Literature Report 1

Total Synthesis of Stephadiamine

Reporter: Xiang Li
Checker: Hong-Qiang Shen
Date: 2018-11-19

Hartrampf, N.; Winter, N.; Pupo, G.; Stoltz, B. M.; Trauner, D.
J. Am. Chem. Soc. **2018**, *140*, 8675.
Volpin, G.; Vepřek, N. A.; Bellan, A. B.; Trauner, D.
Angew. Chem. Int. Ed. **2017**, *56*, 897.

CV of Dirk Trauner

Dirk Trauner

Education:

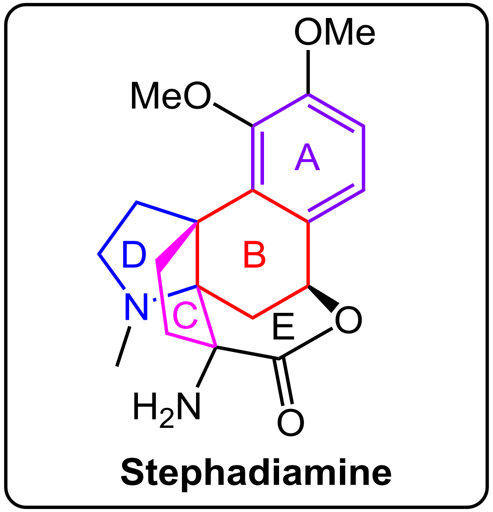
- ☐ **1986–1991** B.S., University of Vienna
- ☐ **1992–1995** M.S., Free University of Berlin
- ☐ **1996–1997** Ph.D., University of Vienna
- ☐ **1998–2000** Postdoctor, Memorial Sloan Kettering Cancer Center
- ☐ **2001–2008** Associate Professor, University of California, Berkely
- ☐ **2009–2018** Professor, University of Munich and New York University

Research:

- ➢ Chemical synthesis, natural product chemistry;
- ➢ Neuroscience, cell biology and photopharmacology.

Contents

Introduction



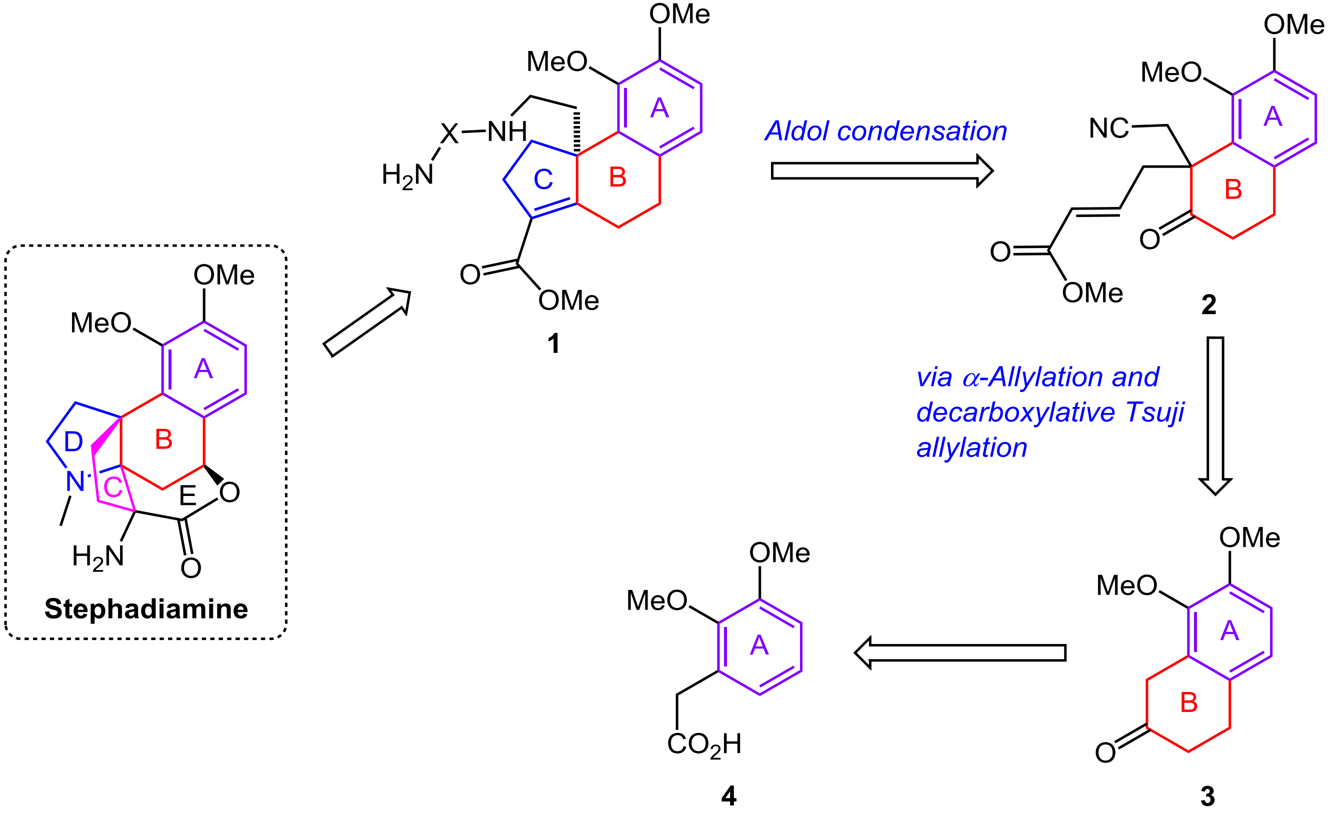
Stephadiamine

Vine stephania japonica

- Isolated from the *Vine stephania japonica* in 1984 by Taga *et al*;
- A highly strained pentacyclic skeleton arranged around an *aza*[4.3.3] propellane core;
- Four stereocenters, including a benzylic quaternary carbon and two adjacent *α*-tertiary amines in a *cis*-1,2 relationship.

Trauner, D. *et al*. *J. Am. Chem. Soc.* **2018**, *140*, 8675.

Retrosynthetic Analysis of Stephadiamine



Stephadiamine

1

Aldol condensation

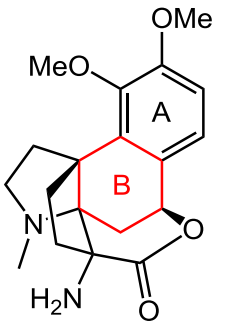
2

via α-Allylation and decarboxylative Tsuji allylation

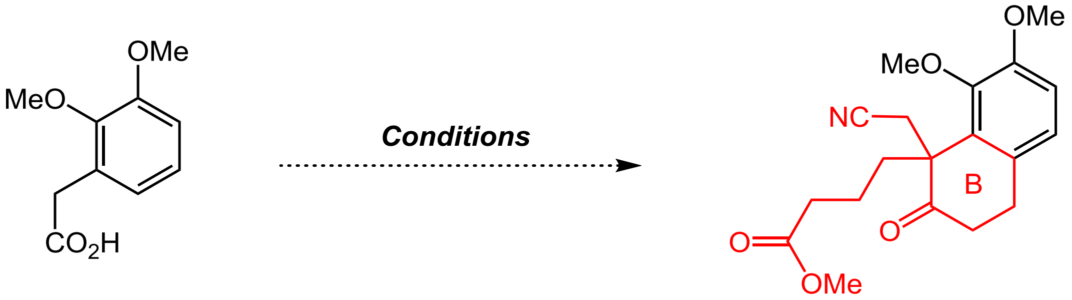
3

4

Total Synthesis of Stephadiamine



Stephadiamine

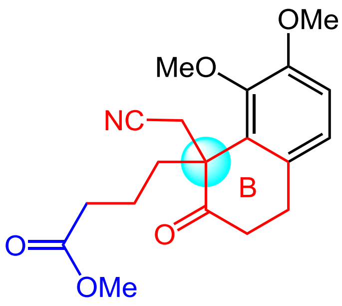


Conditions

4

7

Total Synthesis of Stephadiamine



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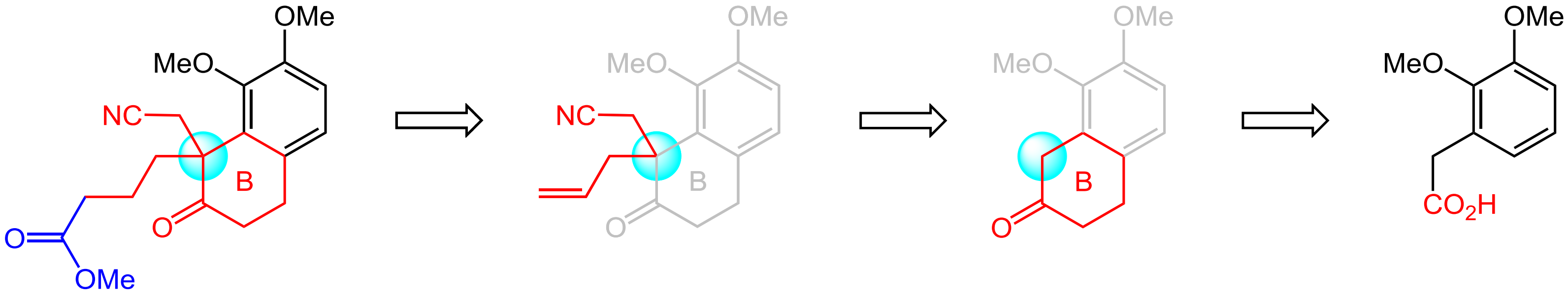
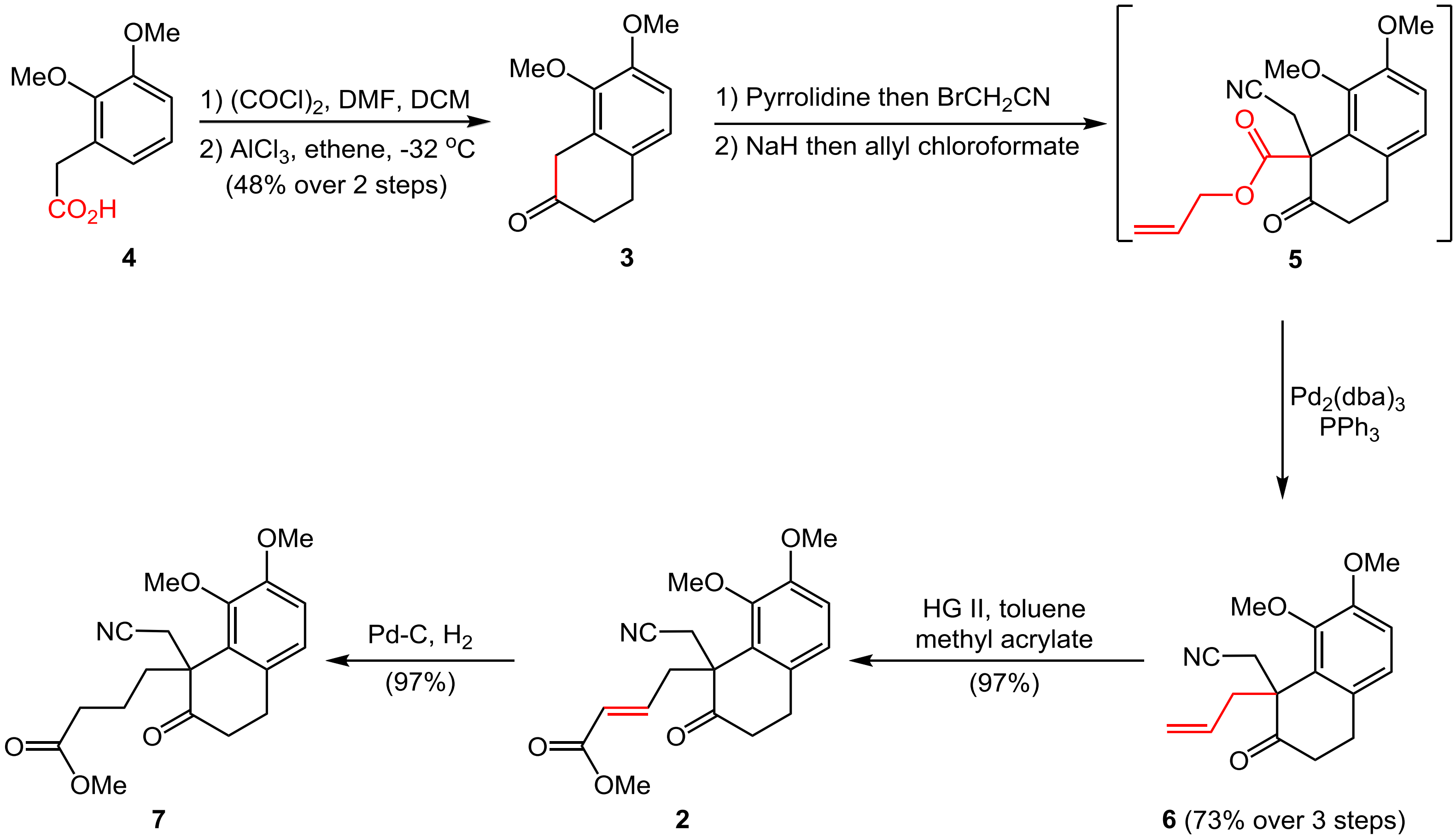
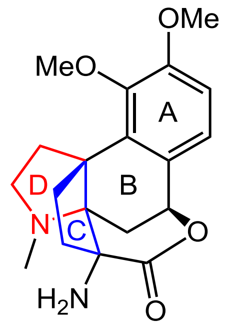


7 **3** **4**

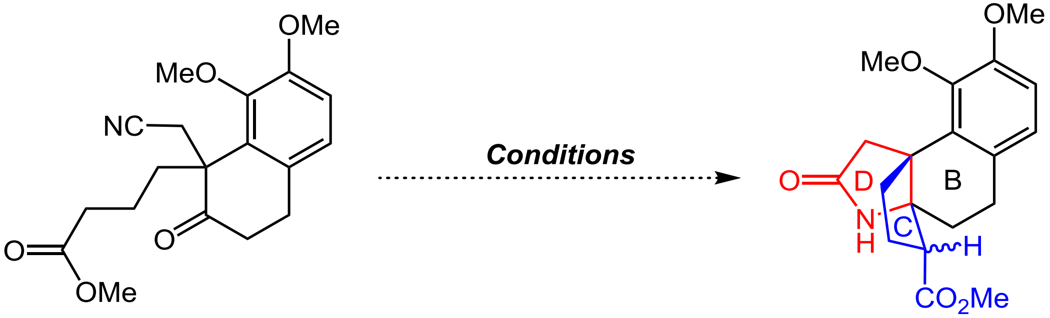
Total Synthesis of Stephadiamine



Total Synthesis of Stephadiamine



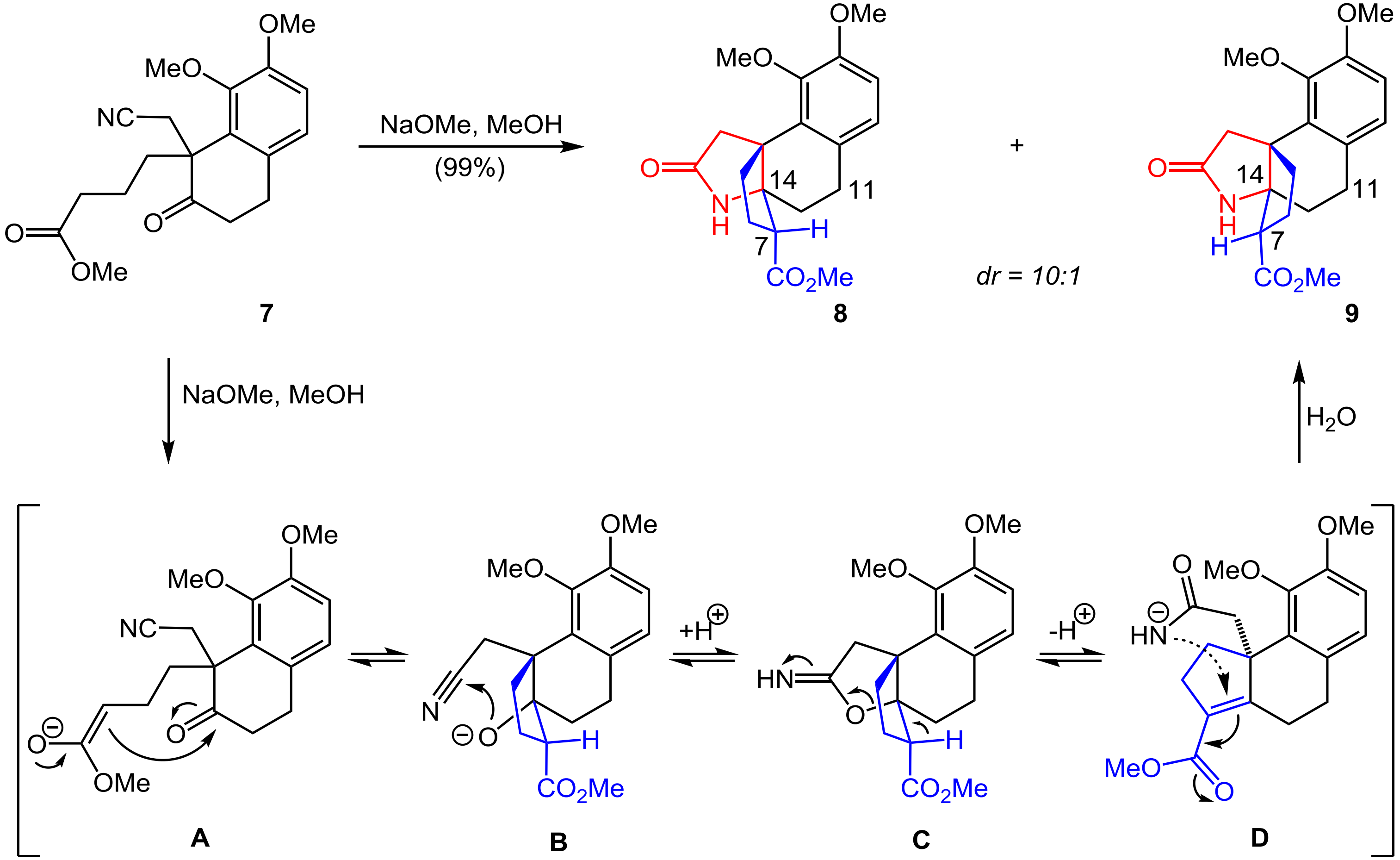
Stephadiamine



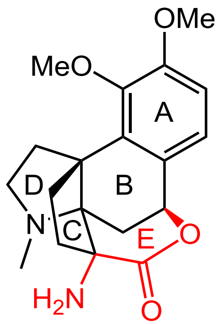
7

8 + 9

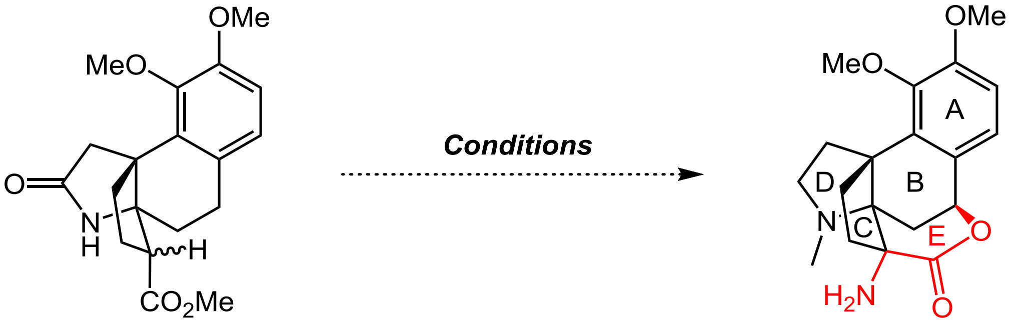
Aldol Condensation



Total Synthesis of Stephadiamine



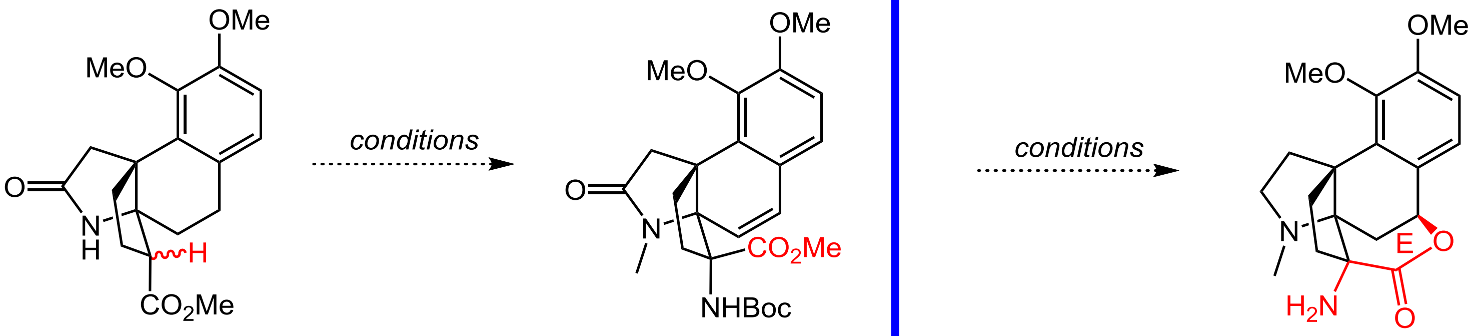
Stephadiamine



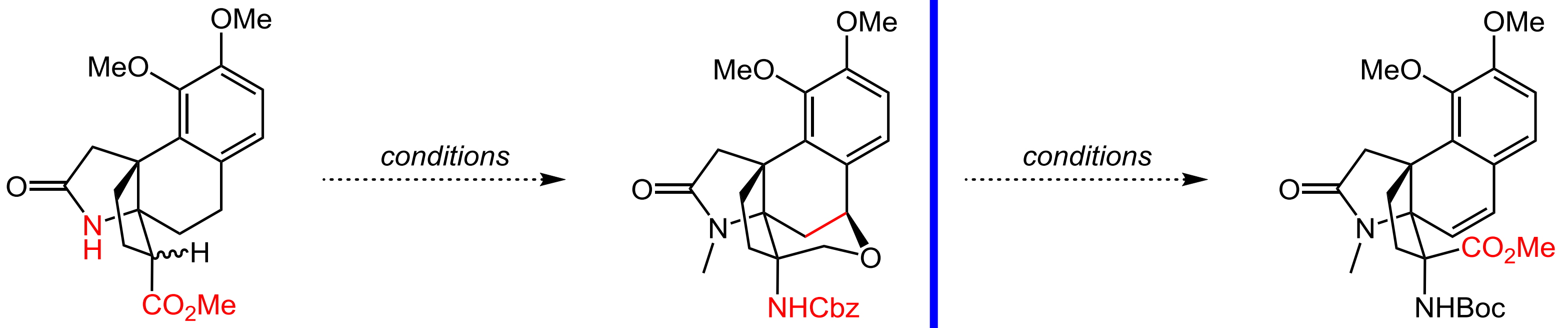
8 + 9

Stephadiamine

Total Synthesis of Stephadiamine

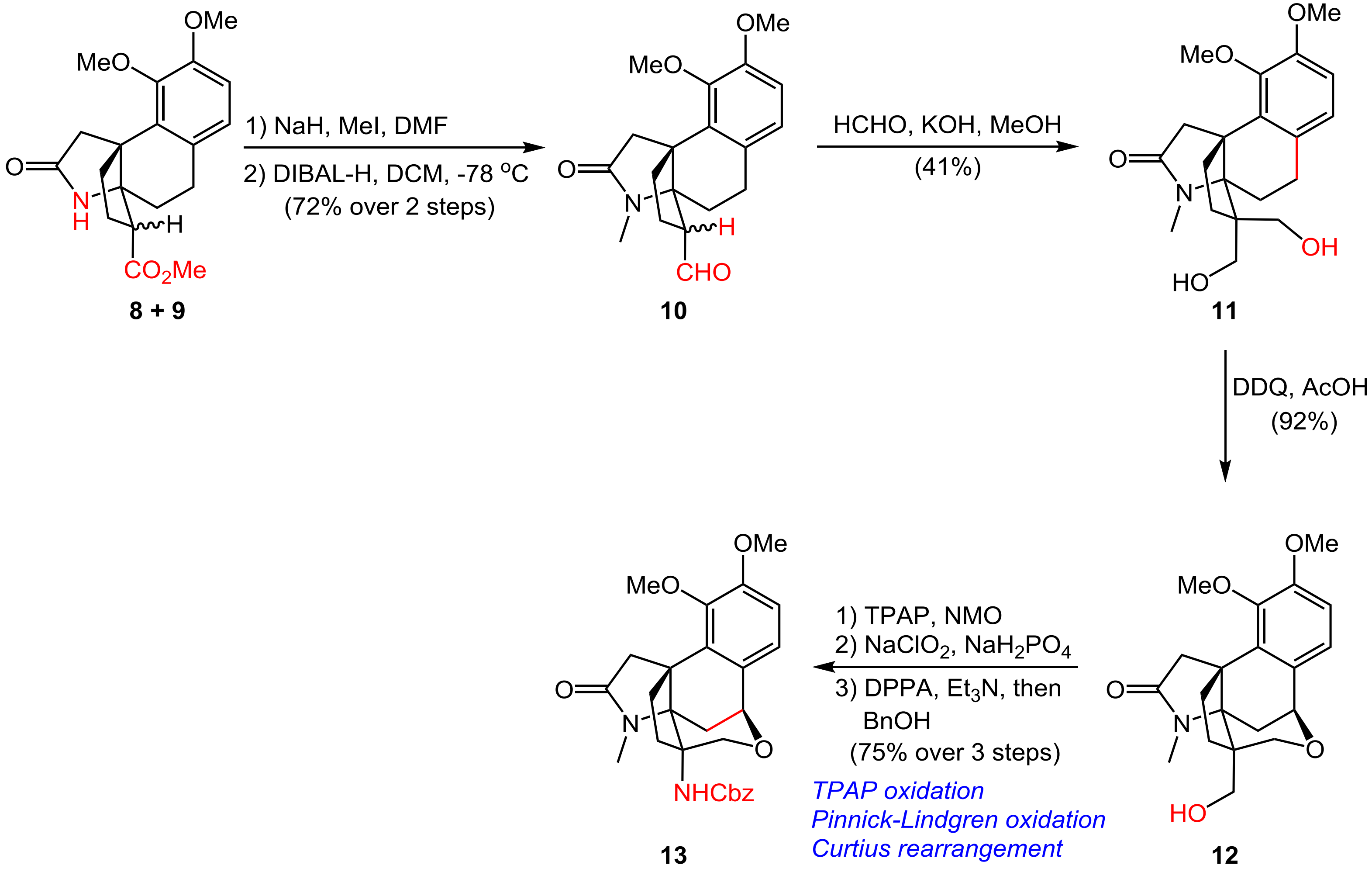


8 + 9 **17** **Stephadiamine**



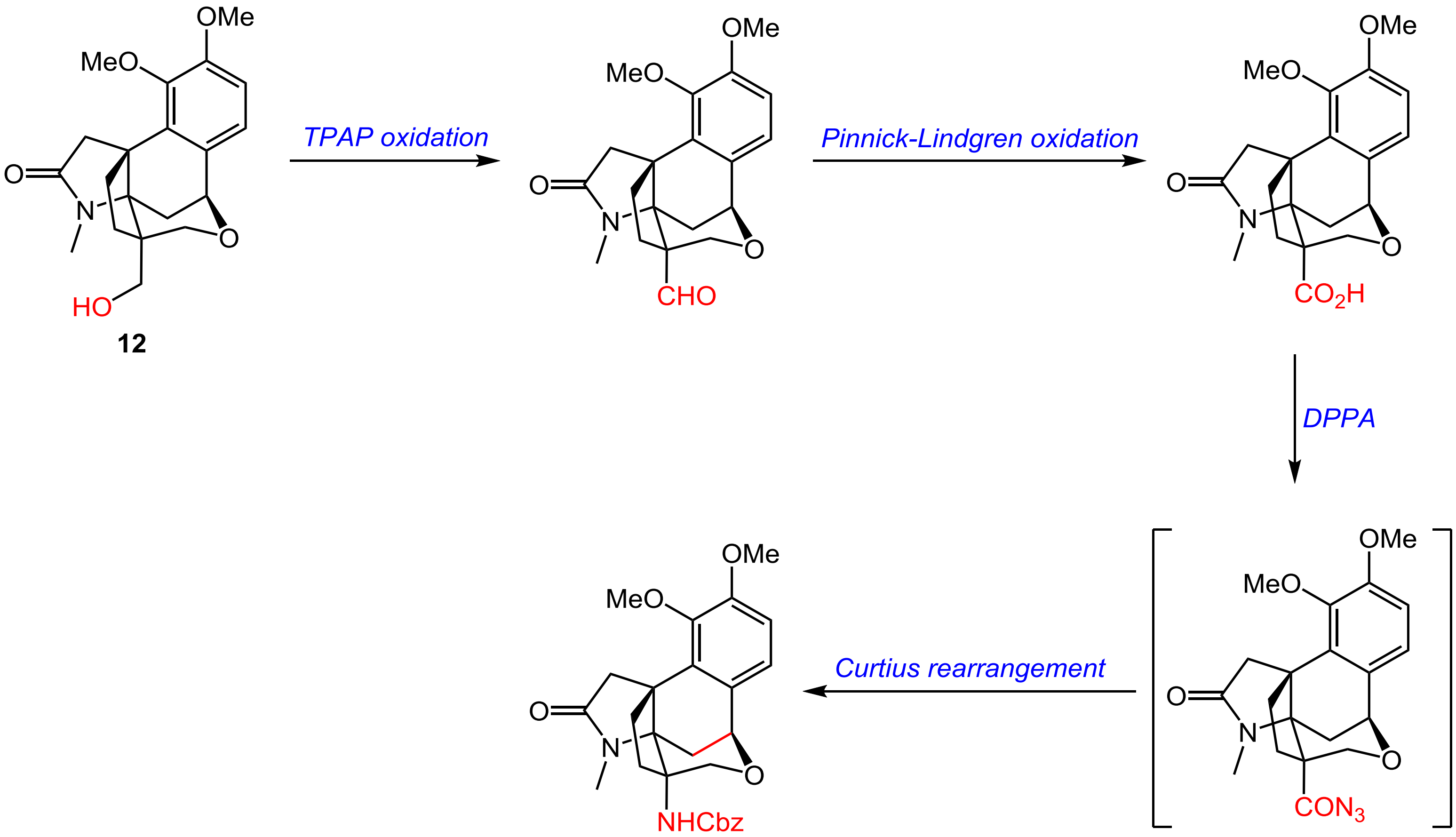
8 + 9 **13** **17**

Total Synthesis of Stephadiamine



TPAP oxidation
Pinnick-Lindgren oxidation
Curtius rearrangement

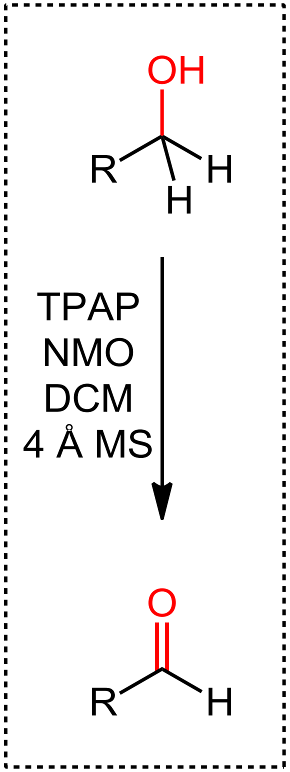
Total Synthesis of Stephadiamine

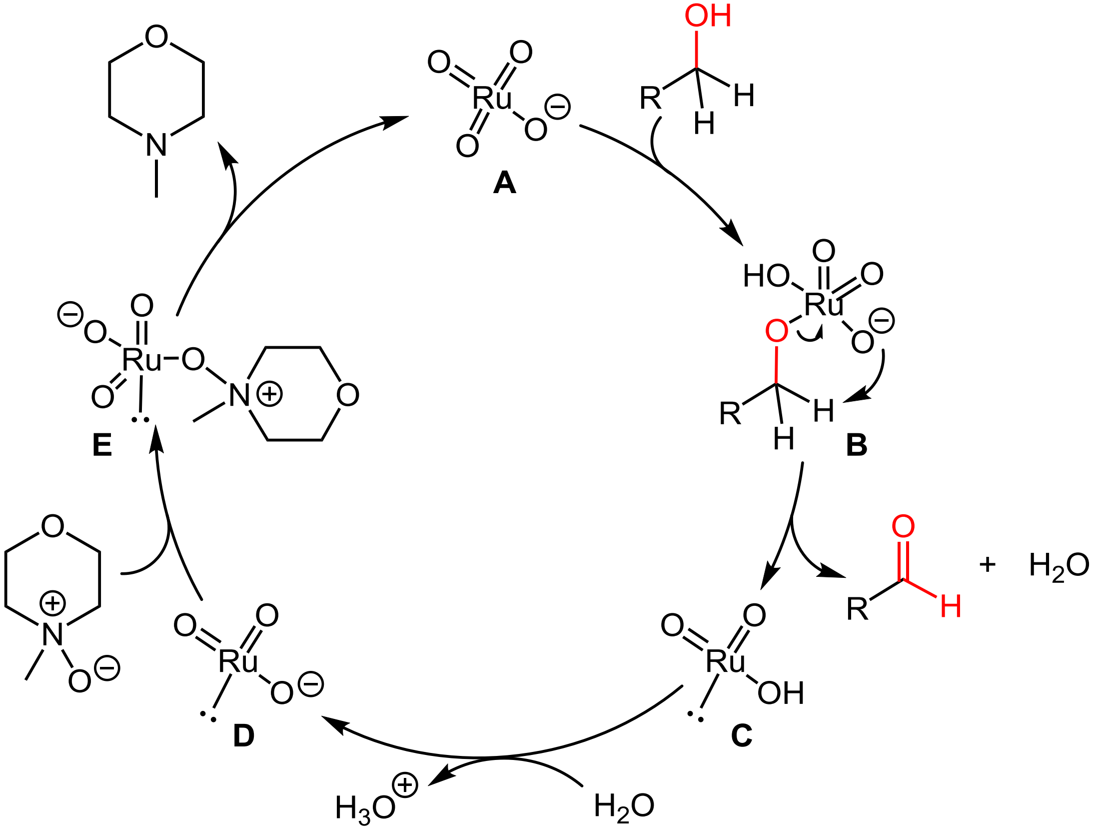


12

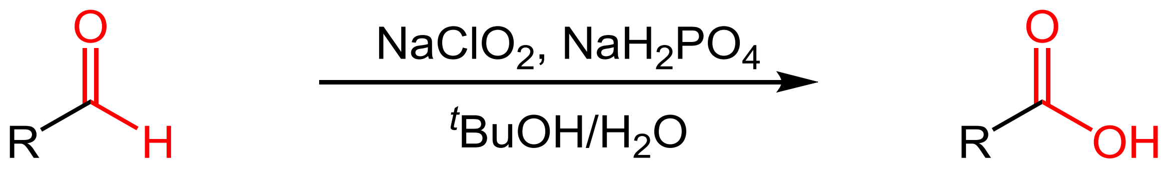
13

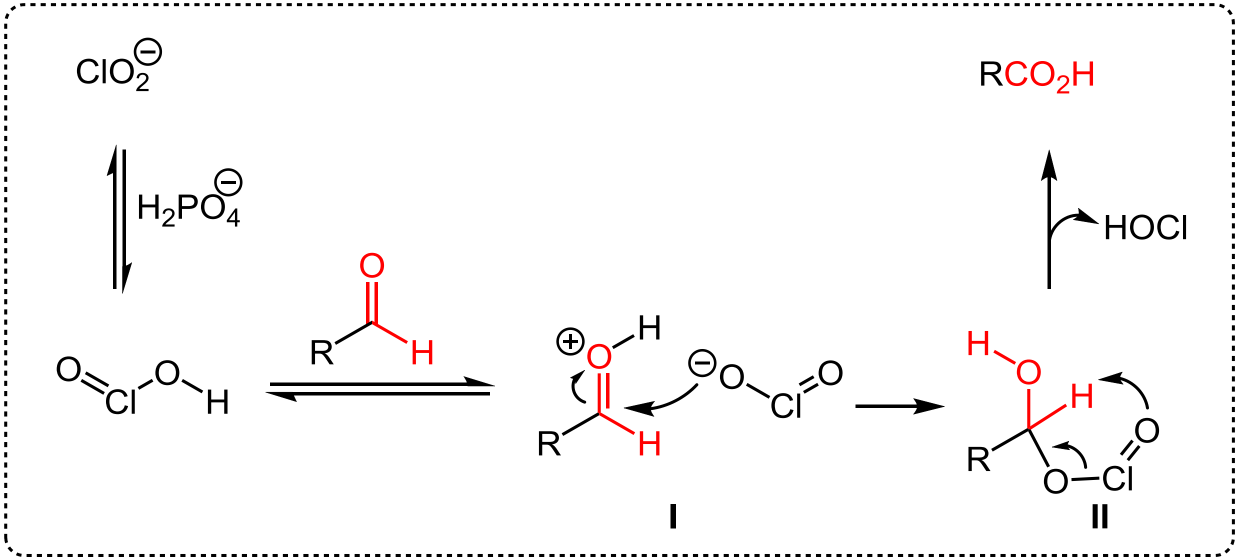
TPAP Oxidation



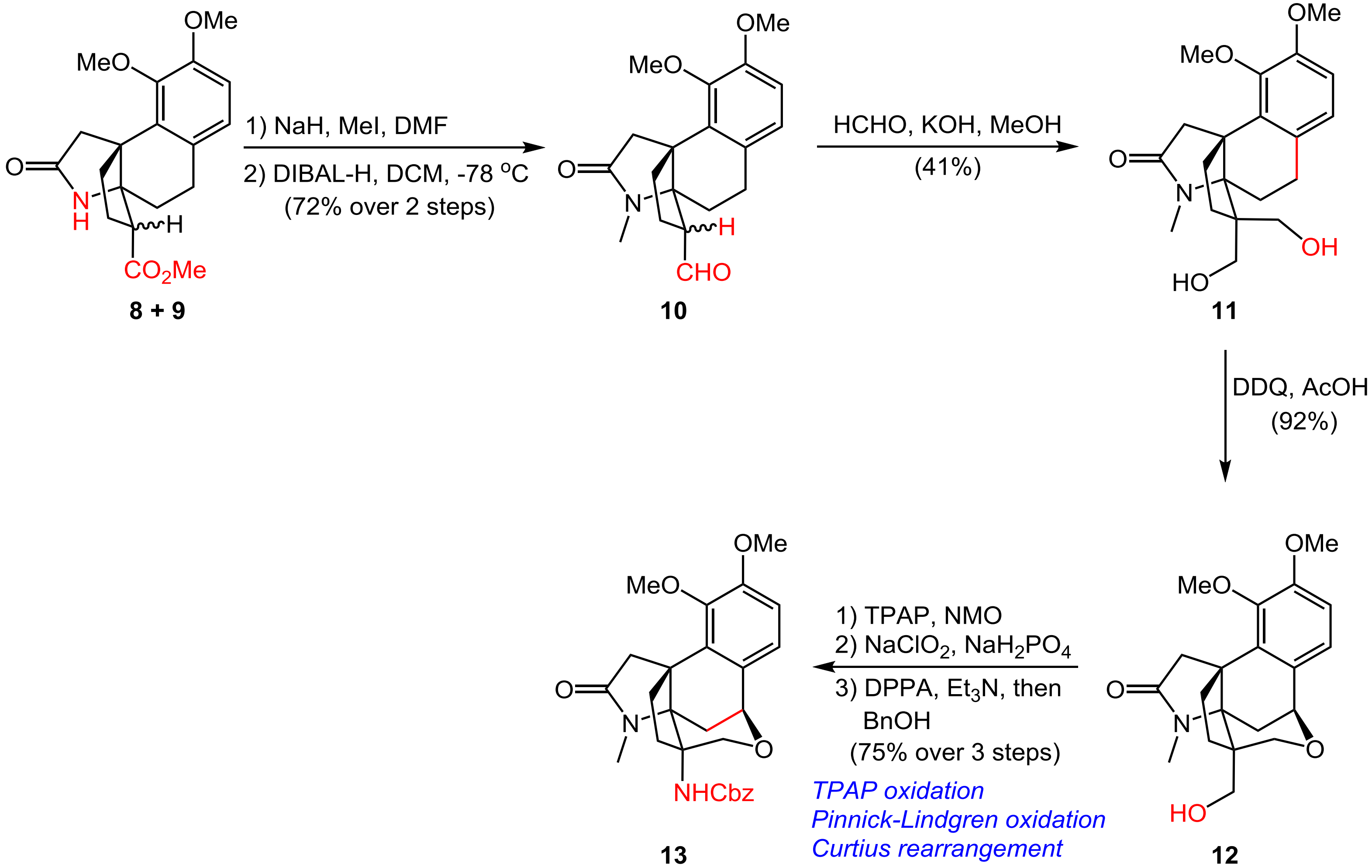


Pinnick-Lindgren Oxidation





Total Synthesis of Stephadiamine



8 + 9

1) NaH, MeI, DMF
2) DIBAL-H, DCM, -78 °C
(72% over 2 steps)

10

HCHO, KOH, MeOH
(41%)

11

DDQ, AcOH
(92%)

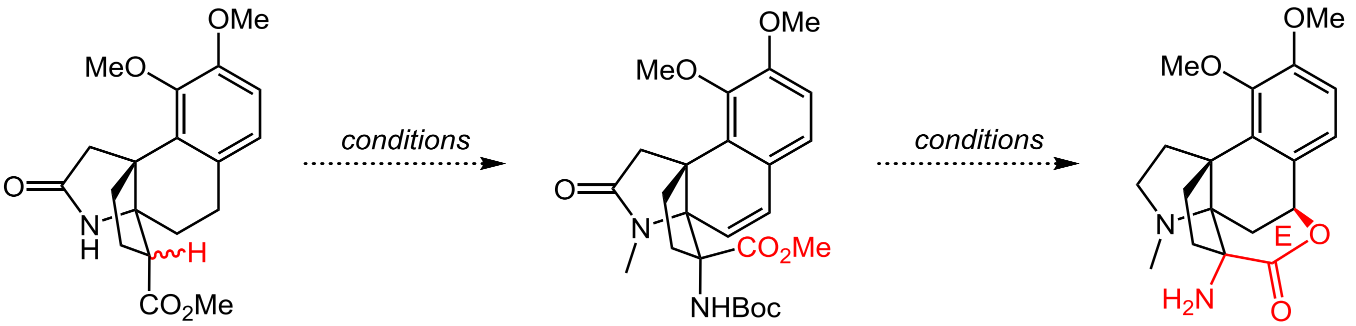
12

1) TPAP, NMO
2) $NaClO_2$, NaH_2PO_4
3) DPPA, Et_3N, then
BnOH
(75% over 3 steps)

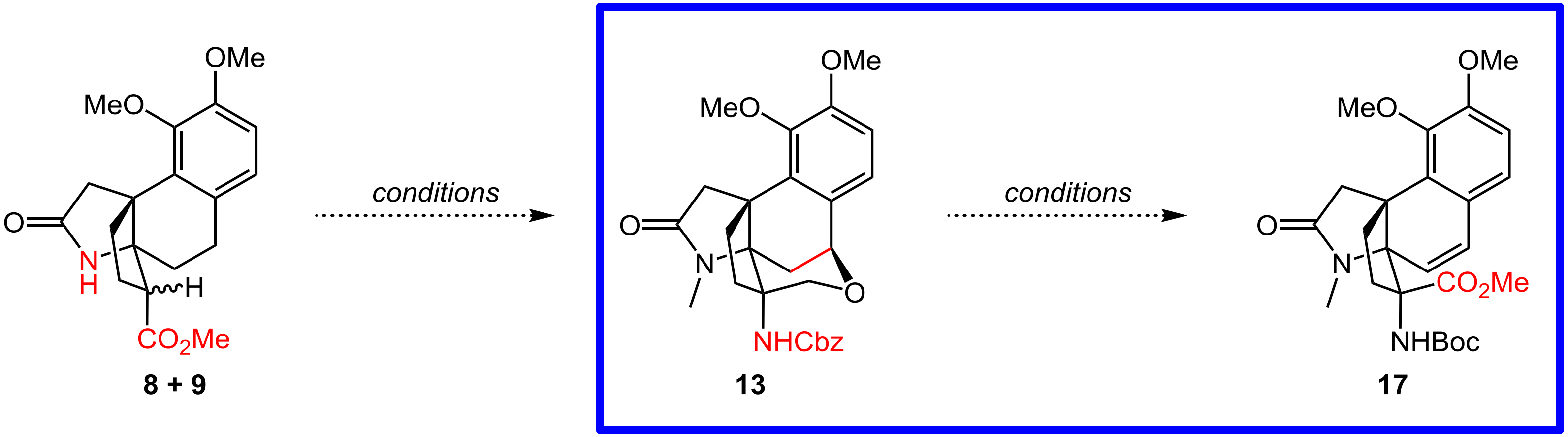
TPAP oxidation
Pinnick-Lindgren oxidation
Curtius rearrangement

13

Total Synthesis of Stephadiamine

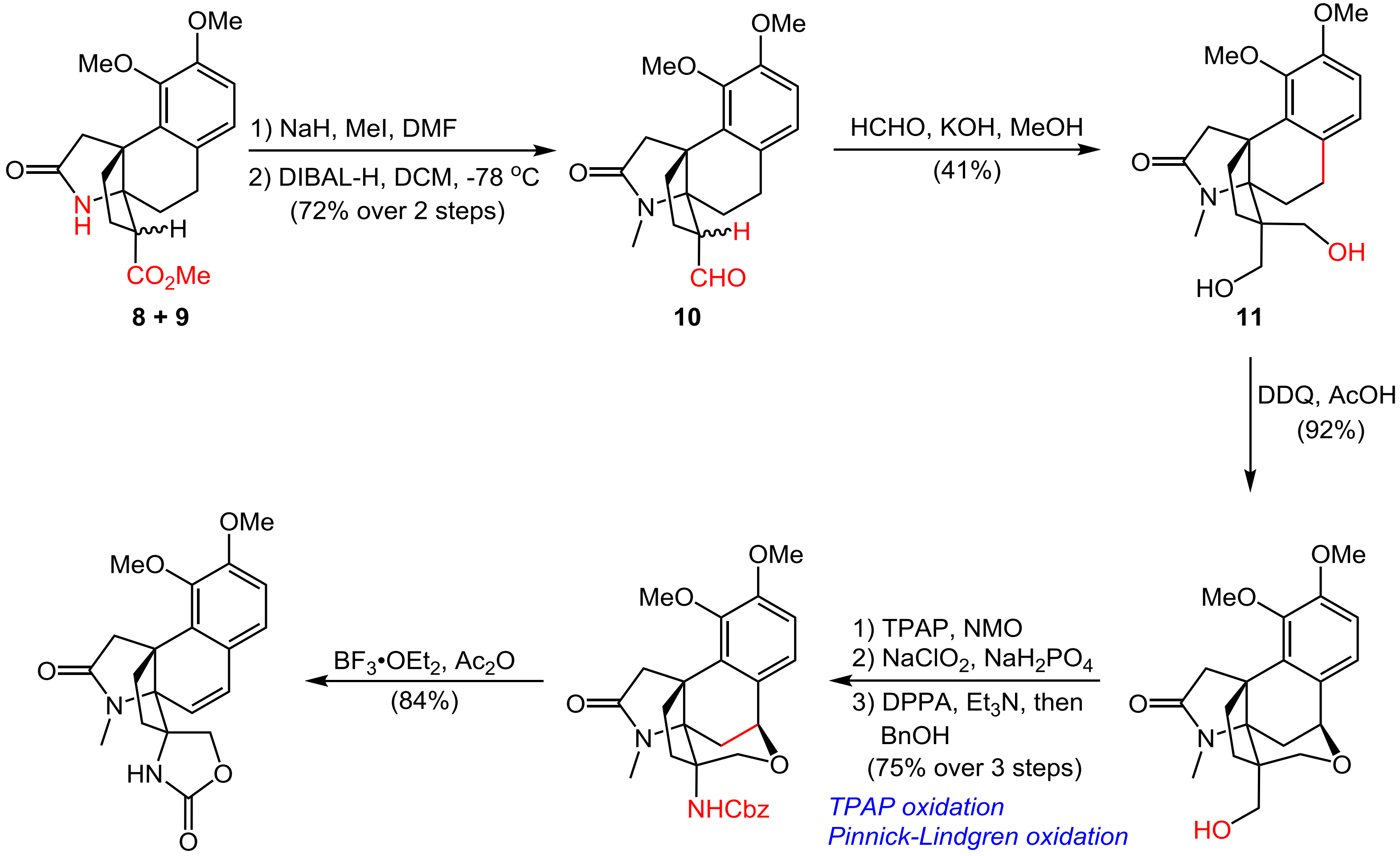


8 + 9 **17** **Stephadiamine**



8 + 9 **13** **17**

Total Synthesis of Stephadiamine



8 + 9

1) NaH, MeI, DMF

2) DIBAL-H, DCM, -78 °C
(72% over 2 steps)

10

HCHO, KOH, MeOH
(41%)

11

DDQ, AcOH
(92%)

12

1) TPAP, NMO
2) NaClO$_2$, NaH$_2$PO$_4$
3) DPPA, Et$_3$N, then
BnOH
(75% over 3 steps)

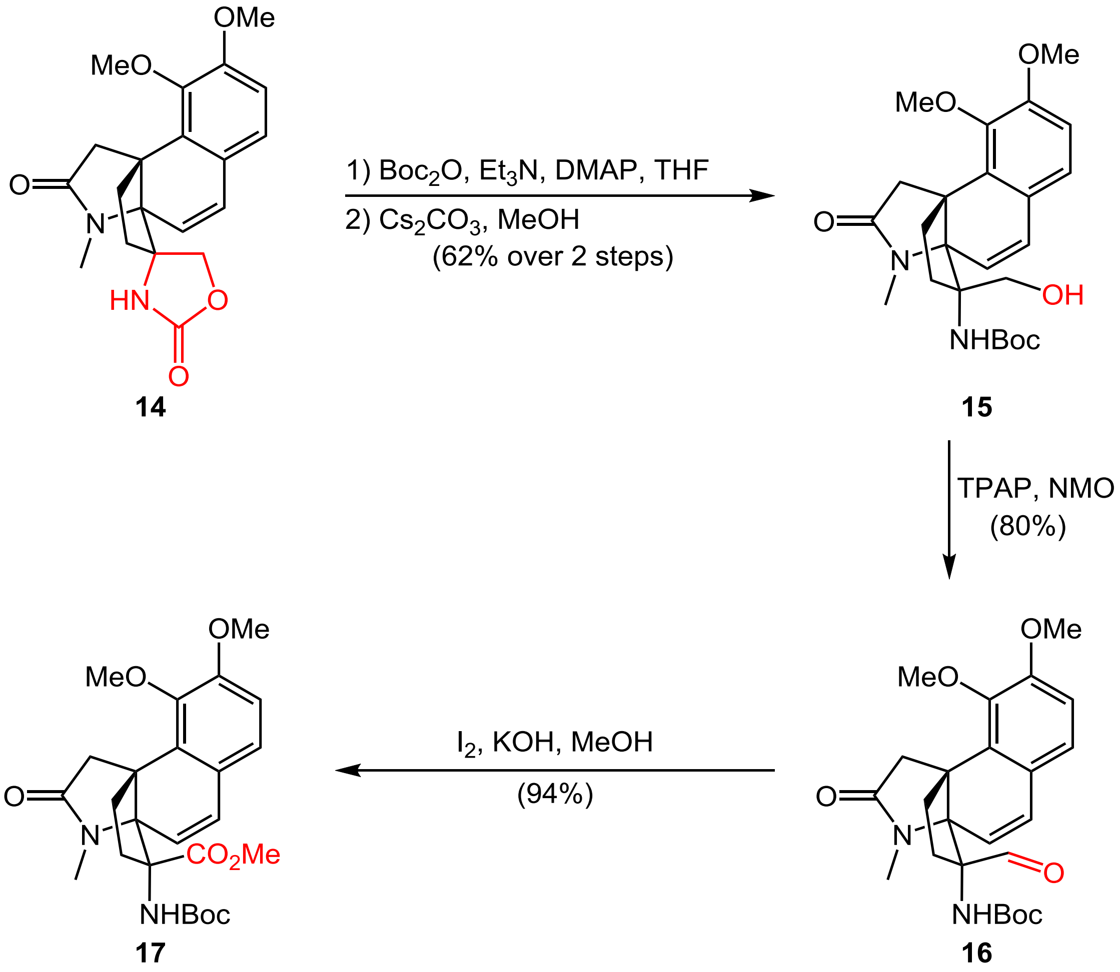
TPAP oxidation
Pinnick-Lindgren oxidation
Curtius rearrangement

13

BF$_3$•OEt$_2$, Ac$_2$O
(84%)

14

Total Synthesis of Stephadiamine

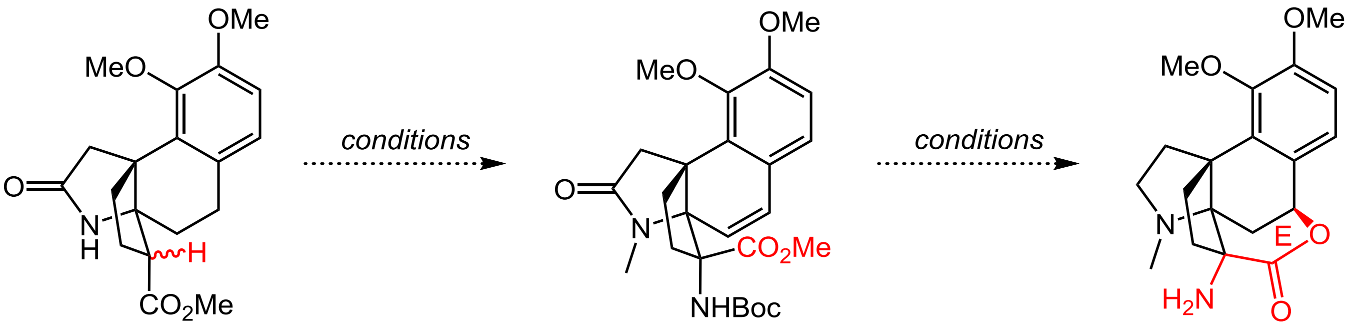


1) Boc_2O, Et_3N, DMAP, THF
2) Cs_2CO_3, MeOH
(62% over 2 steps)

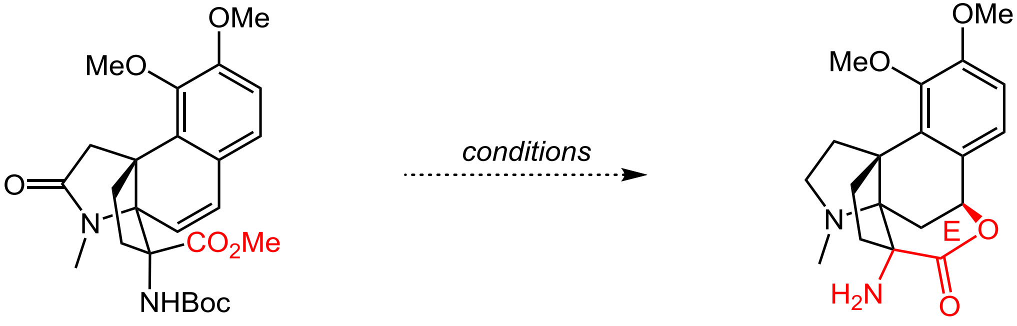
TPAP, NMO
(80%)

I_2, KOH, MeOH
(94%)

Total Synthesis of Stephadiamine

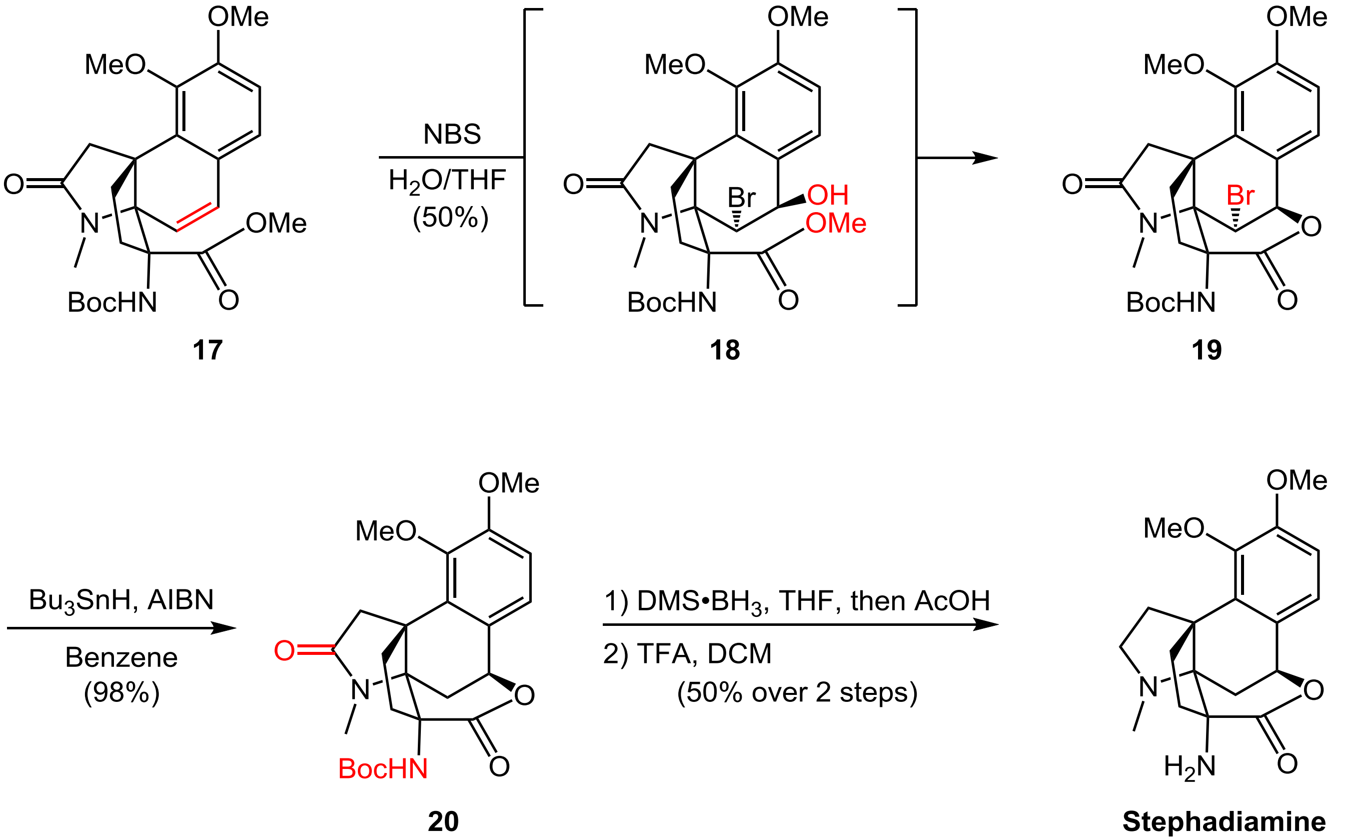


8 + 9 **17** **Stephadiamine**

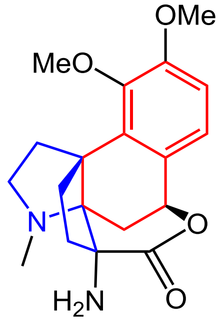


17 **Stephadiamine**

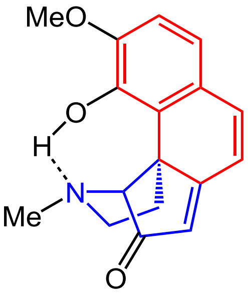
Total Synthesis of Stephadiamine



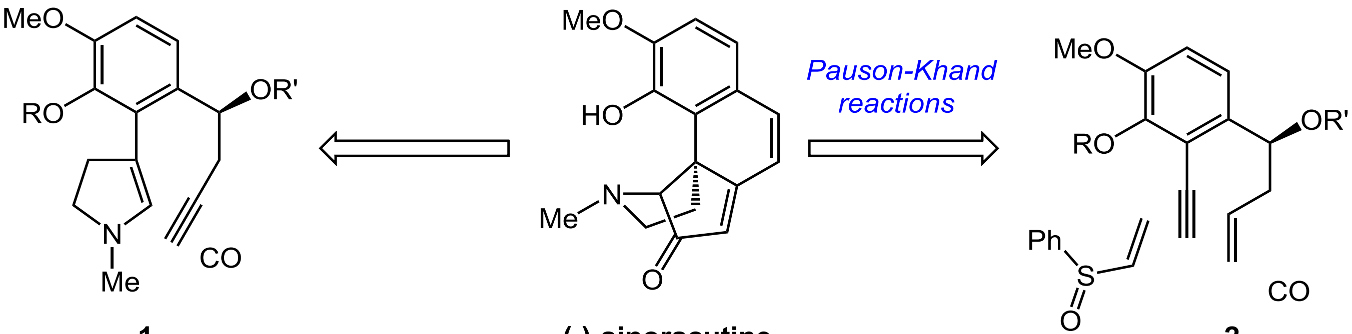
Retrosynthetic Analysis of (-)-Sinoracutine



Stephadiamine



(-)-Sinoracutine



Pauson-Khand reactions

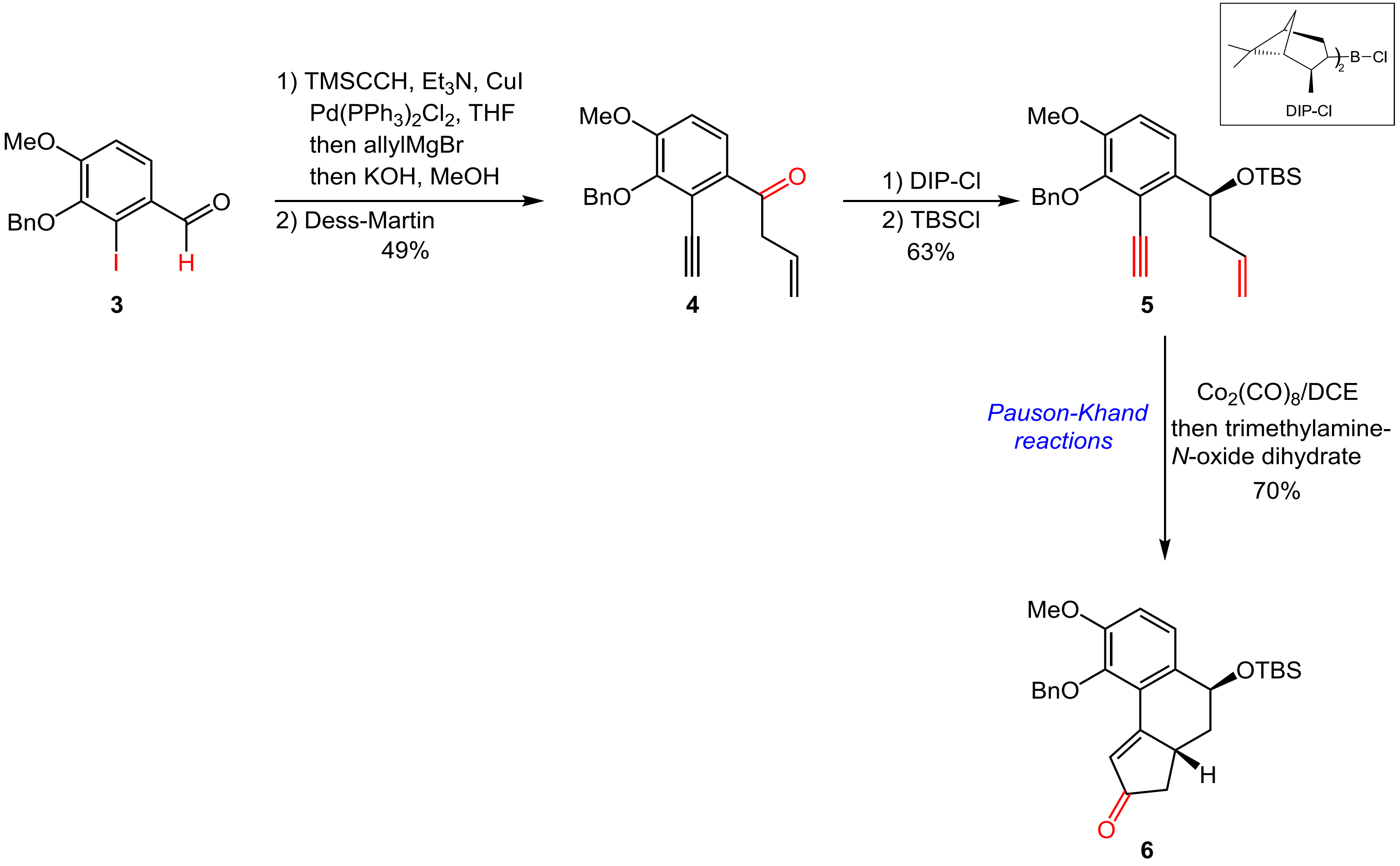
1

(-)-sinoracutine

2

Trauner, D. *et al*. *Angew. Chem. Int. Ed*. **2017**, *56*, 897.

Total Synthesis of (-)-Sinoracutine



3

1) TMSCCH, Et_3N, CuI
$Pd(PPh_3)_2Cl_2$, THF
then allylMgBr
then KOH, MeOH

2) Dess-Martin
49%

4

1) DIP-Cl
2) TBSCl
63%

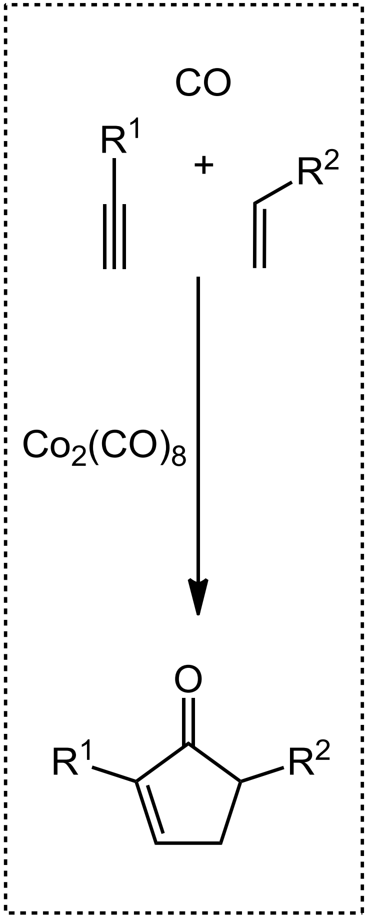
5

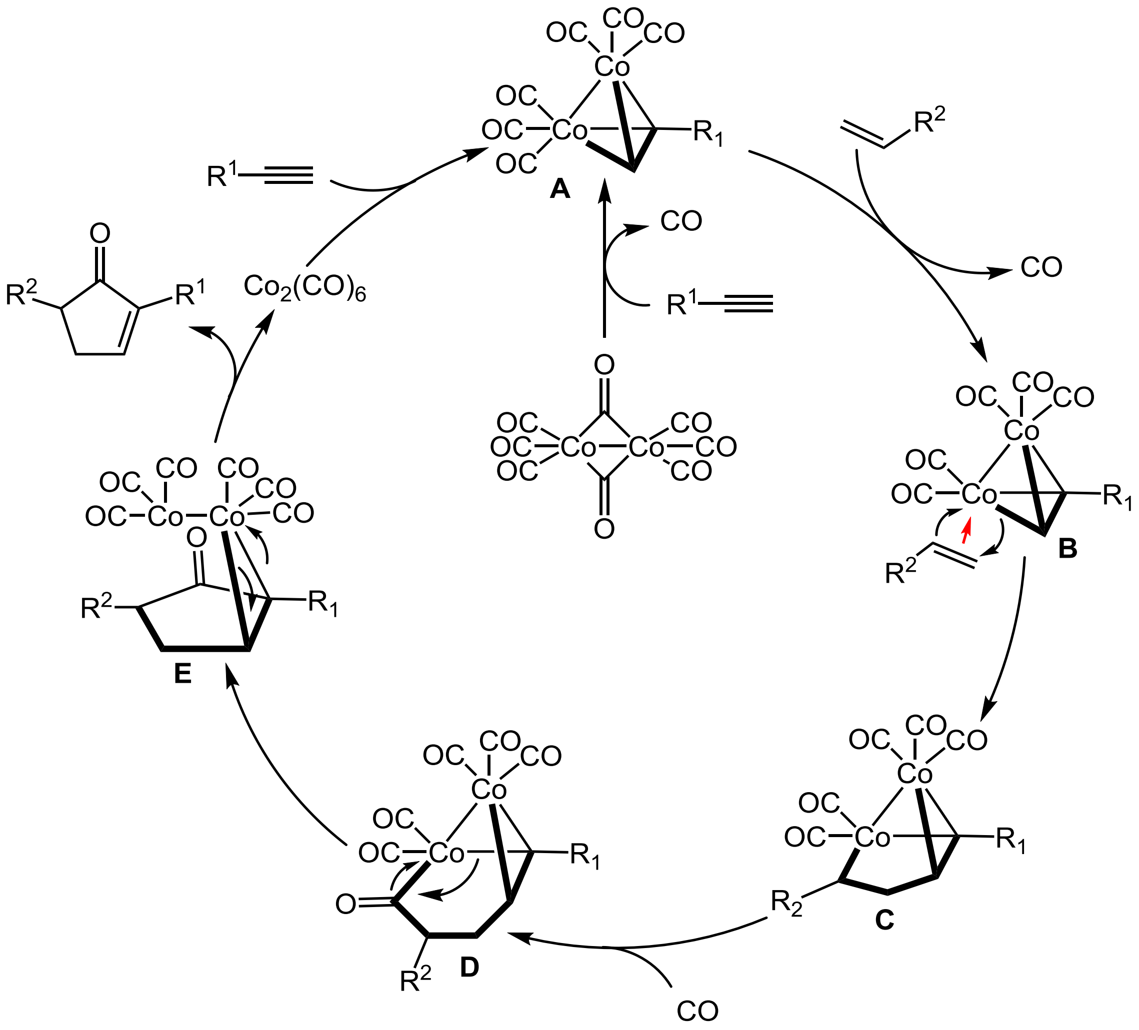
Pauson-Khand reactions

$Co_2(CO)_8$/DCE
then trimethylamine-*N*-oxide dihydrate
70%

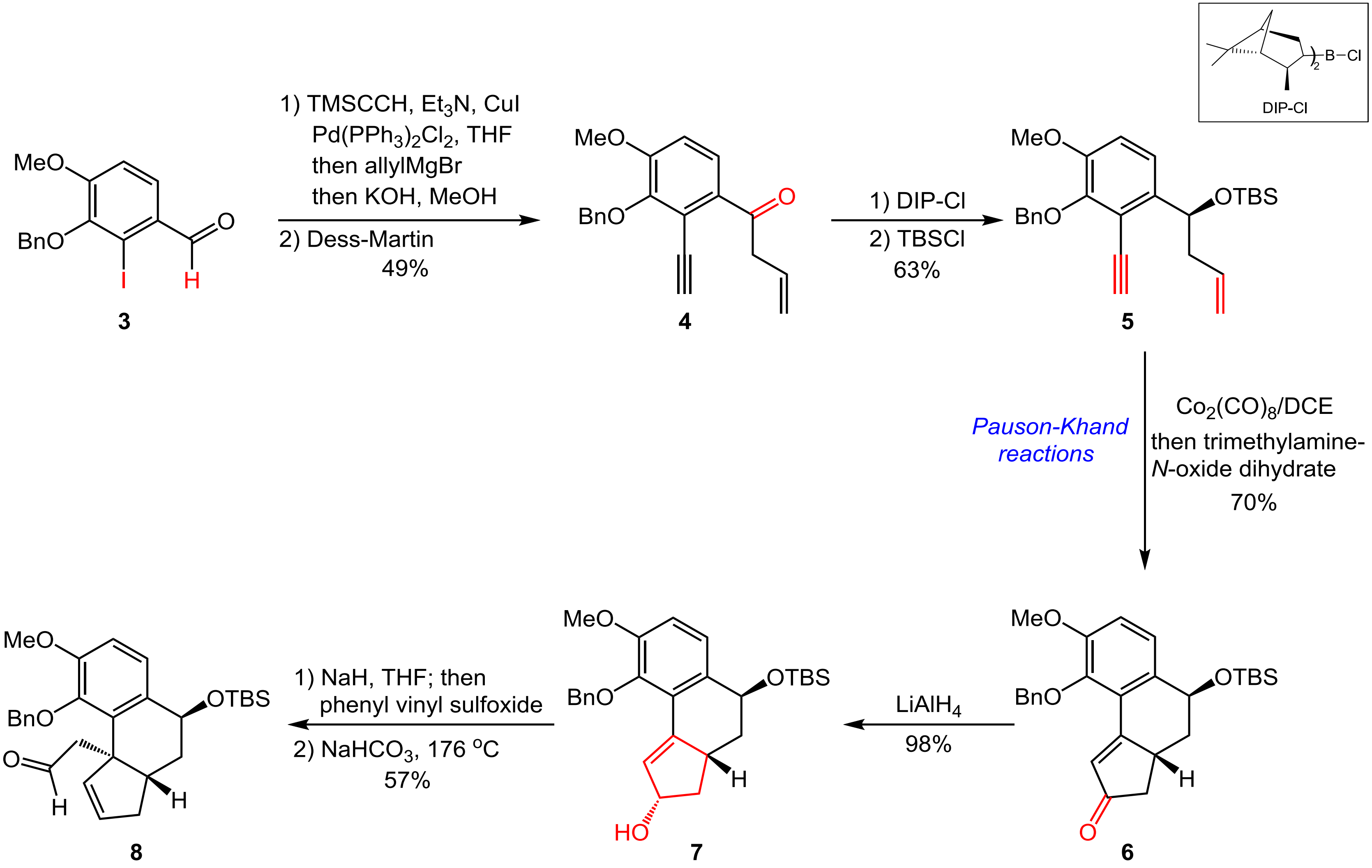
6

Pauson-Khand Reaction





Total Synthesis of (-)-Sinoracutine



1) TMSCCH, Et_3N, CuI
$Pd(PPh_3)_2Cl_2$, THF
then allylMgBr
then KOH, MeOH
2) Dess-Martin
49%

1) DIP-Cl
2) TBSCl
63%

Pauson-Khand reactions

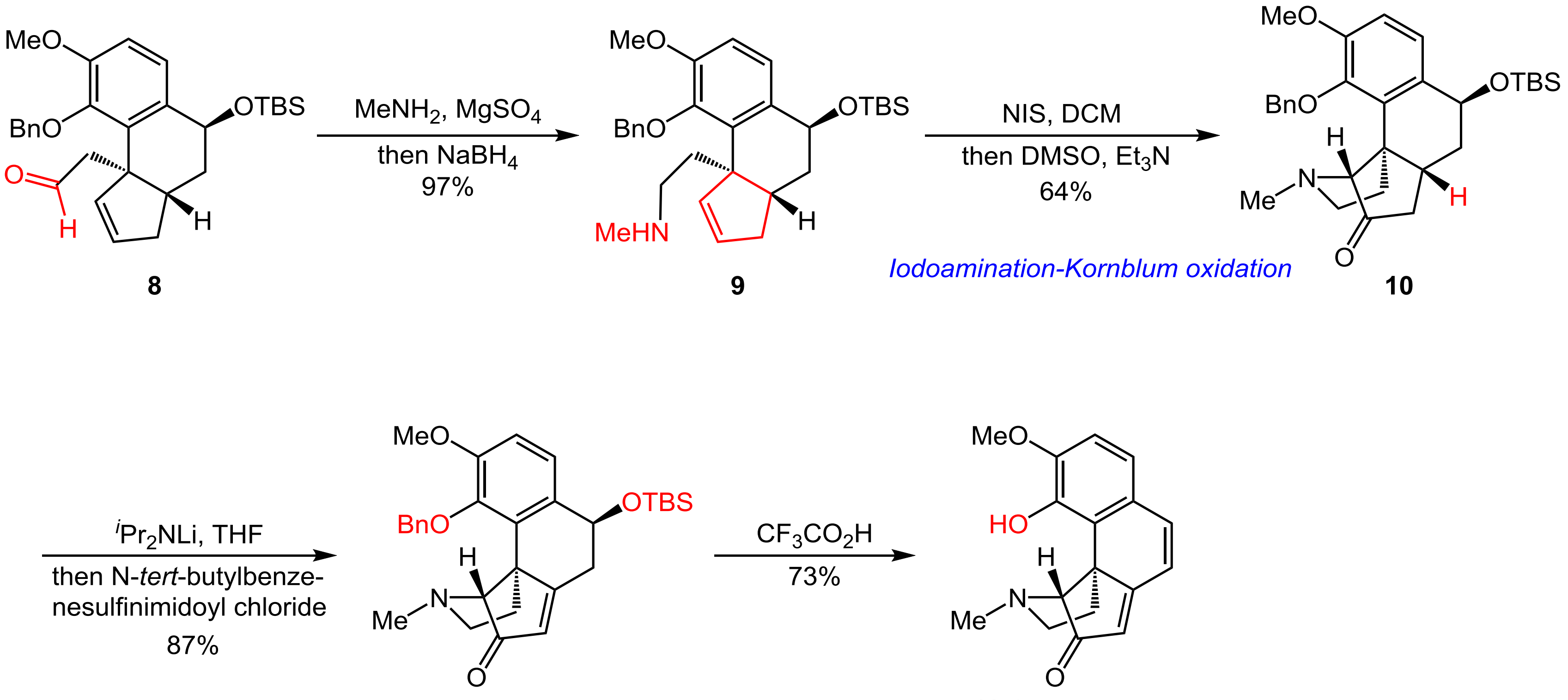
$Co_2(CO)_8$/DCE
then trimethylamine-*N*-oxide dihydrate
70%

$LiAlH_4$
98%

1) NaH, THF; then phenyl vinyl sulfoxide
2) $NaHCO_3$, 176 °C
57%

3 **4** **5** **6** **7** **8**

Total Synthesis of (-)-Sinoracutine



8

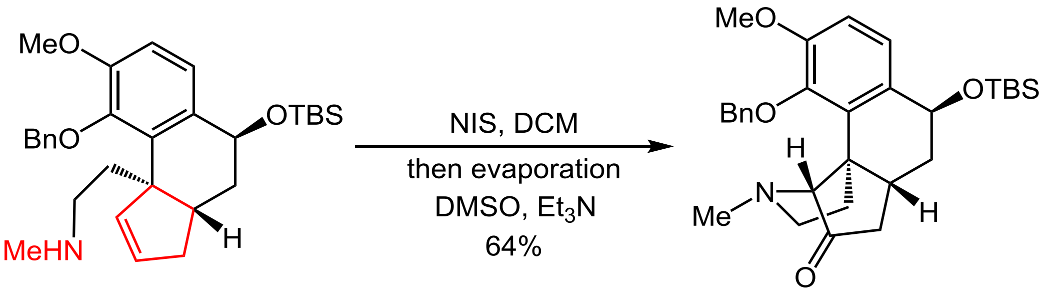
9

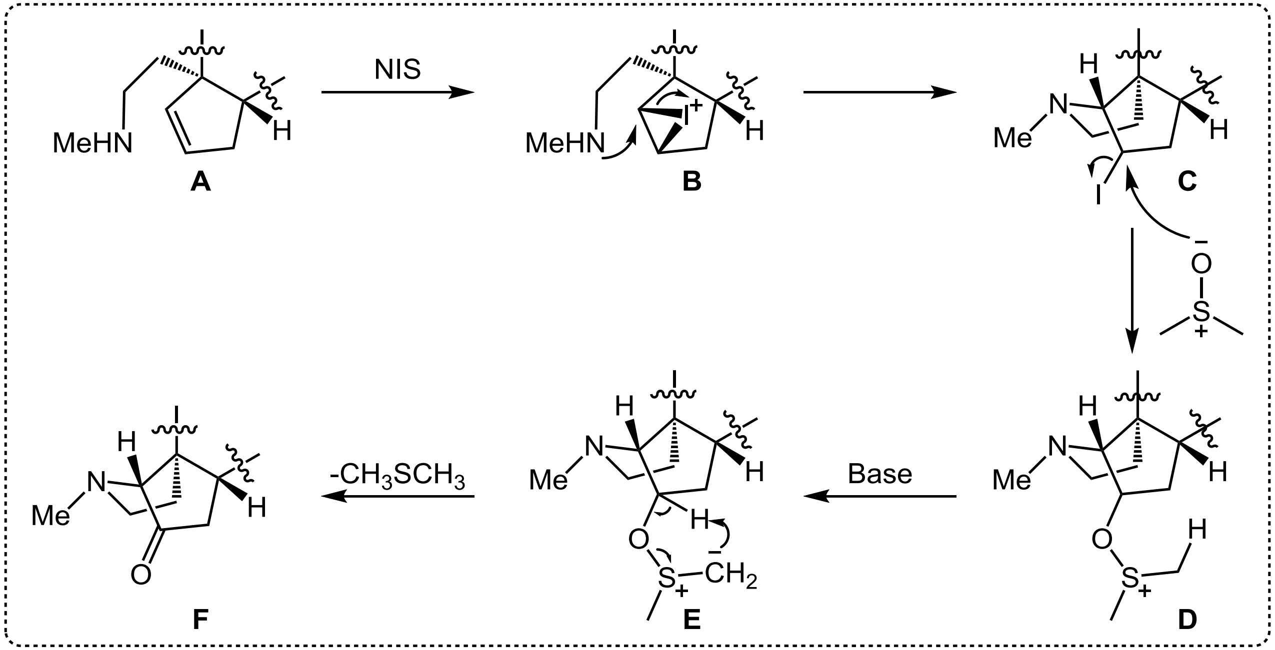
10

11

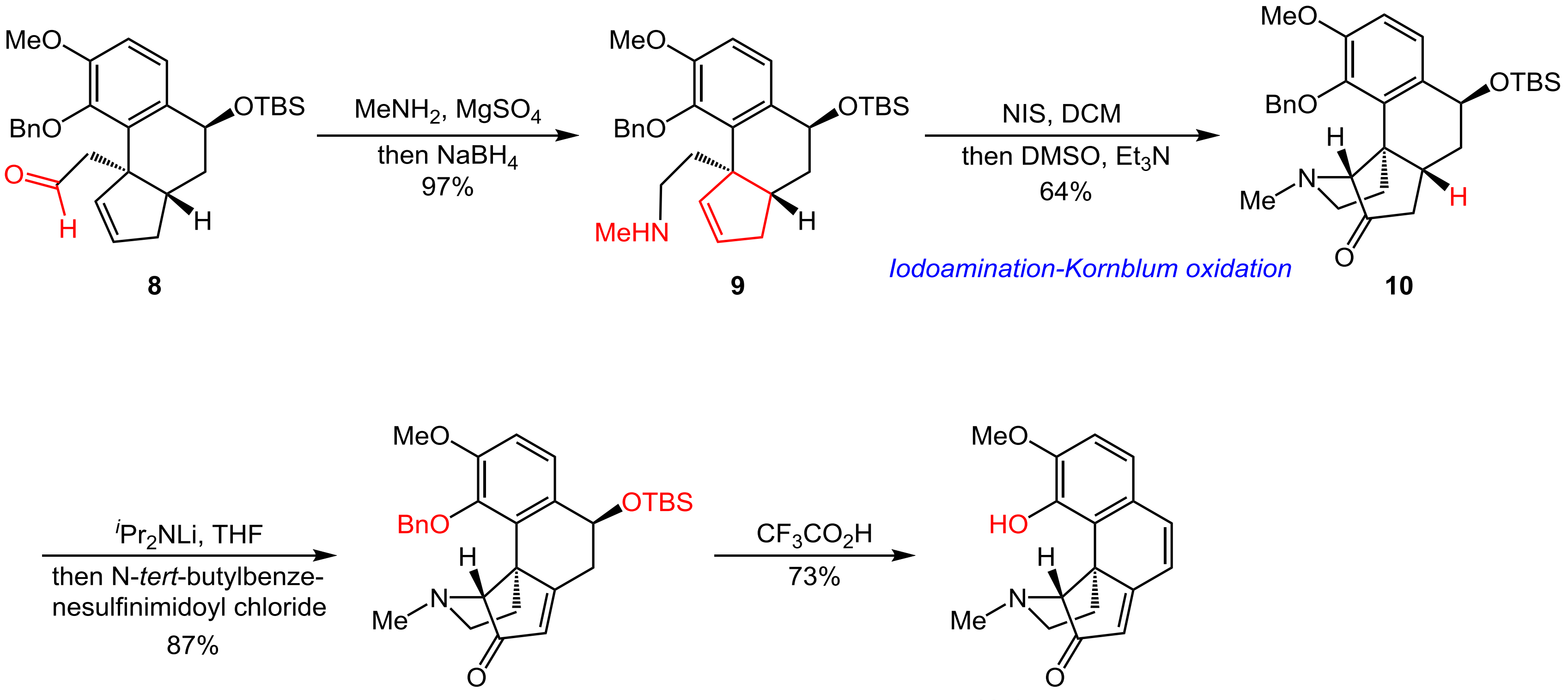
(-)-Sinoracutine

Iodoamination-Kornblum Oxidation





Total Synthesis of (-)-Sinoracutine



8

MeNH$_2$, MgSO$_4$
then NaBH$_4$
97%

9

NIS, DCM
then DMSO, Et$_3$N
64%

Iodoamination-Kornblum oxidation

10

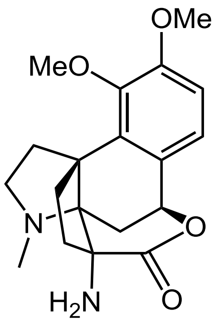
^{i}Pr$_2$NLi, THF
then N-*tert*-butylbenzenesulfinimidoyl chloride
87%

11

CF$_3$CO$_2$H
73%

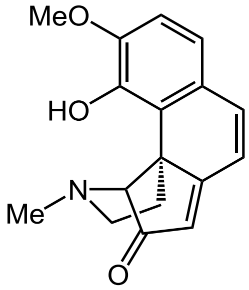
(-)-Sinoracutine

Summary



- 24 Steps, 0.64% overall yield;
- The first total synthesis of stephadiamine;
- *α*-Allylation and decarboxylative Tsuji allylation;
- Aldol condensation.

Trauner, D. *et al*. *J. Am. Chem. Soc.* **2018**, *140*, 8675.



- 12 Steps, 6.72% overall yield;
- Pauson-Khand reaction;
- Claisen Type rearrangement;
- Iodoamination-Kornblum oxidation.

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The First Paragraph

Morphine and hasubanan alkaloids have inspired synthetic chemists for decades. Following the pioneering work of Gates on 1952, more than 30 total and formal syntheses of morphine have been published, some of them very recently. Many syntheses of hasubanonine and its congeners have appeared in the literature since the isolation of the first hasubanan alkaloid was reported by Konto et al. in 1951. Therefore, it is surprising that one of the most beautiful and challenging molecules in the series, stephadiamine, has been virtually ignored by the synthetic community.

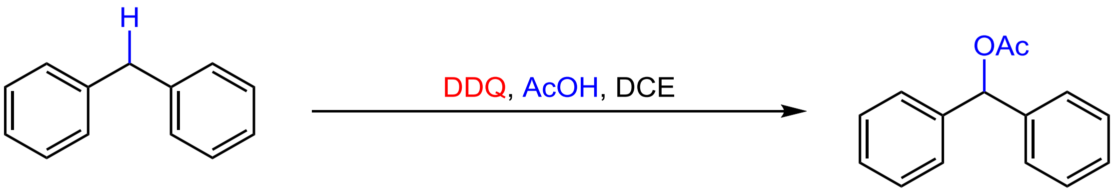
The Last Paragraph

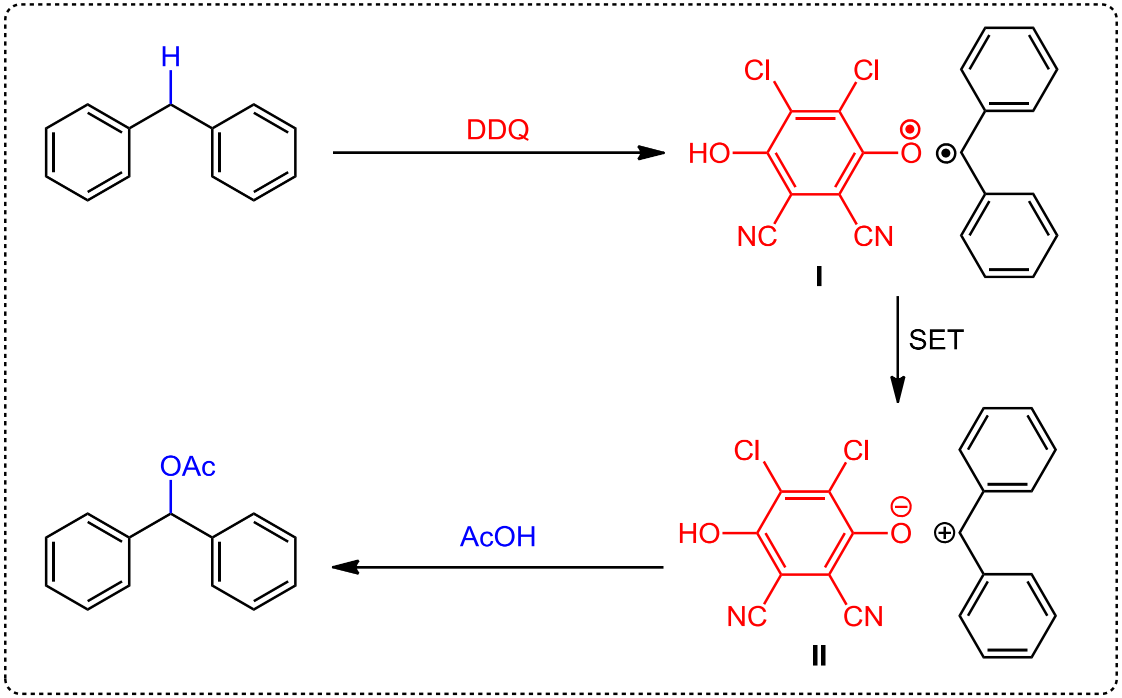
In summary, we have achieved the first synthesis of the unusual alkaloid stephadiamine, in racemic form. Our synthesis is marked by a practical *β*-tetralone synthesis, the facile construction of the benzylic quaternary center through 2-fold alkylation, and a remarkably efficient cascade to forge the azapropellane core of 3. The installation of the α-amino lactone moiety proved to be difficult but could eventually be achieved using a very small base and electrophile. It also required a carefully orchestrated sequence of oxidation and reductions in a densely functionalized setting. Finally, we have elaborated a pathway for the asymmetric synthesis of stephadiamine. The building blocks developed in this context, (*R*)-8 and (*S*)-8, could serve as valuable intermediates in the synthesis of a variety of hasubanan and morphine alkaloids, respectively.

Acknowledgement

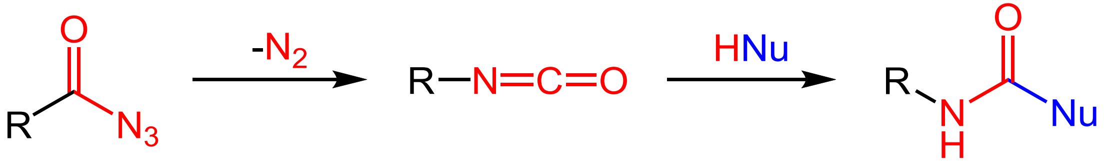
Thanks
for your attention

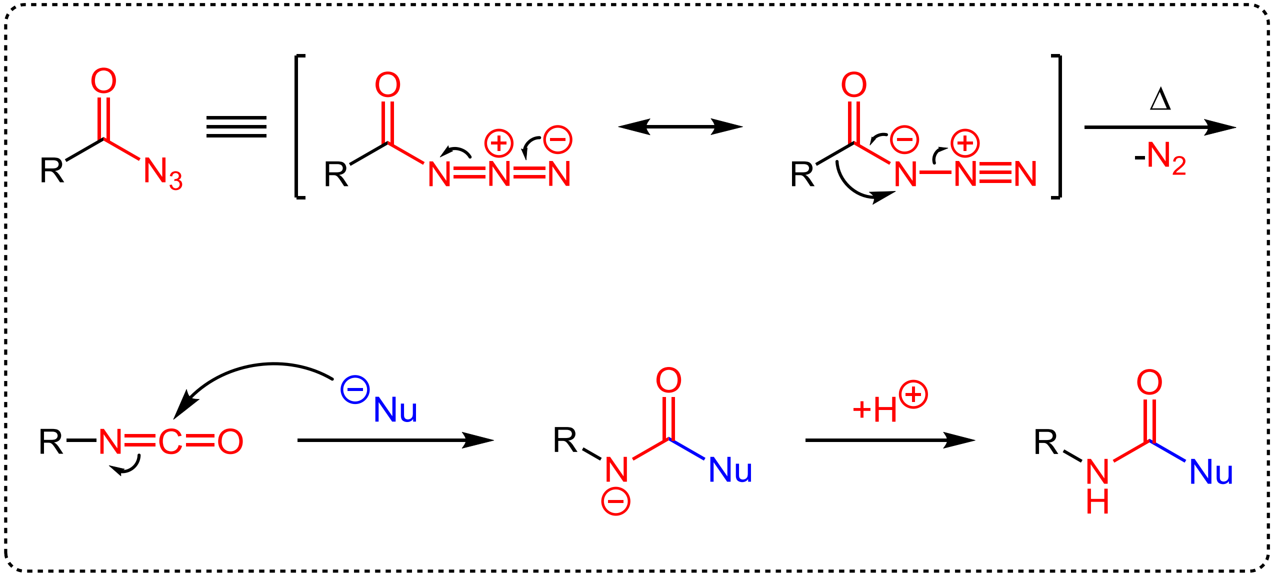
Benzylic Oxidation with DDQ





Curtius Rearrangement





Mukaiyama Oxidation