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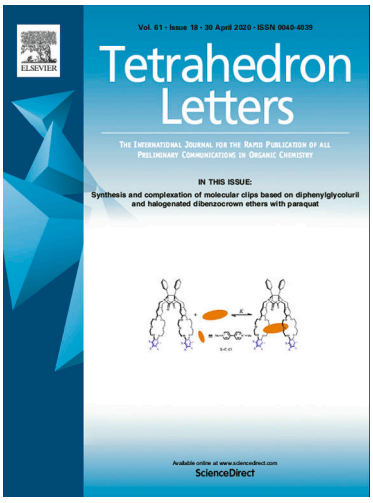

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An alternative synthesis for iloprost via a key bicyclic aldehyde intermediate

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ABSTRACT

An alternative synthesis for iloprost has been accomplished in 13 steps via a convergent synthesis starting from commercially available (-)-Corey lactone diol. The syntheses employ a new and key chiral bicyclic aldehyde (**4**) intermediate, which is primed for attachment of the required α-side chain and ω-side chain.

1. Introduction

Prostacyclin (**1**) (**Fig. 1**), which plays an important role in the vascular and central nervous system and in inflammation, has attracted the attention of chemistry, biology, and medicine[1-3]. Unfortunately, its medicinal application is hampered by the inherent chemical and metabolic instability[4]. Therefore, intensive efforts have been made to find new and stable analogues as alternatives to the natural prostacyclin[5]. Iloprost (**2**) (**Fig. 1**) is a biologically highly potent and chemically stable alternative that has been developed by Bayer Schering Pharma[6]. Currently, iloprost has already been marketed as Ilomedin for the treatment of severe thrombo-angiitis obliterans and as Ventavis for the treatment of pulmonary arterial hypertension[7-11].

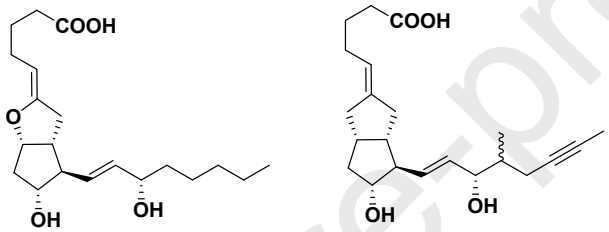
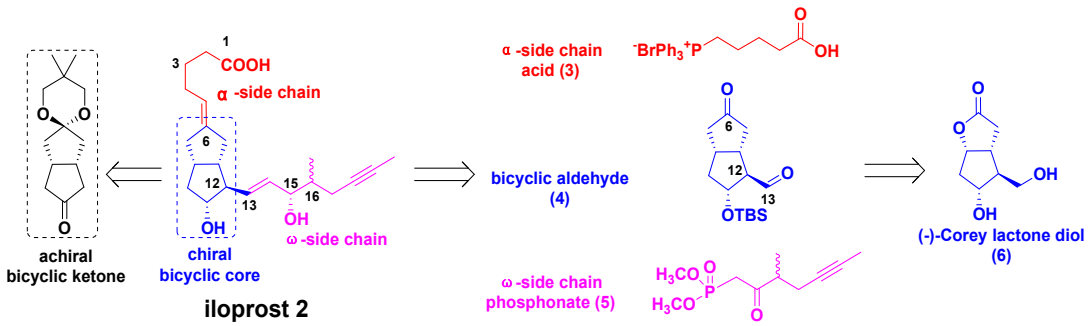


Figure 1. Structures of prostacyclin (**1**) and iloprost (**2**).

Structurally, the iloprost (**2**) consisted of three main parts: α-side chain, chiral bicyclic core and ω-side chain (**Scheme. 1**). Among them, the building blocks of α-side chain and ω-side chain can be commercially purchased or easily synthesized in a few steps[12], while the construction of the appropriately substituted chiral C6-C13 bicyclic core is the key-step of the iloprost synthesis. Previously, one of the most attractive synthetic methods to prepare the chiral C6-C13 bicyclic core mainly started from achiral bicyclic ketone via a enantioselective synthesis to establish the enantiopure functional groups at C12 of iloprost[13-15]. Although these synthetic methods are imaginative, some drawbacks still remained, such as harsh conditions (-100°C), expensive chiral reagents, lengthy synthetic sequences. Thus, it would be highly interesting to have an easy access to chiral C6-C13 bicyclic core, which allows an efficient and alternative synthesis for iloprost (**2**).

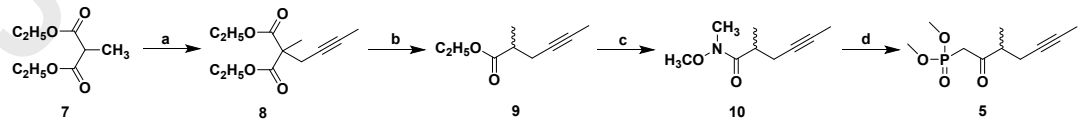


Scheme 1. Retrosynthetic analysis for iloprost (**2**)

2. Results and discussion

Our synthesis for iloprost (**2**) has the following key features (**Scheme 1**): (1) Retrosynthetically, iloprost was disconnected into three main parts: α-side chain acid (**3**), chiral C6-C13 bicyclic aldehyde (**4**) as a new and key intermediate and ω-side chain phosphonate (**5**). (2) Our synthetic method to prepare chiral C6-C13 bicyclic aldehyde (**4**) started from commercially available (-)-Corey lactone diol (**6**), which allowed an easy access to chiral bicyclic core. (3) We reported a short synthesis of iloprost in 13 steps.

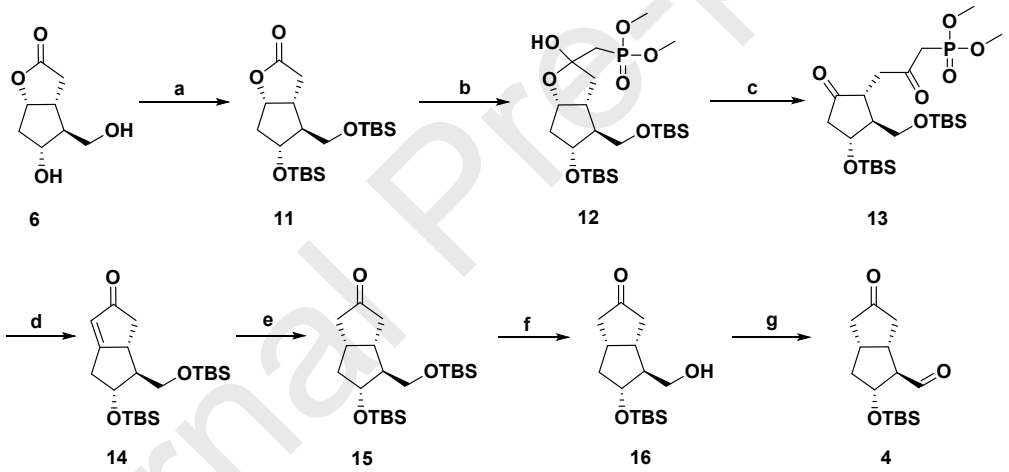
Initially, the synthesis of ω-side chain phosphonate (**5**) was carried out by the known procedures[12](**Scheme 2**). The alkylation of commercially available diethyl methylmalonate (**7**) with 1-bromobut-2-yne gave diester (**8**) in 91% yield. Then, diester (**8**) was subjected to high temperature (170°C) with LiCl to generate the monoester (**9**) in 78% yield, amidation of which with N,O-dimethylhydroxylamine hydrochloride provided the corresponding amide (**10**) in 91% yield. Reaction of amide (**10**) with dimethyl methylphosphonate in the presence of n-BuLi furnished the phosphonate (**5**) in 85% yield. Therefore, the ω-side chain phosphonate (**5**) was obtained in 55% overall yield over 4 steps.



Scheme 2. Preparation of ω-side chain (**5**). Reagents and conditions: (a) 1-bromobut-2-yne, *t*-BuOK, THF, 0°C, 30 mins, 91%; (b) LiCl, DMSO, H_2O, 170°C, 5 hrs, 78%; (c) N,O-dimethylhydroxylamine hydrochloride, isopropylmagnesium chloride, THF, -20°C, 30 mins, 91%; (d) Dimethyl methylphosphonate, n-BuLi, THF, -78°C, 3 hrs, 85%.

The synthesis of the key chiral bicyclic aldehyde (**4**), as depicted in **Scheme 3**,

commenced from commercially available and optically pure (-)-Corey lactone diol (**6**), which was silylated with TBSCl gave silyl ether (**11**) in 95% yield. The silyl ether (**11**) was treated with dimethyl methylphosphonate in the presence of n-BuLi afforded hemiketal (**12**) in 88% yield. A modified PCC oxidation of hemiketal (**12**) was performed to give the desired diketone (**13**) in 86% yield, which was subsequently cyclized by intramolecular Horner-Wadsworth-Emmons reaction to generate the enone (**14**) in 75% yield. The hydrogenolysis of enone (**14**) in the presence of 10% Pd/C provided octanone (**15**) in 90% yield. Subsequent treatment of octanone (**15**) with PPTS allowed selective removal of the TBS-protecting group to give alcohol (**16**) in 72% yield. The oxidation of alcohol (**16**) with oxidant DMP afforded the key chiral bicyclic aldehyde (**4**) in 75% yield. Therefore, the chiral bicyclic aldehyde (**4**) was obtained from (-)-Corey lactone diol (**6**) in 26% overall yield over 7 steps.

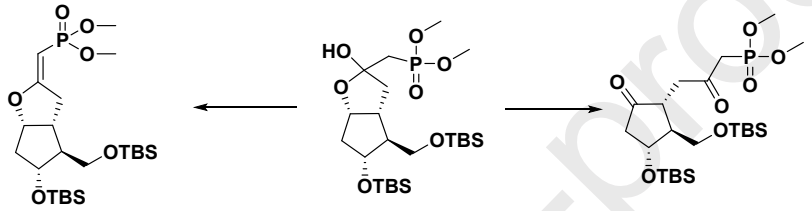


Scheme 3. Preparation of bicyclic aldehyde (**4**). Reagents and conditions: (a) TBSCl, imidazole, DCM, 0°C-40°C, 24 hrs, 95%; (b) Dimethyl methylphosphonate, n-BuLi, THF, -78°C, 3 hrs, 88%; (c) PCC, sodium propionate, DCM, reflux, 6 hrs, 86%; (d) K_2CO_3, 18-crown-6, toluene, 75°C, 6 hrs, 75%; (e) 10% Pd/C, HCO_2H, Et_3N, toluene, 85°C, 1 hr, 90%; (f) PPTS, EtOH, 25°C, 24 hrs, 72%; (g) Dess-Martin periodinane, $NaHCO_3$, DCM, 0°C-10°C, 3 hrs, 75%.

And, the reaction conditions from hemiketal (**12**) to diketone (**13**) was optimized in our lab. Firstly, the Collins condition of hemiketal (**12**) afforded the desired product (**13**) in 40% yield along with β-eliminated by-product (**13-BP**) in 40% yield following the previous method[16]. The main reason to generate **13-BP** was due to acidic condition of oxidation. So, a range of oxidants (DMP, PDC, and PCC) were screened and PCC was more efficient than the others (Table 1, entry 4). In order to reduce the

acidic condition, several bases were investigated and the sodium propionate showed the best efficiency, which could give diketone (**13**) in 86% yield (Table 1, entry 6). Subsequently, the screening of the amount of oxidant and base revealed that decreasing the amount of PCC and sodium propionate to 4.0 equivalents had no influence on the isolated yield (Table 1, entry 8), while further decreasing the amount to 2.0 equivalents led to lower yield (Table 1, entry 9). Therefore, 1.0 eq. of hemiketal (**12**), 4.0 eq. of PCC, and 4.0 eq. of sodium propionate were selected as the optimal reaction conditions.

Table 1. Optimization for the synthesis of intermediate (**13**).



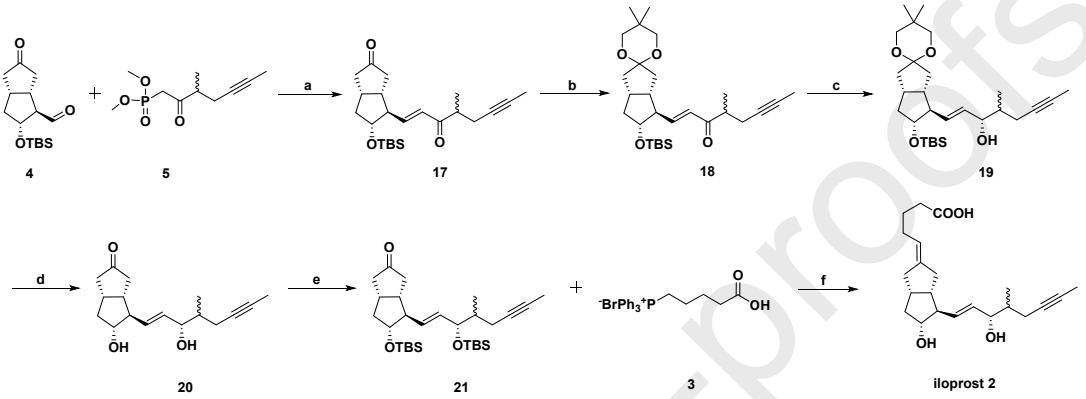
13-BP **12** **13**

Entry	Oxidant (eq.)	Base (eq.)	Yield (%)[d]
1	Collins (6.0)	--	40%
2	DMP[a] (6.0)	--	38%
3	PDC[b] (6.0)	--	45%
4	PCC[c] (6.0)	--	60%
5	PCC (6.0)	Sodium acetate (6.0)	78%
6	PCC (6.0)	Sodium propionate (6.0)	86%
7	PCC (6.0)	Sodium Butyrate (6.0)	82%
8	PCC (4.0)	Sodium propionate (4.0)	86%
9	PCC (2.0)	Sodium propionate (2.0)	45%

[a] DMP: Dess-Martin periodinane; [b] PDC: Pyridinium dichromate; [c] PCC: Pyridinium chlorochromate; [d] Isolated yield.

With two key fragments (**4** & **5**) in hand, we turned to the Horner-Wadsworth -Emmons reaction as a mean of constructing α,β-unsaturated ketone (**17**). Detailedly, the ω-side chain phosphonate (**5**) was treated with NaH and to this was added the chiral bicyclic aldehyde (**4**) to afford α,β-unsaturated ketone (**17**) in 78% yield. The protection of α,β-unsaturated ketone (**17**) with 2,2-dimethylpropane-1,3-diol gave intermediate (**18**) in 90% yield, which was converted to its corresponding enol (**19**) through a diastereoselective reduction with R-(+)-Me-CBS with the yield of 75%[17]. The deprotection of enol (**19**) was achieved with p-TsOH to generate diol (**20**) in 90%

yield, which was further protected with TBSCl to generate silyl ether (**21**) in 85% yield. Finally, the Wittig olefination and silyl deprotection of silyl ether (**21**) with commercially available α-side chain acid (**3**) delivered a mixture of iloprost (**2**) and its Z isomer in a ratio of 65:35, the separation of which by preparative HPLC afforded iloprost (**2**) in 31% yield (**Scheme 4**). Thus, we have achieved an alternative synthesis for iloprost **(2)**.



Scheme 4. Preparation of iloprost (**2**). Reagents and conditions: (a) NaH, THF, 25°C, 1 hr, 78%; (b) 2,2-dimethylpropane-1,3-diol, PPTS, toluene, reflux, 45 min, 90%; (c) R-(+)-Me-CBS, borane dimethyl sulfide, DCM, -5 °C-10°C, 30 mins, 75%; (d) p-TsOH·H_2O, acetone, H_2O, 30°C, 12 hrs, 90%; (e) TBSCl, imidazole, DCM, 0°C-40°C, 24 hrs, 85%; (f) KHMDS, THF, 25°C, 24 hrs, 31%.

3. Conclusion

In summary, an alternative synthesis for iloprost (**2**) was achieved in 13 steps via a convergent synthesis starting from commercially available (-)-Corey lactone diol (**6**). We have prepared a new and key chiral bicyclic aldehyde (**4**) intermediate, which was subsequently elaborated to iloprost (**2**). To the best of our knowledge, the synthetic route presented here is shorter than those previously reported. Further studies on the application of this approach are in progress in our lab.

Acknowledgments

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Supplementary Material

Supplementary data associated with this article can be found. This material

includes detailed experimental procedures and analytical data (^{1}H NMR and MS & HRMS).

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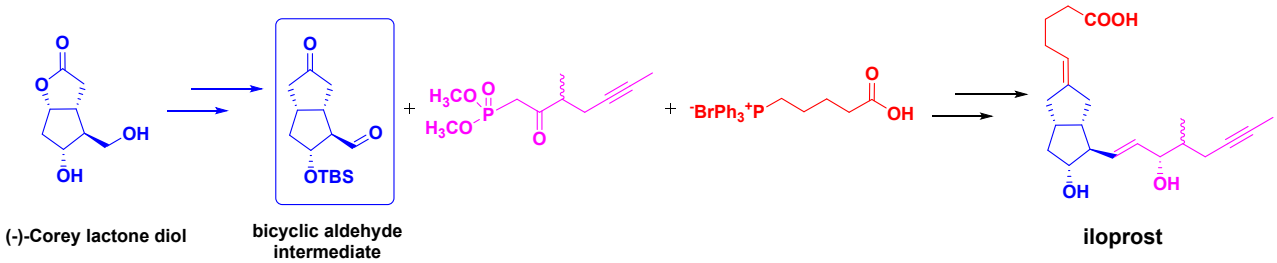
Graphical abstract



18.

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Highlights

- An alternative synthesis for iloprost is presented.
- The shortest synthetic approach for iloprost was achieved in 14 steps.
- The synthesis started from commercially available (-)-Corey lactone diol.

19.