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A Facile Route for Synthesis of Structural Analogs for Latanoprost: An Anti-Glaucoma Agent

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A facile synthetic approach has been developed for latanoprost analogs, (±) 13,14-dehydro latanoprost (**2**), (±) 16-nor-13,14-dehydro latanoprost (**3**) and (±) 16-homo-13,14-dehydro latanoprost (**4**) in five steps starting from key intermediate (**5**), through Wittig reaction and separation of diasteromers as the key steps.

Key Words: Prostaglandins, Anti-glaucoma, (±) 13,14-Dehydro latanoprost, (±) 16-Nor-13,14-dehydro latanoprost and (±) 16-Homo-13, 14-dehydro latanoprost.

INTRODUCTION

Glaucoma is a disease in which the optic nerve of the eye is damaged, leading to progressive, irreversible loss of vision. It is often, but not always, associated with increased pressure of the fluid in the eye. Latanoprost (**1**) belongs to small group of prostaglandin derivatives (PGF analogs) that have found use in the treatment of glaucoma[1]. Latanoprost is a selective FP receptor agonist with an ocular hypertensive effect and increases uveoscleral outflow and thereby reduces intraocular pressure[2-6].

Latanoprost is an effective antiglaucoma agent and continues to hold a key position in the anti-glaucoma market, although certain newer prostaglandin analogs have shown high levels of intraocular pressure reduction in clinical trails[7-10]. In this paper, we report a general synthetic approach for latanoprost analogs, exemplified by the synthesis of (±) 13,14-dehydrolatanoprost (**2**), (±) 16-nor-13,14-dehydrolatanoprost (**3**) and (±) 16-homo-13,14-dehydro latanoprost (**4**) in five steps from the key intermediate (**5**). 13,14-Dehydro latanoprost (**2**) can easily be converted into the latanoprost (**1**) based on the methods reported in the literature[11]. Synthesis of versatile key intermediate (5) was reported earlier by us from the (±) Corey latone[12].

EXPERIMENTAL

All reactions were performed either under argon or nitrogen atmosphere, unless otherwise mentioned. The progress of the reactions was monitored by thin layer chromatography (TLC) over silica gel 60F (E. Merck) thin layers (0.25 mm). The chromatograms were visualized by irradiation with UV light or by heat staining with polyphosphoric 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 300 MHz Bruker Avance-II NMR Spectrometer using $CDCl_3$ as solvent. Infrared spectra were recorded on a Perkin-Elmer FTIR 1605 spectrometer. Mass spectra were measured on Waters Quatro Micro mass spectrometer.

Preparation of compound 7: (General procedure): A suspension of 55 % sodium hydride (71.1 mmol) in dimethoxy ethane (DME) (80 mL) was cooled to -5 ºC under nitrogen atmosphere. Compound **6**[6] (69.0 mmol) was dissolved in DME (40 mL) and added slowly into the reaction mass at -5 to 0 °C and stirred for 15 min at 0 °C. Reaction mass temperature was raised to 25 °C and stirred for 1 h at 25 °C. Reaction mass temperature was cooled to -5 °C and compound **5** (19.78 mmol) dissolved in DME (40 mL) was added slowly into the reaction mass for 0.5 h at -5 °C. The temperature of the reaction mass was raised to 25 °C and stirred for 1.5 h at which TLC indicates completion of the reaction. The reaction mixture was cooled to 10 °C and added saturated ammonium chloride solution (100 mL). Then the reaction mass temperature was raised to 25 °C and stirred for 10 min and concentrated under vacuum at 40 °C. The residue was dissolved in EtOAc (50 mL) and separated both the layers; aqueous layer was extracted with

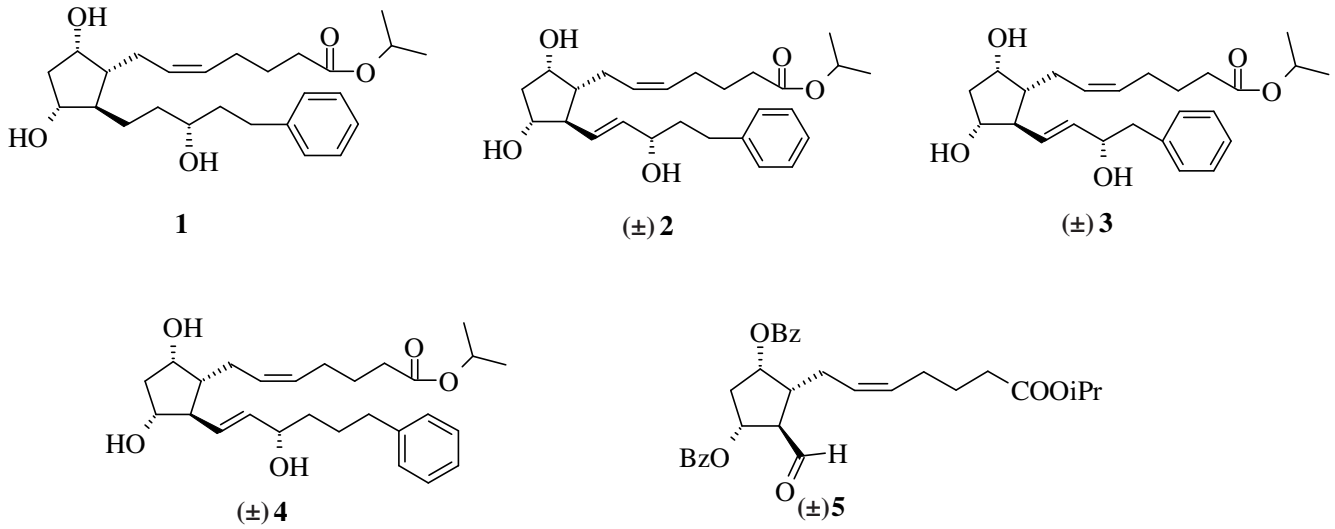


Fig. 1.

EtOAc (3 × 50 mL). Combined organic layers were washed with brine dried over Na_2SO_4 and concentrated under vacuum at 40 °C. Obtained crude was purified by flash column chromatography on silica gel (230-400 mesh) with an ethyl acetate-hexane (1:9) as eluent to give compound **7**. Using the described procedure, following compounds were obtained.

4-[(*Z*)-7-isopropoxy-7-oxohept-2-enyl]-5-[(*E*)-3-oxo-4-phenylbut-1-enyl]cyclopentane-1,3 diyl dibenzoate (7a): Pale yellow colour viscous liquid, Yield : 65 %. ^{1}H NMR (300 MHz) ($CDCl_3$) δ (ppm): 1.18 (6H, d, *J* = 6.3, HC-$(CH_3)_2$), 1.50 (1H, m, CH), 1.54 (2H, m, -CH_2-CH_2-CH_2-$COOCH(CH_3)_2$), 1.84 (2H, m, cyclopentyl CH_2), 2.04 (2H, m, -CH_2-CH_2-CH_2-$COOCH(CH_3)_2$), 2.11-2.28 (4H, m, CH_2-CH=CH (*cis*)-CH_2), 2.37 (1H, m, cyclopentyl HC-CH=CH(*trans*)), 3.87 (2H, s, Ph-CH_2), 4.94 (1H, m, HC-$(CH_3)_2$), 5.29 (1H, m, cyclopentyl OBz-HC-), 5.31 (1H, m, cyclopentyl OBz-HC-), 5.31 (1H, m, CH_2-CH=CH(*cis*)), 5.45 (1H, m, CH_2-CH=CH(*cis*)), 6.30 (1H, d, *J* = 15.0, (*trans*)-CH=CH-C=O)), 6.92 (1H, dd, *J* = 15.0, 8.7, CH-CH=CH(*trans*)), 7.18 - 7.61 (11H, m, H_{Ar}), 7.89 (2H, d, *J* = 8.4, OBz-C-$(CH)_2$, H_{Ar}), 8.06 (2H, d, *J* = 8.4, OBz-C-$(CH)_2$, H_{Ar}). MS (ES): m/z 623 $(M+H)^+$.

4-[(*Z*)-7-Isopropoxy-7-oxohept-2-enyl]-5-[(*E*)-3-oxo-5-phenylpent-1-enyl]cyclopentane-1,3-diyl dibenzoate (7b): Pale yellow colour viscous liquid, Yield: 70 %. ^{1}H NMR (300 MHz) ($CDCl_3$) δ (ppm): 1.17 (6H, d, *J* = 6.3, HC-$(CH_3)_2$), 1.35-1.76 (4H, m, $2CH_2$), 1.78-2.45 (6H, m, $3CH_2$), 2.55-3.15 (6H, m, $2CH_2$, 2CH), 4.94 (1H, m, $CH(CH_3)_2$), 5.30 (1H, m, cyclopentyl CH-OBz), 5.35 (1H, m, cyclopentyl CH-OBz), 5.46 (2H, m, HC=CH(*cis*)), 6.25 (1H, d, *J* = 15.9, O=C-CH (*trans*)), 6.84 (1H, dd, *J* = 15.9, 8.7, HC-CH (*trans*)), 7.10-7.38 (7H, m, H_{Ar}), 7.44 (2H, d, *J* = 7.2 Hz, H_{Ar}), 7.50 (1H, t, *J* = 7.5 Hz, H_{Ar}), 7.59 (1H, t, *J* = 7.5 Hz, H_{Ar}), 7.90 (2H, m, H_{Ar}), 8.06 (2H, m, H_{Ar}). MS (ES): m/z 659 $(M+Na)^+$. HRMS (ESI): Calcd. for $C_{40}H_{44}O_7$ $[M+H]^+$ 637.316; found 637.3178.

4-[(*Z*)-7-Isopropoxy-7-oxohept-2-enyl]-5-[(*E*)-3-oxo-6-phenylhex-1-enyl]cyclopentane-1,3-diyl dibenzoate (7c): Pale yellow colour viscous liquid, Yield : 70 %. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18 (6H, d, *J* = 6.3 Hz, HC-$(CH_3)_2$), 1.49 (2H, m, CH_2), 1.73-2.49 (10H, m), 2.62 (5H, m, $2CH_2$, CH), 2.98 (1H, m, CH), 4.93 (1H, m, $CH(CH_3)_2$), 5.33-5.47 (4H, m, HC=CH(*cis*), OBz-$(CH)_2$), 6.24 (1H, dd, *J* = 15.9, 0.6 Hz, O=C-CH (*trans*)), 6.80 (1H, dd, *J* = 15.9, 9.0 Hz, HC-CH (*trans*)), 7.18 (3H, m, H_{Ar}), 7.24-7.35 (4H, m, H_{Ar}), 7.42-7.65 (4H, m, H_{Ar}), 7.90 (2H, m, H_{Ar}), 8.07 (2H, m, H_{Ar}). MS (ES): m/z 651 $(M+H)^+$ and 673 $(M+Na)^+$. HRMS (ESI): Calcd. for $C_{41}H_{46}O_7$ NH_4 $[M+NH_4]^+$ 668.3582; found 668.3589.

Preparation of compound 8: (General procedure): A solution of compound **7** (13.36 mmol) in methanol (85.0 mL) was cooled to 0 °C and sodium borohydride (26.7 mmol) was added at 0 °C and stirred for 10 min. The reaction mass temperature was raised to 25 °C and stirred for 0.5 h at which TLC indicates complete conversion of the reaction. Solvent was distilled under vacuum at 40 °C. Ammonium chloride solution (85 mL) was added to the residue at 25 °C and stirred for 10 min and the layers were separated, the aqueous layer was extracted with EtOAc (3 × 85 mL). Organic layer was dried over Na_2SO_4 and concentrated under vacuum at 40 °C. Crude product was purified by flash column chromatography on silica gel (230-400 mesh) using ethyl acetate-hexane (2:8) as eluent. The pure fractions were combined and the solvent was removed *in vacuo* at 40 °C to give compound **8**. Using the described procedure, following compounds were obtained.

4-[(*E*)-3-Hydroxy-4-phenylbut-1-enyl]-5-[(*Z*)-7-isopropoxy-7-oxohept-2-enyl]cyclopentane-1,3-diyl dibenzoate (8a): Pale yellow colour viscous liquid, Yield: 85 %, ^{1}H NMR (300 MHz) ($CDCl_3$) δ (ppm): 1.18 (6H, d, *J* = 6.3, HC-$(CH_3)_2$), 1.51 (1H, m, CH), 1.55 (2H, m, -CH_2-CH_2-CH_2-$COOCH(CH_3)_2$), 1.96 (2H, m, -CH_2-CH_2-CH_2-$COOCH(CH_3)_2$), 2.02-2.10 (4H, m, CH_2-CH=CH (*cis*)-CH_2), 2.32 (1H, m, cyclopentyl HC-CH=CH(*trans*)), 2.63 (1Ha, m, cyclopentyl-CH_2), 2.90 (1Hb, m, cyclopentyl-CH_2), 3.86-3.97 (2H, m, Ph-CH_2), 4.56 (1H, m, OH-HC-CH=CH(*trans*)), 4.94 (1H, m, HC-$(CH_3)_2$), 5.28 (1H, m, cyclopentyl CH-OBz), 5.31 (1H, m, cyclopentyl CH-OBz), 5.40 (1H, m, CH_2-CH=CH(*cis*)), 5.45 (1H, m, CH_2-CH=CH(*cis*)), 5.81 (1H, m, (*trans*)-CH=CH-C=O)), 5.89 (1H, m, CH-CH=CH(*trans*)), 6.87 (2H, m, H_{Ar}), 6.92 (1H, m, H_{Ar}), 7.23-7.65 (8H, m, H_{Ar}), 7.93 (2H, m, OBz-C-$(CH)_2$, H_{Ar}), 8.07 (2H, m, OBz-C-$(CH)_2$, H_{Ar}). MS (ES): m/z 663 $(M+K)^+$.

4-[(*E*)-3-hydroxy-5-phenylpent-1-enyl]-5-[(*Z*)-7-isopropoxy-7-oxohept-2-enyl]cyclopentane-1,3-diyl dibenzoate (8b): Pale yellow colour viscous liquid, Yield: 82 %, ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (6H, d, *J* = 6.3 Hz, HC-$(CH_3)_2$), 1.64 (2H, m, CH_2), 1.70-2.35 (12H, m), 2.69 (2H, m, CH_2), 4.10 (2H, m, OH-CH, HC-$(CH_3)_2$), 4.97 (1H, m, cyclopentyl CH-OBz), 5.33 (1H, m, cyclopentyl CH-OBz), 5.45-5.49 (2H, m, HC=CH(*cis*)), 5.58 (2H, m, HC-CH (*trans*)), 7.08-7.68 (11H, m, H_{Ar}), 8.03 (2H, m, H_{Ar}), 8.06 (2H, m, H_{Ar}). MS(ES): m/z 661 $(M+Na)^+$. HRMS (ESI): Calcd. for $C_{40}H_{46}O_7$ NH_4 $[M^+ NH_4]^+$ 656.3582; found 656.3589.

4-[(*E*)-3-Hydroxy-6-phenylhex-1-enyl]-5-[(*Z*)-7-isopropoxy-7-oxohept-2-enyl]cyclopentane-1,3-diyl dibenzoate (8c): Pale yellow colour viscous liquid, Yield: 80 %, ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (6H, d, *J* = 6.3 Hz, HC-$(CH_3)_2$), 1.48-1.82 (11H, m), 2.04-2.29 (5H, m, $2CH_2$, CH), 2.63 (2H, t, *J* = 7.5 Hz, CH_2), 3.94 (1H, m, HO-CH), 4.10 (1H, m, cyclopentyl CH-OBz), 4.20 (1H, t, *J* = 3.6 Hz, cyclopentyl CH-OBz), 5.00 (1H, m, $HC(CH_3)_2$), 5.40 (2H, m, HC=CH(*cis*)), 5.55 (2H, m, HC-CH (*trans*)), 7.13-7.30 (5H, m, H_{Ar}), 7.40-7.62 (6H, m, H_{Ar}), 7.98-8.10 (m, 4H, H_{Ar}). MS (ES): m/z 675 $(M+Na)^+$.

Preparation of compound 9: (General procedure): To a mixture of compound **8** (11.75 mmol) in MeOH (75 mL) potassium carbonate (46.95 mmol) was added into the reaction mixture at 25 °C and stirred for 5 h at which TLC indicates complete conversion of the reaction. DM water (75 mL) was added to the reaction mixture at 25 °C and stirred for 10 min. pH of the reaction mixture was adjusted to 2 with 10 % citric acid (75 mL) solution and aqueous layer was extracted with EtOAc (3 × 75 mL). Organic layers were dried over Na_2SO_4 and concentrated under vacuum at 40 °C to obtain crude product. Crude product contains two diastereo isomers and desired isomer was purified by flash column chromatography on silica gel (230-400 mesh) with ethyl acetate-hexane (6:4) as eluent. The pure fractions were combined and the solvent was removed in vacuum at 40 °C to give compound **9**. Using the described procedure, following compounds were obtained.

(*Z*)-methyl 7-(3,5-dihydroxy-2-[(*E*)-3-hydroxy-4-phenylbut-1-enyl]cyclopentyl)hept-5-enoate (9a): Pale yellow colour viscous liquid, Yield: 25 %, ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.54 (1H, m, CH), 1.63 (2H, m, CH_2-CH_2-CH_2), 1.77-1.82 (4H, m, $2CH_2$), 2.01-2.16 (4H, m, $2CH_2$), 2.30, (1H, m, HC-CH (*trans*)-CH_2-CH), 2.85 (2H, m, Ph-CH_2), 3.65 (3H, s, O-CH_3), 3.90 (1H, m, HO-CH), 4.00 (1H, m, cyclopentyl CH-OH), 4.53 (1H, m, cyclopentyl CH-OH), 5.31-5.48 (2H, m, HC=CH(*cis*)), 5.58-5.76 (2H, m, HC=CH(*trans*)), 7.20 (2H, m, H_{Ar}), 7.23 (1H, m, H_{Ar}), 7.28 (2H, m, H_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.66, 24.70, 33.30, 42.64, 43.84, 49.76, 51.46, 52.28, 70.96, 71.64, 7718, 126.68, 129.08, 129.39, 129.43, 130.24, 134.23, 135.21, 137.87 and 174.26. MS (ES): m/z 411 $(M+Na)^+$.

(*Z*)-Methyl-7-(3,5-dihydroxy-2-[(*E*)-3-hydroxy-5-phenylpent-1-enyl]cyclopentyl)hept-5-enoate (9b): Pale yellow colour viscous liquid, Yield: 30 %, ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.47 (1H, m, CH), 1.65 (2H, m, CH_2-CH_2-CH_2), 1.74-2.28 (10H, m, $5CH_2$), 2.34, (1H, m, HC-CH (*trans*)-CH_2-CH), 2.69 (2H, m, Ph-CH_2), 3.67 (3H, s, O-CH_3), 3.93 (1H, m, HO-CH), 4.08 (1H, m, cyclopentyl CH-OH), 4.12 (1H, m, cyclopentyl CH-OH), 5.35-5.40 (2H, m, HC=CH(*cis*)), 5.50-5.61 (2H, m, HC=CH(*trans*)), 7.18 (2H, m, H_{Ar}), 7.19 (1H, m, H_{Ar}), 7.26 (2H, m, H_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.66, 25.29, 26.49, 31.72, 33.30, 38.59, 42.69, 50.40, 51.47, 55.33, 71.44, 72.30, 77.79, 125.68, 128.25, 128.30, 129.46, 131.92, 133.22, 135.13, 141.82, 174.32. MS (ES): m/z 402 $(M+H)^+$. HRMS (ESI): Calcd. for $C_{24}H_{34}O_5$ Na $[M+Na]^+$ 425.2298; found 425.2318.

(*Z*)-Methyl-7-(3,5-dihydroxy-2-[(*E*)-3-hydroxy-6-phenylhex-1-enyl]cyclopentyl)hept-5-enoate (9c): Pale yellow colour viscous liquid, Yield: 28 %, ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40-1.88 (4H, m), 2.00-2.48 (11H, m, $5CH_2$, CH), 2.63 (3H, m, CH_2, CH), 3.66 (3H, s, $COOCH_3$), 3.94 (1H, m, HO-CH), 4.11 (2H, m, cyclopentyl $(CH\text{-}OH)_2$), 5.38 (2H, m, HC=CH(*cis*)), 5.53 (2H, m, HC-CH (*trans*)), 7.16 (3H, m, H_{Ar}), 7.26 (2H, m, H_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.6, 25.44, 26.43, 27.19, 33.23, 35.67, 36.65, 42.81, 50.55, 51.53, 55.43, 72.11, 72.79, 77.95, 125.60, 128.18, 128.29, 129.14, 129.39, 131.83, 134.63, 142.25, 174.40. MS (ES): m/z 439 $(M+Na)^+$. HRMS (ESI): Calcd. for $C_{25}H_{36}O_5$ Na $[M+Na]^+$ 439.2455; found 439.2475.

Preparation of compound 10: (General procedure): To a mixture of compound **9** (3.24 mmol) in THF (13 mL), lithium hydroxide monohydrate (12.85 mmol) was added into the reaction mixture at 25 °C and stirred for 2 h at which TLC indicates complete conversion of the reaction. DM water (13 mL) was added to the reaction mixture at 25 °C and stirred for 10 min. pH of the reaction mixture was adjusted to 2 with 10 % citric acid (13 mL) and aqueous layer was extracted with EtOAc (3 × 25 mL). Organic layers were dried over Na_2SO_4 and concentrated under *vacuo* at 40 °C to obtain crude. Crude product was purified by column chromatography on silica gel (230-400 mesh) with EtOAc/hexane with gradient system as eluent. The pure fractions were combined and the solvent was removed *in vacuo* at 40 °C to give compound **10**. Using the described procedure, following compounds were prepared.

(*Z*)-7-(3,5-Dihydroxy-2-[(*E*)-3-hydroxy-4-phenylbut-1-enyl]cyclopentyl)hept-5-enoic acid (10a): Colourless viscous liquid, Yield: 70 %. IR (KBr, ν_{max}, cm^{-1}): 3375 (acid -OH str.), 3029, 3004 (Ar C-H str.), 2935, 2868 (Ali C-H str.), 1710 (C=O), 1608 (Ali C=C), 1450, 1456 (Ar C=C), 1244, 1049 (C-O), 751. ^{1}H NMR (300 MHz) ($CDCl_3$) δ (ppm): 1.48 (1H, m, CH), 1.62 (2H, m, -CH_2-CH_2-CH_2-COOH), 1.74 (1Ha, m, cyclopentyl CH_2), 2.10-2.23 (4H, m, CH_2-CH=CH (*cis*)-CH_2), 2.24 (1Hb, m, cyclopentyl CH_2), 2.33 (2H, m, -CH_2-CH_2-CH_2-COOH), 2.35 (1H, m, cyclopentyl HC-CH=CH(*trans*)), 2.69 (2H, m, -CH_2-Ph), 3.90 (1H, m, cyclopentyl OH-HC-HC-CH=CH(*trans*)), 4.10 (1H, m, cyclopentyl CH-OH), 4.13 (1H, m, cyclopentyl CH-OH), 5.32 (1H, m, CH_2-CH=CH(*cis*)), 5.42 (1H, m, CH_2-CH=CH(*cis*)), 5.46 (1H, m, CH-CH=CH(*trans*)), 5.63 (1H, m, CH-CH=CH(*trans*)), 7.19 (1H, m, H_{Ar}), 7.17 (2H, m, H_{Ar}), 7.20 (2H, m, H_{Ar}). ^{13}C NMR (75 MHz) ($CDCl_3$) δ (ppm): 24.39, 25.12, 26.15, 32.83, 42.63, 45.23, 50.01, 55.20, 72.21, 72.33, 125.70, 128.26, 128.30, 129.00, 129.54, 132.92, 134.66, 141.70 and 177.10. MS (ES): m/z 397 $(M+Na)^+$.

(*Z*)-7-(3,5-Dihydroxy-2-[(*E*)-3-hydroxy-5-phenylpent-1-enyl]cyclopentyl)hept-5-enoic acid (10b): Colourless viscous liquid, Yield: 80 %. IR (KBr, ν_{max}, cm^{-1}): 3373 (acid

-OH str.), 3025, 3006 (Ar C-H str.), 2933, 2863 (Ali C-H str.), 1708 (C=O), 1603 (Ali C=C), 1496, 1454 (Ar C=C), 1242, 1050 (C-O), 749. ^{1}H NMR (300 MHz) ($CDCl_3$) δ (ppm): 1.46 (1H, m, CH), 1.64 (2H, m, -CH_2-CH_2-CH_2-COOH), 1.72 (1Ha, m, cyclopentyl CH_2), 1.80-1.91 (2H, m, -CH_2-CH_2-Ph), 2.11-2.21 (4H, m, CH_2-CH=CH (*cis*)-CH_2), 2.26 (1Hb, m, cyclopentyl CH_2), 2.30 (2H, m, -CH_2-CH_2-CH_2-COOH), 2.33 (1H, m, cyclopentyl HC-CH=CH(*trans*)), 2.67 (2H, m, -CH_2-CH_2-Ph), 3.92 (1H, m, cyclopentyl OH-HC-HC-CH=CH (*trans*)), 4.13 (1H, m, cyclopentyl CH-OH), 4.13 (1H, m, (cyclopentyl CH-OH), 5.35 (1H, m, CH_2-CH=CH(*cis*)), 5.44 (1H, m, CH_2-CH=CH(*cis*)), 5.48 (1H, m, CH-CH=CH(*trans*)), 5.60 (1H, m, CH-CH=CH(*trans*)), 7.16 (1H, m, H_{Ar}), 7.17 (2H, m, H_{Ar}), 7.25 (2H, m, H_{Ar}). ^{13}C NMR (75 MHz) ($CDCl_3$) δ (ppm): 24.36, 25.15, 26.17, 31.71, 32.80, 38.41, 42.65, 50.04, 55.21, 72.24, 72.36, 125.72, 128.28, 128.32, 129.02, 129.56, 132.90, 134.64, 141.76 and 177.16. MS (ES): m/z 411 $(M+Na)^+$ and 427 $(M+K)^+$.

(*Z*)-7-(3,5-Dihydroxy-2-[(*E*)-3-hydroxy-6-phenylhex-1-enyl]cyclopentyl)hept-5-enoic acid (10c): Colourless viscous liquid, Yield: 75 %, IR (KBr, ν_{max}, cm^{-1}): 3389 (acid -OH str.), 3005 (Ar C-H str.), 2931, 2859 (Ali C-H str.), 1708 (C=O), 1453 (Ali C=H bending). ^{1}H NMR (300 MHz) ($CDCl_3$) δ (ppm): 1.48 (1H, m, CH), 1.55 (2H, m, -CH_2-CH_2-CH_2-Ph), 1.63 (2H, m, -CH_2-CH_2-CH_2-COOH), 1.75 (2H, m, cyclopentyl CH_2), 1.76-1.81 (2H, m, -CH_2-CH_2-CH_2-Ph), 2.08-2.17 (4H, m, CH_2-CH=CH (*cis*)-CH_2), 2.28 (2H, m, -CH_2-CH_2-CH_2-COOH), 2.34 (1H, m, cyclopentyl HC-CH=CH(*trans*)), 2.63 (2H, m, CH_2-CH_2-CH_2-Ph), 3.95 (1H, m, cyclopentyl OH-HC-HC-CH=CH(*trans*)), 4.13 (1H, m, cyclopentyl CH-OH), 4.21 (1H, m, cyclopentyl CH-OH), 5.32 (1H, m, CH_2-CH=CH(*cis*)), 5.41 (1H, m, CH_2-CH=CH(*cis*)), 5.53 (1H, m, CH-CH=CH(*trans*)), 5.58 (1H, m, CH-CH=CH(*trans*)), 7.11-7.34 (5H, m, H_{Ar}). MS (ES): m/z 425 $(M+Na)^+$.

Preparation of compound 2 (General procedure): A solution of compound **10** (1.80 mmol) in acetone (20 mL) was cooled to -5 °C and DBU (10.85 mmol) was added slowly into reaction mass at -5 °C. The reaction mass temperature raised to 25 °C and stirred for 0.5 h at 25 °C. Isopropyl iodide (12.61 mmol) was slowly added to the reaction mass at 25 °C and stirred for 12 h at 25 °C at which TLC indicates complete conversion. The reaction mass was concentrated under vacuum at 40 °C and residue was diluted with EtOAc (40 mL). 10 % citric acid (20 mL) solution added and stirred for 10 min at 25 °C (clear solution was observed). Organic layer was separated and washed with 10 % citric acid (20 mL), 5 % sodium bicarbonate solution (40 mL) followed by brine solution (10 mL). Organic layer was dried over Na_2SO_4 and concentrated under vacuum at 40 °C to get compound **2**. Using this procedure, following compounds were obtained.

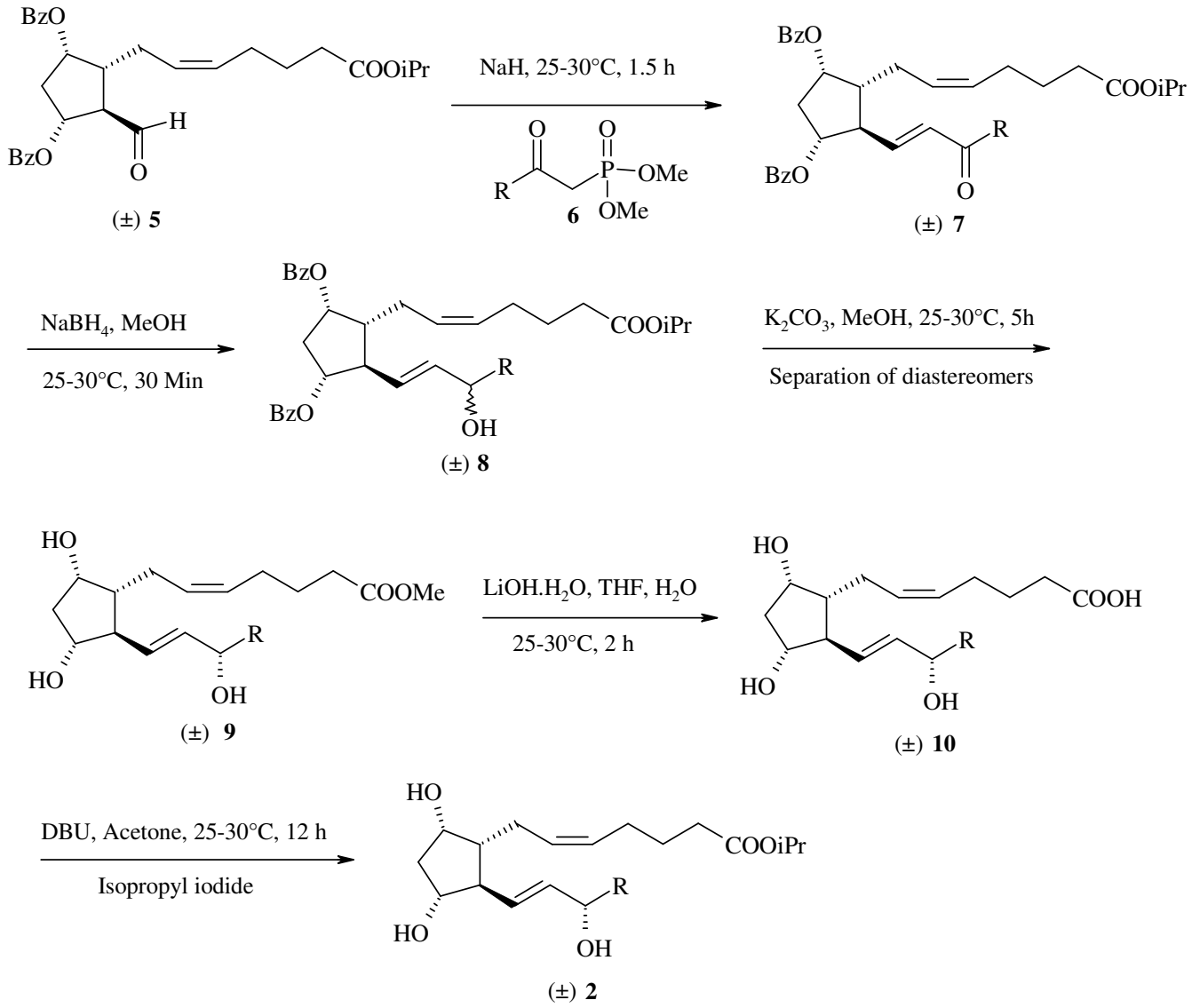
(±)13,14-Dehydro latanoprost (2): Pale yellow viscous liquid, Yield: 65 %. IR (KBr, ν_{max}, cm^{-1}): 3390 (-OH str.), 3063 (Ar C-H str.), 2980, 2932 (Ali C-H str.), 1727, 1714 (C=O), 1455 (Ali C=H bending). ^{1}H NMR (300 MHz) ($CDCl_3$) δ (ppm): 1.21 (6H, d, *J* = 6.3, HC-$(CH_3)_2$, 1.38 (1H, m, CH), 1.69 (2H, m, -CH_2-CH_2-CH_2- $COOCH(CH_3)_2$), 1.80-1.91 (2H, m, -CH_2-CH_2-Ph), 1.86 (2H, m, cyclopentyl CH_2), 2.11- 2.19 (4H, m, CH_2-CH=CH (*cis*)-CH_2), 2.27 (2H, t, *J* = 7.2, CH_2-CH_2-$COOCH(CH_3)_2$), 2.34 (1H, m, cyclopentyl HC-CH=CH(*trans*)), 2.69 (2H, m, -CH_2-CH_2-Ph), 3.92 (1H, m, cyclopentyl OH-HC-HC-CH=CH(*trans*)), 4.11 (1H, m, cyclopentyl CH-OH), 4.13 (1H, m, cyclopentyl CH-OH), 4.98 (1H, m, $CH(CH_3)_2$), 5.38 (1H, m, CH_2-CH=CH(*cis*)), 5.40 (1H, m, CH_2-CH=CH(*cis*)), 5.49 (1H, m, CH-CH=CH(*trans*)), 5.59 (1H, m, CH-CH=CH(*trans*)), 7.15-7.30 (5H, m, H_{Ar}). ^{13}C NMR (75 MHz) ($CDCl_3$) δ (ppm): 21.73, 24.77, 26.52, 31.72, 33.93, 38.63, 38.66, 42.74, 50.20, 55.61, 67.58, 72.11, 77.82, 125.71, 128.27, 128.32, 128.89, 129.69, 132.94, 134.90, 141.80, 173.41. MS (ES): m/z 453 $(M+Na)^+$. HRMS (ESI): Calcd. for $C_{26}H_{38}O_5$ Na $[M+Na]^+$ 453.2611; found 453.2618.

(±)16-Nor-13, 14-dehydro latanoprost (3): Pale yellow viscous liquid, Yield: 60 %. IR (KBr, ν_{max}, cm^{-1}): 3393 (-OH str.), 3068 (Ar C-H str.), 2979, 2930 (Ali C-H str.), 1729, 1718 (C=O), 1455 (Ali C=H bending). ^{1}H NMR (300 MHz) ($CDCl_3$) δ (ppm): 1.20 (6H, d, *J* = 6.3, HC-$(CH_3)_2$, 1.40 (1H, m, CH), 1.70 (2H, m, -CH_2-CH_2-CH_2- $COOCH(CH_3)_2$), 1.89 (2H, m, cyclopentyl CH_2), 2.10-2.22 (4H, m, CH_2-CH=CH (*cis*)-CH_2), 2.29 (2H, t, *J* = 7.2, CH_2-CH_2-$COOCH(CH_3)_2$), 2.36 (1H, m, cyclopentyl HC-CH=CH(*trans*)), 2.66 (2H, m, -CH_2-Ph), 3.94 (1H, m, cyclopentyl OH-HC-HC-CH=CH(*trans*)), 4.10 (2H, m, cyclopentyl $(CH\text{-}OH)_2$), (4.96 (1H, m, $CH(CH_3)_2$), 5.35 (1H, m, CH_2-CH=CH(*cis*)), 5.42 (1H, m, CH_2-CH=CH(*cis*)), 5.47(1H, m, CH-CH=CH(*trans*)), 5.56 (1H, m, CH-CH=CH(*trans*)), 7.13-7.33 (5H, m, H_{Ar}). ^{13}C NMR (75 MHz) ($CDCl_3$) δ (ppm): 21.75, 24.79, 26.48, 33.96, 38.69, 42.78, 45.62, 50.26, 55.67, 67.60, 72.16, 77.86, 125.74, 128.30, 128.33, 128.85, 129.74, 132.90, 134.95, 141.83, 173.44. MS (ES): m/z 439 $(M+Na)^+$. HRMS (ESI): Calcd. for $C_{25}H_{36}O_5$ Na $[M+Na]^+$ 439.2557; found 439.2561.

(±)16-Homo-13,14-dehydro latanoprost (4): Pale yellow viscous liquid, Yield: 58 %. IR (KBr, ν_{max}, cm^{-1}): 3394 (-OH str.), 2929, 2857 (Ali C-H str.), 1726 (C=O), 1648 (Ali C=C), 1453 (Ar C=C), 1261, 1108 (C-O). ^{1}H NMR (300 MHz) ($CDCl_3$) δ (ppm): 1.22 (6H, d, *J* = 6.3, HC-$(CH_3)_2$), 1.57 (1H, m, CH), 1.59 (2H, m, -CH_2-CH_2-CH_2-Ph), 1.67 (2H, m, -CH_2-CH_2-CH_2-$COOCH(CH_3)_2$), 1.70 (2H, m, cyclopentyl CH_2), 1.72-1.82 (2H, m, -CH_2-CH_2-CH_2-Ph), 2.04-2.12 (4H, m, CH_2-CH=CH (*cis*)-CH_2), 2.27 (2H, m, -CH_2-CH_2-CH_2-$COOCH(CH_3)_2$), 2.35 (1H, m, cyclopentyl HC-CH=CH(*trans*)), 2.63 (2H, m, CH_2-CH_2-CH_2-Ph), 3.94 (1H, m, cyclopentyl OH-HC-HC-CH=CH(*trans*)), 4.10 (1H, m, cyclopentyl CH-OH), 4.20 (1H, m, cyclopentyl CH-OH), 5.00 (1H, m, HC-$(CH_3)_2$), 5.35 (1H, m, CH_2-CH=CH(*cis*)), 5.41 (1H, m, CH_2-CH=CH(*cis*)), 5.53 (1H, m, CH-CH=CH(*trans*)), 5.57 (1H, m, CH-CH=CH (*trans*)), 7.15-7.34 (5H, m, H_{Ar}). ^{13}C NMR (75 MHz) ($CDCl_3$) δ (ppm): 21.84, 24.83, 26.58, 27.78, 33.98, 35.74, 36.95, 42.71, 50.01, 55.07, 67.72, 71.66, 73.90, 77.06, 125.78, 128.59, 128.79, 128.96, 129.78, 133.22, 135.10, 142.52, 173.55. MS (ES): m/z 467 $(M+Na)^+$. HRMS (ESI): Calcd. for $C_{27}H_{40}O_5$ Na $[M+Na]^+$ 467.2768; found 467.2782.

RESULTS AND DISCUSSION

Synthesis of (±)13,14-dehydro latanoprost (2) (Scheme-I): Wittig reaction of compound **5** with phosphonate ester reagent, **6**[13-22] in presence of 55 % sodium hydride in dimethoxyethane (DME) for 2 h at 0-5 °C followed by work-up and flash chromatography afforded **7**[23-29] in 70 % yield. Towards synthesis of compound **7**, we have studied reactions



Scheme-I

in various solvents such as tetrahydrofuran, DMF, 2-methyl THF and DME and found that best results were obtained using DME as a solvent. Reduction of keto group on compound **7** with sodium borohydride in methanol at 25 °C for 0.5 h afforded compound **8** in 82 % yield. For initial studies, column chromatography was used for purification of compound **8** and to remove non-polar impurities, but subsequently we have incorporated washing with hexanes to remove impurities from crude product and thus could avoid column purifications. Deprotection of both benzoyl groups on compound **8** 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 **9** in *ca.* 30 % yield. Trans-esterification was observed from

isopropyl ester to methyl ester during deprotection of compounds **8** to **9** in methanol/K_2CO_3 conditions. Ester hydrolysis of compound **9** with LiOH·H_2O in THF/water for 2 h at room temperature yielded **10** in 80 % yield. Esterification of compound **10** with isopropyl iodide using DBU in acetone at room temperature for 12 h followed by flash column purification gave 13-14-dehydro latanoprost (**2**)[1,30] in 65 % yield. Using a similar reaction sequence, we have synthesized 16-nor-13,14-dehydro latanoprost (**3**) and 16-homo-13,14-dehydro latanoprost (**4**) as shown in **Scheme-I**.

Conclusion

Using a common intermediate (**5**), three structural analogs of "latanoprost" were synthesized in a facile route.

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