

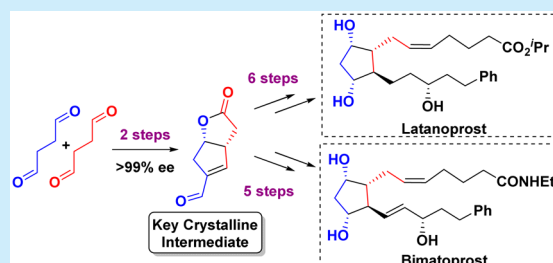
Synthesis of Prostaglandin Analogues, Latanoprost and Bimatoprost, Using Organocatalysis via a Key Bicyclic Enal Intermediate

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Supporting Information

ABSTRACT: Two antiglaucoma drugs, bimatoprost and latanoprost, which are analogues of the prostaglandin, $\text{PGF}_{2\alpha}$, 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., $\text{PGF}_{2\alpha}$) 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

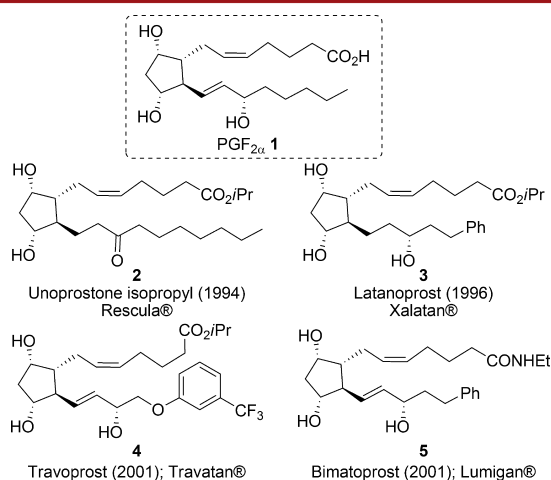
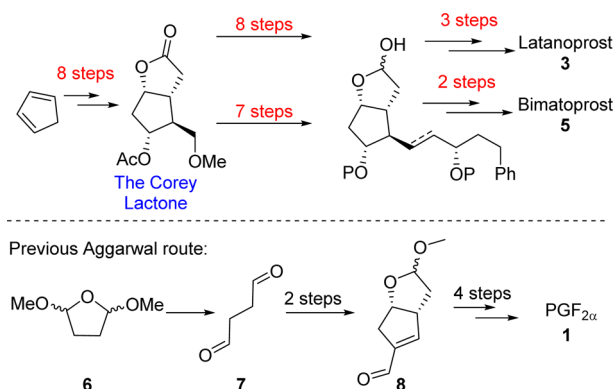


Figure 1. FDA-approved first-line antiglaucoma agents.

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



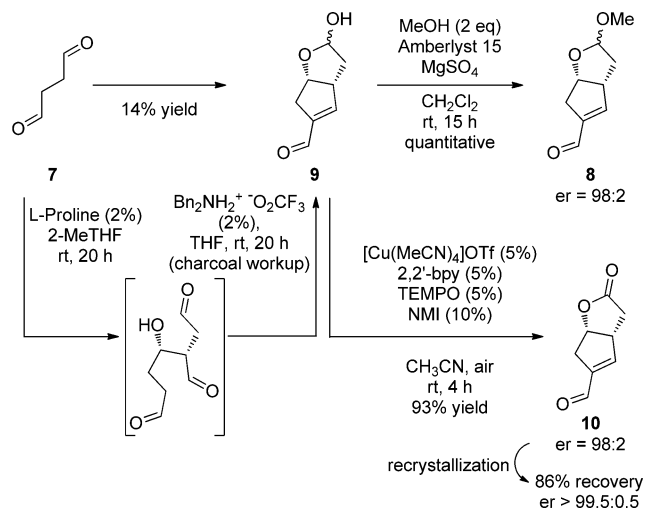
a short synthesis of the related natural product, $\text{PGF}_{2\alpha}$ in just 7 steps from dimethoxy tetrahydrofuran.⁹ Hayashi has also recently reported a short synthesis of PGE_1 methyl ester using organocatalysis.¹⁰ We were keen to broaden the reach of this chemistry and in particular to demonstrate 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



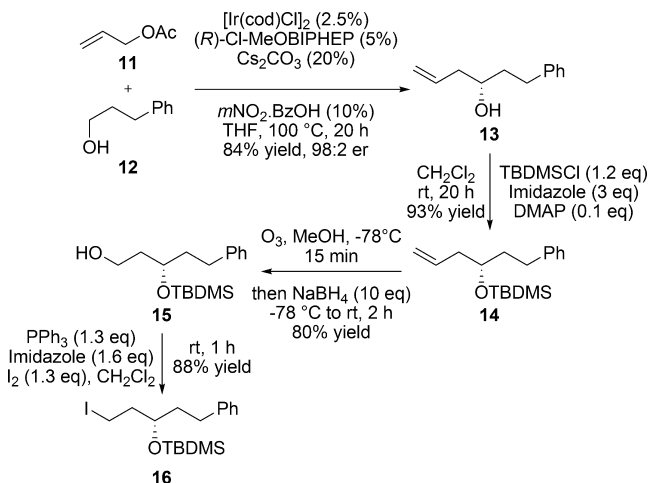
intermolecular aldol reaction between two molecules of succinaldehyde in high er, and then DBA catalyzes the second intramolecular aldol reaction and dehydration. By using our original optimized conditions, enal 8 can be isolated in 14% yield, but occasionally, valuable material is lost upon workup. 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.

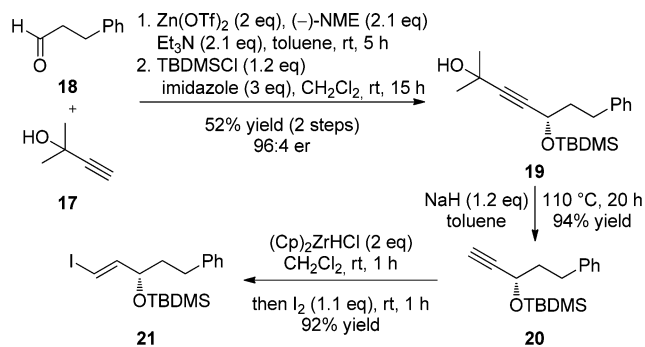
The lower side chain for latanoprost was prepared in 4 steps from allyl acetate 11 and 3-phenyl-1-propanol 12 (Scheme 3). An isohypsic asymmetric iridium-catalyzed allylation reaction between allyl acetate 11 and 3-phenyl-1-propanol 12 gave homoallylic alcohol 13 in 84% yield and 98:2 er.¹³ Silyl protection, 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 16¹⁸ 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 NaBH₄ 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_{2α}.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

8: $X^1 = H, X^2 = OMe$
10: $X^1 = X^2 = O$

23: $X^1 = H, X^2 = OMe$
24: $X^1 = X^2 = O$

25: $X^1 = H, X^2 = OMe$: 62% yield (2 steps)
26: $X^1 = X^2 = O$: 64% yield (2 steps)

25

 HCl (1.5% aq) / THF 3:2, rt, 16 h

27

 $BrPh_3P$ (6 eq), $tBuOK$ (12 eq), THF, 0 °C to rt, 1.5 h, 45% yield, > 95:5 (Z:E) (2 steps)

29

 CS_2CO_3 (1.5 eq), DMF, rt, 18 h, 64%

latanoprost 3

26

 $DIBAL-H$ (2.2 eq), CH_2Cl_2 , -78 °C, 2 h

30

 $BrPh_3P$ (4 eq), $tAmyLOK$ (8 eq), THF, 0 °C to rt, 1.5 h, 84% yield, > 95:5 (Z:E) (2 steps)

31

 HCl (1.5% aq) / THF 3:2, rt, 17 h, 87% yield

[illegible]

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

- (1) (a) Bindra, J. S.; Bindra, R. *Prostaglandin Synthesis*; Academic Press: 1977. (b) Funk, C. D. *Science* **2001**, *294*, 1871. (c) Das, S.; Chandrasekhar, S.; Yadav, J. S.; Grée, R. *Chem. Rev.* **2007**, *107*, 3286. (d) Dams, I.; Wasyluk, J.; Prost, M.; Kutner, A. *Prostaglandins Other Lipid Mediators* **2013**, 109.
- (2) (a) Collins, P. W.; Djuric, S. W. *Chem. Rev.* **1993**, *93*, 1533. (b) Nair, S. K.; Henegar, K. E. Latanoprost (Xalatan): A Prostanoid FP Agonist for Glaucoma. In *Modern Drug Synthesis*; Li, J. J., Johnson, D. S., Eds.; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2010; pp 329–338.
- (3) Full-year results for 2010 were reported by Pfizer: http://www.pfizer.com/files/investors/presentations/q4performance_020111.pdf.
- (4) (a) Noecker, R. S.; Dirks, M. S.; Choplin, N. T.; Bernstein, P.; Batoosingh, A. L.; Witcup, S. M. *Am. J. Ophthalmol.* **2003**, *135*, 55. (b) Simmons, S. T.; Dirks, M. S.; Noecker, R. J. *Adv. Ther.* **2004**, *21*, 754. (c) Dams, I.; Chodyński, M.; Krupa, M.; Pietraszek, A.; Zezula, M.; Cmocho, P.; Kosińska, M.; Kutner, A. *Chirality* **2013**, *25*, 170.
- (5) Fagien, S. *Clin. Cosmet. Invest. Dermatol.* **2010**, *3*, 39.
- (6) Corey, E. J.; Winshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675.
- (7) For previous syntheses of latanoprost, see: (a) Obadalová, I.; Pilarčík, T.; Slavíková, M.; Hájíček, J. *Chirality* **2005**, 109. (b) Martynow, J. G.; Józwik, J.; Szelejewski, W.; Achmatowicz, O.; Kutner, A.; Wiśniewski, K.; Winiarski, J.; Zegrock-Stendel, O.; Golebiewski, P. *Eur. J. Org. Chem.* **2007**, 689. (c) Zanon, G.; D'Alfonso, A.; Porta, A.; Feliciani, L.; Nolan, S. P.; Vidari, G. *Tetrahedron* **2010**, *66*, 7472. (d) Harikrishna, M.; Mohan, H. R.; Dubey, P. K.; Shankar, M.; Subbaraju, G. V. *Asian J. Chem.* **2011**, *23*, 3121. (e) Mariani, E.; Orru, G.; Montorsi, M.; Andriolo, E.; Bandini, M.; Contento, M.; Tolomelli, A. *Eur. Pat. Appl.* (2012) EP 2495235 A1 20120905. (f) Contento, M. L.; Zambelli, P.; Galafassi, S.; Tamborini, L.; Pinto, A.; Conti, P.; Molinari, F.; Romano, D. *J. Mol. Catal. B: Enzym.* DOI: 10.1016/j.molcatb.2014.05.022.
- (8) For previous syntheses of bimatoprost, see: (a) Ham, W.-H.; Oh, C.-Y.; Kim, Y.-H.; Lee, Y.-S.; Lee, K.-Y. World Patent Application, No. 02/090324A1, 2002. (b) Obadalová, I.; Pilarčík, T.; Slavíková, M.; Hájíček, J. *Chirality* **2005**, *17*, 109. (c) Dominic De, S.; Albert, M.; Sturm, H. World Patent Application, No. 2009153206A2, 2009. (d) Sandoz AG European Patent Application, No. EP2135860A1, 2009.
- (e) Harikrishna, M.; Rama Mohan, H.; Dubey, P. K.; Shankar, M.; Subbaraju, G. V. *Synth. Commun.* **2012**, *42*, 1288. (f) Dams, I.; Chodyński, M.; Krupa, M.; Pietraszek, A.; Zezula, M.; Cmocho, P.; Kosińska, M.; Kutner, A. *Chirality* **2013**, *25*, 170.
- (9) Coulthard, G.; Erb, W.; Aggarwal, V. K. *Nature* **2012**, 489, 278.
- (10) Hayashi, Y.; Umamiya, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 3450.
- (11) Aggarwal, V. K.; Coulthard, G.; Erb, W. *PCT Int. Appl.* (2013) WO 2013/186550 A1.
- (12) (a) Hoover, J. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2011**, *133*, 16901. (b) Hoover, J. M.; Ryland, B. L.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 2357.
- (13) (a) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 14891. (b) Hassan, A.; Lu, Y.; Krische, M. J. *Org. Lett.* **2009**, *11*, 3112.
- (14) (a) Victor Paul Raj, I.; Sudalai, A. *Tetrahedron Lett.* **2008**, *49*, 2646. (b) Fernández, E.; Pietruszka, J.; Frey, W. *J. Org. Chem.* **2010**, *75*, 5580. (c) Denmark, S. E.; Heemstra, J. R., Jr. *J. Am. Chem. Soc.* **2005**, *128*, 1038. (d) Denmark, S. E.; Wilson, T. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 3236. (e) Nunez, M. T.; Martín, V. S. *J. Org. Chem.* **1990**, *55*, 1928. (f) Peng, F.; Hall, D. G. *Tetrahedron Lett.* **2007**, *48*, 3305.
- (15) (a) Bovall, D.; López, F.; Sasaki, H.; Frantz, D.; Carreira, E. M. *Org. Lett.* **2000**, *2*, 4233. (b) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806. Carreira reported that addition of the acetylide anion to the primary aliphatic aldehyde, hexanal, only gave 51% ee using 1.2 equiv of NME and 1.1 equiv of Zn(OTf)₂ but 98% ee using 2.1 equiv of NME and 2.0 equiv of Zn(OTf)₂. As such we used the latter conditions.
- (16) For the original work on (nuncatalytic) asymmetric addition of acetylide anions to aldehydes and ketones, see: (a) Niwa, S.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 937. (b) Ramos Tombo, G. M.; Didier, E.; Loubinoux, B. *Synlett* **1990**, 547. (c) Tan, L.; Chen, C.; Tillyer, R. D.; Grabowski, E. J. J.; Reider, P. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 711. (d) Li, Z.; Upadhyay, V.; DeCamp, A. E.; DiMichele, L.; Reider, P. J. *Synthesis* **1999**, 1453. For the first application of the catalytic methodology in total synthesis, see: (e) Hale, K. J.; Grabski, M.; Manaviyar, S.; Maczka, M. *Org. Lett.* **2014**, *16*, 1164. (f) Hale, K. J.; Hatakeyama, S.; Urabe, F.; Ishihara, J.; Manaviyar, S.; Grabski, M.; Maczka, M. *Org. Lett.* **2014**, *16*, 3536.
- (17) (a) Clark, D. A.; Kulkarni, A. A.; Kalbarczyk, K.; Schertzer, B.; Diver, S. T. *J. Am. Chem. Soc.* **2006**, *128*, 15632. (b) World International Application, No. WO2005058812A2, 2005. (c) Kiyotsuka, Y.; Katayama, Y.; Acharya, H. P.; Hyodo, T.; Kobayashi, Y. *J. Org. Chem.* **2008**, *74*, 1939. (d) Makida, Y.; Ohmiya, H.; Sawamura, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 4122.
- (18) Lipshutz, B. H.; Kozlowski, J. A.; Parker, D. A.; Nguyen, S. L.; McCarthy, K. E. *J. Organomet. Chem.* **1985**, *285*, 437.
- (19) To test the effect of base on the efficiency of the Wittig reaction, the reaction of unprotected alcohol **27** with phosphonium salt **28** was performed with tAmylOK. 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.