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Novel synthetic approach to alfaprostol key intermediates *via* Stille coupling with an alkyne

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ABSTRACT

Novel intermediates based on the Corey skeleton for preparation of the ω-chain of non-halogenated unnatural prostaglandin analogues containing a triple bond at position 13–14 (PG numbering) were synthesized. The utilization of a novel synthetic approach towards a new tin intermediate, and subsequent Stille coupling opens up new possibilities for preparing these important pharmaceutical intermediates.

The synthesis of natural or synthetic analogs of prostaglandin (PG) has been of significant interest to synthetic chemists since its discovery by Von Euler.[1,2] Their use in human and veterinary practice and the complexity of their preparation is one reason for the continued fascination of organic chemists. Synthetic analogs moreover show greater biological activity, better stability, or allow for more preferred methods of application to the organism.[3–5] The basis for the synthesis of natural PG was first reported by Corey and co-workers, and this approach still forms the basis for laboratory synthesis as well as industrial applications.[6] Recent studies have described the synthesis of PG without Corey intermediates; fewer steps are the main advantage of these approaches.[7–9] Despite these promising studies, there is still scope for optimizing existing routes, as well as for the application of modern approaches to the synthesis of PG using Corey intermediates.

The synthesis of natural PGs and their synthetic analogues based on Corey intermediates can be divided into two phases, each involving several synthetic steps. Individual phases include construction of the ω-chain (Phase 1) and subsequent synthesis of the α-chain (Phase 2). The α-chain of PGs is connected using the Wittig reaction (Fig. 1).[6,9,10]

In this study, attention was focused on synthesis of the ω-chain of the non-halogenated synthetic PG derivative alfaprostol (AP). AP is used in veterinary practice, however, compared to $PGF2_\alpha$ it is characterized by greater stability and specific activity.[11] Comparing the structure of AP with $PGF2_\alpha$, position 13–14 (PG numbering) contains a triple bond instead of an alkene. Additionally, the ω-chain of AP is terminated by a saturated six-membered ring and the α-chain contains a carboxylic acid methyl ester (Fig. 2).

Due to the presence of the triple bond, a specific approach for the synthesis of this molecule is required. In this case, it is not appropriate to simply apply Horner-Wadsworth-Emmons reaction

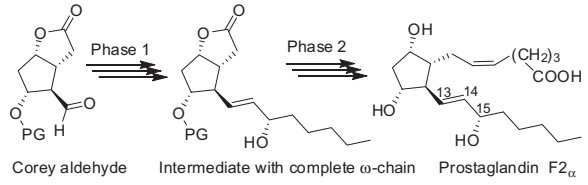

Fig. 1. Representative example of a general approach towards prostaglandins using natural $PGF2_\alpha$.

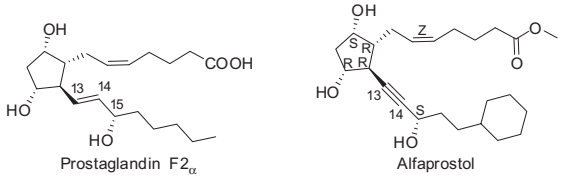

Fig. 2. Comparison of $PGF_{2\alpha}$ and AP structures.

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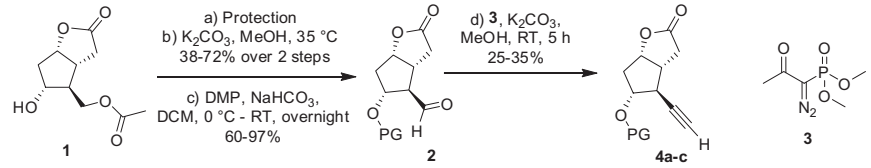
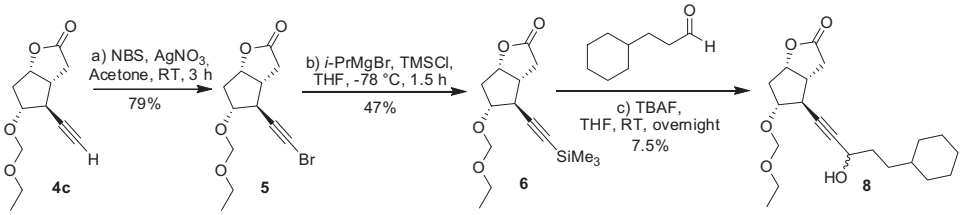


Scheme 1. Synthesis of key intermediates for further modification. **4a** PG = TBDPS; **4b** PG = TBDMS; **4c** PG = EOM.



Scheme 2. Application of the Chintareddy synthetic pathway (step c) to the novel Corey intermediates **4c**, **5** and **6**.

conditions which allow the Corey aldehyde to react with an appropriate phosphonate, yielding an *E*-alkene at position 13–14. This reaction is commonly used for the synthesis of precursors of various PGs containing double bonds at the mentioned position.[6]

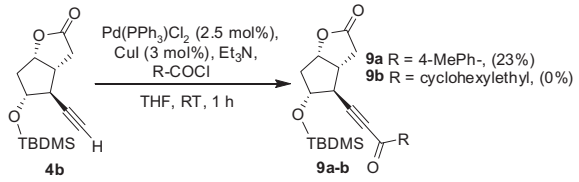
Several methods to synthesize intermediates containing a triple bond at position 13–14 for various PGs have been described.[12–14] Gandolfi and co-workers reported a sequence utilizing a phosphonate reaction with the protected Corey aldehyde.[12,13] In the first step, the appropriate *E*-alkene was generated and subsequently reacted with bromine. Double dehydrohalogenation followed to yield the desired triple bond at position 13–14 of the future PG ω-chain. A stereoselective reduction was also performed during this synthesis to obtain the final ω-chain. Klar and co-workers reported an alternative method, where a one-step reaction produced a "bromo-enone" derivative which was dehydrohalogenated using CsOAc in the presence of 18-crown-6 ether.[14] Both of these studies involved reactions with phosphonates, a dehydrohalogenation step, and stereoselective reduction of the carbonyl group.

Based on retrosynthetic analyses, we proposed an alternative methodology for synthesis of the ω-chain containing a triple bond at position 13–14. This approach included synthesis of the protected Corey aldehyde, followed by Seyfert–Gilbert homologation. The targeted intermediate was synthesized *via* formation of a new C—C bond; a scheme comparing our and Gandolfi and co-workers synthetic approach can be found in the ESI.

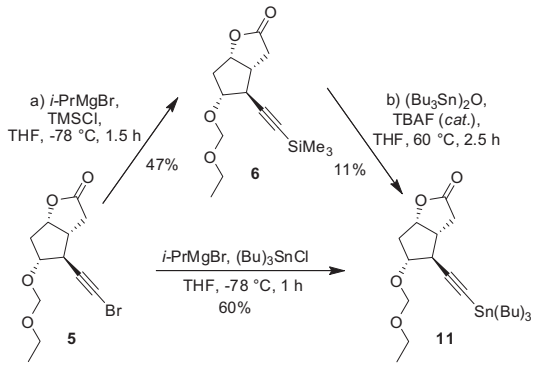
The starting gamma-lactone **1** (supplied by Cayman Pharma) was first protected with *tert*-butyldimethylsilyl (other groups were also tested for the protection of the Corey skeleton) and the ester group hydrolyzed under basic conditions. The resulting Corey alcohol was oxidized using Dess-Martin periodinane to give the protected Corey aldehyde **2**, which was the starting material for further experiments (see ESI for detailed procedures as well as compound characterization). In order to directly obtain the terminal alkyne, alkynylation by treatment of the aldehyde with lithiotrimethylsilyldiazomethane was attempted,[15,16] but resulted in substrate decomposition. Therefore, it was decided to use the Ohira Bestmann reagent **3** which was prepared according to the literature procedure.[17] The terminal alkynes **4a-c** were prepared in 25–35% isolated yield (Scheme 1).[18] *tert*-Butyldimethylsilyl (TBDMS), *tert*-butyldiphenylsilyl (TBDPS) and eventually the ethylmethyl ether (EOM) group were used for hydroxyl group protection.

The synthesis of propargyl alcohols from terminal alkynes and aldehydes is widely described and presents the possibility of controlling individual isomers. In general, these synthetic methodologies use a strong base, e.g. butyllithium, for activation of the triple bond.[19,20] The conditions of several studies were applied to the reaction of **4a** or **4b** with cyclohexylpropanal. While the reaction of **4a** and cyclohexylpropanal in the presence of BuLi in THF[21,22] resulted in starting material decomposition, the reaction in the presence of diethylzinc and *N*-methylimidazole in DCM[23] or chromium(II) chloride in DMF[24] did not proceed. See ESI, Table S1 for all reaction conditions.

Persisting with our efforts to prepare propargylic alcohols, Chintareddy and co-workers described the formation of propargyl alcohols from the corresponding trimethylsilyl derivative in the presence of TBAF.[25] However, in order to carry out this approach it was necessary to use a new protecting group. Ethyl methyl ether (EOM) was chosen as a simple protecting group and compound **4c**

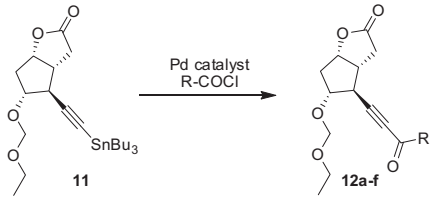


Scheme 3. Sonogashira coupling reaction with Corey intermediate **4b**.



Scheme 4. Comparison of the literature approach to intermediate **11** *via* compound **6** and our novel one-step synthetic approach.

Table 1
Comparison of palladium catalysts for the reaction of tributyl tin derivative **11** with R-COCl.



Entry	R-COCl	Pd catalyst	Conditions	Product	Yield (%)
1	-Ph	$Pd(PPh_3)_4$	1	**12a**	4[a]
2		$Pd(PPh_3)_2Cl_2$	2		40[b]
3	-Ph-4-CH_3	$Pd(PPh_3)_4$	1	**12b**	56[a]
4		$Pd(PPh_3)_2Cl_2$	2		45[b]
5	-Ph-4-OCH_3	$Pd(PPh_3)_4$	1	**12c**	17[a]
6		$Pd(PPh_3)_2Cl_2$	2		29[b]
7	-Ph-4-NO_2	$Pd(PPh_3)_4$	1	**12d**	NF[a]
8		$Pd(PPh_3)_2Cl_2$	2		56[b]
9	-Ph-4-Cl	$Pd(PPh_3)_4$	1	**12e**	5[a]
10		$Pd(PPh_3)_2Cl_2$	2		61[b]
11	-CH_2CH_2Ch	$Pd(PPh_3)_4$	1	**12f**	17[a]
12		$Pd(PPh_3)_2Cl_2$	2		35[b]

[a] Determined by HPLC.
[b] Isolated yields, NF – not found, Reagents and conditions: (1) $Pd(PPh_3)_4$ (10 mol%), DMF, 65 °C, 2.5 h. (2) $Pd(PPh_3)_2Cl_2$ (2.5 mol%), MeCN, reflux, 2 h.

was successfully transformed into bromo-derivative **5** in 79% yield.[26] Compound **6** was then reacted with 3-cyclohexylpropanal **7** in the presence of TBAF to afford the desired product **8** (PG = EOM, R = cyclohexylethyl) in 7.5% isolated yield (Scheme 2). This result was not surpassed either upon repeated experiments or after reaction condition optimisation. Experimental procedures as well as characterisation data for compounds **5**, **6** and **8** can be found in the ESI.

Because we were not able to obtain the appropriate propargyl alcohol in good yield, we then concentrated our efforts on propargyl ketones which can be easily reduced to the desired alcohol. The Sonogashira coupling reaction initially seemed ideal to apply to our system.[27] On the basis of this, compound **4b** was reacted with *p*-toluoyl chloride in presence of $PdCl_2(PPh)_2$, CuI and Et_3N. The expected ketone derivatives **9a** was isolated in 23% yield; however, the reaction with 3-cyclohexylpropanoyl chloride **10** did not proceed (Scheme 3).

These disappointing results led us to select another type of reaction which could produce the desired propargylic ketone. The Stille coupling reaction has been reported as a useful method for the preparation of propargylic ketones.[28] In a first attempt, compound **6** was transformed into the appropriate tributyl tin compound **11** in 11% yield.[29] Due to the low yield of the isolated tin compound, a one-step synthetic approach was developed where compound **5** was directly transformed into tributyl tin compound **11** in 60% yield (Scheme 4). The reaction of **11** with several substituted benzoylchlorides (R-COCl) as well as cyclohexylpropanoyl chloride **10** was investigated using $Pd(PPh_3)_4$ and $Pd(PPh_3)_2Cl_2$ as catalysts. While $Pd(PPh_3)_4$ gave the desired product **12** in low yields, Pd $(PPh_3)_2Cl_2$ led to the targeted ketones **12a–f** in moderate to good yields (Table 1). The terminal alkyne was also detected by TLC but not isolated.

In conclusion, it was determined that it is possible to modify Corey intermediates to obtain terminal alkynes **4a–c**. Nevertheless, despite a number of available literature reports, their application in the preparation of propargyl alcohols was not successful. As a consequence, the alkyne was modified using an original approach to yield a tin derivative **11** which was suitable for the Stille coupling reaction. Under these conditions the desired ketone **12f** was synthesized which can be used as a key intermediate in the preparation of AP. This study may open up several possibilities for future studies in the preparation of active PGs with a triple bond at position 13–14.

Acknowledgments

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A. Supplementary data

General experimental information, experimental details, spectral characterization data for compounds which are not cited in references, their NMR and MALDI-TOF spectra. Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2017.04.091.

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