



ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

Total Synthesis of Actinophyllic Acid

Group Seminar

Guang Li (Jieping Zhu's Lab)

Laboratory of Synthesis and Natural Products (LSPN)

Ecole Polytechnique Fédérale de Lausanne (EPFL)

Outline

- ❖ 1. Introduction
- ❖ 2. Proposed Biosynthesis
- ❖ 3. Total synthesis of Actinophyllic acid
 - Overman's **aza-cope-mannich** strategy
 - Martin's **carbocation/ π -nucleophile cascade reaction** strategy
 - Kwon's **phosphine-catalyzed [3 + 2] annulation** strategy
 - Chen's **desymmetrization** strategy
- ❖ 4. Summary and Outlook

Outline

❖ 1. Introduction

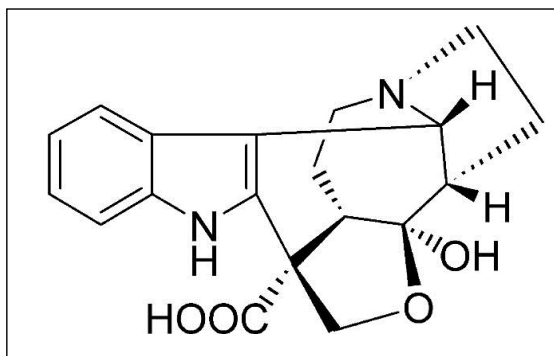
❖ 2. Proposed Biosynthesis

❖ 3. Total synthesis of Actinophyllic acid

- Overman's aza-cope-mannich strategy
- Martin's carbocation/ π -nucleophile cascade reaction strategy
- Kwon's phosphine-catalyzed [3 + 2] annulation strategy
- Chen's desymmetrization strategy

❖ 4. Summary and Outlook

Introduction



Actinophyllic Acid

0.0072%



Alstonia actinophylla

Structure Characters:

- *Indole alkaloid;*
- *Six rings;*
- *Five contiguous stereocenters;*

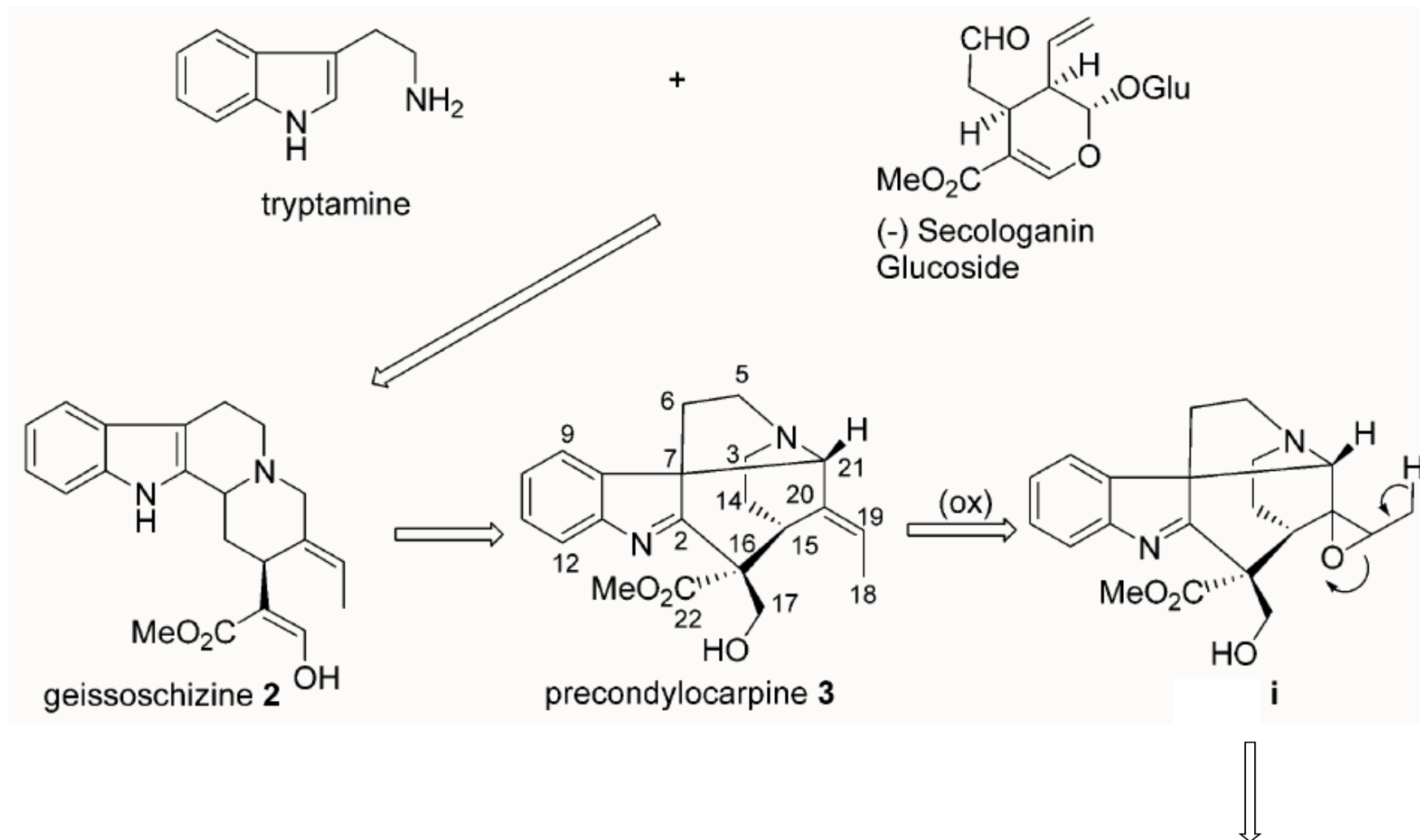
Biological activity:

A potent inhibitor of the zinc-dependent carboxypeptidase U (CPU), with an IC_{50} of $0.84 \mu M$. CPU is an endogenous inhibitor of fibrinolysis, the breakage of fibrin clots.

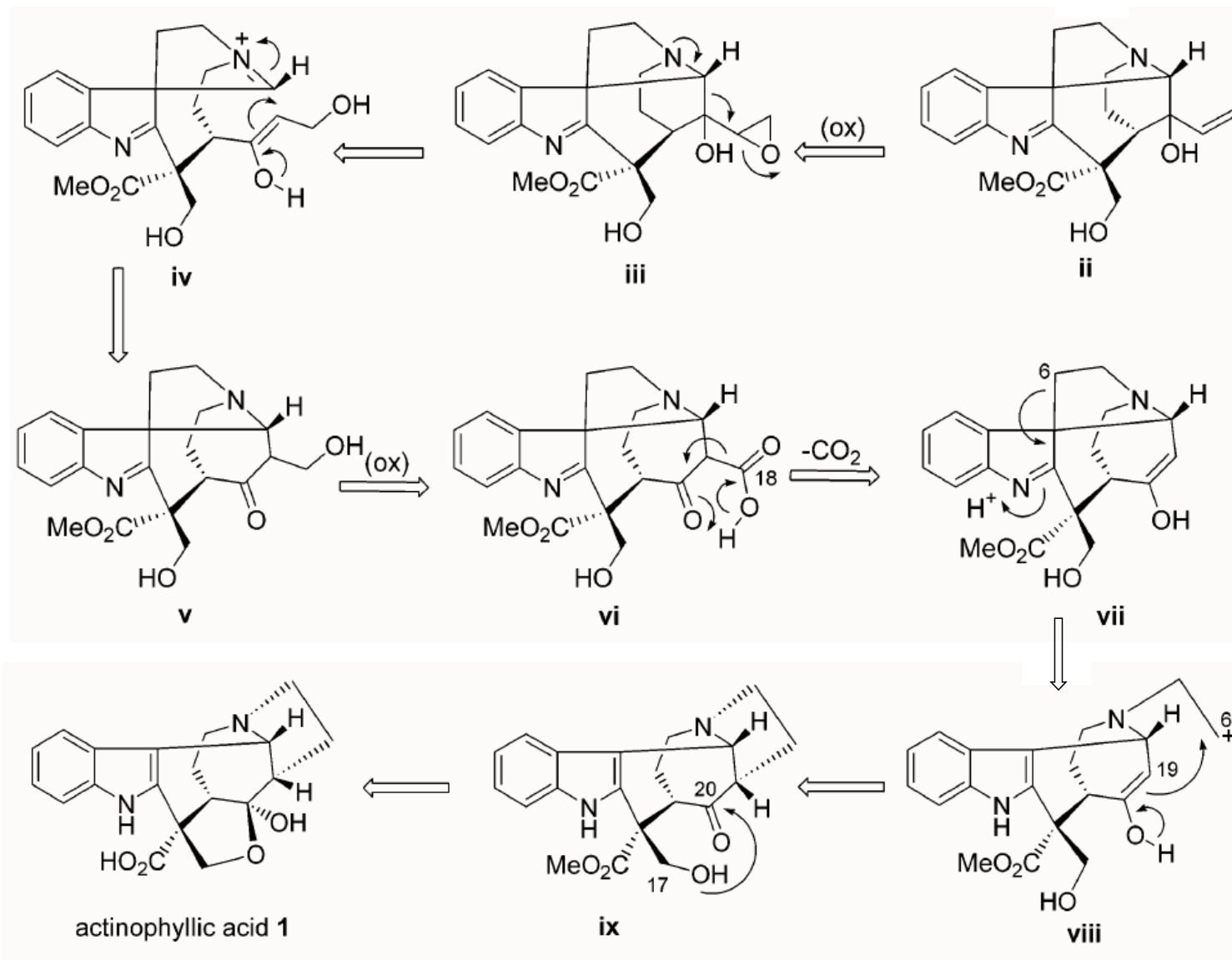
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Proposed Biosynthesis



Proposed Biosynthesis

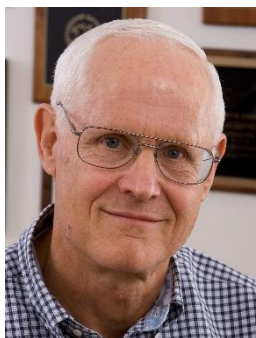


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Total synthesis of Actinophyllic acid

Total synthesis



Larry E. Overman
JACS. **2008**, *130*, 4894.
JACS. **2010**, *132*, 4532.



Stephen F. Martin
JACS. **2013**, *135*, 12984.
T. **2014**, *70*, 4094.



Ohyun Kwon
JACS. **2016**, *138*, 3298.



David Y.-K. Chen
ACIE. **2017**, *56*, 12277.

Progress of total synthesis



John L. Wood
OL. **2009**, *11*, 4532.



Tsuyoshi Taniguchi
OL. **2014**, *14*, 1656.



Luis A. Maldonado
TL. **2013**, *54*, 2180.

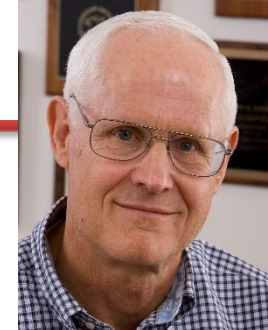


Iain Coldham
TL. **2014**, *55*, 1255.

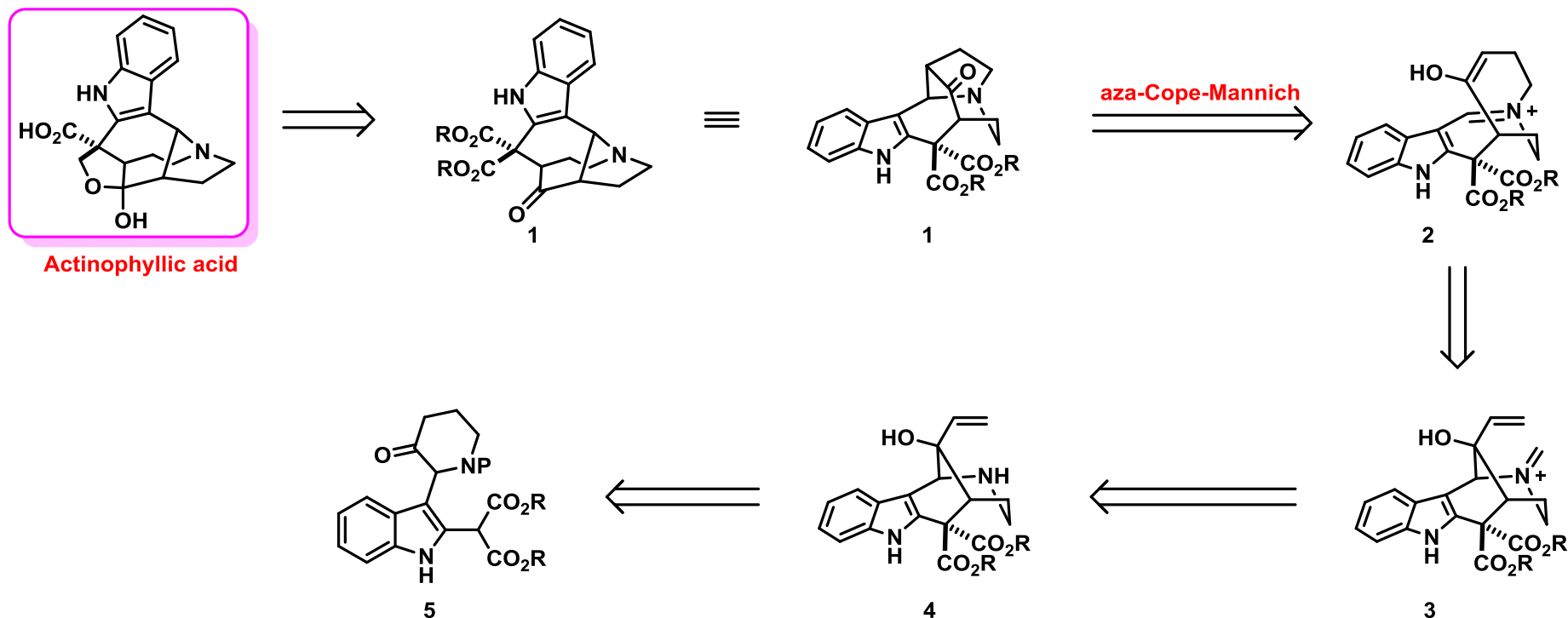


Yong Qin
T. **2017**, *73*, 2109.

Overman's total synthesis

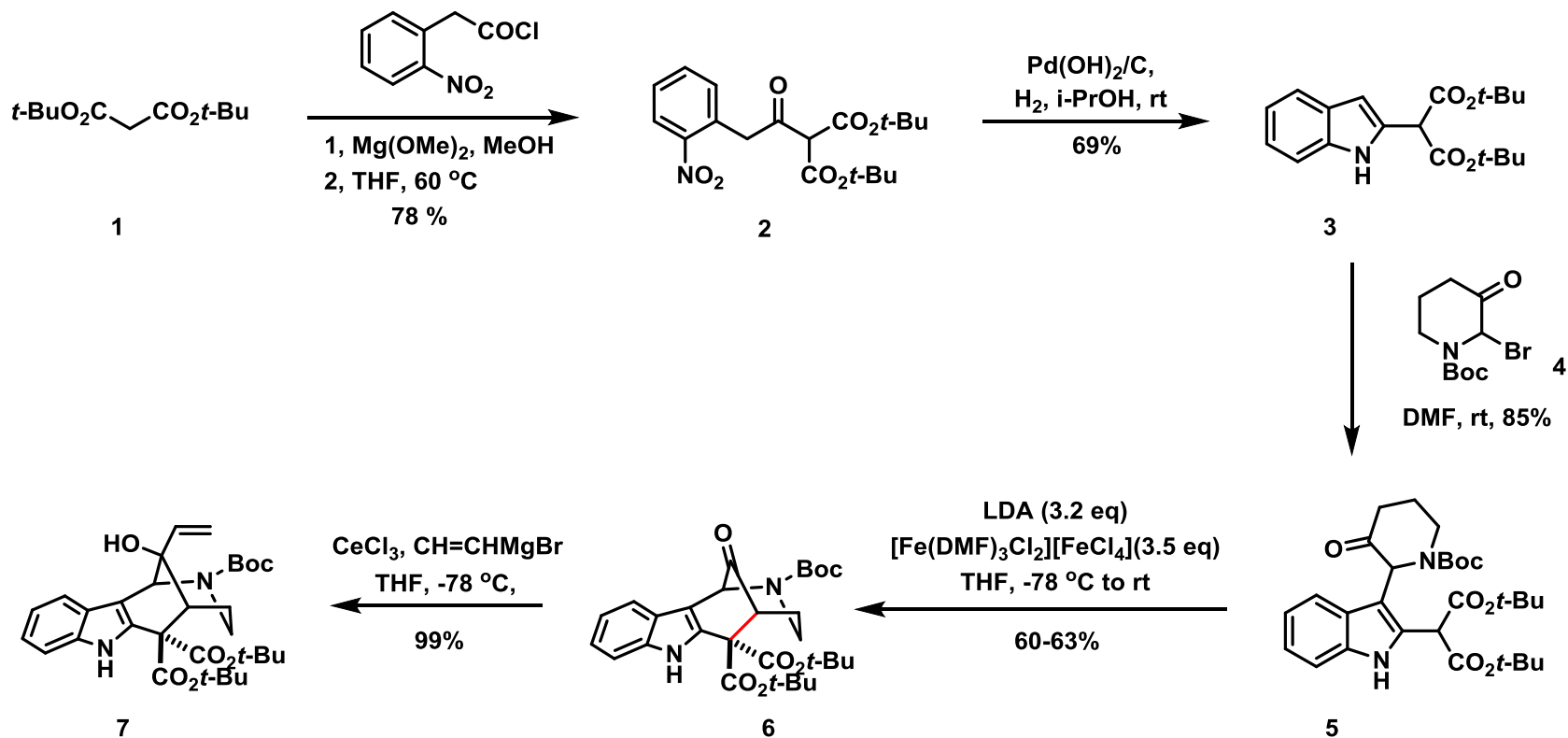


Retrosynthetic Analysis of Actinophyllic Acid



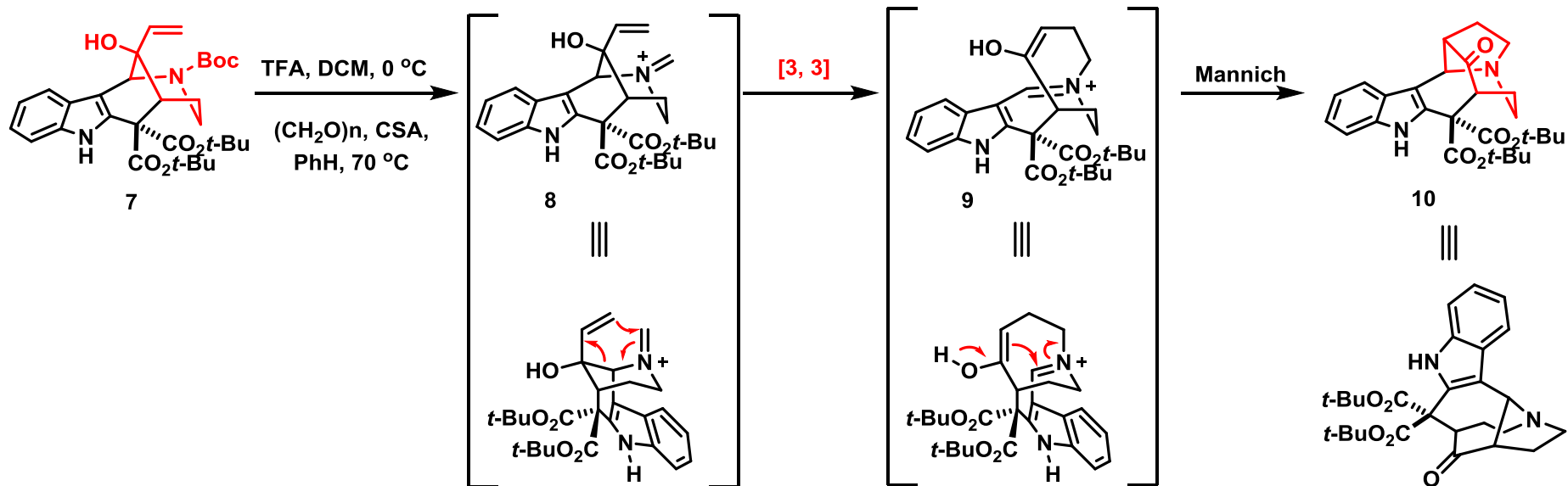
Overman's total synthesis

First-Generation total synthesis



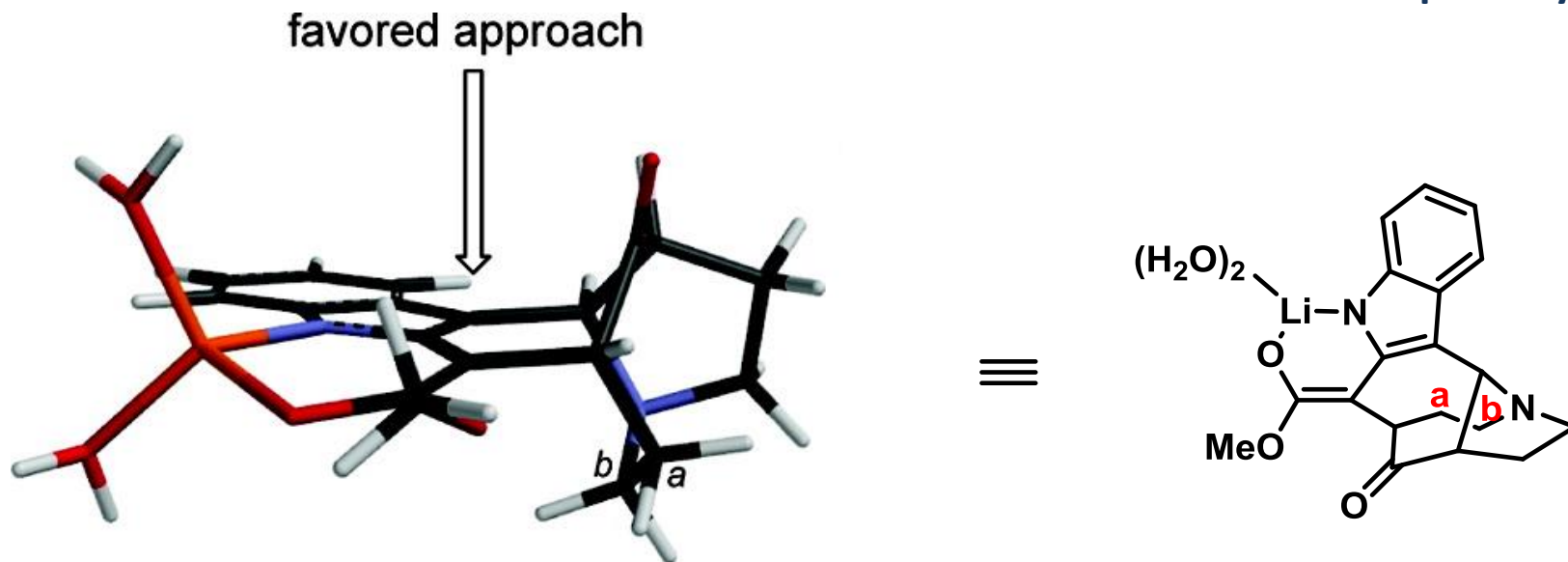
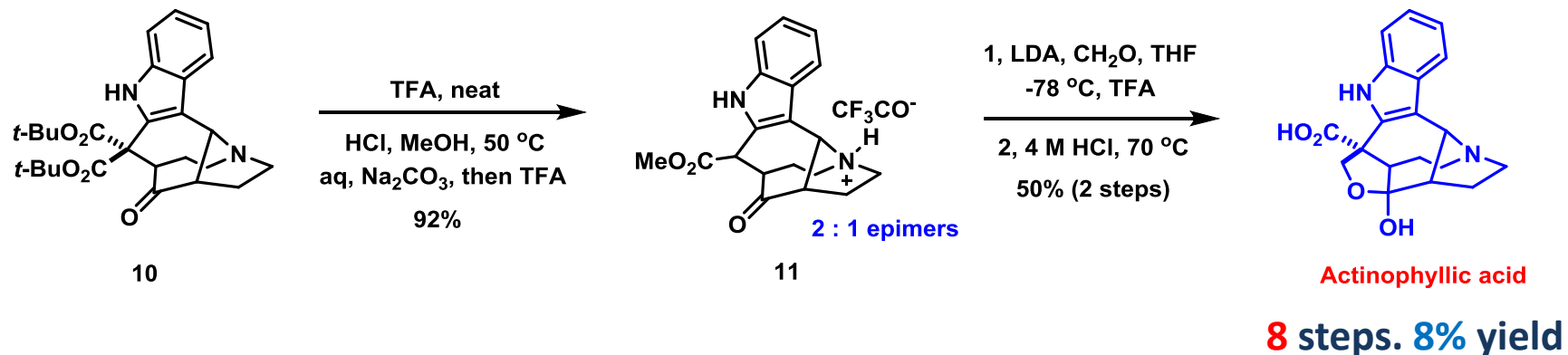
Overman's total synthesis

First-Generation total synthesis



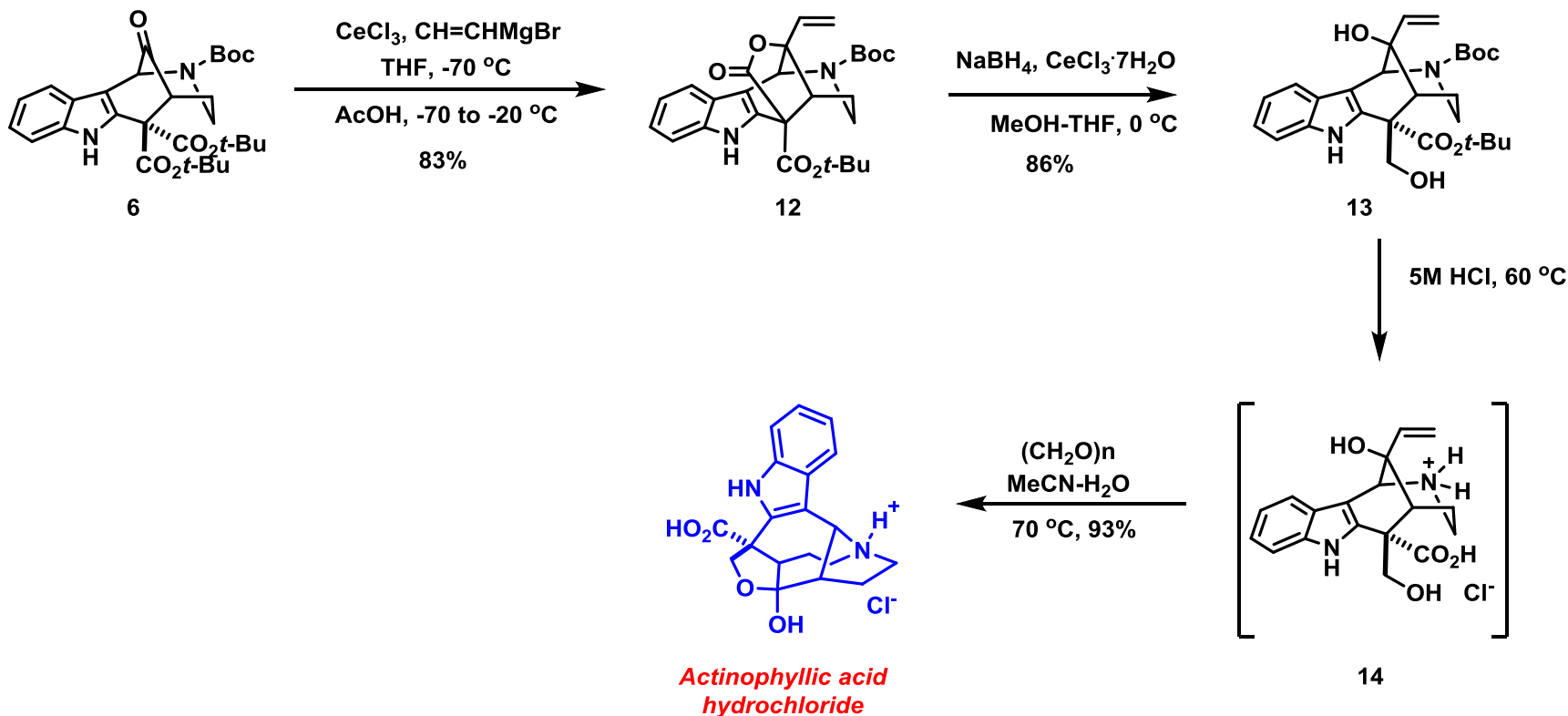
Overman's total synthesis

First-Generation total synthesis



Overman's total synthesis

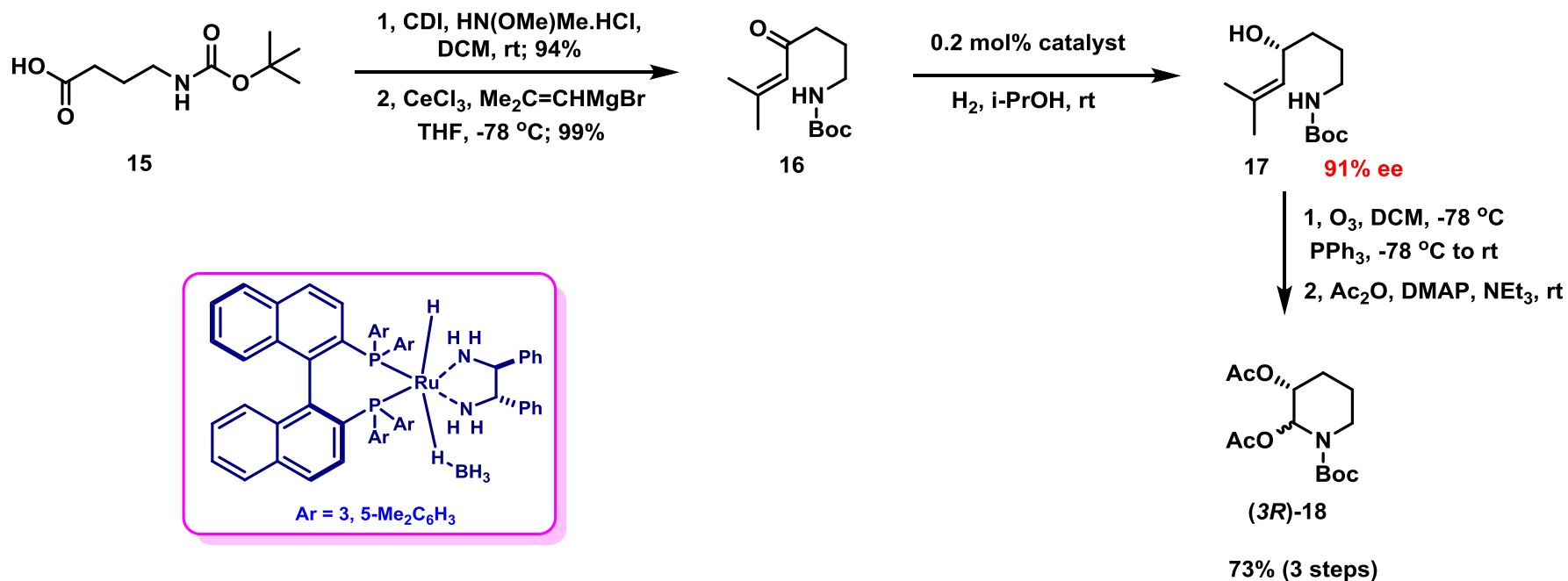
Second-Generation total synthesis



7 steps. 22% yield

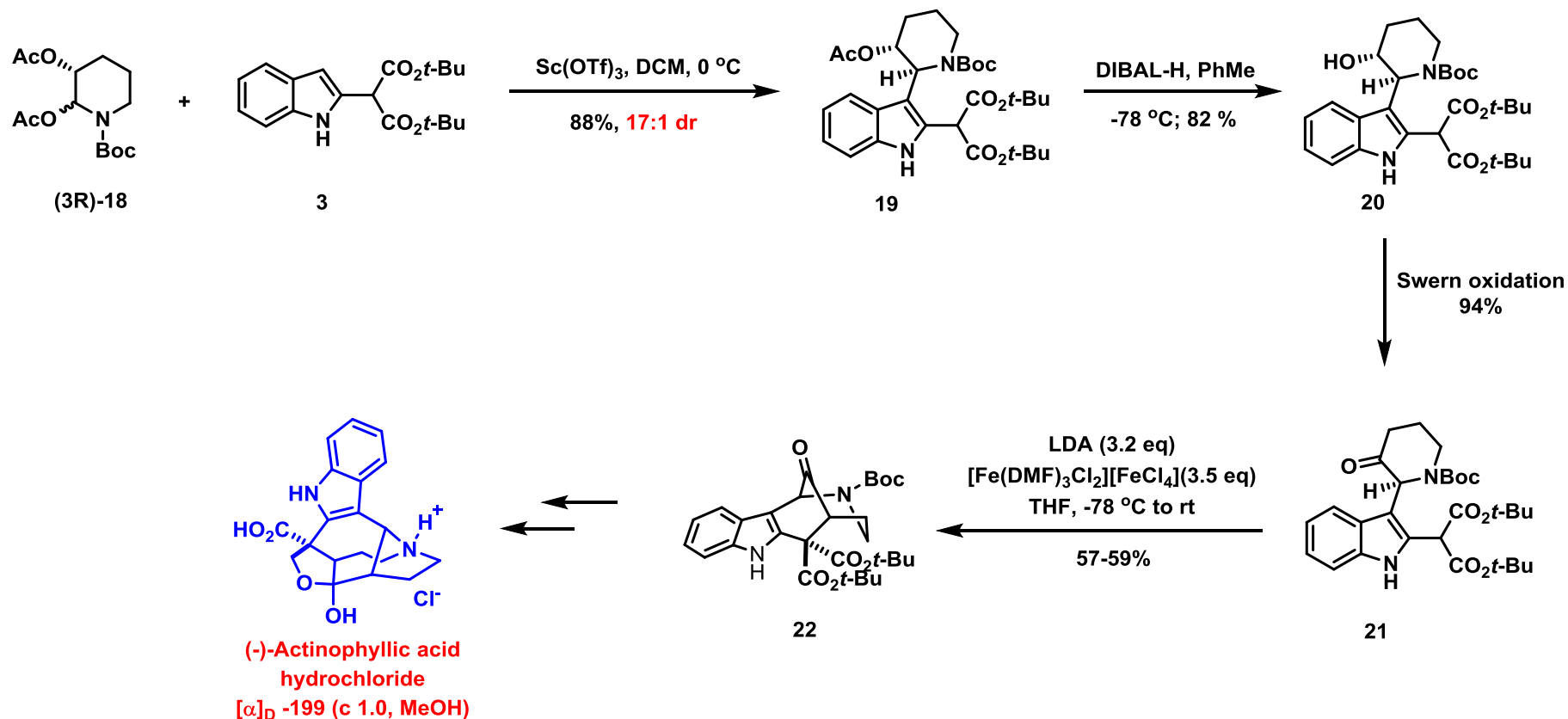
Overman's total synthesis

Enantioselective total synthesis of (-)-Actinophyllic Acid



Overman's total synthesis

Enantioselective total synthesis of (-)-Actinophyllic Acid

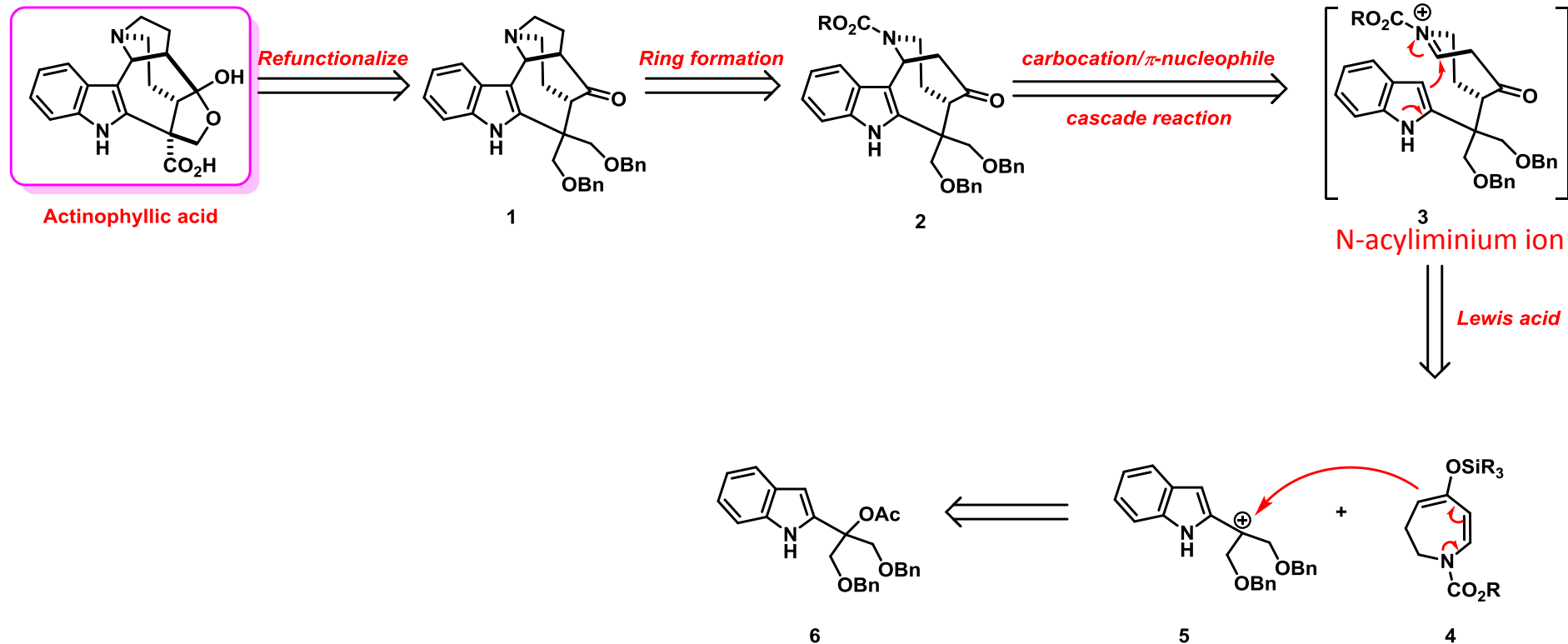


11 steps. 18% yield

Martin's total synthesis

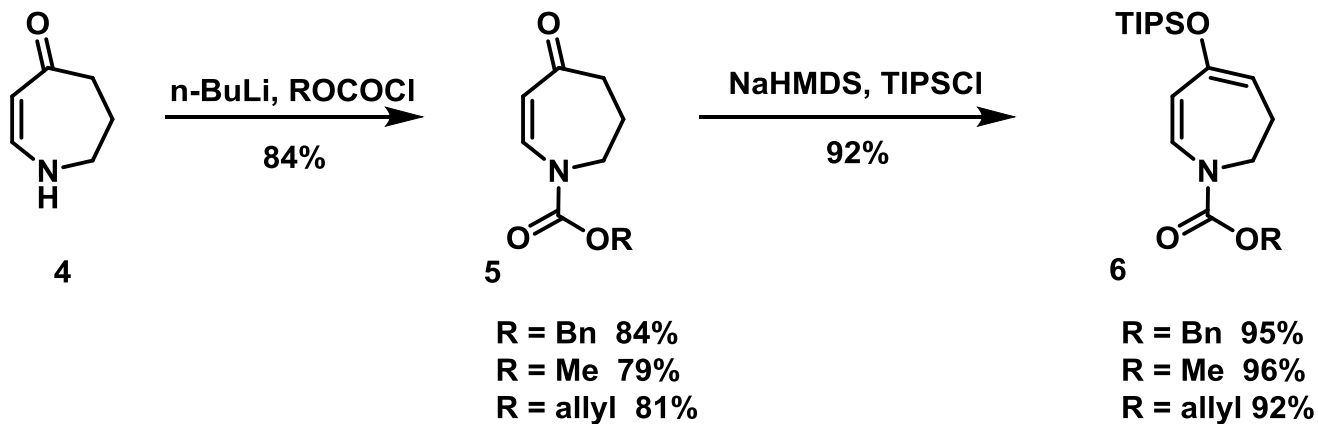
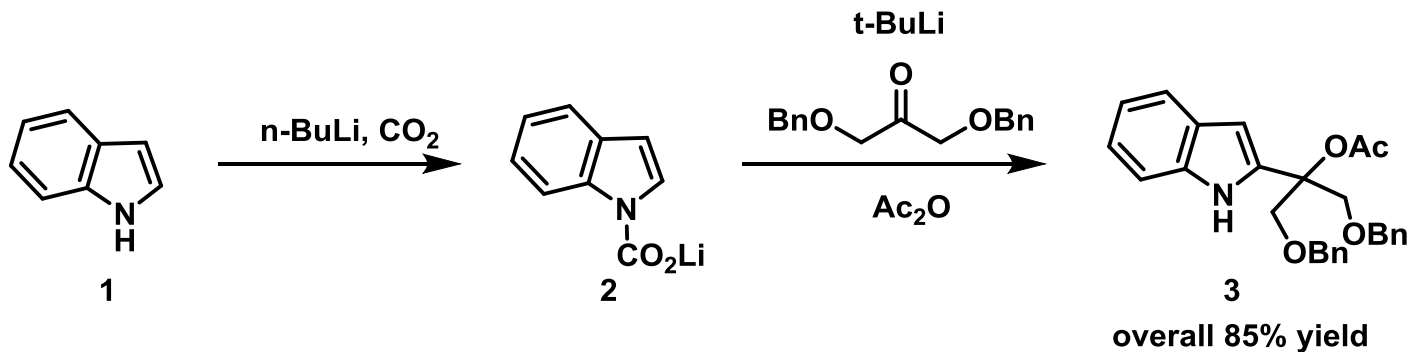


Retrosynthetic Analysis of Actinophyllic Acid



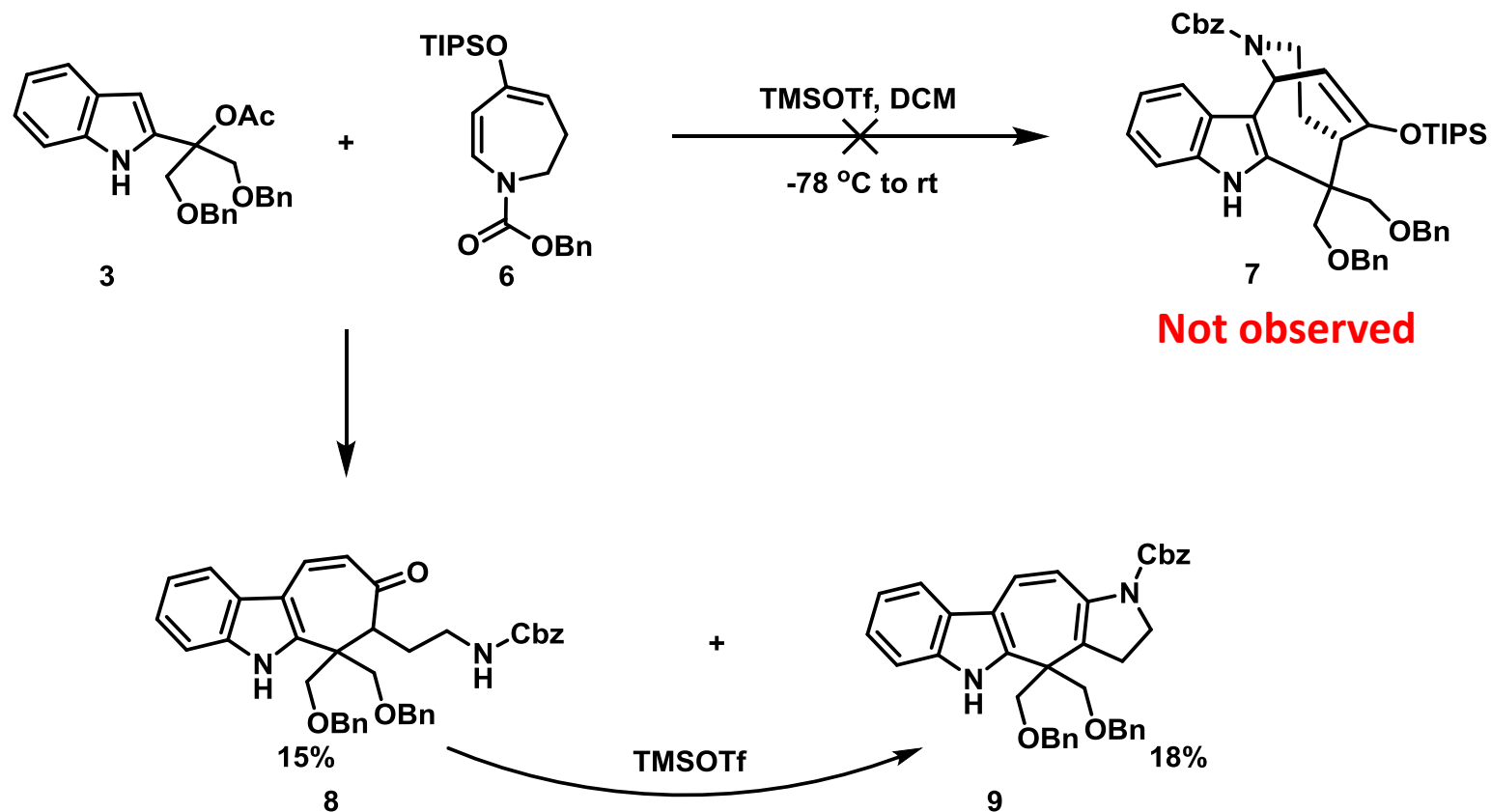
Martin's total synthesis

Preparation of starting materials



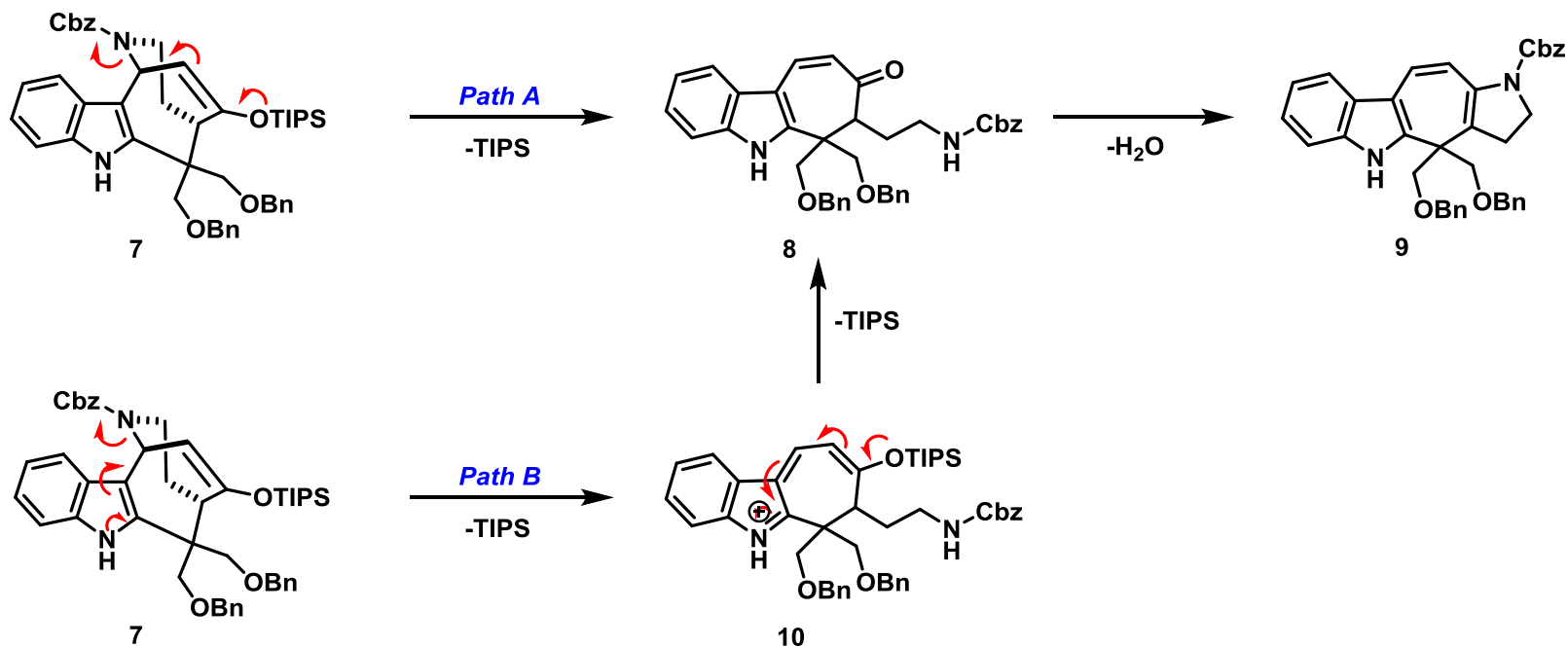
Martin's total synthesis

Failed cascade reaction

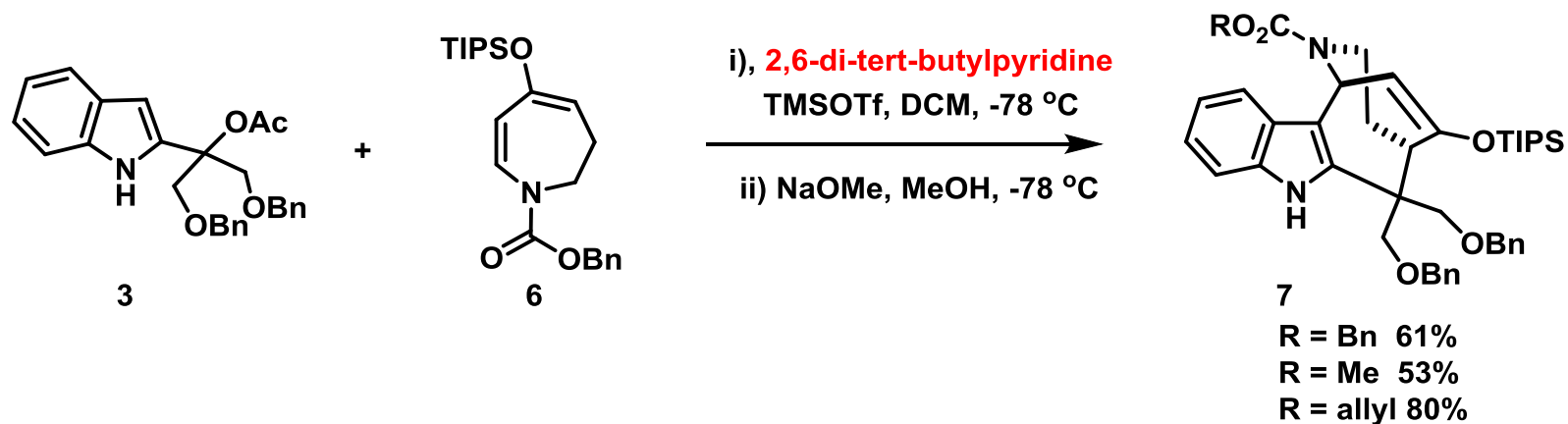


Martin's total synthesis

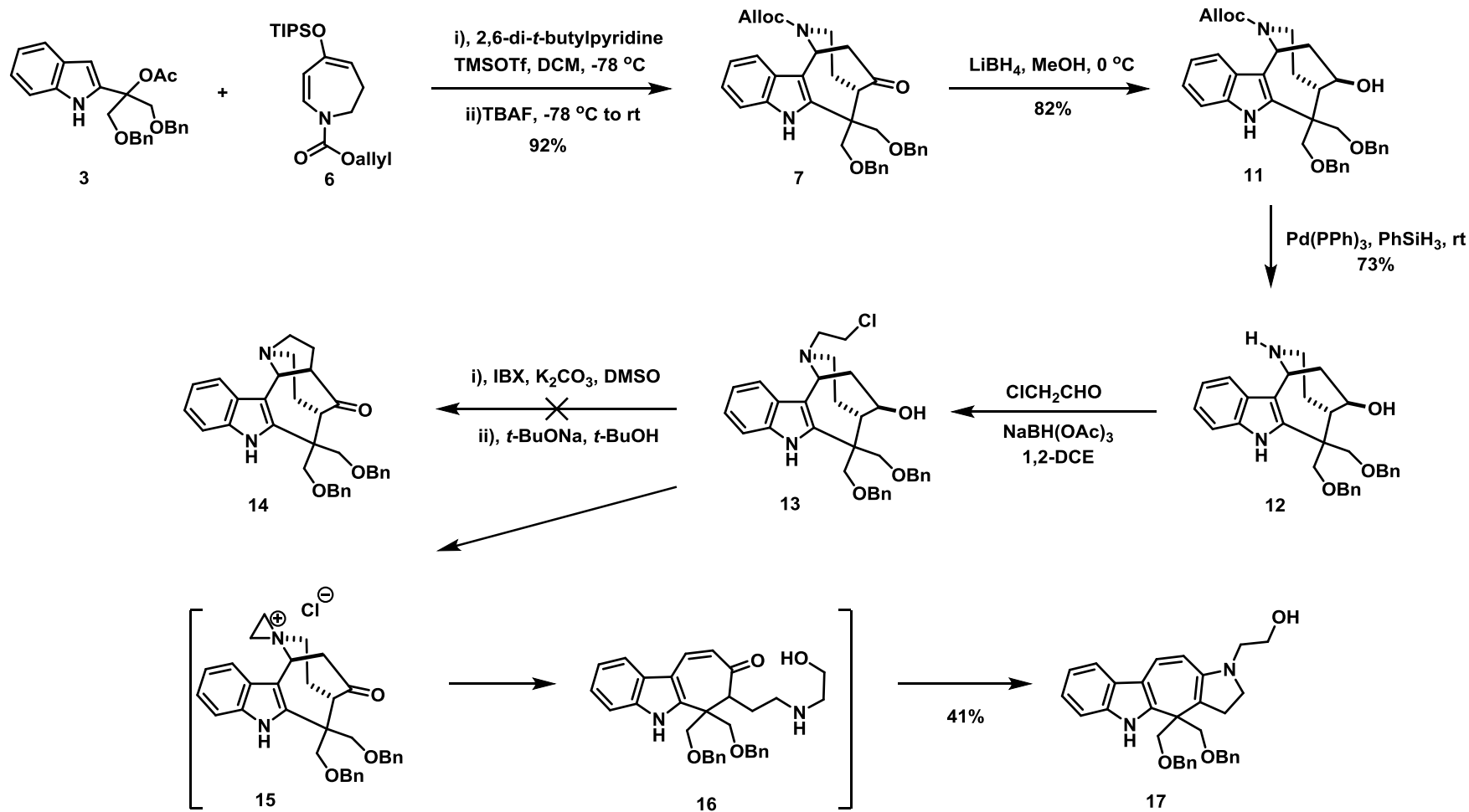
Proposed fragmentation pathways



Martin's total synthesis

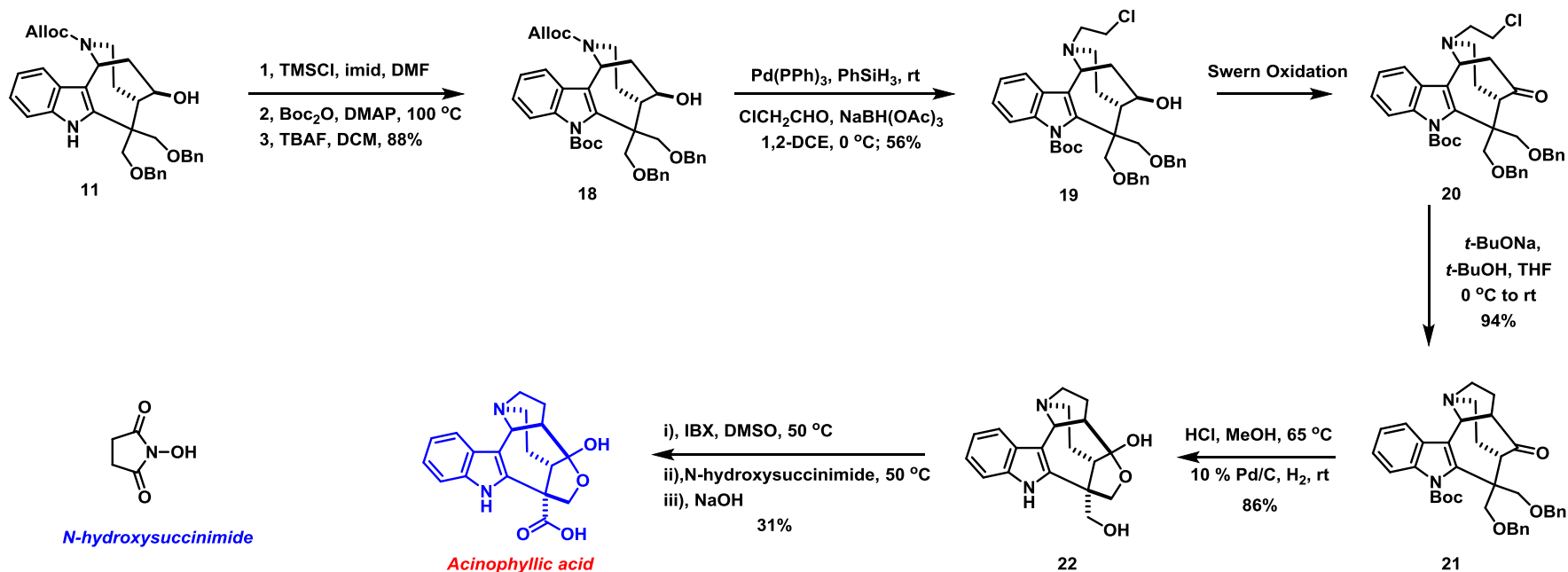


Martin's total synthesis



Martin's total synthesis

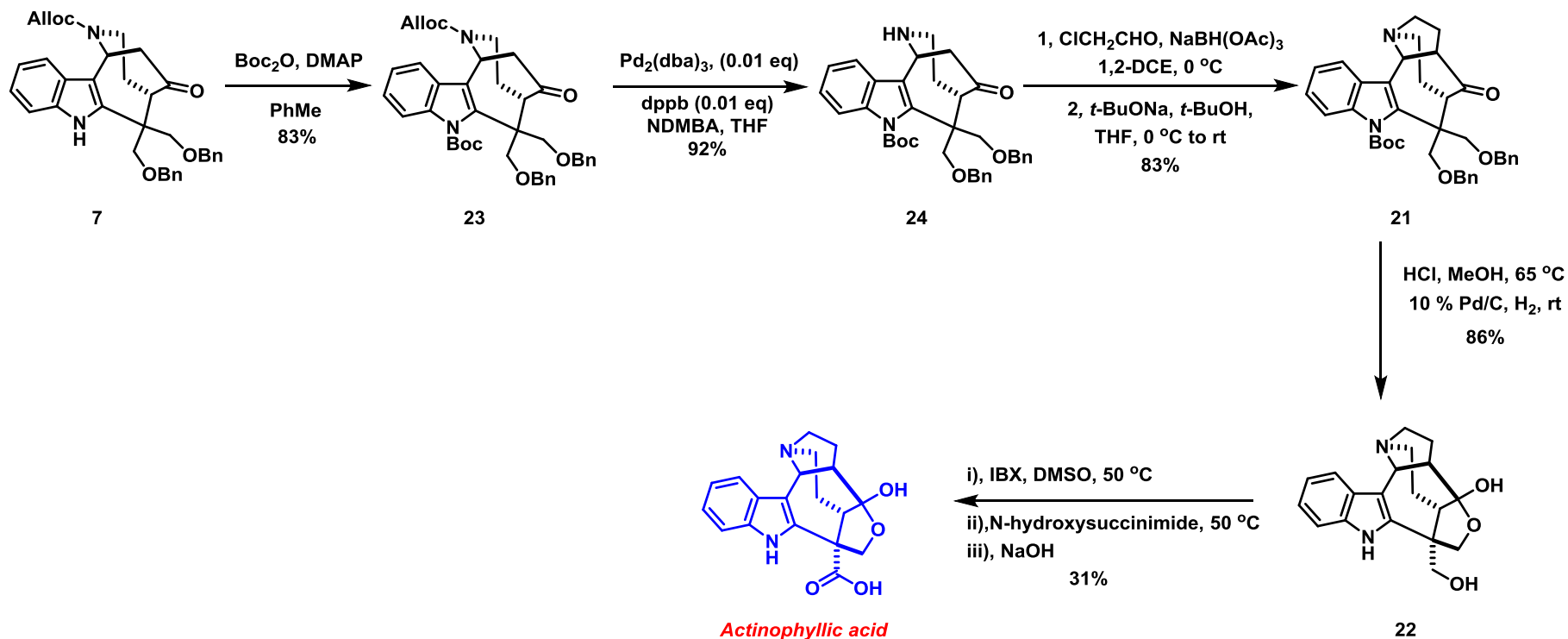
First-Generation total synthesis



14 steps. 5% yield

Martin's total synthesis

Second-Generation total synthesis

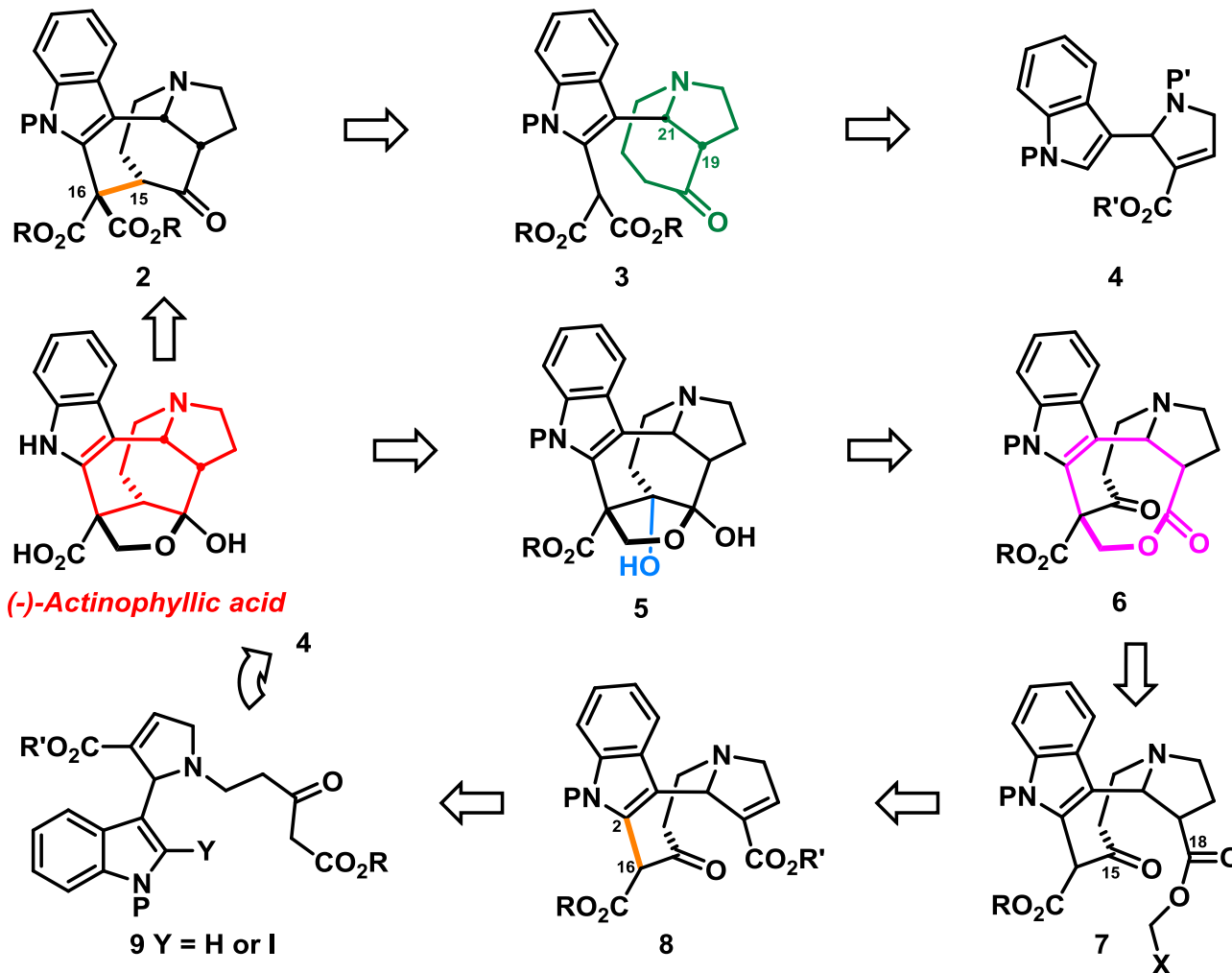


10 steps. 10% yield

kwon's total synthesis

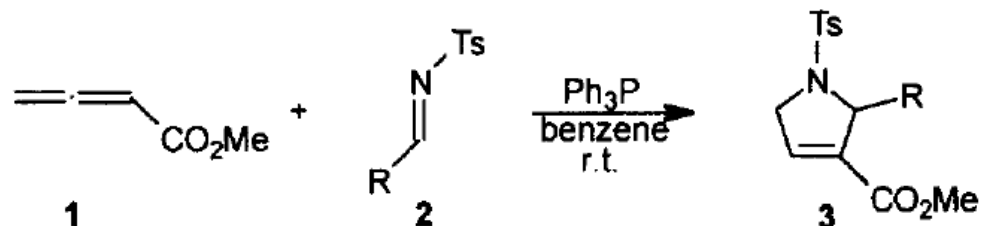


Retrosynthetic Analysis of Actinophyllic Acid

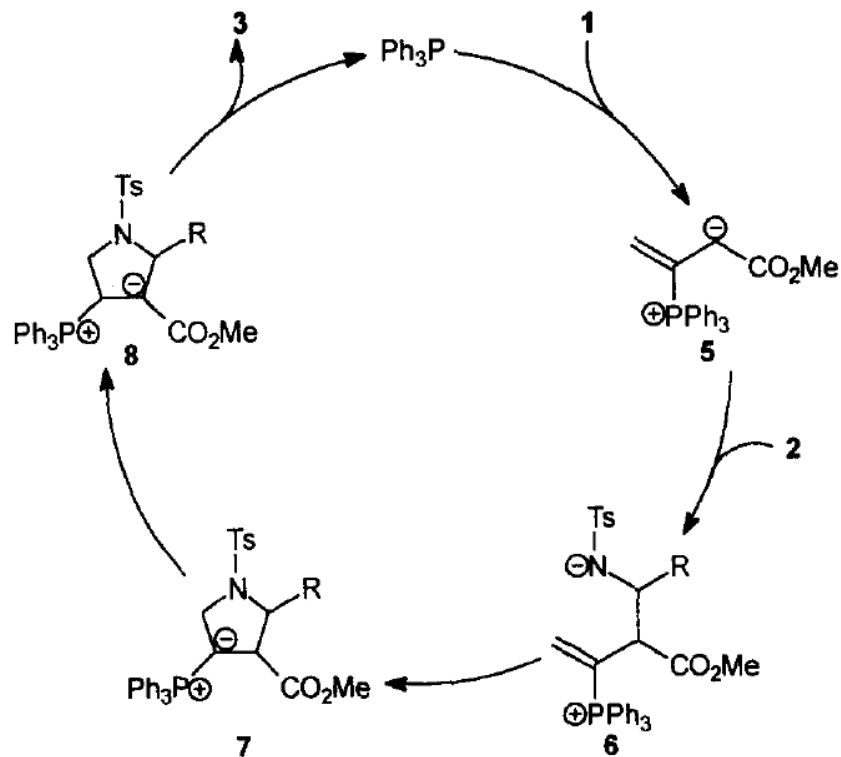


kwon's total synthesis

Mechanism of [3+2] annulation reaction

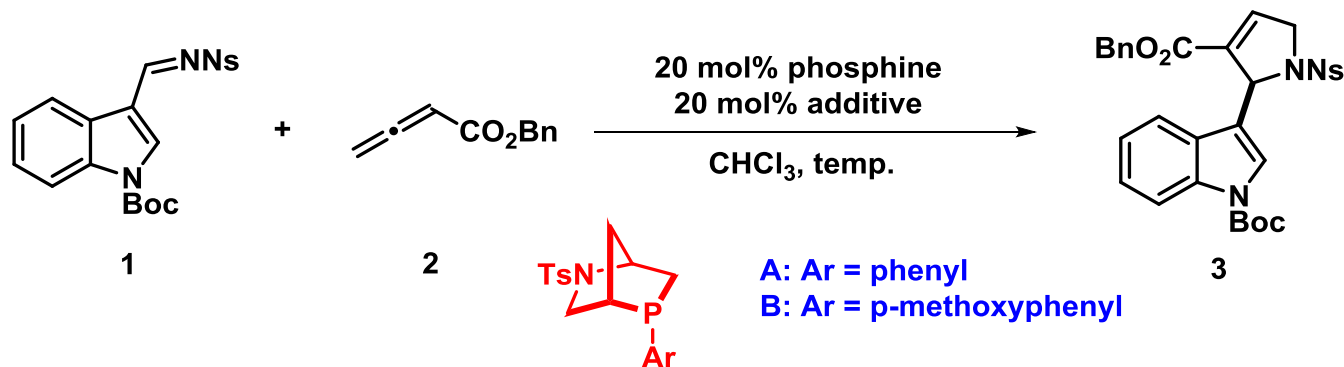


Xu, Z.; Lu, X. *Tetrahedron Lett.* **1997**, 38, 3461.



kwon's total synthesis

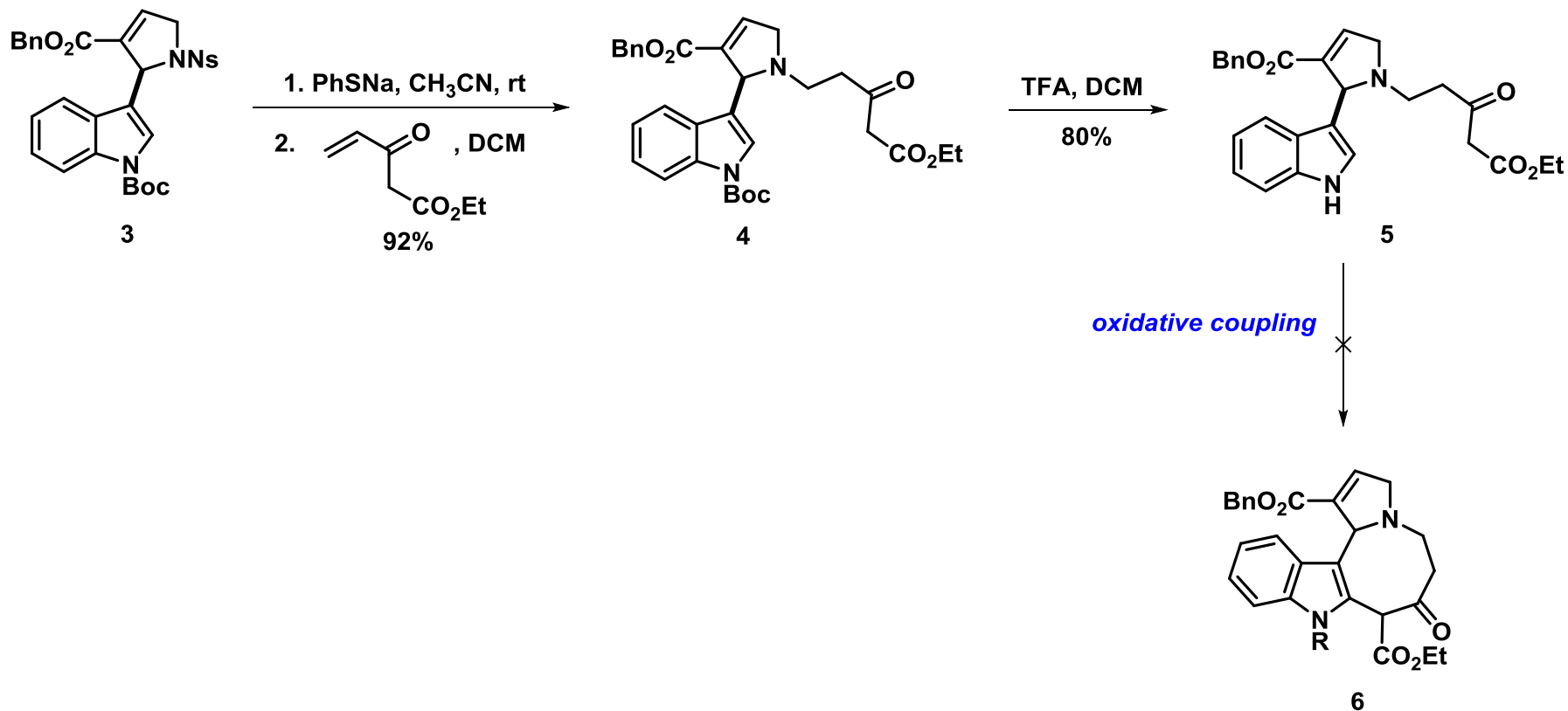
Phosphine-Catalyzed Pyrrolidine Synthesis



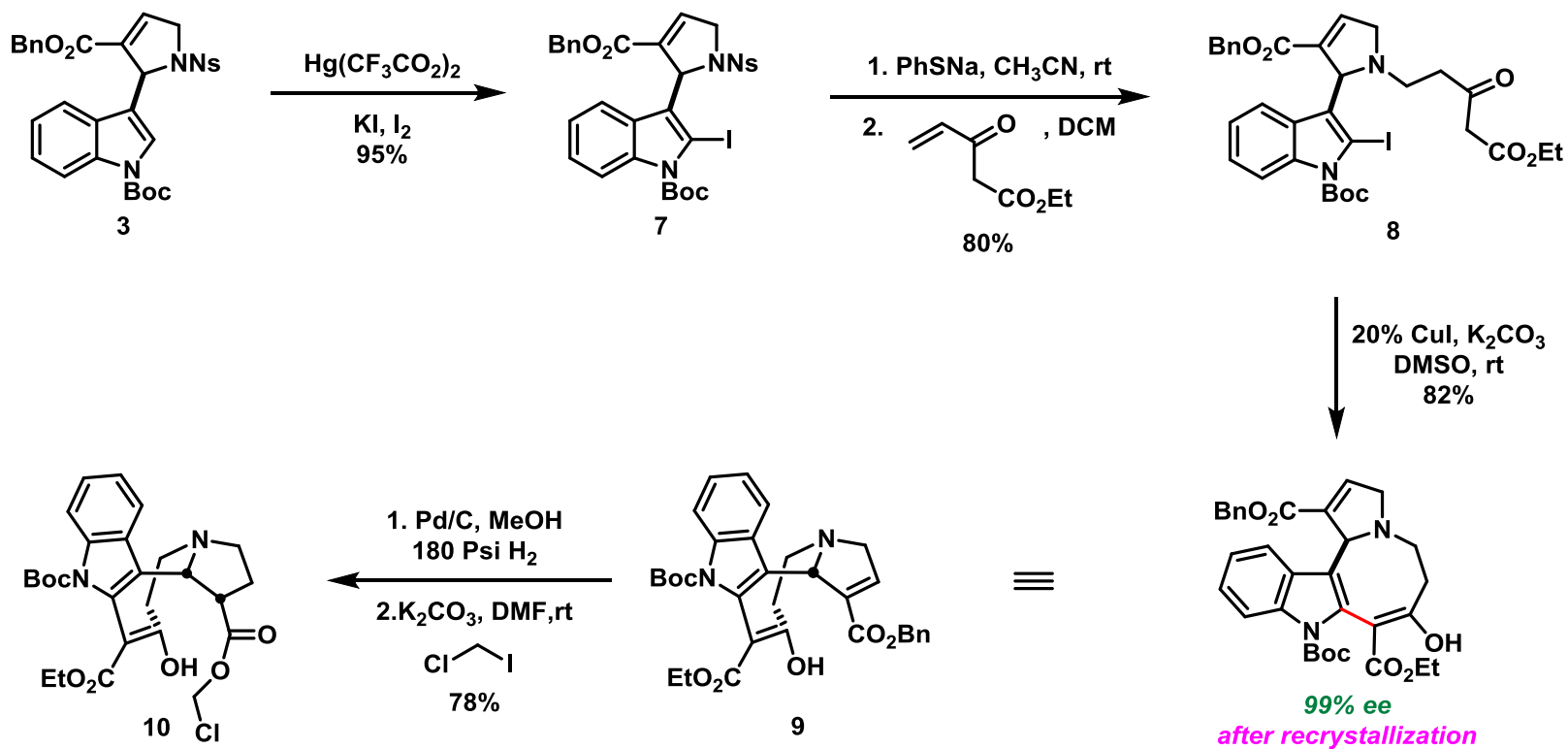
entry	cat.	temp. (°C)	additive	time (h)	yield (%) ^a	ee (%) ^b
1	PPh ₃	rt		6	99	
2	A	rt		5	97	75
3	B	rt		5	99	83
4	B	0		5	99	91
5	B	0	phenol	2	99	91
6	B	0	biphenol	2	99	91
7	B	0	<i>s</i> -BINOL	2	99	94
8	B	0	<i>r</i> -BINOL	2	99	94

kwon's total synthesis

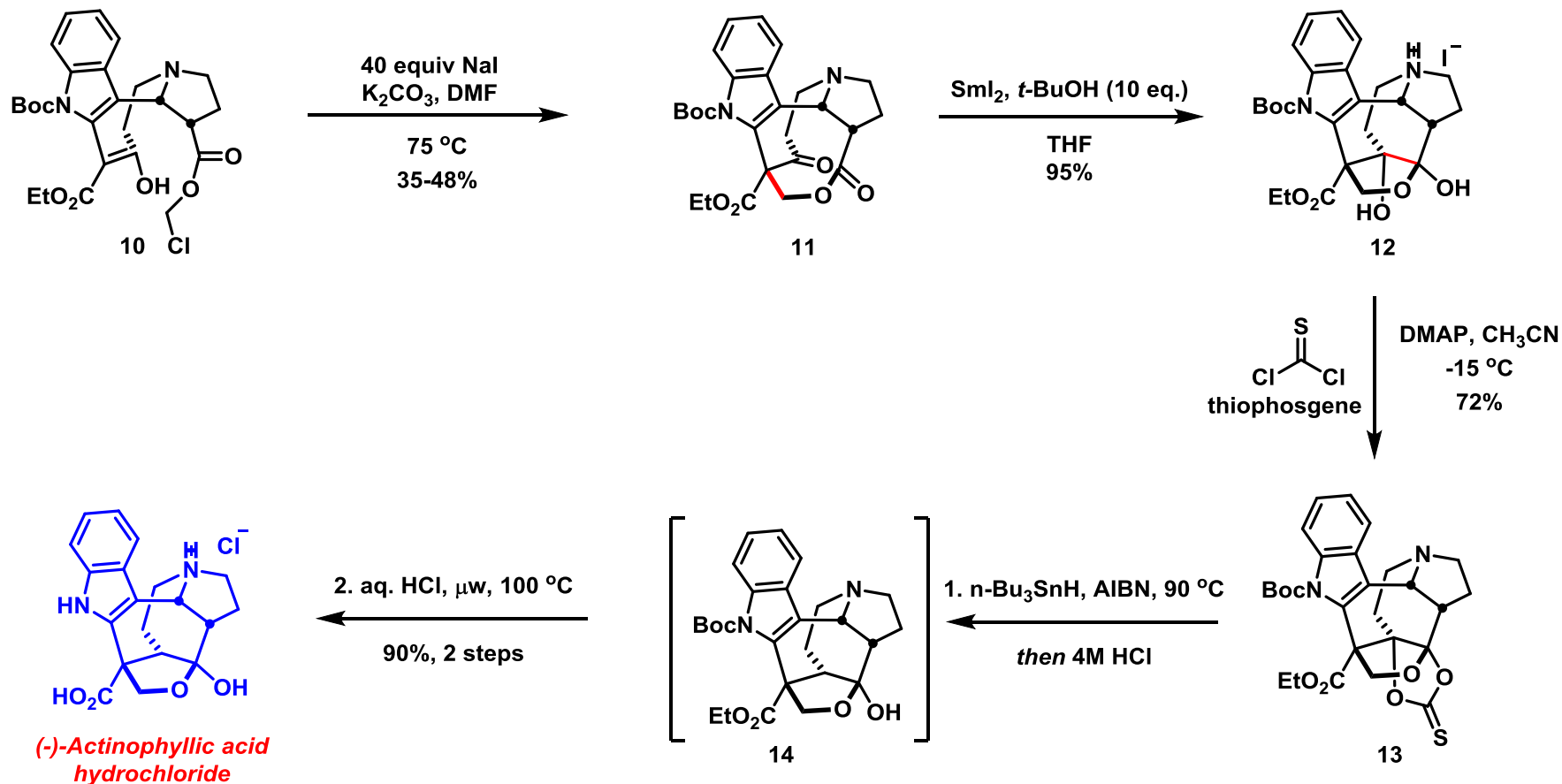
Attempted Oxidative Coupling



kwon's total synthesis



kwon's total synthesis

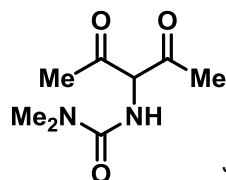


13 steps. **12.4%** yield

Chen's total synthesis



Desymmetrization-based strategy

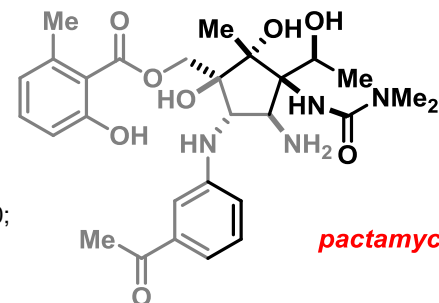


"desymmetrization"

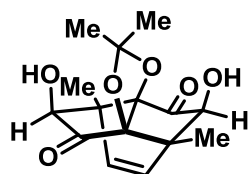


Johnson: 13 steps

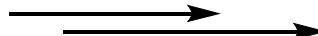
J. S. Johnson et al, *Science* **2013**, 340, 180;
J. Am. Chem. Soc. **2013**, 135, 17990.



pactamycin

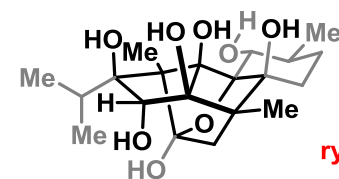


"desymmetrization"



Inoue: 22 steps

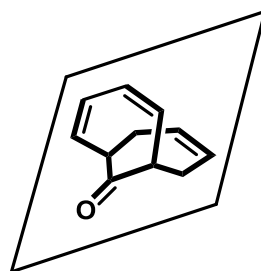
M. Inoue et al, *J. Am. Chem. Soc.* **2014**, 136, 5916.



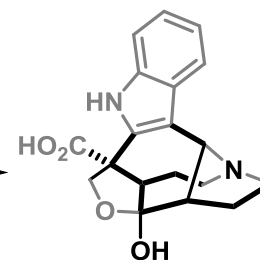
ryanodol



≡



"desymmetrization"

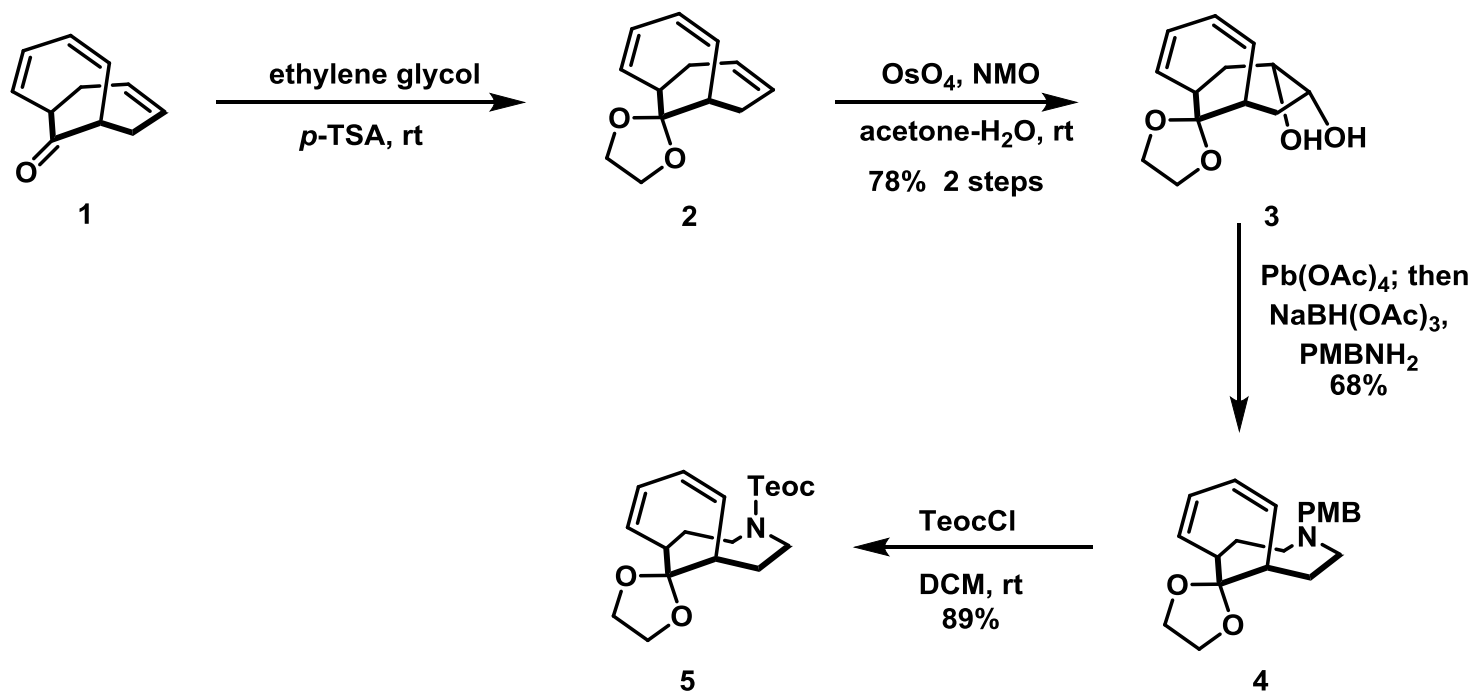


actinophyllic acid

olefin differentiation
plane of symmetry

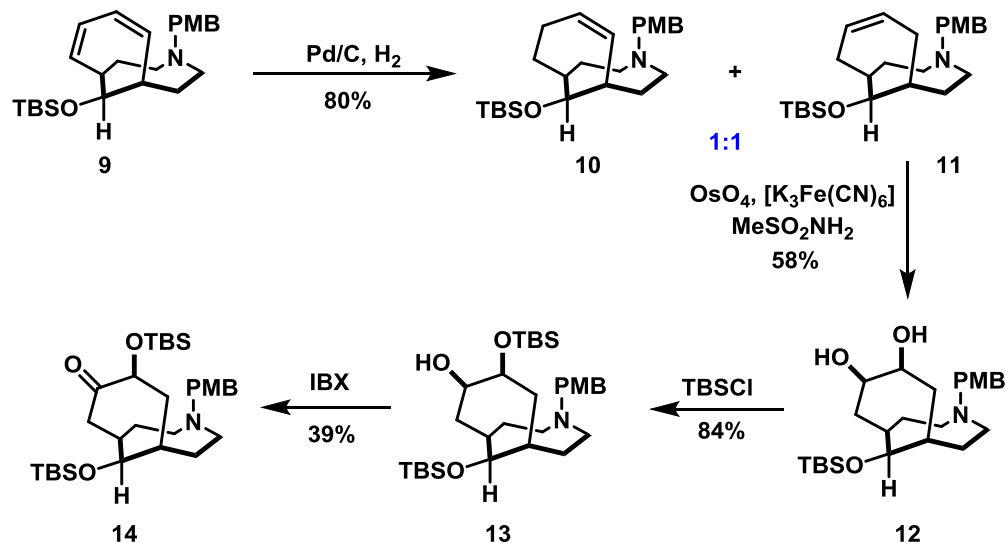
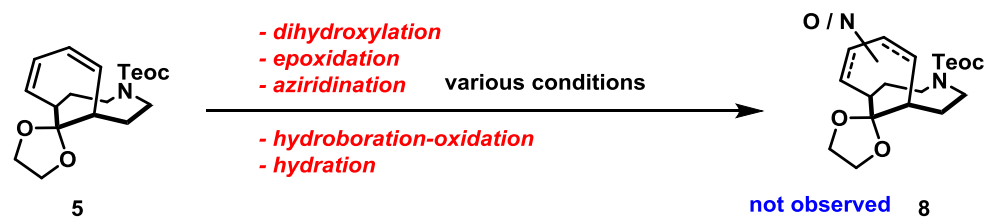
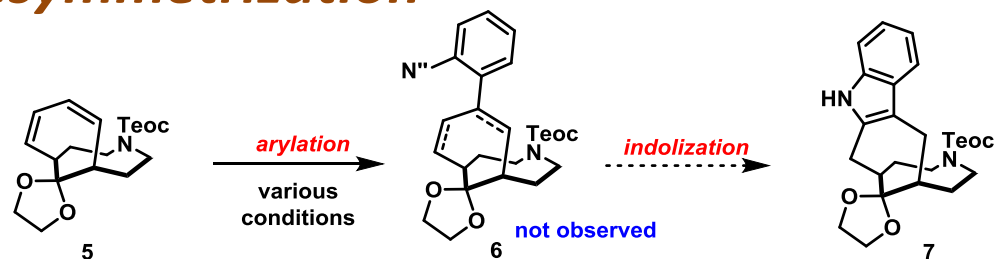
Chen's total synthesis

Preparation of precursor for Desymmetrization



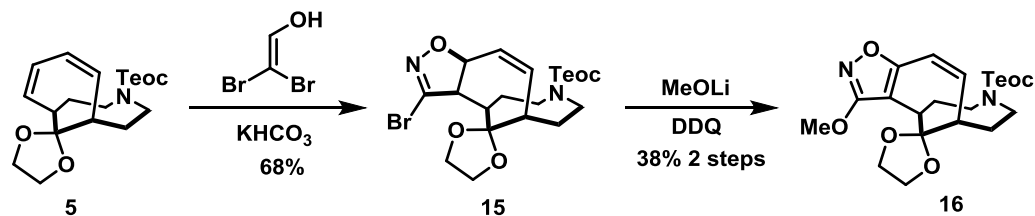
Chen's total synthesis

Exploration of desymmetrization

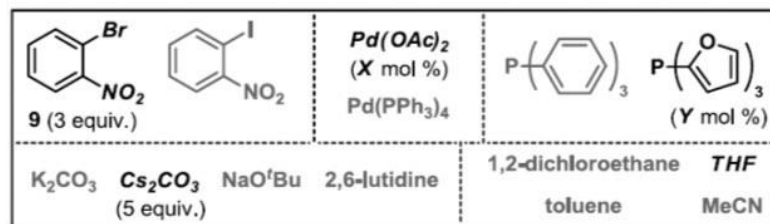
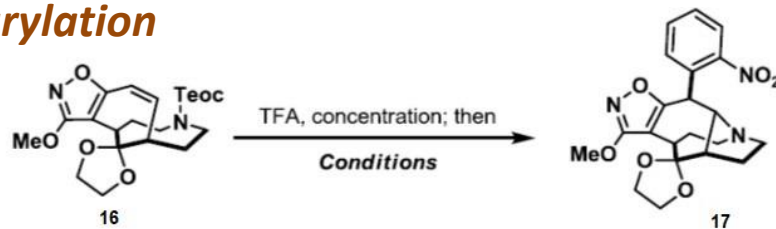


Chen's total synthesis

[3+2] cycloaddition desymmetrization



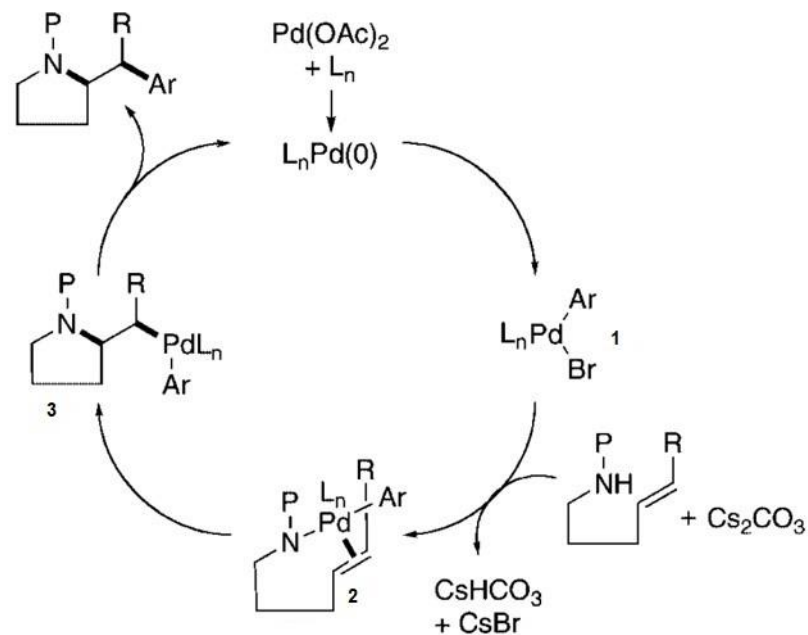
Optimization of the aminoarylation



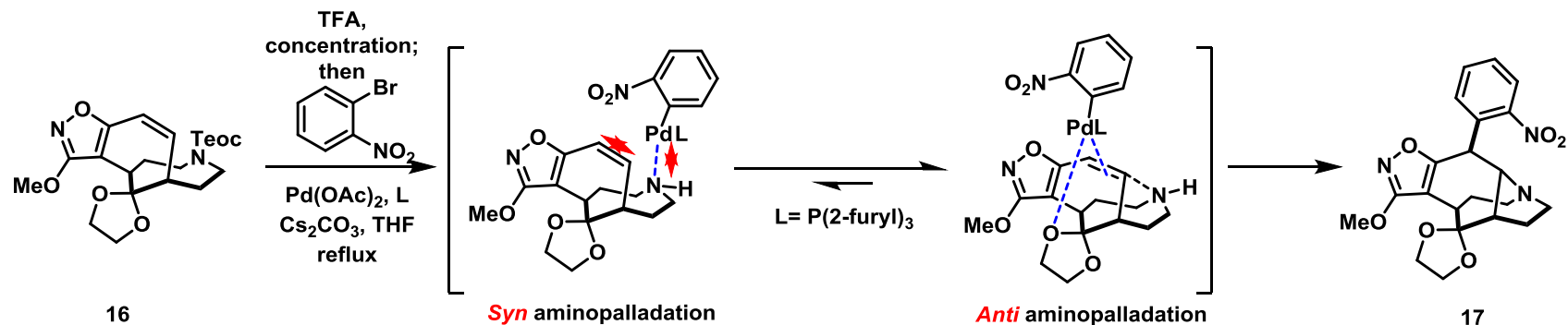
^a Entry	X	Y	17 (% yield)
1	10	20	Trace
2	20	40	11%
3	30	60	35%
4	40	80	41%
5	50	100	42%
6	60	120	42%
7	70	140	52%
8	80	160	65%
9	100	200	45%

Chen's total synthesis

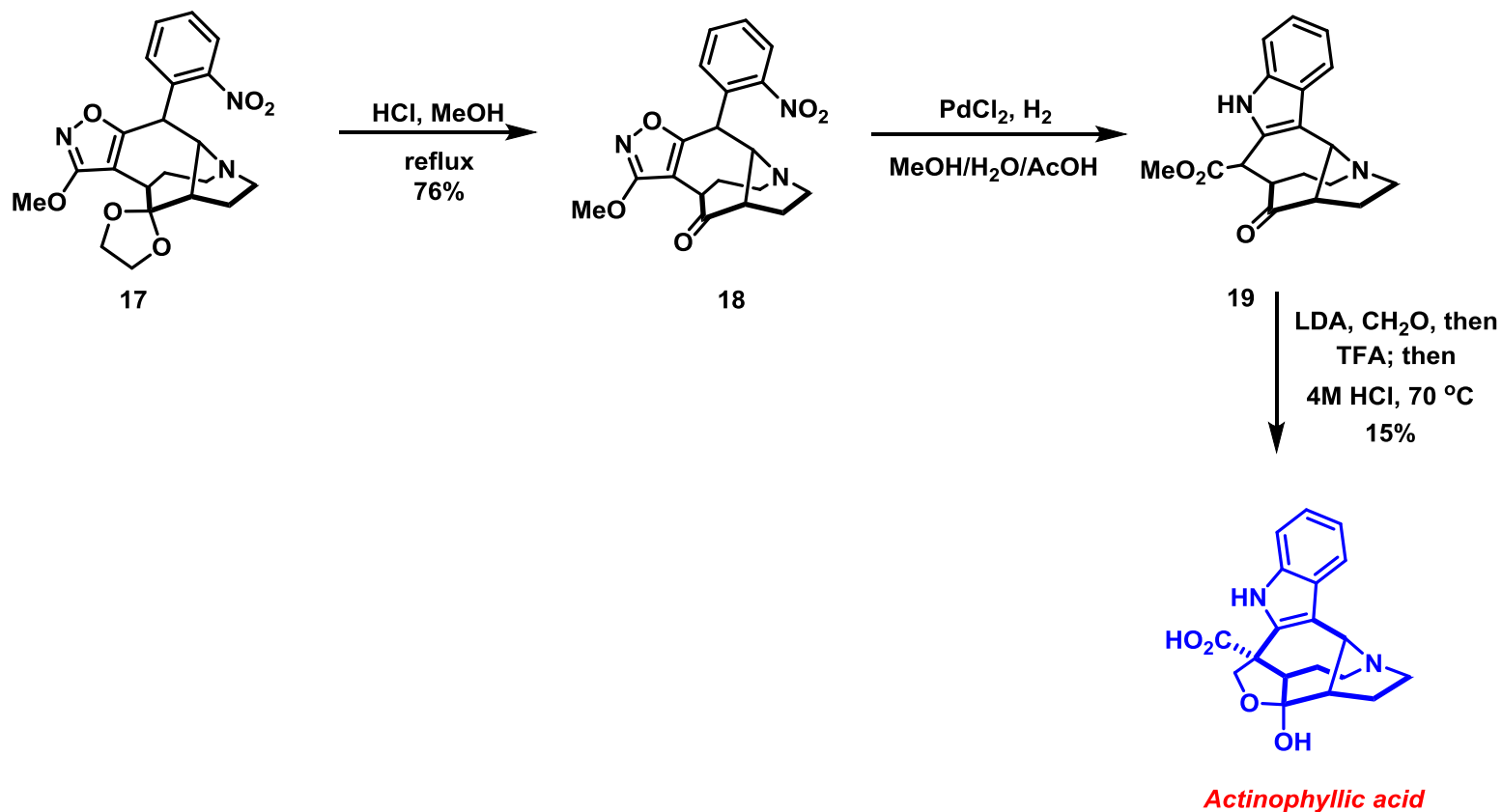
Simplified catalytic cycle



J. P. Wolfe, *J. Org. Chem.* **2008**, *73*, 8851



Chen's total synthesis



11 steps. 0.8% yield

Summary

Overman's

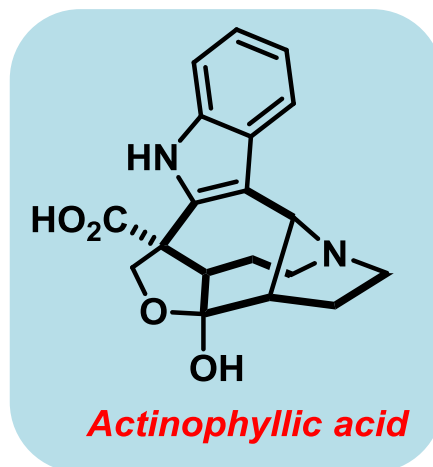
Racemic: **7** steps. **22%** yield

Asymmetric: **11** steps. **18%** yield

Key steps:

Oxidative coupling

Aza-cope/mannich reaction



Kwon's

13 steps. **12.4%** yield

Key steps:

Phosphine-catalyzed [3+2] annulation.

Pinacol coupling and regioselective removal of tertiary alcohol.

Martin's

10 steps. **10%** yield

Key steps:

carbocation/ π -nucleophiles
cascade reaction

Chen's

11 steps. **0.8%** yield

Key steps:

[3+2] desymmetrization
Aminoarylation

Thanks for your attention !