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 $et$ $al.$
  - 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).

1.2. Proline Organocatalyst

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

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.
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.

- 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.
  - $[\text{Bn}_2\text{NH}_2][\text{OCOCF}_3]$ was effective in conversion of 11.

Figure 3. Retrosynthesis of PGF$_2$α (1).

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

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.

<table>
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<th>(S)-proline (mol%)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
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<tr>
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<td>14</td>
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</tr>
<tr>
<td>1</td>
<td>24</td>
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‘Time’ refers to the time before [Bn₂NH₂][OCOCF₃] was added.

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

2.2. Total Synthesis of PGF₂α

- Using the developed preparation of bicyclic enal 5, total synthesis of PGF₂α 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 NaBH₄ 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.
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