Baars, H., Classen, M. J., & Aggarwal, V. K. (2017). Synthesis of Alfaprostol and $\text{PGF}_{2\alpha}$ through 1,4-Addition of an Alkyne to an Enal Intermediate as the Key Step. *Organic Letters*, 19(21), 6008-6011. <https://doi.org/10.1021/acs.orglett.7b03057>

Peer reviewed version

Link to published version (if available):
[10.1021/acs.orglett.7b03057](https://doi.org/10.1021/acs.orglett.7b03057)

[Link to publication record in Explore Bristol Research](#)
PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via ACS Publications at <http://pubs.acs.org/doi/abs/10.1021/acs.orglett.7b03057>. Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:
<http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/>

Synthesis of Alfaprostol and PGF_{2α} Through 1,4-Addition of an Alkyne to an Enal Intermediate as the Key Step

Hannah Baars[‡], Moritz J. Classen[‡], Varinder K. Aggarwal^{*}

School of Chemistry, University of Bristol, Cantock's Close, Bristol, BS8 1TS, U.K.

Supporting Information Placeholder

ABSTRACT: The veterinary drug Alfaprostol and prostaglandin PGF_{2α} have been synthesized in just 9 steps. The strategy involved the conjugate addition of an alkyne to a bicyclic enal, available in three steps by a proline-catalyzed aldol reaction of succinaldehyde. In the case of Alfaprostol, this resulted in the shortest synthesis reported to date. For PGF_{2α}, this approach improved our previous route by making the 1,4-addition and ozonolysis more operationally simple.

Prostaglandins are involved in many reproductive processes in mammals.¹ Control of such processes, particularly in veterinary medicine, is critical to food production and animal welfare.² For example, prostaglandin PGF_{2α} (1) is known for its luteolytic effect (degradation of the corpus luteum) in cattle.³ This activity is exploited in veterinary practice for the timing of insemination and increasing reproductive efficiency. Alfaprostol (2) was developed as a more stable and selective analogue of PGF_{2α} and is widely used as a potent luteolytic agent in cows⁴ and mares.⁵ In addition to its application in the treatment of glaucoma,⁶ continued research on PGF_{2α} and its analogues (including Alfaprostol) have uncovered a diverse array of new biological activity from reduction of adipose tissue,⁷ to the treatment of neuropsychiatric conditions (e.g. bipolar disorders).⁸ These new applications warrant renewed and improved syntheses of this important class of compounds.⁹

Figure 1. Prostaglandin PGF_{2α} and its synthetic analogue Alfaprostol.

Whilst numerous diverse strategies have been reported for the synthesis of PGF_{2α},^{1c} strategies towards Alfaprostol have been more limited. In fact, they all utilize the Corey lactone as an intermediate, only differing in the method for the introduction of the alkyne moiety (Scheme 1A). Gandolfi *et al.* applied a sequence of HWE olefination, bromination and double dehydrobromination to install the triple bond.¹⁰ Monteiro *et al.* used a Seyferth-Gilbert homologation to give the alkyne directly, which was converted into a stannane and finally

coupled with acyl chloride in a Stille coupling.¹¹ Both approaches required ca. 17 steps from cyclopentadiene.

Scheme 1. Previous and current strategy towards Alfaprostol.

We recently reported a 7-step synthesis of PGF_{2α},¹² and similarly short syntheses of Latanoprost and Bimatoprost.¹³ We employed the (L)-proline catalyzed aldol reaction of

succinaldehyde as the key step to rapidly assemble the bicyclic enal, which was ideally set up to enable the stereoselective incorporation of the remaining side chains (Scheme 1B). Herein, we report the application of this strategy to an 9-step synthesis of Alfacprostol based on the conjugate addition of an alkyne to our key enal intermediate.

1,4-Additions of alkynes to α,β -unsaturated aldehydes are challenging as alkynes usually form stable complexes with copper¹⁴ (in fact, they have been used as non-transferable groups in mixed organocuprates) and alternative organometallics either led to undesired 1,2-addition or no reaction. There is just one report of the addition of copper acetylides to an enal, which employed iodotrimethylsilane as an activator.¹⁵ We initially tested this methodology on lactone **3**¹³ with the commercially available alkyne **4** (protected as a silyl ether; Scheme 2A).⁷ Under the reported conditions (at -40°C), we were pleased to find that the addition product **5** was formed, after acidic work up, in good yield (48% ¹H NMR yield). The yield could be increased to 83% (by ¹H NMR) by lowering the temperature to -78°C . Crucial for high yields was the quality of the TMSI, which had to be stored under the exclusion of light, air and moisture.¹⁶

Scheme 2 Model Studies to investigate (a) the 1,4-addition to enal **3 and (b) a 1,4 addition/ozonolysis sequence.**

Next, we explored whether the conditions were also suitable for the 1,4-addition and subsequent ozonolysis with the required hemiacetal **6**. Thus, the crude reaction mixture obtained following 1,4-addition was subjected directly to ozonolysis (Scheme 2B). Our standard protocol used in our previous prostaglandin synthesis¹² involved reaction with ozone, followed by flushing the reaction mixture with a stream of N_2 and subsequent addition of NaBH_4 to reduce the ozonide and reduce the ketone intermediate. However, under these conditions an allenic side product was formed instead of the desired alcohol **7**. This problem was overcome by reducing the ozonide with PPh_3 before addition of NaBH_4 ,¹⁷ leading to the formation of alcohol **7** in 50% yield over the 2 steps.

Having established that the conjugate addition to our enal substrate was feasible, we moved on to the synthesis of Alfacprostol itself. The lower side chain **11** was prepared in 4 steps starting from 3-cyclohexylpropanoic acid (**8**; Scheme 3). Transformation of acid **8** into the corresponding Weinreb amide, and subsequent coupling with ethynylmagnesium bromide, gave alkyne **9** in 85% yield over 2 steps. Chiral alcohol **10** was obtained by asymmetric CBS-reduction¹⁸ in 87% yield and 97:3 er. Alcohol **10** was protected as a silyl ether in 93% yield in the final step.

Scheme 3 Synthesis of the ω side chain.

To complete the synthesis of Alfacprostol (Scheme 4), copper acetylide **12** was generated from alkyne **11** and added to enal **6**, to form intermediate silyl enol ether **13**. Subsequent ozonolysis and reduction with NaBH_4 furnished alcohol **14** in 56% yield over the two steps, and with complete stereocontrol over the two newly created stereogenic centers at C_{11} and C_{12} . Double deprotection of the silyl and acetal groups under acidic conditions gave the hemiacetal intermediate **15**, which was used without purification in the subsequent Wittig reaction. Accordingly, treatment of hemiacetal **15** with the commercially available Wittig salt gave *Z*-alkene **16** with essentially perfect selectivity. Finally, esterification¹⁹ of acid **16** with methyl iodide completed an 9-step synthesis of Alfacprostol (**2**) with complete stereocontrol.

By synthesizing Alfacprostol, we recognized that the conjugate addition of an alkyne to enals **3/6** could also be beneficial for the synthesis of $\text{PGF}_{2\alpha}$, and other prostaglandin analogues, for three reasons. Firstly, our original 1,4-addition to the enal required the formation of an organocuprate bearing the required vinyl substituent and a non-transferable thiophene ligand,¹² and its preparation was time consuming, laborious, and required the use of *t*-BuLi. Secondly, we had previously required a more functionalized vinyl iodide rather than using the commercially available alkyne directly. Thirdly, the ozonolysis would become simpler and more reliable due to the absence of a second competing double bond, and so timing of the addition of ozone would become less critical. We therefore revisited the synthesis of $\text{PGF}_{2\alpha}$ (Scheme 5). From our initial studies, we found that the sequence of 1,4-addition of alkyne **4** to enal **6** followed by ozonolysis and reduction with sodium borohydride gave alcohol **7** in good yield and full stereocontrol, over 2 steps (Scheme 2). The alkyne was converted into *E*-allylic alcohol **18** by deprotection of the TBDMS group with

Scheme 4. Synthesis of Alfaprostol

Scheme 5. Synthesis of PGF_{2α}

TBAF and subsequent Chan-reduction²⁰ with Red-Al. Finally, deprotection of the acetal and Wittig olefination gave PGF_{2α} **1**.

In conclusion, we have developed short routes towards Alfaprostol (9 steps longest linear sequence, 12 steps in total) and prostaglandin PGF_{2α} (9 steps longest linear sequence, 10 steps in total). Alfaprostol and PGF_{2α} were synthesized in 23% and 18% overall yields from **6**, respectively (both were obtained in ~3% overall yield from succinaldehyde; the optimization for the synthesis of **6** is currently ongoing in our laboratories). In comparison to the previous syntheses of Alfaprostol, our key enal intermediate is not only accessed in substantially fewer steps compared to the Corey lactone, but it is also perfectly set up to introduce the alkyne side chain in an efficient, single-step fashion. This resulted in the marked step count reduction reported here. Furthermore, the conjugate addition of an alkyne to the enal intermediate simplifies both the 1,4-addition and subsequent ozonolysis significantly. The alkyne functionality can be retained or converted into either an alkene or alkane, thereby providing access to an even broader array of important prostaglandin analogues which are currently used in the clinic.

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>.

AUTHOR INFORMATION

Corresponding Author

* Email: v.aggarwal@bristol.ac.uk

Author Contributions

‡These authors contributed equally.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We thank EPSRC for support of this work (EP/M012530/1). H.B. thanks the Deutsche Forschungsgemeinschaft (DFG) for a postdoctoral fellowship. We thank Dr. Jonathan P. Knowles and James Smith (University of Bristol) for helpful discussion.

REFERENCES

- (a) Bindra, J. S.; Bindra, R. *Prostaglandin Synthesis*; Academic Press, Inc: London, 1977; Chapter 1, pp 1–5. (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. (e) Clark, K.; Myatt, L. *Glob. libr. women's med. (ISSN: 1756-2228)*, **2008**; DOI 10.3843/GLOWM.10314. (f) Alfirevic, Z.; Keeney, E.; Dowswell, T.; Welton, N. J.; Dias, S.; Jones, L. V.; Navaratnam, K.; Caldwell, D. M. *BMJ*, **2015**;350:h217.
- (2) Weems, C. W.; Weems, Y. S.; Randel, R. D. *Vet J.* **2006**, *171*, 206.
- (3) (a) Lauderdale, J. W. *J. Anim. Sci.* **2009**, *87*, 801 (b) Rowson, L. E. A.; Tervit, R.; Brand, A., *J. Reprod. Fertil.* **1972**, *29*, 145.
- (4) Maffeo, G.; Ballabio, R.; Olgiati, V.; Guidobono, F. *Prostaglandins* **1983**, *25*, 541.
- (5) Howey, W. P.; Jochle, W.; Barnes, W. J. *Aust. Vet. J.* **1983**, *60*, 180.
- (6) (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.; Wiley, Hoboken, NJ, 2010; Chapter 21, pp 329–338.
- (7) Singer, M. S.; Kalayoglu, M. V. **2016**, US 20160067263 A1.
- (8) Mastronardi, F. G. **2012**, WO 2012/100347.
- (9) For reviews, see: (a) Peng, H.; Chen, F.-E. *Org. Biomol. Chem.* **2017**, *15*, 6281. (b) Corey, E. J. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*,

455. For recent organocatalytic approaches to PGs, see: (c) Hayashi, Y.; Umemiya, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 3450. (d) Umemiya, S.; Sakamoto, D.; Kawauchi, G.; Hayashi, Y. *Org. Lett.* **2017**, *19*, 1112.
- (10) Gandolfi, C.; Pellegata, R.; Ceserjani, R.; Usardi, M. M. US Patent Application, **1977**, No.4035415.
- (11) (a) Monteiro, S.; Imramovsky, A.; Pauk, K.; Pavlik, J. *Tetrahedron Lett.* **2017**, *58*, 2228. (b) Imramovsky, A.; Pauk, K.; Elias, Z. **2015**, CZ 305221 B6 20150617.
- (12) Coulthard, G.; Erb, W.; Aggarwal, V. K. *Nature* **2012**, *489*, 278.
- (13) Prevost, S.; Thai, K.; Schützenmeister, N.; Coulthard, G.; Erb, W.; Aggarwal, V. K. *Org. Lett.* **2015**, *17*, 504.
- (14) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210.
- (15) (a) Eriksson, M.; Ilieski, T.; Nilsson, M.; Olsson, T. *J. Org. Chem.* **1997**, *62*, 182. This paper did not appear in a SciFinder search of this reaction which may account for its low uptake in the community. However, the methodology has been used by Tanaka. See: (b) Takeishi, K.; Sugishima, K.; Sasaki, K.; Tanaka, K. *Chem. Eur. J.* **2004**, *10*, 5681. (c) Tanaka, K.; Hagiwara, Y.; Hirano, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 2734. (d) Tanaka, K.; Mimura, M.; Hojo, D. *Tetrahedron* **2009**, *65*, 9008.
- (16) A commercial source (Sigma Aldrich) of TMSI was used without further purification. The TMSI was stored over copper turnings, under an inert atmosphere, and in a freezer.
- (17) Körner, M.; Hierseman, M. *Synthesis* **2016**, *48*, 2466.
- (18) (a) Parker, K. A.; Ledebor, M. W., *J. Org. Chem.* **1996**, *61*, 3214. (b) Corey E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551.
- (19) Gutman, A.; Rukhman, I.; Tishin, B.; Yudovich, L.; Vilwinsky, A.; Pertsikov, B.; Nisnevich, G. US Patent Application No. US2011/0288179A1, 2011.
- (20) (a) Shang, S.; Iwadare, H.; Macks, D. E.; Ambrosini, L. M.; Tan, D. S. *Org. Lett.* **2007**, *9*, 1895. (b) Chan, K.-K.; Cohen, N.; De Noble, J. P.; Specian, A. C., Jr.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3497. (c) Marshall, J. A.; DeHoff, B. S. *J. Org. Chem.* **1986**, *51*, 863. (d) Corey, E. J.; Katzenellenbogen, J. A.; Posner, G. H. *J. Am. Chem. Soc.* **1967**, *89*, 4245.