Synthesis of (±) Travoprost and its Analogs

Harikrishna Mudduluru[a], Rama M. Hindupur*[,a], Pramod K. Dubey[b], Shankar Madhavaram[a], Lakshmikumar Tatini[a] and Gottumukkala V. Subbaraju[c]

[a]*Aptuit Laurus Private Limited, ICICI Knowledge Park, Turkapally, Shameerpet, Hyderabad 500 078, India*

[b]*Department of Chemistry, College of Engineering, J N T University, Kukatpally, Hyderabad 500 085, India*

[c]*Lakshmi Surya, A-16, Nalanda Nagar, Tirupati-517502, Índia*

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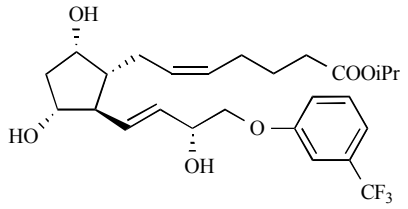
Abstract: A new synthetic approach for the antiglaucoma agent, travoprost (**1**) has been developed in four steps from key intermediate (**2**). Key transformations include Horner–Wadsworth–Emmons reaction and separation of diastereomers to obtain (±) travoprost (**1**) and its analogs.

Keywords: Prostaglandins, antiglaucoma, (±) travoprost.

INTRODUCTION

Glaucoma is one of the most common, but serious eye diseases that can lead to optic nerve damage and result in blindness if not appropriately treated [1]. A main risk factor is thought to be elevated intraocular pressure (IOP). Since the discovery of PGF2α known to reduce IOP in an animal model [2], extensive efforts have been dedicated to develop PGF receptor (FP) agonists as a new antiglaucoma agent [3].



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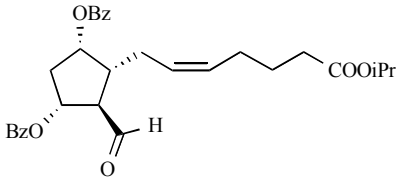

(±) **2**

Fig. (1).

The prostaglandin analog 16-[3-(trifluoromethyl) phenoxy]-17, 18, 19, 20-tetranor $PGF_{2\alpha}$ and its ester derivatives, in particular the isopropyl ester, travoprost (**1**) as shown in Fig. (**1**), are potent for the treatment of glaucoma and ocular hypertension [4]. Additionally, certain phenyl substituted prostaglandins are known to be potent and are selective anti-glaucoma agents [3b]. In this note we report the synthesis of (±) travoprost (**1**) and its analogs such as phenyl substituted prostaglandins from the racemic key intermediate (**2**). Synthesis of the versatile key intermediate (**2**) was reported earlier by us [5].

RESULTS AND DISCUSSION

Synthesis for Phosphonate Ester Derivatives, 7a-e

Attempted alkylation of **3a-e** with methyl bromoacetate (**4**) using a combination of K_2CO_3 and acetone was successful for preparation of compounds **5a** and **5e** [6]. The same method did not give desired products for **3b-d**. Alternate base and solvent combinations have to be used for obtaining products **5b**, **5c** and **5d** [7]. Details of these reaction conditions are reported in Table **1**. However the esters, **5a-e** reacted with dimethyl methane phosphonate (**6**) [8] using *n*-BuLi and THF gave the desired phosphonate esters, **7a-e** [9] as shown in Scheme **1.** Reaction yields have been noted in Table **1**.

Synthesis of (±) Travoprost, 1 and its Analogs, 11-14

Horner–Wadsworth–Emmons reaction of key intermediate, **(2)** with phosphonate esters, **7a-e** in the presence of sodium hydride in dimethoxyethane (DME) for 4 h at room temperature under nitrogen atmosphere followed by column chromatography yielded **8a-e** [3b, 10]. Mole ratio of NaH was found to be critical for the reaction and it should be 1:1 with respect to phosphonate esters, **7a-e** for the preparation of **8a-e**. Use of excess sodium hydride led to the formation of non-polar impurities based on TLC analysis and consequently lower yields. Keto group reduction of **8a-e** with sodium borohydride in methanol at room temperature for 1 h gave the desired products **9a-e.** However, during preparation of **9d** we observed formation of non-polar impurity which was separated by column chromatography. Diastereomeric mixture was formed during preparation of **9a-e** in the ratio of 3:2 based in TLC (the diastereomers are very close in TLC and separation was difficult by column

*Address correspondence to this author at the Aptuit Laurus Private Limited, ICICI Knowledge Park, Turkapally, Shameerpet, Hyderabad 500 078, India; Tel: +91-40-23480480; Fax: +91-40-23480481;
E-mail: mohan.hindupur@aptuitlaurus.com

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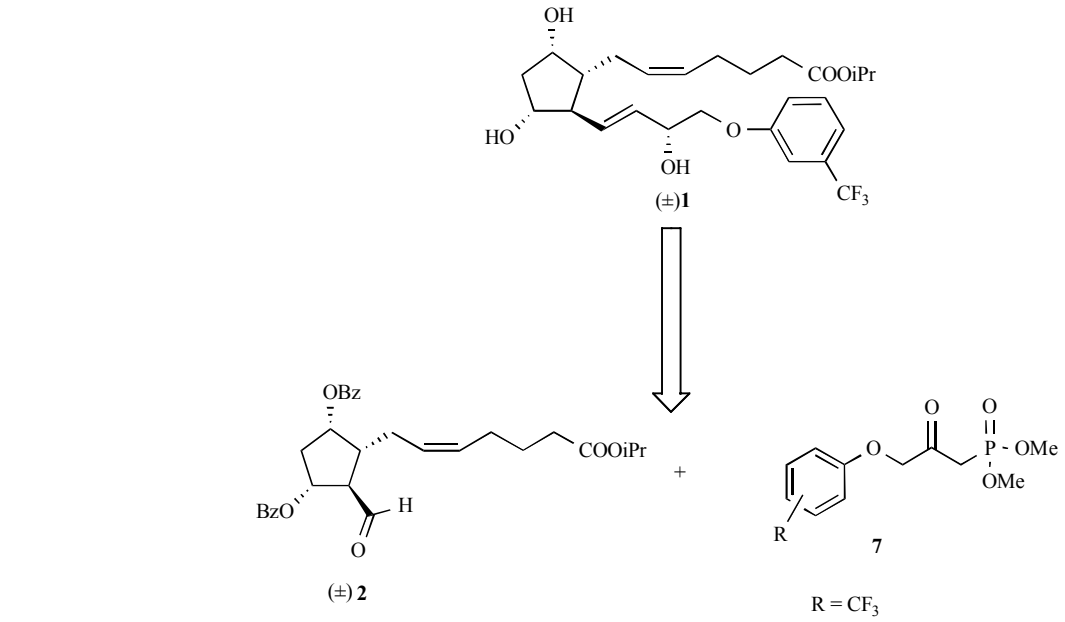
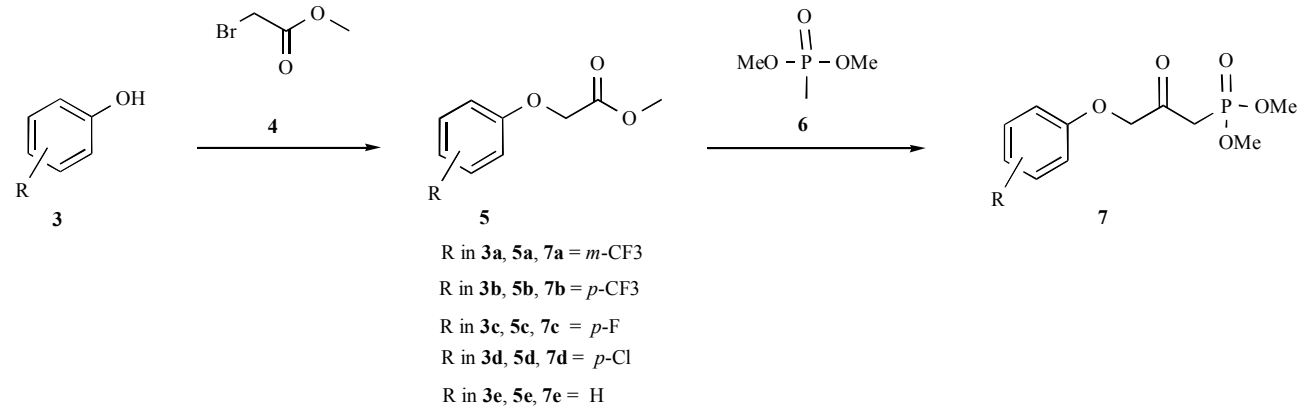


Fig. (2). Retrosynthetic scheme of (±) Travoprost.

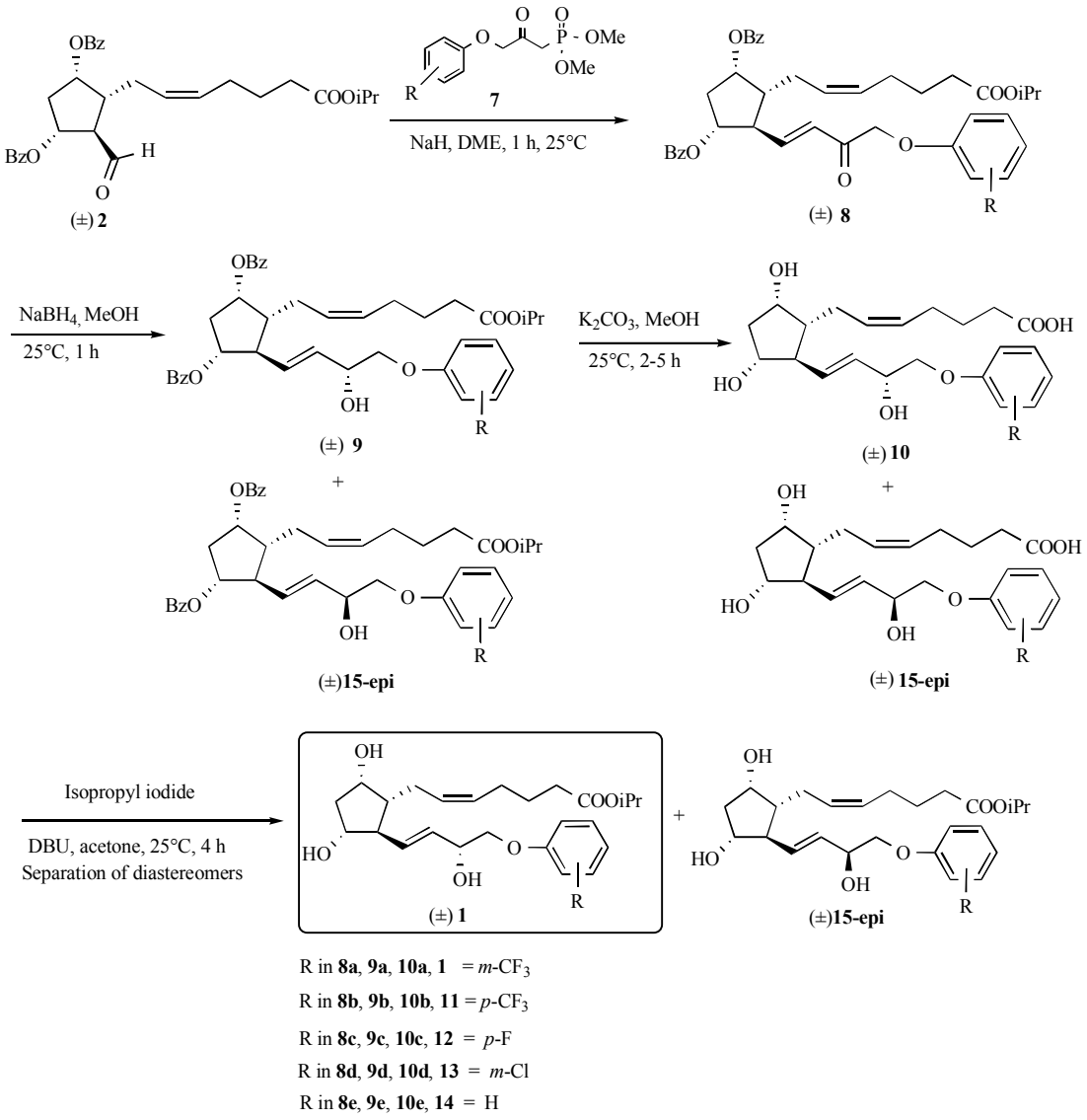


Scheme 1.

Table 1. Reaction Conditions and Yields for 5a-e and 7a-e [10]

Compound-5	Conditions	Yield	Compound-7	Conditions	Yield
5a	K_2CO_3, Acetone, 4 h, 56°C	80 %	**7a**	n-BuLi, THF, -78°C, 2 h	66 %
5b	Cs_2CO_3, ACN,15 h, RT	85 %	**7b**	n-BuLi, THF, -78°C, 2 h	82 %
5c	NaH, THF, 4 h, 65°C	61 %	**7c**	n-BuLi, THF, -78°C, 2 h	66 %
5d	NaH, THF, 4 h, 65°C	65 %	**7d**	n-BuLi, THF, -78°C, 2 h	82 %
5e	K_2CO_3, Acetone, 4h, 56°C	90 %	**7e**	n-BuLi, THF, -78°C, 2 h	83 %

chromatography at this stage) and the mixture was taken for further stages without separation. Diasteromeric mixture of compounds of **9a-e** were taken for deprotection of both benzoyl groups in K_2CO_3/methanol conditions for 2-5 h at room temperature followed by column chromatography gave respective products **10a-e** (diasteromeric mixture, 3:2). We have observed partial hydrolysis of isopropyl group during debenzoylations of **9a-e**. Esterification of **10a-e** with isopropyl iodide using DBU in acetone at room temperature for 4 h followed by usual work up gave the diastereomeric mixtures of Travoprost (both diastereomers are clearly separated in TLC in the ratio of 3:2 and the Rf difference was found to be around 0.2) , (±) **(1)** [11] and its analogs, (±)**11-14.** Diastereomers were separated by flash column chromatography using silica gel by elution with ethyl acetate/ hexane (70/30, 80/20) gradient mobile phase, which



Scheme 2.

Table 2. Reaction Yields Details from 8a-e to 1, 11-14

Compound-8	Yields	Compound-9	Yields	Compound-10	Yields	Compound-1	Yields
8a	50 %	**9a**	66 %	**10a**	55 %	**1**	35 %
8b	55 %	**9b**	82 %	**10b**	60 %	**11**	30 %
8c	45 %	**9c**	66 %	**10c**	58 %	**12**	36 %
8d	50 %	**9d**	82 %	**10d**	60 %	**13**	38 %
8e	60 %	**9e**	83 %	**10e**	59 %	**14**	40 %

afforded (±)**1** and (±) **11, 12, 13** and **14** (Scheme **2**). Stereochemistry of (±) **1** was ascertained based on literature and spectral data of (±) 1 which compared well with those reported for travoprost [10d]. All other analogs prepared were also assigned similar stereochemistry, in view of minor structural changes at remote location to the reaction centre were involved. Yields for these reactions have been reported in Table **2**.

EXPERIMENTAL

Materials and Instruments

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 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- and ^{13}C- NMR spectra were recorded on a Bruker 300 MHz NMR unit using $CDCl_3$ as solvent. Infrared spectra were recorded on a Perkin-Elmer FTIR 1605 spectrometer. Mass spectra were measured on JEOL DX-303 and JEOL HX-110 mass spectrometer.

Preparation of 5a and 5e: (Typical procedure)

Compound **3** (10.0 g, 61.68 mmol), K_2CO_3 (12.78 g, 92.53 mmol), acetone (100 mL) and **4** (14.15 g, 92.53 mmol) were refluxed under stirring for 4 h. Reaction mixture was cooled to RT and stirred for 12 h at 25 °C at which TLC indicates complete conversion of the reaction. Reaction mixture was filtered and the residue was distilled under vacuum. The residue was dissolved in water and extracted into EtOAc (100.0 mL). Organic layer was washed with 0.1 M K_2CO_3 (50.0 mL), water (50.0 mL), 0.01 M HCl (50.0 mL), water (50.0 mL), dried (Na_2SO_4) and distilled under vacuum at 40 °C to obtain the product.

Methyl 2-(3-(trifluoromethyl) phenoxy) acetate (5a)

Colorless liquid**.** ESI-MS: m/z 257 ($[M+Na]^+$). IR (KBr, υ_{max}, cm^{-1}): 3079, 2959, 1762, 1594, 1494, 1210, 1066, 875 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.81 (s, 3H), 4.67 (s, 2H), 7.07 (m, 1H), 7.14 (br, 1H), 7.26 (m, 1H), 7.40 (t, J=8.1 Hz, 1H).

Methyl 2-phenoxyacetate (5e)

Colorless liquid. ESI-MS: m/z 167 and 189 ($[M+H]^+$ and $[M+Na]^+$). IR (KBr, υ_{max}, cm^{-1}): 3.65, 2955, 1761, 1742, 1600, 1495, 1438, 1207, 1090, 888 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.80 (s, 3H), 4.64 (s, 2H), 6.89 - 6.92 (m, 2H), 6.99 (t, J=8.4 Hz, 1H), 7.29 (t, J= 6.6 Hz, 2H).

Methyl 2-(4-(trifluoromethyl) phenoxy) acetate (5b)

Compound **3b** (10.0 g, 61.68 mmol), Cs_2CO_3 (30.15 g, 92.53 mmol), acetonitrile (100.0 mL) and **4** (14.15 g, 92.53 mmol) were stirred at RT for 15 h at which TLC indicates complete conversion of the reaction. Water (100.0 mL) was added into the reaction mass at 25°C and compound was extracted into EtOAc (2x50.0 mL) dried (Na_2SO_4) and distilled under vacuum at 40 °C to obtain the product **5b**. Colorless liquid.

ESI-MS: m/z 273 ($[M+K]^+$). IR (KBr, υ_{max}, cm^{-1}): 3008, 2959, 1760, 1617, 1594, 1520, 1440, 1331, 1214, 1063, 838 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.80 (s, 3H), 4.67 (s, 2H), 6.96 (d, J=8.4 Hz, 2H), 7.55 (d, J=8.7 Hz, 2H).

Preparation of 5c and 5d

A suspension of 55 % sodium hydride (1.41 g, 107 mmol) in DMF (50.0 mL) was taken at room temperature under nitrogen atmosphere. Compound **3c** (10.0 g, 89.2 mmol) in DMF (100.0 mL) was slowly added to the suspension at room temperature under nitrogen atmosphere. **4** (20.4 g, 133.8 mmol) was added slowly to the reaction mixture at room temperature and heated to 90 °C and maintained for 3-4 h at which TLC indicates completion of the reaction. Reaction mixture was cooled to RT and 10 % ammonium chloride solution (100.0 mL) was added to the reaction mixture. Compound was extracted into EtOAc (2x100.0 mL), washed with water (3x100.0 mL), dried (Na_2SO_4) and distilled under vacuum at 40 °C to obtain the product.

Methyl 2-(4-fluorophenoxy) acetate (5c)

White colour solid**.** ESI-MS: m/z 185 and 207 ($[M+H]^+$ and $[M+Na]^+$). IR (KBr, υ_{max}, cm^{-1}): 3080, 2957, 1767, 1506, 1439, 1209, 1079, 847, 808 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.79 (s, 3H), 4.59 (s, 2H), 6.82 – 6.87 (m, 2H), 6.94 – 7.00 (m, 2H).

Methyl 2-(3-chlorophenoxy) acetate (5d)

Colorless liquid. ESI-MS: m/z 201 and 223 ($[M+H]^+$ and $[M+Na]^+$). IR (KBr, υ_{max}, cm^{-1}): 3080, 2957, 1767, 1602, 1506, 1439, 1210, 1079, 847 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.81 (s, 3H), 4.62 (s, 2H), 6.77 – 6.81 (m, 1H), 6.90 (t, J=2.1 Hz, 1H), 6.96 – 7.00 (m, 1H), 7.18 (t, J=8.1 Hz, 1H).

General Procedure for the Synthesis of Compounds 7a-e

Compound **6** (12.7 g, 102.48 mmol) in THF (100.0 mL) was cooled to -78 °C under nitrogen atmosphere. 1.6 M n-Butyl lithium (66.7 mL, 106.75 mmol) was added slowly under nitrogen atmosphere and stirred for 30 min at -78 °C. Compound **5** (10.0 g, 42.7 mmol) in THF (50.0 mL) was added slowly at -78 °C and stirred for 2 h at -78 °C under nitrogen atmosphere and further 30 min at RT. Acetic acid (20.0 mL) was added slowly into reaction mass and extracted compound with EtOAc (2x100 mL). The combined extracts were washed with water, dried (Na_2SO_4) and evaporated to dryness to obtain crude product. Crude product was purified by column chromatography using EtOAc/hexane (9:1) as eluent to get pure product.

Dimethyl 2-oxo-3-(3-(trifluoromethyl) phenoxy) propylphosphonate (7a)

Pale yellow colour liquid. ESI-MS: m/z 327 and 349 ($[M+H]^+$ and $[M+Na]^+$). IR (KBr, υ_{max}, cm^{-1}): 2961, 2925, 1737, 1594, 1494, 1451, 1331, 1252, 1030, 877 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.26 (d, J=22.8 Hz, 2H), 3.79 (d, J=11.8 Hz, 6H), 4.79 (s, 2H), 7.10 (m, 1H), 7.13 (br, 1H), 7.24 (m, 1H), 7.40 (t, J=8.1 Hz, 1H).

Dimethyl 2-oxo-3-(4-(trifluoromethyl) phenoxy) propylphosphonate (7b)

Pale yellow color liquid**.** ESI-MS: m/z 327 and 349 ($[M+H]^+$ and $[M+Na]^+$). IR (KBr, υ_{max}, cm^{-1}): 2959, 1735, 1618, 1522, 1239, 1036, 839 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.26 (d, J=22.8 Hz, 2H), 3.80 (d, J=11.1 Hz, 6H), 4.79 (s, 2H), 6.70 (d, J=8.4 Hz, 2H), 7.55 (d, J=8.4 Hz, 2H).

Dimethyl 3-(4-fluorophenoxy)-2-oxopropylphosphonate (7c)

Pale yellow colour liquid**.** ESI-MS: m/z 277 and 299 ($[M+H]^+$ and $[M+Na]^+$). IR (KBr, υ_{max}, cm^{-1}):3077, 2960, 1737, 1507, 1456, 1208, 1032, 831 cm^{-1}. ^{1}H NMR (300

MHz, $CDCl_3$) δ (ppm): 3.26 (d, J=22.8 Hz, 2H), 3.78 (d, J=11.4 Hz, 6H), 4.66 (s, 2H), 6.83 – 6.87 (m, 2H), 6.94 – 7.00 (m, 2H).

Dimethyl 3-(3-chlorophenoxy)-2-oxopropylphosphonate (7d)

White colour solid. ESI-MS: m/z 293 ($[M+H]^+$). IR (KBr, υ_{max}, cm^{-1}): 3098, 2960, 1733, 1598, 1486, 1237, 1027, 861, 824 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.26 (d, J=22.8 Hz, 2H), 3.80 (d, J=11.1 Hz, 6H), 4.72 (s, 2H), 6.79 – 6.83 (m, 1H), 6.91 (t, J=2.1 Hz, 1H), 6.96 – 7.00 (m, 1H), 7.21 (t, J=8.1 Hz, 1H).

Dimethyl 2-oxo-3-phenoxypropylphosphonate (7e)

Colour less liquid**.** ESI-MS: m/z 258 ($[M+H]^+$). IR (KBr, υ_{max}, cm^{-1}): 3027, 2957, 1718, 1497, 1401, 1259, 1031, 852 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.31 (d, J=22.5 Hz, 2H), 3.79 (d, J=11.1 Hz, 6H), 4.68 (s, 2H), 6.88 – 6.91 (m, 2H), 6.99 (t, J=7.5 Hz, 1H), 7.26 – 7.32 (m, 2H).

General Procedure for the Synthesis of Compounds 8a-e

A suspension of 55 % sodium hydride (0.41 g, 31.62 mmol) in dimethoxyethane, DME (40.0 mL) under nitrogen atmosphere was cooled to -5 °C. Compound **7** (9.66 g, 29.64 mmol) dissolved in DME (20.0 mL) was added slowly into the reaction mixture at -5 to 0 °C and stirred for 15 min at 0 °C. Reaction mixture temperature was raised to 25 °C and stirred for 1 h at 25 °C. Reaction mixture temperature was cooled to -5 °C and compound **2** (5.0 g, 9.88 mmol) dissolved in DME (20.0 mL) was added slowly into the reaction mass for 30 min 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 (50.0 mL). Then the reaction mixture temperature was raised to 25 °C and stirred for 10 min and concentrated under vacuum at 40°C. The residue was dissolved in EtOAc (50.0 mL) and separated the layers; aqueous layer was extracted with EtOAc (3x40.0 mL). Combined organic layers were washed with brine dried over Na_2SO_4 and concentrated under vacuum at 40 °C. Crude product obtained was purified by flash column chromatography on silica gel (230-400 mesh) with an ethyl acetate-hexane (1:9) as eluent to give compound **8**.

4-((Z)-7-isopropoxy-7-oxohept-2-enyl)-5-((E)-3-oxo-4-(3-(trifluoromethyl)phenoxy)but-1-enyl) cyclopentane-1,3-diyl dibenzoate (8a)

Pale yellow color viscous liquid. ESI-MS: m/z 707 ($[M+H]^+$). IR (KBr, υ_{max}, cm^{-1}): 3065, 2979, 1720, 1623, 1492, 1453, 1271, 1069, 712 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.17 (d, J=6.3 Hz, 6H), 1.94 – 1.22 (m, 2H), 1.34 – 1.57 (m, 4H), 1.87 – 2.36 (m, 4H), 2.66 (m, 1H), 3.03 (m, 1H), 4.80 (s, 2H), 4.92 (m, 1H), 5.34 – 5.39 (m, 3H), 5.48 (t, J=4.2 Hz, 1H), 6.58 (d, J=15.9 Hz, 1H), 7.10 – 7.62 (m, 11H), 7.89 (m, 2H), 8.06 (m, 2H).

4-((Z)-7-isopropoxy-7-oxohept-2-enyl)-5-((E)-3-oxo-4-(4-(trifluoromethyl)phenoxy)but-1-enyl) cyclopentane-1,3-diyl dibenzoate (8b)

Pale yellow color viscous liquid. ESI-MS: m/z 707 ($[M+H]^+$). IR (KBr, υ_{max}, cm^{-1}): 2927, 2856, 1719, 1615, 1452, 1328, 1269, 1112, 837 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.17 (d, J=6.3 Hz, 6H), 1.43 – 1.77 (m, 3H), 1.80 – 2.45 (m, 7H), 2.69 (m, 1H), 3.05 (m, 1H), 4.81 (s, 2H), 4.92 (m, 1H), 5.33 – 5.39 (m, 3H), 5.48 (t, J=4.5 Hz, 1H), 6.55 (d, J=8.7 Hz, 1H), 6.94 (d, J=8.7 Hz, 2H), 7.11 (dd, J=15.9, 9.0 Hz, 1H), 7.31 (t, J=8.1 Hz, 2H), 7.48 (m, 1H), 7.43 (t, J=7.5 Hz, 2H), 7.52 (d, J=8.7 Hz, 2H), 7.62 (m, 1H), 7.89 (m, 2H), 8.07 (m, 2H).

4-((E)-4-(4-fluorophenoxy)-3-oxobut-1-enyl)-5-((Z)-7-isopropoxy-7-oxohept-2-enyl)cyclopentane-1,3-diyl dibenzoate (8c)

Pale yellow color viscous liquid. ESI-MS: m/z 679 ($[M+H]^+$). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.18 (d, J=6.3 Hz, 6H), 1.40 – 1.54 (m, 3H), 1.90 (m, 2H), 2.01 – 2.35 (m, 5H), 2.69 (m, 1H), 3.03 (m, 1H), 4.71 (s, 2H), 4.93 (m, 1H), 5.33 – 5.36 (m, 3H), 5.47 (t, J=4.2 Hz, 1H), 6.57 (dd, J=15.6, 0.6 Hz, 1H), 6.82 (m, 2H), 6.94 (m, 2H), 7.09 (dd, J=15.6, 8.7 Hz, 1H), 7.32 (t, J=7.5 Hz, 2H), 7.45 (t, J=7.5 Hz, 2H), 7.51 (t, J=7.5 Hz, 1H), 7.59 (t, J=7.5 Hz, 1H), 7.89 (dd, J=8.1, 0.6 Hz, 2H), 8.07 (dd, J=8.1, 0.6 Hz, 2H).

4-((*E*)-4-(3-chlorophenoxy)-3-oxobut-1-enyl)-5-((*Z*)-7-isopropoxy-7-oxohept-2-enyl)cyclopentane-1,3-diyl dibenzoate (8d)

Pale yellow color viscous liquid. ESI-MS: m/z 696 ($[M+Na]^+$). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.17 (d, J=6.3 Hz, 6H), 1.48 – 1.55 (m, 3H), 1.89 (m, 2H), 2.02 – 2.35 (m, 5H), 2.68 (m, 1H), 3.04 (m, 1H), 4.73 (s, 2H), 4.93 (m, 1H), 5.32 – 5.37 (m, 3H), 5.48 (t, J=4.5 Hz, 1H), 6.56 (d, J=15.9 Hz, 1H), 6.75 (m, 1H), 6.90 (t, J=2.1 Hz, 1H), 6.95 (m, 1H), 7.11 (dd, J=15.9, 9.0 Hz, 1H), 7.17 (t, J=8.1 Hz, 1H), 7.32 (t, J=7.5 Hz, 2H), 7.45 (t, J=7.5 Hz, 2H), 7.51 (t, J=7.5 Hz, 1H), 7.59 (t, J=7.2 Hz, 1H), 7.89 (m, 2H), 8.07 (m, 2H).

4-((Z)-7-isopropoxy-7-oxohept-2-enyl)-5-((E)-3-oxo-4-phenoxybut-1-enyl)cyclopentane-1,3-diyl dibenzoate (8e)

Pale yellow color viscous liquid. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.16 (d, J=6.3 Hz, 6H), 1.47 – 1.57 (m, 3H), 1.87 (m, 2H), 2.04 – 2.34 (m, 5H), 2.68 (m, 1H), 3.03 (m, 1H), 4.73 (s, 2H), 4.93 (m, 1H), 5.29 – 5.36 (m, 3H), 5.47 (t, J=4.2 Hz, 1H), 6.60 (dd, J=15.9, 0.9 Hz, 1H), 6.88 (m, 2H), 6.95 (t, J=7.2 Hz, 1H), 7.09 (dd, J=15.9, 9.0 Hz, 1H), 7.23 (m, 2H), 7.31 (t, J=7.8 Hz, 2H), 7.45 (t, J=7.5 Hz, 2H), 7.51 (t, J=7.2 Hz, 1H), 7.59 (t, J=7.5 Hz, 1H), 7.89 (m, 2H), 8.07 (m, 2H).

General Procedure for the Synthesis of Compound 9a-e

Compound **8** (4.0 g, 5.66 mmol) in methanol (40.0 mL) was cooled to 0 °C and sodium borohydride (0.42 g, 11.31 mmol) was added at 0 °C and stirred for 10 min. The reaction mixture temperature was raised to 25 °C and stirred for 30 min at which TLC indicates complete conversion of the reaction. Solvent was distilled under vacuum at 40 °C. Ammonium chloride solution (40.0 mL) was added to the residue at 25 °C and stirred for 10 min. Both the layers were separated and the aqueous layer was extracted with EtOAc (3x40.0 mL). Organic layer was dried (Na_2SO_4) and

concentrated under vacuum at 40 °C to obtain the crude product. Crude product was purified by flash column chromatography using silica gel (230-400 mesh) by eluting ethyl acetate-hexane (2:8). Pure fractions were combined, and the solvent was distilled under vacuum at 40 °C to give **9**.

4-((E)-3-hydroxy-4-(3-(trifluoromethyl)phenoxy)but-1-enyl)-5-((Z)-7-isopropoxy-7-oxohept-2-enyl)cyclopentane-1,3-diyl dibenzoate (9a)

Colorless viscous liquid. ESI-MS: m/z 726 ($[M+NH_4]^+$). IR (KBr, υ_{max}, cm^{-1}): 3067, 2980, 1717, 1602, 1451, 1329, 1271, 1111, 712 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.18 (d, J=6.1 Hz, 6H), 1.51 – 1.55 (m, 2H), 1.89 – 2.11 (m, 4H), 2.30 (m, 2H), 2.66 (m, 1H), 2.89 (m, 1H), 3.88 – 4.04 (m, 2H), 4.58 (m, 1H), 4.94 (m, 1H), 5.27 – 5.48 (m, 4H), 5.80 – 5.95 (m, 2H), 7.02 – 7.58 (m, 10H), 7.91 (m, 2H), 8.06 (m, 2H).

4-((E)-3-hydroxy-4-(4-(trifluoromethyl)phenoxy)but-1-enyl)-5-((Z)-7-isopropoxy-7-oxohept-2-enyl)cyclopentane-1,3-diyl dibenzoate (9b)

Colorless viscous liquid. ESI-MS: m/z 731 ($[M+Na]^+$). IR (KBr, υ_{max}, cm^{-1}): 3485, 3064, 2980, 1719, 1615, 1587, 1519, 1452, 1270, 1112, 1069, 837 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.19 (d, J=6.1 Hz, 6H), 1.53 (m, 2H), 1.85 – 2.12 (m, 6H), 2.31 (m, 2H), 2.63 – 2.92 (m, 2H), 3.94 – 4.01 (m, 2H), 4.58 (br, 1H), 4.93 (m, 1H), 5.38 – 5.47 (m, 4H), 5.71 – 6.04 (m, 2H), 6.92 (dd, J=8.4, 5.7 Hz, 2H), 7.31 (m, 2H), 7.40 – 7.61 (m, 6H), 7.91 (m, 2H), 8.06 (m, 2H).

4-((E)-4-(4-fluorophenoxy)-3-hydroxybut-1-enyl)-5-((Z)-7-isopropoxy-7-oxohept-2-enyl)cyclopentane-1,3-diyl dibenzoate (9c)

Colorless viscous liquid. ESI-MS: m/z 681 ($[M+Na]^+$). IR (KBr, υ_{max}, cm^{-1}): 3437, 2980, 2934, 1717, 1602, 1451, 1329, 1271, 1111, 1068, 712 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.18 (d, J=6.3 Hz, 6H), 1.53 (m, 2H), 1.91 – 2.11 (m, 3H), 2.31 (m, 2H), 2.61 – 2.72 (m, 2H), 2.90 (m, 1H), 3.79 – 3.96 (m, 2H), 4.55 (br, 1H), 4.94 (m, 1H), 5.26 – 5.47 (m, 4H), 5.75 – 5.85 (m, 2H), 6.76 – 6.97 (m, 4H), 7.32 (t, J=7.8 Hz, 2H), 7.44 (t, J=7.8, 2H), 7.50 (t, J=7.5 Hz, 2H), 7.58 (t, J=7.5 Hz, 2H), 7.92 (m, 2H), 8.07 (m, 2H).

4-((E)-4-(3-chlorophenoxy)-3-hydroxybut-1-enyl)-5-((Z)-7-isopropoxy-7-oxohept-2-enyl)cyclopentane-1,3-diyl dibenzoate (9d)

Colorless viscous liquid. ESI-MS: m/z 697 ($[M+Na]^+$). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.81 (d, J=6.3 Hz, 6H), 1.58 (m, 2H), 1.90 – 2.73 (m, 8H), 3.81 – 3.98 (m, 2H), 4.55 (m, 1H), 4.90 – 4.99 (m, 1H), 5.18 – 5.48 (m, 4H), 5.74 – 5.87 (m, 2H), 6.75 (m, 1H), 6.87 – 6.94 (m, 2H), 7.16 (m, 1H), 7.32 (t, J=7.5 Hz, 2H), 7.45 (t, J=7.5, 2H), 7.50 (t, J=7.5 Hz, 2H), 7.58 (t, J=7.5 Hz, 2H), 7.93 (d, J=7.5 Hz, 2H), 8.07 (m, 2H).

4-((E)-3-hydroxy-4-phenoxybut-1-enyl)-5-((Z)-7-isopropoxy-7-oxohept-2-enyl)cyclopentane-1,3-diyl dibenzoate (9e)

Colorless viscous liquid. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.17 (d, J=6.3 Hz, 6H), 1.52 (m, 2H), 1.88 – 2.67 (m, 8H), 3.85 – 4.01 (m, 2H), 4.57 (m, 1H), 4.94 (m, 1H), 5.26 – 5.47 (m, 4H), 5.79 – 5.92 (m, 2H), 6.86 – 6.97 (m, 3H), 7.23 (m, 2H), 7.31 (t, J=7.8 Hz, 2H), 7.44 (t, J=7.5 Hz, 2H), 7.50 (t, J=7.2 Hz, 1H), 7.58 (t, J=7.5 Hz, 1H), 7.93 (m, 2H), 8.07 (m, 2H).

General Procedure for the Synthesis of Compound 10a-e

Compound **9** (3.2 g, 4.51 mmol), potassium carbonate (2.5 g, 18.05 mmol) and MeOH (32.0 mL) were stirred at RT for 5 h at which TLC indicates complete conversion of the reaction. Demineralized water (32.0 mL) was added to the reaction mixture at 25 °C and stirred for 10 min. pH of the reaction mixture was adjusted to 2-5 with 10% citric acid (32.0 mL) and aqueous layer was extracted with EtOAc (3x32.0 mL). Organic layers were dried over Na_2SO_4 and concentrated under vacuum at 40 °C to obtain crude product. Crude product was purified by flash column chromatography using silica gel (230-400 mesh) by eluting ethyl acetate-hexane (6:4). Pure fractions were combined, and solvent was removed under vacuum at 40 °C to give Compound **10**.

(Z)-7-(3,5-dihydroxy-2-((E)-3-hydroxy-4-(3-(trifluoromethyl)phenoxy)but-1-enyl)cyclopentyl)hept-5-enoic acid (10a)

Colorless viscous liquid. ESI-MS: m/z 481 ($[M+Na]^+$). IR (KBr, υ_{max}, cm^{-1}): 3395, 3010, 2930, 1712, 1592, 1493, 1450, 1330, 1125, 792cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.50 – 2.36 (m, 8H), 3.94 – 4.08 (m, 3H), 4.25 (m, 1H), 4.62 (m, 1H), 5.38 – 5.78 (m, 4H), 7.09 (d, J=8.4 Hz, 1H), 7.15 (d, J=1.5 Hz, 1H), 7.22 (d, J=8.4 Hz, 1H), 7.39 (t, J=8.1 Hz, 1H).

(Z)-7-(3,5-dihydroxy-2-((E)-3-hydroxy-4-(4-(trifluoromethyl)phenoxy)but-1-enyl)cyclopentyl)hept-5-enoic acid (10b)

Colorless viscous liquid. ESI-MS: m/z 481 ($[M+Na]^+$). IR (KBr, υ_{max}, cm^{-1}): 3392, 3009, 2930, 1712, 1615, 1591, 1438, 1330, 1259, 1112, 1069, 837 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.41 – 1.91 (m, 4H), 2.00 – 2.51 (m, 8H), 3.95 – 4.04 (m, 3H), 4.20 (m, 1H), 4.59 (m, 1H), 5.42 (m, 2H), 5.70 (m, 2H), 6.97 (d, J=8.7 Hz, 2H), 7.54 (d, J=8.7 Hz, 2H).

(Z)-7-(2-((E)-4-(4-fluorophenoxy)-3-hydroxybut-1-enyl)-3,5-dihydroxycyclopentyl)hept-5-enoic acid (10c)

Colorless viscous liquid. ESI-MS: m/z 431 ($[M+Na]^+$). IR(KBr, υ_{max}, cm^{-1}): 3392, 2925, 1708, 1506, 1455, 1207, 1032, 829 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.18 – 1.84 (m, 4H), 2.08 – 2.35 (m, 8H), 3.85 – 4.01 (m, 3H), 4.22 (m, 1H), 4.56 (m, 1H), 5.34 – 5.76 (m, 4H), 6.85 (m, 2H), 6.97 (m, 2H).

(Z)-7-(2-((E)-4-(3-chlorophenoxy)-3-hydroxybut-1-enyl)-3,5-dihydroxycyclopentyl)hept-5-enoicacid (10d)

Colorless viscous liquid. ESI-MS: m/z 447 ($[M+Na]^+$). IR(KBr, υ_{max}, cm^{-1}): 3369, 2929, 1718, 1595, 1477, 1232, 1034, 864 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.50 – 1.82 (m, 4H), 2.10 – 2.38 (m, 8H), 3.89 – 4.01 (m, 3H), 4.21 (m, 1H), 4.57 (m, 1H), 5.37 – 5.74 (m, 4H), 6.80 (m, 1H), 6.90 – 6.96 (m, 2H), 7.19 (td, J=8.1, 1.5 Hz, 1H).

(Z)-7-(2-((E)-4-phenoxy-3-hydroxybut-1-enyl)-3,5-dihydroxycyclopentyl)hept-5-enoicacid (10e)

Colorless viscous liquid. ESI-MS: m/z 413 ($[M+Na]^+$). IR(KBr, υ_{max}, cm^{-1}): 3363, 2929, 1718, 1643, 1557, 1454, 1246, 1031, 972 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.57 – 1.85 (m, 5H), 2.07 – 2.42 (m, 7H), 3.79 – 4.64 (m, 5H), 5.31 – 5.81 (m, 4H), 6.88 – 7.01 (m, 3H), 7.30 (m, 2H).

General Procedure for the Synthesis of (±) Travoprost (1) and its Analogues (11-14)

Compound 10 (1.0 g, 2.18 mmol) in acetone (25.0 mL) was cooled to -5 °C and DBU (2.0 g, 13.08 mmol) was added slowly under nitrogen atmosphere at -5 °C. Reaction mixture temperature was raised to room temperature and stirred for 30 min. Isopropyl iodide (1.85 g, 10.9 mmol) was added at room temperature into the reaction mixture and stirred for 4 h at which TLC indicates completion of the reaction. Reaction mixture was concentrated under vacuum to remove acetone and to get residue. Residue was dissolved in EtOAc (30.0 mL) and washed with 10 % citric acid (20.0 mL) solution followed by 5 % $NaHCO_3$ solution (20.0 mL), brine (20.0 mL) and dried (Na_2SO_4) to obtain crude product. Crude product contains two diastereomers and desired isomer was separated by column chromatography using silica gel (230-400 mesh) by eluting EtOAc / hexane (3:7) to give pure product.

(Z)-6-(3,5-dihydroxy-2-((E)-3-hydroxy-4-(3-(trifluoromethyl)phenoxy)but-1-enyl)cyclopentyl)hex-4-enyl isobutyrate ((±)Travoprost) (1) [10d]

Pale yellow color viscous liquid. ESI-MS: m/z 523 ($[M+Na]^+$). HRMS (ESI): Calcd. for $C_{26}H_{35}F_3O_6$ Na $[M+Na]^+$ 523.2278; found 523.2299. IR (KBr, υ_{max}, cm^{-1}): 2980, 2935, 1719, 1492, 1450, 1330, 1126, 1061, 793 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.21 (d, J=6.3 Hz, 6H), 1.50 – 1.83 (m, 5H), 2.04 – 2.44 (m, 7H), 3.91 – 4.04 (m, 3H), 4.19 (t, J=3.9 Hz, $1H_a$), 4.54 (m, $1H_b$), 4.98 (m, 1H), 5.35 – 5.42 (m, 2H), 5.66 (dd, J=15.3, 5.7 Hz, 1H), 5.76 (dd, J=15.3, 5.7 Hz, 1H), 7.08 (dd, J=8.1, 2.1 Hz, 1H), 7.14 (br, 1H), 7.22 (d, J=7.8 Hz, 1H), 7.39 (t, J=8.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 21.67, 24.71, 25.27, 26.47, 33.90, 42.69, 49.89, 55.48, 67.61, 70.85, 71.86, 72.34, 111.40 (q, J_{C-F}=3.8 Hz), 117.61 (q, J_{C-F}=4.5 Hz), 117.95, 123.79 (q, J_{C-F}=270.8 Hz), 128.83, 129.64, 129.93, 130.01, 131.74 (q, J_{C-F}=32.3 Hz), 135.48, 158.60, 173.48.

(Z)-isopropyl7-(3,5-dihydroxy-2-((E)-3-hydroxy-4-(4-(trifluoromethyl)phenoxy)but-1-enyl)cyclopentyl) hept-5-enoate (11)

Pale yellow color viscous liquid. ESI-MS: m/z 523 ($[M+Na]^+$). HRMS (ESI): Calcd. for $C_{26}H_{35}F_3O_6$ Na $[M+Na]^+$ 523.2278; found 523.2295. IR (KBr, υ_{max}, cm^{-1}): 3393, 2980, 2934, 1724, 1615, 1520, 1375, 1330, 1259, 1111, 837 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm):1.21 (d, J=6.3 Hz, 6H), 1.53 – 1.84 (m, 5H), 2.05 – 2.41 (m, 7H), 3.90 – 4.06 (m, 3H), 4.21 (t, J=3.9 Hz, 1H), 4.55 (m, 1H), 4.99 (m, 1H), 5.36 – 5.44 (m, 2H), 5.63 – 5.80 (m, 2H), 6.98 (d, J=8.7 Hz, 2H), 7.54 (d, J=8.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm):21.69, 24.74, 25.42, 26.50, 33.90, 42.80, 50.26, 55.78, 67.61, 70.67, 71.85, 72.71, 114.50, 123.22 (q, J_{C-F}=32.3 Hz), 124.25 (q, J_{C-F}=269.3 Hz), 126.84 (q, J_{C-F}=3.8 Hz), 128.82, 129.53, 129.63, 129.74, 135.22, 160.90, 173.40.

(Z)-isopropyl7-(2-((E)-4-(4-fluorophenoxy)-3-hydroxybut-1-enyl)-3,5-dihydroxycyclopentyl)hept-5-enoate (12)

Yellow color viscous liquid. ESI-MS: m/z 473 ($[M+Na]^+$). HRMS (ESI): Calcd. for $C_{25}H_{35}FO_6$ Na $[M+Na]^+$ 473.231; found 473.2337. IR (KBr, υ_{max}, cm^{-1}):3399, 2932, 1725, 1507, 1453, 1375, 1249, 1210, 1108, 971, 829 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.22 (d, J=6.3 Hz, 6H), 1.52 – 1.84 (m, 4H), 2.05 – 2.43 (m, 6H), 3.82 – 4.00 (m, 3H), 4.20 (br, 1H), 4.52 (br, 1H), 4.99 (m, 1H), 5.37 – 5.42 (m, 2H), 5.61 – 5.79 (m, 2H), 6.85 (m, 2H), 6.97 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 21.70, 24.74, 25.31, 26.50, 33.93, 42.72, 49.94, 55.52, 67.58, 70.92, 72.39, 115.57 (q, J_{C-F}=1.5 Hz), 115.78 (q, J_{C-F}=17.3 Hz), 128.88, 129.62, 130.08, 135.23, 154.60 (q, J_{C-F}=2.3 Hz), 157.33 (q, J_{C-F}=237.0 Hz), 173.40.

(Z)-isopropyl7-(2-((E)-4-(4-chlorophenoxy)-3-hydroxybut-1-enyl)-3,5-dihydroxycyclopentyl)hept-5-enoate(13)

Yellow color viscous liquid. ESI-MS: m/z 489 ($[M+Na]^+$). HRMS (ESI): Calcd. for $C_{25}H_{35}ClO_6$ Na $[M+Na]^+$ 489.2014; found 489.2034. IR(KBr, υ_{max}, cm^{-1}): 3389, 2931, 1725, 1595, 1479, 1374, 1248, 1107, 1035, 773 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.22 (d, J=6.3 Hz, 6H), 1.55 – 1.84 (m, 4H), 2.09 – 2.40 (m, 8H), 3.88 (dd, J=9.6, 7.8 Hz, 1H), 4.00 (m, 2H), 4.21 (t, J=4.2 Hz, 1H), 4.52 (m, 1H), 4.99 (m, 1H), 5.40 (m, 2H), 5.61 – 5.78 (d, 2H), 6.80 (ddd, J=8.4, 2.4, 0.9 Hz, 1H), 6.91 – 6.96 (m, 2H), 7.20 (t, J=8.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 21.70, 24.74, 25.25, 26.49, 33.94, 42.71, 49.80, 55.38, 67.57, 70.85, 71.85, 72.21, 113.01, 115.03, 121.12, 128.89, 129.58, 130.15, 130.20, 134.74, 135.43, 159.24, 173.44.

(Z)-isopropyl7-(3,5-dihydroxy-2-((E)-3-hydroxy-4-phenoxybut-1-enyl)cyclopentyl)hept-5-enoate(14)

Yellow color viscous liquid. ESI-MS: m/z 455 ($[M+Na]^+$). HRMS (ESI): Calcd. for $C_{25}H_{36}O_6$ Na $[M+Na]^+$ 455.2404; found 455.2394. IR(KBr, υ_{max}, cm^{-1}): 3369, 2928, 2859, 1726, 1634, 1599, 1496, 1375, 1246, 1108, 1040, 970 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.21 (d, J=6.3 Hz, 6H), 1.64 – 1.83 (m, 4H), 1.98 – 2.30 (m, 8H), 3.91 (dd, J=9.3, 7.5 Hz, 1H), 3.97 – 4.02 (m, 2H), 4.19 (t, J=4.2 Hz, 1H), 4.53 (m, 1H), 4.99 (m, 1H), 5.41 (m, 2H), 5.70 (m, 2H), 6.87 – 7.00 (m, 3H), 7.30 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 21.71, 24.77, 25.41, 26.50, 29.56, 33.95, 50.09, 55.65, 58.44, 67.49, 70.90, 71.71, 72.42, 114.54, 120.95, 129.03, 129.37, 129.49, 130.19, 135.12, 158.50, 173.32.

CONCLUSION

The advanced racemic key intermediate (**2**) was successfully converted in to (±) travoprost and its analogs establishing the generality of the synthetic approach.

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