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.*
- 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.°
    - An efficient synthesis platform of pactamycin and its derivatives is needed.

1-2. Previous work

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

*Scheme 1*. 32-step total synthesis of pactamycin 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.](image)

1-4. Author’s strategy

- As a starting material for the asymmetric synthesis of pactamycin, authors chose a symmetrical α-ureido-2,4-pentanediione 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 Mannich reaction.
- Diastereoselective diketone monoreduction provides the cyclopentane skeleton of Pactamycin.

![Figure 3.](image)

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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. (1R,2R,7S)-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 cyclization 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.