STUDIES ON BIMATOPROST, HOMOBIMATOPROST AND NORBIMATOPROST

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ABSTRACT:
The PG ocular hypertensives are PGF2 analogs where the α-side chain converted into either ester or amide functionality and in these the ω-side chain is modified with aromatic units. In previous chapter, we reported the development of a versatile key Intermediate (148) from racemic Corey lactone (140) and it can be elaborated in to variety of prostaglandins and their derivatives. As a demonstration of this general approach, we discussed conversion of key intermediate (148) in to (±) Bimatoprost (3), (±) Homobimatoprost (168) and (±) Norbimatoprost (172) and details are discussed in this article.

Keywords: Bimatoprost, Homobimatoprost, Norbimatoprost
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1. INTRODUCTION:

Glaucoma, a potentially blinding eye disorder, is characterized by increased intraocular pressure (IOP), excavation of optic nerve head, and gradual loss of visual field.In recent years, attention has been focused on prostaglandins (PGs), primarily prostaglandin F2α estersand there are currently four prostaglandin analogues latanoprost, bimatoprost, travoprost and uniprostoneapproved for Glaucoma treatment by the USFDA. [1-6] Several studies have established that PGs of the F2α type reduce IOP by increasing uveoscleral outflow of aqueous humor. [7-8]

2. BIMATOPROST:

Bimatoprost is a synthetic prostamide and structural prostaglandin analogue with ocular hypotensive activity. Bimatoprost mimics the effects of the endogenous prostamides and reduces intraocular pressure by increasing outflow of aqueous humor through both the pressure-sensitive outflow pathway (the trabecular meshwork), and the pressure-insensitive outflow pathway (the uveoscleral routes). It is not clear whether bimatoprost lowers intraocular pressure by stimulating F-Prostanoid receptors or by acting on specific prostamide receptors.

Bimatoprost, also known as Latisse or Lumigan, belongs to a group of drugs called prostamides, which are synthetic structural analogs of prostaglandin. Bimatoprost, marketed by Allergan, is administered in both the ophthalmic solution and implant form. It has the ability to reduce ocular hypotension, proving effective in conditions such as ocular hypertension and glaucoma. Bimatoprost is also used to treat eyelash hypotrichosis, or sparse eyelash growth. It was initially approved by the FDA in 2001 for ocular hypertension and later approved for hypothrichosis in 2008, as eyelash growth became a desirable adverse effect for patients using this drug.

This medication is used to treat patients with not enough or inadequate eyelashes. Bimatoprost makes the eyelashes more

noticeable by causing more eyelashes to grow and making them longer, thicker, and darker. Bimatoprost is similar to a natural chemical in the body (prostaglandin). Bimatoprost is also used to treat glaucoma.

3. RETROSYNTHESIS OF BIMATOPROST AND ITS ANALOGS:

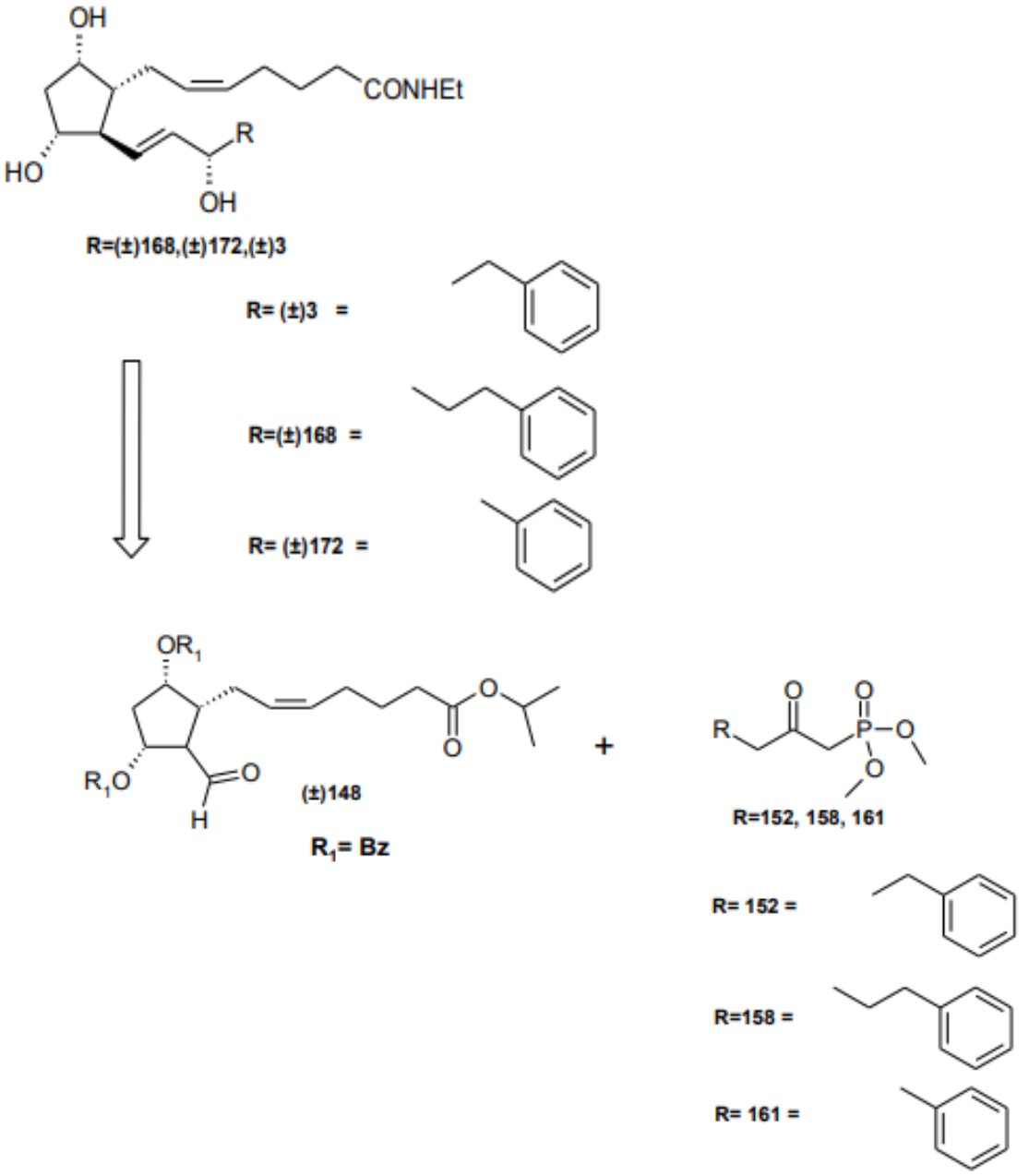


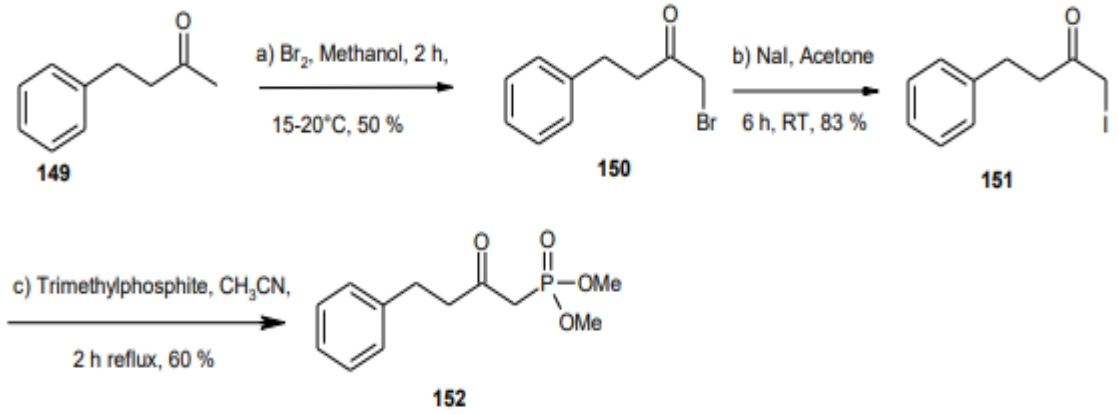
Figure 3. 1 Retrosynthesis of (±)-Bimatoprost and analogs

Restrosynthetic analysis of "Bimatoprost" led to two key fragments, key intermediate (148) for which synthesis has been described in detail in chapter-2, and the phosphonate ester, part of the "ω" side chain.

SYNTHESIS OF DIMETHYL 2-OXO-4-PHENYLBUTYLPHOSPHONATE (152):

Bromination of benzylacetone (149) with bromine in methanol solvent at 10-15 °C for 2 h

followed by selective recrystallization (dibromo compound remains in the mother liquor) using hexane gave 150 in 50% yield. Iodination of 150 with sodium iodide in acetone for 6 h at neat ambient temperature gave 151 in 83% yield, after recrystallization with ethyl alcohol. Reaction of 151 with trimethyl phosphite in acetonitrile at reflux temperature for 2 h followed by column purification afforded 152 with 60% yield.

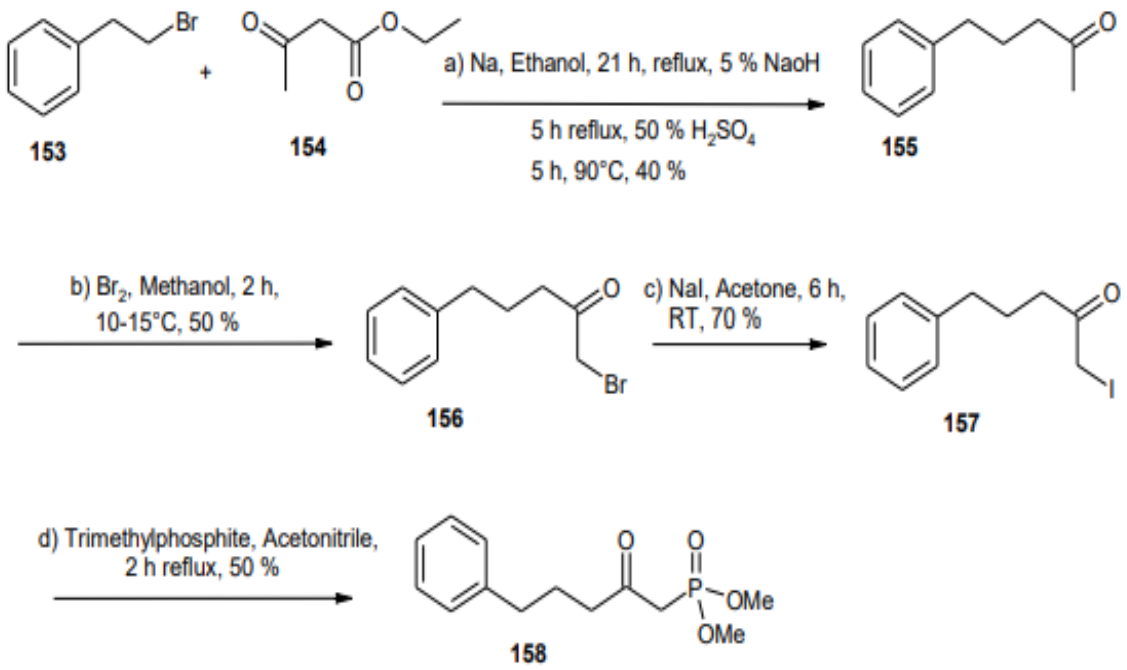


149 150 151 152

Scheme-3.0

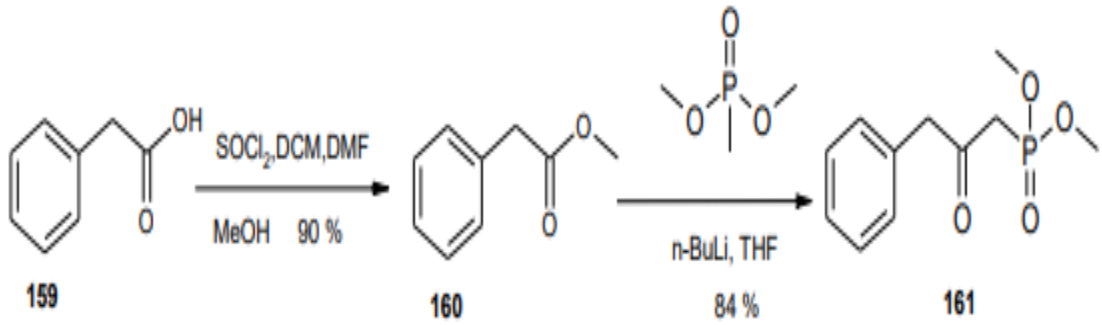
SYNTHESIS OF DIMETHYL 2-OXO-5-PHENYLPENTYLPHOSPHONATE (158):

Alkylation reaction of phenylethyl bromide 153 with ethyl acetoacetate, 154 in presence of sodium metal in ethanol at reflux temperature followed by usual work up gave residue which was treated with 5% sodium hydroxide at 90°C for ester hydrolysis followed by treatment with 50% sulphuric acid for decarboxylation at 90 °C for 5 h gave 155 in 40% yield. Bromination of 155 with bromine in methanol at 10-15 °C for 2 h yielded 156 with 50% yield. Iodination of 156 with NaI / acetone condition at RT for 6 hours yielded 157 in 70% and the reaction of 157 with trimethylphosphite in acetonitrile at reflux temperature for 2h followed by flash column chromatography gave 158 with 50% yield.



Scheme-3.1

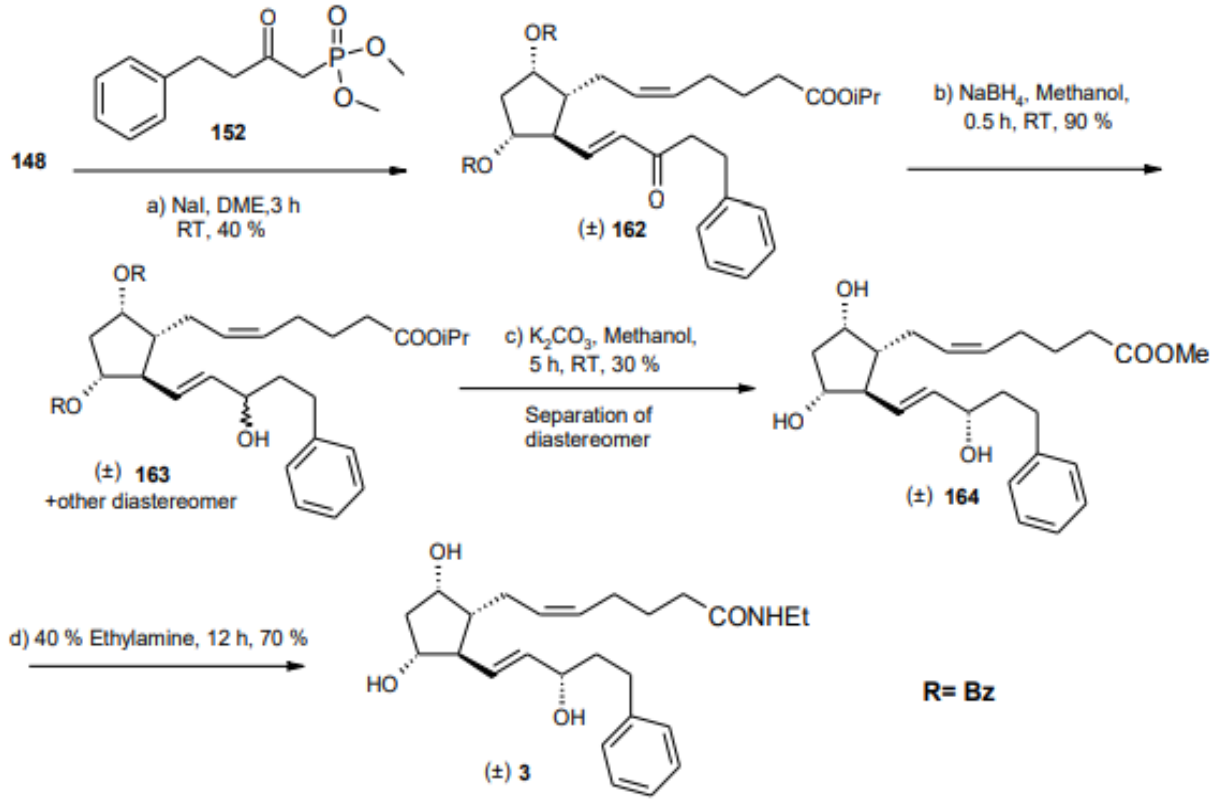
SYNTHESIS OF DIMETHYL (2-OXO-3-PHENYLPROPYL) PHOSPHONATE:



Scheme-3.2

Reaction of phenyl acetic acid (159) with catalytic amount of DMF in presence of thionyl chloride in dichloromethane at 5-10°C for 60 min and further treated with methanol at 25-35°C for 2 h gave 160 in 90 % yield and the reaction of 160 with dimethyl methane phoshonate in the presence of n- Butyl lithium in THF at -78°C for 1 h afforded 161 with 84 % yield.

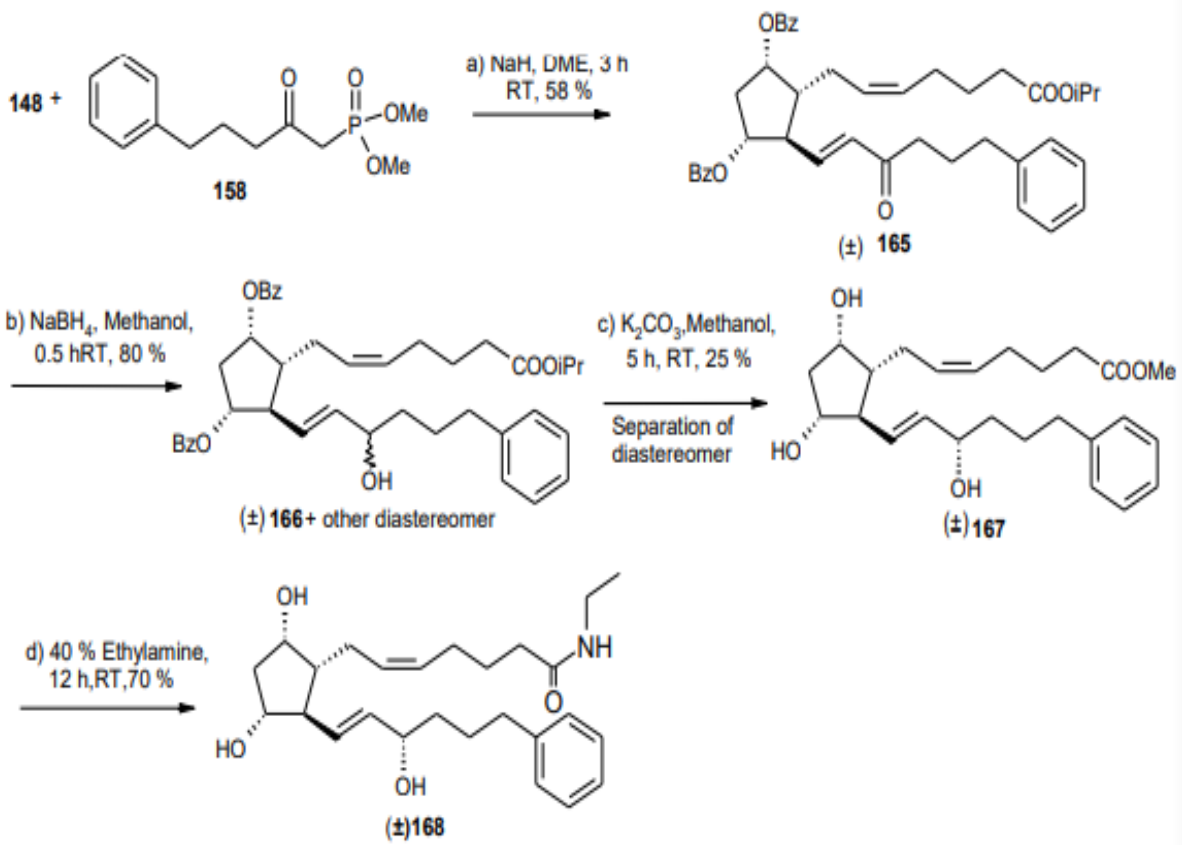
SYNTHESIS OF (±) BIMATOPROST (3): RESULTS AND DISCUSSION:



Scheme-3.3

Horner-Wadsworth-Emmons reaction of 148 with phosphonate reagent 152 using NaH in DME solvent for 65 min at 0-5 °C followed by flash chromatography afforded 162 with 40% yield.Towards synthesis of compound 162, we have studied the reaction in different solvents such as tetrahydrofuran, 2-methyl THF and DME and found that best results were obtained using DME as a solvent. More impurities observed based on TLC in tetrahydrofuran and 2-methyl THF for 162 preparation. Reduction of keto group on 162 with sodium borohydride in methanol at 25 °C for 30 min yielded compound 163 in 90% yield. During carbonyl group reduction with sodium borohydride, observed 3:2 ratio of diastereomeric mixture by TLC which are very close and separation is very critical at this stage by flash chromatography. Hence separation of diastereomer could not be achieved. Deprotection of both benzoyl groups of 163 with potassium carbonate in methanol for 5 h at RT gave 164 in 30% yield and its diastereo isomer was well separated by column chromatography. Here separation of diastereomers could be achieved easily as 0.2 Rf difference was observed by TLC (mobile phase 80 % ethyl acetate/hexane) and separation of desired diastereomer was not critical at this stage. Trans esterification was observed from isopropyl ester to methyl ester during deprotection of 163 to 164 in methanol / K2CO3 conditions. Reaction of 164 with 70% ethylamine solution in water for 12 h at 25-30°C followed by flash column purification gave 3 with 70% yield. Spectral data (±) 3 compares well with those reported for Bimatoprost.

SYNTHESIS OF (±) HOMOBIMATOPROST (168):

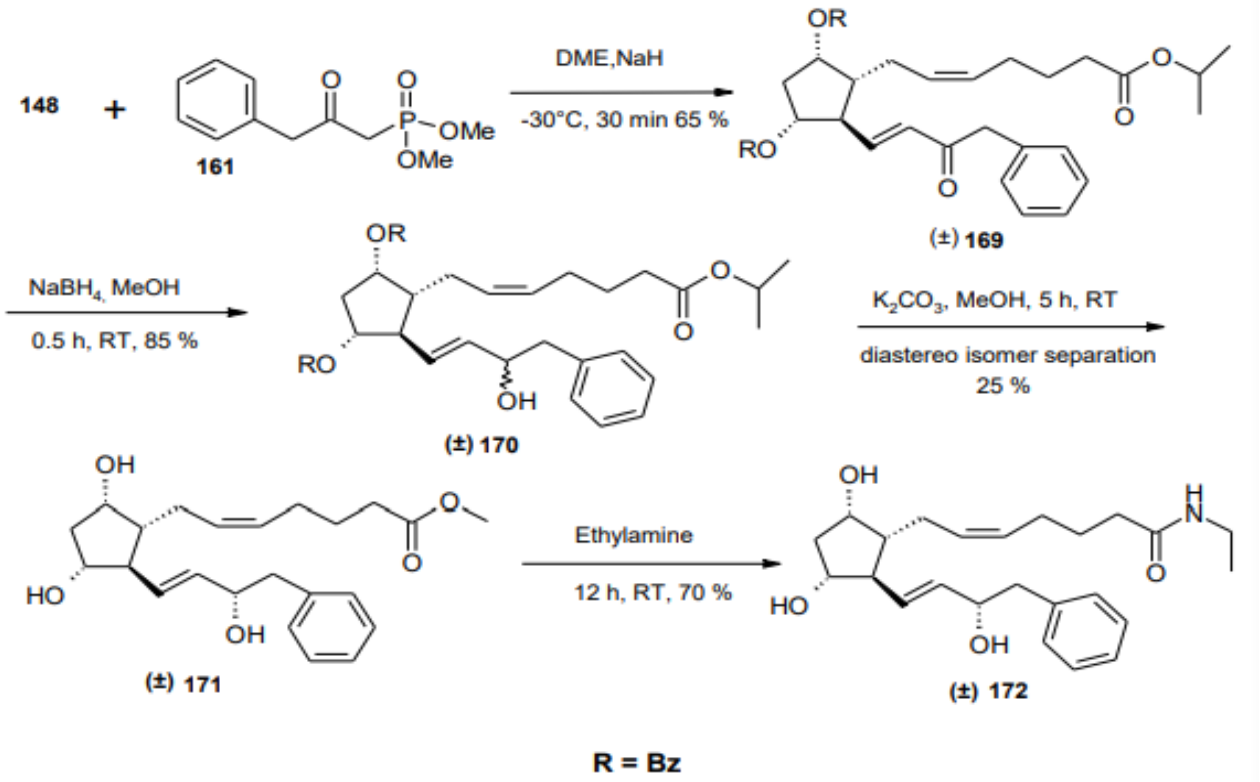


Scheme-3.4

Horner-Wadsworth-Emmons reaction of 148 with phosphonate reagent, 158in presence of sodium hydride in dimethoxyethane (DME) solvent in 30 min at -30 °C followed by flash chromatography gave 165[40,41] in 58 % yield and observed more impurities when we carried reaction at 0-5 °C. Reduction of keto group on 165 with NaBH4 in methanol at 25 °C for 30 min gave 166 with 80% yield followed by removal of benzoyl groups of 166 using K2CO3/ MeOH condition for around 6-8 hours at RT yielded a mixture of diastereomers (Ratio 3:2). Desired diastereo isomer, 167, was separated by column chromatography with 25 % yield. Reaction of 167 with 70% ethylamine solution in water for 12 h at RT yielded 168[47] with 70 % yield.

Product obtained was well characterized with ^{1}HNMR, ^{13}CNMR, and HRMS data.

SYNTHESIS OF (±) NOR-BIMATOPROST (172):



Scheme-3.5

HWE reaction of 148 with phosphonate, 161in presence of sodium hydride in dimethoxyethane (DME) solvent in 30 min at -30 °C followed by flash chromatography gave 169in 65% yield and observed more impurities when reactions carried out at 0-5 °C. Reduction of keto group on 169 using NaBH4 / MeOH at 25 °C for 0.5 hours achieved 170 with 85% yield and observed mixture of diastereomers approximately 3:2 ratio based on thin layer chromatographic analysis during carbonyl group reduction of 169. Separation of desired diasteromer was critical at this stage due to very close Rf observed by TLC and, hence product obtained was taken for next transformation. Deprotection of benzoyl groups of 170 with K_2CO_3 in methanol for 6 h at room temperature yielded a mixture of diastereomers. Desired diastereo isomer, 171, was separated by flash column chromatography and obtained around 25% yield. Reaction of 171 with 70% ethylamine solution in water for 12 h at RT afforded 172[47] with 70 % yield. Product obtained was well characterized with ^{1}HNMR, ^{13}CNMR, HRMS

4. CONCLUSION:

A versatile intermediate 148 obtained from (±)-Corey lactone, can be elaborated into all clinical ophthalmic prostaglandins. (±)-Bimatoprost, homobimatoprostand norbimatoprost were synthesized using 148. Using the same strategy optically pure Bimatoprost and its analogs can be obtained starting from chiral pure Corey lactone. [9-12]

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