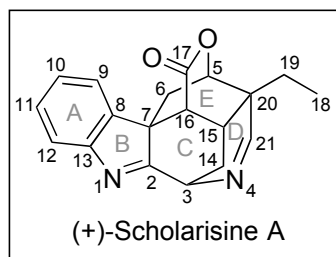


Problem Session (2) -Answer-

2015.05.23. Hideyuki Sawada

Topic: Total synthesis of (+)-Scholarisine A

0. Introduction.



Scholarisine A is one of akkumamine monoterpene indole alkaloids. Akkumamine alkaloids are ones that are derived biosynthetically from geissoschizine (**0-1**) via a cyclization leading to a bond between C-7 and C-16¹.

Here, details of scholarisine A were shown.

0-1. Details of (+)-scholarisine A.

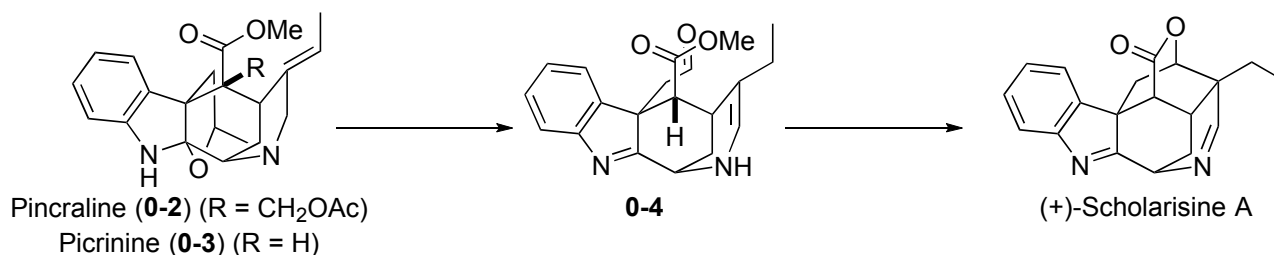
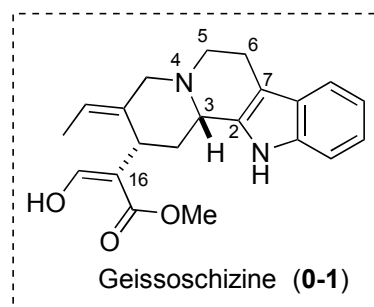
0-1-1. Isolation: *Alstonia scholaris* ²⁾

0-1-2. Structural feature:

- architecturally intricate cage-like scaffold
- bridged lactone
- aliphatic imine
- indolenine core.

0-1-3. Biological activity:

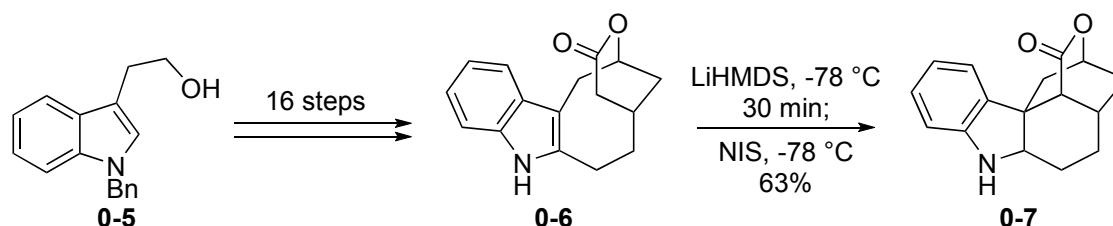
- The activity of scholarisine A is unexplored to date.
- Pincraline (**0-2**), congeners of a putative biosynthetic precursor picrinine (**0-3**), selectively inhibits SGLT2, a renal cortex membrane protein that regulates glucose reabsorption, which was validated as a target for type-II diabetes intervention³⁾. For SGLT2 inhibitors in detail, see [131214_LS_Kamimura](#).



0-1-4. Synthetic study and total synthesis of scholarisine A.

0-1-4-1. Smith, III et. al. (In 2008, first total synthesis) → **Problem 1**

0-1-4-2. Higuchi et. al. (In 2013, synthetic study)⁴⁾



0-1-4-3. Snyder, S. A. et. al. (In 2013, total synthesis) → **Problem 2**

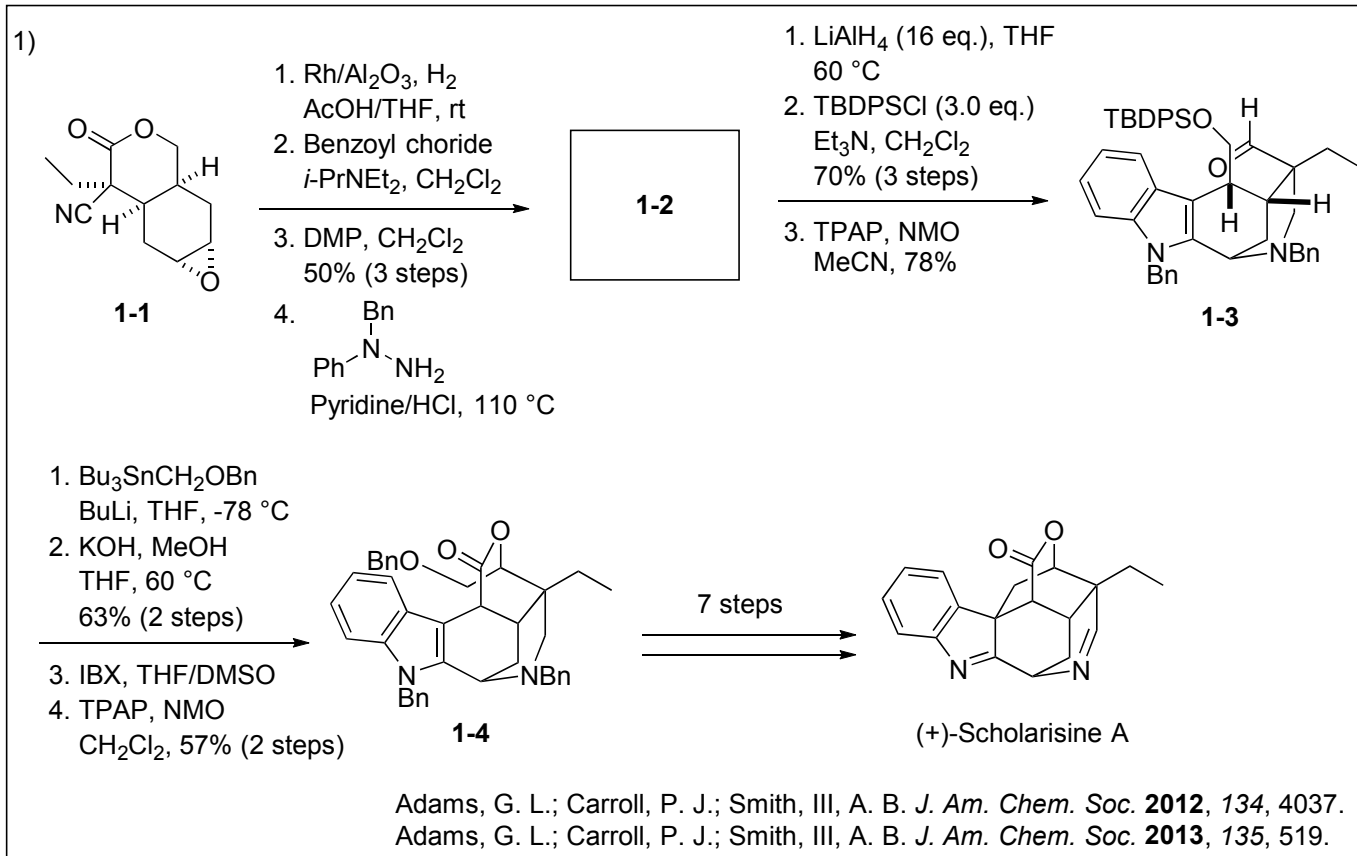
1) a) Ramirez, A.; Garcia-Rubio, S. *Curr. Med. Chem.* **2003**, *10*, 1891. b) Llopart, C. C.; Joule, J. A. *ARKIVOC* **2004**, No. x, 20-38.

2) Cai, X.-H.; Tan, Q.-C.; Liu, Y.-P.; Feng, T.; Du, Z.-Z.; Li, W.-Q.; Luo, X.-D. *Org. Lett.* **2008**, *10*, 577.

3) Arai, H.; Hirasawa, Y.; Rahman, A.; Kusumawati, I.; Zaini, N. C.; Sato, S.; Aoyama, C.; Takeo, J.; Morita, H. *Bioorg. Med. Chem.* **2010**, *18*, 2152.

4) Watanabe, T.; Kato, N.; Umezawa, N.; Higuchi, T. *Chem. Eur. J.* **2013**, *19*, 4255.

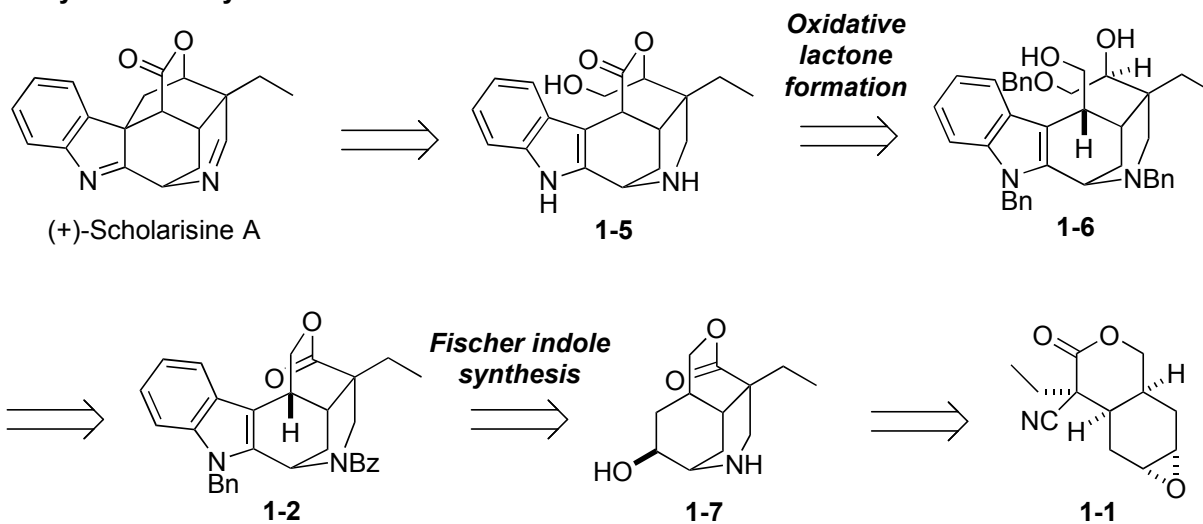
Problem 1: Smith's report



Key steps:

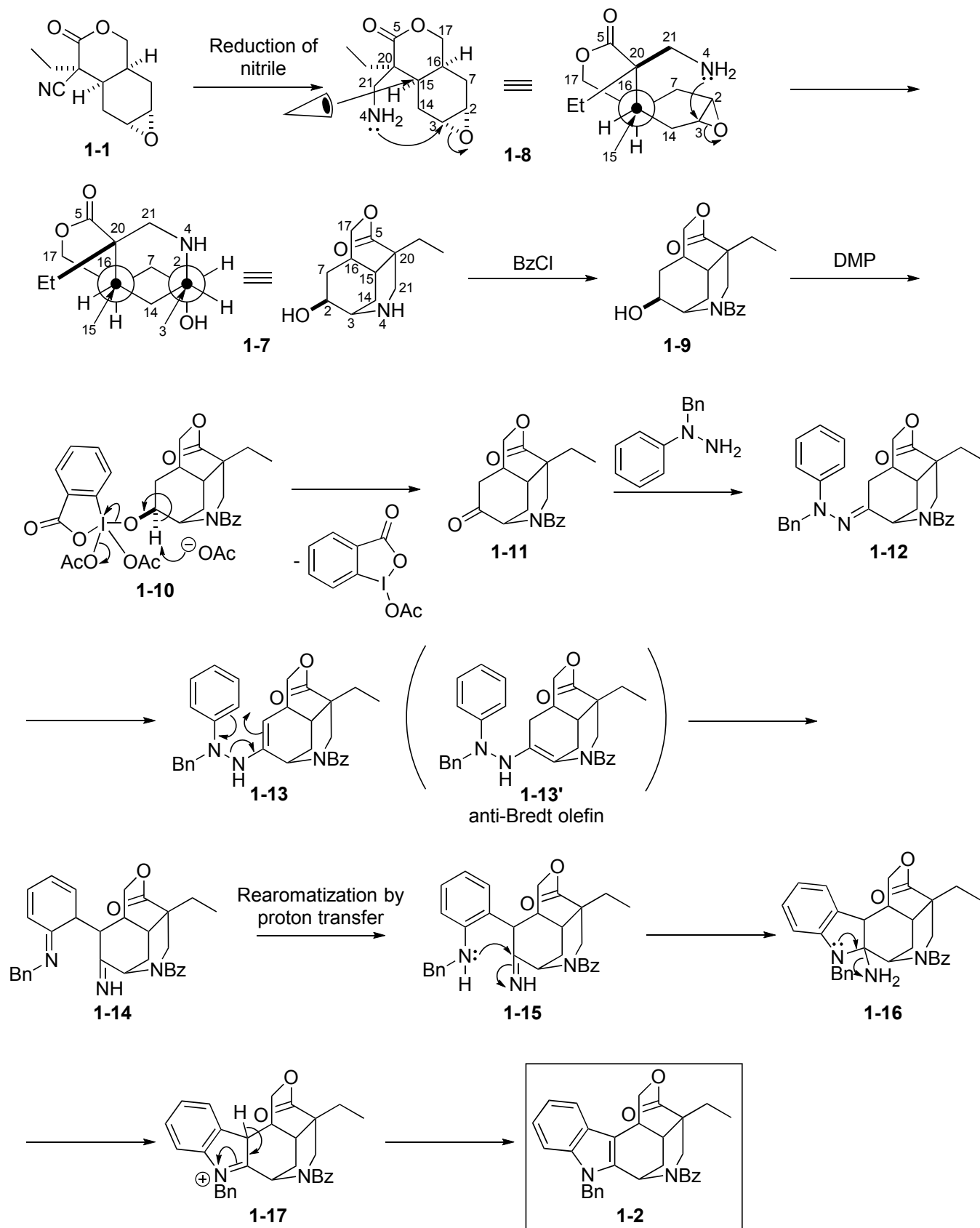
1. Fischer indole synthesis
2. Oxidative lactone formation.

Retrosynthetic analysis:

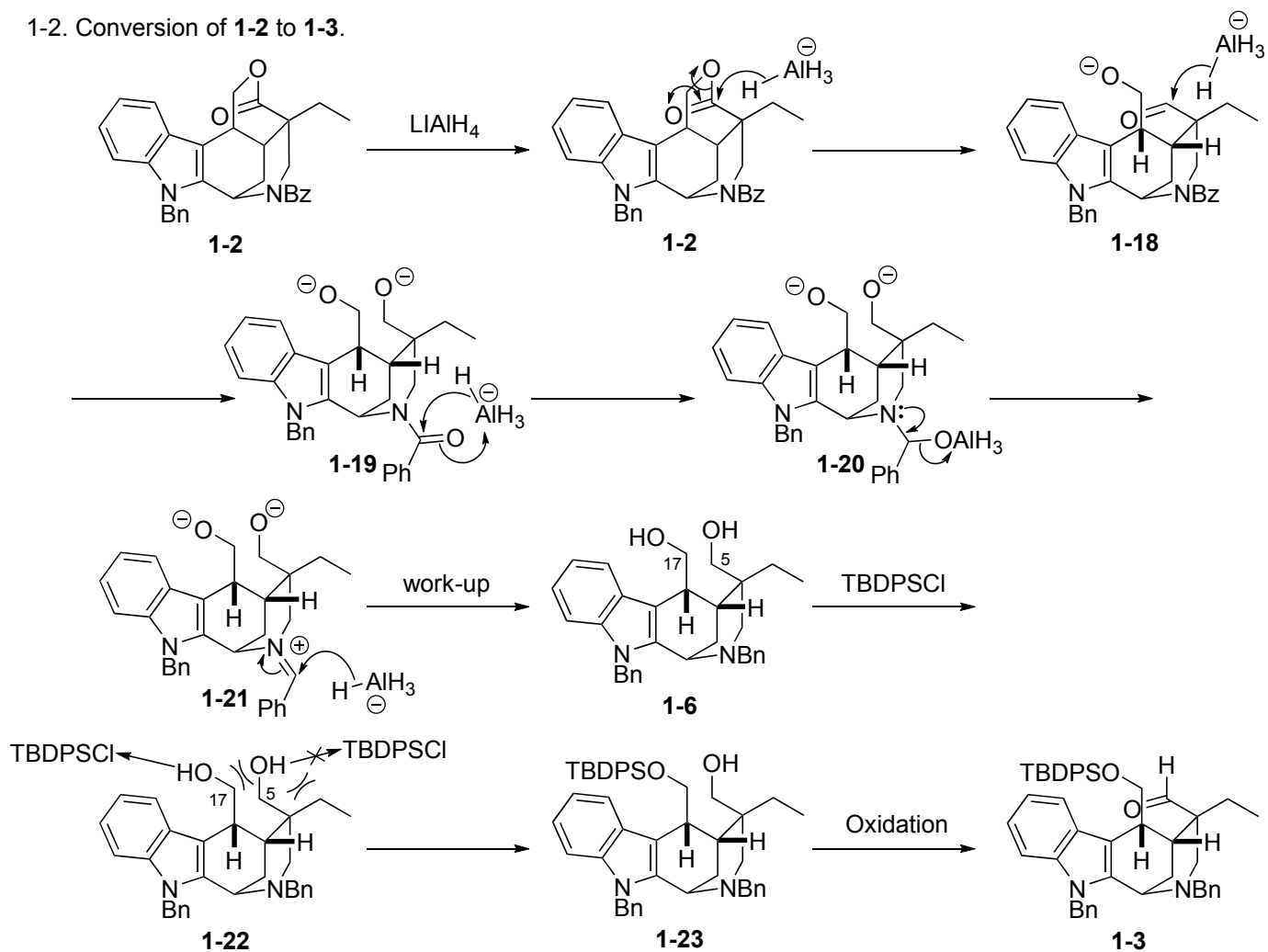


Answer:

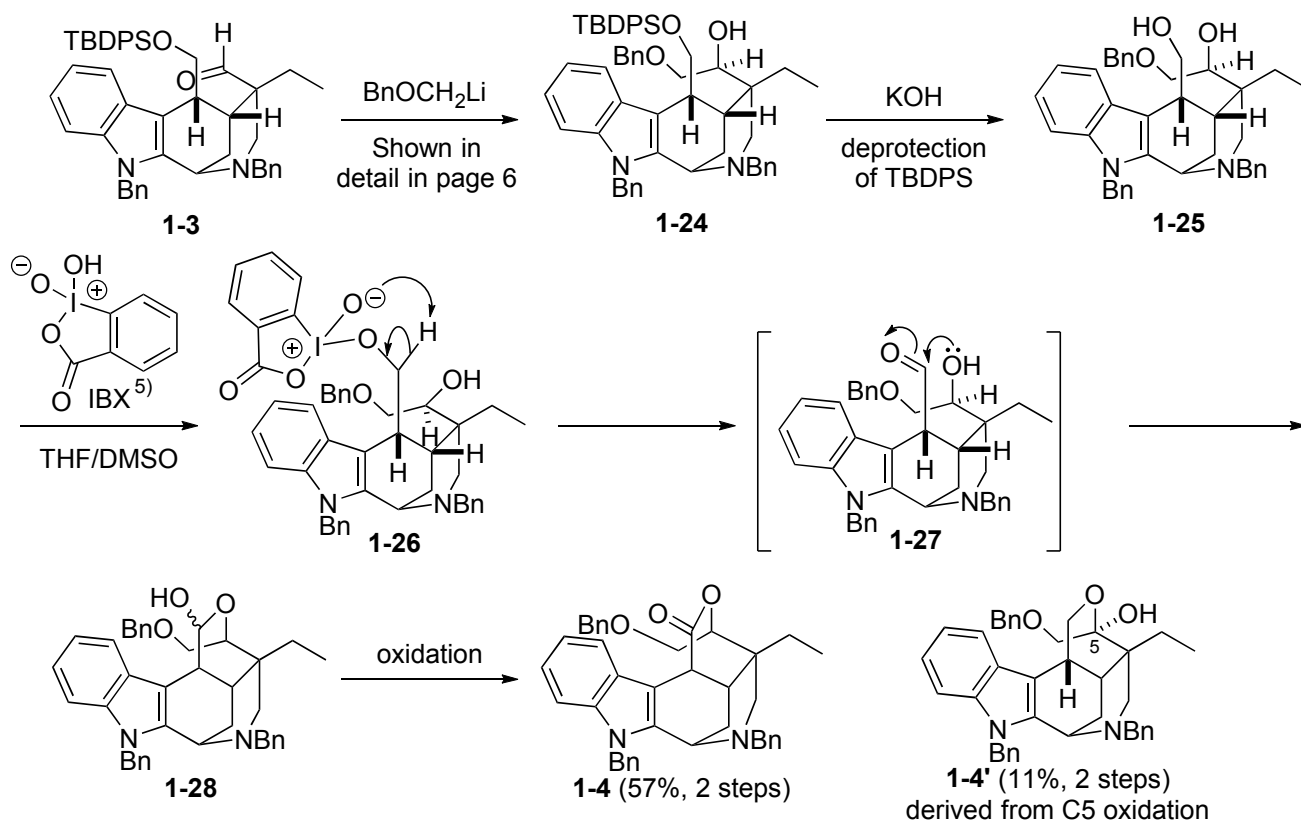
1-1. Conversion of 1-1 to 1-2.



1-2. Conversion of 1-2 to 1-3.



1-3. Conversion of 1-3 to 1-4.

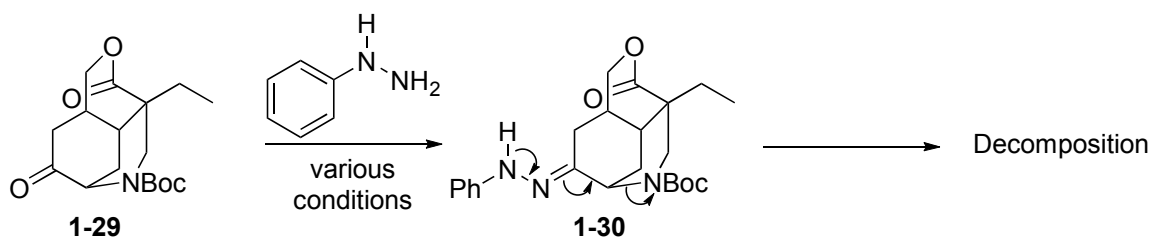


5) IBX convert 1,4-diol to γ -lactol selectively. See : a) 最新有機合成法 p98. b) Corey, E. J.; Palani, A. *Tetrahedron. Lett.* **1995**, 36(44), 7945. c) Corey, E. J.; Palani, A. *Tetrahedron. Lett.* **1995**, 36(20), 3485.

Discussion:

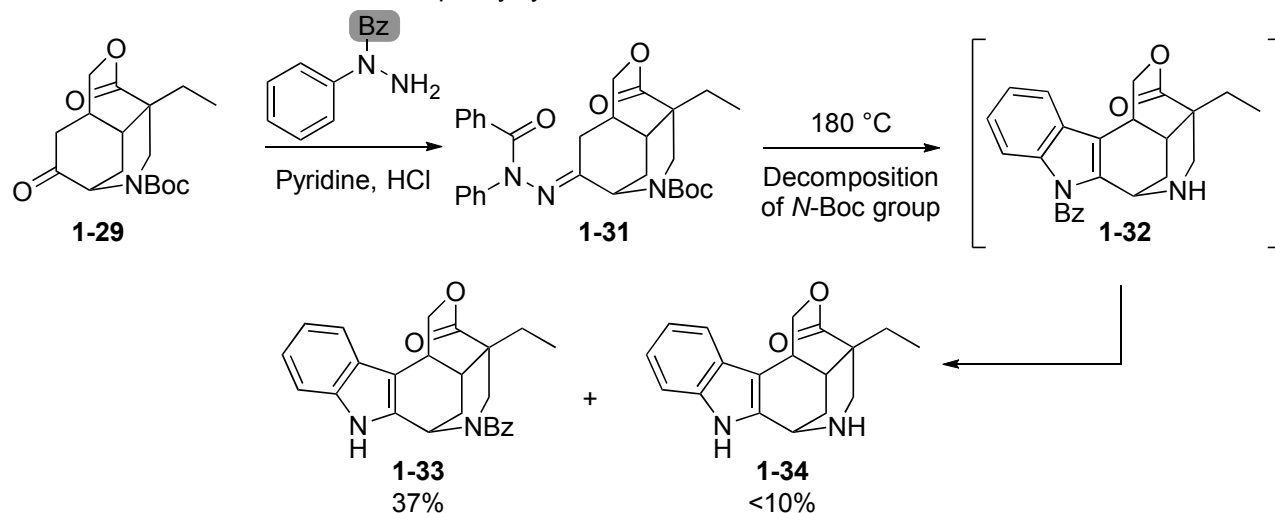
1-4. Initial indole synthesis.

1-4-1. Reaction with phenylhydrazine.



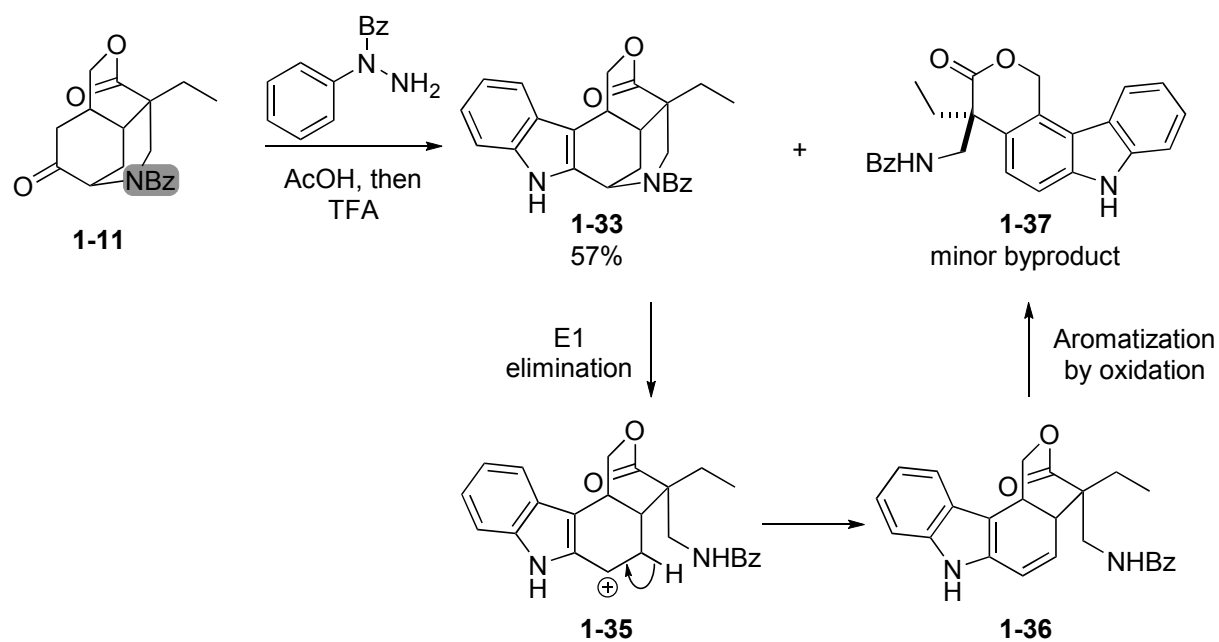
⇒ Deprotonation of phenylhydrazone derived from electron withdrawing ability of *N*-Boc group was problematic.

1-4-2. Reaction with *N*-Bz substituted phenylhydrazine.



⇒ This result shows the possibility of intramolecular or intermolecular benzoyl migration. So this route was problematic in term of scale up synthesis.

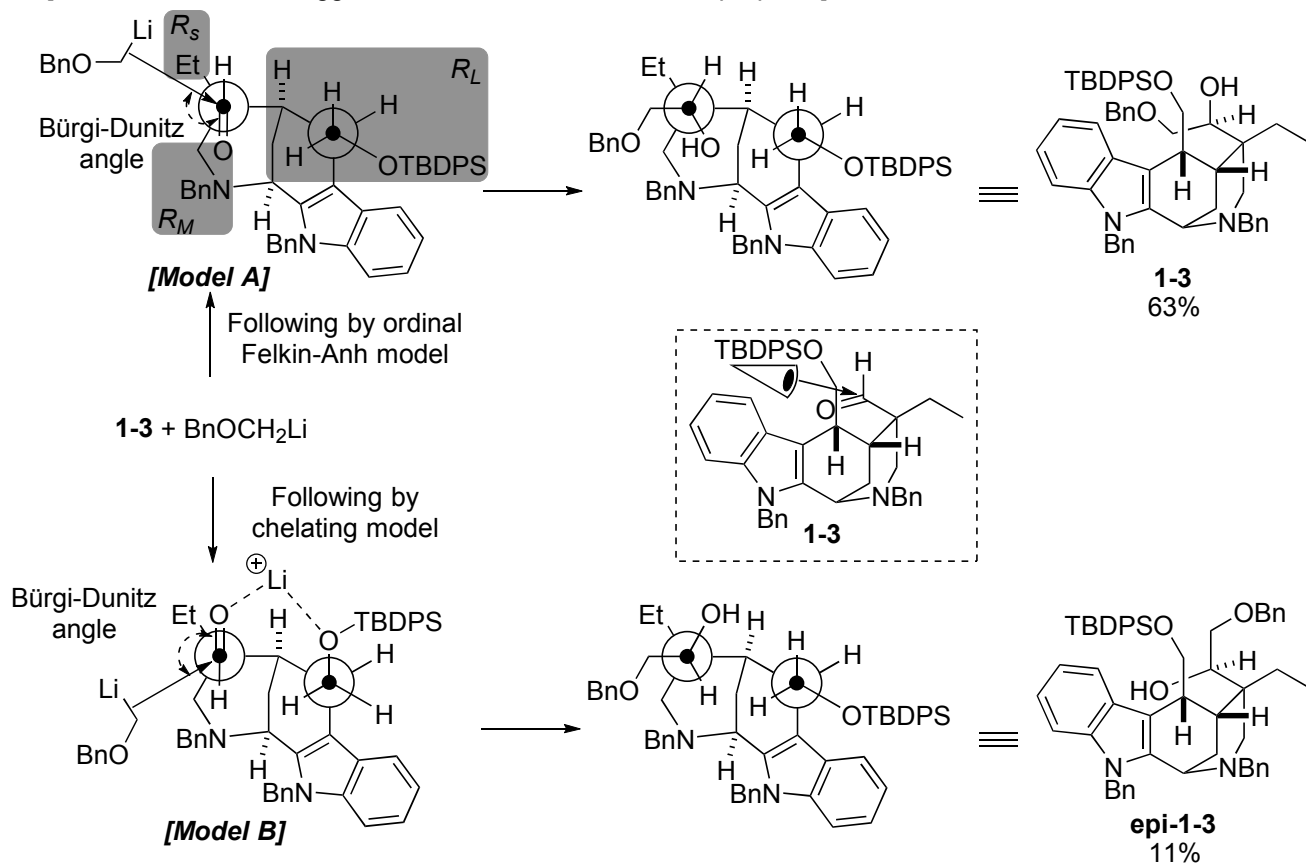
1-4-3. Reaction of *N*-Bz type substrate.



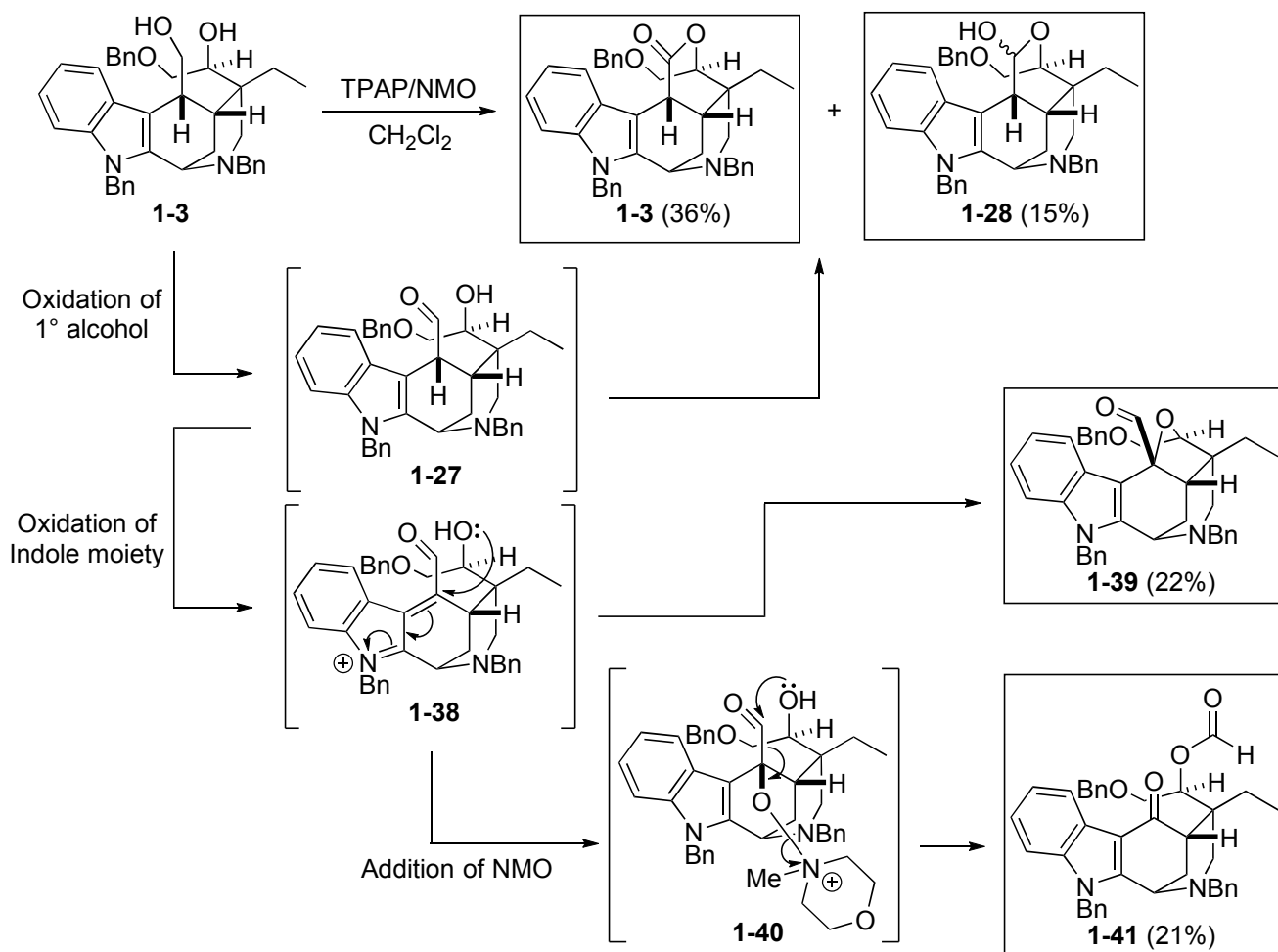
⇒ The formation of minor byproduct **1-37** supports the decomposition pathway shown in 1-4-1.

1-5. Selectivity of addition of BnOCH_2Li to aldehyde

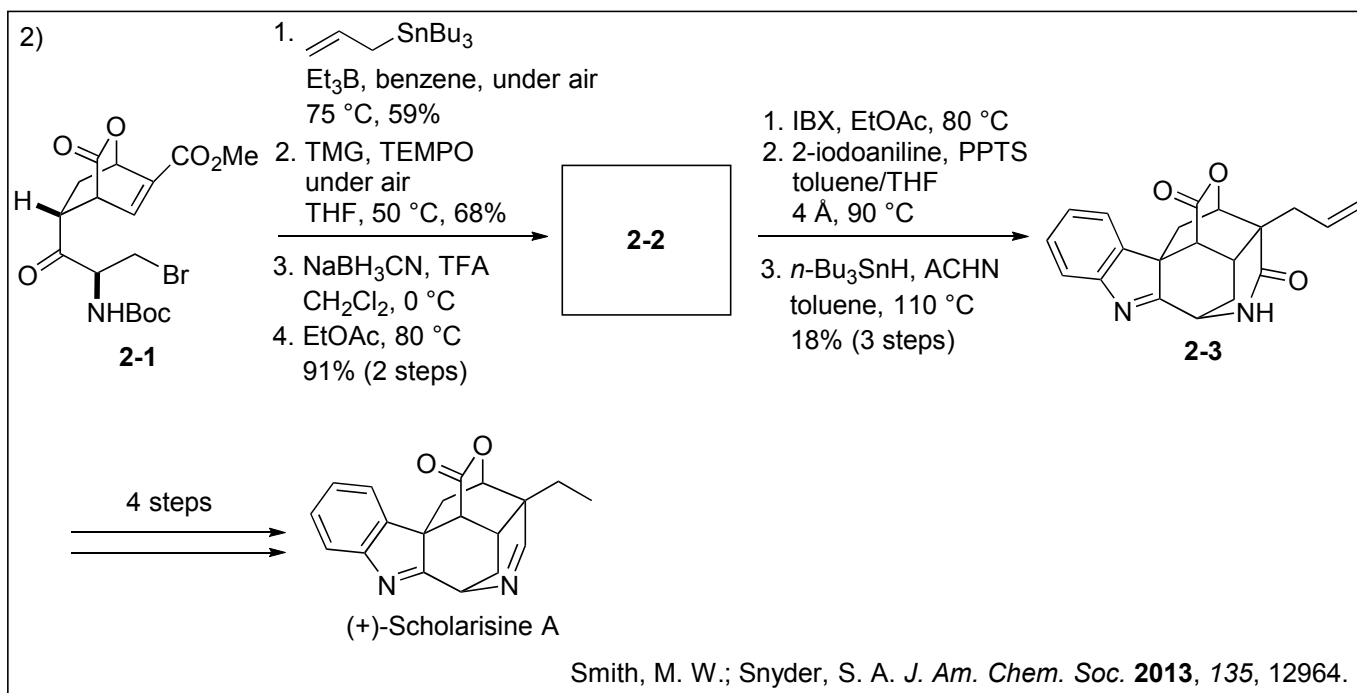
[Model A is author's suggest, while model B is Sawada's proposal].



1-6. Direct TPAP oxidation of **1-25**.



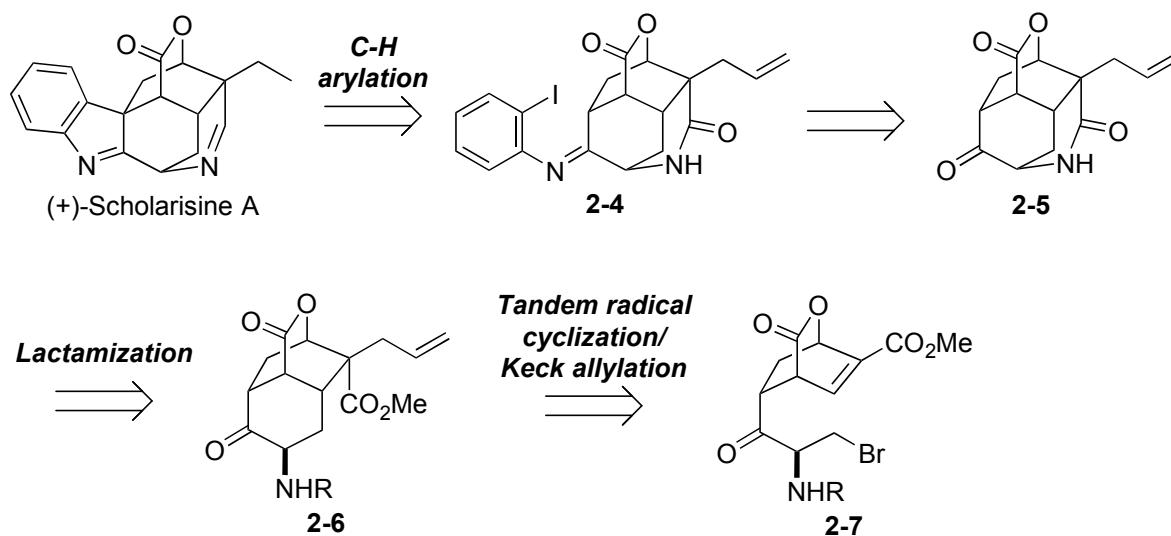
Problem 2: Snyder's report



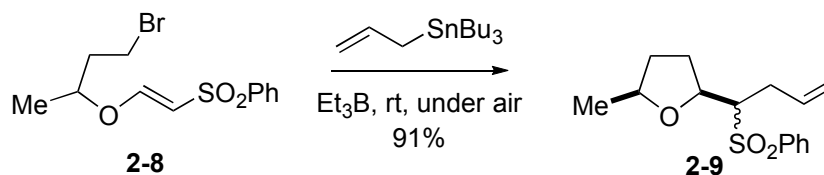
Key steps:

1. Tandem radical cyclization followed by Keck allylation.
2. Lactamization.
3. Indolenine formation by C-H arylation

Retrosynthetic analysis:



■ Another example of tandem radical cyclization/Keck allylation⁶⁾.

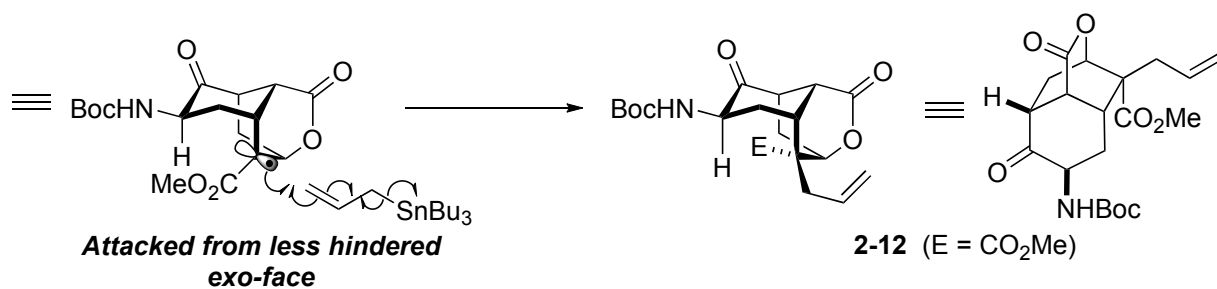
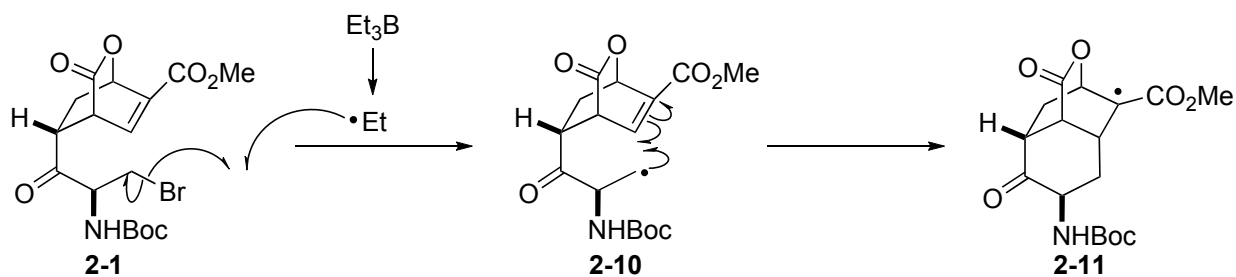


6) Evans, P. A.; Manangan, T. *Tetrahedron Lett.* **1997**, *38*, 8165.

Answer:

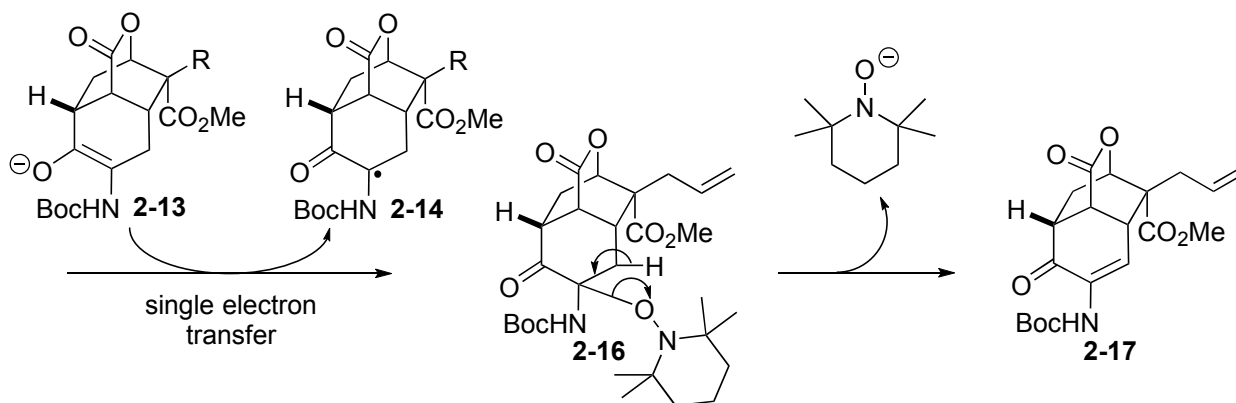
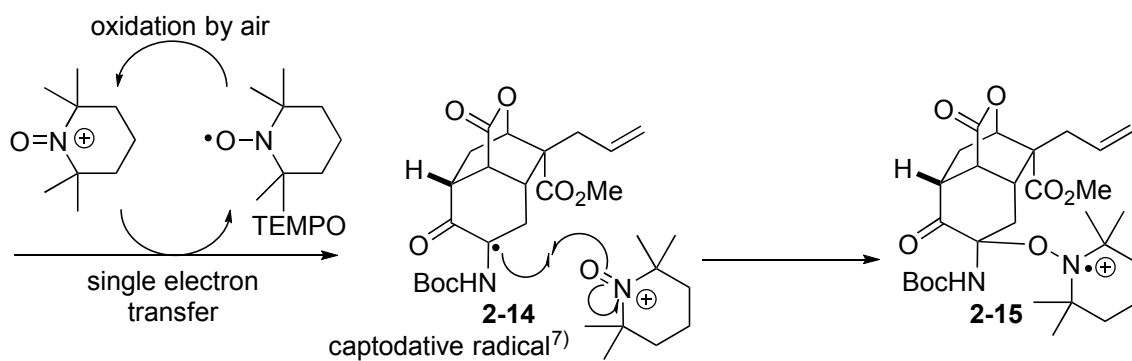
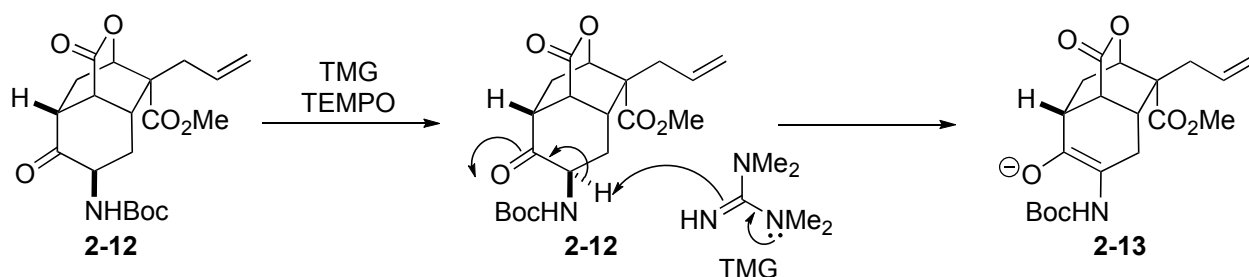
2-1. Conversion of **2-1** to **2-2**.

2-1-1. Conversion of **2-1** to **2-12**.



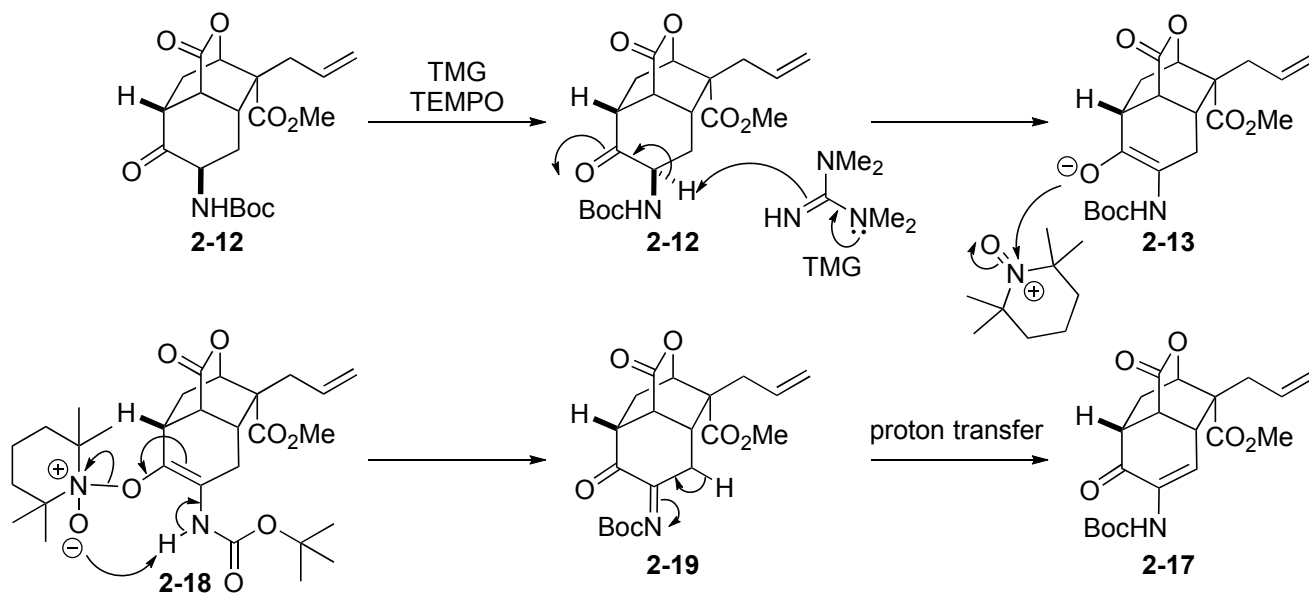
2-1-2. TMG, TEMPO oxidation step.

[Path A ~ captodative radical pathway ~]

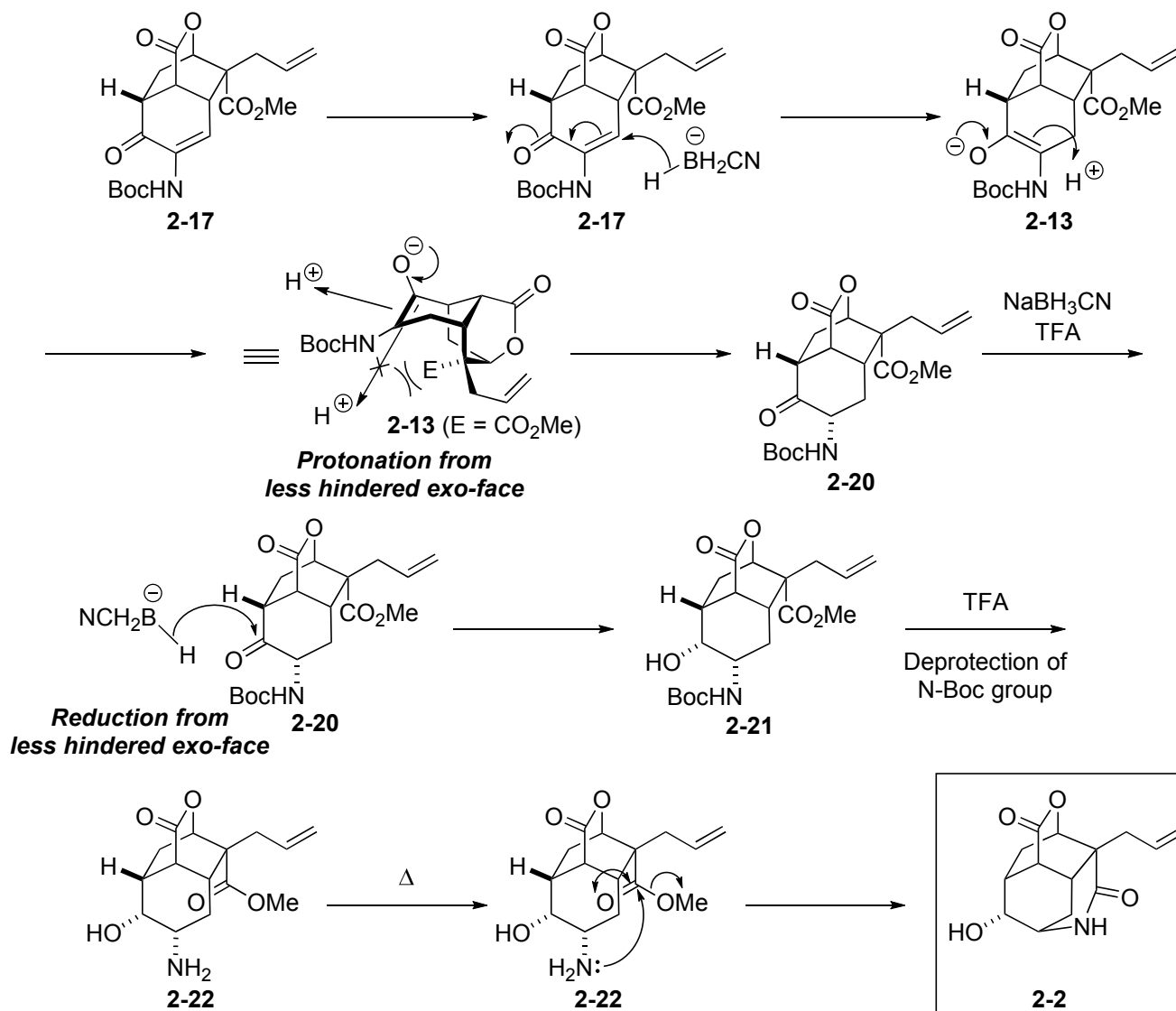


7) Viehe, H. G.; Janousek, Z.; Merenyi, R. *Acc. Chem. Res.* **1985**, *18*, 148.

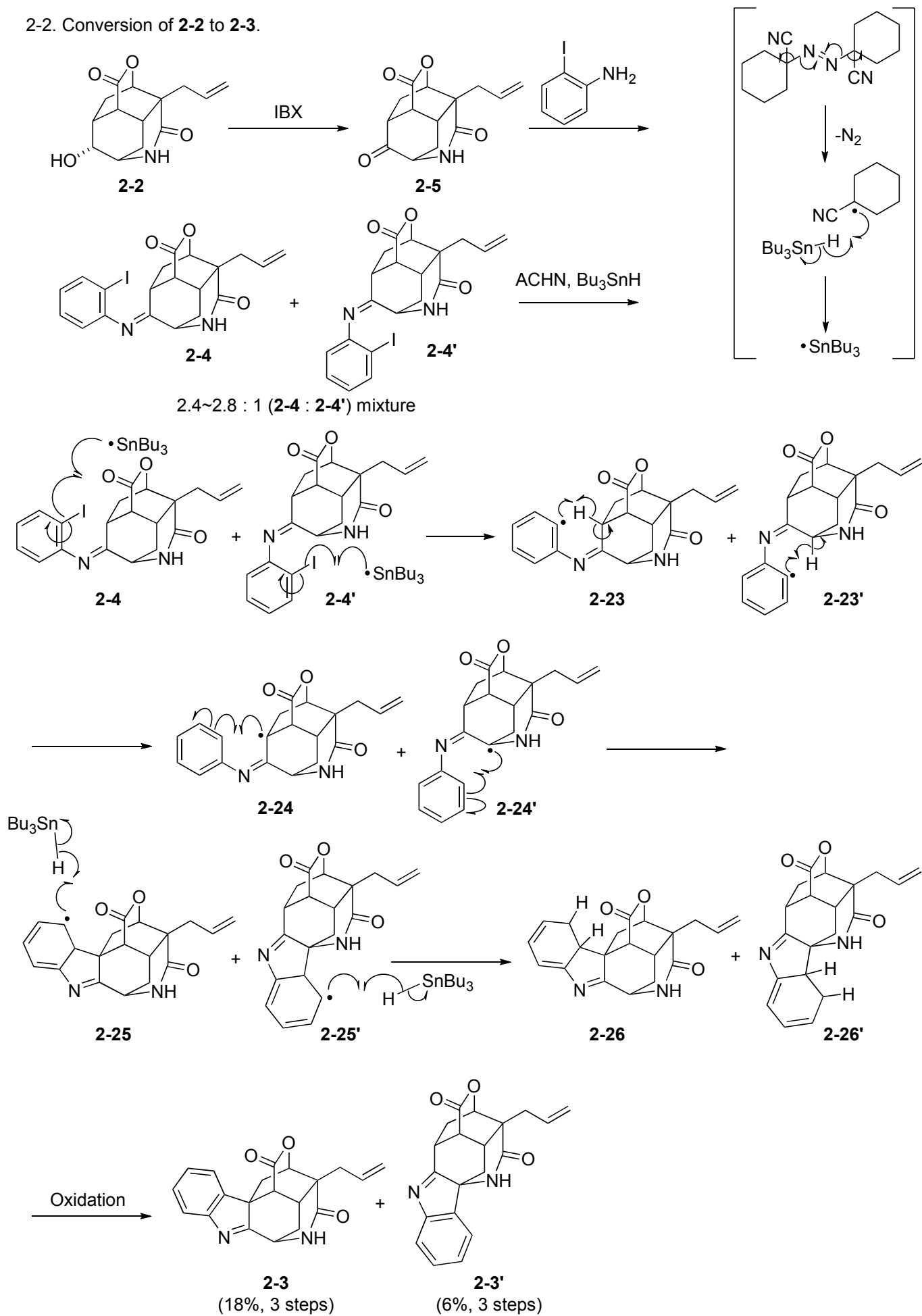
[Path B ~ general TEMPO oxidation-like pathway ~]



2-1-3. Conversion of **2-17** to **2-2**.



2-2. Conversion of 2-2 to 2-3.

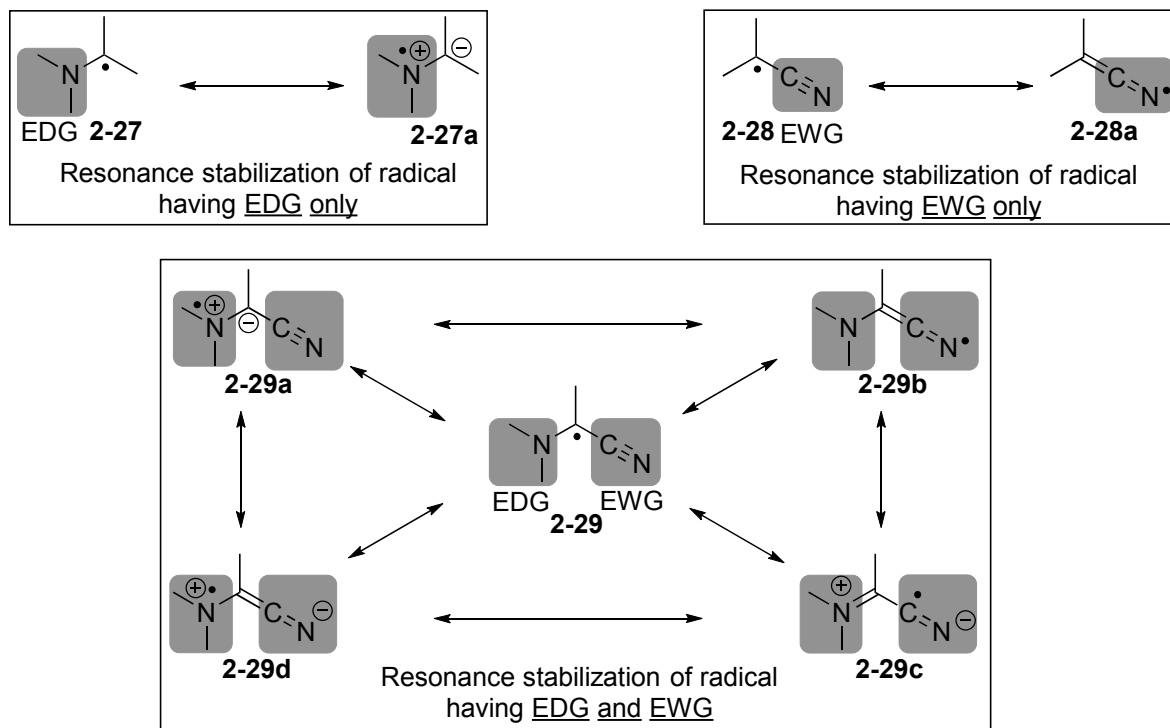


Discussion:

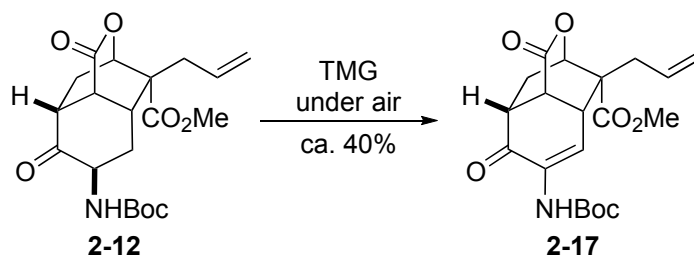
2-3. Appendix of TMG, TEMPO oxidation step.

2-3-1. Captodative effect.

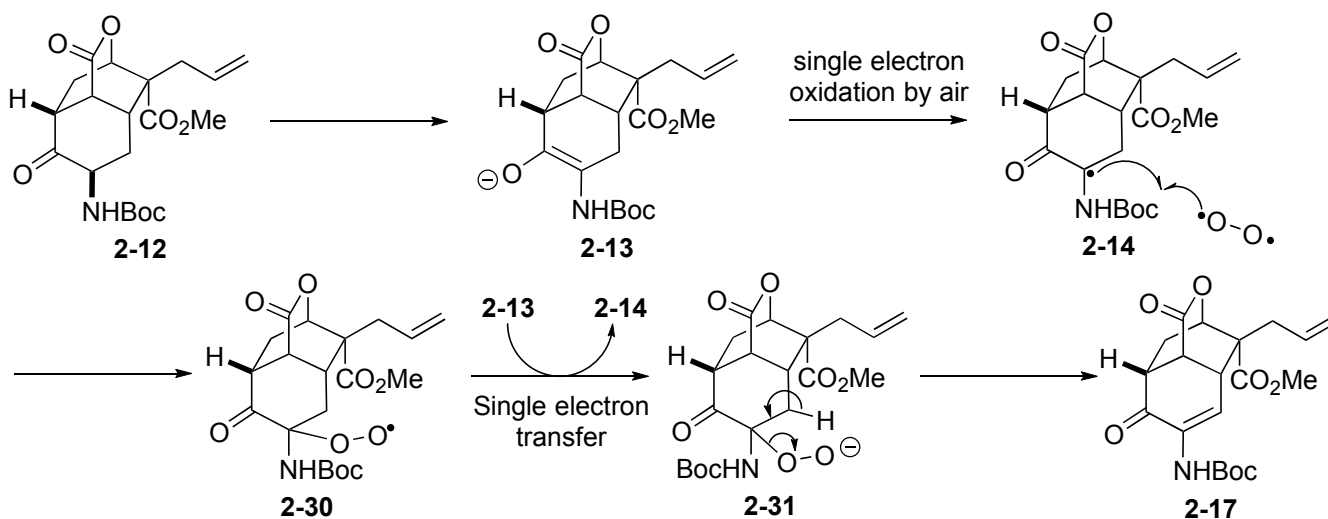
Captodative effect is the stabilization effect of radicals by the synergistic effect of an electron withdrawing group (EWG) and electron donating group (EDG). The name originates as the EWG is sometimes called the "captor" group, while the EDG is the "donor" group.



2-3-2. Result of reaction from 2-12 to 2-17 without TEMPO.

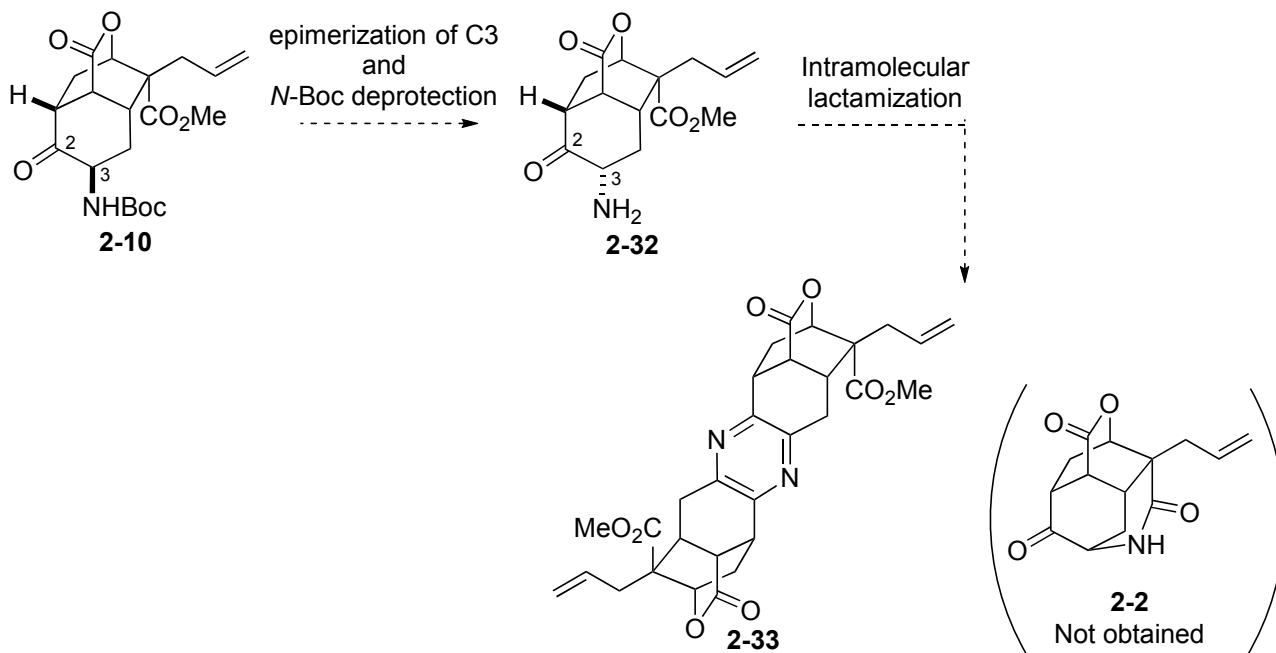


[Proposed mechanism]



⇒ I consider that captodative radical pathway is more plausible.

2-4. Attempt via epimerization and intramolecular lactamization.



⇒ This result shows that reduction of C2 ketone moiety is essential to work intramolecular lactamization well.

Appendix:

TMG, TEMPO oxidation step based on Nagatomo-san and Prof. Inoue's suggestion.

