Enantioselective Synthesis of Pactamycin, a Complex Antitumor Antibiotic

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1. Introduction

1-1. Pactamycin

- Pactamycin **1** (*Figure 1*) was isolated from *Streptomyces pactum* var. *pactum* in 1961 by Argoudelis *et al*.[1].
- The bioactivity profile of pactamycin is notable; it displays antitumor property.
- However, pactamycin's therapeutic benefits have yet to be realized due to its high cytotoxicity.

  ➔ Reducing cytotoxicity is necessary for medicinal application.
- Genetic engineering studies have reignited its possibility for medicinal application; 7-deoxy– and 8''-hydroxy–derivatives displayed diminished cytotoxicity.[2]

  ➔ An efficient synthesis platform of pactamycin and its derivatives is needed.

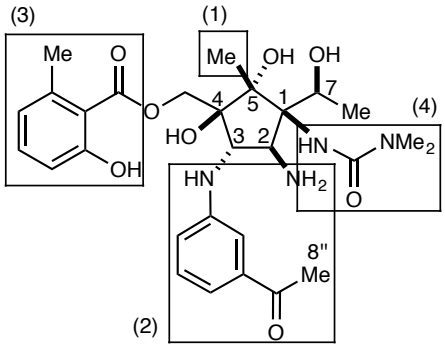
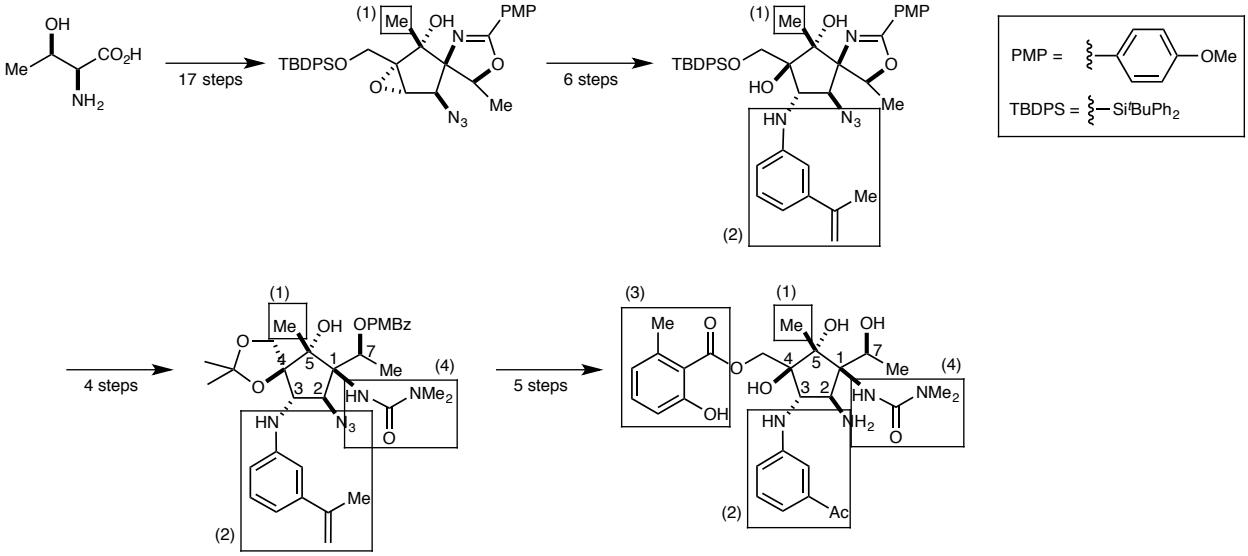


Figure 1. Pactamycin **1**. Four functional groups are attached to cyclopentane core.

1-2. Previous work

- 32-step total synthesis of pactamycin **1** was realized by Hanessian and co-workers (*Scheme 1*).[3]

Scheme 1. 32-step total synthesis of pactamycine by Hanessian and co-workers.



- Stepwise construction of functional groups.

  ➔ It is difficult to apply this methodology to the synthesis of other derivatives.

  ➔ A more practical synthesis solution is needed.

1-3. This work

- 15-step total synthesis of pactamycin was achieved.
- Modular construction (*Figure 2*); after the formation of the cyclopentanone structure (a core skeleton of pactamycin), four functional groups were introduced.
  - ➔ Easily applicable to the synthesis of other derivatives!

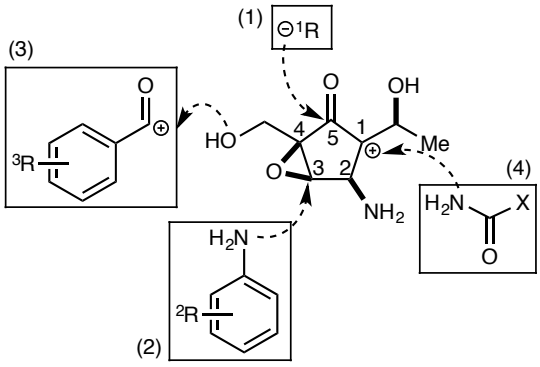


Figure 2. Modular introduction of functionality.

1-4. Author's strategy

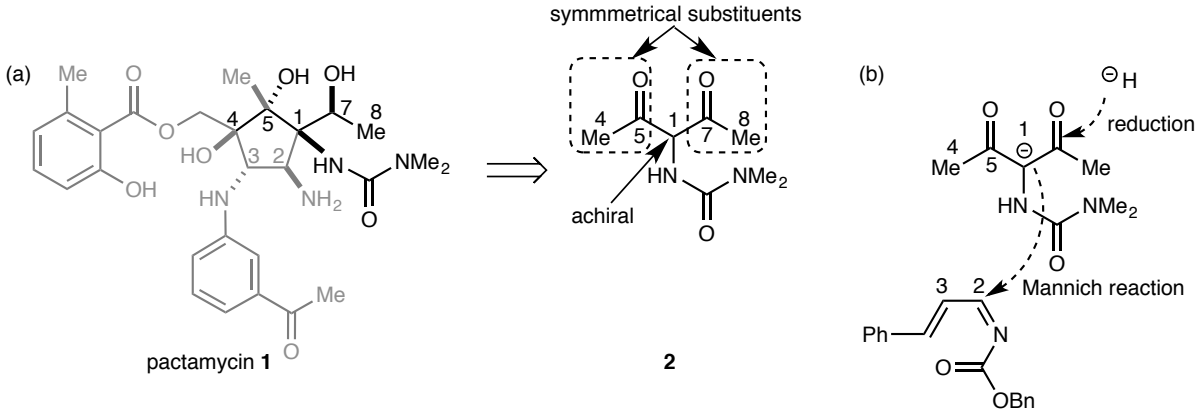


Figure 3. (a) Authors' choice of starting material. (b) Mannich addition and reduction steps.

- As a starting material for the asymmetric synthesis of pactamycin, authors chose a symmetrical α-ureido-2,4-pentanedione **2** as a starting material (***Figure 3***).
- In the C1–C2 bond construction (Mannich reaction), diastereoselectivity considerations are prevented due to the symmetrical methyl ketone substituents at C1 center.
  - ➔ They could focus on the enantioselective C2–amino incorporation in Mannnich reaction.
- Diastereoselective diketone monoreduction provides the cyclopentane skeleton of Pactamycin.

(1) Argoudelis, A. D., *et al*. *Antimicrob*. *Agents Chemother*. **1962**, *1962*, 191–197.

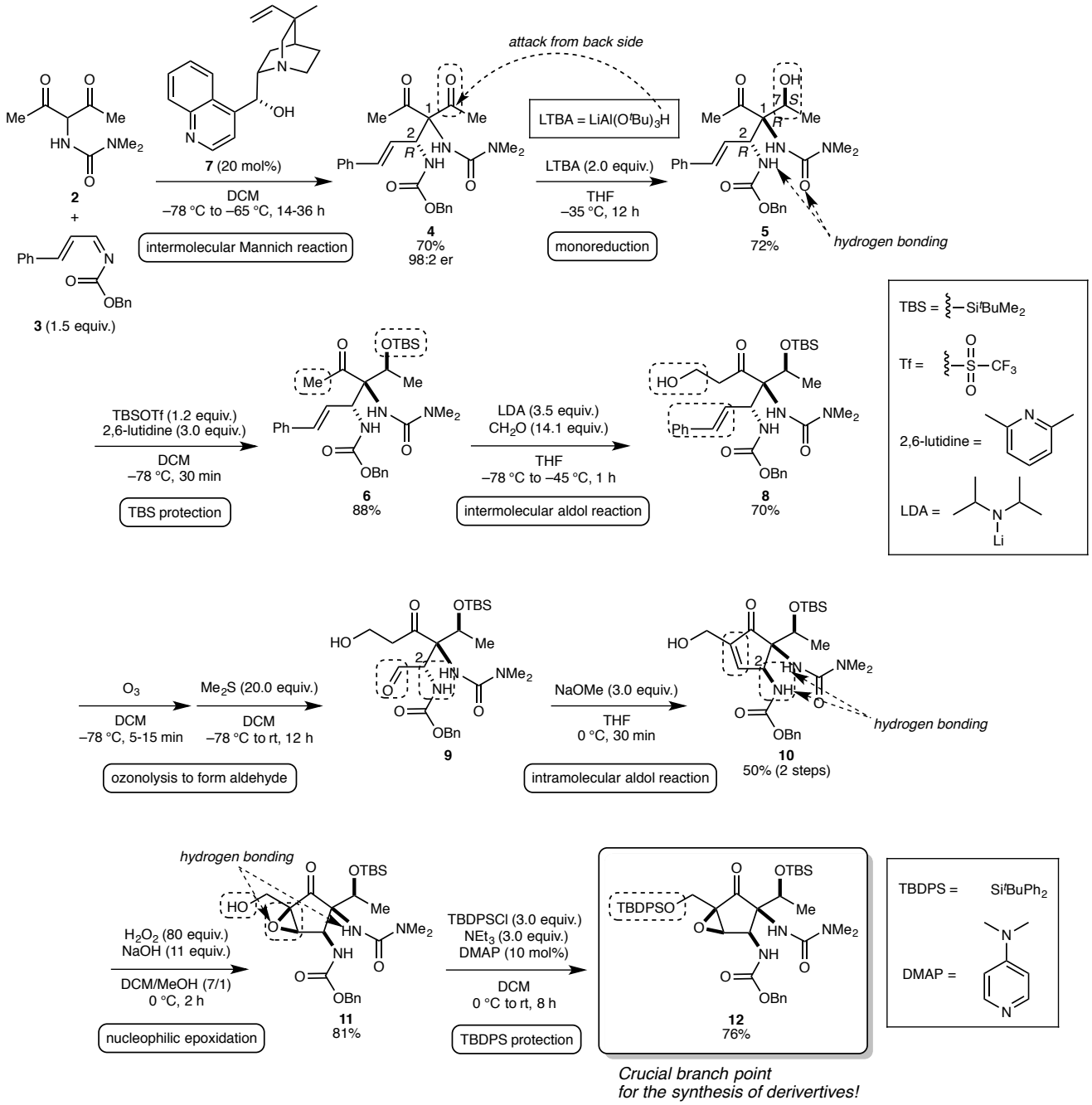
(2) Iwasaki, M., *et al*. *Antibiot*. **2012**, *65*, 169–171.

(3) Hanessian, S., *et al*. *J*. *Org*. *Chem*. **2012**, *77*, 9458–9472.

2. Results and Discussion

2-1. Formation of cyclopentanone core structure

Scheme 2. Formation of cyclopentanone core structure.



- **2→4** (intermolecular Mannich reaction): Mannich product **4** was obtained in (*R*) conformation at C-2 (98:2 enantiomeric ratio) because diketone and catalyst form complex (*Figure 4*).
- **4→5** (monoreduction): The monoreduction of diketone proceeded with high diastereoselectivity. (1*R*,2*R*,7*S*)-product was selectively obtained, probably because of the hydrogen bonding between N and H atoms and steric hindrance.

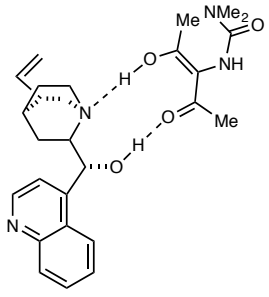
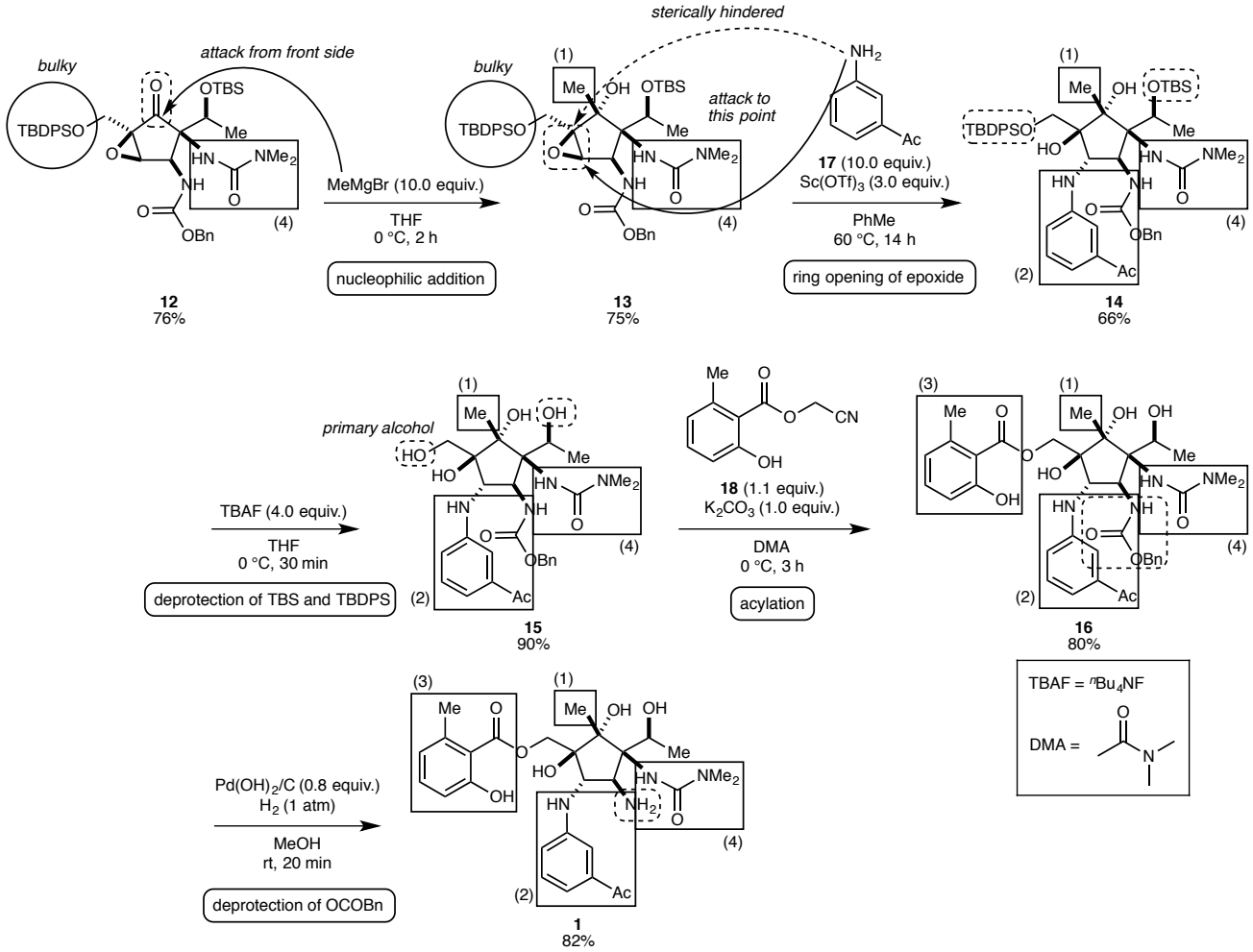


Figure 4. A complex formed by diketone **2** and catalyst **7**.

- **9→10** (intramolecular aldol reaction): C2 stereocenter was inverted during the cylization to form the correct C2 isomer, probably because the formed isomer can be stabilized by the hydrogen bonding between N and H atoms.
- **10→11** (nucleophilic epoxidation): Nucleophilic epoxidation proceeded with high diastereoselectivity, probably because of the hydrogen bonding between O and H atoms.

2-2. Modular introduction of functionality to complete the synthesis of pactamycin 1

Scheme 3. Modular introduction of functionality to complete the synthesis of pactamycin **1**.



- **12→13** (nucleophilic addition): Because of the sterically demanding TBDPS group, Grinard reagent attacks from the front side.
- **13→14** (ring opening of epoxide): Because of the sterically demanding TBDPS group, 3-acetylaniline **17** attacks the less hindered side of epoxide.
- **15→16** (acylation): Only a highly reactive primary alcohol was acylated.

3. Conclusion

- The authors achieved the total synthesis of pactamycin in 15 steps and 1.9% overall yield.
- The modular construction enables the synthesis and investigation of pactamycin derivatives.