Stereocontrolled Organocatalytic Synthesis of Prostaglandin $PGF_{2\alpha}$ in Seven Steps

Graeme Coulthard, William Erb, and Varinder K. Aggarwal

Nature **2012**, *489*, 278–281.

1. Introduction

1.1. Prostaglandin in Physiology

- Prostaglandins are a group of compounds that act as chemical messengers and regulate many physiological activities inside the body.
- Prostaglandin analogs are used as pharmaceuticals, but the syntheses require many steps.
  - Costs time and energy; generates a large amount of wastes.
- Many noble chemists developed syntheses of prostaglandins, including 17-step synthesis of the most complex prostaglandin $PGF_{2\alpha}$ (**1**) by E. J. Corey *et al*.[1]
  - From Corey lactone (**3**), the whole family of prostaglandins can be synthesized.
- Latanoprost (**2**), which is an analog of $PGF_{2\alpha}$, is manufactured using synthetic methods based on Corey's work and is a billion-dollar drug to treat glaucoma (緑内障).

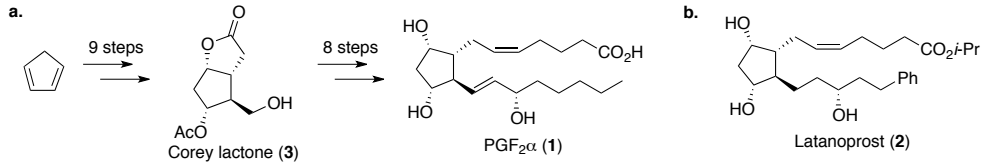


Figure 1. a. General outline of Corey's synthesis of $PGF_{2\alpha}$. **b.** Structure of Latanoprost.

1.2. Proline Organocatalyst

- First studied by B. List.[2]
- Enantioselective aldol reaction of aldehydes using proline was developed by MacMillan.[3]
- Cheap, non-toxic, and readily available in both enantiomers.
- Can be easily separated due to its solubility in water.

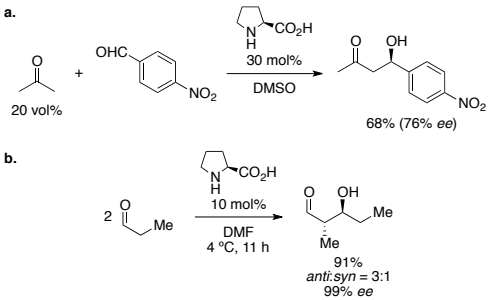


Figure 2. a. Proline-catalyzed asymmetric aldol reaction by List. **b.** Proline-catalyzed enatioselective aldol reaction of aldehydes by MacMillan.

1.3. Idea of This Work

- Synthesis of $PGF_{2\alpha}$ via bicyclic enal **5** (Figure 3).
  - Upper side-chain can be connected with Wittig reaction.
  - Lower side-chain can be stereoselectively added by Michael addition.
  - Bicyclic enal **5** can also be intermediates for other prostaglandins.
- Bicyclic enal **5** can be prepared through aldol cascade reaction of succinaldehyde (**6**) using proline as a catalyst.
  - Seemingly simple reaction, but actually very difficult.

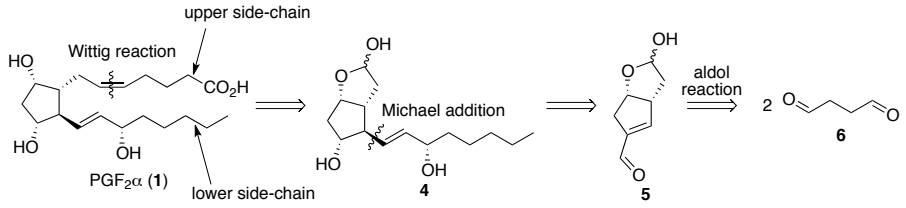


Figure 3. Retrosynthesis of $PGF_{2\alpha}$ (**1**).

2. Results and Discussion

2.1. Preparation of Key Bicyclic Enal Intermediate

- Simple treatment of succinaldehyde with proline did not derive the desired compound **5** but gave oligomeric material, due to many "potential pitfalls" (Figure 4).
  - Aldol **7** must form the less favored hemiacetal **8**.
  - However, aldol **7** can undergo further aldol reactions, leading to oligomers.

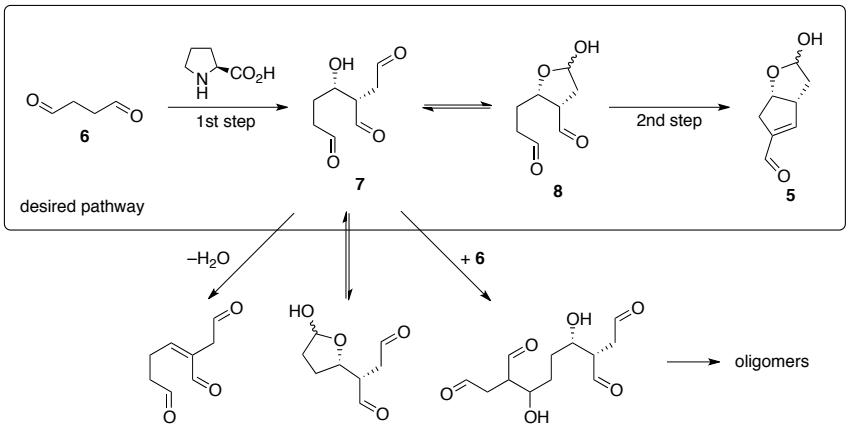


Figure 4. Potential pathway of proline-catalyzed aldol reaction of succinaldehyde (**6**).

- Model reactions were performed to determine which of the two aldol steps was the problem (Figure 5).
  - Model aldehyde **9** was converted into aldol product **10** in moderate yield; Aldehydes with a carbonyl group at the 4-position are suitable for the first step.
  - Low conversion of model dialdehyde **11** with proline.
  - $[Bn_2NH_2][OCOCF_3]$ was effective in conversion of **11**.

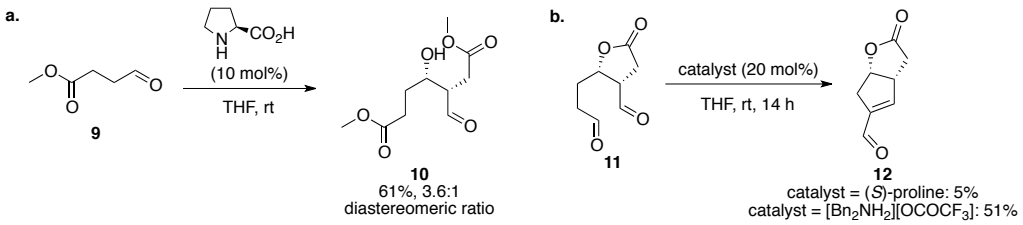
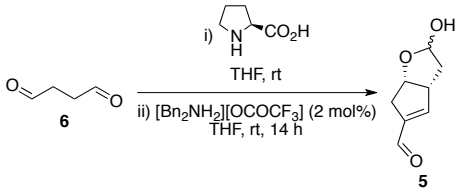


Figure 5. Model reactions. **a.** Model for first step. **b.** Model for second step.

- Authors developed a sequenced addition method of the two catalysts (Table 1).
  - Low yield due to oligomerization but high enantioselectivity (98% *ee*).
  - Timing to add the second catalyst depended on the amount of proline; must be added before trialdehyde **7** increases too much and oligomerization increases.
  - Removal of oligomeric material lead to relatively pure crude; easy work-up.
  - Diastereomeric isomers were consumed by oligomerization.
  - Can be conducted with low loading of catalyst and under high concentration (2 M).

Table 1. Effect of catalyst loading and time delay on yield.

(*S*)-proline (mol%)	Time (h)	Yield (%)
10	2	14
5	2	16
5	4	19
2	0	~2
2	4	10
2	6	16
2	10	20
2	24	20
1	24	18



'Time' refers to the time before $[Bn_2NH_2][OCOCF_3]$ was added.

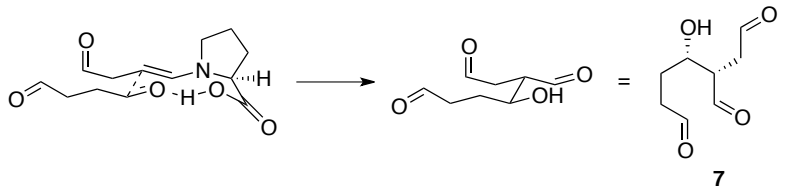


Figure 6. Proposed transition state structure that leads to the observed enantioselectivity.

2.2. Total Synthesis of $PGF_{2\alpha}$

- Using the developed preparation of bicyclic enal **5**, total synthesis of $PGF_{2\alpha}$ was performed (Figure 7).
  - Succinaldehyde (**6**) was prepared by heating 2,5-dimethoxytetrahydrofuran (**13**) in water.
  - Hemi-acetal **5** was subsequently converted into methoxy acetal **14**.
- Lower side-chain was added by conjugate addition of mixed vinyl cuprate **15** to methoxy acetal **14**, followed by treatment with TMSCl, leading to silyl enol ether **16**. Then controlled ozonolysis of **16** and treatment with $NaBH_4$ yielded alcohol **17**.
  - Mixed cuprate **15** is prepared with only 1 eq of vinyl substrate.
  - 2 steps with complete stereoselectivity.
- Upper side-chain was added to **17** by simultaneous deprotection of acetal and silyl ether followed by Wittig reaction with phosphonium salt **18**.

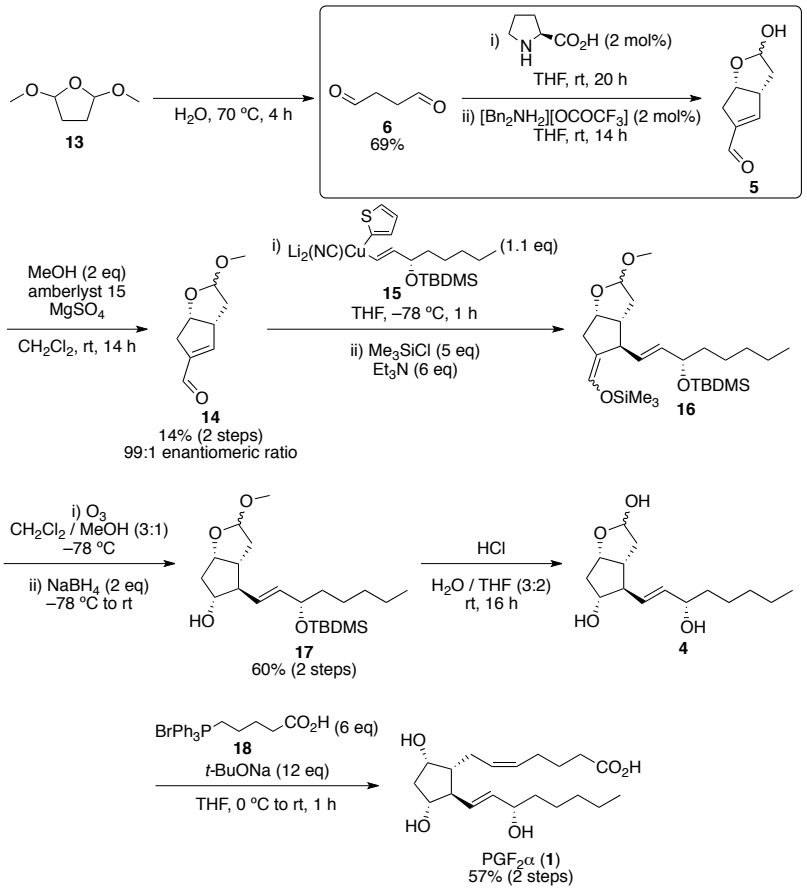


Figure 7. Complete Synthesis of $PGF_{2\alpha}$

3. Conclusion

- Total synthesis of prostaglandin $PGF_{2\alpha}$ was achieved in 7 steps with a total yield of 3%.
  - Less time, energy, and waste compared to prior methods.
- Key step is organocatalytic aldol dimerization of succinaldehyde in high enantioselectivity.
  - Yield is low, but purification is easy and can be performed on multi-gram scale.
- Bicyclic enal **5** can be used as a cost-effective starting material for prostaglandin-based drugs and can lead to rapid exploration of other prostaglandin analogs.

4. References

1. Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675–5677.
2. List, B.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.
3. Northrup, A. B.; MacMillan D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798–6799.