Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX-XXX

pubs.acs.org/OrgLett

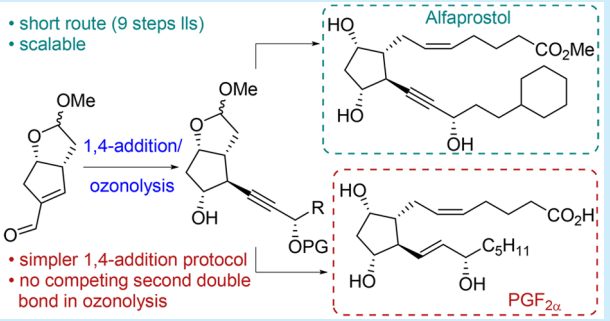
Synthesis of Alfaprostol and $PGF_{2\alpha}$ through 1,4-Addition of an Alkyne to an Enal Intermediate as the Key Step

Hannah Baars,[†] Moritz J. Classen,[†] and Varinder K. Aggarwal*

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

Supporting Information

ABSTRACT: The veterinary drug Alfaprostol and prostaglandin $PGF_{2\alpha}$ have been synthesized in just nine 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 $PGF_{2\alpha}$, 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 $PGF_{2\alpha}$ (**1**) is known for its luteolytic effect (degradation of the corpus luteum) in cattle (Figure 1).[3] This activity is exploited in veterinary practice for

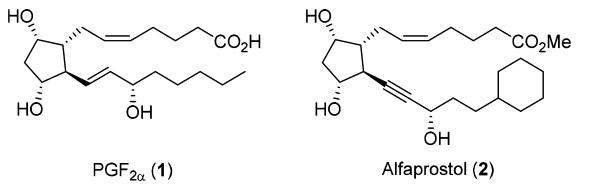
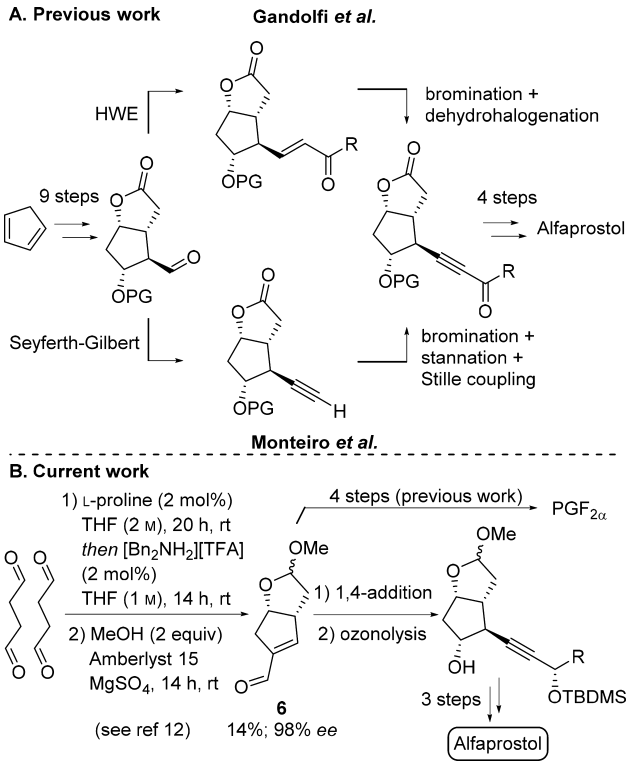


Figure 1. Prostaglandin $PGF_{2\alpha}$ and its synthetic analogue Alfaprostol.

the timing of insemination and increasing reproductive efficiency. Alfaprostol (**2**) was developed as a more stable and selective analogue of $PGF_{2\alpha}$ and is widely used as a potent luteolytic agent in cows[4] and mares.[5] In addition to its application in the treatment of glaucoma,[6] continued research on $PGF_{2\alpha}$ 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]

While numerous diverse strategies have been reported for the synthesis of $PGF_{2\alpha}$,[1c] strategies toward 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 Horner–Wadsworth–Emmons olefination, bromination, and double dehydrobromination to install the triple bond.[10] Monteiro et al. used a Seyferth–Gilbert homologation

Scheme 1. Previous and Current Strategy toward Alfaprostol



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.

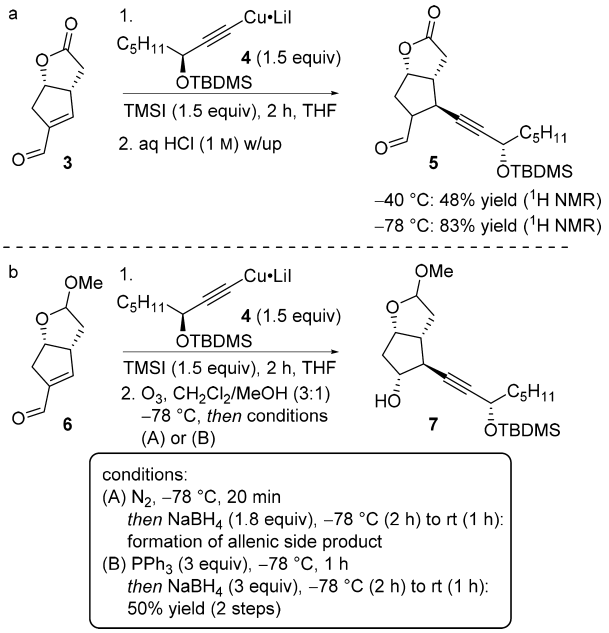
Received: September 29, 2017

DOI: 10.1021/acs.orglett.7b03057
Org. Lett. XXXX, XXX, XXX–XXX

We recently reported a seven-step synthesis of $PGF_{2\alpha}$[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 a nine-step synthesis of Alfaprostol 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 copper[14] (in fact, they have been used as nontransferable 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

Scheme 2. Model Studies To Investigate (a) the 1,4-Addition to Enal 3 and (b) a 1,4 Addition/Ozonolysis Sequence

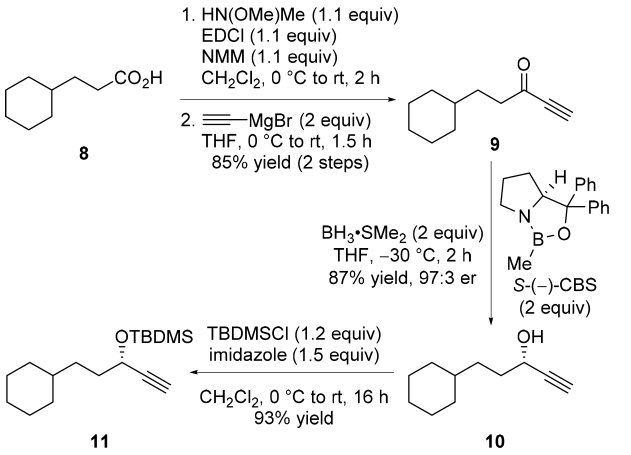


were pleased to find that the addition product **5** was formed, after acidic workup, in good yield (48% ^{1}H NMR yield). The yield could be increased to 83% (by ^{1}H NMR) by lowering the temperature to −78 °C. Crucial for high yields was the quality of the TMSI, which had to be stored under the exclusion of light, air, and moisture.[16]

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 synthesis[12] 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 two steps.

Having established that the conjugate addition to our enal substrate was feasible, we moved on to the synthesis of Alfaprostol itself. The lower side chain **11** was prepared in four steps starting from 3-cyclohexylpropanoic acid (**8**; Scheme 3).

Scheme 3. Synthesis of the ω Side Chain



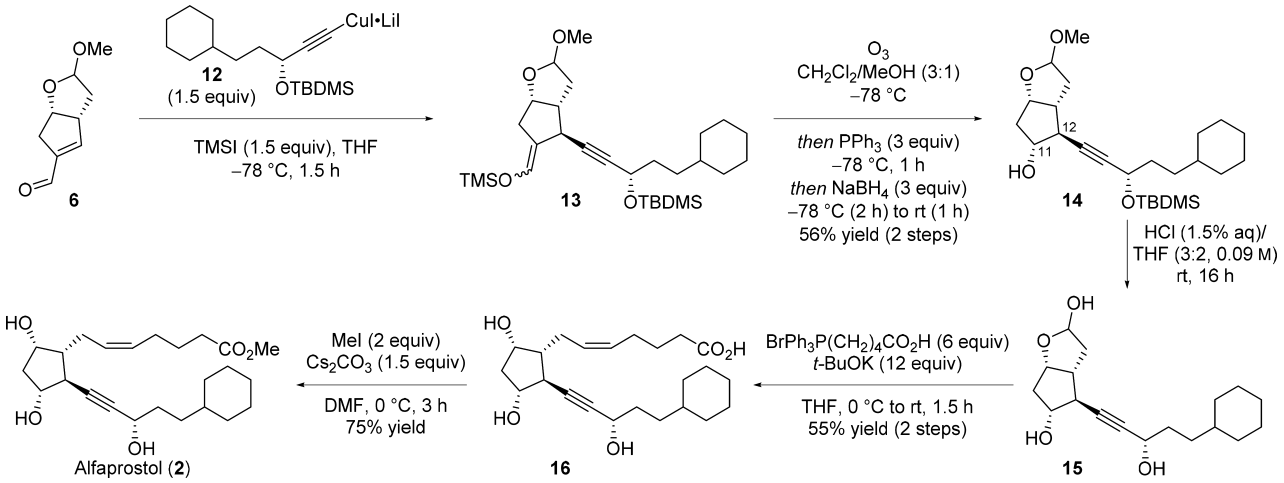
Transformation of acid **8** into the corresponding Weinreb amide, and subsequent coupling with ethynylmagnesium bromide gave alkyne **9** in 85% yield over two steps. Chiral alcohol **10** was obtained by asymmetric CBS-reduction[18] in 87% yield and 97:3 er. Alcohol **10** was protected as a silyl ether in 93% yield in the final step.

To complete the synthesis of Alfaprostol (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, esterification[19] of acid **16** with methyl iodide completed a nine-step synthesis of Alfaprostol (**2**) with complete stereocontrol.

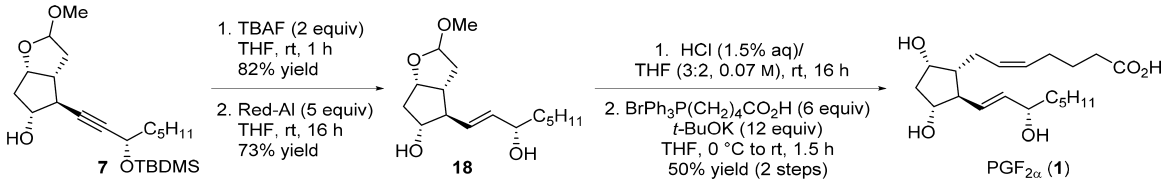
By synthesizing Alfaprostol, we recognized that the conjugate addition of an alkyne to enals **3**/**6** could also be beneficial for the synthesis of $PGF_{2\alpha}$, and other prostaglandin analogues, for three reasons. First, our original 1,4-addition to the enal required the formation of an organocuprate bearing the required vinyl substituent and a nontransferable thiophene ligand,[12] and its preparation was time-consuming and laborious and required the use of *t*-BuLi. Second, we had previously required a more functionalized vinyl iodide rather than using the commercially available alkyne directly. Third, 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 $PGF_{2\alpha}$ (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 two steps (Scheme 2). The alkyne was converted into *E*-allylic

DOI: 10.1021/acs.orglett.7b03057
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 4. Synthesis of Alfaprostol



Scheme 5. Synthesis of $PGF_{2\alpha}$



alcohol **18** by deprotection of the TBDMS group with TBAF and subsequent Chan reduction[20] with Red-Al. Finally, deprotection of the acetal and Wittig olefination gave $PGF_{2\alpha}$ **1**.

In conclusion, we have developed short routes toward Alfaprostol (9 steps longest linear sequence, 12 steps in total) and prostaglandin $PGF_{2\alpha}$ (9 steps longest linear sequence, 10 steps in total). Alfaprostol and $PGF_{2\alpha}$ were synthesized in 23% and 18% overall yields from **6**, respectively (both were obtained in ~3% overall yield from succinaldehyde; further 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 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

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03057.

Experimental procedures, characterization data, and NMR spectra for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: v.aggarwal@bristol.ac.uk.

ORCID

Varinder K. Aggarwal: 0000-0003-0344-6430

Author Contributions

†H.B. and M.J.C. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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 discussions.

■ REFERENCES

(1) (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**, *104-105*, 109. (e) Clark, K.; Myatt, L. *Glob. Libr. Women's Med.* (ISSN: 1523-7060), **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.* **2008**, *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.

DOI: 10.1021/acs.orglett.7b03057
Org. Lett. XXXX, XXX, XXX–XXX

(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. U.S. 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.; Iliefski, 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.; Hiersemann, M. *Synthesis* **2016**, *48*, 2466.
(18) (a) Parker, K. A.; Ledeboer, 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.; Vilwnsky, A.; Pertsikov, B.; Nisnevich, G. U.S. 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.

DOI: 10.1021/acs.orglett.7b03057
Org. Lett. XXXX, XXX, XXX−XXX