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

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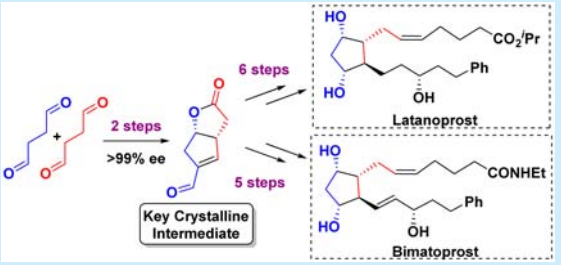
Supporting Information

ABSTRACT: Two antiglaucoma drugs, bimatoprost and latanoprost, which are analogues of the prostaglandin, $PGF_{2\alpha}$, 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., $PGF_{2\alpha}$) are not just of academic interest,[1] 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.[2] These include unoprostone isopropyl (**2**, Rescula, 1994), latanoprost (**3**, Xalatan, 1996), travoprost (**4**, Travatan, 2001), and bimatoprost (**5**, Lumigan, 2001) (Figure 1). Although

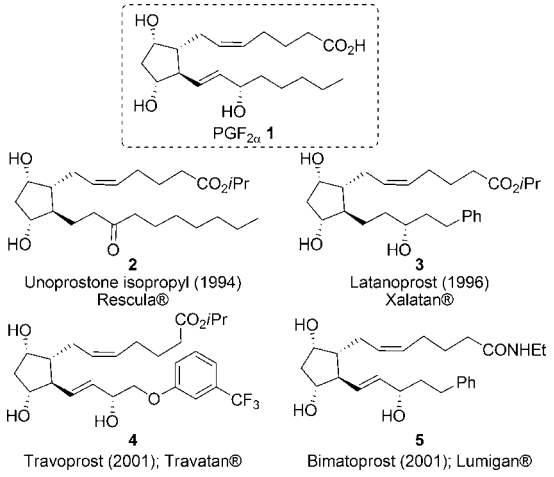
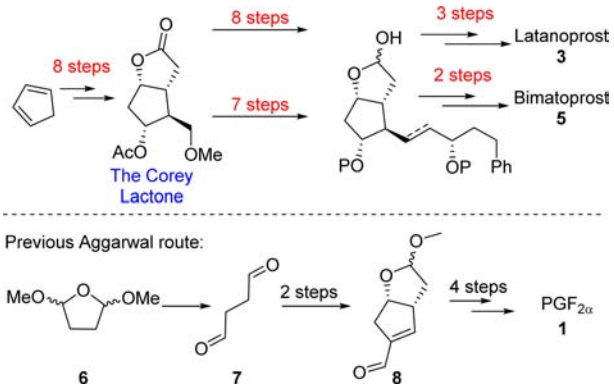


Figure 1. FDA-approved first-line antiglaucoma agents.

latanoprost quickly became a "blockbuster" drug for Pfizer, with sales of $1.75 billion in 2010,[3] bimatoprost ($849 million in sales in 2011) was found to have greater efficiency in intraocular pressure reduction than latanoprost.[4] Bimatoprost is also an active ingredient in Latisse, a new prescription medicine to treat hypotrichosis of eyelashes.[5]

Latanoprost and bimatoprost are currently manufactured using a method developed by Corey in 1969,[6] a process that requires more than 17 steps (Scheme 1).[7,8] We recently reported

Scheme 1. Previous Syntheses of Prostaglandin Analogues, Latanoprost and Bimatoprost, and the Aggarwal Route



a short synthesis of the related natural product, $PGF_{2\alpha}$, in just 7 steps from dimethoxy tetrahydrofuran.[9] Hayashi has also recently reported a short synthesis of PGE_1 methyl ester using organocatalysis.[10] 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, **8**, 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.

Our reported synthesis of enal **8** involved the dimerization of succinaldehyde **7** by using two amine organocatalysts, L-proline and dibenzylammonium trifluoroacetate (DBA), which were

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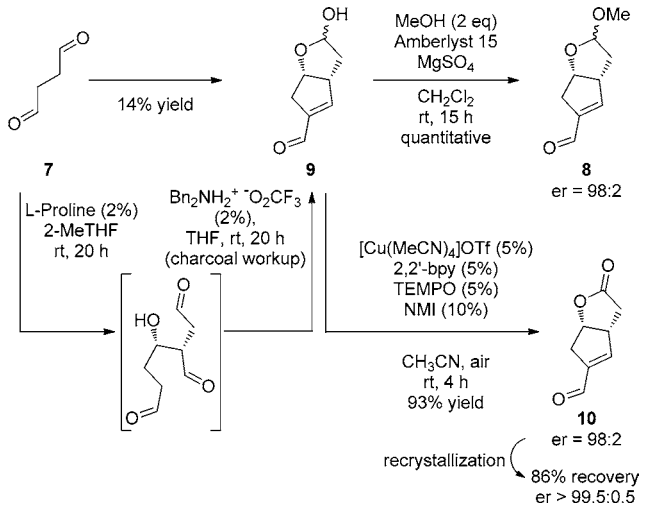
used at low (2 mol % each) loading (Scheme 2). These two catalysts function independently: L-proline catalyzes the first

Scheme 2. Synthesis of the Key Bicyclic Enals 8 and 10



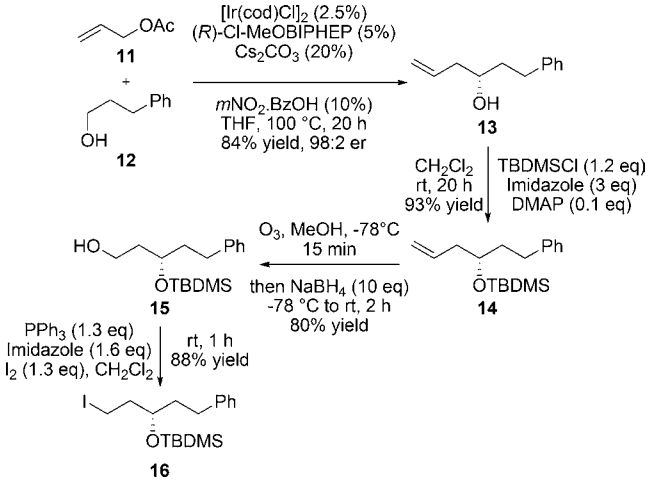
intermolecular aldol reaction between two molecules of succinaldehyde in high er, and then DBA catalyzes the second intramolecular aldol reaction and dehydration. By using our original optimized conditions, enal **8** can be isolated in 14% yield, but occasionally, valuable material is lost upon workup. 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 solid intermediates so that enantiopurity could be increased (from 98:2 er) by crystallization. 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 form at an early stage in the synthesis, despite such a strategy lengthening the processes by one step. The lactone **10** was prepared efficiently from lactol **9** through copper-mediated oxidation in the presence of air (Scheme 2).[12] Furthermore, lactone **10** was crystalline and simple recrystallization from TBME improved the er to >99.5:0.5. In order to adequately assess the advantages of carrying out the synthesis at a higher level of oxidation, we decided to explore the syntheses of both latanoprost **3** and bimatoprost **5** by using both the acetal- and lactone-containing moieties.

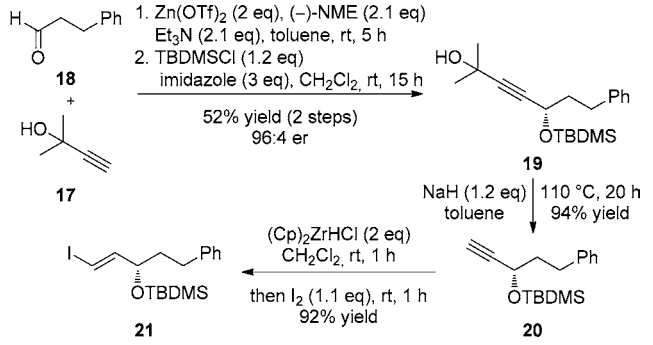
The lower side chain **16** for latanoprost was prepared in 4 steps from allyl acetate **11** and 3-phenyl-1-propanol **12** (Scheme 3). An isohypsic asymmetric iridium-catalyzed allylation reaction between allyl acetate **11** and 3-phenyl-1-propanol **12** gave homoallylic alcohol **13** in 84% yield and 98:2 er.[13] Silyl protection, followed by reductive ozonolysis of the resultant alkene **14**, furnished alcohol **15**, which was converted into iodide **16**. This route to **16** is significantly shorter and more selective than previous routes, which involve 4 to 6 steps to intermediate **15**.[14]

The lower side chain of bimatoprost was also prepared in 4 steps (Scheme 4) and began with alkynylation of hydro-

Scheme 3. Synthesis of the α Side Chain of Latanoprost



Scheme 4. Synthesis of the Bimatoprost α Side Chain



cinnamaldehyde **18** by using (−)-*N*-methylephedrine and $Zn(OTf)_2$.[15,16] After silyl protection of the secondary alcohol, alkyne **19** was obtained in 52% yield and 96:4 er over 2 steps. Following deprotection of the alkyne, hydrozirconation and iodination gave vinyl iodide **21**. Again, this route is significantly shorter and more stereoselective than previous routes to the same intermediate (4 to 6 steps to intermediate **20**).[17]

To complete the synthesis of latanoprost (Scheme 5), mixed cuprate **22** was generated from alkyl iodide **16**[18] and added to enal **8** in a 1,4 manner to form the isolable (but not purified) silyl enol ether **23**. Ozonolysis of **23** followed by addition of $NaBH_4$ 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 $PGF_{2\alpha}$.[9] In the case of acetal **25**, subsequent silyl and acetal deprotection with aqueous HCl gave triol intermediate **27**, which, without purification, was subjected to a Wittig reaction with phosphonium salt **28** to give acid **29**. From lactone **26**, DIBAL-H reduction followed by a Wittig reaction and silyl deprotection gave the same acid, **29**. Despite requiring one more step, the route involving lactone **10** led to a higher overall yield, as it avoided the unstable hemiacetal **27** bearing the unprotected C-15 alcohol. Additionally a single diastereoisomer was carried through the sequence.

Finally, esterification under the same reaction conditions used in the Pfizer commercial process[2b] completed the synthesis of latanoprost **3**.

The route described above was also applied to the synthesis of bimatoprost **5** (Scheme 6). Mixed cuprate **32**, which was

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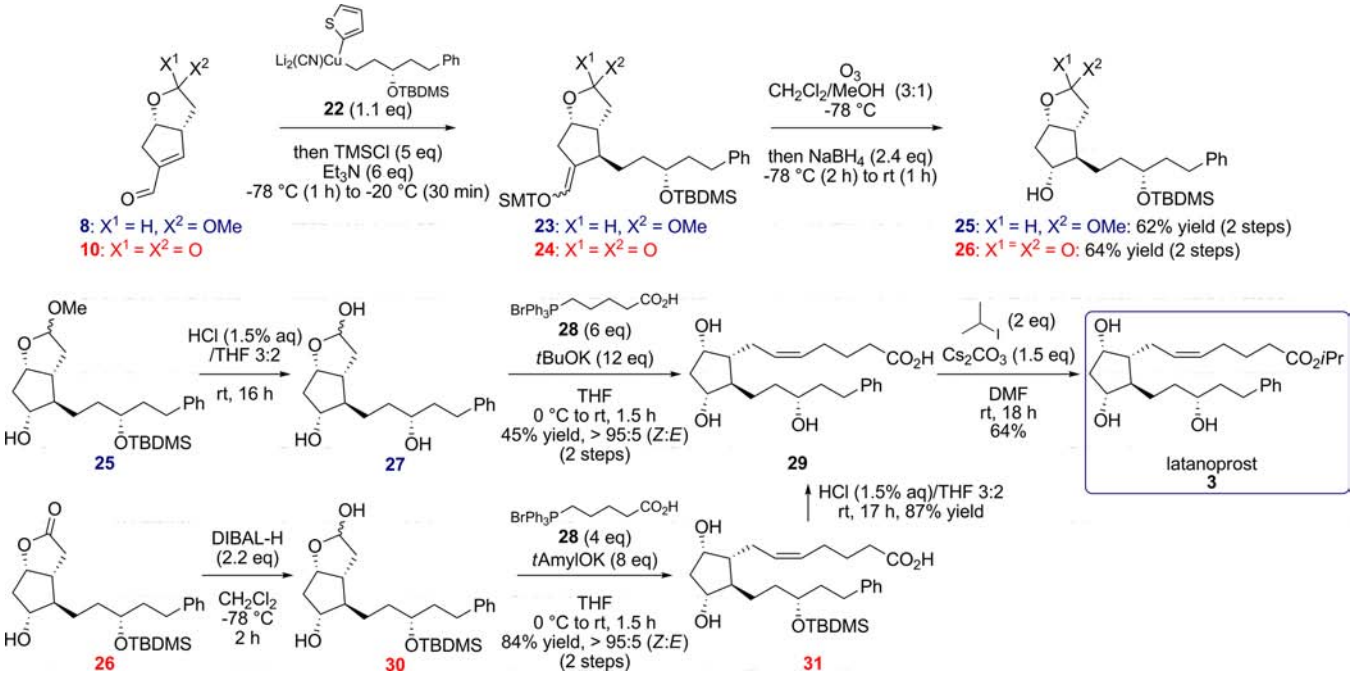
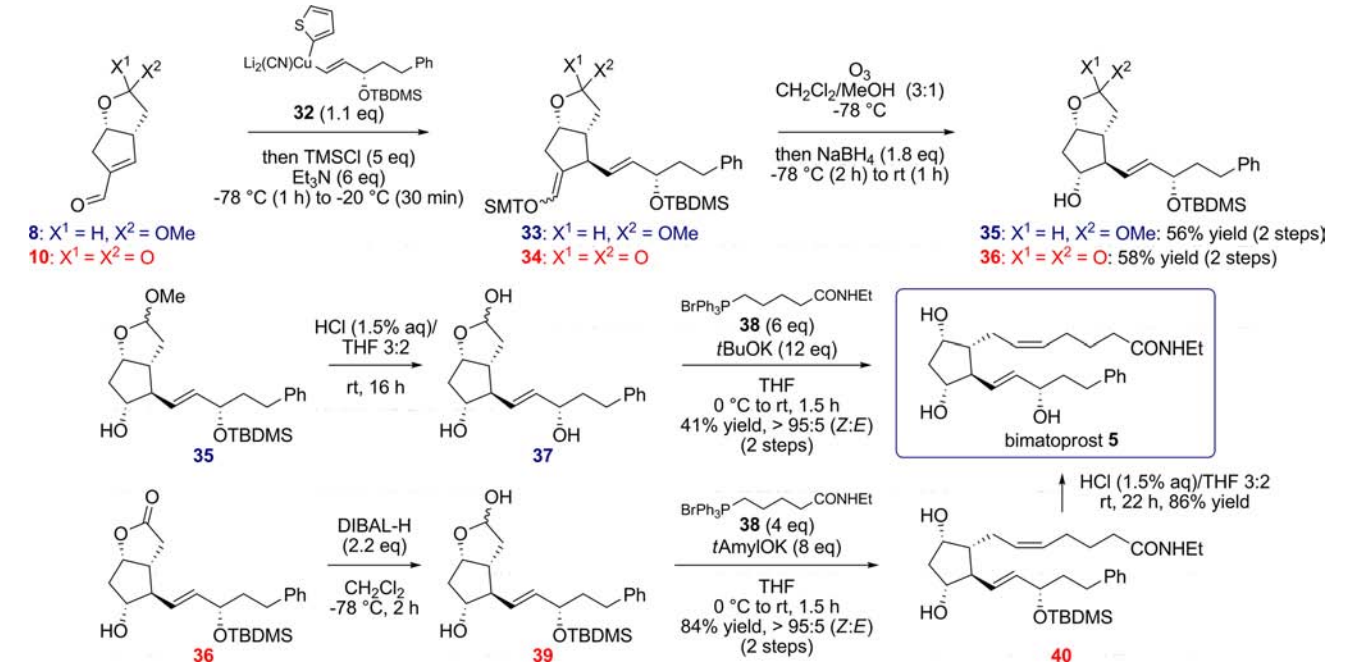
Org. Lett. 2015, 17, 504−507

Scheme 5. Synthesis of Latanoprost



Scheme 6. Synthesis of Bimatoprost



generated from vinyl iodide **21**, was added to enal **8** to form silyl enol ether **33**. Subsequent ozonolysis followed by addition of $NaBH_4$ 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

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Org. Lett. 2015, 17, 504−507

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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