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AN EFFICIENT AND LABORATORY FRIENDLY SYNTHESIS OF ANTI-GLAUCOMA AGENT OF BIMATOPROST

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ABSTRACT: An alternative, economically viable, and laboratory-friendly synthetic method described for the preparation of Bimatoprost, an anti-glaucoma drug. Stereospecific synthesis of Bimatoprost has been achieved with commercially available (-) Corey lactone *i.e.*, diol, as a starting material. To our delight, the replacement of the benzoyl (Bz) group with Tetrahydropyranyl ether (Thp) protection resulted in yield improvement. Tetrahydropyranyl ether (Thp) is notorious as a useful protecting group for alcohols in organic synthesis. It has numerous benefits, such as low cost, ease of insertion, general stability to most non-acidic conditions. It offers good solubility and easy to remove if the functional group it protects requires manipulation. Moreover, it described the successful application of luche's reduction for the conversion of α, β-unsaturated ketone 8 to allylic alcohol 9 using $CeCl_3$ $7H_2O$, $NaBH_4$. This lanthanide combination with borohydride enables the selective 1, 2-hydride attack on the carbonyl group, instead of an undesired 1, 4-hydride attack, which leads to the formation of desired allylic alcohol without disturbing the double bond.

INTRODUCTION: Prostaglandins represent a class of organic compounds containing a cyclo-pentane ring with a variety of substituents and two aliphatic carbon chains on adjacent carbons of the cyclopentane ring. Ketone and hydroxyl or two hydroxyl functionalities are the most common combinations resided on cyclopentane. Based on the substituents present on the cyclopentyl ring, Prostaglandin molecules are characterized. The $PGF_{2\alpha}$ prostaglandin analogs generally have two hydroxyl groups in *cis* orientation relative to the cyclopentane ring.

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The two side chains are in a trans-configuration relative to each other, and each side chain has one double bond in upper α-chain at C_5-C_6, this double bond is in E-orientation. The other double bond in the lower β-chain at C_{13}-C_{14} is in *Z*-orientation. A PGF2α prostaglandin analog shows biological activity, especially in eye diseases such as glaucoma and anti-inflammatory. Bimatoprost (Lumigan) A[1], (Z)-7-[(1R, 2R, 3R, 5S)-3, 5 - Dihydroxy - 2 - [(1E, 3S) - 3 - hydroxyl - 5 - phenyl - 1 - pentenyl] cyclopentyl] - 5 - N - ethyl-heptenamide), a glaucoma [2] refraining agent, is an un-natural prostaglandin analogue **Fig. 1**.

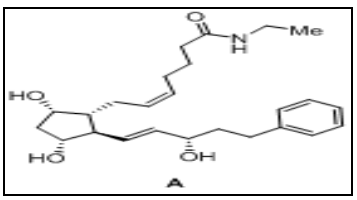


FIG. 1: STRUCTURE OF BIMATOPROST

It is used as eye drops to restrain the progression of open-angle glaucoma and in the management of ocular hypertension. Lowering IOP remains the only reliable treatment for glaucoma [3-5].

EXPERIMENTAL: Proton NMR spectra recorded on 400-MHz spectrometers. Tetramethyl silane (TMS) is used as an internal reference for ^{1}H NMR. All chemical shifts reported in ppm and the coupling constant (*J*) values calculated in hertz (Hz) based on the chemical shifts. Deuterio-chloroform ($CDCl_3$) was used as a solvent for all NMR experiments with residual Chloroform as an internal standard for ^{13}C NMR. IR spectra were recorded on the Perkin Elmer FT-IR spectrophotometer. Mass spectra were obtained by positive chemical ionization (CI) or by the fast atomic bombardment (FAB) technique. All reactions were carried out in oven-dried glassware. Dichloromethane distilled from calcium hydride. Tetrahydrofuran (THF) freshly distilled from sodium metal/benzophenone before use. All solvents for chromatography were obtained commercially and used as received. Reactions monitored by analytical thin-layer chromatographic (TLC) methods, using Pre-coated TLC sheets ALUGRAM® Xtra SIL G/UV_{254} (layer: 0.20 mm silica gel 60 with fluorescent indicator UV_{254}). All spots on TLC plates were either visualized by ultraviolet (UV) light or detected by dipping the plate into a Phospomolybdic acid solution in ethanol and heating. The pure products for characterization were isolated by column chromate-graphy with the use of silica gel, 60-120 mesh, and 100-200 mesh size.

Preparation of (3aR, 4S, 5R, 6a S) – 4 - ((tert – butyl - dimethyl - silyloxy) methyl) – 5 –hydro-xyhexahydro-2H-cyclopenta [b]furan-2-one (2): Added imidazole [2.37 g, 0.0348 moles] to a solution of (3aR, 4S, 5R, 6a S) – 5 - hydroxy 4 - (hydro-xymethyl) hexahydro - 2H –cyclopenta [b] furan – 2 - one [5.0 g, 0.029 moles] (1) in dichloro-methane [50.0 ml] at room temperature. Chilled the reaction mass to 5 °C, then slowly added *tert*-butyldimethylsilyl chloride (TBDMSCl) [4.8g, 0.0319 moles] in a lot wise manner into above solution. After being stirred for 1 h, water was added. Separated the organic layer, extracted the aq layer with dichloromethane (50 ml), combined organic layer washed with water(25 ml), dried over Na_2SO_4, concentrated the organic layer affords **(**3aR, 4S, 5R, 6aS) – 4 - ((tert – butyl dimethyl silyloxy) methyl) - 5-hydroxyhexahydro-2H-cyclo-penta [b] furan - 2 - one (2), 8.4 g, 99.0% yiled. ^{1}HNMR ($CDCl_3$, 400MHz, 4.86 (m,1H, J=2.8Hz), 4.06 (m,1H), 3.65 (m, 1H), 3.55 (m, 1H), 2.7 (m,1H), 2.57 (m,1H), 2.5 (m,1H), 2.4 (m,1H), 1.95 (m,2H), 0.83 (s,9H), 0.005 (s,6H),), the hydroxyl proton is not showing signal due to merged.

Preparation of (3aR, 4S, 5R, 6aS) – 4 - ((tert - butyldimethyl silyloxy) methyl) – 5 - (tetrahydro - 2H – pyran – 2 - yloxy) hexahydro - 2H – cyclopenta [b] furan – 2 – one (3a, 3b): Arranged clean and dry RBF. Charged n-hexane [150.0 ml] and **(**3aR, 4S, 5R, 6aS) - 4 - ((tert-butyldimethyl-silyloxy) methyl) – 5 – hydroxyhexahydro - 2H-cyclopenta [b] furan-2-one (2) [15.0 g, 0.0523 moles] in to RBF under nitrogen atmosphere. Cooled the reaction mass to below 5 °C under nitrogen atmosphere. Added Dihydropyran (3, 4-Dihydro-2H-pyran) [7.5 g, 0.089 moles, 1.7eq] and *p*-Toluenesulfonic acid (PTSA or *p*TsOH) [0.447 g, 0.0026 moles, 0.05eq] to the reaction mass at 0-5 °C under nitrogen atmosphere.

Stirred the reaction mass for 1 h at 0-5 °C under nitrogen atmosphere. Added water [90.0 ml] and Ethyl acetate [150.0 ml] in to reaction mass. Separated the org. layer and reextracted the aq. layer with Ethyl acetate [90.0 ml]. Combined org. Layer washed with 5% aq Sodium bicarbonate solution [150.0 ml].

Dried the org.layer over sodium sulphate. Distilled the org. layer under vacuum at below 40 °C. Crude compound purified by column chromatography by eluting column with cyclo hexane and ethyl acetate. Distilled the pure fractions under vacuum at below 40°C to afford (3aR, 4S, 5R, 6aS)-4-((tert-butyl-dimethylsilyloxy) methyl) – 5 - (tetrahydro - 2H – pyran – 2 - yloxy) hexahydro-2H-cyclopenta[b] furan-2-one (3), 15.8 g, 81.5% yield, ^{1}HNMR, 400.0 MHz, $CDCl_3$, 5.112-5.040 (m,1H, J=2.4Hz), 4.761(s,1H), 4.326 - 4.122 (dq, 1H, J=3.2Hz), 4.010 - 3.890 (m, 1H, J=3.2Hz), 3.688 - 3.638 (m, 2H, J=5.6Hz), 3.621-3.572 (m,1H, J=4.4Hz), 2.957-2.892 (m,1H, J=6.0Hz), 2.848-2.659 (m,1H), 2.607-2.427 (m,1H, J=2.4Hz), 2.357-2.300 (m,1H, J=2.4Hz), 2.259-2.217 (m,1H), 1.939-1.853 (m,1H), 1.811-1.589 (m,6H), 0.991-0.989 (s,9H), 0.148 (s, 6H).

Preparation of (3aR, 4S, 5R, 6a S)-4-((tert-butyldimethyl silyloxy) methyl) - 5 - (tetrahydro-2H-pyran-2-yloxy) hexahydro-2H-cyclopenta [b] furan-2-ol (4): Slowly added diisobutylaluminium hydride (DIBAL-H) ,46.0 ml (25% w/w in toluene) [0.081 moles, 3.0 mole ratio, 11.5 g] to a solution of (3aR, 4S, 5R, 6aS) – 4 - ((tert-butyl-dimethylsilyloxy) methyl) – 5 - (tetrahydro- 2H-pyran-2-yloxy) hexahydro-2H-cyclopenta [b] furan-2-one (3) [10.0 g, 0.027 moles], in tetrahydrofuran [100.0 ml] at -70 °C. After being stirred for 3 h, added methanol (10.0 ml) slowly, vigorous frothing observed, followed by aq ammonium chloride solution (10.0 g in 100.0 ml water) and ethyl acetate. After being stirred for 30 min, filtered through hyflow bed, separate the organic layer, aq layer extracted with ethyl acetate, combined organic layer washed with water, dried over sodium sulphate, distilled the low volatiles under vacuum, afford (3aR,4S,5R,6aS)-4-((tert-butyldimethylsilyl oxy)methyl)-5-(tetrahydro-2H-pyran-2-yloxy)hexahydro-2H-cyclopenta [b]furan-2-ol (4) 10.0 g,100% yield. ^{1}HNMR ($CDCl_3$, 400MHz), 5.390-5.631(1H,m), 4.654-4.684(1H,m), 3.799-3.976(1H,m), 3.450-3.668(3H,m), 2.435-2.618 (2H,m), 2.330-2.403 (1H,m), 2.157-2.295 (1H,m), 1.938-2.101 (2H,m), 1.702-1.907 (2H,m), 1.509-1.605 (6H,m), 0.887 (9H,s), 0.043 (6H,s). m/z:355.5(M-1).

Preparation of (Z)-methyl 7-((1R, 2S, 3R, 5S)-2-((tert-butyldimethylsilyloxy) methyl)-5-hydroxy-3- (tetrahydro-2H-pyran-2-yloxy) cyclopentyl) hept - 5-enoate (5): Potassium *t*-butoxide (19.6 g, 0.174 moles) was added to a solution of(4-Carboxybutyl) triphenylphosphonium bromide (38.70 g, 0.086 moles) and tetrahydrofuran (84 ml). After being stirred for 30 min.cool the reaction mass to 5 °C, slowly added solution of (3aR, 4S, 5R, 6aS)-4-((tert-butyldimethylsilyloxy)methyl)-5-(tetrahydro-2H-pyran-2-yloxy) hexahydro - 2H-cyclopenta [b] furan-2-ol (4) (8.4 g, 0.0291 moles) in tetrahydrofuran (17 ml). stirred the mixture for 2 h, monitored by TLC, water (84 ml) and MTBE (100 ml) was added into reaction mixture, separated layers and aq layer rewashed with MTBE (84 ml). Adjusted the pH of aq layer to 3-4 by adding 10% aq citric acid solution(10 g citric acid in 100 ml water),then extracted the aq layer with MTBE (196 ml) followed by reextracted with MTBE (55 ml), combined organic layer washed with water, dried over sodium sulphate, distilled the low volatiles under vacuum. In an another clean and dry RBF was added above distilled compound, 1,8-Diazabicyclo[5.4.0] undec-7-ene, DBU (35.4 g, 0.233 moles) and acetone, after being stirred for 10 min, slowly added methyl iodide (49.5 g, 0.349 moles) into reaction mixture at RT. Quenched the reaction mass with 10% aq citric acid solution after being stirred the reaction mixture over night, aq layer extracted with ethyl acetate (84 ml*2),organic layer washed with water (50 ml), dried over sodium sulphate, distilled the low volatiles under vacuum. crude compound purified column chromatography afford (Z)-methyl 7-((1R,2S,3R,5S)-2-((tert-butyl-dimethylsilyloxy) methyl) - 5 – hydroxy – 3 -(tetra-hydro-2H- pyran-2- yloxy) cyclopentyl) hept-5-enoate (5), 6.5g, yield:47.74% , 1HNMR ($CDCl_3$, 400 MHz), 5.534-5.459 (m,1H, J=7.6Hz), 5.408-5.345(m,1H, J=7.2Hz), 4.702-4.675(m, 1H, J=3.2Hz), 4.277-4.212 (d, 1H, J=6.0Hz), 4.131-4.095 (m,1H), 3.913-3.824 (m,1H), 3.770-3.735 & 3.664-3.638 (dd, dd, 1H, J=4.0Hz), 3.673(s, 3H), 3.532-3.357 (m, 2H, J=6.8Hz), 2.501-2.285 (m, 4H, J=8.0Hz), 2.258-2.104 (m, 3H, J=8.4Hz), 2.046-2.011 (m, 1H), 1.985-1.900 (m,1H), 1.862-1.652 (m, 6H), 1.536-1.486 (m, 3H), 1.259-1.256 (m,1H), 0.887-0.877 (s,s,9H), 0.039-0.033(s,s,6H). m/z: 469.4(M-1).

Preparation of (Z)-methyl 7-((1R, 2S, 3R, 5S)-2-((tert-butyldimethylsilyloxy) methyl) - 3, 5-bis (tetrahydro- 2H-pyran-2-yloxy) cyclopentyl) hept-5-enoate (6): Arranged clean and dry RBF. Charged n-hexane [150.0 ml] and (Z)-methyl 7-((1R, 2S, 3R, 5S) – 2 - ((tert-butyl-dimethylsilyloxy) methyl) - 5 - hydroxy- 3-(tetrahydro-2H-pyran-2-yloxy) cyclopentyl) hept-5-enoate (5), [15.0g, 0.0523 moles] in to RBF under nitrogen atmosphere. Cooled the reaction mass to 5 °C under nitrogen atmosphere. Added 3,4-Dihydro-2H-pyran [7.5 g, 0.089 moles, 1.7eq] and TsOH [0.447 g, 0.0026 moles, 0.05eq] to the reaction mass at 5°C under nitrogen atmosphere. Stirred the reaction mass for 1 h at 5 °C under nitrogen atmosphere. Added water [90.0 ml] and Ethyl acetate [150.0 ml] in to reaction mass. Separated the org. layer and reextracted the aq. layer with ethyl acetate [90.0 ml]. Combined org. layer washed with 5% aq Sodium bicarbonate solution [150.0 ml]. Dried the org.layer over sodium sulphate. Removed the low volatiles under vacuum

at below 40 °C. Crude compound was purified by column chromatography by eluting column with cyclo-hexane and ethyl acetate. Concentrated the pure fractions under vacuum at below 40 °C to afford (Z)-methyl 7-((1R, 2S, 3R, 5S)-2-((tert-butyl-dimethylsilyloxy) methyl)-3, 5-bis (tetrahydro-2H-pyran -2-yloxy) cyclopentyl) hept-5-enoate (6),15.8 g, 81.5% yield, 1HNMR, 400.0MHz, $CDCl_3$. 5.586-5.531 (m,2H), 4.726-4.703 (m,1H), 4.614-4.607 (m,1H), 4.169-3.739 (m,5H), 3.670 (s,3H), 3.578-3.459 (m,3H), 2.356-2.299 (dt,2H,J=7.8Hz, 5.2Hz), 2.275-2.185 (m,1H), 1.976-1.524 (m,14H), m/z:440.3.

Preparation of (Z)-methyl-((1R, 2S, 3R, 5S)-2-(hydroxymethyl)-3, 5-bis (tetrahydro-2H-pyran-2-yloxy) cyclopentyl) hept-5-enoate (7): Added Tetra-n-butylammonium fluoride [TBAF] (0.92 g, 0.0036 moles) to solution of (Z)-methyl 7-((1R, 2S,3R, 5S)-2-((tert-butyldimethylsilyloxy) methyl)-3,5-bis (tetrahydro- 2H-pyran-2-yloxy) cyclo-pentyl) hept-5-enoate (6) [10.0,0.018 moles], Tetrahydrofuran (50.0 ml) at 5 °C. Stirred the mixture for 6 h at 5 °C. Added 5% aq sodium bi carbonate solution (50.0 ml) and ethyl acetate (50.0 ml)to the reaction mass. Separated the org.layer. Reextracted the aq.layer with Ethyl acetate (25.0 ml).Combined both org. layers and wash with water (25.0 ml) and dried over sodium sulphate (10.0 g). Distilled the org. layer under vacuum at below 40 °C. Dissolved above obtained crude in to pet ether (50.0 ml) and stir for 20 min at 25 to 35 °C. Solid Filtered and washed the solid with pet ether (10.0 ml).Dried the solid under vacuum at below 40 °C to afford (Z)-methyl 7-((1R, 2S, 3R, 5S) - 2 - (hydroxymethyl) - 3, 5 – bis (tetra-hydro - 2H-pyran-2-yloxy) cyclo-pentyl) hept-5-enoate (7) 5.6 gr, 70.5% yield, ^{1}HNMR, 400.0 MHz ($CDCl_3$), 5.586-5.351 (2H,m), 4.756-4.703 (1H,m), 4.614-4.607 (1H,m), 4.169-3.739 (5H,m), 3.670 (3H,s), 3.578-3.459 (3H,m), 2.443-2.299 (3H,m), 2.275-2.185 (2H,m), 2.171-2.003 (5H,m), 1.976-1.771 (3H,m), 1.734-1.663 (4H,m), 1.584-1.560 (8H,m).

Preparation of (Z)-methyl 7-((1R, 2R, 3R, 5S)-2-((E) - 3 – oxo – 5 – phenylpent – 1 - enyl)-3, 5-bis (tetrahydro-2H-pyran-2-yloxy) cyclopentyl) hept-5- enoate (8): Dess-Martin periodinane (7.2 g, 0.017) was added to a solution of (Z)-methyl 7-((1R, 2S, 3R, 5S) - 2 -(hydroxymethyl) - 3, 5-bis (tetrahydro -2H-pyran-2-yloxy) cyclo pentyl) hept-5-enoate (7) (5.0 gr, 0.0113 moles) in dichloromethane (50.0 ml) at 5 °C. After being stirred for 30 min at RT, was added water (50.0 ml) and filtered the unwanted salts, separated the layers into separated flasks, the aq layer reextracted with dichloromethane (25.0 ml), the combined organic layer washed with 5% aq sodium bicarbonate solution (50.0 ml). Concentrated the organic layer under vacuum at 40 °C. Pet ether was added to the above residue and then filtered. The Filtrate was evaporated under vacuum at 40 °C to afford an aldehyde intermediate.

In an another 4 necked RBF was charged dimethyl 2 – oxo – 4 – phenyl -butylphosphonate, MTBE (50.0 ml) and LiOH. H_20, stired the mixture for 30 min, to this solution was added above aldehyde and MTBE (20.0 ml) solution drop wise at 0-5 °C in 5-10 min. Stirred the reaction mass at 0-5°C for 20-30 minutes. Separate the upper organic layer, aq layer reextracted with ethyl acetate (25.0 ml). Combined organic layer washed with water and dried over sodium sulphate. Concentrated the organic layer affords (Z)-methyl 7-((1R, 2R, 3R, 5S)-2-((E) - 3 - oxo - 5 – phenylpent – 1 - enyl) - 3, 5-bis (tetrahydro-2H-pyran -2-yloxy) cyclopentyl) hept-5-enoate (8), 4.2 g, 65.3% Yiled:, ^{1}HNMR, 400MHz, $CDCl_3$, 7.279-7.298 (d, 2H, J=7.6Hz), 7.193-7.211 (3H, m, J=7.2Hz), 6.667-6.785 (1H, m, J=6.4Hz), 6.160-6.244 (1H, m, J=6.4Hz), 5.300-5.474 (2H,m), 4.503-4.713 (2H, m, J=12Hz), 3.942-4.059 (2H,m, J=8.0Hz), 3.838-3.809 (1H,m), 3.765-3.737 (3H,d, J=11.6Hz), 3.644 (3H, s), 3.486-3.362 (2H,m), 3.103-3.047 (1H,d, J=24Hz), 2.970-2.861(5H,m), 2.794-2.591 (1H,m), 2.445-2.346 (1H,m), 2.285-2.324 (2H, t, J=8.4Hz), 2.265-2.172 (1H,m), 1.902-1.915 (4H,m), 1.752-1.865 (5H,m), 1.586-1.697 (6H,m), 1.499-1.522 (10H, m).m/z: 553.30 (568-15) loss of methyl radical.

Preparation of (Z)-methyl 7-((1R, 2R, 3R, 5S)-2-((S, E) – 3 – hydroxyl – 5 – phenylpent – 1 - enyl) - 3, 5 – bis (tetrahydro - 2H – pyran – 2 - yloxy) cyclopentyl) hept-5-enoate (9): Slowly added sodium borohydride (0.26 g, 0.007 moles) in a lot wise manner into a cooled solution of (Z)-methyl 7-((1R, 2R, 3R, 5S)-2-((E)-3- oxo-5-phenylpent-1-enyl) - 3, 5 – bis (tetrahydro-2H-pyran-2-yloxy) cyclopentyl)hept-5-enoate(**8**)[4.0g, 0.007 moles], $CeCl_3.7H_2O$ [2.6g, 0.007 moles] and methanol.

After being stirred for 45 min at 5 °C, checked the TLC, removed the methanol under vacuum, added ethyl acetate and 5% aq ammonium chloride to the residue, mixed for 10min separated the upper organic layer, aq layer extracted with ethyl acetate, combined organic layer was washed with water, dried over sodium sulphate and concentrated under vacuo at below 30 °C. The oily residue contains two major spots on TLC with equal proportions, was purified by column chromatography by eluting with ethyl acetate and petroleum ether affords (Z)-methyl 7-((1R,2R,3R,5S)-2- ((S,E)-3-hydroxy-5-phenylpent-1-enyl) -3,5-bis(tetrahydro-2H -pyran-2-yloxy) cyclopentyl)hept-5-enoate (9),1.6 g,40.0% yield, ^{1}HNMR,CDCl3, 400-MHz, 7.298-7.280 (2H, d, J=7.2Hz), 7.205-7.187 (3H,d, J=7.2Hz), 5.712-5.479 (2H,m, J=6.4Hz), 5.381-5.299 (1H,m, J=7.2Hz), 4.720-4.600 (2H,m, J=11.6Hz), 4.192-4.102 (1H,m, J=6.4Hz), 4.039-3.914 (2H,m, J=7.6Hz), 3.864-3.826 (2H,d, J=10.4Hz) ,3.772-3.745 (d,2H, J=10.8Hz) 3.659-3.646 (2H,d, J=5.2Hz), 3.490 -3.374 (2H,m, J=10.0Hz), 2.850-2.697 (2H,m), 2.602-2.462 (1H,m), 2.428-2.355 (1H,m, J=8.4Hz), 2.318-2.212 (1H,m, J=8.8Hz), 2.196-2.127 (1H,m, J=2.8Hz), 1.950-1.876 (2H,m, J=6.8Hz), 1.805(3H,m), 1.518-1.685 (15H,m), 1.227-1.277 (1H,m).

Preparation of (Z)-methyl 7-((1R, 2R, 3R, 5S)-3, 5- dihedron - xy - 2 -((S,E) - 3 - hydroxy - 5-phenylpent-1-enyl) cyclopentyl) hept-5-enoate (10): P- toluene sulfonic acid (2.0g)was added to the solution of (Z)-methyl 7-((1R,2R,3R,5S)-2-((S, E) – 3 – hydroxyl – 5 – phenylpent - 1- enyl) - 3, 5-bis (tetrahydro-2H-pyran-2-yloxy) cyclopentyl) hept-5-enoate(9) (20.0 g, 0.035 moles), methanol (200.0 ml), Stirred the reaction mass at 25 °C for 90 min. Distill the reaction mass under vacuum at 40 °C. Charge water (200.0ml) and Ethyl acetate (200.0 ml) to the above crude. Stir the mixture at RT for 15 min, settle the layers and separate aq layer and org Distil the org.layer under vacuum at 40 °C till no distillate collected. Crude compound purified by column chromatography afford (Z)-methyl 7-((1R, 2R, 3R, 5S)-3, 5- dihedron- xy-2-((S, E) – 3 – hydroxyl – 5 – phenylpent – 1 - enyl) cyclopentyl) hept-5-enoate (10), 8.5 g, yield 60.3%, ^{1}HNMR, 400MHz, 7.274-7.256 (m,2H,J=4.3Hz), 7.199-7.181 (d,3H, J=7.6Hz), 5.643-5.588 (dd,1H, J=6.8Hz), 5.529-5.469 (dd,1H, J=6.4Hz), 5.446-5.362 (m,2H, J=6.8Hz), 4.166 (t,1H), 4.129-4.076 (q,1H, 7.2Hz), 3.950-3.910 (m,1H, J=6.0Hz), 3.646 (s,3H), 2.722-2.664(q,2H, J=8.0Hz),2.507(bs,2H), 2.314-2.278 (t,2H, J=7.2 Hz), 2.118-2.076 (m,3H), 1.929-1.851 (m,1H), 1.835-1.780 (m,2H), 1.705-1.634 (pentet, 2H, J=6.8 Hz), 1.241(m,2H).

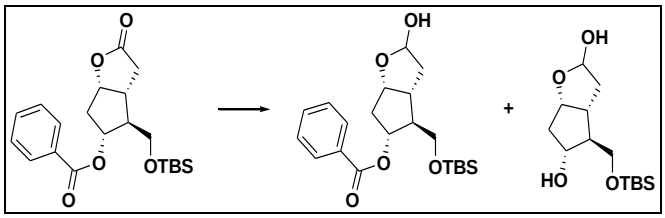
Preparation of (Z)-7-[(1R, 2R, 3R, 5S)-3, 5-Dihydroxy – 2 - [(1E, 3S) - 3-hydroxy - 5-phenyl-1-pentenyl] cyclopentyl] – 5- ethyl-heptenamide (11): (Z)-methyl 7-((1R,2R,3R,5S)-3,5- dihydroxy-2 - ((S, E) – 3 – hydroxyl – 5 – phenylpent - 1 - enyl) cyclopentyl) hept – 5 - enoate (10) [5.0 g, 0.012 moles] was added to the aq solution of ethyl amine [100 ml, 70% in water] at RT, stir reaction mass for 34-36 hrs at 25-30 °C. Removed the low volatiles under vacuum at 45 °C, then added and dichloromethane, Separate the organic layer, aq. Layer extracted with dichloromethane. Combined organic layers dried over sodium sulphate. Removed the low volatiles under vacuum at 40 °C. Charge MTBE at 25 °C. Stir the reaction mass at 25-35°C for 3-4 h. Filter the solid under nitrogen blanketing conditions and wash the solid with MTBE Dry the solid at 40 °C for 3-4 h under vacuum affords (Z)-7-[(1R, 2R, 3R, 5S)- 3,5-Dihydroxy-2-[(1E, 3S) – 3 – hydroxyl – 5 – phenyl -1-pentenyl] cyclopentyl]-5ethylheptenamide (11), 3.0 gr, 58.1% yield.

^{1}HNMR, CDCl3, 7.3-7.25 (m,2H), 7.20-7.17 (m,3H), 5.65- 5.59 (1H,dd, J=6.714Hz), 5.545-5.469 (1H,dd, J=6.714 Hz), 5.443-5.336 (m,2H), 4.179-4.168 (1H,m), 4.142-4.084 (m,1H), 3971-3.954 (m,1H), 3.292-3.223 (m,2H, J=7.6Hz), 3.058-2.991 (dd,2H, J=4.8Hz), 2.789-2.647 (m,3H), 2.374-2.232 (m,2H), 2.182-1.998 (m,6H), 1.918-1.817 (m,4H), 1.806-1.592 (m,2H, J=6.7 Hz), 1.516-1.443(m,1H,J=4.272Hz), 1.136-1.101(t,3H,J=6.714Hz).m/z: 398.4(M+H).IR: 3423, 3322, 3025, 2930, 1640, 1620, 1547, 1496, 1454, 1373, 748,696. m/z:385.3, 367.32, 349.2., 13CNMR173, 142, 135, 133, 130, 129, 128.4, 128.3, 126, 78, 72.4, 72.2, 55.56, 50.26, 42.91, 38.75,35.84,34.36,32,27, 26,15. m/z: 438.3 (M+Na). 398.3 (M-18) loss of water molecule.

RESULTS AND DISCUSSION: Large-scale processing of Bimatoprost synthesis [6, 7] is highly challenging. The compound (3aR, 4S, 5R, 6aS)-(-)-Hexahydro – 5 – hydroxyl – 4 - (hydroxymethyl)-2H-cyclopent [b] furan-2-one 1, is commercially

available and its trade name is (-) Corey lactone diol used as a critical starting material for the preparation of Bimatoprost [8]. General development of prostaglandins from Corey-lactone diol involves the protection of primary and secondary alcoholic groups and the selective deprotection of primary alcoholic groups in the presence of protected secondary alcohol; further oxidation and coupling are crucial steps. On the other hand, the reduction of keto functionality of the cyclopentane ring and Wittig reaction are the key transformations to accomplish Bimatoprost in another way. Benzoyl group is a commonly used protecting group among these strategies.

Low yield was observed during the benzoyl group deprotection. Transesterification and ester hydrolysis are the significant disadvantages noted during the benzoyl group deprotection. As it involves the use of either sodium methoxide in methanol or potassium carbonate in methanol. Pyridine is a widely used base for benzoyl protection, which is associated with health hazards, and removal of pyridine from the reaction mixture is tedious and problematic. Benzoyl group is labile to the bases such as sodium hydroxide, lithium hydroxide, sodium hydride, and at pH more than [9]. It does not survive during the reduction with DIBAL-H to make lactone to lactol.



SCHEME 1: BENZOYL GROUP HYDROLYSIS DURING THE DIBAL-H REDUCTION

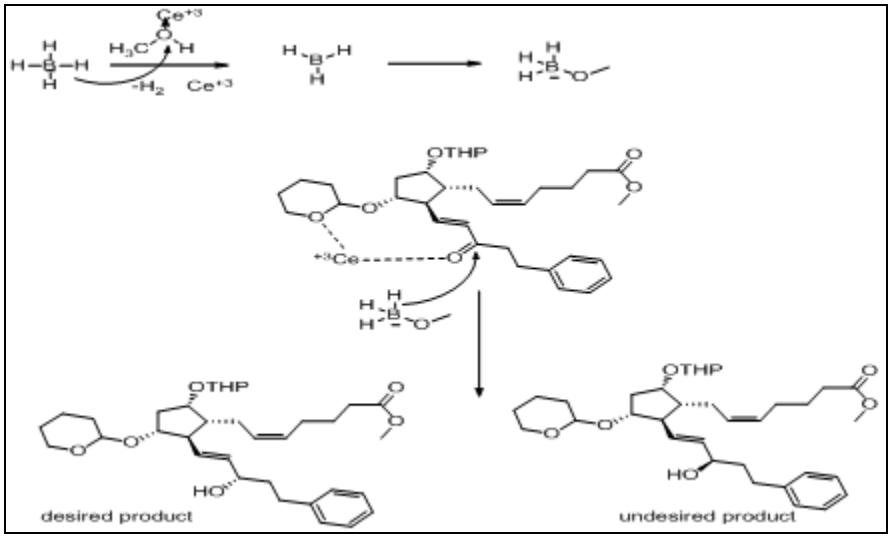
Moreover, electronic effects will hinder the insertion of a second benzoyl group. Also, by debenzoylation takes place at elevated temperatures, which led to the methyl ester group generation and getting hydrolyzing. Tetrahydropyranyl ether (Thp) protecting group chosen to overcome the difficulties, as mentioned earlier. To our delight, the replacement of the benzoyl (Bz) group with Tetrahydropyranyl ether (Thp) protection resulted in yield improvement. Tetrahydropyranyl ether (Thp) is renowned as a useful protecting group for alcohols in organic synthesis. It has several benefits, such as inexpensive, ease of insertion, general stability to most non-acidic conditions. It offers good solubility and easy to remove if the functional group it protects requires manipulation. Thp has the advantage over benzoyl and benzyl-based protecting groups, such as triphenyl methyl (Trt), diphenylmethyl (Dpm), (4-methoxyphenyl) diphenylmethyl (methoxytrityl, Mmt) or benzyloxymethyl (Bom) because it lacks aromaticity and offers enhanced solubility. The tetrahydropyranyl ethers (Thp) offer stability towards strong bases such as sodium hydride (NaH), Potassium tert-butoxide (KOtBu), Lithium diisopropylamide (LDA), Lithium tetra-methylpiperidine (LiTMP).

The tetrahydropyranyl ethers (Thp) protecting group is stable towards many reagents that would generally consume alcohol. These tetrahydropyranyl ethers are stable towards organometallics such as alkyl lithium (RLi, R=Me,n-Bu), Grignard reagents (RMgBr, R=Methyl, Ethyl, Butyl). Metal hydrides such as Na/NH_3, $NaBH_4$, $LiAlH_4$, DIBAL-H, nucleophiles such asalkoxides **(**NaOR, R= Methyl, Ethyl), lithiumenolates, $Ph_3P=CH_2$, reductants such as H_2 and Ni or Pd, oxidants such as OsO_4, PCC/PDC, Swern, H_2O_2, Sodium hypochlorite in combination with TEMPO.

A drawback with tetrahydropyranyl ether (Thp) groups is to generate diastereomeric mixtures when reacts with chiral alcohols. Simple laboratory affordable methods applied for the synthesis of Bimatoprost A. $NaBH_4$ is the most widely used reducing agent for the effective conversion of carbonyl compounds to the corresponding alcohols [9-12]. The $NaBH_4$ reduction of conjugated carbonyl compounds takes place in an uncontrolled fashion and gives a substantial amount of saturated alcohols.

However, the usage of $NaBH_4$ in combination with $CeCl_3$. $7H_2O$ (Luche's reduction) [13-17] arrests this problem. The Luche reduction can be adopted to convert α, β-unsaturated ketones into allylic alcohols by using the combination of lanthanide salts such as $CeCl_3$ anhydrous or $CeCl_3.7H_2O$, $NaBH_4$ and methanol (or ethanol) as a solvent. The leading role of cerium(III) ion is to coordinate with the alcoholic solvent such as methanol, making its proton more acidic, which can then be abstracted by the carbonyl oxygen of the keto group.

After the addition of $NaBH_4$, it also reacts with the cerium activated methanol and forms methoxyborohydride. methoxyborohydride is "hard reagent." It facilitates the selective 1, 2-hydride attack on the carbonyl group instead of an undesired 1, 4-hydride attack, which leads to the formation of desired allylic alcohol without disturbing the double bond. Besides, the use of $CeCl_3$ offers the possibility of coordinating with the oxygen atom of the carbonyl group and with the oxygen atom of the pyran group, which results in shielding of the front side. Due to this shielding effect, the desired backside hydride attack should be more favored. The incursion of a cerium ion on the oxygen atom of the carbonyl group allows the formation of a cerium complex that helps the axial attack of borohydride and ensuring the creation of the equatorial hydroxy group. Adopting the Luche's reduction prevented the over reduction, thus delivered the corresponding alcohols through regioselective reduction. The plausible reduction mechanism with Luche's is shown in **Scheme 2**.

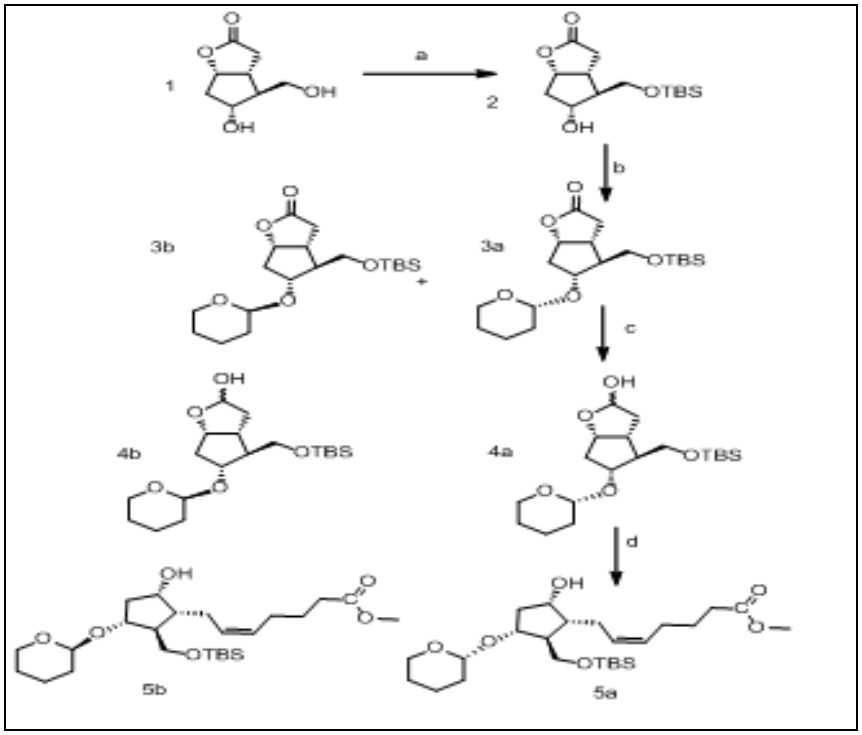


SCHEME 2: THE PLAUSIBLE MECHANISM OF LUCHE'S REDUCTION

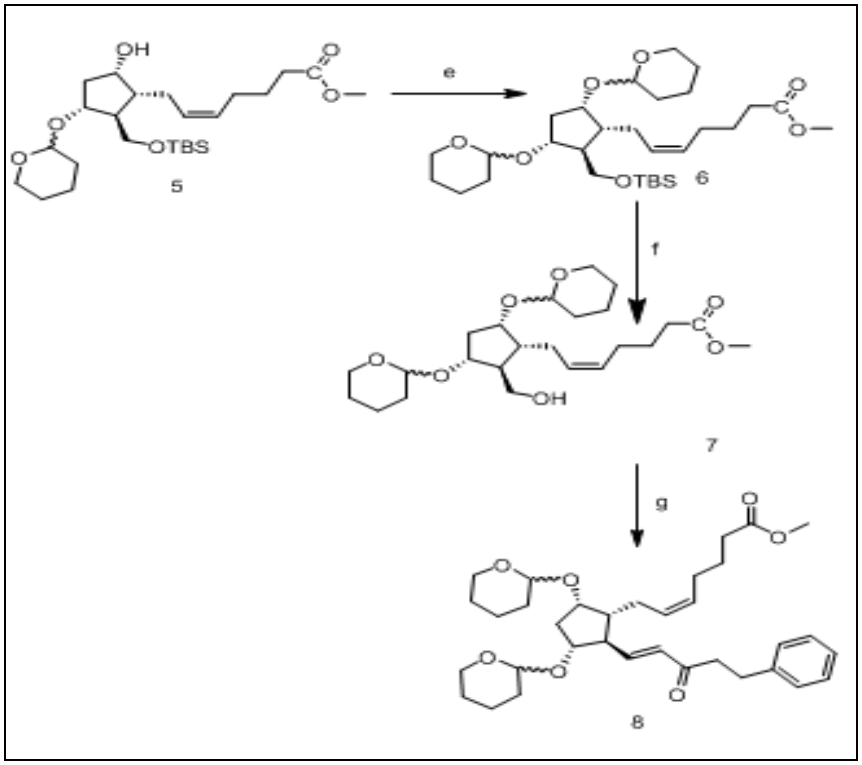
The primary alcoholic group of (-)-Corey lactone diol 1 protected with a tert butyl dimethylsilyl group by using tert-butyldimethylsilyl chloride (TBDMSCl) [18-20] and imidazole in dichloromethane yields the desired lactone 2 in quantitative yield. On the other hand, the secondary alcohol of compound 2 protected with tetrahydropyranyl ether (Thp) [21] group by reacting with 3,4-dihydro-2*H*-pyran in the presence of a catalytic amount of *para*-toluene sulphonic acid (PTSA) in the presence of hexane solvent medium gave the compound 3 in 90% yield, which on further, reduction with diisobutyl aluminum hydride (DIBAL-H) [22] in tetrahydrofuran obtained the lactol 4. Treatment of Lactol 4 with commercially available (4-carboxybutyl) triphenylphosphonium bromide [23] and potassium tertiary butoxide in tetrahydrofuran solvent medium forms cis-olefinic acid intermediate [24] through the generation of an unstabilized ylide [wittig reaction] [25]. Esterification of olefinic acid intermediate with methyl iodide and 1, 8-Diazabicyclo (5.4.0) undec-7-ene (DBU) [26] in acetone afforded hydroxyl ester 5 **Scheme 3.**

Tert-butyldimethylsilyl chloride, imidazole, dichloromethane, RT, 1 h, 95%; b. 3, 4-dihydro-2H-pyran, PTSA; c. di isobutyl aluminum hydride, tetrahydrofuran, -78 °C, 3 h, 98%; d. (4-carboxybutyl) triphenylphosphonium bromide, potassium *tert*-butoxide, tetrahydrofuran, 0-5 °C, CH_3I, DBU, acetone.

The free hydroxy group in ester 5 protected with 3, 4-dihydro-2H-pyran by using a catalytic amount of *p*-toluene sulphonic acid in the presence of hexane to give the corresponding compound 6 in quantitative yield. The deprotection of the TBDMS group of 6 with Tetra-(n-butyl) ammonium fluoride (TBAF) [27] in tetrahydrofuran solvent medium forms the hydroxy ester compound 7 in a quantitative yield. Compound 7 was treated with Dess-Martin periodinane [28] in the dichloromethane solvent medium to yield an aldehyde intermediate, which is further reacted with dimethyl-2-oxo-4-phenyl-butyl phosphonate to afford a conjugated carbonyl 8 as an *E*-isomer *via* a stabilized ylide [29, 30] **Scheme 4.**

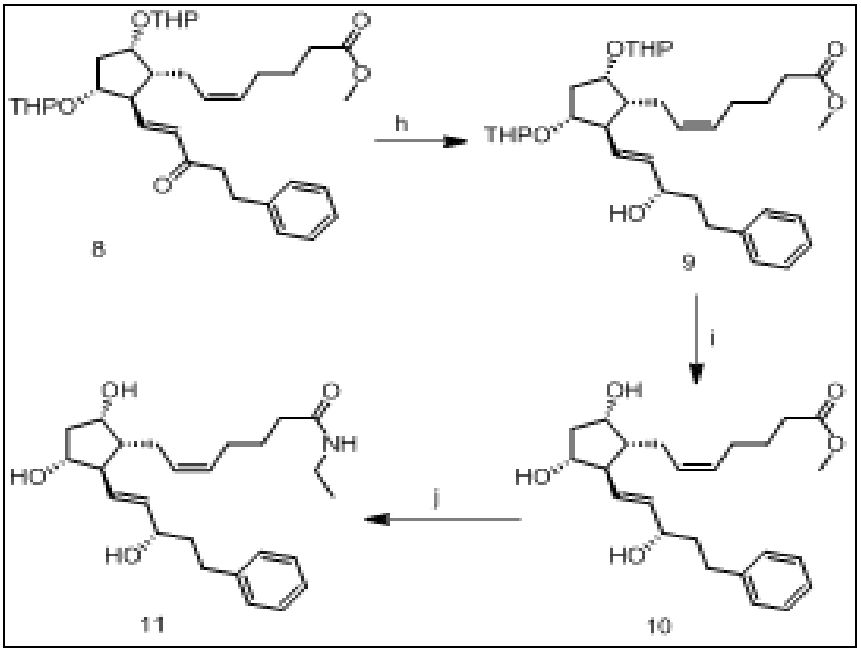


SCHEME 3: PREPARATION OF HYDROXYL ESTER



SCHEME 4: PREPARATION OF CONJUGATED ENONE

3, 4 - dihydro - 2*H* - pyran, PTSA; Tetra(n-butyl) ammonium fluoride, tetrahydrofuran, RT, 10 h, 87%; Des-Martin periodinane, lithium hydroxide, methyl tert-butyl ether, dimethyl-2-oxo-4-phenyl-butyl phosphonate, RT. The conjugated enone 8 is further reduced with sodium borohydride in the presence of cerium trichloride-heptahydrate in the presence of methanol to yield hydroxy ester 9. Both the tetrahydropyranyl (Thp) groups of the alcoholic ester 9 deprotected with PTSA in water and THF mixture to produce trihydroxy ester 10. Finally, the trihydroxy ester reacted with ethyl-amine in the water medium to give the desired amide, bimatoprost 11 (A) **Scheme 5.**



SCHEME 5: PREPARATION OF TRIHYDROXY ESTER h. CH_3OH, $CeCl_3 \bullet 7H_2O$, $NaBH_4$, -70 °C; i. CH_3OH, TsOH, RT; j. Ethylamine, water.

CONCLUSION: First time successfully introduced the large scale method able to isolate, synthesize and characterize the antigalucoma agent of Bimatoprost. In summary, we have successfully prepared the anti-glaucoma agent bimatoprost from commercially available (-)-Corey lactone diol with the use of the tetrahydropyranyl group (Thp) as a protecting group. Moreover, in this synthesis, we described the successful application of luche's reduction for the conversion of α,β-unsaturated ketone to corresponding alcohol without disturbing the double bond. Although using this route augmented yields are obtained.

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CONFLICTS OF INTEREST: Nil

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