, Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, vol. 39, B. No. 3. New Delhi, India.
12. J. Brenner, T. Fishburne, Braaksma and C.H. Hendricks, *Obstet. Gynec.*, **39**, 892 (1972).
13. M. Sakurai, M. Araie, T. Oshika, M. Mori, K. Masuda, R. Ueno and M. Takase, *Jpn. J. Ophthalmol.*, **35**, 156 (1991).
14. B. Resul, J. Stjernschantz, K. No, C. Liljebris, G. Selen, M. Astin, M. Karlsson and L.Z. Bito, *J. Med. Chem.*, **36**, 243 (1993).
15. P.A. Netland, T. Landry, E.K. Sullilvan, R. Andrew, L. Silver, A. Weiner, S. Mallick, J. Dickerson, M.V. Bergamini, S.M. Robertson and A.A. Davis, *Am. J. Ophthalmol.*, **132**, 472 (2001).
16. R.F. Brubaker, E.O. Schoff, C.B. Nau, S.P. Carpenter, K. Chen and A.M. Vandenburgh, *Am. J. Ophthalmol.*, **131**, 19 (2001).
17. M. Harikrishna, H.R. Mohan, P.K. Dubey, M. Shankar and G.V. Subbaraju, *Synth. Commun.*, **42**, 1288 (2012)
18. M. Harikrishna, H.R. Mohan, P.K. Dubey, M. Shankar, G.V. Subbaraju and T. Lakshmikumar, *Lett. Org. Chem.*, **8**, 234 (2011).
19. M. Harikrishna, H.R. Mohan, P.K. Dubey, M. Shankar and G.V. Subbaraju, *Asian J. Chem.*, **23**, 3121 (2011).
20. W.Y. Ernest, A. Udo and L.B. Gordon, *J. Am. Chem. Soc.*, **96**, 5865 (1974).
21. C. Earil and W.Y. Ernest, *J. Am. Chem. Soc.*, **96**, 5876 (1974).
22. P.W. Collins and S.W. Djuric, *Chem. Rev.*, **93**, 1533 (1993).
23. S. Das, S. Chandrasekhar, J.S. Yadav and G. Rane, *Chem. Rev.*, **107**, 3286 (2007).
24. B. Helferich and W. Schaefer, *Org. Synth. Coll.*, **1**, 147 (1941).
25. J. Avila-Zarraga, R. Gustavo, Martinez, *Synth. Commun.*, **31**, 2177 (2001).
26. F. Mathey and P. Savignac, *Tetrahedron*, **34**, 649 (1978).
27. I. Martin, J. Anvelt, T. Valimae, T. Pehk and O. Lille, *Synth. Commun.*, **20**, 2597 (1990).
28. S.W. Hwang, M. Adiyaman, S. Khanapure, L. Schio and J. Rokach, *J. Am. Chem. Soc.*, **116**, 10829 (1994).
29. B. Resul, J. Stjernschantz, K. No, C. Liljebris, G. Selen, M. Astin, M. Karlsson and L.Z. Bito, *J. Med. Chem.*, **36**, 243 (1993).
30. G.Q. Long and K.C. Jin, *J. Am. Chem. Soc*., **124**, 12424 (2002).
31. A. Neil, Sheddan and M. Johann, *Org. Lett.*, **8**, 3101 (2006).
32. S.R. Ruben, G. Sylvain, M.Z.S. Alexandra, P. Alessio, D.A. Alessandro, Z. Giuseppe and P.N. Steven, *Organometallics*, **29**, 3665 (2010).
33. A.S. Neil, B.A. Vladimir and M. Johann, *Tetrahedron Lett.*, **47**, 6689 (2006).
34. M. Shizuka and M.L. Snapper, *Synthesis*, 2397 (2007).
35. C.B. Francisco, R.R. Alessandra and C.F.S. Marcela, *Lett. Org. Chem.*, **4**, 1 (2007).
36. K. Weinges, W. Huber, U. Huber-Patz, H. Irngartinger, M. Nixdorf and H. Rodewald, *Liebigs Ann. Chem.*, **4**, 761 (1984).
37. G.L. Bundy, D.C. Peterson, J. C. Cornette, W.L. Miller, C.H. Spilman and J.W. Wilks, *J. Med. Chem.*, **26**, 1089 (1983).
38. Astrazeneca Pharma India Limited, Astrazeneca UK Limited, WO2008/81191 (2008).
39. L.B. Gordon and M. Kalamazoo, U.S. Patent, 3804890 (1974).
40. L.B. Gordon and M. Portage, U.S. Patent, 3904679 (1975).