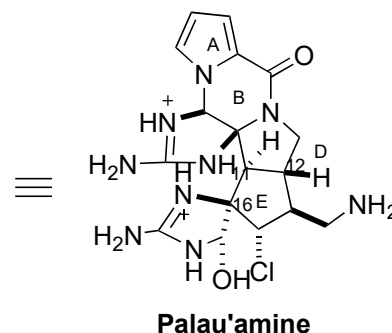
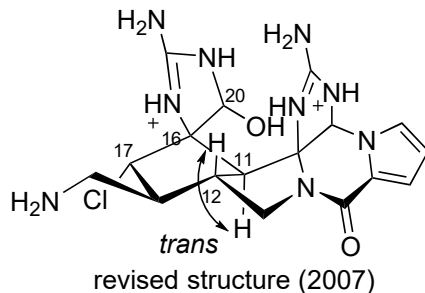
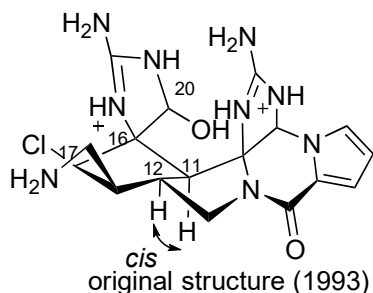


## Problem session (1)-Answer

2017.1.12 Yuri Takada

Palau'amine (Pyrrole-imidazole alkaloid)



### <Isolation>

From the sponge, *Stylotella agminata* in the Western Caroline Islands.

(P. J. Scheuer et al. *J. Am. Chem. Soc.* **1993**, *115*, 3376.)

### <Structural determination>

Firstly: P.J. Scheuer determined (P. J. Scheuer et al. *J. Am. Chem. Soc.* **1993**, *115*, 3376.)

Revised structural determination (M. Kock et al. *Angew. Chem., Int. Ed.* **2007**, *46*, 2320

R. J. Quinn et al. *J. Org. Chem.* **2007**, *72*, 2309. S. Matsunaga et al. *Tetrahedron Lett.* **2007**, *48*, 2127.)

### <Bioactivity>

antifungal, antitumour, immunosuppressive activity (Kinnel, R. B. et. al. *J. Am. Chem. Soc.* **1993**, *115*, 3376. and

### <structural feature>

*J. Org. Chem.* **1998**, *63*, 3281.)

- 1) two spiroguanidine units polycyclic framework containing
- 2) highly strained trans-azabicyclo[3,3,0]octane subunit.(D,E-ring)
- 3) All substituted cyclopentane core containing spiro guanidine core (E-ring)

### <Total synthesis>

first total synthesis (**problem 2**)

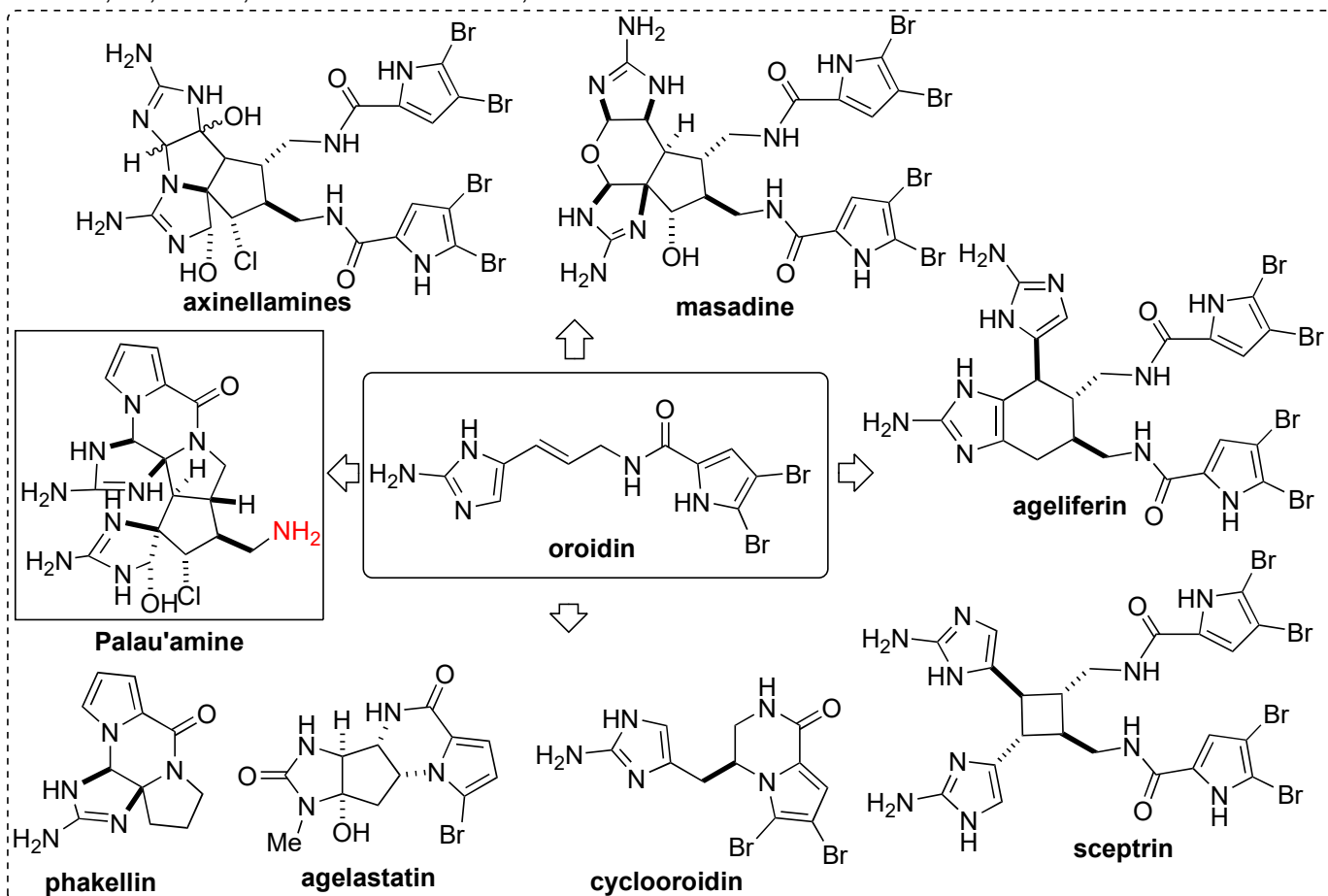
Seiple, I. B.; Su, S.; Young, I. S.; Lewis, C. A.; Yamaguchi, J.; Baran, P. S. *Angew. Chem. Int. Ed.* **2010**, *49*, 1095.

Seiple, I. B.; Su, S.; Young, I. S.; Nakamura, A.; Yamaguchi, J.; Jørgensen, L.; Rodriguez, R. A.; O'Malley, D. P.;

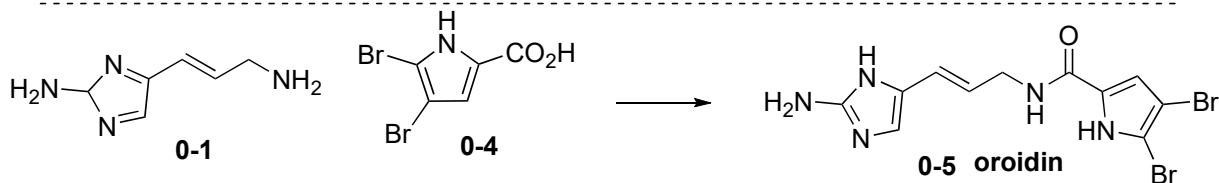
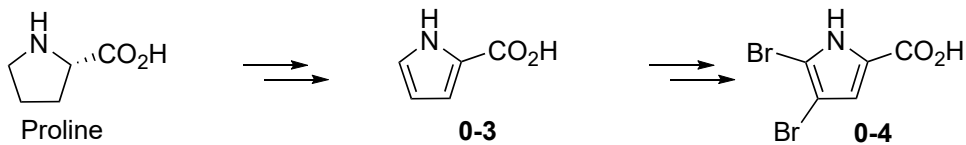
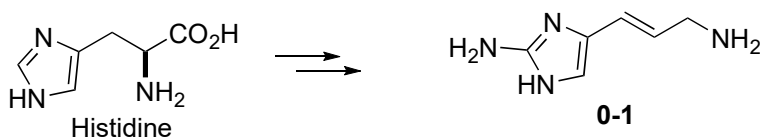
Gaich, T.; Köck, M.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 14710.

second total synthesis (**problem 1**) Namba, K.; Takeuchi, K.; Kaihara, Y.; Oda, M.; Nakayama, A.; Nakayama, A.;

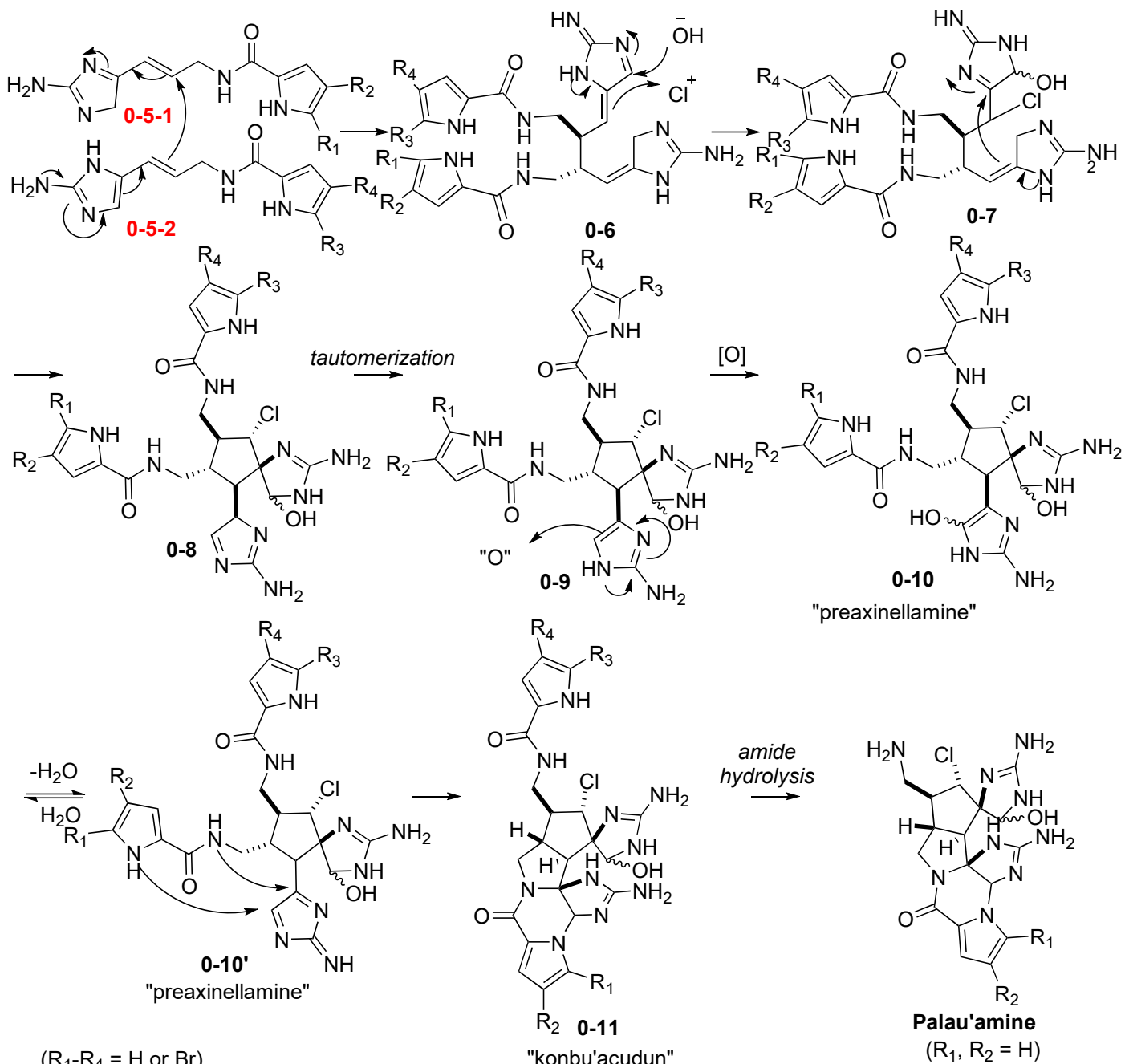
Yoshida, M.; Tanino, K. *Nat. Commun.* **2015**, *1*.



<Biosynthesis of Palau'amine>



Mourabit, A. A.; Potier, P. *Eur. J. Org. Chem.* **2001**, 237.



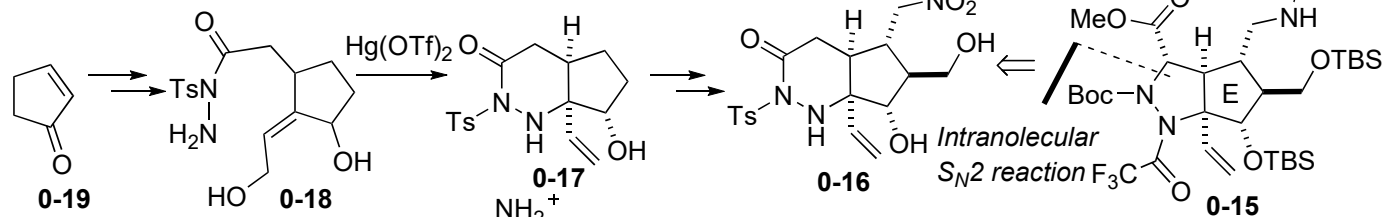
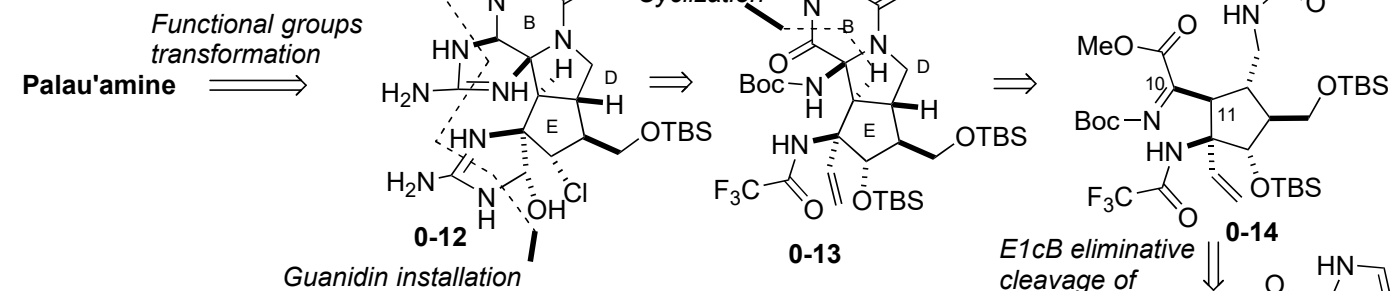
( $R_1$ - $R_4 = H$  or Br)

Köck, M.; Grube, A.; Seiple, I. B.; Baran, P. S. *Angew. Chem. Int. Ed.* **2007**, 46, 6586.

• Namba K. et al.

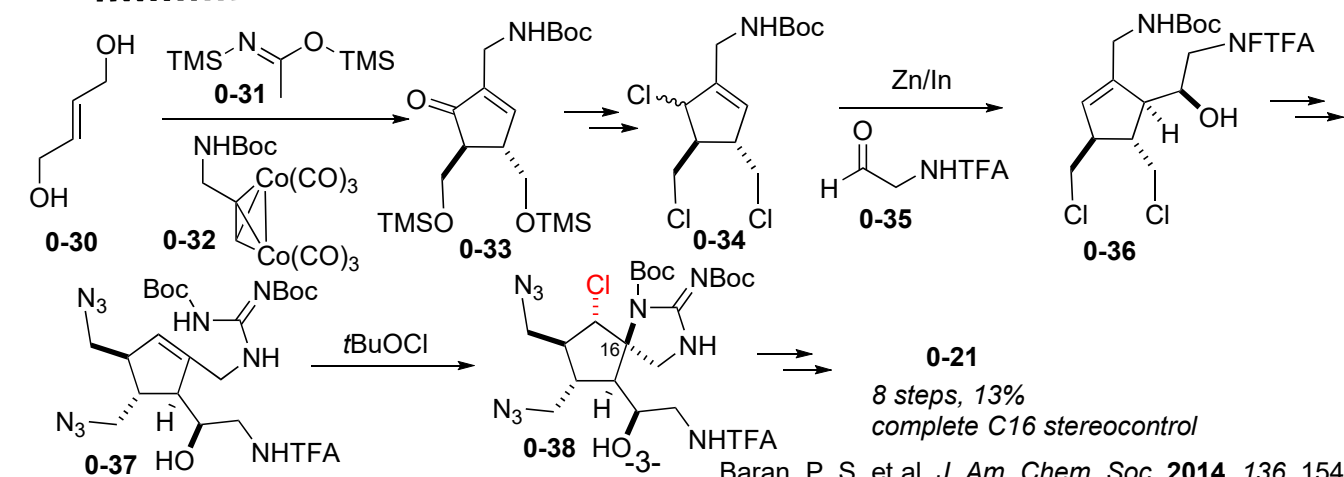
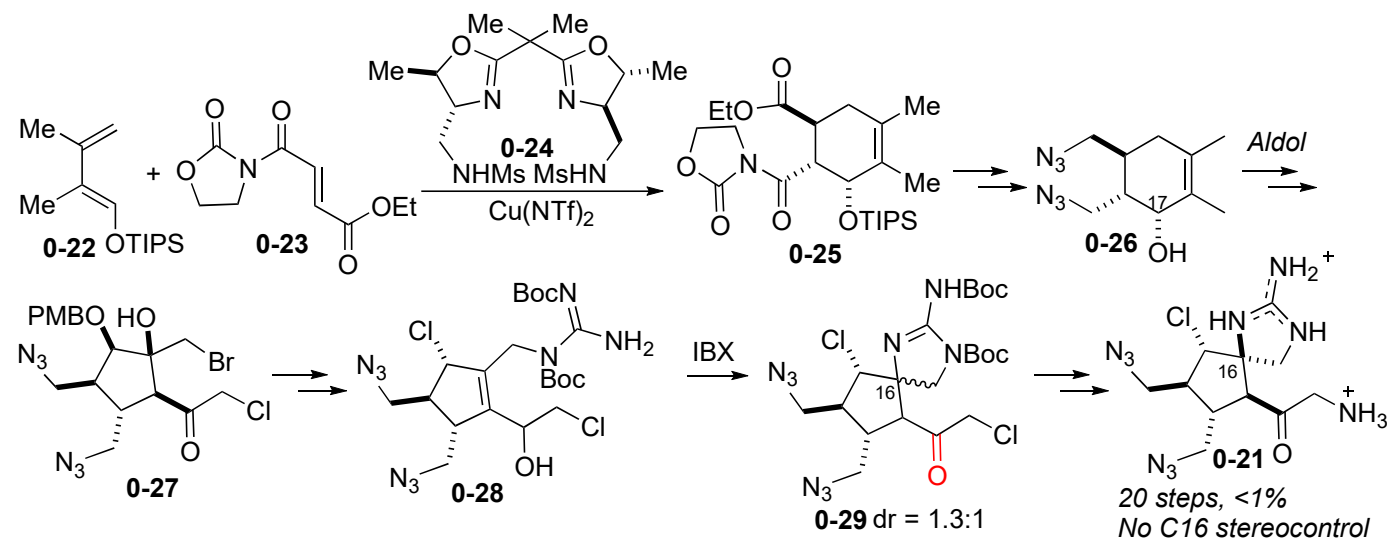
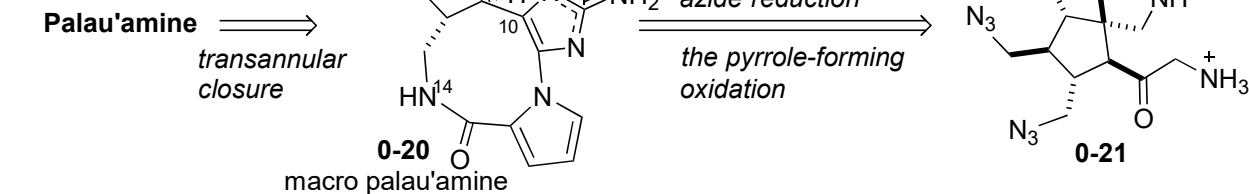
Basic ring system

would be constructed at early stage

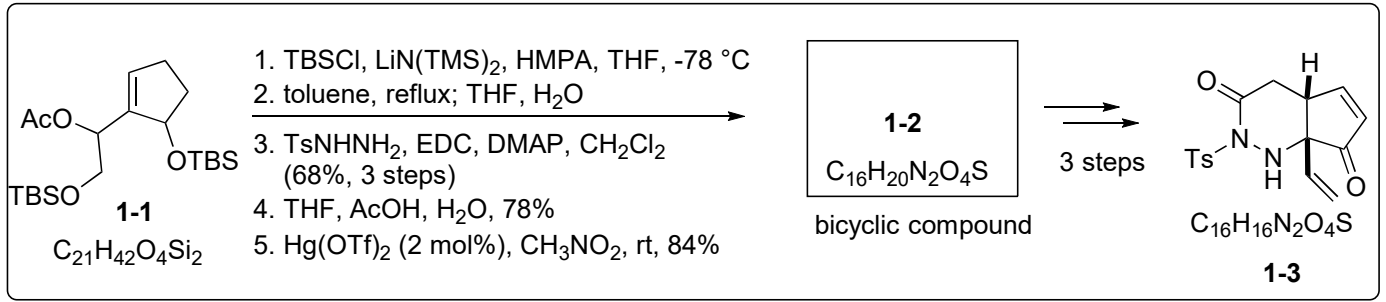


• Baran, P. S. et al

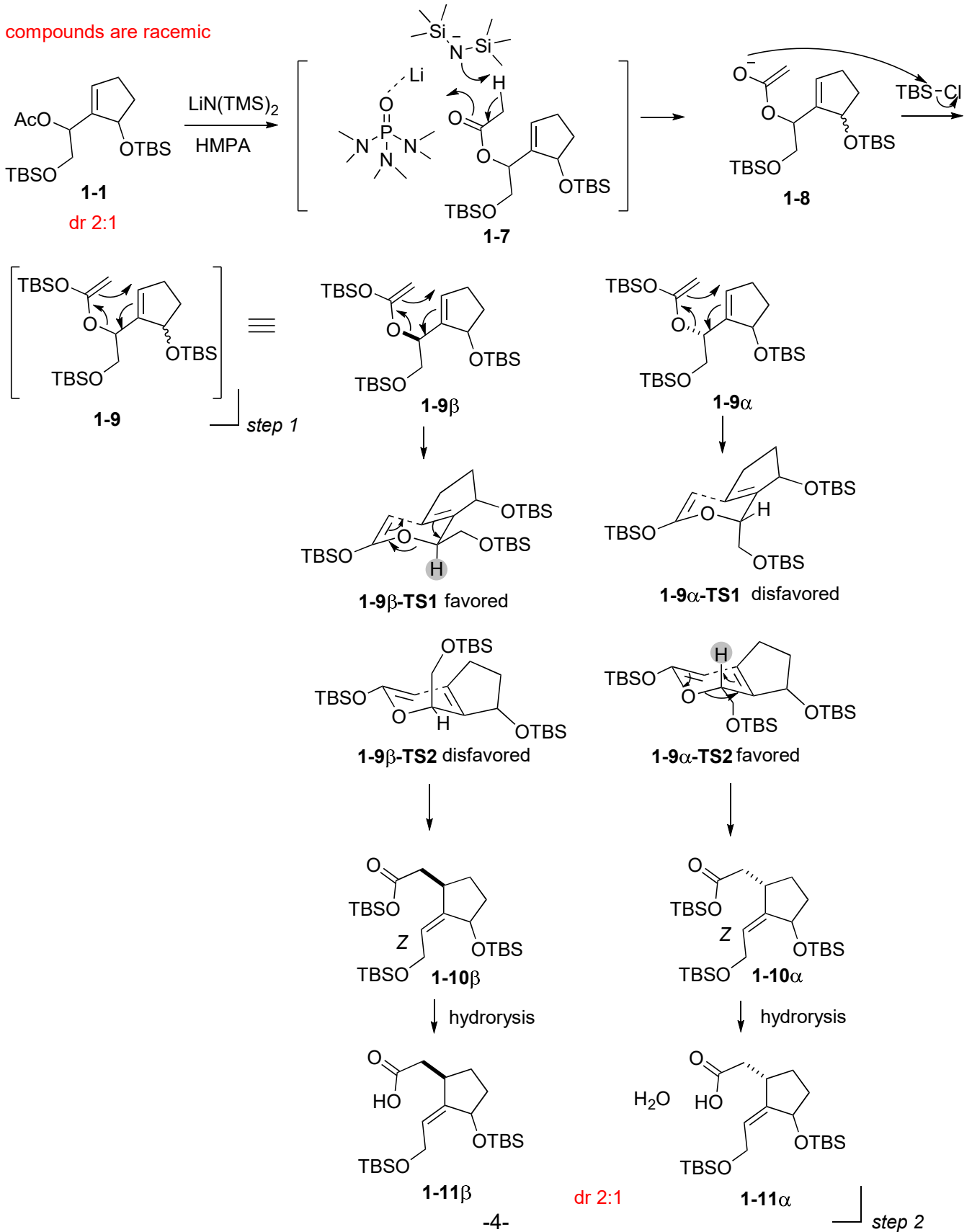
Construction of basic ring system at first step

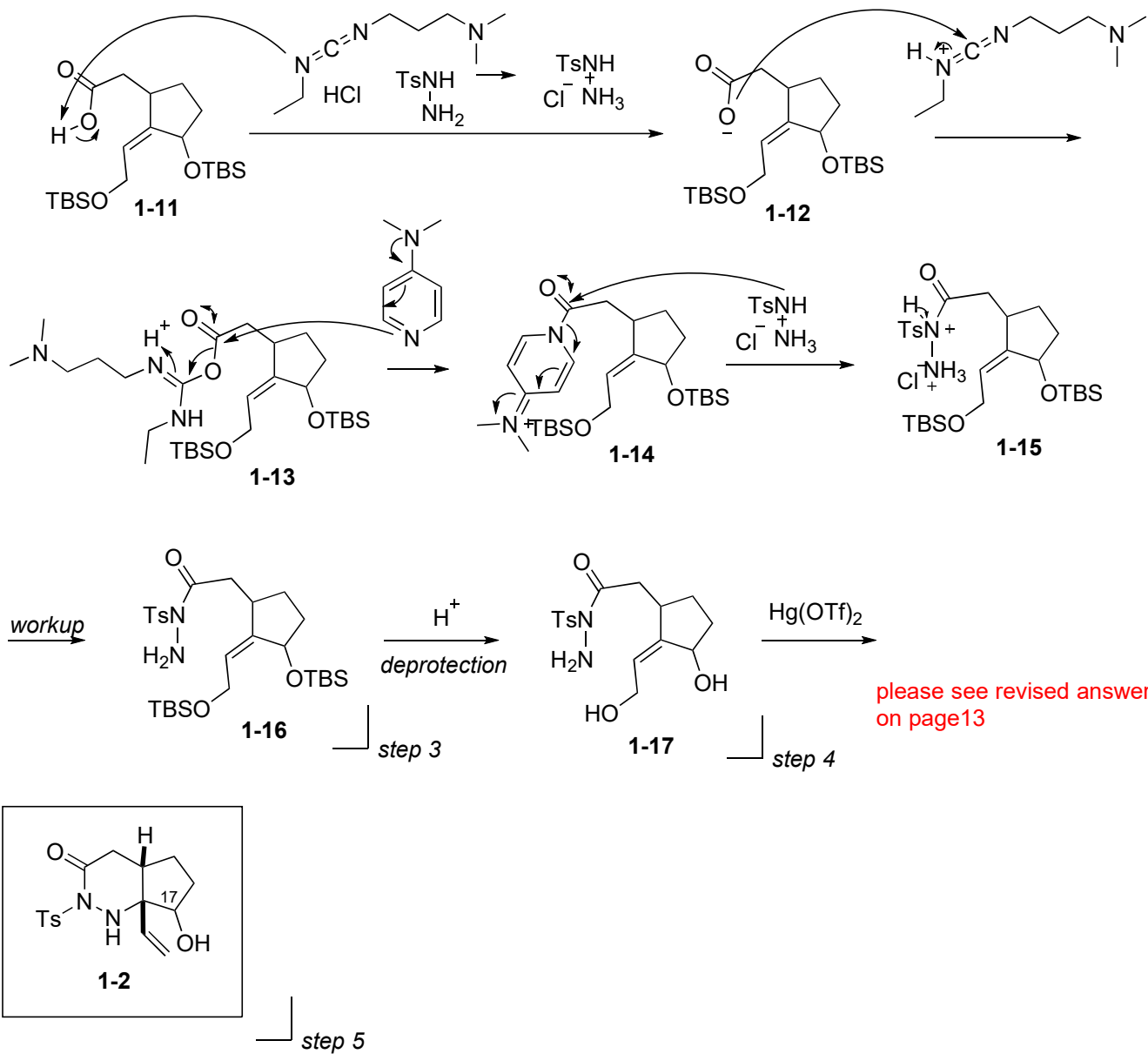


Baran, P. S. et al. *J. Am. Chem. Soc.* **2014**, *136*, 15403.

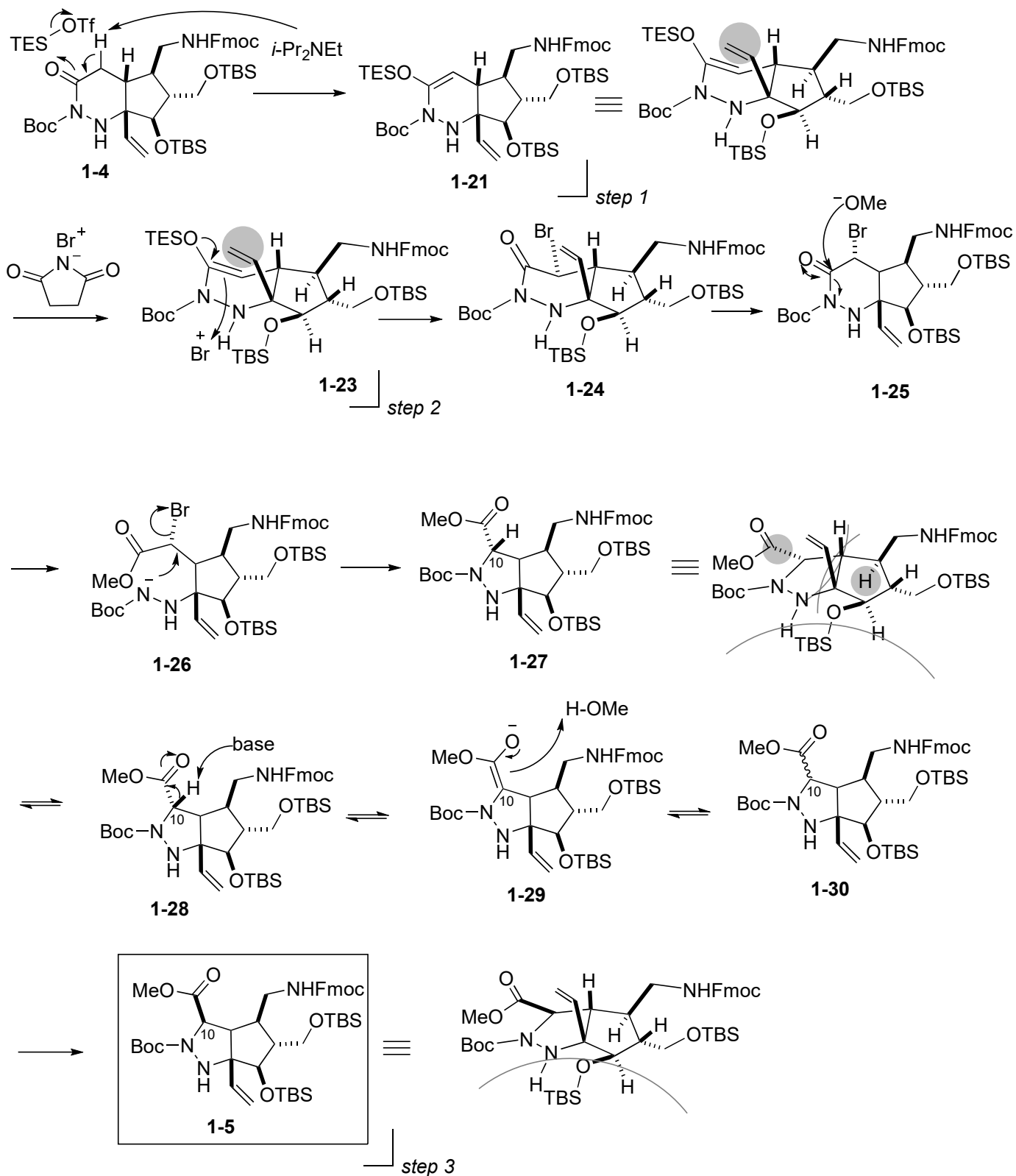
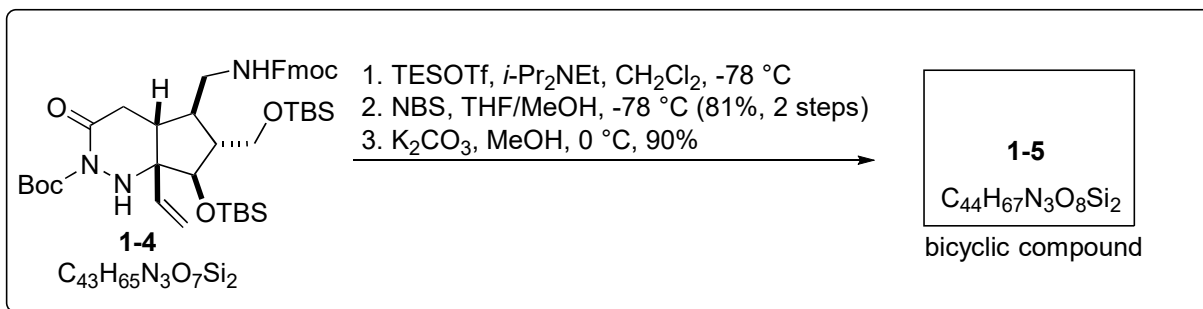


compounds are racemic

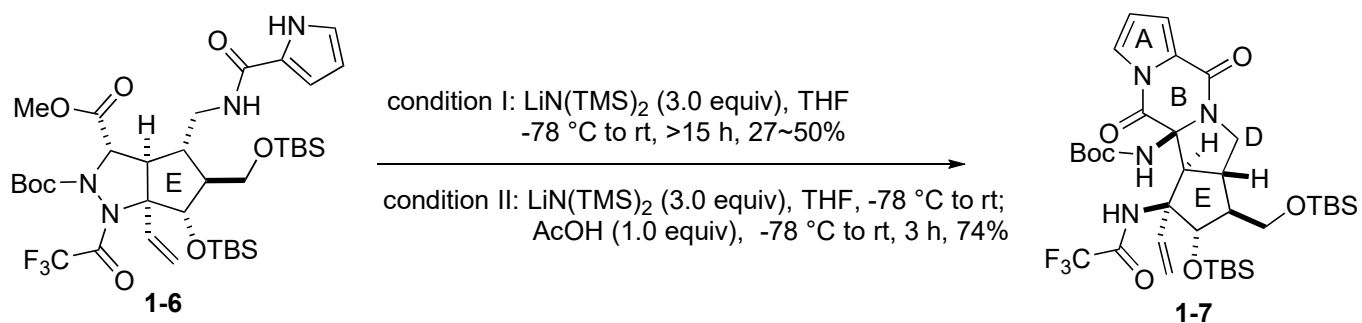




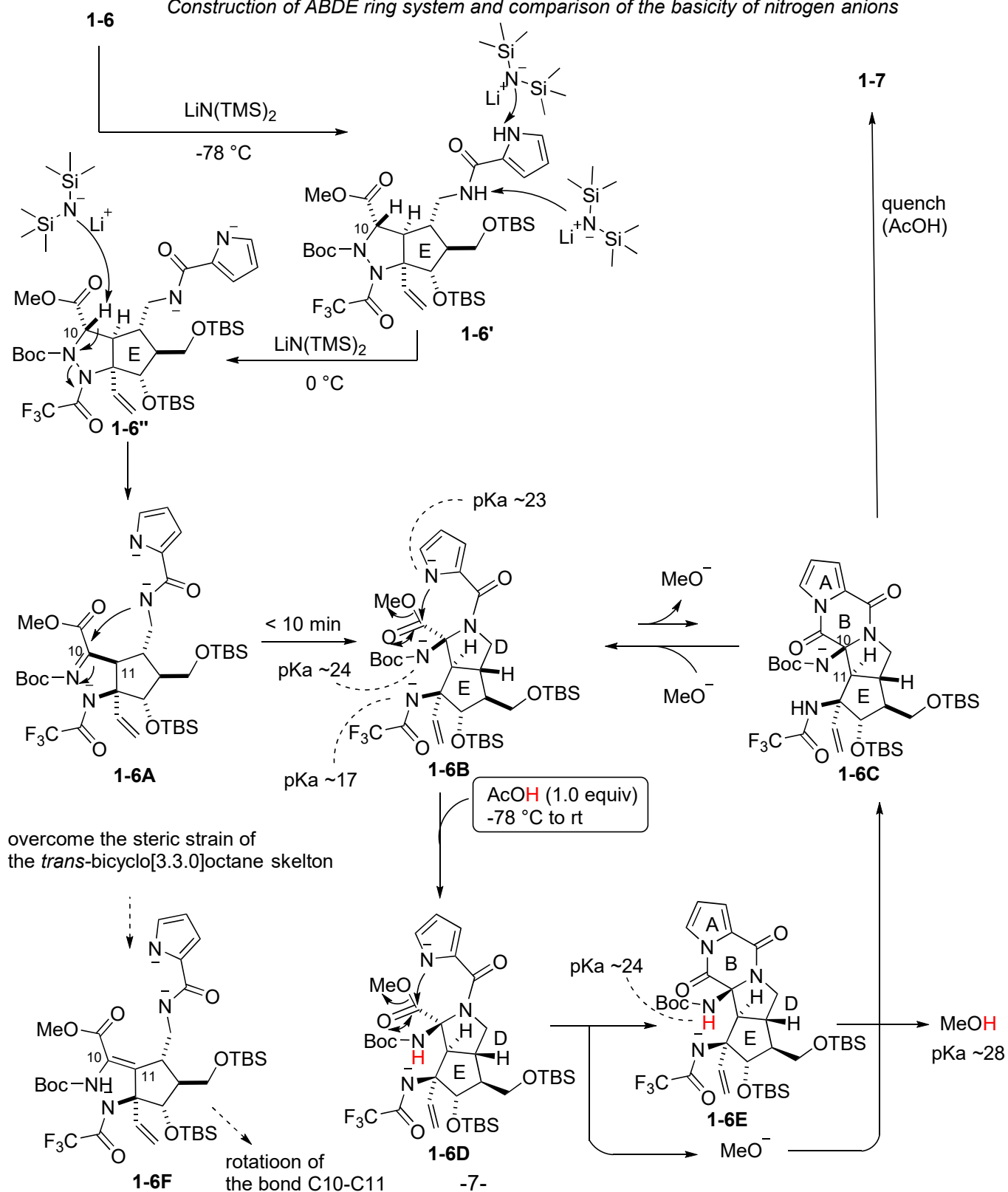
please see revised answer on page 13



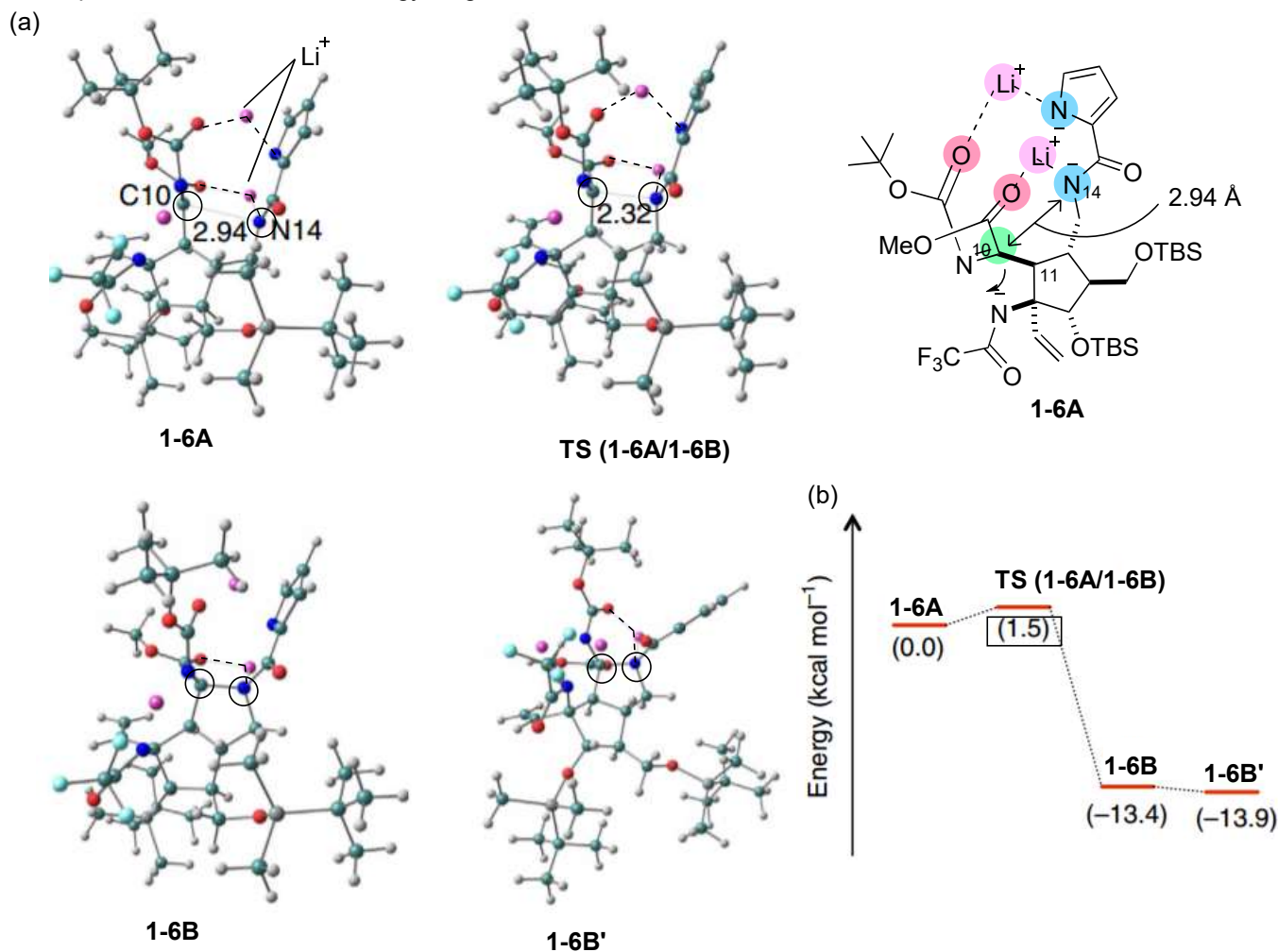
1-2. Please provide the mechanism of the following reactions and role of AcOH. (Compounds are racemic.)



Construction of ABDE ring system and comparison of the basicity of nitrogen anions



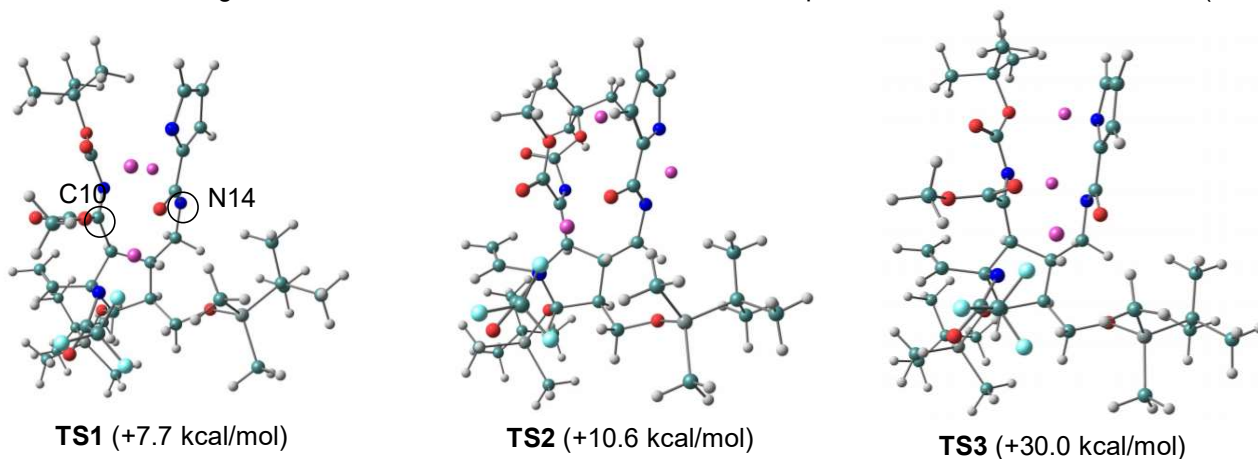
Optimized structures and energy diagram of **1-6**



(a) Optimized structures of **1-6A**, **1-6B**, **TS (1-6A/1-6B)** and **1-6B'**.  
**TS (1-6A/1-6B)** is a transition-state structure connecting **1-6A** and **1-6B**.  
**1-6B'** represents a structure after the translocation of a lithium atom.

(b) Potential energy profile for the cyclization reaction (**1-6A**→**1-6B**).  
 Calculations were performed by the density functional theory (DFT) using M06-2X with the 6-31G\* basis set.  
 The solvent effects are taken into account by the self-consistent reaction field (THF).  
 The potential energies (in kcal/mol) relative to **1-6A** are shown in parentheses.  
 All calculations were performed by the Gaussian 09 package.

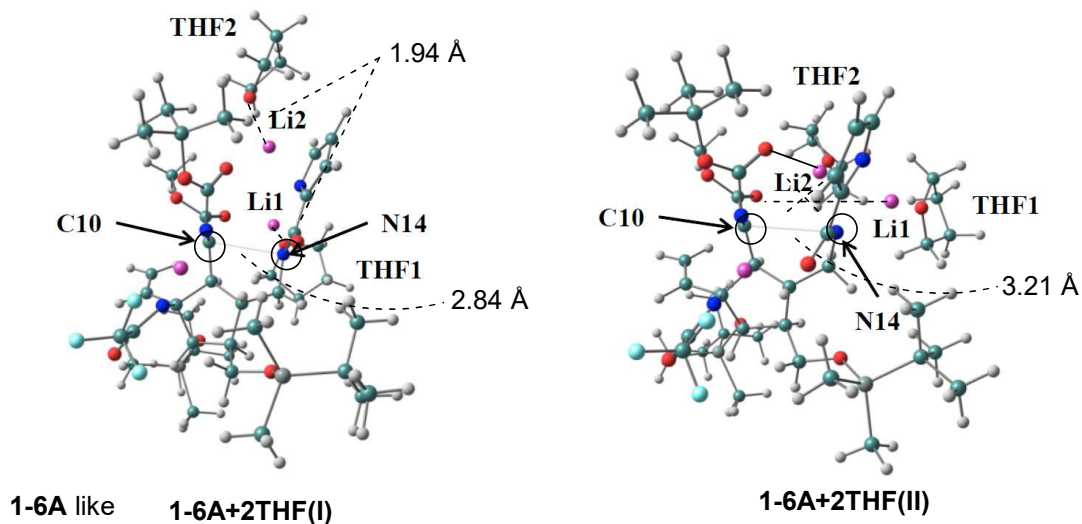
If the rotation of the single bond C10-C11 was occurred before the nucleophilic addition of the amide anion (N14).



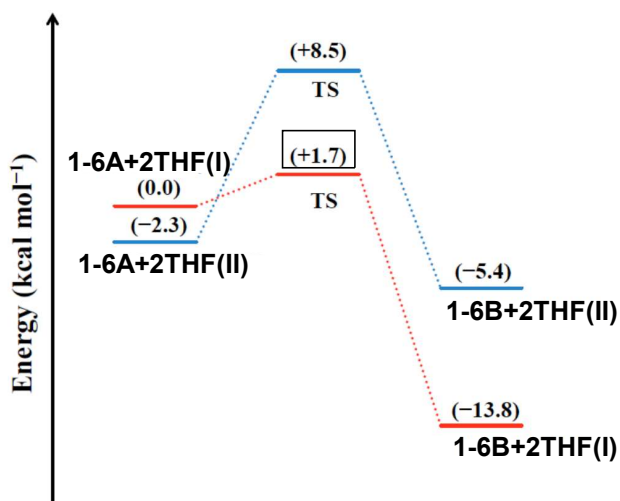


**Table 1**

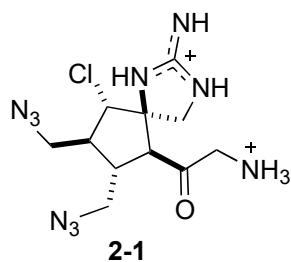
base	additive	T (°C)	results
LiN(TMS) <sub>2</sub>	—	-78 °C to 0 °C	70%
LiN(TMS) <sub>2</sub>	HMPA (3.6 eq)	-78 °C to 0 °C	complex mixture desired cyclized (D/E ring) products and related intermediates were not detected no cyclized (D/E ring) products
NaN(TMS) <sub>2</sub>	—	-78 °C to 0 °C	
KN(TMS) <sub>2</sub>	—	-78 °C to 0 °C	
LiN(TMS) <sub>2</sub>	—	0 °C	10 ~ 20%



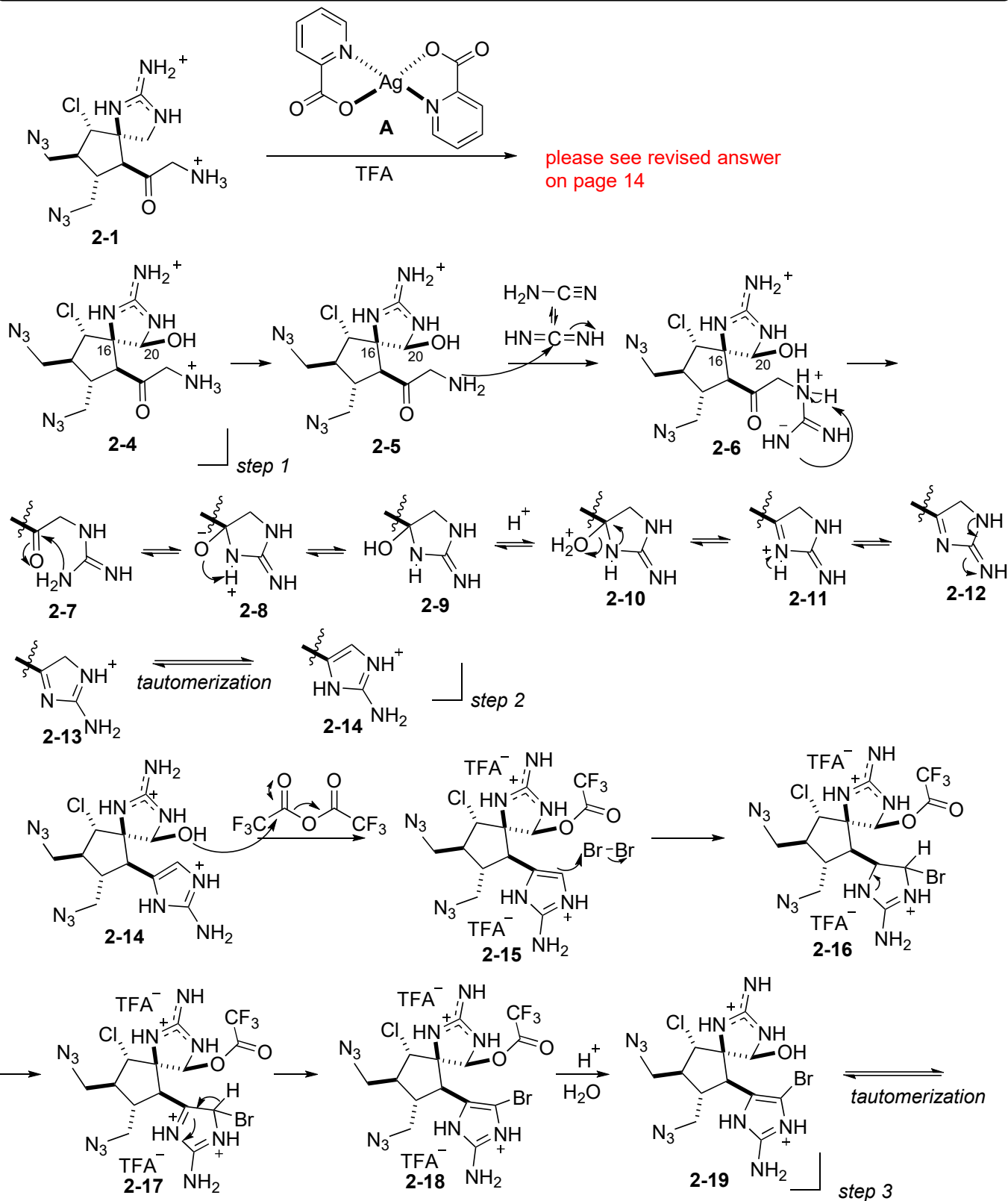
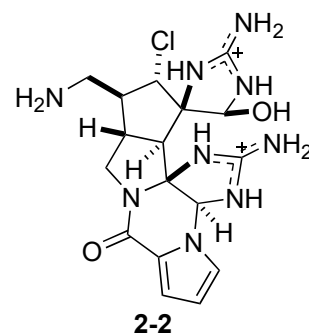
**1-6A+2THF(II)** is slightly more stable than **1-6A+2THF(I)** by 2.3 kcal/mol.



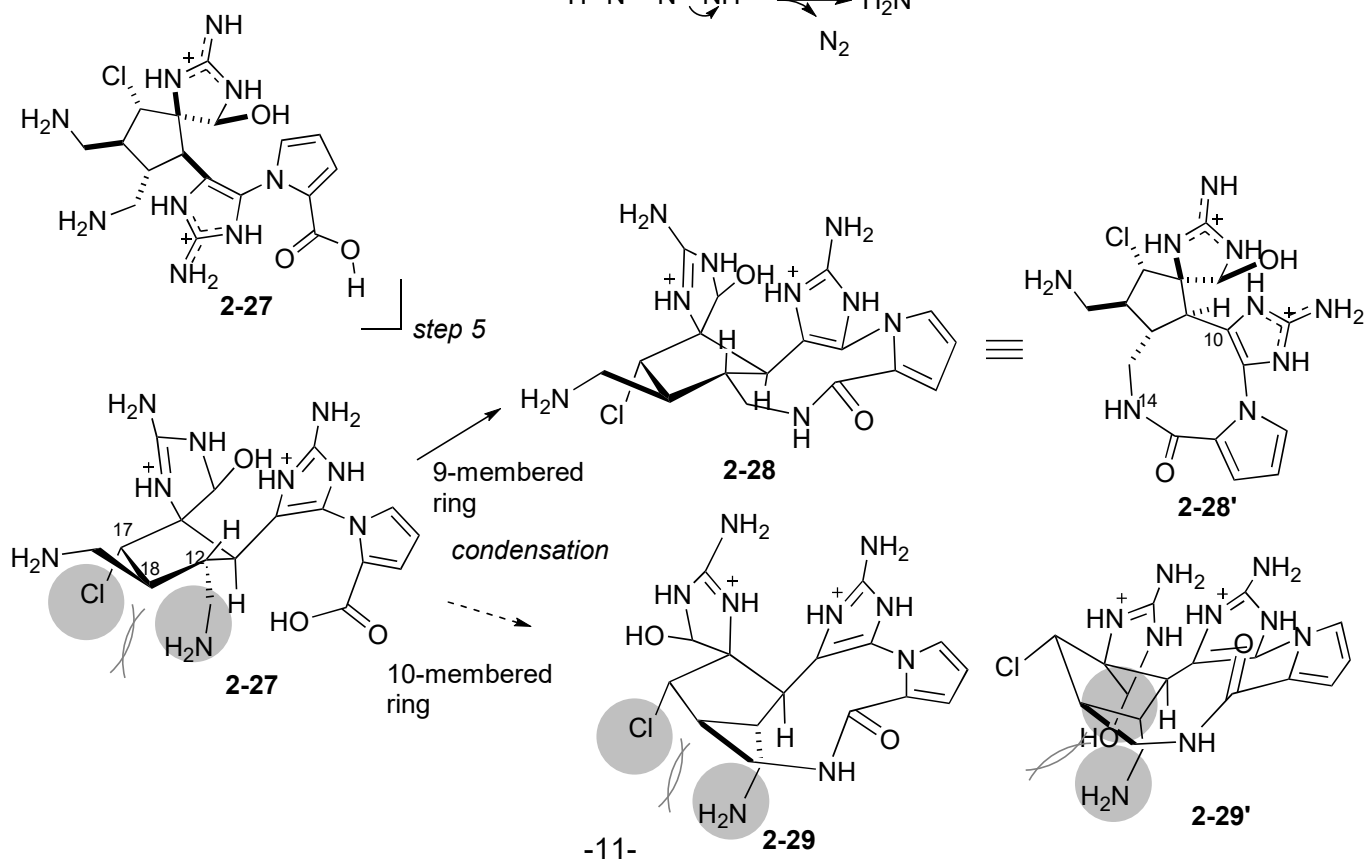
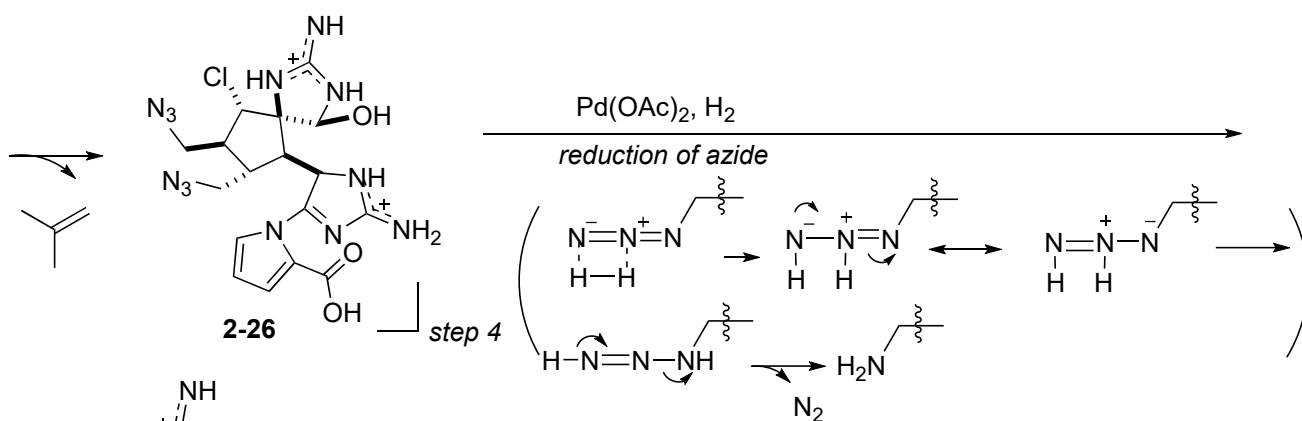
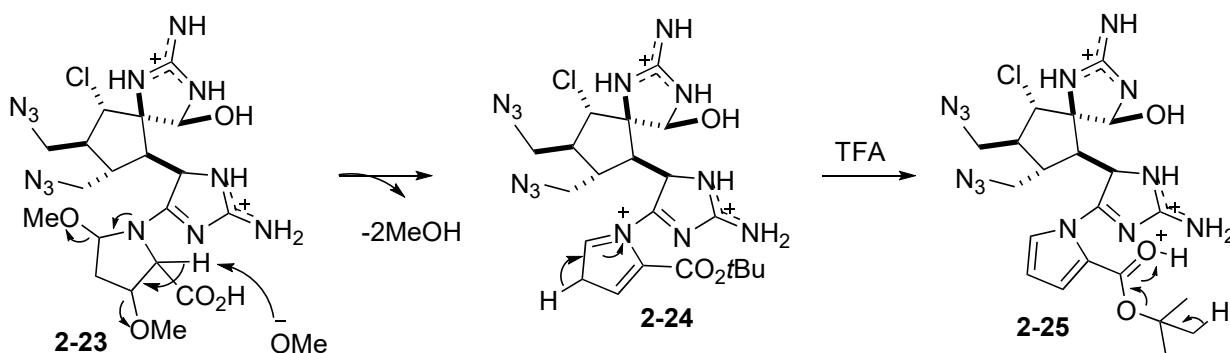
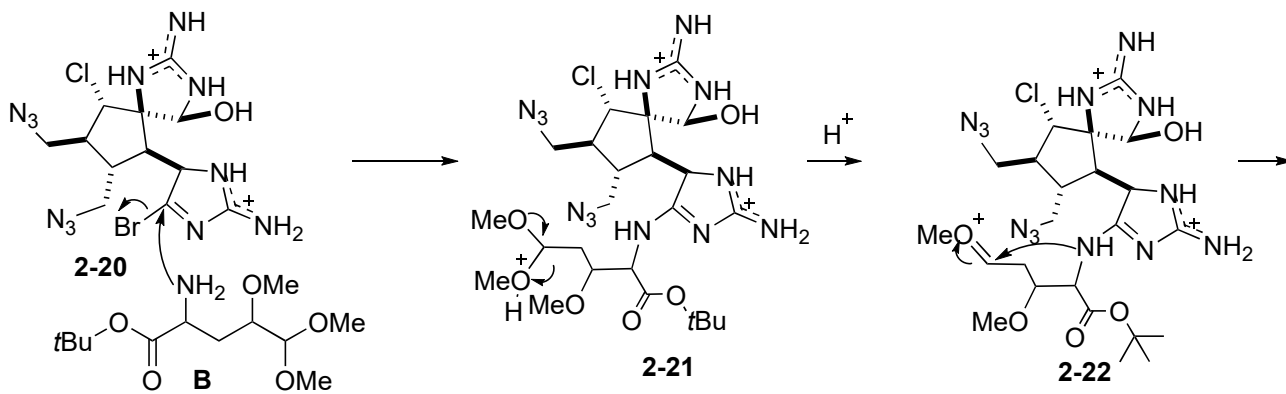
2. Please provide the mechanism of the following reactions.

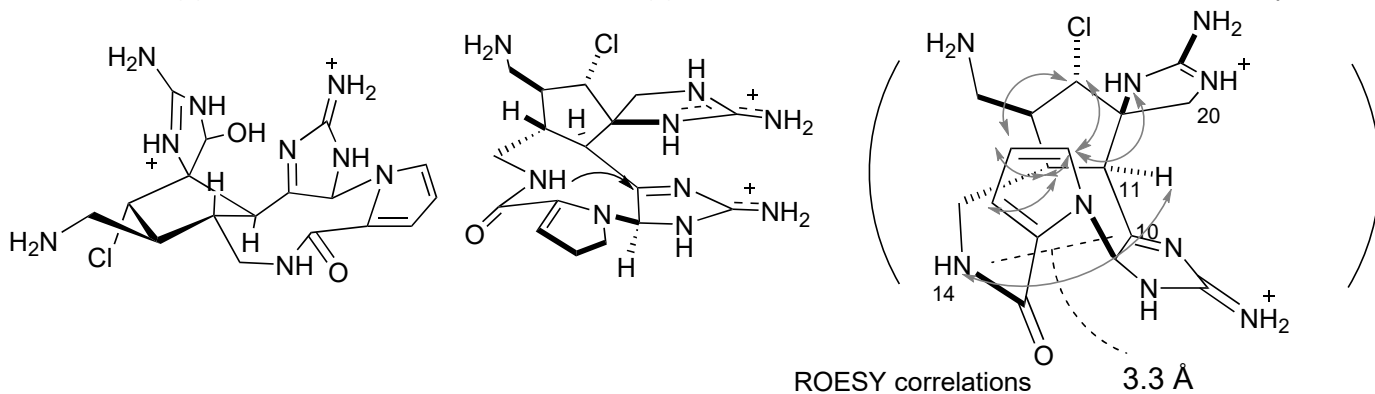
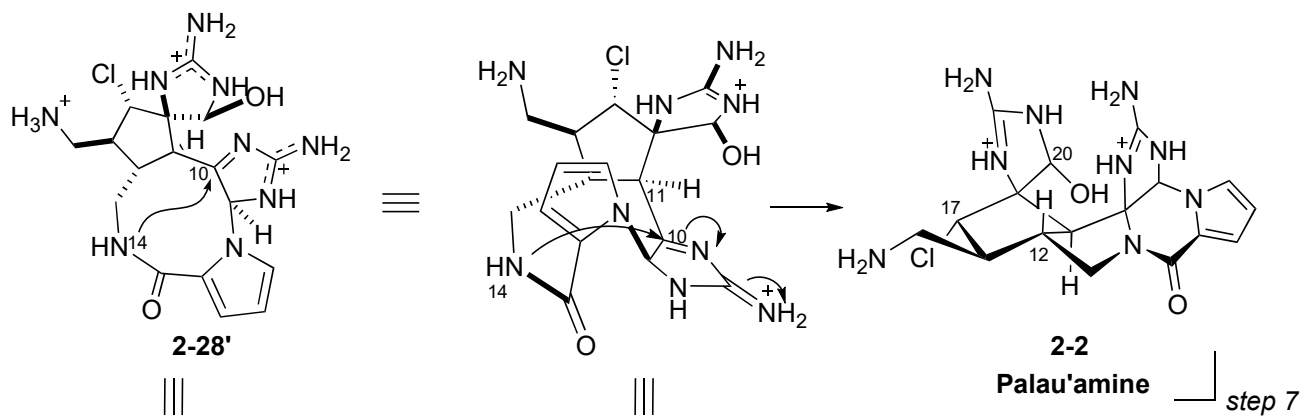
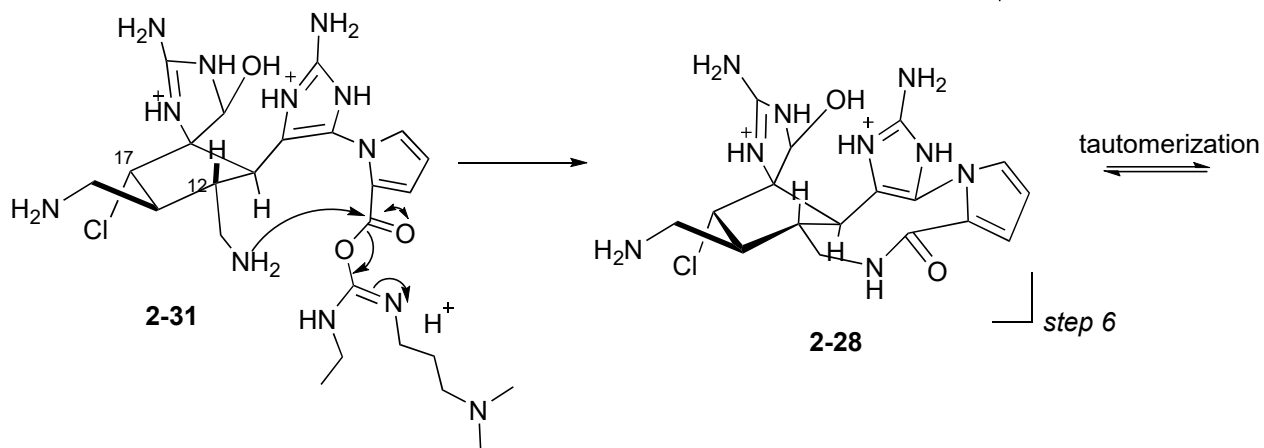
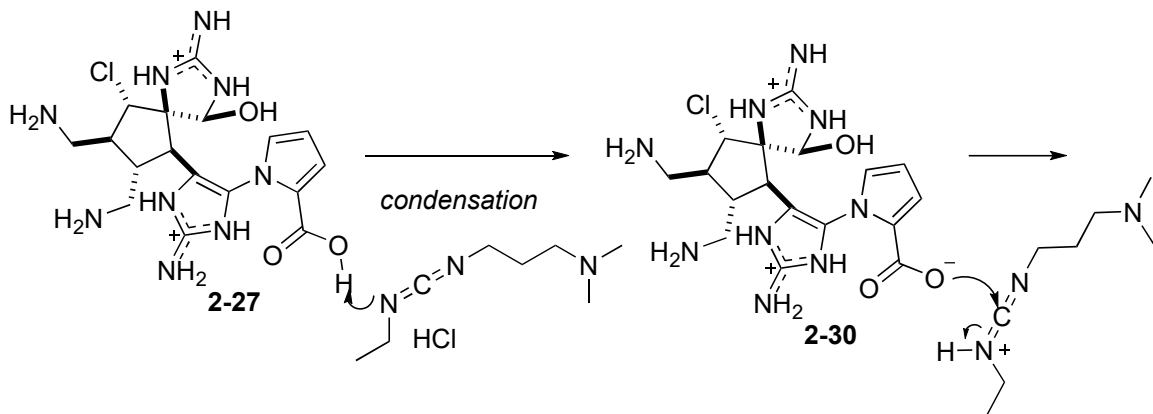


- A** (2.5 equiv), 10% TFA/H<sub>2</sub>O, 23 °C, 69%
- H<sub>2</sub>NCN (40 equiv), pH 5, brine, 70 °C, 65%
- TFAA: TFA (1:1); Br<sub>2</sub> (2.0 equiv); TFA: H<sub>2</sub>O (1:1), 38 °C, 54%
- AcOH (3.0 equiv), **B** (3.0 equiv), THF, 38 °C; TFA:CH<sub>2</sub>Cl<sub>2</sub> (1:30 to 1:1), 23 °C, 44%
- Pd(OAc)<sub>2</sub> (1.6 equiv), H<sub>2</sub> (1 atm), TFA: H<sub>2</sub>O (1:9), 23 °C
- EDC (3.0 equiv), DMF, 23 °C;
- TFA, 70 °C (17%, 3 steps)

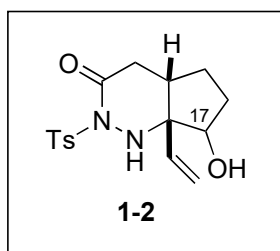
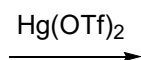
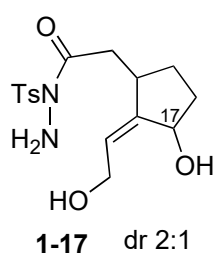


please see revised answer on page 14

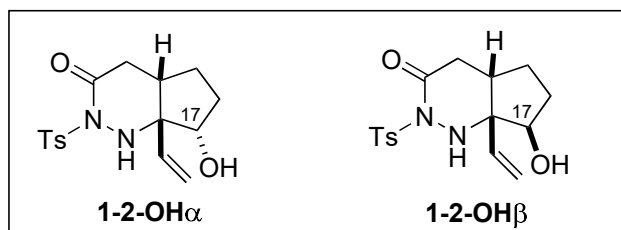
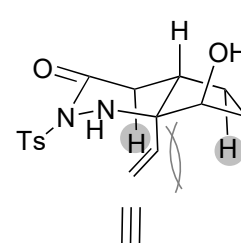
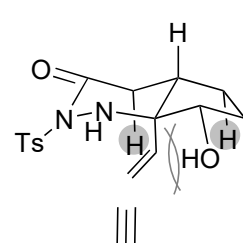
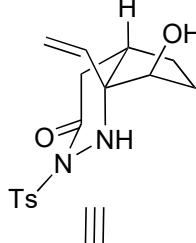
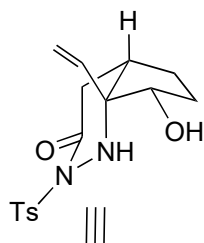
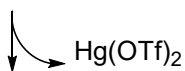
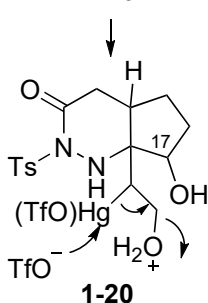
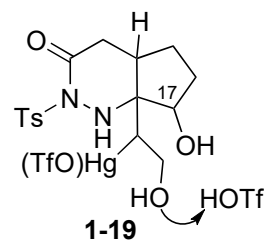
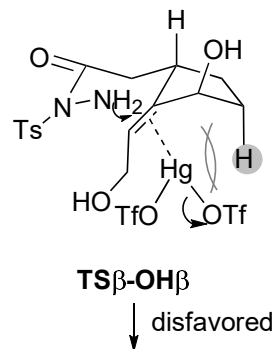
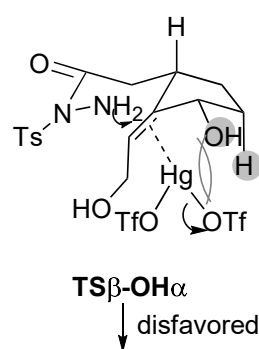
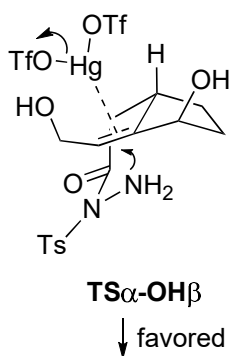
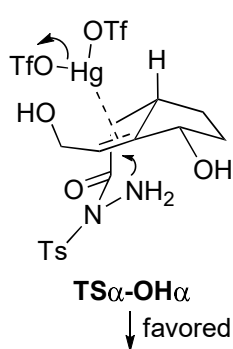
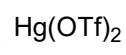




Revised answer:



**1-17** dr 2:1



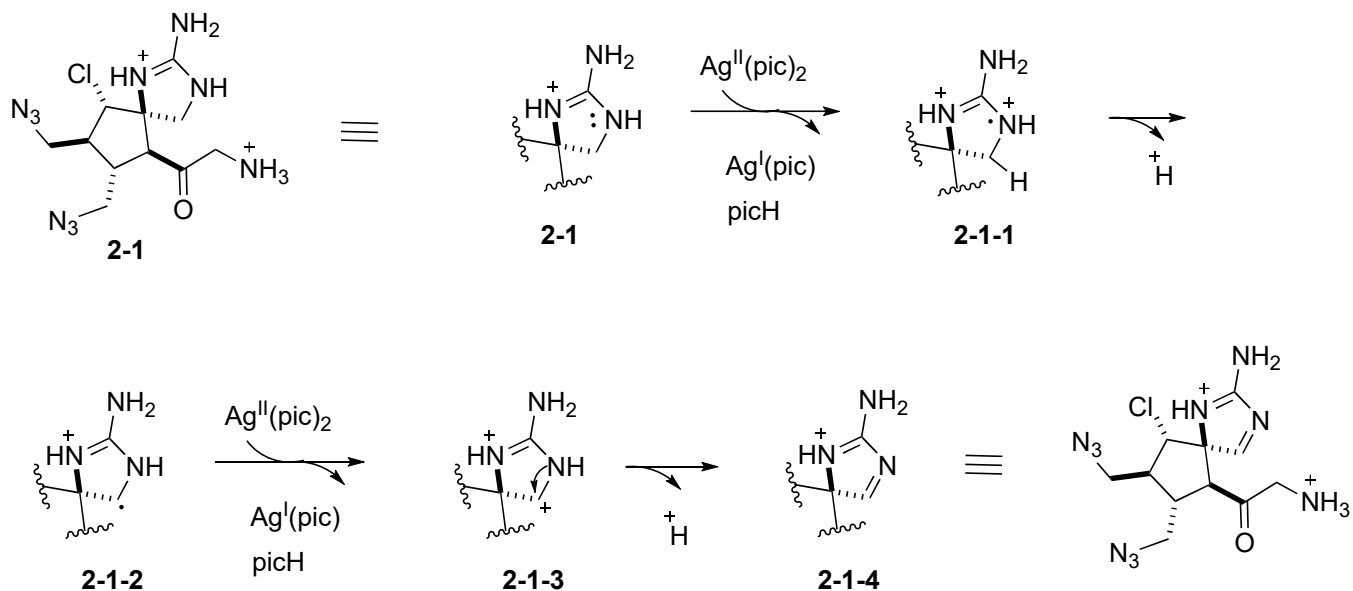
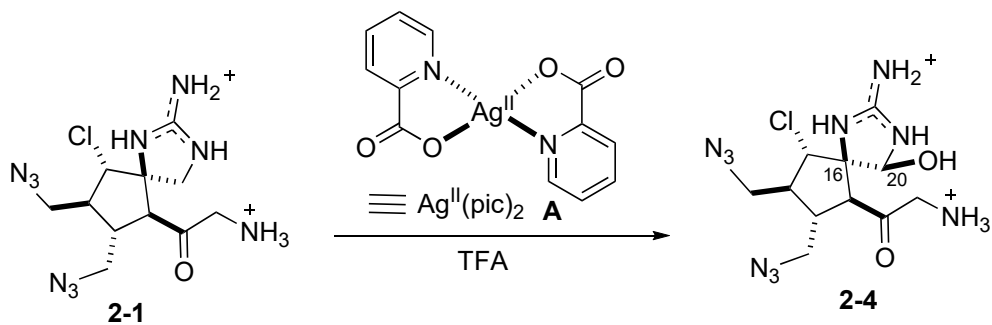
*cis*-OH $\alpha$

dr 1 : 2

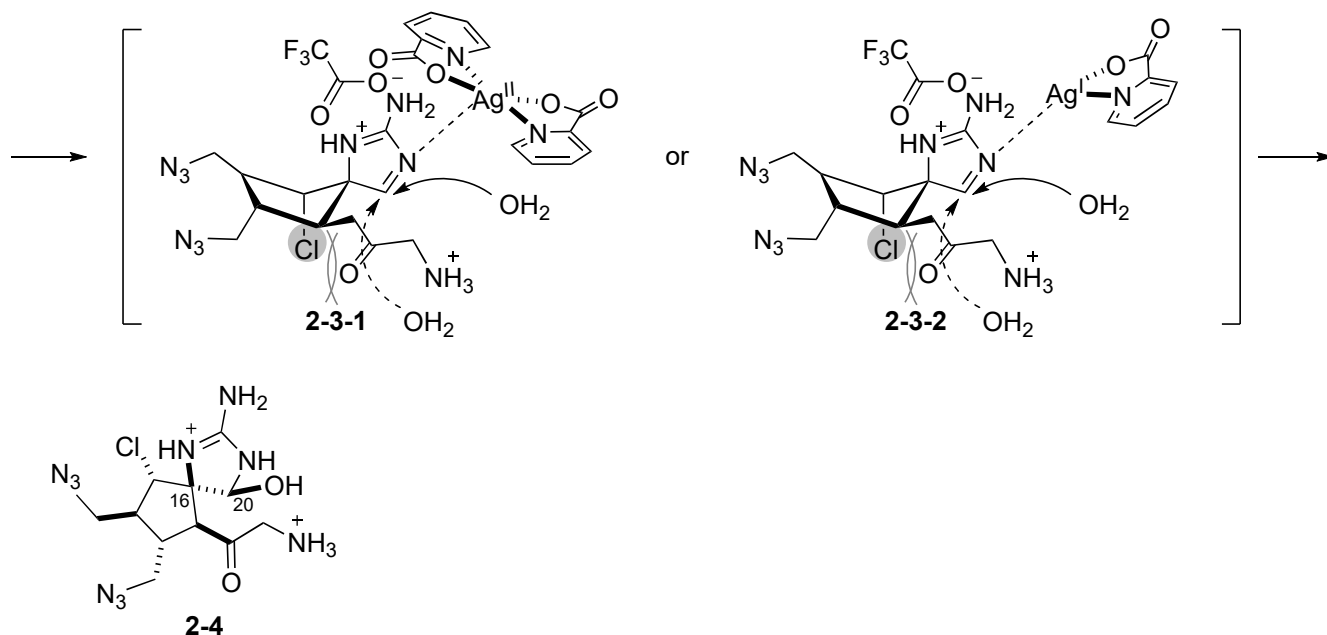
*cis*-OH $\beta$

*trans*- $\alpha$ OH

*trans*- $\beta$ OH



Reaction undergoes the equivalent of a one-electron change giving silver(I) picolinate as product.\*



\*Glarke, T. G.; Hampson, N. A.; Lee, J. B.; Morley, J. R.; Scanlon, B. *Can. J. Chem.* **1969**, *47*, 1649.