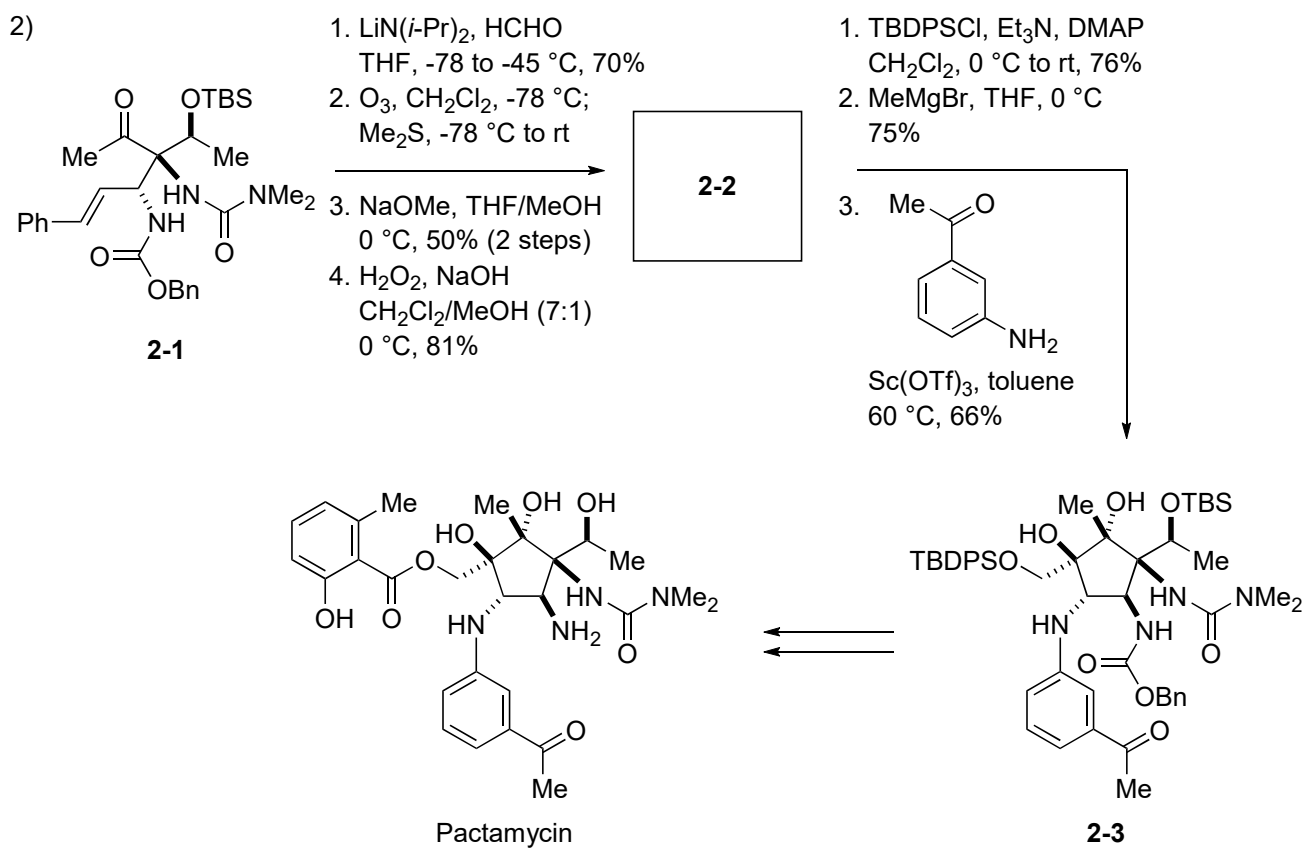
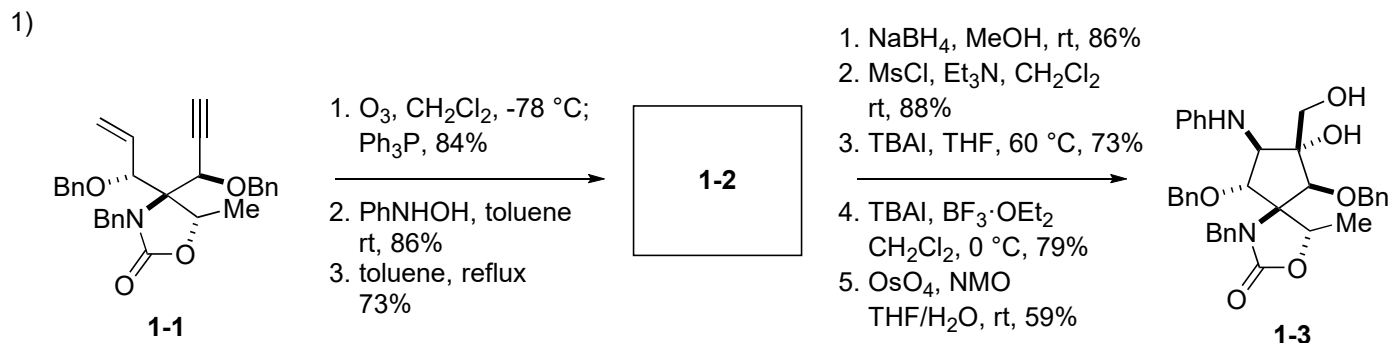


# Problem Session (3)

2016.05.21 Hideyuki Sawada

Please fill in the blanks and provide the reaction mechanisms.



# Problem Session (3) -Answer-

## Topic: Total synthesis of Pactamycin

2016.05.21. Hideyuki Sawada

### 0. Introduction.

#### 0-1. Details of pactamycin

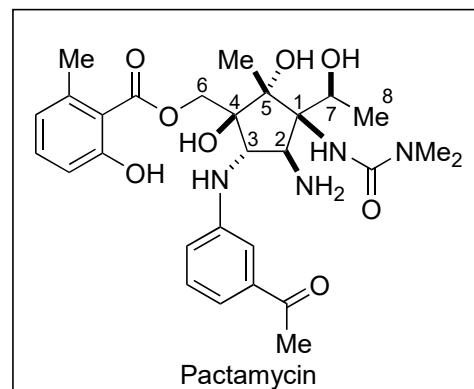
##### 0-1-1. Isolation: *Streptomyces pactum* var. *pactum* <sup>1)</sup>

##### 0-1-2. Structural elucidation

- ◆ Proposed structure: 1970 <sup>2)</sup>
- ◆ Revised structure: 1972 <sup>3)</sup>

##### 0-1-3. Structural feature:

- ◆ densely functionalized cyclopentane core
- ◆ six contiguous stereogenic centers
- ◆ three of quaternary carbon



##### 0-1-4. Biological activity: <sup>4)</sup>

- ◆ Antitumor, antimicrobial, antiviral, antiprotozoal properties.

##### 0-1-5. Synthetic study toward pactamycin

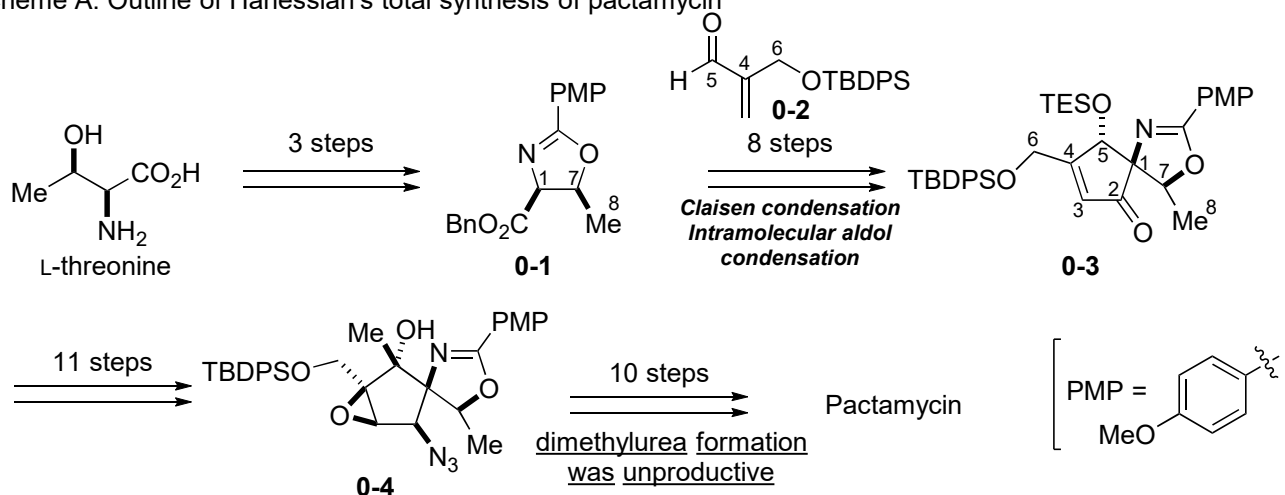
###### 0-1-5-1. Synthetic study

- ◆ Tsujimoto, T.; Nishikawa, T.; Urabe, D.; Isobe, M. *Synlett* **2005**, 433.
- ◆ Knapp, S.; Yu, Y. *Org. Lett.* **2007**, *9*, 1359.
- ◆ Haussener, T. J.; Looper, R. E. *Org. Lett.* **2012**, *14*, 3632.
- ◆ Matsumoto, N.; Tsujimoto, T.; Nakazaki, A.; Isobe, M.; Nishikawa, T. *RSC Adv.* **2012**, *2*, 9448. → **Problem 1**
- ◆ Mslinowski, J. T.; McCarver, S. J.; Johnson, J. S. *Org. Lett.* **2012**, *14*, 2878.

###### 0-1-5-2. Total synthesis

- ◆ Hanessian, S.; Vakiti, R. R.; Dorich, S.; Banerjee, S.; Lecomte, F.; DelValle, J. R.; Zhang, J.; Deschênes-Simard, B. *Angew. Chem. Int. Ed.* **2011**, *50*, 3497.
- ◆ Hanessian, S.; Vakiti, R. R.; Dorich, S.; Banerjee, S.; Deschênes-Simard, B. *J. Org. Chem.* **2012**, *77*, 9458.

##### Scheme A. Outline of Hanessian's total synthesis of pactamycin



- ◆ Malinowski, J. T.; Sharpe, R. J.; Johnson, J. S. *Science* **2013**, *340*, 180. → **Problem 2**
- ◆ Sharpe, R. J.; Malinowski, J. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2013**, *135*, 17990.

1) Argoudelis, A. D.; Jahnke, H. K.; Fox, J. A. *Antimicrob. Agents Chemother.* **1962**, 191.

2) Wiley, P. F.; Jahnke, H. K.; MacKellar, F.; Kelly, R. B.; Argoudelis, A. D.; *J. Org. Chem.* **1970**, *35*, 1420.

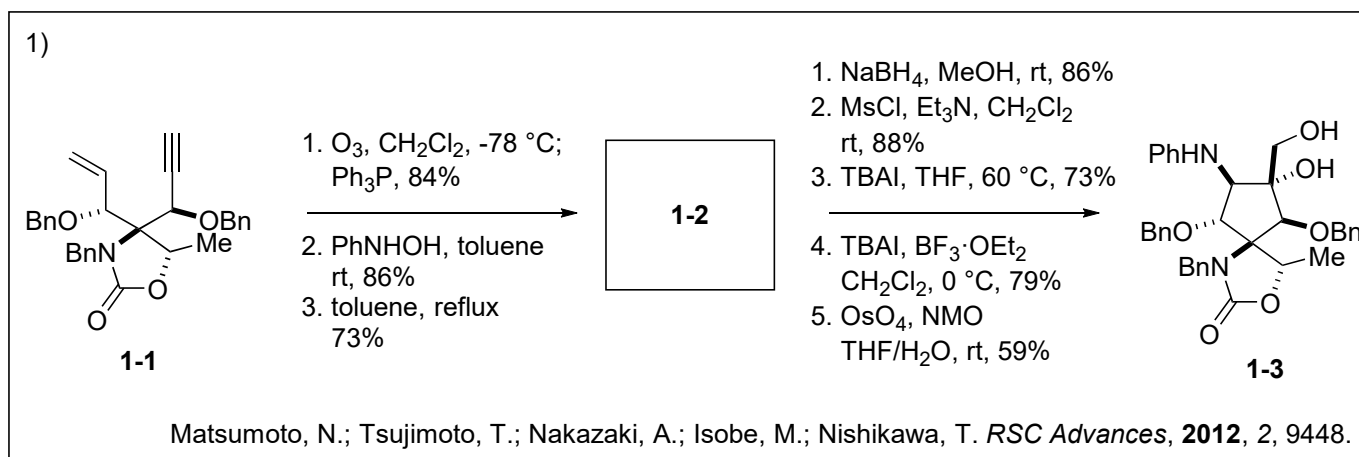
3) Duchamp, D. J. Abstracts, American Crystallographic Association Winter Meeting; Albuquerque, NM, 1972; 23.

4) (a) Bhuyan, B. K.; Dietz, A.; Smith, C. G.; *Antimicrob. Agents Chemother.* **1962**, 184.

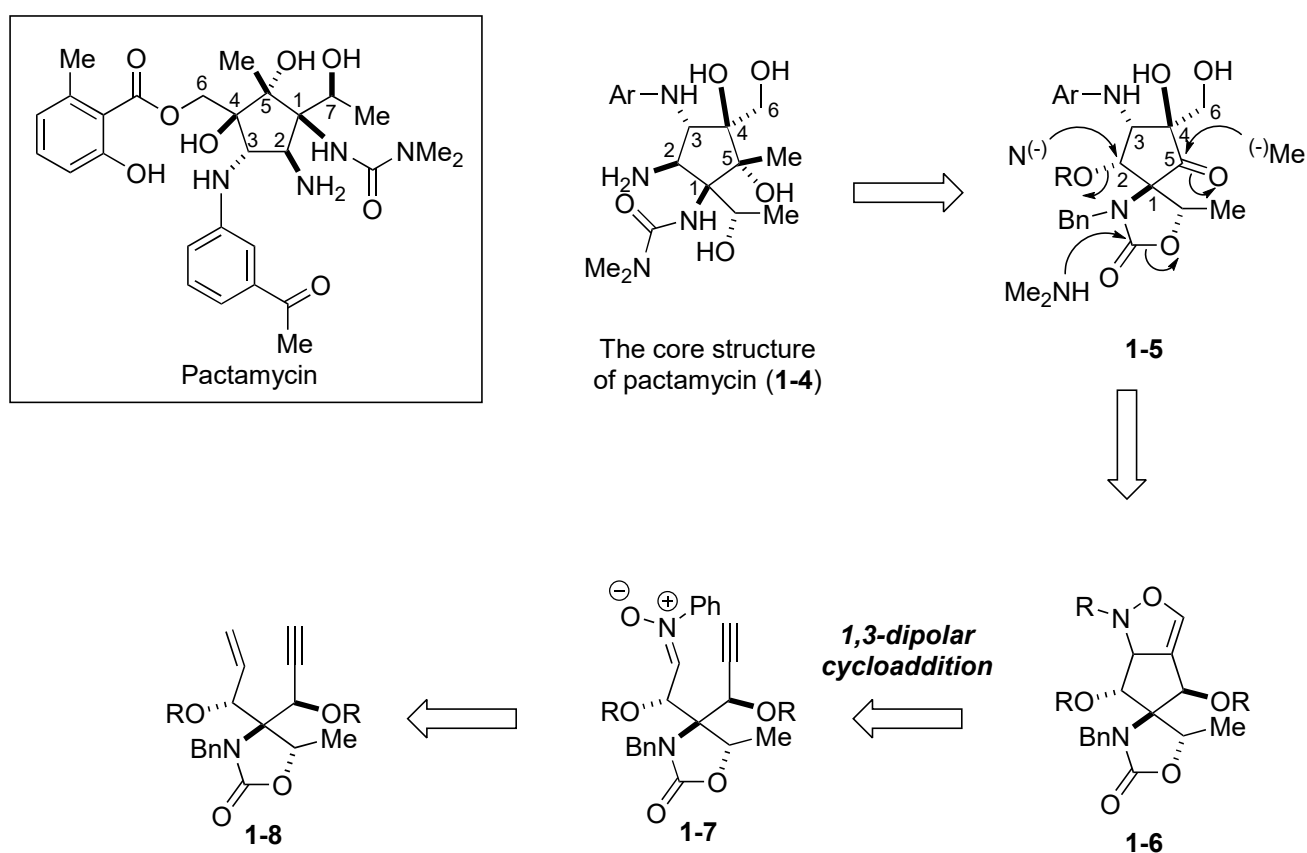
(b) Iwatsuki, M.; Nishihara-Tsukashima, A.; Ishiyama, A.; Namatame, M.; Watanabe, Y.; Handasah, S.; Pranamuda, H.; Marwoto, B.; Matsumoto, A.; Takahashi, Y.; Otoguro, K.; Omura, S. *J. Antibiot.* **2012**, *65*, 169.

(c) Taber, R.; Reksh, D.; Baltimore, D. *J. Virol.* **1971**, *8*, 395.

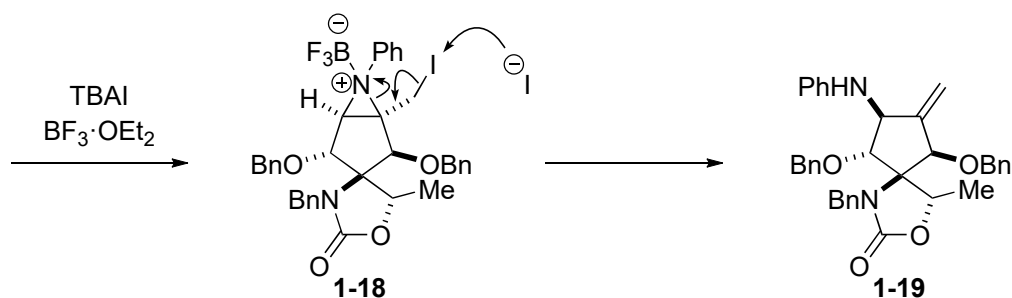
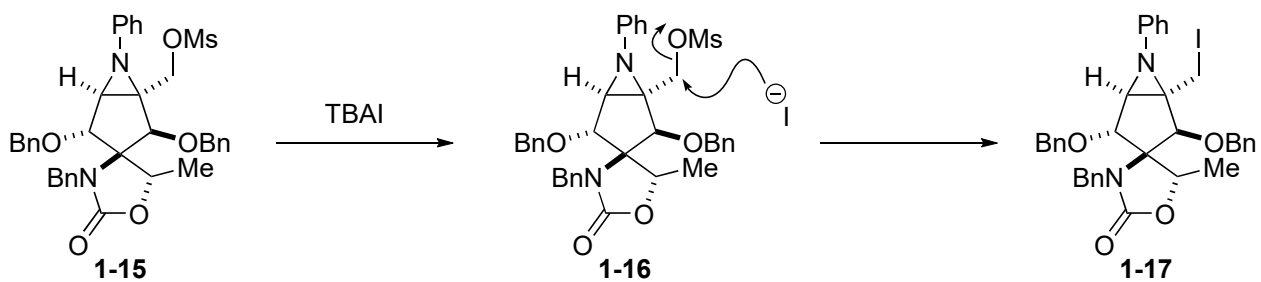
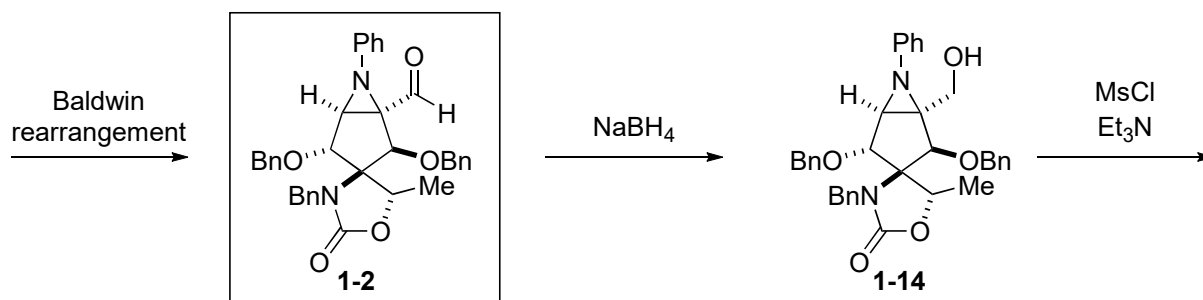
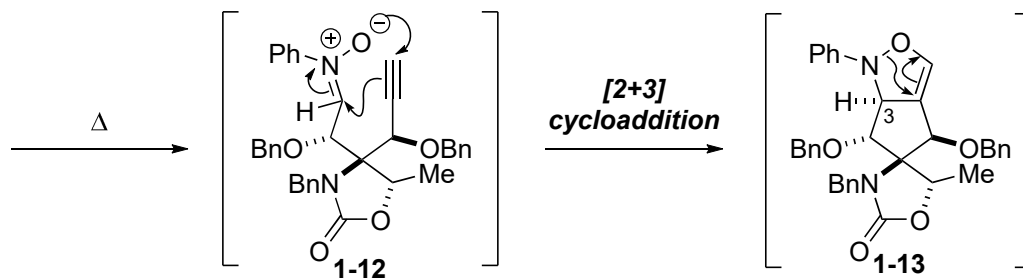
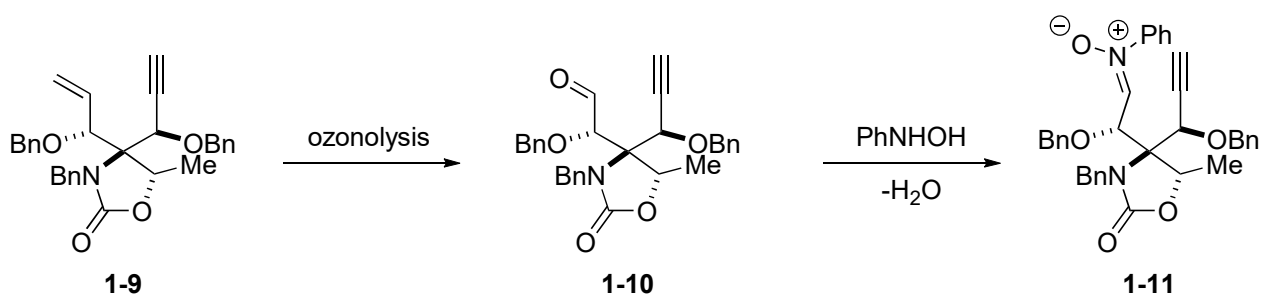
**Problem 1: Synthetic study by Nishikawa**

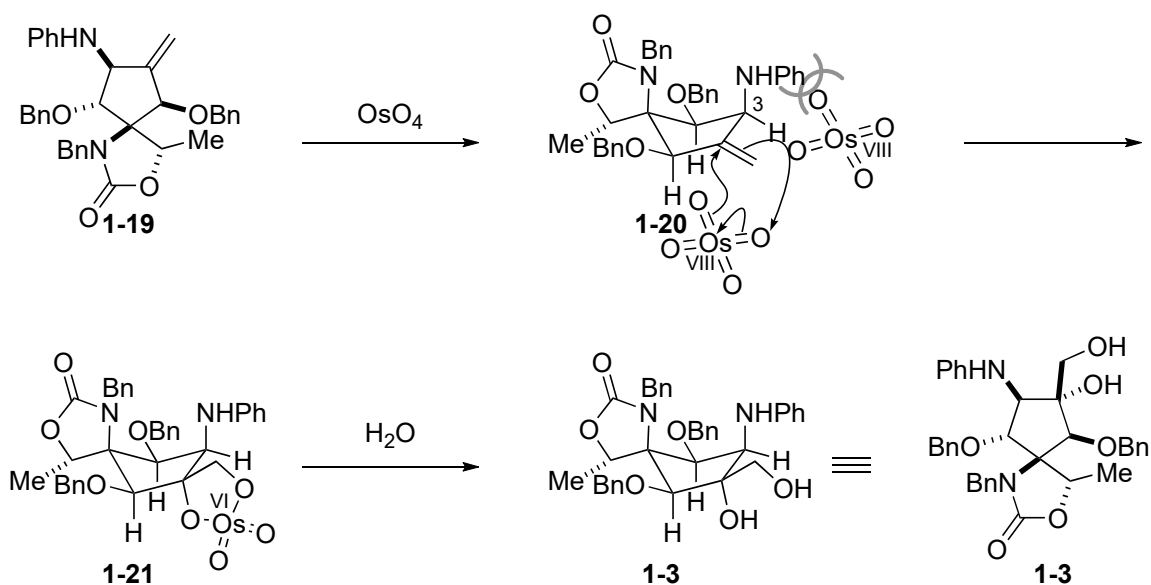


**Retrosynthetic analysis:**



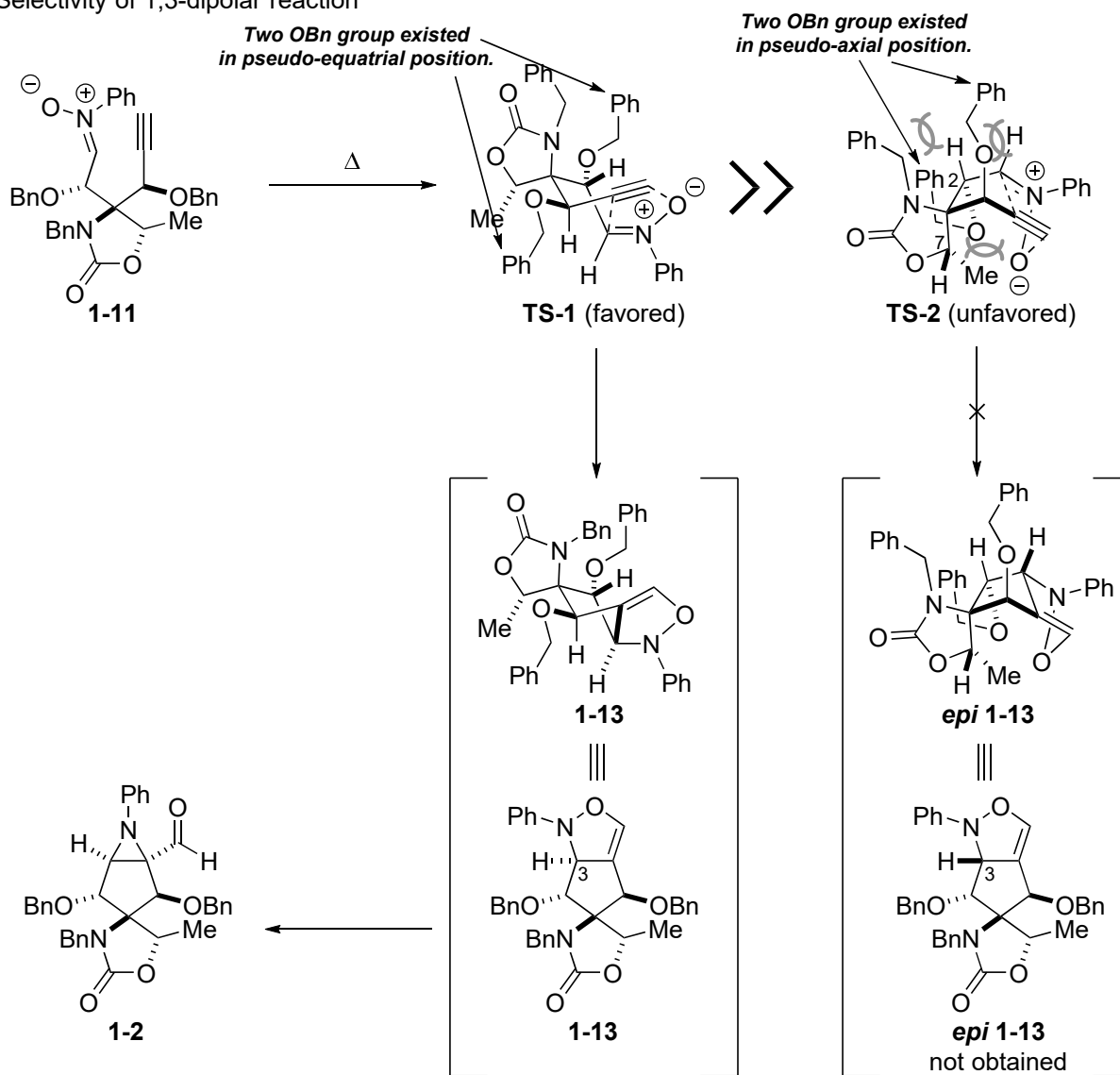
Answer:



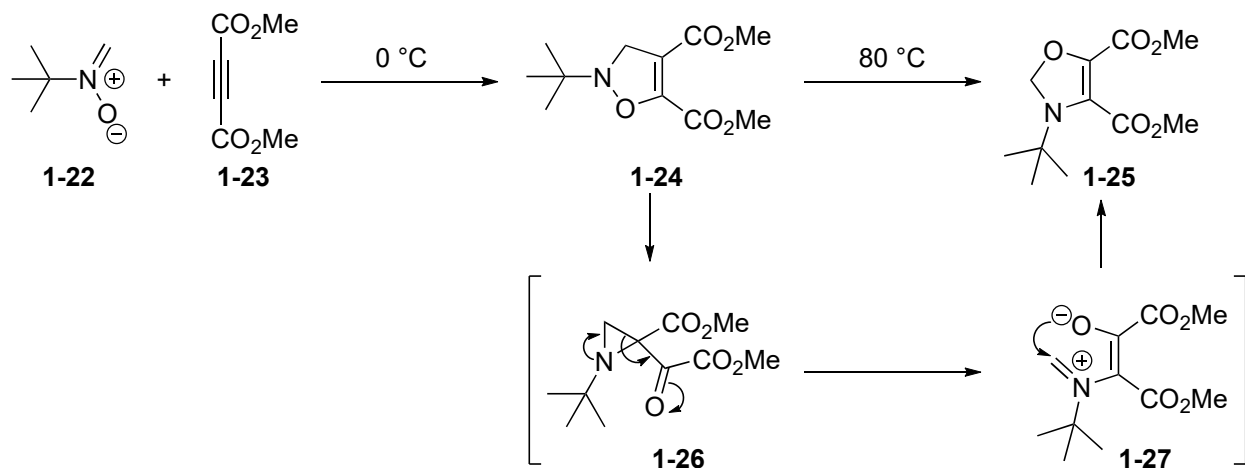


### Discussion:

#### 1. Selectivity of 1,3-dipolar reaction

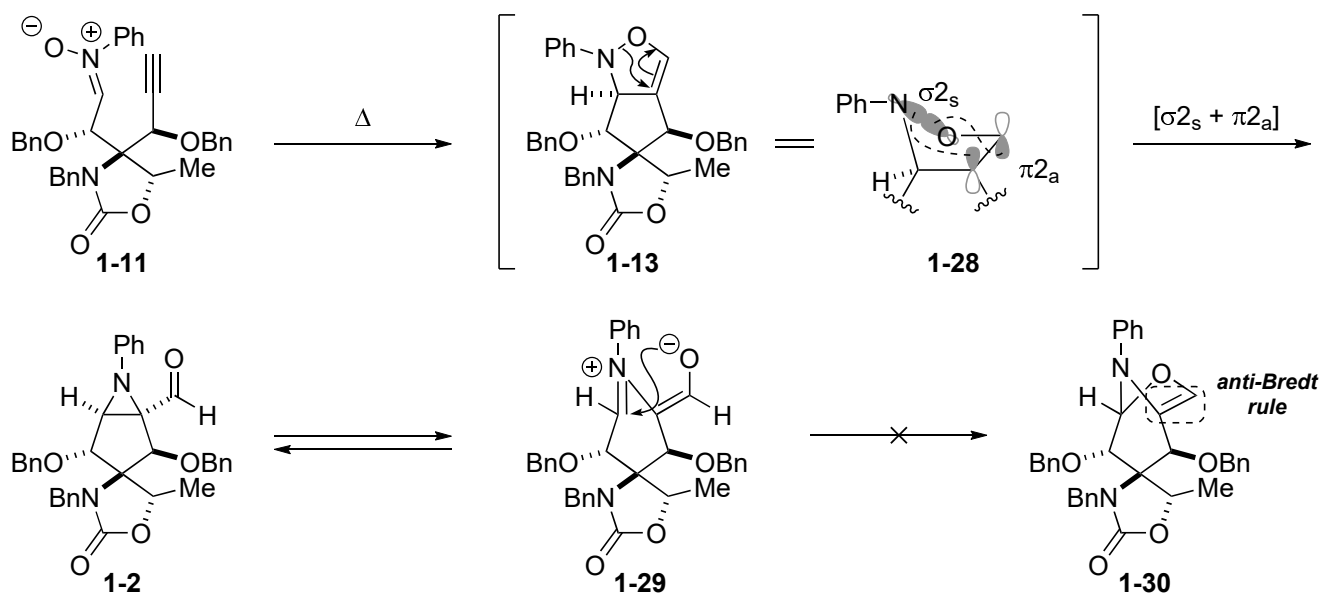


## 2. Baldwin rearrangement

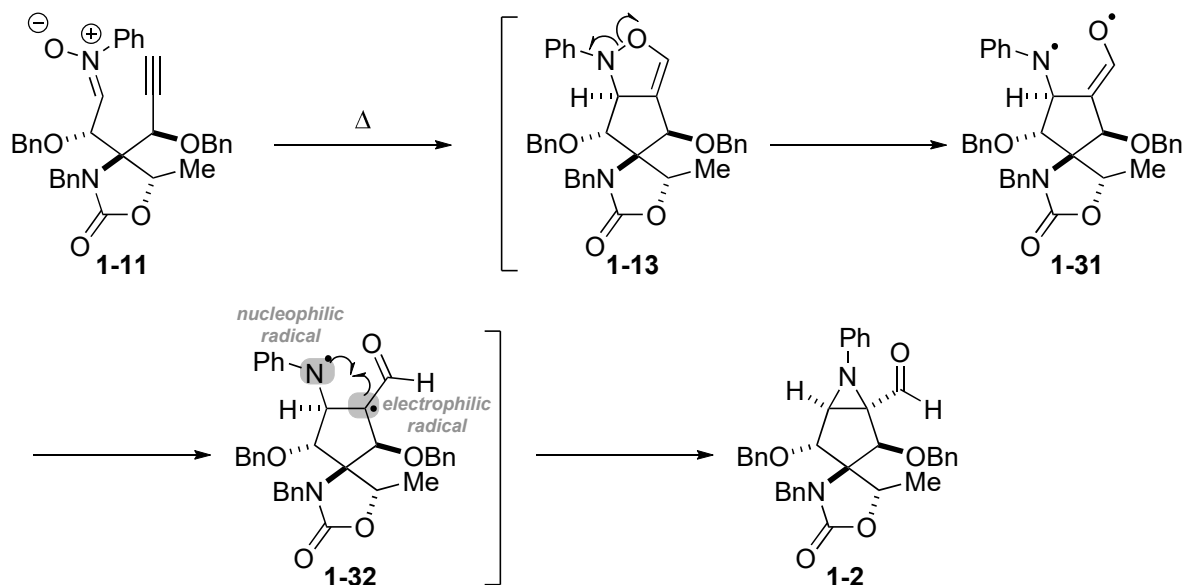


Baldwin, J. E.; Pudussery, R. G.; Qureshi, A. K.; Sklarz, B. *J. Am. Chem. Soc.* **1968**, *90*, 5325.

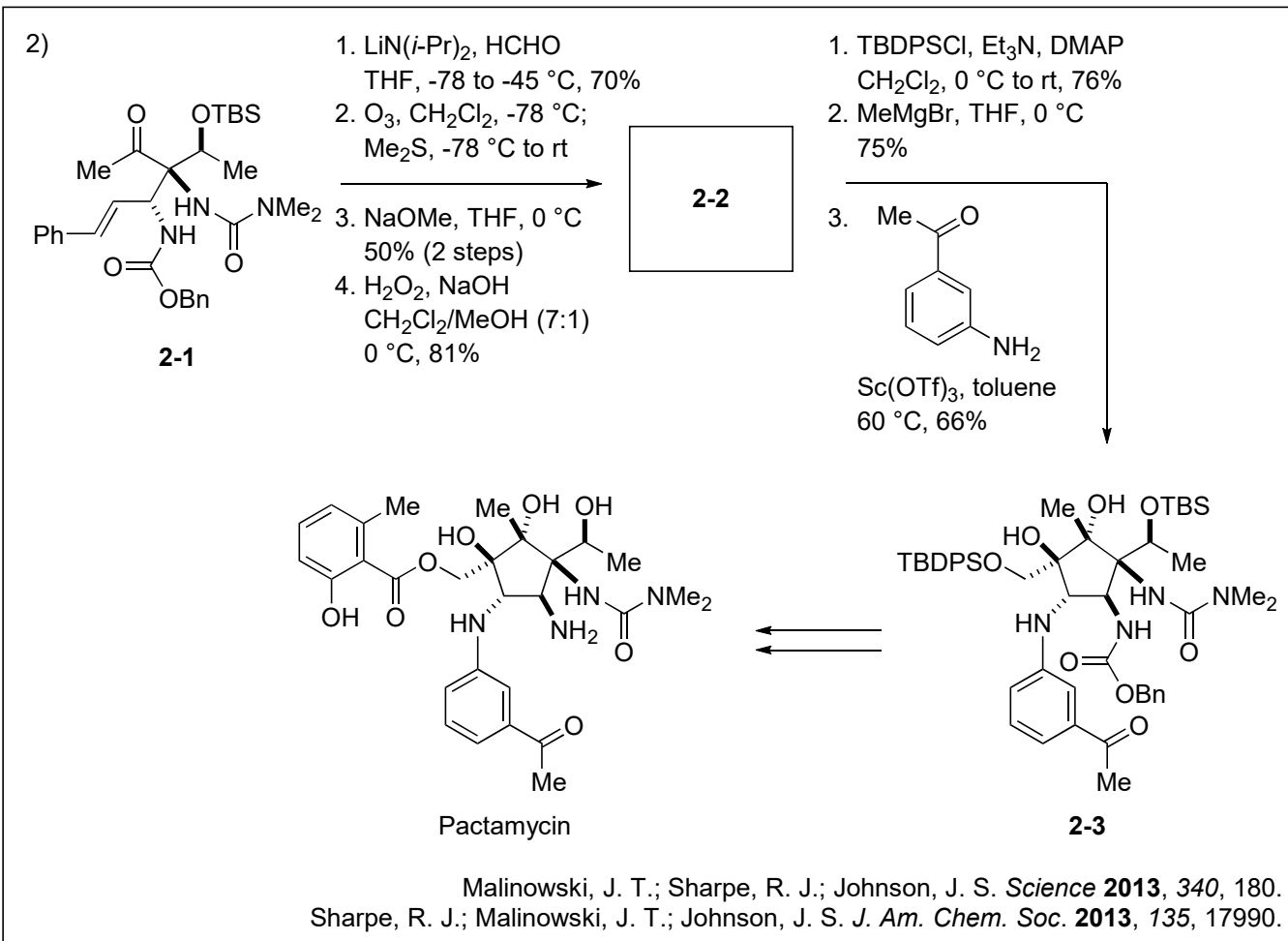
[Proposed mechanism 1, [1,3]-sigmatropic rearrangement pathway]



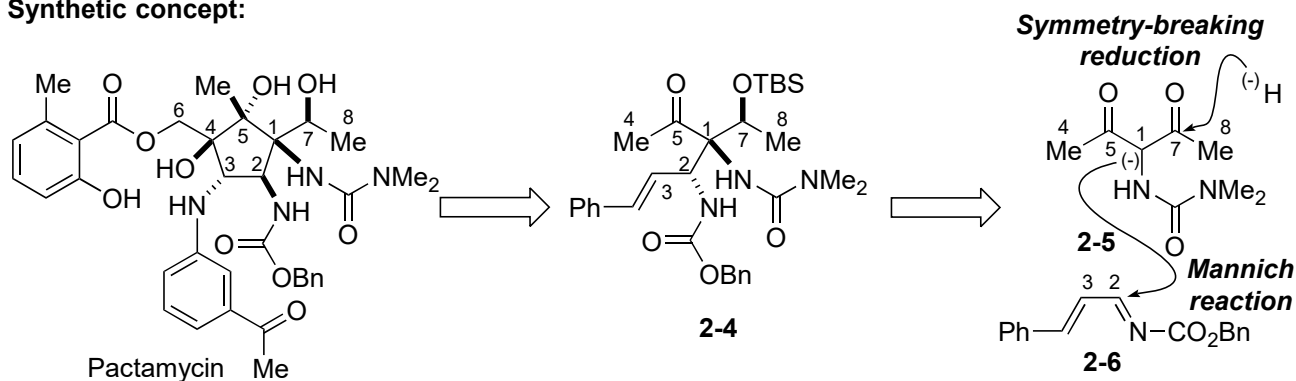
[Proposed mechanism 2, radical pathway]



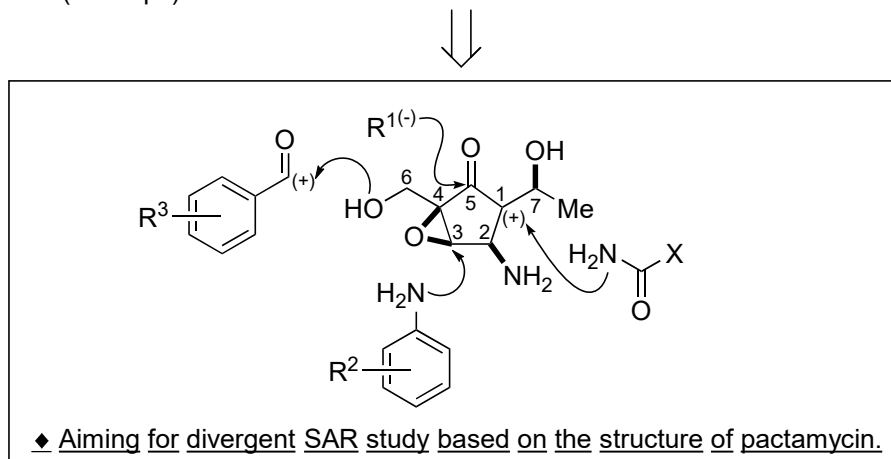
**Problem 2: Total synthesis by Johnson**



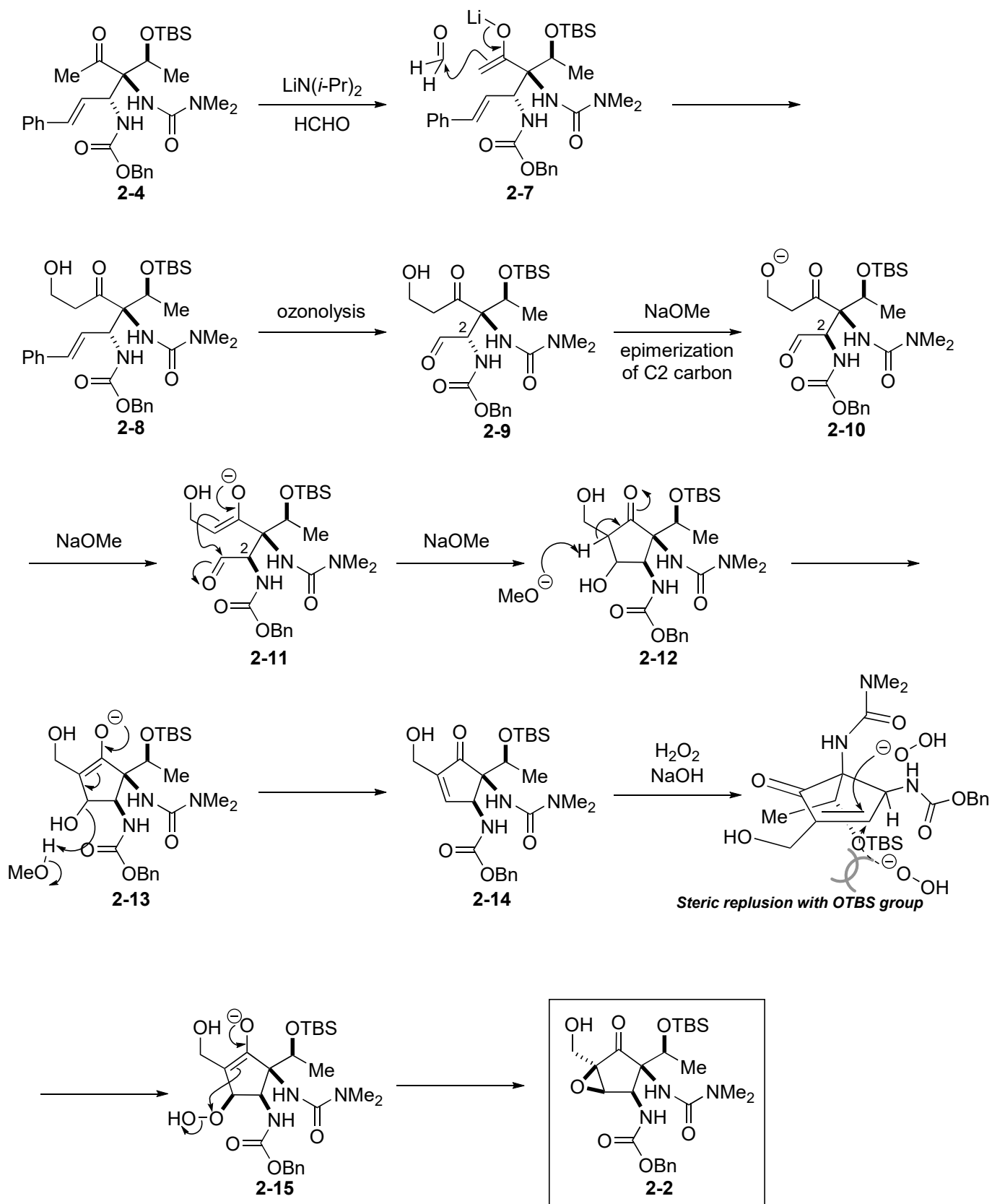
**Synthetic concept:**



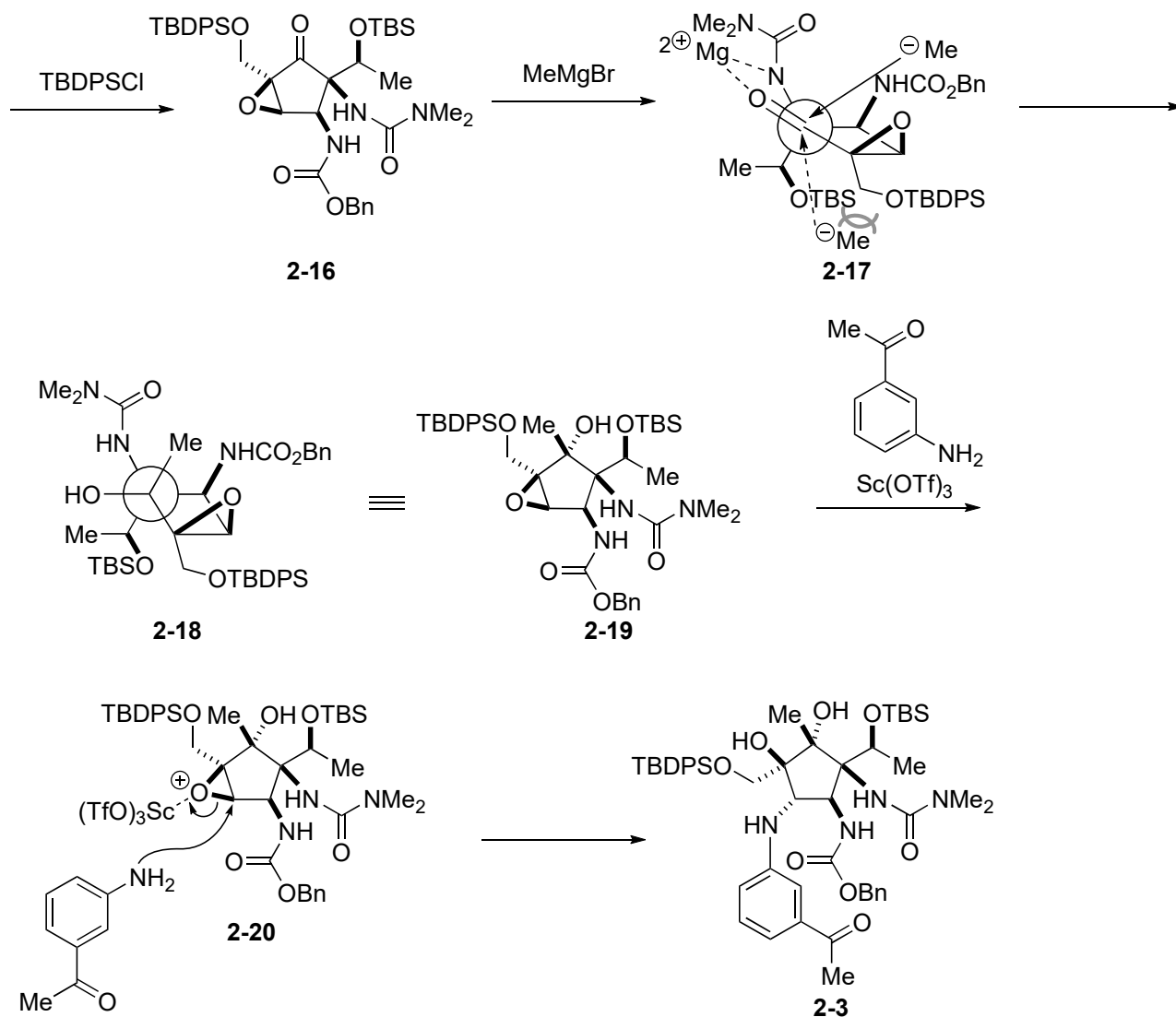
- ◆ By introducing dimethylurea moiety in initial stage, total steps were shortened to 15 steps, compared to Hanessian's route (32 steps).



Answer:



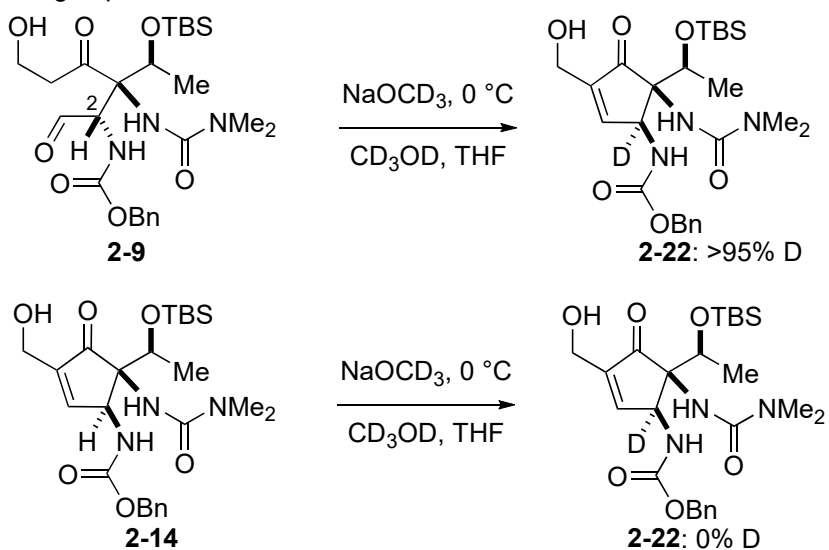




## Discussion:

### 1. C2 epimerization

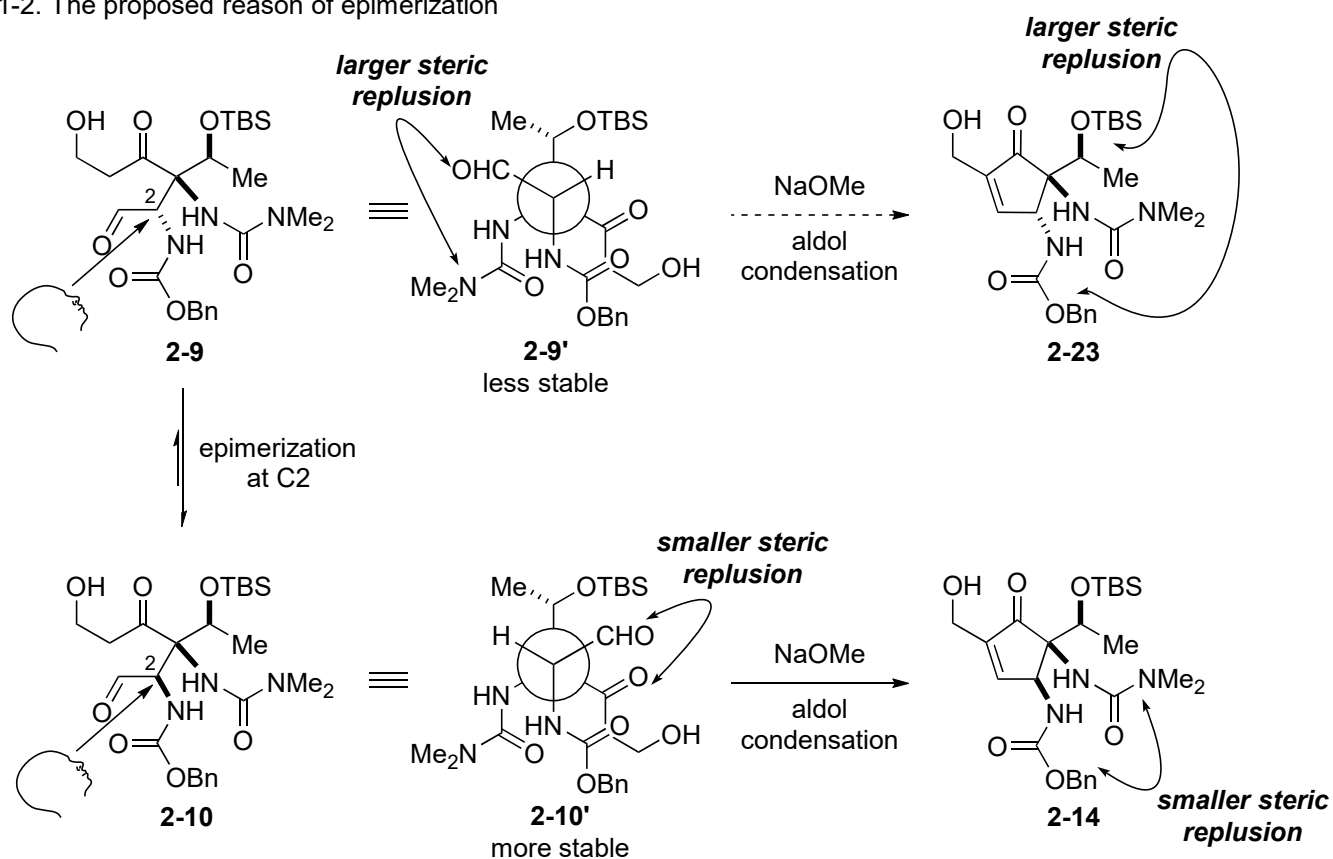
#### 1-1. Deuterium-labeling experiments



Sharpe, R. J.; Malinowski, J. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2013**, *135*, 17990.

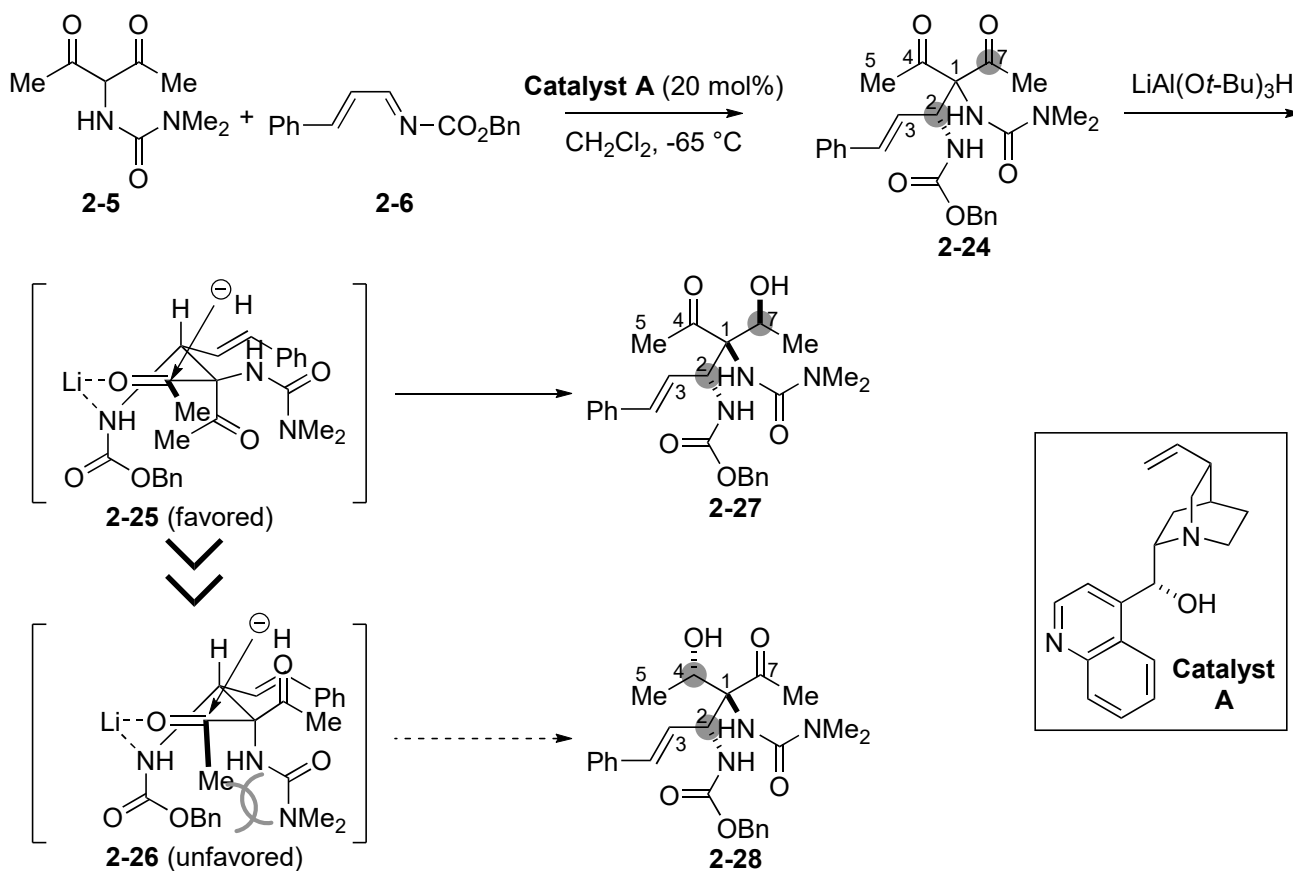
⇒ It seemed that epimerization was occurred before aldol condensation.

1-2. The proposed reason of epimerization



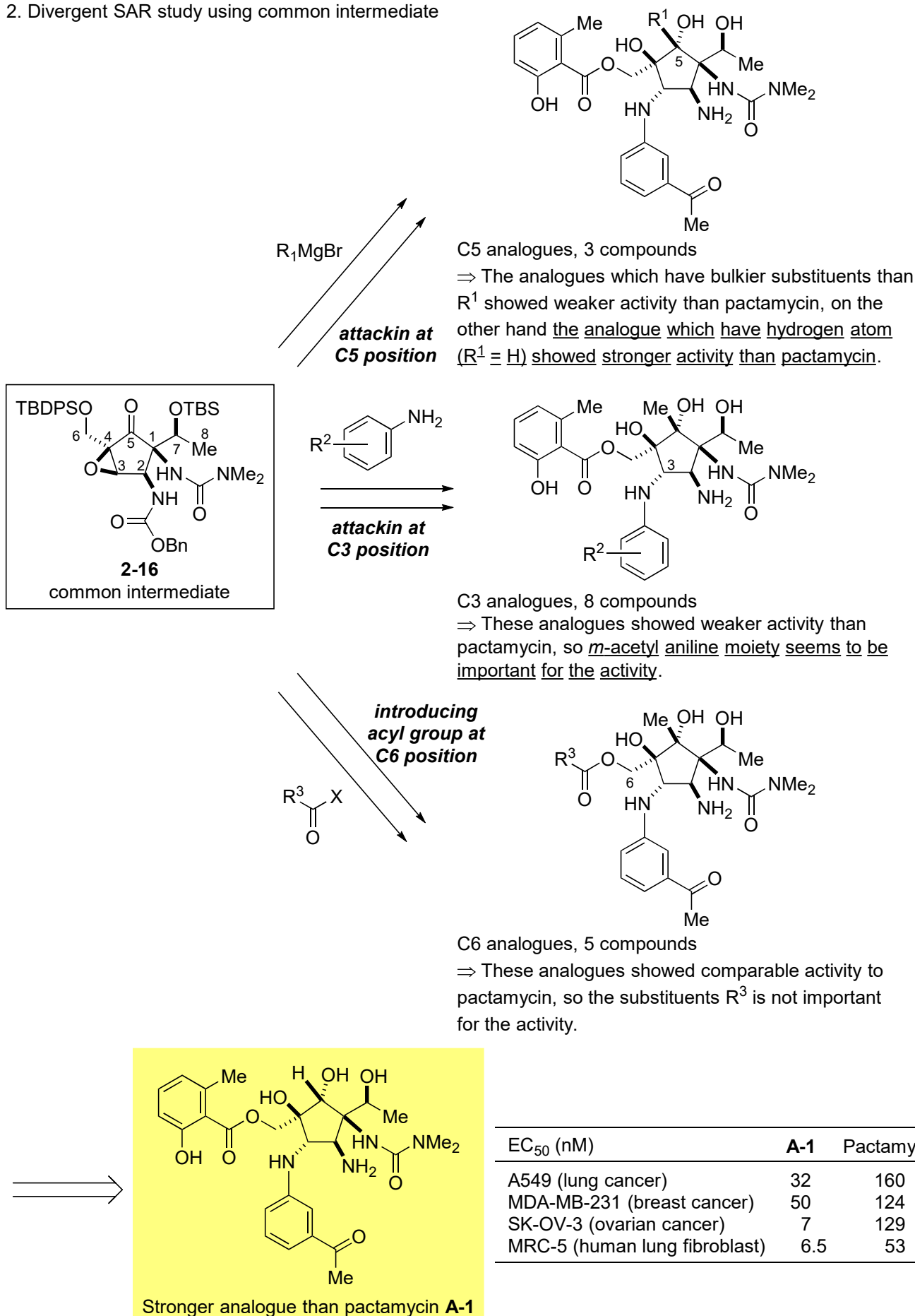
**Appendix:**

1. Proposed stereochemical model for LTBA reduction



⇒ This result shows that "incorrect" C2 stereochemistry was helpful to construct C7 asymmetric carbon stereoselectivity.

## 2. Divergent SAR study using common intermediate



Sharpe, R. J.; Malinowski, J. T.; Sorana, F.; Luft, J. C.; Bowerman, C. J.; DeSimone, J. M.; Johnson, J. S. *Bioorg. Med. Chem.* **2015**, *23*, 1849.