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Synthesis of Advanced Prostaglandin Intermediates

Thesis of the Doctoral Dissertation

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References

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ABSTRACT

Prostaglandins are a group of lipid mediators with multiple pharmaceutical and veterinary applications.

This thesis describes the efforts made in the development of a new strategy for the synthesis of Alfaprostol ω-chain. More specifically, several attempts were made in the preparation of the propargyl alcohol connection present in this molecule.

Literature described two main methodologies for preparation of optically active propargylic alcohols, namely: asymmetric reduction of a propargylic ketone or the asymmetric alkynylation of a carbonyl group. Both mentioned methodologies were studied and applied to target molecule.

Stille coupling has been successfully used to afford propargylic ketone susceptible of asymmetric reduction.

The direct preparation of propargylic alcohol with adequate stereoselectivity using Corey lactone derivatives and 3-cyclohexylpropanal as starting materials was also deeply studied. Furthermore, it has also been used in the stereoselective studies made afterwards.

Keywords

Alfaprostol, Alkynylation, Propargyl alcohol, Propargyl ketone, Prostaglandins, Stille coupling.

ABSTRAKT

Prostaglandiny jsou skupinou fyziologicky aktivních látek odvozených od kyseliny arachidonové. Prostaglandiny a jejich syntetická analoga mají široké uplatnění v klinické humánní i veterinární praxi.

Tato dizertační práce popisuje návrh a experimentální ověření nové strategie pro syntézu ω-řetězce Alfaprostolu. Popisuje několik různých přístupů k budování propargyl alkoholového uspořádání v cílové molekule.

Literatura popisuje dva základní přístupy ke stereospecifické syntéze propargylalkoholového uspořádání. Konkrétně se jedná o asymetrickou redukci propargyl ketonu, nebo o asymetrickou alkylaci karbonylové skupiny. Oba přístupy byly podrobně studovány a experimentálně ověřovány při syntéze cílové molekuly.

Úspěšně byla využita reakce organociničitých sloučenin s chloridy karboxylových kyselin za přítomnosti palladia (Stille coupling) poskytující propargylketonové uspořádání, což je meziprodukt vhodný pro asymetrickou redukci.

Přímá stereoselektivní syntéza meziproduktu Alfaprostolu obsahující propargyl alkoholové uspořádání, vycházející z derivátu Corey laktonu a 3-cyklohexylpropanalu byla taktéž intenzivně studována. Tato reakce se stala také součástí stereoselektivní studie, popisující vznik uvedeného uspořádání.

Klíčová slova:

Alfaprostol, Propargyl alcohol, Propargyl keton, Prostaglandiny, Stille coupling.

TABLE OF CONTENT

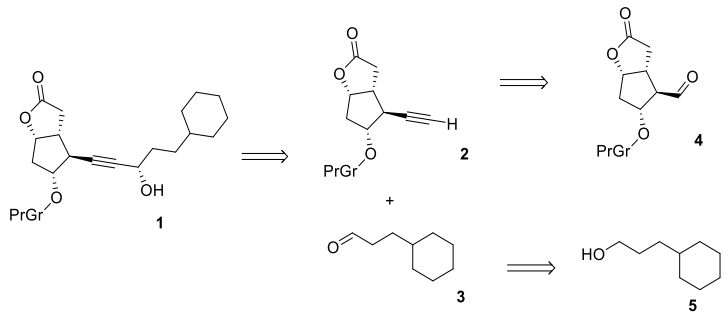
INTRODUCTION

Prostaglandins (PG) are a group of lipid mediators with a general skeleton of 20 carbons, including a five-membered ring and two lateral chains. They have multiple pharmaceutical and veterinary applications, reason why they are being synthesized for more than 50 years and represent a market of millions of dollars every year.

Alfaprostol is a synthetic $PGF_{2\alpha}$ methyl ester analogue used as a veterinary agent with luteolytic activity with a propargyl alcohol skeleton at position 13. Its relevance in the veterinary context such as cow, mare and goat industry is well known. However, even if its first synthesis has been reported in 1979, until 2014 no other synthetic alternative was published for this molecule.[1] The lack of studies, at the time this study started (year of 2014), opens the possibility for further investigation. In this context, the main proposal of this work is the development of new synthetic approaches for the preparation of alfaprostol molecule, using new synthetic methodologies. Having Corey lactone diol as starting material, different modifications were proposed and tested. Experimental validation of suggested approaches and their summarization was done, and the resumed results are presented in the next pages.

There are two main ways how to prepare an optically active propargyl alcohol moiety: asymmetric reduction of a propargyl ketone or asymmetric alkynylation between an alkyne terminal and a carbonyl compound.[2] Comparing both strategies, the one-pot asymmetric alkynylation presents undeniable advantageous. While the asymmetric reduction requires first the preparation of ketone intermediate, followed by reduction, the alkynylation should be a straightforward protocol for propargyl alcohol intermediate (**1**).

The enantioselective alkynylation of aldehydes is widely described in the literature.[2,3] It normally involves an intermetalation step of an alkyne followed by the nucleophilic attack to a ketone or aldehyde. The process is normally assisted by a chiral auxiliary which determines the outcome configuration of the final compound.



Scheme 1 – Simplified retrosynthetic analyses of alfaprostol intermediate (**1**). PrGr - Protecting group

From our retrosynthetic analyses (**Scheme 1**) we suggested that compound **1** could be a crucial intermediate in the preparation of alfaprostol. From literature search we assumed that asymmetric alkynylation of compound **2** and **3** should be an effective way to compound **1**. On the other hand, while alkyne **2** could be prepare from aldehyde **4**, aldehyde **3** could be synthesize from commercially available 3-cyclohexylpropanol, compound **5**.

AIMS

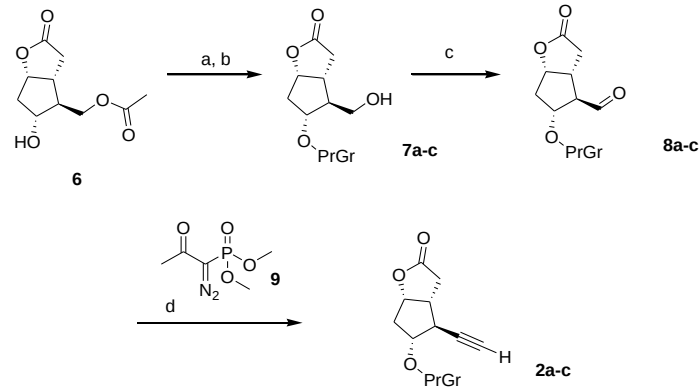
The main goals of this thesis are:

- Revision of the literature and the current state of the art related with PG synthesis. A special focus was put on the synthesis of 13,14-dehydroPG;
- Preparation of adequate intermediates useful in the synthesis of alfaprostol, with possibility of application in the synthesis of other 13,14-dehydroPG intermediates;
- Extension of our previous knowledge in the synthesis of alfaprostol molecule and adequate intermediates.
- One-pot synthesis of propargyl alcohol moiety from a Corey alkyne intermediate and adequate aldehyde;
- Enantioselective alkynylation of an alkyne and aldehyde in the preparation of alfaprostol ω-chain;
- Comprehension of the reality of the industrial and technological concerns of PG production.

RESULTS AND DISCUSSION

Synthesis of intermediate Corey alkynes

With the previous retrosynthetic analyse in mind, Corey alkynes **2a-c** have been prepared according **Scheme 2.**

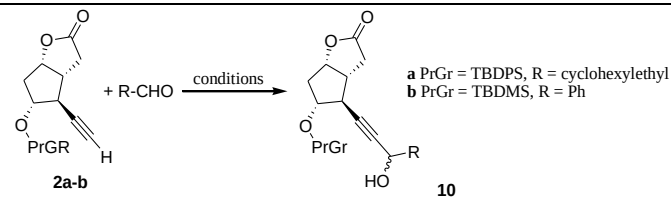


Scheme 2 – Synthesis of terminal alkynes via Ohira Bestmann reagent (**9**). **Protecting groups: a=** TBDPS; **b=** TBDMS; **c=** EOM. Reagent: a) Protection; b) K_2CO_3, MeOH, 35 °C, (38-72 %, 2 steps); c) DMP, $NaHCO_3$, DCM, 0 °C to rt, overnight (60-97%); d) K_2CO_3, MeOH, rt, 5h, (25-35 %).

Starting from protected Corey lactone alcohol **6** (also known as gamma-lactone, which was kindly provided to our laboratory by Cayman Pharma Ltd.), the first step was the protection of the free alcohol. Firstly, silyl ethers were used as PrGr (*tert*-butyldiphenylsilyl (TBDPS) and *tert*-butyldimethylsilyl (TBDMS)) and later ethyl methyl ether (EOM) was also used. Appropriate chlorides were used in the presence of a base. While in the case of the silyl ether the crude product of the protection was used without further purification, EOM-protected gamma-lactone was prepared and isolated in 95 % yield. Hydrolysis of the ester group by K_2CO_3 and MeOH afforded the alcohols **7a-c**. The silyl ethers **7a** and **7b** were obtained in 50 and 38 % yield respectively, over two steps. EOM-protected alcohol **7c** was prepared in 72 % yield over two steps. Thus, even if part of the initial experiments were made using the silyl ethers as PrGr, on the later experiments EOM PrGr was the preferred choice.

Oxidation with Dess-Martin periodinane (DMP) successfully yielded aldehydes **8a-c**. Yields varied between 60 and 94 %. Lastly, Seyfert-Gilbert homologation, using Ohira Bestmann reagent (1-diazo-2-oxopropylphosphonate, **9**), allowed the preparation of terminal alkyne **2a-c** under mild conditions (K_2CO_3 in MeOH). Yields differed from 25 to 35 %. With terminal alkynes **2a-c** in hands different attempts have been performed in order to prepare propargyl alcohol. 3-Cyclohexyl-1-propanal (**3**) or benzaldehyde have been used as testing aldehydes. Despite the use of conditions described in different literature sources, as described in **Table 1**, it was not possible to prepare the desired intermediate **10.**

Table 1: Conditions and results of initial experiments to afford propargyl alcohols.

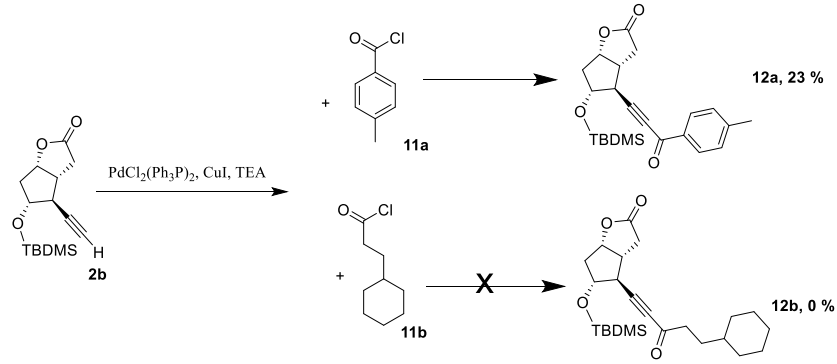


Entry	Starting material	R	Conditions	Expected product	Yield (%)
1	**2a**	-CH_2CH_2Ch (**3**)	BuLi [4,5]	**10a**	0 %
2	**2a**	-CH_2CH_2Ch (**3**)	$ZnEt_2$, NMI, DCM, 20 h, rt [6]	**10a**	0%
3	**2a**	-CH_2CH_2Ch (**3**)	$CrCl_2$, DMF, 20 h, rt [7]	**10a**	0%
4	**2b**	Ph	$Zn(OTf)_2$, (-)NME, TEA, Toluene, rt [8,9]	**10b**	0%
5	**2b**	Ph	$Zn(OTf)_2$, (-)NME, Toluene, rt [8,9]	**10b**	0%
6	**2b**	Ph	(*S*)-Binol, Cy_2NH $Ti(OiPro)_4$, NME, $ZnEt_2$, THF, rt [10]	**10b**	0%
7	**2b**	Ph	*t*-BuOK, THF/DMSO (1:1), rt [11]	**10b**	0%
8	**2b**	Ph	$InBr_3$, (*S*)-Binol, Cy_2NMe, DCM [12]	**10b**	0%

Synthesis of Prostaglandin intermediates *via* Stille coupling.

After the unsatisfying results described above, attention has been concentrated in the preparation of propargyl ketone. The ketone intermediate could be later reduced to the appropriate alcohol. Propargyl ketone, could be prepared using a coupling between a terminal alkyne and an acyl chloride. Sonogashira coupling was the selected protocol, because it could allow the use of the terminal alkynes **2a-c** without further modifications. In general, Sonogashira coupling uses a palladium catalyst and a copper co-catalyst.[13,14]

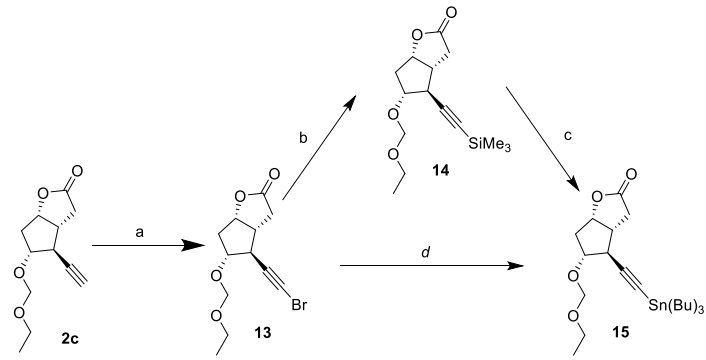
In a first attempt alkyne **2b** was coupled with *p*-toluoyl chloride **11a** in the presence of bis(triphenylphosphine)palladium(II) dichloride, copper iodide and triethylamine. Propargyl ketone **12a** was isolated in 23 % yield (**Scheme 3**). The next step was the preparation of intermediate chloride **11b** from correspondent acid, followed by coupling with compound **2b**. Unfortunately, the use of Sonogashira coupling did not afford desired intermediate **12b**.



Scheme – Synthesis of propargyl ketone **12a-b** using Sonogashira coupling.

The disappointing results forced subsequent efforts to the selection of a different type of coupling. Stille coupling appeared as an attractive alternative since the tributyl tin derivative (**15**) preparation from **13** *via* **14** is described (**Scheme 4**).[15] Compound **13** has been previously prepared from alkyne **2c** using bromination with NBS (*N*-Bromosuccinimide).

However, the results were not as expected, since compound **15** was prepared in just 11 % from **14** and in 5 % overall yield from **13**. Because of the low yield, a direct one-step synthesis of **15** from **13** was developed, and the desired compound was prepared in 60 % yield. This represents a big improvement when compared with the process described in literature and in the best of our knowledge was not previously reported. **Scheme 4** compare both strategies.

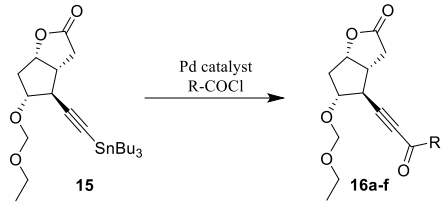


Scheme 4 – Synthesis of tributyl tin derivative (**15**) by to different approaches and their comparison. Reagents: a) NBS, $AgNO_3$, acetone, rt, 3h (79 %); b) *i*-PrMgCl, TMS-Cl, THF, –78 °C, 1.5 h (47 %); c) $((Bu_3Sn)_2O$, TBAF, THF, 60 °C, 2.5 h (11 %); d) *i*-PrMgCl, $(Bu)_3$-Sn-Cl, THF, –78 °C, 1h (60 %).

With compound **15** in hands, a series of reactions between **15** and several acyl chlorides were set. Two different palladium catalysts were investigated, and the results are compared in **Table 2**. In general, the desired propargyl ketones were successfully prepared in modest yields when $Pd(PPh_3)_2Cl_2$ was used as catalyst. On the other side the use of $Pd(PPh_3)_4$ afforded the product in much lower yields, and in some cases, final propargyl ketone was not even detected in the reaction mixture.

With this study it was proved that tributyl tin intermediate **15** is a good substrate to undergo Stille coupling. Additionally, Stille coupling may be of interest in the preparation of different PG intermediates. In conclusion, different propargyl ketones were prepared, among which compound **16f** is an appropriate intermediate for the preparation of alfaprostol.

Table 2 – Comparison of the use of two different palladium catalysts for the reaction of tributyl tin derivative **15** with different acyl chlorides.



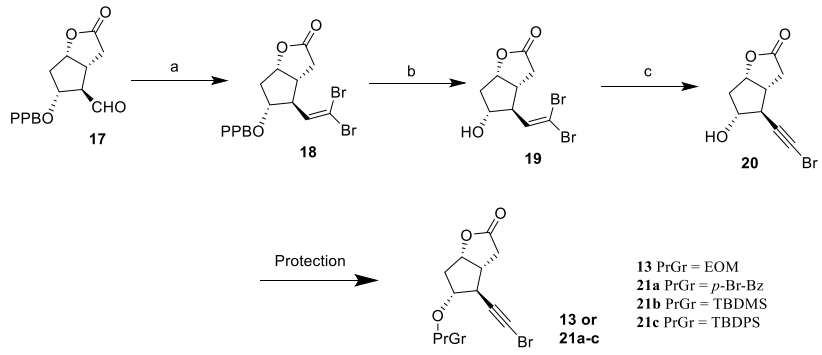
Entry	R	Pd catalyst	Conditions	Product	Yield (%)
1	-Ph	$Pd(PPh_3)_4$	1	**16a**	4[a]
2		$Pd(PPh_3)_2Cl_2$	2		40[b]
3	-Ph-4-CH_3	$Pd(PPh_3)_4$	1	**16b**	56[a]
4		$Pd(PPh_3)_2Cl_2$	2		45[b]
5	-Ph-4-OCH_3	$Pd(PPh_3)_4$	1	**16c**	17[a]
6		$Pd(PPh_3)_2Cl_2$	2		29[b]
7	-Ph-4-NO_2	$Pd(PPh_3)_4$	1	**16d**	NF[a]
8		$Pd(PPh_3)_2Cl_2$	2		56[b]
9	-Ph-4-Cl	$Pd(PPh_3)_4$	1	**16e**	5[a]
10		$Pd(PPh_3)_2Cl_2$	2		61[b]
11	-CH_2CH_2Ch	$Pd(PPh_3)_4$	1	**16f**	17[a]
12		$Pd(PPh_3)_2Cl_2$	2		35[b]

Legend: [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.

Use of Corey bromoalkyne in the preparation of PG intermediates

A reflection on the previous work, made possible to highlight the importance and potential of the Corey bromoalkyne **13**. The direct preparation of organostannane **15** from **13** renewed the hypothesis of activating the triple bond to conduct direct alkynylation. A literature search has also proved the existence of some protocols which could potentially be applied in this system.[16,17]

At this point efforts were focused in the preparation of Corey bromoalkyne **20**. Compound **20** was prepared from PPB-protected Corey aldehyde in a more straightforward way and with improved yields, when compared with previous approach. The strategy here applied had previously been reported in a patent published by our group and it was the base for the direct preparation of bromoalkynes (**Scheme 5)**.[18,19]



Scheme 5 – Synthesis of Corey bromoalkyne **20**. Reagents: a) CBr_4, PPh_3, DCM, –78 °C, 2h (85 %); b) K_2CO_3, MeOH, 35 °C, 3h, (85 %); c) TBAF·$3H_2O$, DMF, 60 °C, 2h, (60 %).

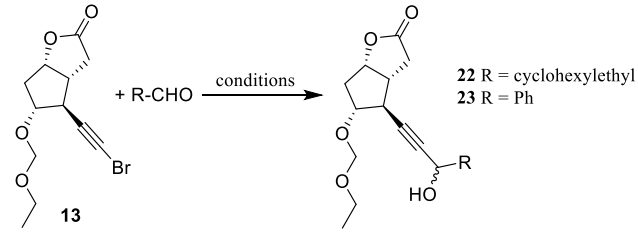
Lactone diol (**17**), which was kindly provided by Cayman Pharma, was converted into dibromoalkene **18** under Corey-Fuchs conditions. The use of TBAF as base seems as an appropriate choice for the structure of molecule **18**. However, due the instability of PPB group under dehydrohalogenation conditions, it was initially necessary to hydrolyze the protecting group. Unprotected dibromoalkene **19** could then undergo dehydrohalogenation in the presence of TBAF·H_2O in

DMF at 60 ºC, affording the desired bromoalkyne **20** in 60 % yield. With this protocol Corey bromoalkyne **20** was obtained in approximately 45 % yield from Corey aldehyde **17** in just 3 steps. Protection of **20** with several groups afforded compounds **13** and **21a-c** which could then be used according convenience.

Synthesis of racemic propargyl alcohol from protected Corey bromoalkyne

After synthesis of the appropriately protected Corey bromoalkyne, the preparation of propargyl alcohol was attempted. The transformation is a connection between molecule **13** and either benzaldehyde (as a readily available aldehyde) or the non-commercial intermediate 3-cyclohexylpropanal (**3**). **Table 3** resumes the conducted attempts for the alkynylation of Corey bromoalkyne **13**.

Table 3 – Conditions and results of alkylation with Corey bromoalkyne **13**.

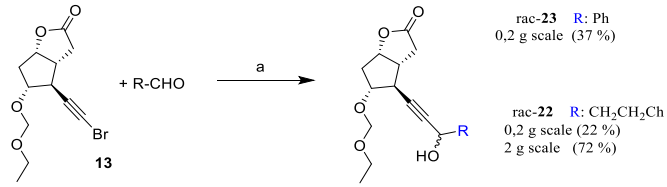


Entry	Starting material	R	Conditions	Expected product	Yield (%)	Terminal alkyne 2c (yield %)
1	**13**	Ph	$Ti(OiPr)_4$, *i*Pr-MgCl, TFH, –80 to –30 °C, 4h [17]	**23**	47	20
2		-CH_2CH_2Ch (**3**)	$Ti(OiPr)_4$, *i*Pr-MgCl, TFH, –80 to –30 °C, 4h [17]	**22**	-	-
3		Ph	$ZnEt_2$, toluene, rt, 5h	**23**	-	-
4		-CH_2CH_2Ch (**3**)	$ZnEt_2$, PPh_3, DCM, rt, 2h[16]	**22**	-	detected

Unfortunately, the reaction between compound **13** and aldehyde **3** did not proceed under the described conditions. And once more it was not possible to prepare desired propargyl alcohol.

Synthesis of Alfaprostol Key Intermediate Ynol via Br/Mg Exchange

After first attempts failed, Corey bromoalkyne **13** has been used in the preparation of alfaprostol ynol intermediate *via* Br/Mg exchange. From previous work, it was possible to conclude that the use of *i*-PrMgCl was able to activate the bromoalkyne terminal. Nucleophilic addition of activated **13** to selected aldehydes was tested. Small scale reaction (200 mg of **13**) with benzaldehyde provided ***rac*-23** (racemic mixture of C15) in 37 % yield. The same protocol was applied using 3-cyclohexylpropanal (**3**) and afforded the desired alfaprostol intermediate ***rac*-22** (racemic mixture of C15) in 22 % yield (**Scheme 6**).[20] These preliminary results were only the inspiration and it was a pleasure to later find out that when the reaction was performed in larger scale (2.00 g of **13**), compound ***rac*-22** was isolated in 72 % yield.



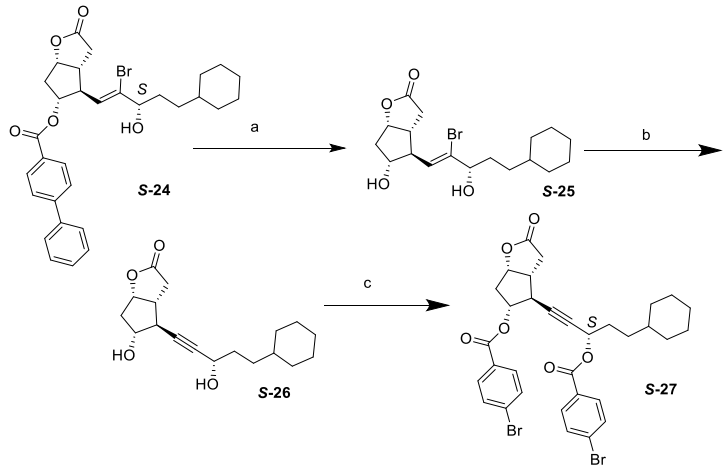
Scheme 6 – Novel approach to synthesis of alfaprostol intermediate using Br/Mg-exchange ***rac*-22**. Reagents: a) *i*-PrMgCl, THF, –78 °C, 30 minutes.

Stereoselective study of alkynylation via Br/Mg Exchange

In order to make the stereoselective study of the previous reaction it was first necessary to prepare C15-*R* and *S* standards. These standards were analysed via HPLC (using a chiral column Chiralpak AD-H) and allowed the identification of further ratio of enantiomers. The

preparation of standards was made using either enantiomeric pure samples provided by Cayman Pharma or using commercially available reducing agents as seen in **Scheme 7** and **Scheme 8**.

Pure ***S*-24** has been provided by Cayman Pharma and used to prepare standard ***S*-27** in 3 steps (**Scheme 7**). Deprotection of compound ***S*-24** provided free diol ***S*-25** which underwent dehalogenation in the presence of NaH to afford the desired triple bond moiety (***S*-26**). Protection of ***S*-26** with *p*-Br-Bz group afforded ***S*-27**. Compound ***S*-27** was identified using chiral HPLC-UV as one single peak. Compound ***S*-27** was isolated as a single crystal and it was possible to measure its X-ray. **Figure 26** shows the ORTEP view of ***S*-27.**



Scheme 7 – Synthesis of standard ***S*-27**. a) K_2CO_3, MeOH, 35 °C, 2h (62 %); b) NaH, THF:DMF (1:1), 2h (87 %); c) *p*-Br-Bz-Cl, DMAP, Et_3N, DCM, rt, 10 minutes (70 %).

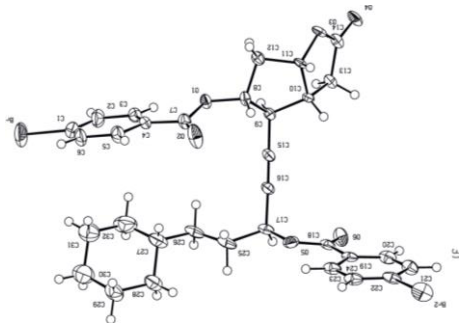
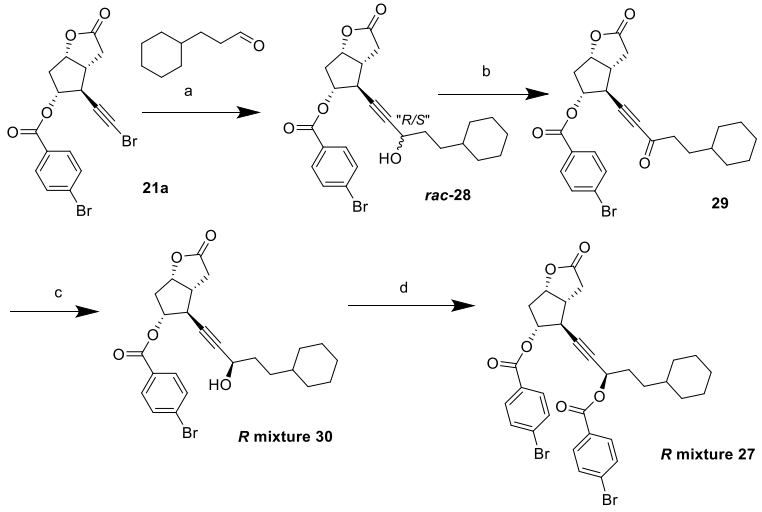


Figure 26 – ORTEP view of compound ***S*-27.**



Scheme 8 – Preparation of *R*-enriched mixtures by the use of (–)DIP-Cl. Reagent: a) *i*-PrMgCl, THF, –78 °C, 30 minutes; b) DMP, DCM, rt, 3h, (92 %); c) (–)DIP-Cl, THF, 0 °C to rt, overnight (93 % , S/R ratio 20/80); d) *p*-Br-Bz-Cl, DMAP, Et_3N, DCM, rt, 10 minutes (60 % , S/R ratio 26/74).

Starting from the previously mentioned **21a** (including a *p*-Br-Bz PrGr), ***rac*-28** was prepared followed by oxidation with DMP to obtain ketone **29**. Ketone **29** was then reduced using (–)-DIP-Cl in order to obtain mixture **30** with one isomer in excess. After protection of

compound **30** it was possible to isolate the mixture **27**. HPLC analyses of this mixture shown a predominance of *R* isomer comparing with *S*.

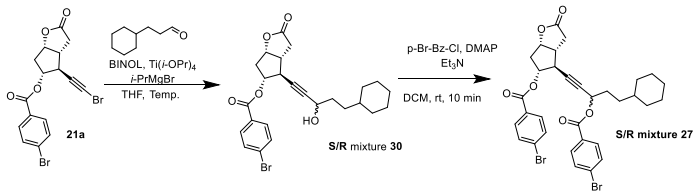
At this point the goal was the development of a strategy which could influence the outcome configuration of the C15 alcohol. The use of a chiral ligand is of common use in organic chemistry.

At the beginning two chiral ligands were tested; more specifically *N*-methylephedrine (NME) and 1,1′-bi-2-naphthol (BINOL). While NME failed to influence the outcome configuration of C15 (a racemic mixture was obtained), the use of (*S*)-BINOL afforded an excess of *R* isomer (S/R ratio 34:66). Having the previous results as starting point, the influence of BINOL in the reaction system was investigated. Parameters such as solvent, temperature, the use of additives and the use of other similar ligands have been studied. **Table 4** resumes the most significant attempts and the resulting influence to the stereochemistry of the system.

As a result, the most suitable solvent was found to be THF. The use of excess of BINOL proved to be the most effective (exp. m and r). Two equivalents of titanium(IV) isopropoxide (Ti(iOPr)4) as a reaction additive was found to be essential (exp. g-i). The ideal reaction temperature was determined to be –78 °C.

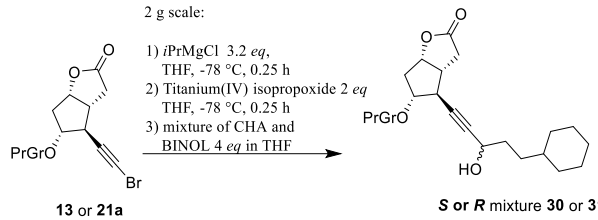
In order to conclude the stereoselectivity study, it was decided to make a scale up of the best conditions previously achieved. This way it was aimed to make a final confirmation of the yield and the stereoselectivity. As previously attempted, 2 grams of starting bromoalkyne were used. **Scheme 9** shows the scale-up conditions used for preparation of ***S*** or ***R*** **mixtures 30** and **31**. The results obtained during the scale-up are summarized in **Table 5**.

Table 4 - Results of stereoselective influence in the formation of alfaprostol ω-chain



Entry	BINOL (type - equiv[a])	Ti(*i*-OPr)$_4$ (equiv[a])	Temp. (°C)	Ratio (*S*/*R* mixture **30**)[b]	Ratio (*S*/*R* mixture **27**)[b]
1	*S* - 2	0	–78	40:60	-
2	*S* - 1	0	–78	40:60	-
3	*S* - 0,4	0	–78	45:55	-
4[c]	*S* - 1	0	–20[d]	50:50	-
5[e]	*S* - 1	2	–78	53:57	-
6	*S* - 1	0	0-rt	NF	-
7	*S* - 1	2	–78	34:66	-
8	*S* - 1	1	–78	40:60	-
9	*S* - 1	0,5	–78	46:54	-
10	*S* - 2	2	–78	30:70	-
11	*S* - 1	2	–50	NF	-
12	*S* - 1	2	–100	48:52	-
13	*S* - 4	2	–78	25:75	-
14	1[g]	2	–78	50:50	-
15	0,4[h]	2	–78	NF	-
16	*R* - 1	2	–78	60:40	-
17	*R* - 1	0	–78	64:36	63:34
18	*R* - 4	2	–78	82:18	82:18

[a]Equiv. relative to 4. [b]Measurement by chiral HPLC. [c]Starting material not soluble at lower temperatures. [d]Et_2O used has solvent at –20°C (starting material not soluble at lower temperatures). [e]toluene used has solvent [f]Using 2-(dimethylamino)ethyl ether instead of Ti(*i*-OPr)$_4$.[21] [g](S)-Vanol [h](*S*)-(–)-3-3′-bis(3,5-bis(trifluoromethyl)phenyl)-1,1′-bi-2-naphthol. NF No final compound observed.



Scheme 9 – Scale-up preparation of enriched **mixture 32** and **35** using optimized conditions described in **Table 4, entry 13** and **18**.

As shown in **Table 5** yields from scale-up reactions differed from 15 to 28 %. These yields, although higher than the obtained in small scale, are still far from the 72 % obtained for the non-mediated reaction. In question of stereoselectivity, the reactions have proved their reproducibility, and similar ratios to the ones obtained in the small-scale protocols, where achieved.

Table 5: Binol mediated asymmetric alkylation of Corey lactone derivative in 2g scales reaction

Entry	Starting material	BINOL	Yield (%)	*S:R* Ratio (mixture 30[a] or 31)[b]
1	**13**	*S*	28	28:72
2	**21a**	*S*	22	20:80
3	**21a**	*R*	15	80:20

Legend: **mixture 30** was functionalized with *p*-Br-Bz group; b) measurement by chiral HPLC.

As conclusion, it was possible to influence the stereoselectivity of the alcohol formed during the alkylation of aldehyde **10** to bromoalkynes **13** and **21a**. However, a significant reduction in yield of targeted intermediates **mixtures 30** and **31** was observed.

CONCLUSION

In this thesis is described the preparation of several valuable intermediates for the synthesis of PG and their synthetic analogues. A special effort was dedicated to the development of an adequate methodology for the preparation of the propargyl alcohol connection present in alfaprostol molecule.

Two main synthetic approaches were found to provide the desired intermediates for the synthesis of alfaprostol. Stille coupling provided propargyl ketone **16f** which can easily be reduced to afford alfaprostol omega chain. On the other side the use of Corey bromoalkynes (**13** and **21a-c**) allowed the preparation of intermediates Ynol such as ***rac*-22** *via* Br/Mg exchange. ***Rac*-22** was prepared in a one-pot synthesis between Corey bromoalkyne **13** and an appropriate aldehyde, as it was our initial goal. The direct use of Corey alkynes **2a-c** in either a Sonogashira coupling or as starting material for alkylation, was not proved to be successful.

In an extension of the previous study, the enantioselective alkynylation of bromoalkynes **13** and **21a** was evaluated. As before, the Br/Mg exchange strategy was used, however the addition of different chiral ligands and additives was taken in consideration. The influence of the alkylation stereoselectivity was performed and desired intermediates prepared with either an excess of *S* or *R* isomer (*S* or *R* mixtures **30** or **31**). However, due the drop in the overall yield (from 72 to 20 %) as well as the difficulty in the separation of both isomers by conventional techniques, the industrial application of this method is unlike.

The application of Corey alkynes and bromoalkynes in the synthesis of other PG with a triple bond in their skeleton is of much value and most likely deserves further investigation. For the synthesis of Corey bromoalkynes **13** and **21a-c** two strategies were described. In a first attempt the bromination of Corey alkynes was an easy methodology when alkynes are available. Furthermore, the preparation of Corey bromoalkynes via Corey Fuchs reaction followed by dehalogenation with TBAF is a valuable technique to directly prepare bromoalkynes from commercially available Corey diol.

Regarding the synthesis of PG, an intense literature search has been made and is presented in the introduction of this thesis. A special focus has been given to the synthesis of 13,14-dehydroPG. Due the structural differences, this group of PG requires a special synthetic approach for the introduction of the omega chain. However, from our search it was revealed that the information about their synthesis was mainly fragmented and sometimes included in long papers focus on the synthesis of general PG. Thus, a structured review on the topic as a consequence of the literature search entitled "Synthesis of 13,14-Dehydro-prostaglandins Synthetic Analogues: A Review" has been published by our group.[22]

All compounds prepared in the basis of this thesis have been fully characterized. NMR, Maldi-TOF and Elemental Analysis have been used as basic tools for characterization. When necessary, HPLC, melting point and X-ray have also been used. Compounds **13**, **18**, **19**, **20** and **21a** have been reported before in the patents of the group however their single crystals presented in this thesis for the first time. Furthermore, compounds ***S*-27** have been reported for the first time in question of synthesis and X-ray analyses.

The results of this thesis were presented in several domestic and international scientific conferences and have been published in 3 scientific publications (two experimental and one review).

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LIST OF STUDENT PUBLICATIONS

Publications related with the dissertation thesis:

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