Synthesis of Prostaglandin Analogues, Latanoprost and Bimatoprost, Using Organocatalysis via a Key Bicyclic Enal Intermediate

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Supporting Information

ABSTRACT: Two antiglaucoma drugs, bimatoprost and latanoprost, which are analogues of the prostaglandin, PGF2α, have been synthesized in just 7 and 8 steps, respectively. The syntheses employ an organocatalytic aldol reaction that converts succinaldehyde into a key bicyclic enal intermediate, which is primed for attachment of the required lower and upper side chains. By utilizing the crystalline lactone, the drug molecules were prepared in >99% ee.

Prostaglandins (e.g., PGF2α) are not just of academic interest, owing to a number of analogues having emerged as important drugs, particularly in the treatment of glaucoma, the second leading cause of blindness worldwide after cataracts. These include unoprostone isopropyl (2, Rescula, 1994), latanoprost (3, Xalatan, 1996), travoprost (4, Travatan, 2001), and bimatoprost (5, Lumigan, 2001) (Figure 1). Although latanoprost quickly became a “blockbuster” drug for Pfizer, with sales of $1.75 billion in 2010, bimatoprost ($849 million in sales in 2011) was found to have greater efficiency in intraocular pressure reduction than latanoprost. Bimatoprost is also an active ingredient in Latisse, a new prescription medicine to treat hypotrichosis of eyelashes.

Latanoprost and bimatoprost are currently manufactured using a method developed by Corey in 1969, a process that requires more than 17 steps (Scheme 1). We recently reported a short synthesis of the related natural product, PGF2α, in just 7 steps from dimethoxy tetrahydrofuran. Hayashi has also recently reported a short synthesis of PGE1 methyl ester using organocatalysis. We were keen to broaden the reach of this chemistry and in particular to demonstrate its application to short syntheses of the important antiglaucoma drugs, latanoprost and bimatoprost. Just as the Corey lactone has been used for the preparation of other prostaglandin analogues, we see our enal intermediate, as being perfectly set up for further transformations to access other prostaglandin analogues in an efficient manner. Herein we report short (7–8 steps) syntheses of these important pharmaceuticals.

Figure 1. FDA-approved first-line antiglaucoma agents.

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used at low (2 mol % each) loading (Scheme 2). These two catalysts function independently: l-proline catalyzes the first intramolecular aldol reaction between two molecules of succinaldehyde in high er, and then DBA catalyzes the second intramolecular aldol reaction and dehydration. By using our original optimized conditions, enal 8 can be isolated in 14% yield, but occasionally, valuable material is lost upon workup. To reduce these losses, we undertook further optimization studies and discovered that adding charcoal to the reaction mixture at the end of the process followed by stirring, filtration, and purification led to more efficient removal of oligomeric material without loss of significant quantities of the valuable enal.11 We now have a more reliable process, which consistently provides our key enal intermediate in ca. 14% yield.

We wanted to develop a route that could also form the basis of a viable manufacturing process, and therefore we sought intermediates so that enantiopurity could be increased (from 98:2 er) by recrystallization. Because the diastereoisomeric mixture resulting from the acetal moiety would not be conducive to this goal, we considered conversion of this moiety into the lactone bearing the unprotected C-15 alcohol. Additionally a single diastereoisomer was carried through the sequence. Following deprotection of the acetal, hydrozirconation and iodination gave vinyl iodide 10. The same sequence was applied to lactone 11, which was converted into iodide 16, and added to enal 8 in a 1,4 manner to form the isolable (but not purified) silyl enol ether 9. Ozonolysis of 9 proceeded with perfect stereocontrol, as in accordance with our previously reported synthesis of PGF2α.9 In the case of acetal-protected lactone 11, the route described above was also applied to the synthesis of bimatoprost (Scheme 6). Mixed cuprate 28 was generated from alkyl iodide 27 and added to enal 8 in a 1,4 manner to form the isolable (but not purified) silyl enol ether 25. Ozonolysis of 25 proceeded with perfect stereocontrol, as in accordance with our previously reported synthesis of PGF2α.9 After silyl protection of the secondary alcohol, alkynyl 26 was obtained in 52% yield and 96:4 er over 2 steps. Following deprotection of the alcohol, hydrozirconation and iodination gave vinyl iodide 27. The same sequence was applied to lactone 11. The same sequence was applied to lactone 10, which gave alcohol 26 in similar yields. For both intermediates, the addition of the side chain and the subsequent reduction proceeded with perfect stereocontrol, as in accordance with our previously reported synthesis of latanoprost.20c The route described above was also applied to the synthesis of the side chain of bimatoprost (Scheme 5). Mixed cuprate 22 was generated from alkyl iodide 16 and added to enal 8 in a 1,4 manner to form the isolable (but not purified) silyl enol ether 23. Ozonolysis of 23 proceeded with perfect stereocontrol, as in accordance with our previously reported synthesis of PGF2α.9 In the case of acetal 25, the subsequent silyl and acetal deprotection with aqueous HCl gave alcohol 25. The same sequence was applied to lactone 10, which gave alcohol 26 in similar yields. For both intermediates, the addition of the side chain and the subsequent reduction proceeded with perfect stereocontrol, as in accordance with our previously reported synthesis of latanoprost.20c The route described above was also applied to the synthesis of bimatoprost (Scheme 5). Mixed cuprate 22, which was...
generated from vinyl iodide 21, was added to enal 8 to form silyl enol ether 33. Subsequent ozonolysis followed by addition of NaBH₄ gave alcohol 35. For this particular transformation, careful monitoring of the ozonolysis reaction was required to prevent overoxidation of the alkene moiety in the side chain. The same sequence was applied to lactone 10, which gave alcohol 36. As before, the incorporation of the side chain and reduction of the ketone proceeded with perfect stereocontrol. In the case of the acetal 35, subsequent deprotection of the alcohol and acetal with aqueous HCl gave triol intermediate 37, which, without purification, was subjected to a Wittig reaction with phosphonium salt 38 to give bimatoprost 5. From lactone 36, DIBAL-H reduction followed by a Wittig reaction and deprotection gave bimatoprost.

It should be noted that the yields in the Wittig reactions are consistently higher when the C-15 hydroxyl group is protected even when using potassium amylate as the base.¹⁹

In conclusion, we have developed an improved process for the preparation of our key bicyclic enal intermediate, which was subsequently elaborated into latanoprost and bimatoprost, two blockbuster drugs used in the treatment of glaucoma. The synthetic routes presented here are considerably shorter than those previously reported. This reduction in step count was made possible not only by easily generating lactol 9 but also by devising...
shorter and more efficient syntheses of the lower side chains. Furthermore, as a result of using the crystalline lactone 10 as an intermediate, these compounds were prepared with very high enantiopurity. The significantly reduced step count should lead to lower costs in the production of these important drugs, thus enabling more people to have access to these effective medicines.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES


(3) Full-year results for 2010 were reported by Pfizer: http://www.pfizer.com/files/presentations/q4performance_201111.pdf.


(19) To test the effect of base on the efficiency of the Wittig reaction, the reaction of unprotected alcohol in yield between similar to that obtained with phosphonium salt was performed with tBuOK. This gave alkene 29 in 45% yield (2 steps), similar to that obtained with tBuOK showing that the marked difference in yield between 27 and 30 is due to the protection of the C-15 hydroxyl group and not the base used.

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