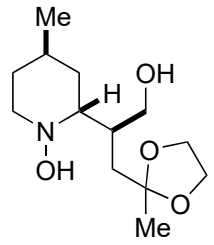
Problem Session (5) Answer

Topic: Total synthesis of Chilocorine C

2020/9/12 Takumi Fukuda

1-1. Reaction mechanism

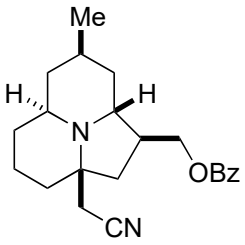
(1)



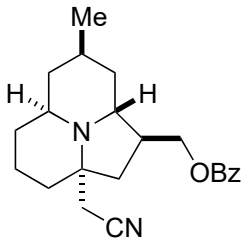
1-1

1. IBX (1.1 eq), $MgSO_4$, CH_2Cl_2
2. ethyl vinyl ether, toluene;
   BzCl, DMAP, Et_3N, CH_2Cl_2
   68% (2 steps)

3. $Mo(CO)_6$ (1.5 eq)
   CF_3COOH (2.5+2.5 eq)
   CH_3CN/H_2O;
   benzene, 90 °C*;
   $NCCH_2COOK$ (1.6+2.4 eq)
   i-PrOH, 100 °C to 120 °C



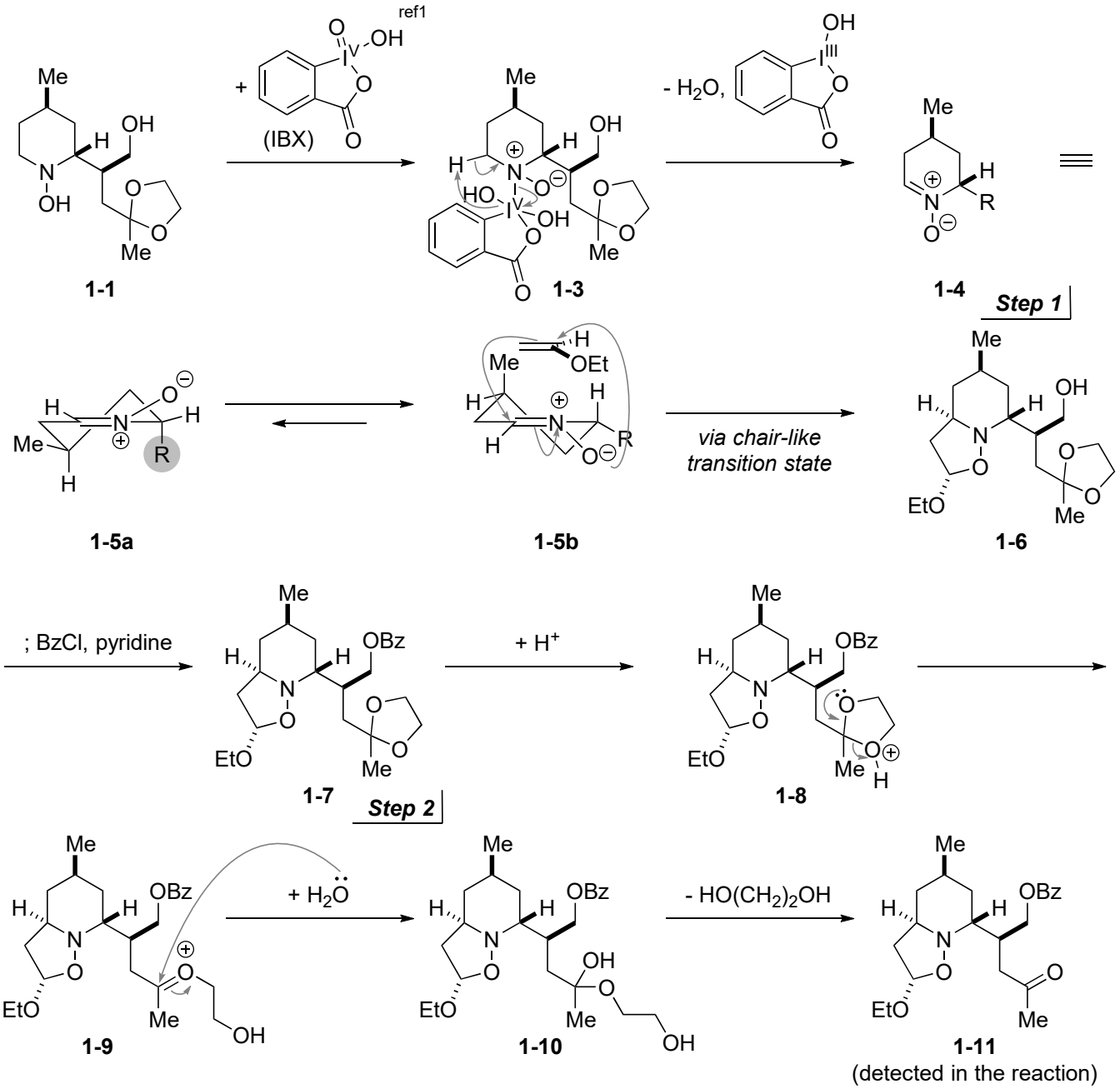
1-2a
47%

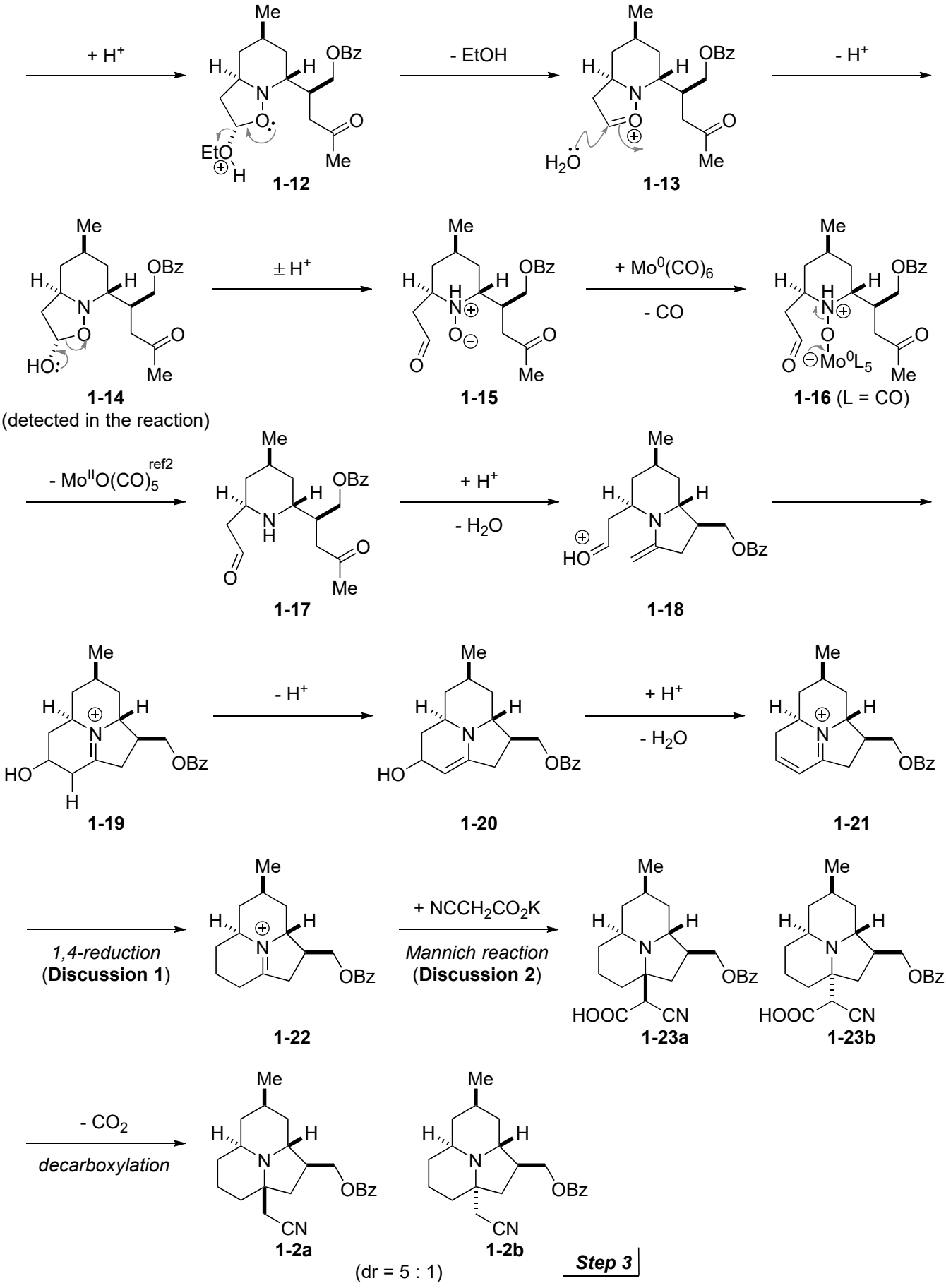


1-2b
9%

* Condenser was replaced with a Dean-Stark trap.

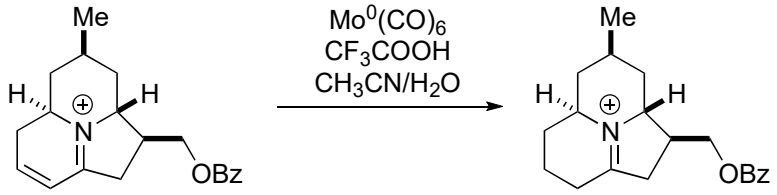
Lisnyak, V. G.; Snyder, S. A. *J. Am. Chem. Soc.* **2020**, *142*, 12027.




+ H+
- EtOH
- H+
1-12
1-13
± H+
+ Mo0(CO)6
- CO
1-14
(detected in the reaction)
1-15
1-16 (L = CO)
- MoIIO(CO)5
ref2
+ H+
- H2O
1-17
1-18
- H+
+ H+
- H2O
1-19
1-20
1-21
1,4-reduction
(Discussion 1)
+ NCCH2CO2K
Mannich reaction
(Discussion 2)
1-22
1-23a
1-23b
- CO2
decarboxylation
1-2a
1-2b
(dr = 5 : 1)
Step 3

1-2. 1,4-reduction (**Discussion 1**)

1-2-1. Mechanistic study



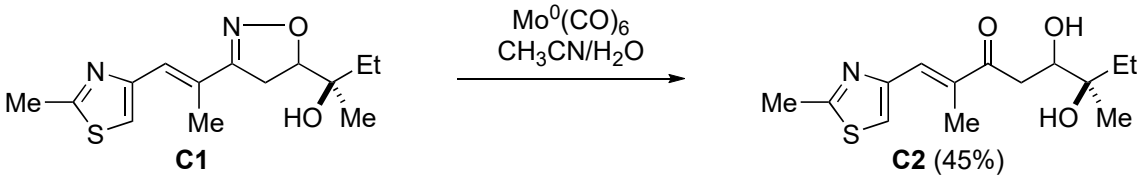
1-21
(isolated)

1-22
not obtained

When **1-21** was subjected to the cascade cyclization conditions with $Mo^0(CO)_6$, no 1,4-reduction occured. This result rejects one electron reduction to **1-21** from $Mo^0(CO)_6$. Furthermore, when the reaction was carried out in D_2O, full incorporation of deuterium was observed at the β-position.

Smiliar 1,4-reduction was reported by Carreira group.

Bode, J. W.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 1587.



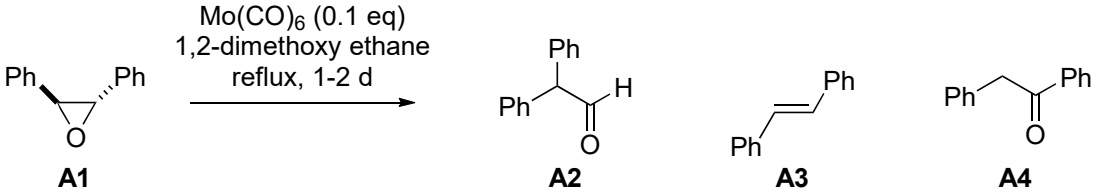
C1

C2 (45%)

C3 (20%)

These results suggest that Mo^{II} species, formed as a result the N-O reduction, are responsible for the 1,4-reduction. However, detailed reaction mechanisms were still unknown.

1-2-2. $Mo(CO)_6$-catalyzed rearrangement of epoxides
(Alper, H. Roches, D. D.; Durst, T.; Legault, R. *J. Org. Chem.* **1976**, *41*, 3611.)



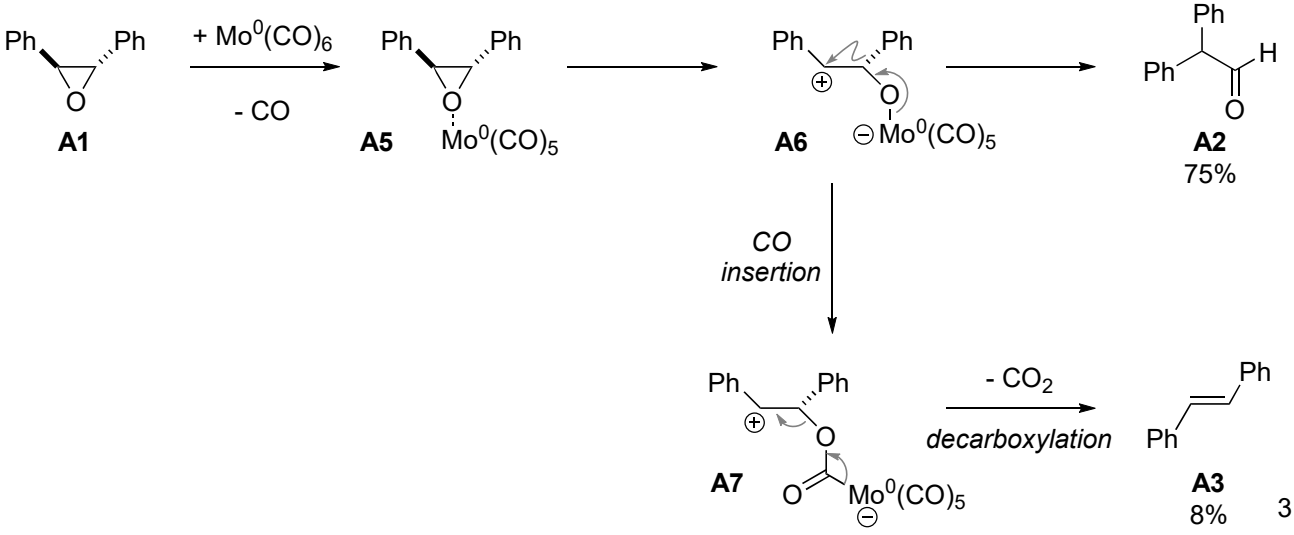
A1

A2
75%

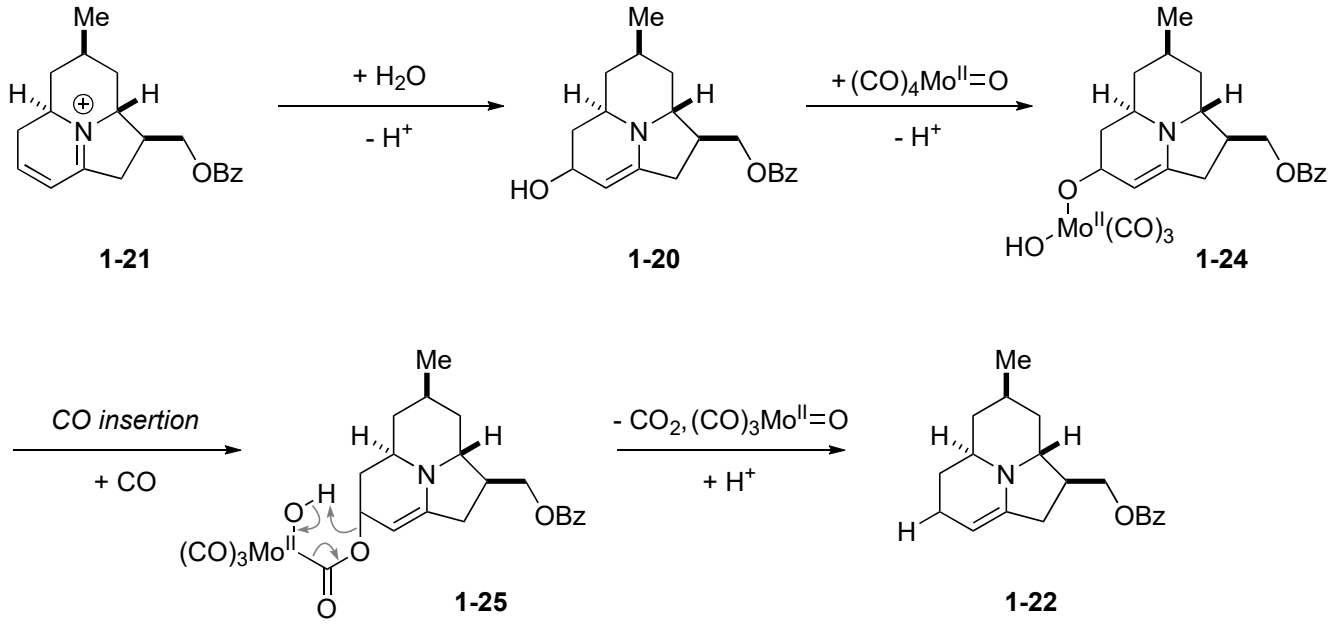
A3
8%

A4
3%

Proposed mechanism:



1-2-3. Proposed mechanism (my proposal)



1-21 **1-20** **1-24** **1-25** **1-22**

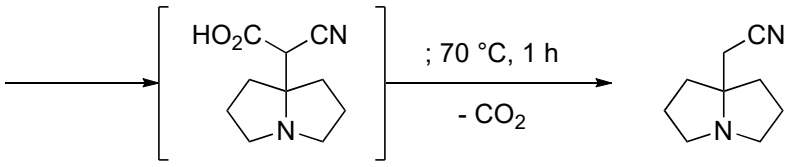
1-3. Decarbonylative Mannich reaction (**Discussion 2**)

1-3-1. The order of the reactions

Snyder group reported that the addition preceded decarbonylation on the basis of MS analysis of the crude reaction mixture.

Also, the following reactions support the above hypothesis.
(Oka, M.; Baba, K.; Suzuki, T.; Matsumoto, Y. *Heterocycles* **1997**, *45*, 2317.)

M1 **M2**

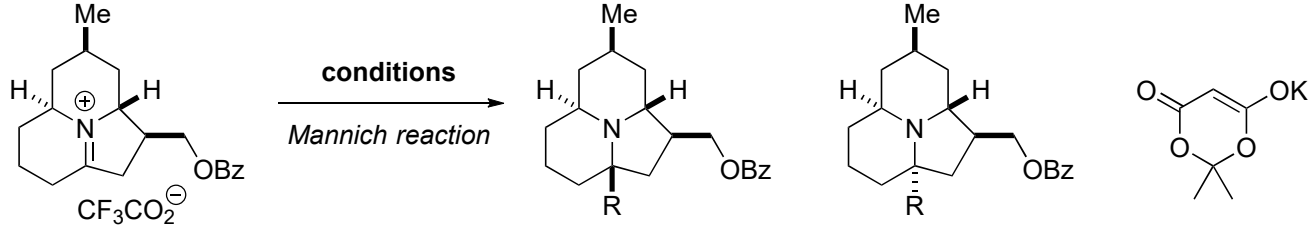


M3
(detected by NMR)

M4
54%

1-3-2. Stereoselectivity

1-3-2-1. Other nucleophiles



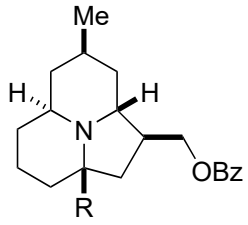
1-26 **1-23a** **1-23b** **Nu1**

KCN (6 eq), THF, 23 °C, 2h 67% (**1-23a** : **1-23b** = 1 : 5)[a)]

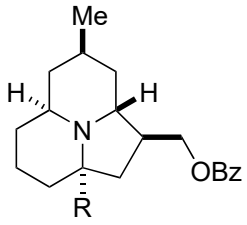
Nu1 (2.2 eq), MeOH, 23 °C, 2h 54% (**1-23a** : **1-23b** = 8 : 1)

a) Upon storage, the ratio of **1-23a** to **1-23b** changes to 1 : 8.

1-3-2-2. Relative stability calculated using DFT

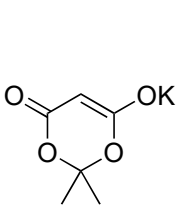


1-23a

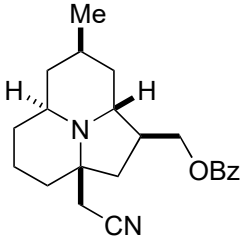


1-23b

Nu	dr (**1-23a**/**1-23b**)	$\Delta\Delta G^0_{298K}$ (**1-23a** - **1-23b**)
KCN	1 : 8	+2.1 kcal/mol
Nu1	8 : 1	-1.5 kcal/mol
$NCCH_2COOK$	5 : 1	+1.1 kcal/mol



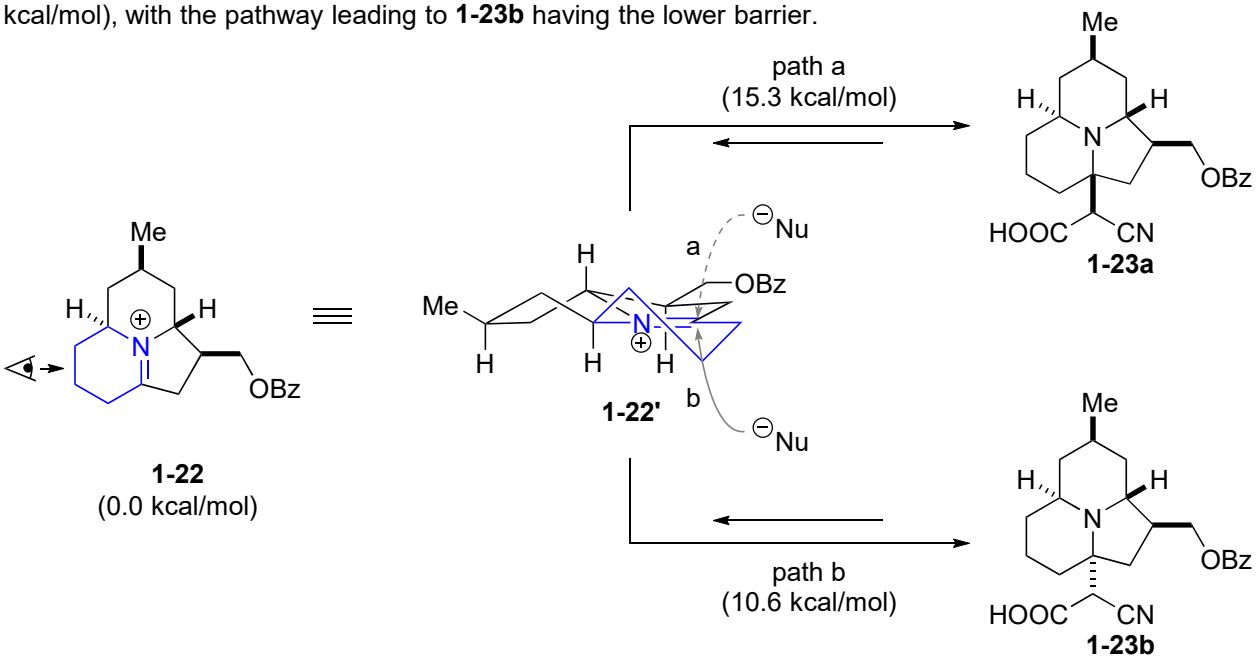
Nu1



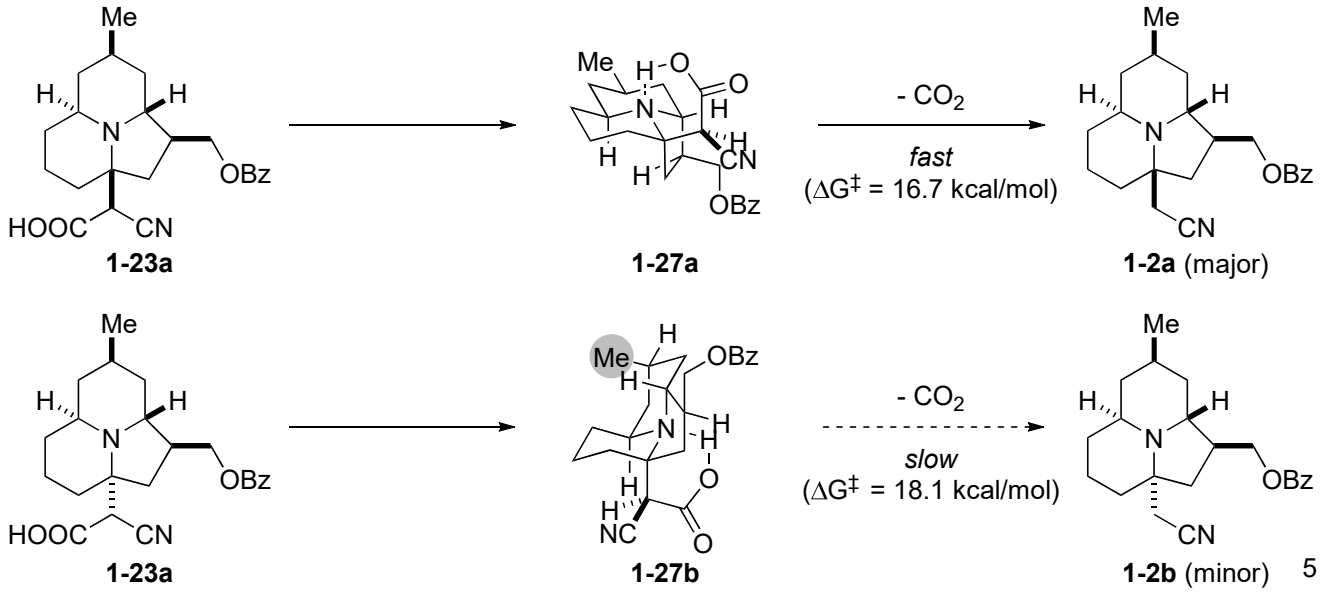
1-2a

In the case of $NCCH_2COOK$, **1-23b** is the thermodynamically favored product, but **1-2a** was obtained as a major product. It suggests that this reaction was kinetically controlled.

However, DFT calculations revealed that the barriers of the Mannich reaction differ significantly ($\Delta H^{\ddagger}$ = 4.7 kcal/mol), with the pathway leading to **1-23b** having the lower barrier.

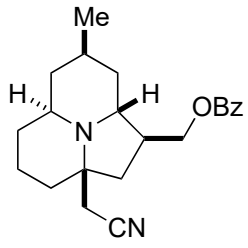


Thus, the selectivity are controlled in the decarboxylation step.
The energy of the decarboxylation transition state that leads to **1-2a** is lower than the transition state that gives **1-2b**.



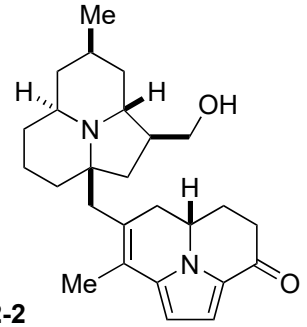
2-1. Reaction mechanism

(2)

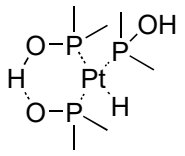


2-1

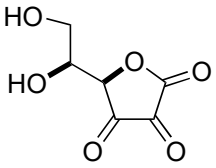
1. **A**, EtOH/H_2O; PhI(OH)OTs (1.2+0.8 eq) *p*-TsOH•H_2O, CH_3CN/H_2O, 65%;
2. **B** (3.0 eq), DMF; 1 M aq. HCl, 60%
3. **C** (1.2 eq.), *i*-Pr_2NLi (1.5 eq), THF, -78 °C; *p*-TsOH (7.0 eq), -78 °C to 23 °C; benzene, 50 °C, 60%
4. $Mn(dpm)_3$, $MeSi(OEt)_2H$, *i*-PrOH, CH_2Cl_2
5. MeLi (4 eq), THF; *p*-TsOH•H_2O (10 eq); DMSO (10 eq), 6 M aq. HCl 1,4-dioxane, 42% (2 steps)



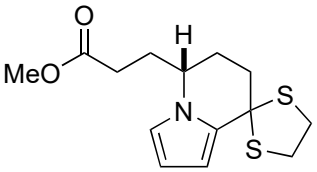
2-2



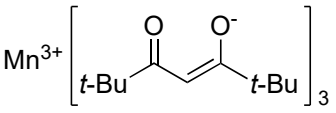
A



B

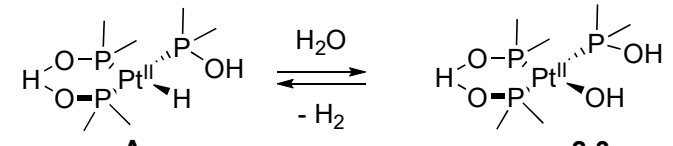


C



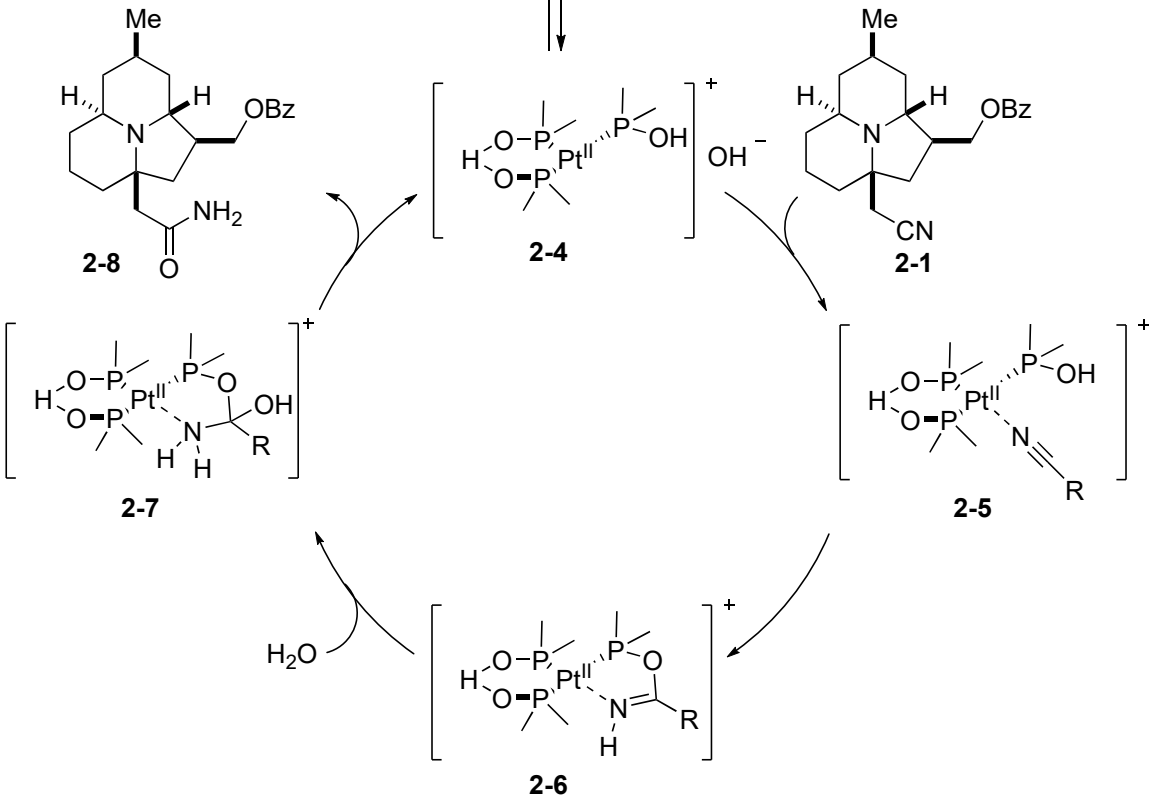
$Mn(dpm)_3$

Lisnyak, V. G.; Snyder, S. A. *J. Am. Chem. Soc.* **2020**, *142*, 12027.

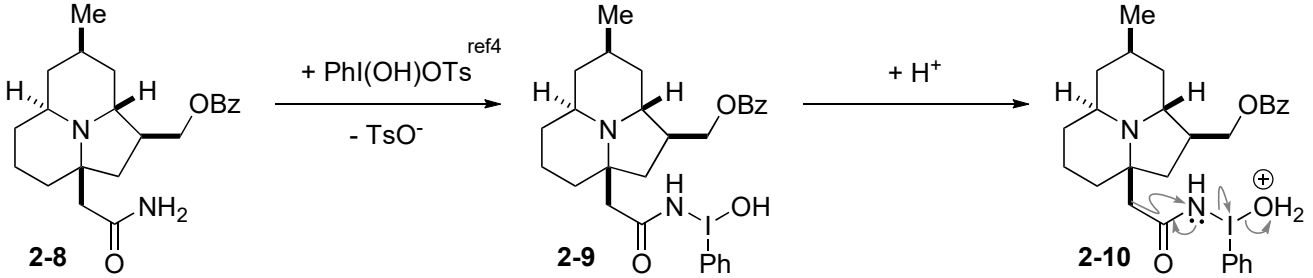


A (Ghaffar-Parkins cat.)[ref3]

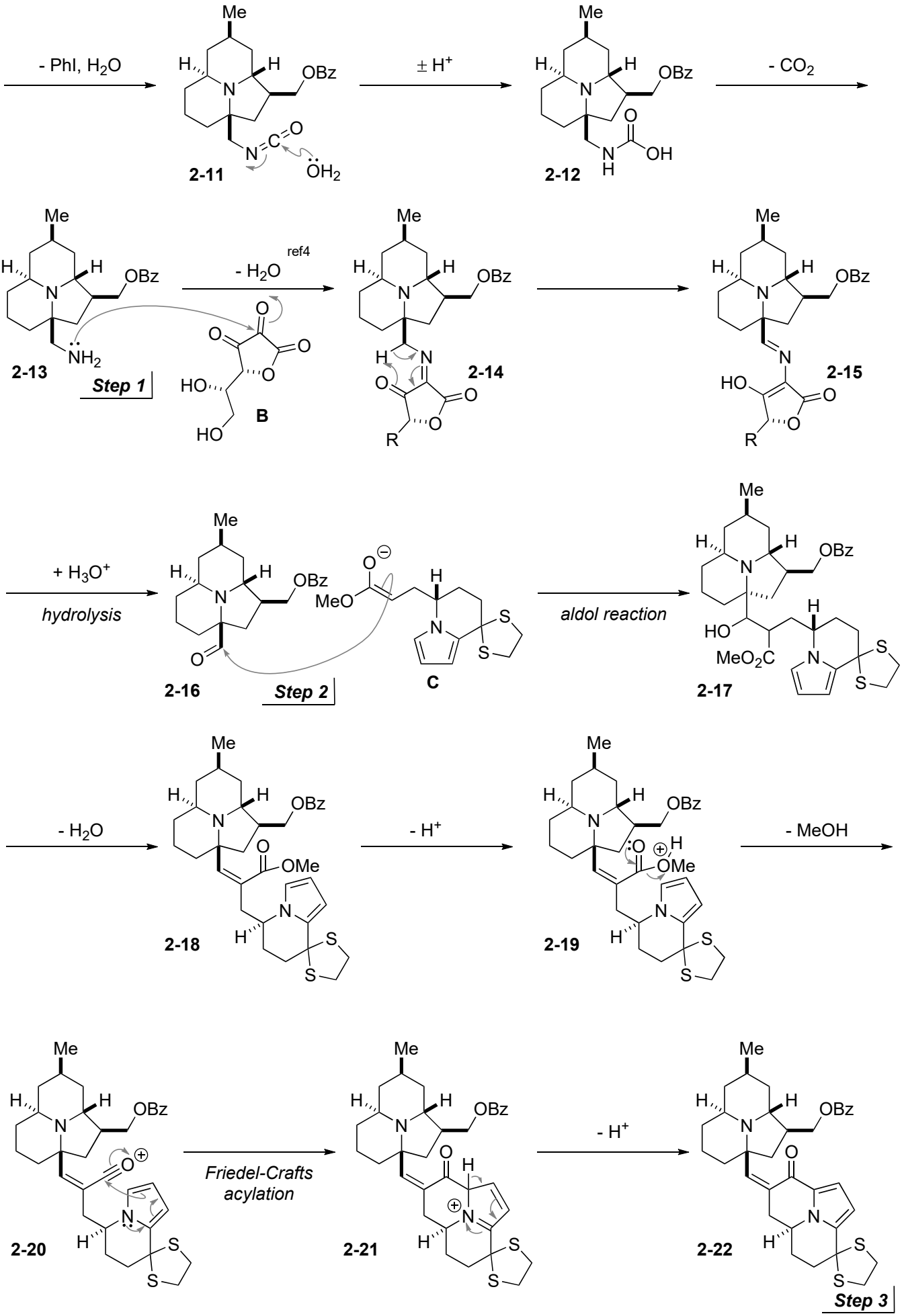
2-3

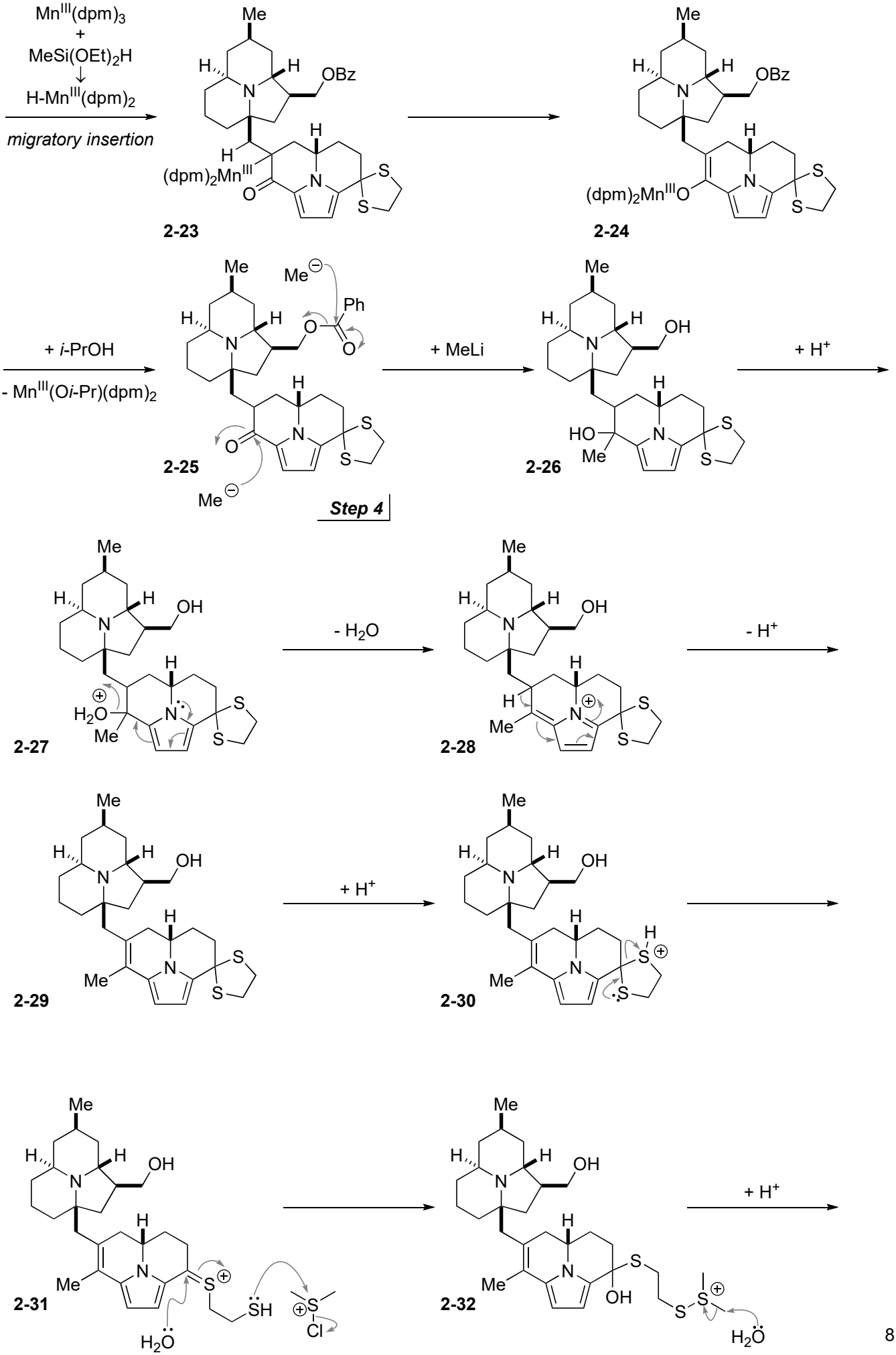


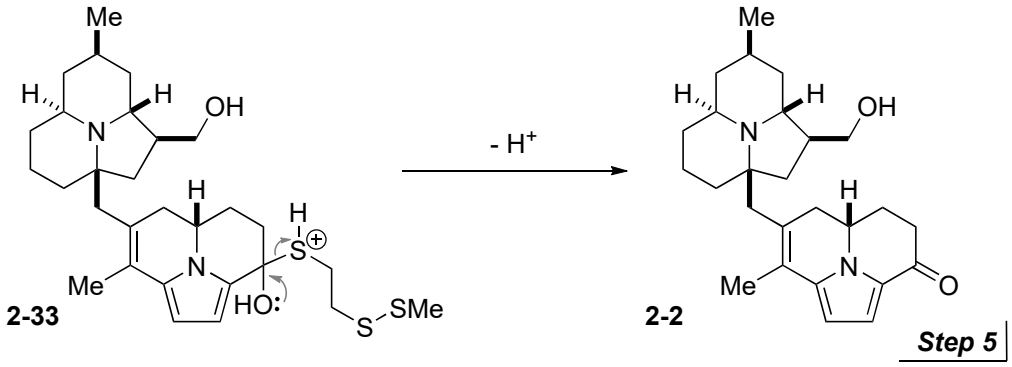
2-8, **2-4**, **2-1**, **2-7**, **2-5**, **2-6**



2-8 → (+ PhI(OH)OTs[ref4], - TsO^-) → **2-9** → (+ H^+) → **2-10**


- PhI, H2O
2-11
± H+
2-12
- CO2
- H2O
ref4
2-13
Step 1
B
2-14
2-15
+ H3O+
hydrolysis
2-16
Step 2
C
aldol reaction
2-17
- H2O
2-18
- H+
2-19
- MeOH
Friedel-Crafts acylation
2-20
2-21
- H+
2-22
Step 3


Mn^III(dpm)3
+
MeSi(OEt)2H
↓
H-Mn^III(dpm)2
migratory insertion
2-23
2-24
+ i-PrOH
- Mn^III(Oi-Pr)(dpm)2
2-25
+ MeLi
2-26
+ H+
Step 4
- H2O
2-27
2-28
- H+
+ H+
2-29
2-30
+ H+
2-31
2-32



Reference

1. Matassini, C.; Parmeggiani, C.; Cardona, F.; Goti, A. *Org. Lett.* **2015**, *17*, 4082.
2. Yoo, B. W.; Choi, J. W.; Yoon, C. M. *Tetrahedron Lett.* **2006**, *47*, 125.
3. (a) Ghaffar, T.; Parkins, A. W. *Tetrahedron Lett.* **1995**, *36*, 8657.
   (b) Ghaffar, T.; Parkins, A. W. *J. Mol. Catal. A* **2000**, *160*, 249.
4. Lazbin, M.; Koser, G. F.; *J. Org. Chem.* **1987**, *52*, 477.
5. Srogl. J.; Voltrova, S. *Org. Lett.* **2009**, *11*, 843.