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A Convenient Synthesis of the Beraprost Intermediate: A Useful Method for Introducing a C3 Unit at the Benzyl Position

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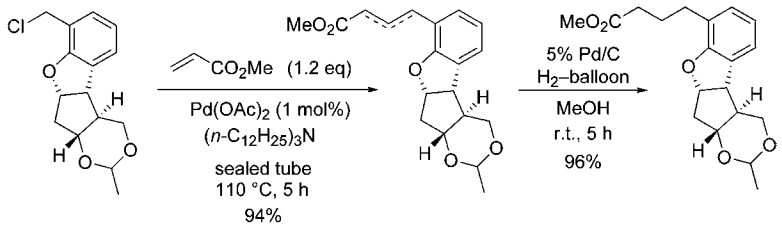
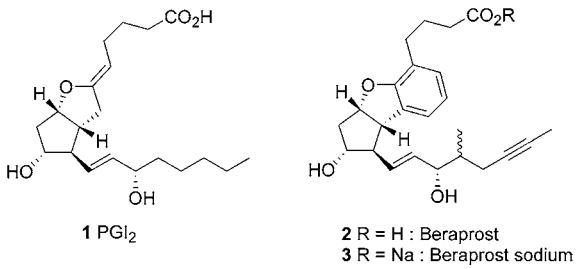
ABSTRACT



The Heck reaction is a more efficient and reliable method than previous ones for introducing a C3 unit at the benzyl position for the synthesis of Beraprost. Especially, trialkylated long-chain amines such as $(n\text{-}C_8H_{17})_3N$ and $(n\text{-}C_{12}H_{25})_3N$ resulted in good yields. This development will be used for the industrial synthesis of Beraprost.

Prostacyclin (PGI_2; **1**) is a naturally occurring bicyclic tetrahydrofuran that acts both as a potent vasodilator and an inhibitor of platelet aggregation.[1,2] In light of these biological effects, it was considered for use as a drug for treating thromboembolic disorders. However, its clinical application was eventually compromised by its poor stability and rapid loss of activity in aqueous solution, which limited its mode of administration to intravenous injection.[3]

Beraprost (**2**) is an orally active antithrombotic prostacyclin derivative that has been developed by Toray Industry.[4] It is a more stable and less cytotoxic compound than other PGI_2 analogues and its sodium salt **3** is now in clinical use as an anti-platelet drug. Ever since **3** was introduced for clinical use its effectiveness against other disease states has been investigated.



1 PGI_2

2 R = H : Beraprost
3 R = Na : Beraprost sodium

Figure 1. PGI_2 and its analogues.

The published synthesis of **2** is achieved by using a Grignard reaction with the benzyl chloride derivative **4a**

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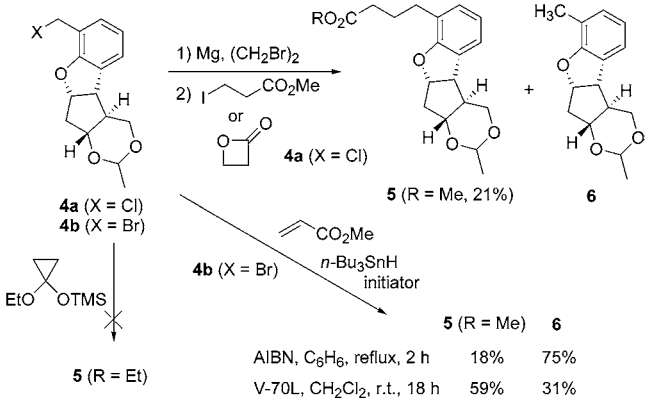
Scheme 1. C3-Unit Insertion to Benzyl Halides



(Scheme 1).[4d] Although this is a very simple method for introducing the C3 unit at the benzyl position in one step, the yield is a problem. When we tried this reaction, the major products were the protonated compound **6**, dimer, and benzyl alcohol with the target adduct **5** being obtained in only 21% yield. Other conditions investigated which included using a zinc reagent also failed to give **5** in good yield.

Therefore, we investigated alternative methods for introducing the C3 unit at the benzyl position of **4**.

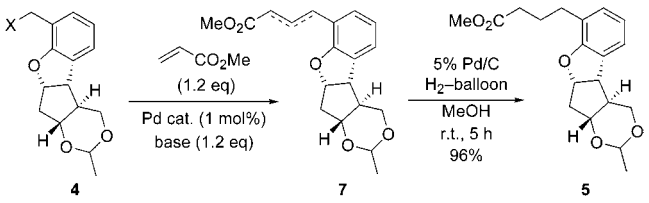
We first attempted an intermolecular radical reaction between **4b** and methyl acrylate. When AIBN was used as a radical initiator, the reduced compound was mainly obtained. In the case of V-70L, which is known as a radical initiator at low temperature,[5] the target adduct **5** was obtained in 59% yield when *n*-Bu_3SnH was slowly added.

Next, we investigated [(1-ethoxycyclopropyl)oxy]trimethylsilane[6] for chain elongation. This reagent is a synthetic equivalent of the β-anion of propionate. However, all our attempts to make this elongation work failed.

Another reaction that has been routinely used for introducing a C3 unit onto a halobenzene is the Heck reaction. However, there are only a few reports of the Heck reaction being applied to benzyl halides after its development by Heck in 1972.[7] This notwithstanding, we now show that the Heck reaction is a reliable method for introducing a C3 unit at the benzyl position of the benzyl chloride derivative **4a** in high yield.

Our first trial with **4a**, $Pd(OAc)_2$, and *n*-Bu_3N in DMF resulted in multiple spots (Table 1, run 1). The desired coupling product **7** could, however be obtained in good yield when this reaction was conducted in a sealed tube (run 2). $Pd(OAc)_2$ gave better results than $Pd(dba)_2$ but there was no improvement with the addition of $Cu(OAc)_2$ (runs 3 and 4). Trialkylated long-chain amines such as $(n\text{-}C_8H_{17})_3N$ and $(n\text{-}C_{12}H_{25})_3N$ were better than *n*-Bu_3N (runs 5 and 6). These conditions did not need a solvent such as DMF or CH_3CN. Because the quantity of the amine increased with the increasing length of the alkyl chain for the same equivalent amount, these amines were used as the reaction solvent. Interestingly, the bromo compound **4b**, which is less stable than the chloro one **4a**, decomposed under these reaction conditions (run 7).

Table 1. Heck Reaction of Beraprost Intermediate (**4**)



run	X	Pd cat.	base	additive	solvent	time, h	**7**, %
1	Cl	$Pd(OAc)_2$	*n*-Bu_3N	none	DMF	15	—[a]
2	Cl	$Pd(OAc)_2$	*n*-Bu_3N	none	DMF	5[b]	83
3	Cl	$Pd_2(dba)_3$	*n*-Bu_3N	PPh_3	DMF	15[b]	21
4	Cl	$Pd(OAc)_2$	*n*-Bu_3N	$Cu(OAc)_2$	DMF	5[b]	64
5	Cl	$Pd(OAc)_2$	$(n\text{-}C_8H_{17})_3N$	none	none	5[b]	86
6	Cl	$Pd(OAc)_2$	$(n\text{-}C_{12}H_{25})_3N$	none	none	5[b]	94
7	Br	$Pd(OAc)_2$	$(n\text{-}C_{12}H_{25})_3N$	none	none	5[b]	0

[a] Many products were obtained. [b] Pressure tube was used.

Catalytic hydrogenolysis of the Heck adduct on 5% Pd/C in MeOH gave the key Beraprost intermediate (**5**) in 96% yield.

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Supporting Information Available: Experimental procedure and full characterization for compound **5** and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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