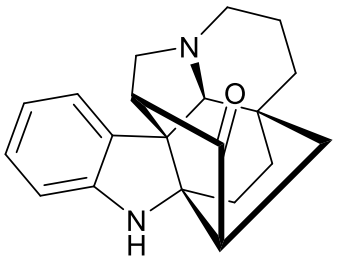
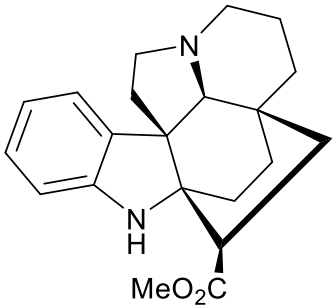
Total Synthesis of *Kopsia* alkaloids



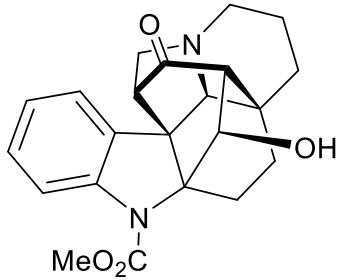
Kopsanone

Magnus
MacMillan



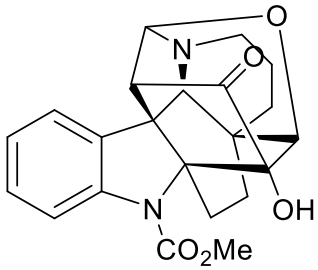
Kopsinine

MacMillan



Fruticosine

Qin



Kopsinitarine E

Ma

Cedric Fung

11-11-2021

*Laboratory of Synthesis and Natural Products (**LSPN**)*

*Ecole Polytechnique Fédérale de Lausanne (**EPFL**)*

Outline

- 1. Introduction
- 2. Total synthesis of *Kopsia* alkaloids
  - Total synthesis of kopsanone, 1983, Magnus
  - Total synthesis of (-)-kopsanone and (-)-kopsinine, 2011, MacMillan
  - Total synthesis of (-)-fruticosine, 2017, Qin
  - Total synthesis of kopsinitarine E, 2020, Ma
- 3. Summary

Outline

- **1. Introduction**
- **2. Total synthesis of *Kopsia* alkaloids**
  - **Total synthesis of kopsanone, 1983, Magnus**
  - **Total synthesis of (-)-kopsanone and (-)-kopsinine, 2011, MacMillan**
  - **Total synthesis of (-)-fruticosine, 2017, Qin**
  - **Total synthesis of kopsinitarine E, 2020, Ma**
- **3. Summary**

Introduction of *Kopsia* alkaloids

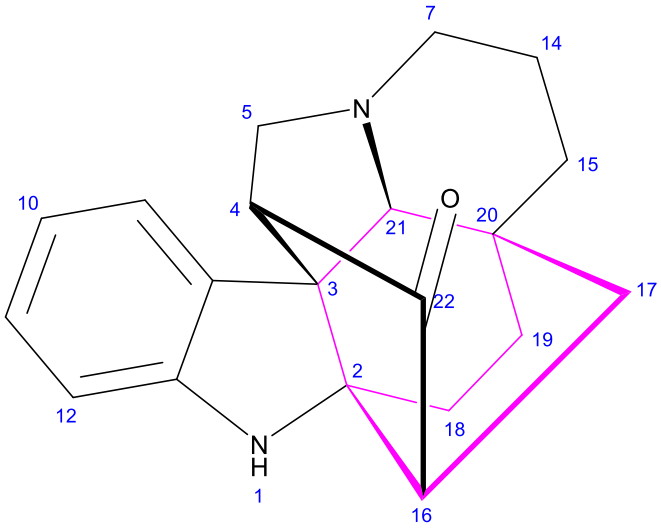
Images from www.excelsagardens.com and Wikimedia.

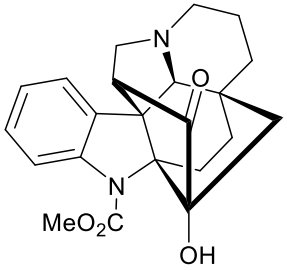
- Shrub or small tree
- Southeast Asia, India, Southern China
- Wide range of biological effects: anti-protozoal, cholinergic, antirheumatism, anti-inflammation among others.
- Intriguing molecular structure

T.-S. Kam, K.-H. Lim in *The Alkaloids: Chemistry and Biology, Vol.66*, Elsevier, **2008**, pp.1-111.
K.-H.Lim, O. Hiraku, K. Komiyama, T. Koyano, M. Hayashi, T.-S. Kam, *J.Nat.Prod.* **2007**, *70*, 1302.

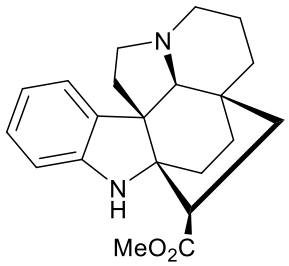
Structure of *Kopsia* alkaloids

Some examples of Kopsia alkaloids

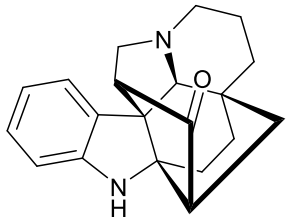




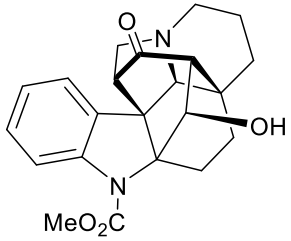
Kopsine



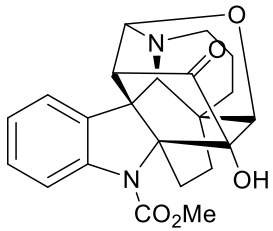
Kopsinine



Kopsanone



Fruticosine



Kopsinitarine E

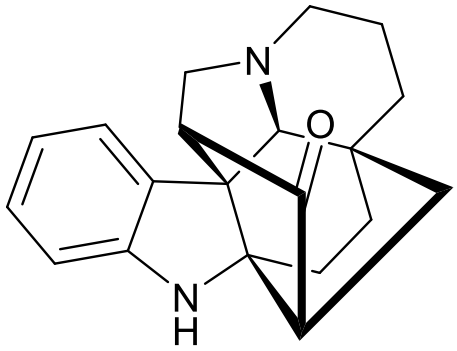
- Hexacyclic to octacyclic framework
- Bicyclo[2,2,2]octane (in purple)
- Multiple contiguous stereogenic centers
- 2 all-carbon quaternary centers at C3 and C20

Outline

- 1. Introduction
- **2. Total synthesis of *Kopsia* alkaloids**
  - **Total synthesis of kopsanone, 1983, Magnus**
  - Total synthesis of (-)-kopsanone and (-)-kopsinine, 2011, MacMillan
  - Total synthesis of (-)-fruticosine, 2017, Qin
  - Total synthesis of kopsinitarine E, 2020, Ma
- 3. Summary

Total synthesis of *Kopsanone*

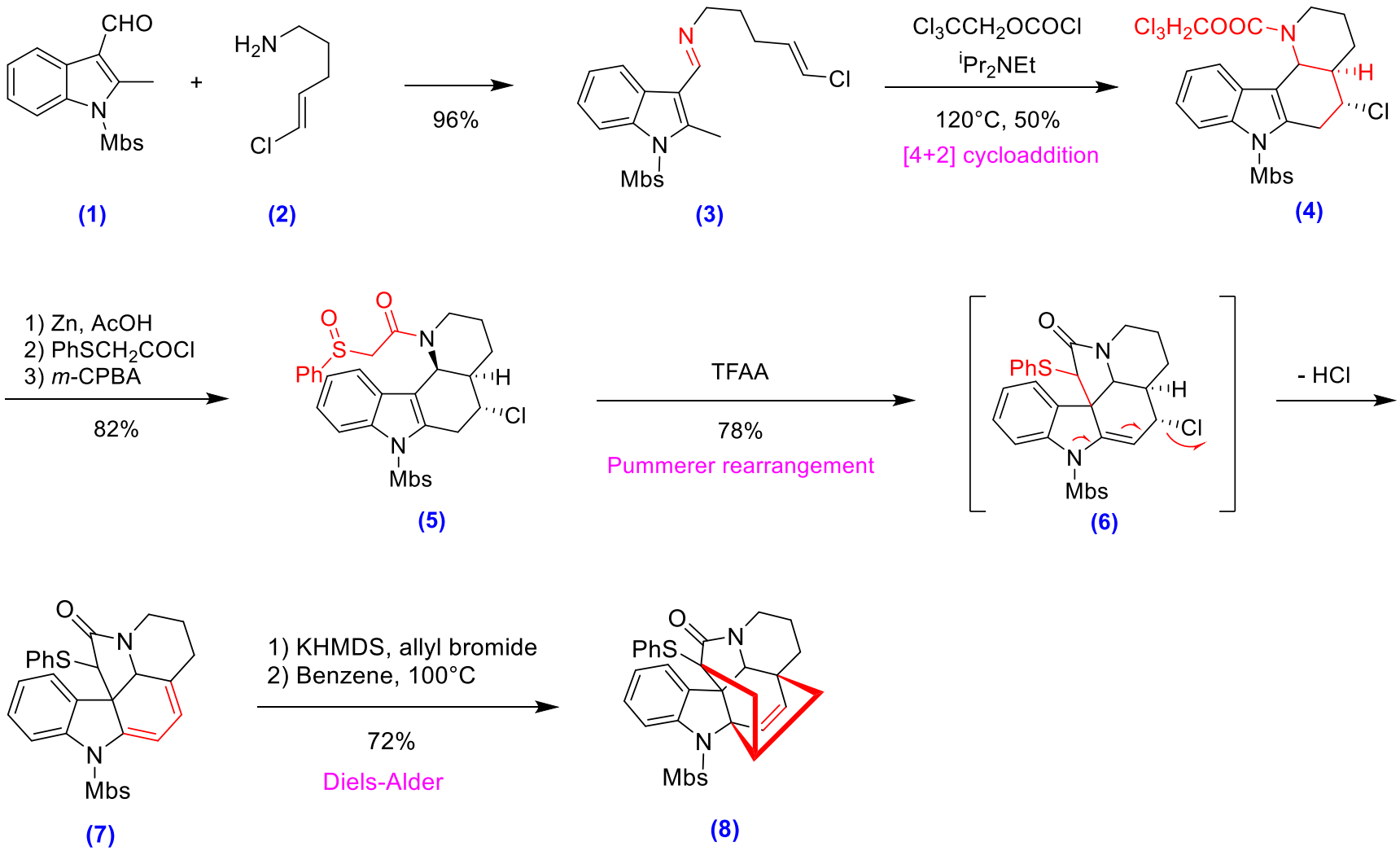
***Brief summary of the total synthesis of* Kopsanone**



- Magnus, 1983, 14 steps
- Kuehne, 1985, 8 steps
- MacMillan, 2011, asymmetric, 11 steps
- Qin, 2017, asymmetric, 21 steps
- Ye, 2020, asymmetric, 19 steps

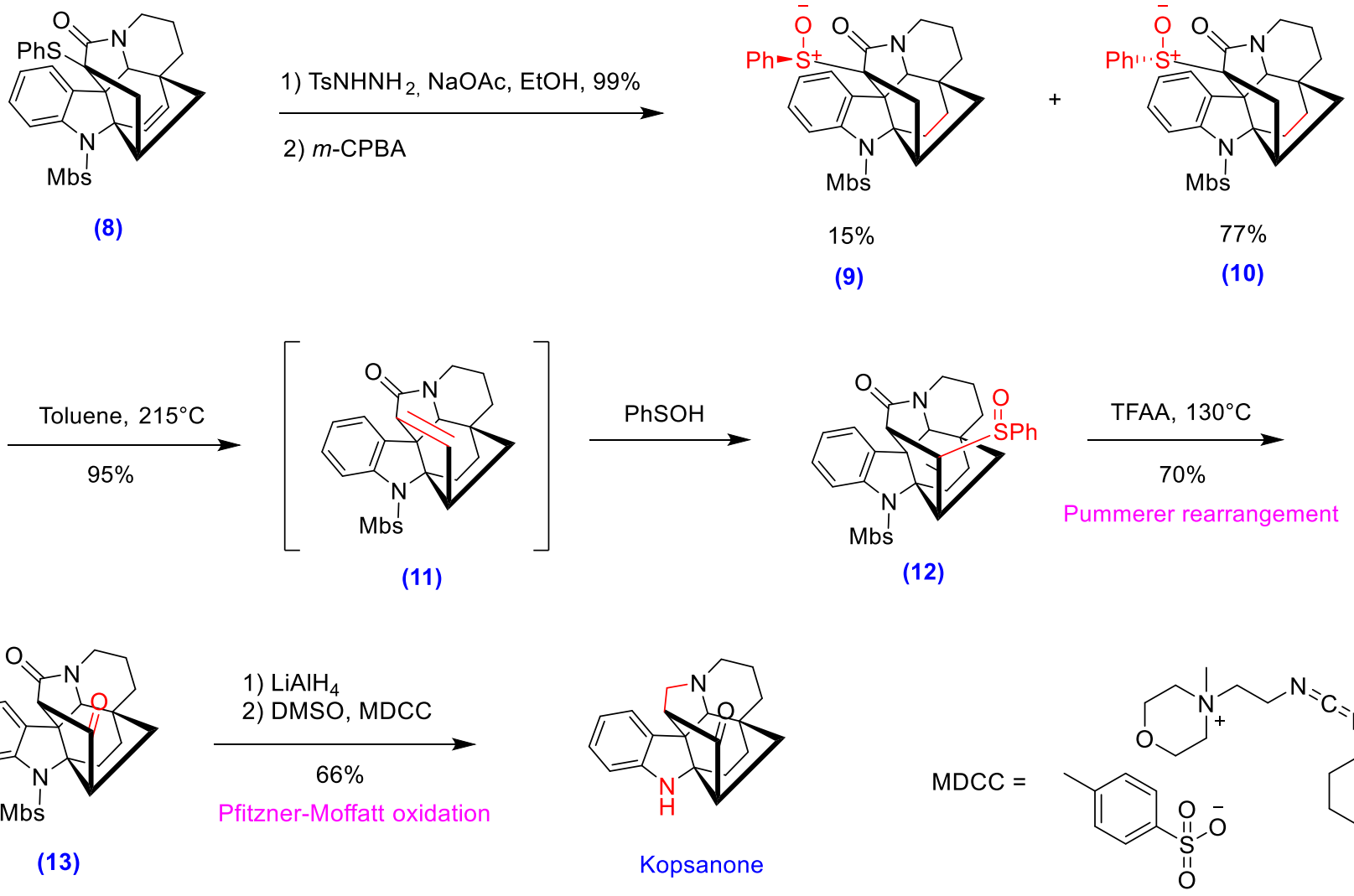
T. Gallagher, P. Magnus, *JACS*, **1983**, *105*, 2086.
P.J. Seaton, M.E. Kuehne, *JOC*, **1985**, *50*, 4790.
S.B. Jones, B. Simmons, A. Mastracchio, D.W.C. MacMillan, *Nature*, **2011**, *475*, 183.
L. Leng, X. Zhou, Q. Liao, F. Wang, H. Song, D. Zhang, X.-Y. Liu, Y. Qin, *ACIE*, **2017**, *56*, 3703.
X. Jia, H. Lei, F. Han, T. Zhang, Y. Chen, Z. Xu, P. Nakliang, S. Choi, Y. Guo, T. Ye, *ACIE*, **2020**, *59*, 12832.

Total synthesis of *Kopsanone* (1)



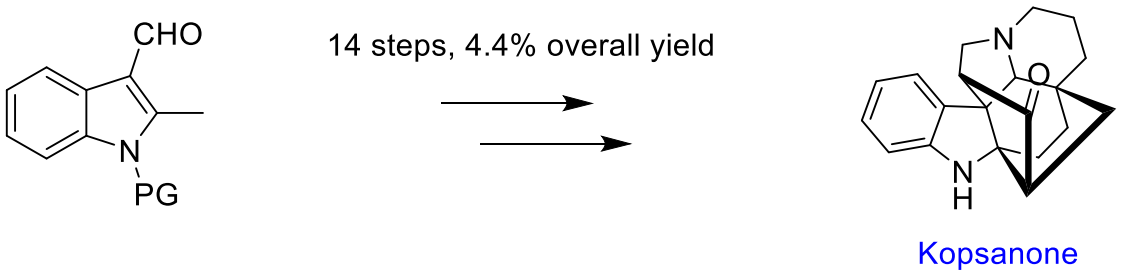
T. Gallagher, P. Magnus, *JACS*, **1983**, *105*, 2086.

Total synthesis of *Kopsanone* (1)



T. Gallagher, P. Magnus, *JACS*, **1983**, *105*, 2086.

Total synthesis of *Kopsanone* (1)



Kopsanone

Key steps:

- Pummerer rearrangement to furnish the pentacyclic core
- Diels-Alder reaction to obtain the bicyclooctane

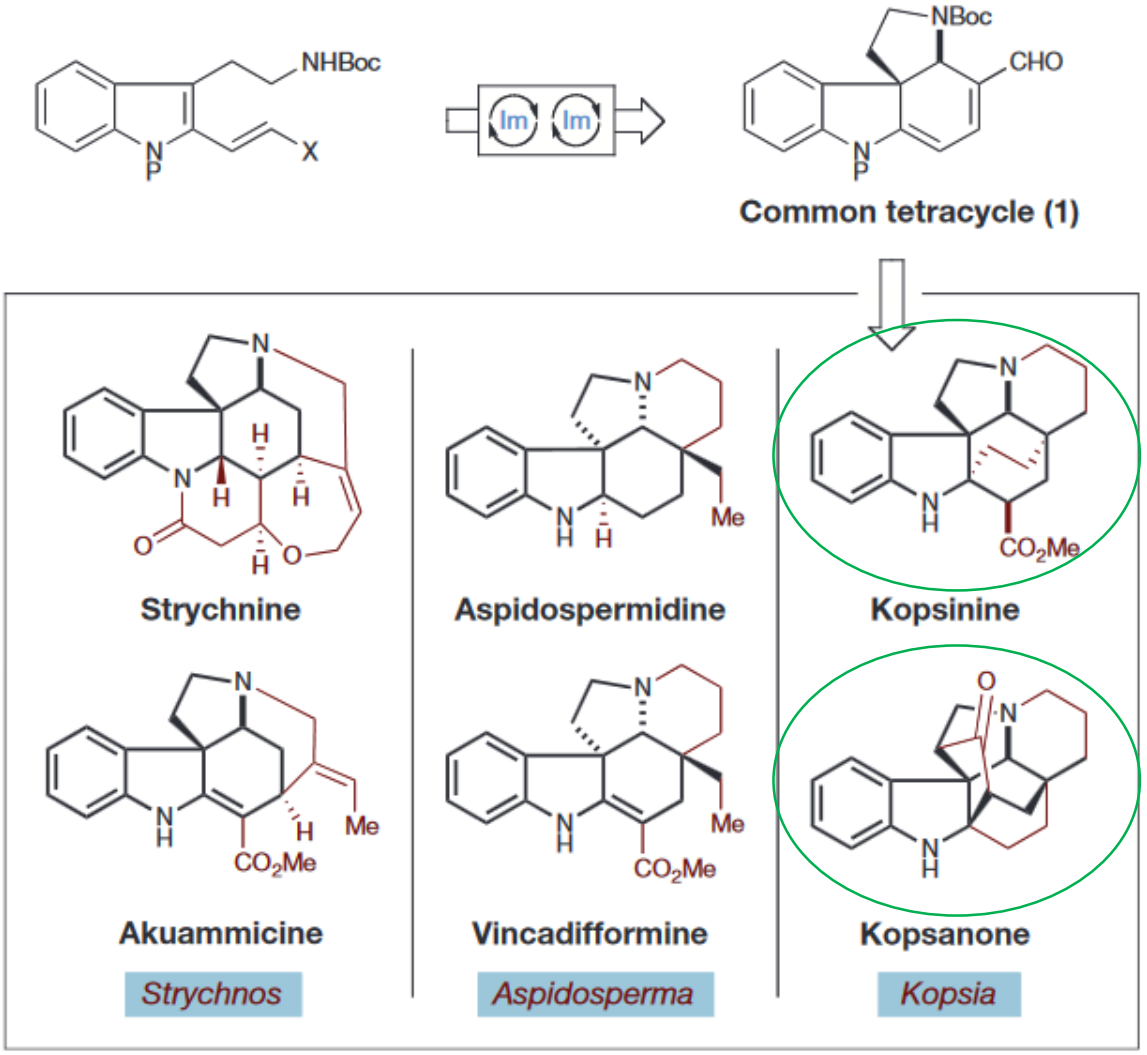
T. Gallagher, P. Magnus, *JACS*, **1983**, *105*, 2086.

Outline

- 1. Introduction
- **2. Total synthesis of *Kopsia* alkaloids**
  - Total synthesis of kopsanone, 1983, Magnus
  - **Total synthesis of (-)-kopsanone and (-)-kopsinine, 2011, MacMillan**
  - Total synthesis of (-)-fruticosine, 2017, Qin
  - Total synthesis of kopsinitarine E, 2020, Ma
- 3. Summary

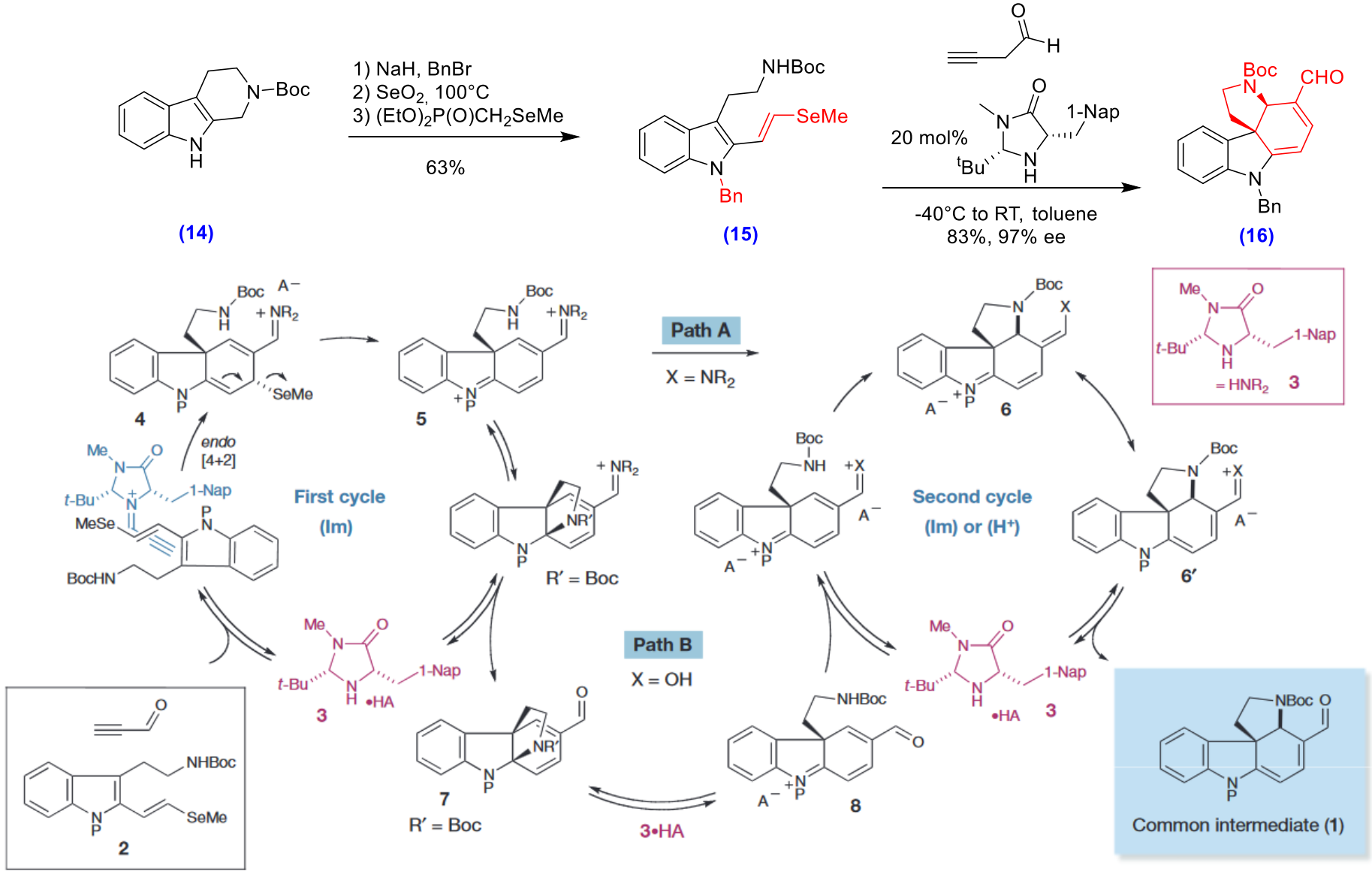
Retrosynthesis of (-)-*Kopsinine* & (-)-*Kopsanone* (2)

Mimic of biosynthesis



S.B. Jones, B. Simmons, A. Mastracchio, D.W.C. MacMillan, *Nature*, **2011**, *475*, 183.

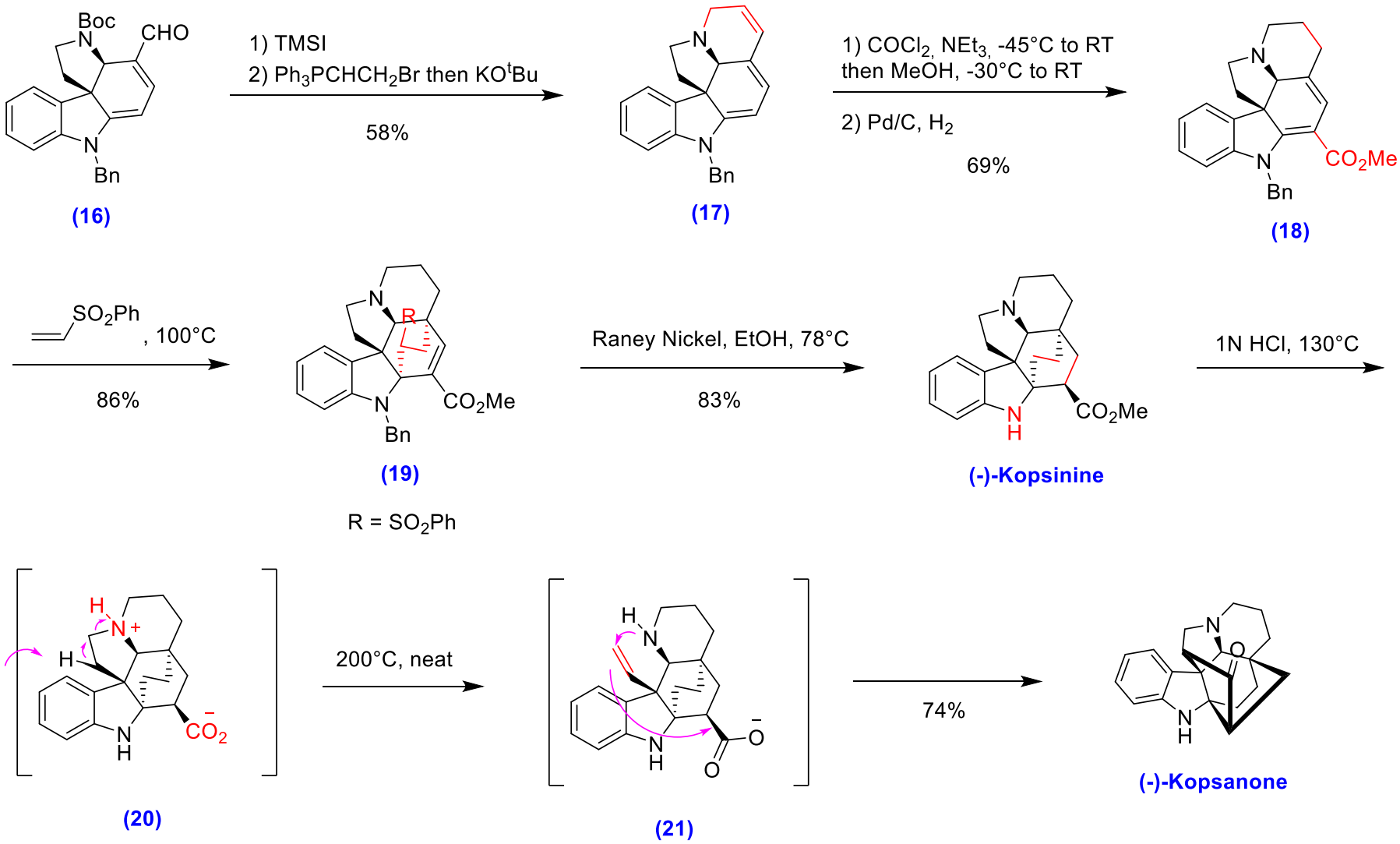
Total synthesis of (-)-*Kopsinine* & (-)-*Kopsanone* (2)



S.B. Jones, B. Simmons, A. Mastracchio, D.W.C. MacMillan, *Nature*, **2011**, *475*, 183.

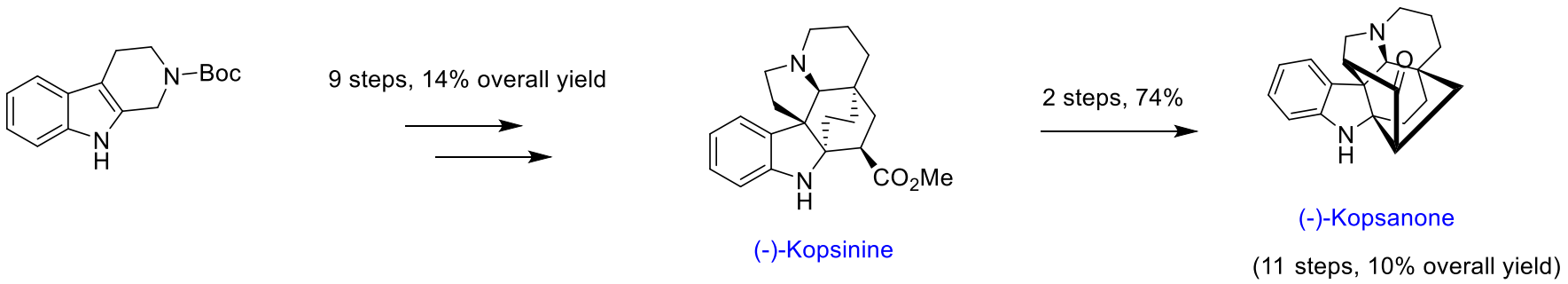
F. Gatta, D. Misiti, *J. Heterocycl. Chem.* **1987**, *24*, 1183

Total synthesis of (-)-*Kopsinine* & (-)-*Kopsanone* (2)



S.B. Jones, B. Simmons, A. Mastracchio, D.W.C. MacMillan, *Nature*, **2011**, *475*, 183.
C. Kump, J.J. Dugan, H. Schmid, *Helv.Chim.Acta.* **1966**, *49*, 1237.

Total synthesis of (-)-*Kopsinine* & (-)-*Kopsanone* (2)



Key steps:

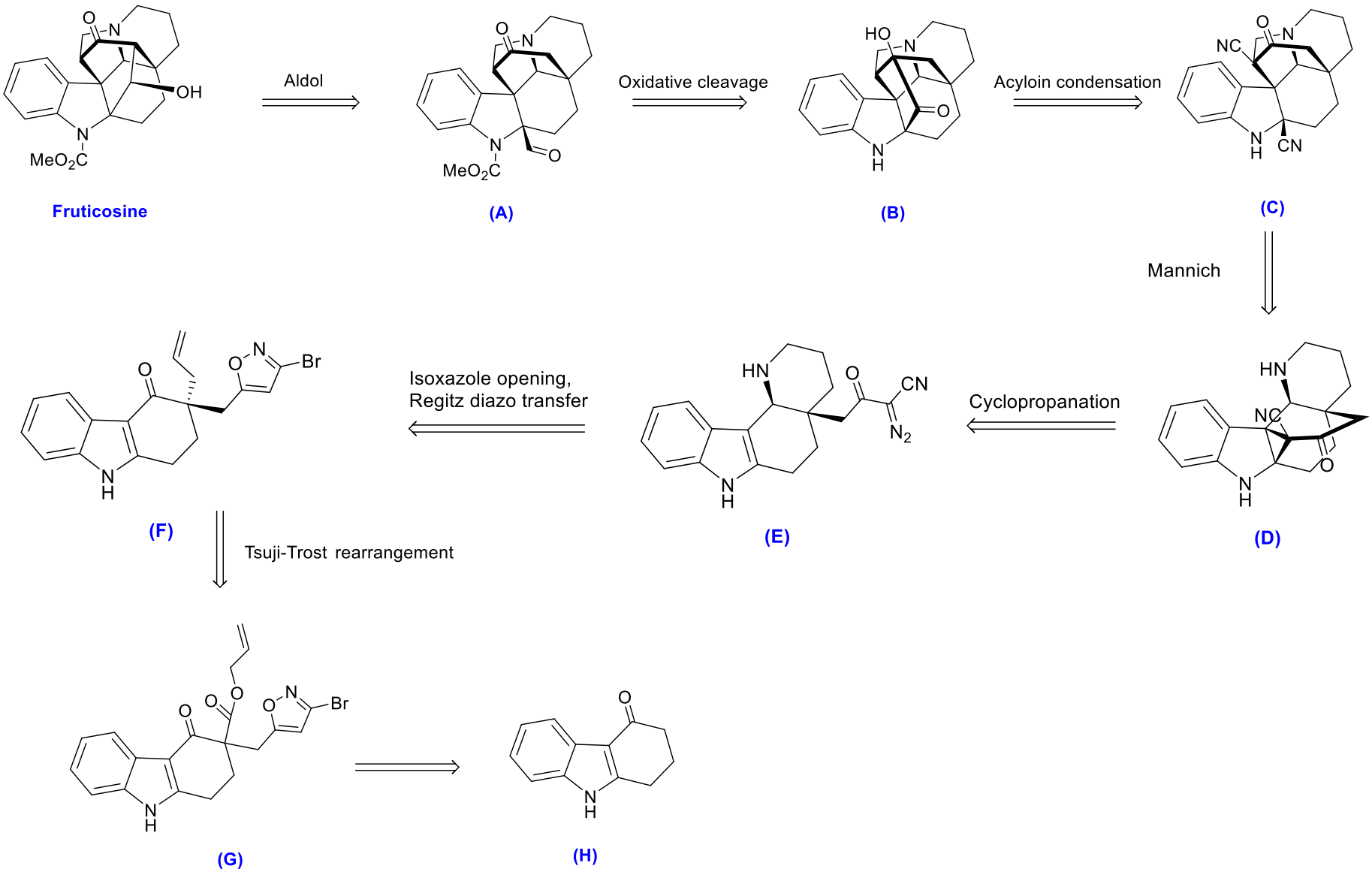
- Biomimetic cascade reaction to an advanced intermediate
- Diels-Alder reaction to obtain the bicyclooctane
- Acid-mediated thermodynamic rearrangement from Kopsinine to Kopsanone

S.B. Jones, B. Simmons, A. Mastracchio, D.W.C. MacMillan, *Nature*, **2011**, *475*, 183.

Outline

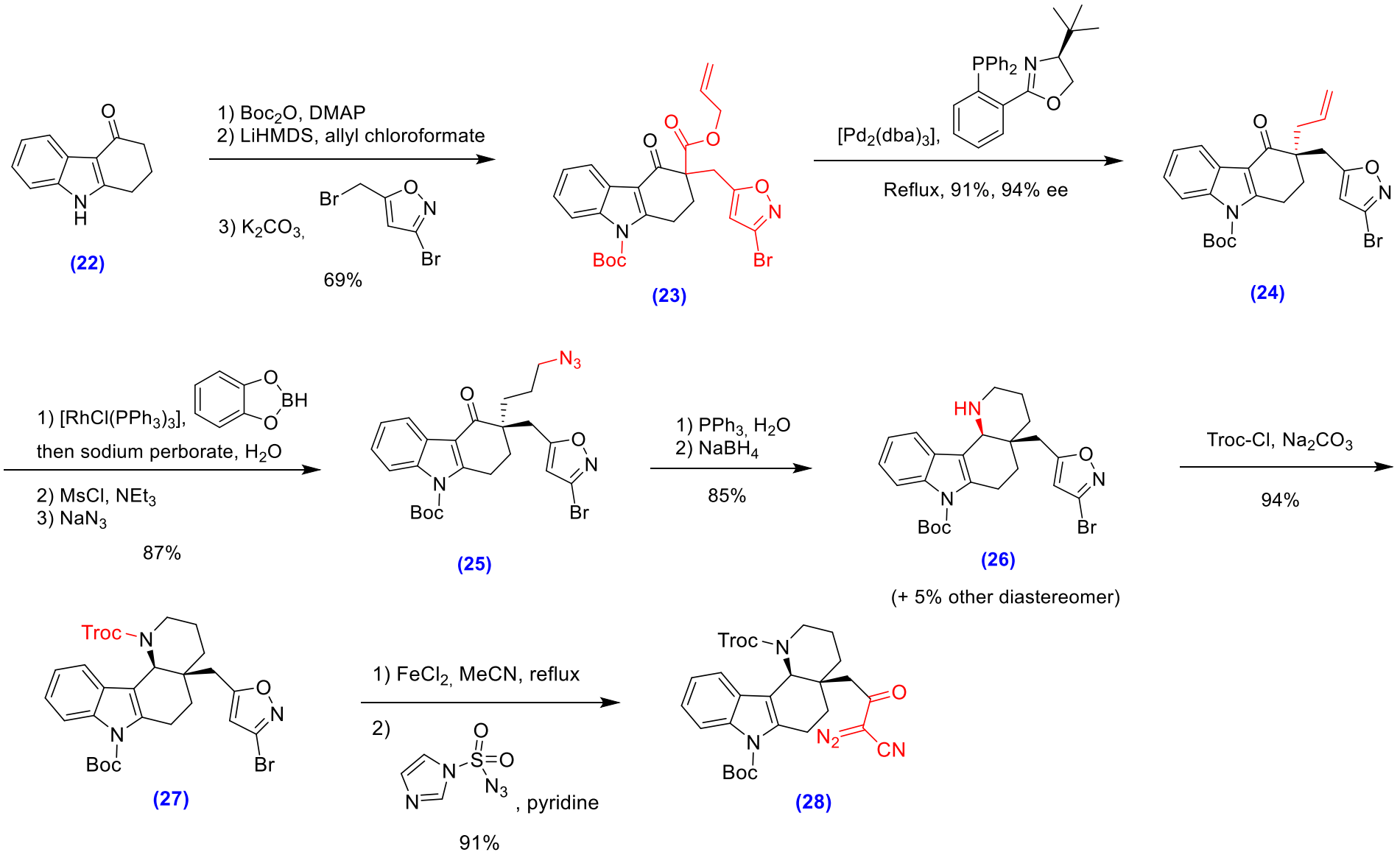
- 1. Introduction
- **2. Total synthesis of *Kopsia* alkaloids**
  - Total synthesis of kopsanone, 1983, Magnus
  - Total synthesis of (-)-kopsanone and (-)-kopsinine, 2011, MacMillan
  - **Total synthesis of (-)-fruticosine, 2017, Qin**
  - Total synthesis of kopsinitarine E, 2020, Ma
- 3. Summary

Retrosynthesis of (-)-*Fruticosine*



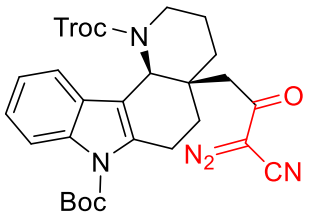
L. Leng, X. Zhou, Q. Liao, F. Wang, H. Song, D. Zhang, X.-Y. Liu, Y. Qin, *ACIE*, **2017**, *56,* 3703.

Total synthesis of (-)-*Fruticosine*



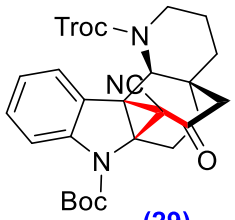
L. Leng, X. Zhou, Q. Liao, F. Wang, H. Song, D. Zhang, X.-Y. Liu, Y. Qin, *ACIE*, **2017**, *56,* 3703.
J.T. Mohr, D.C. Behenna, A.M. Harned, B.M. Stoltz, ACIE, **2005**, *44*, 6924.

Total synthesis of (-)-*Fruticosine*



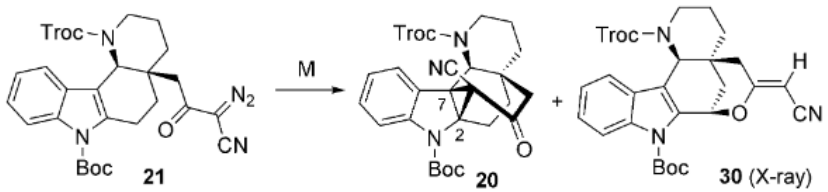
(28)

Conditions



(29)

Table 1: Optimization of cyclopropanation reactions.[a]

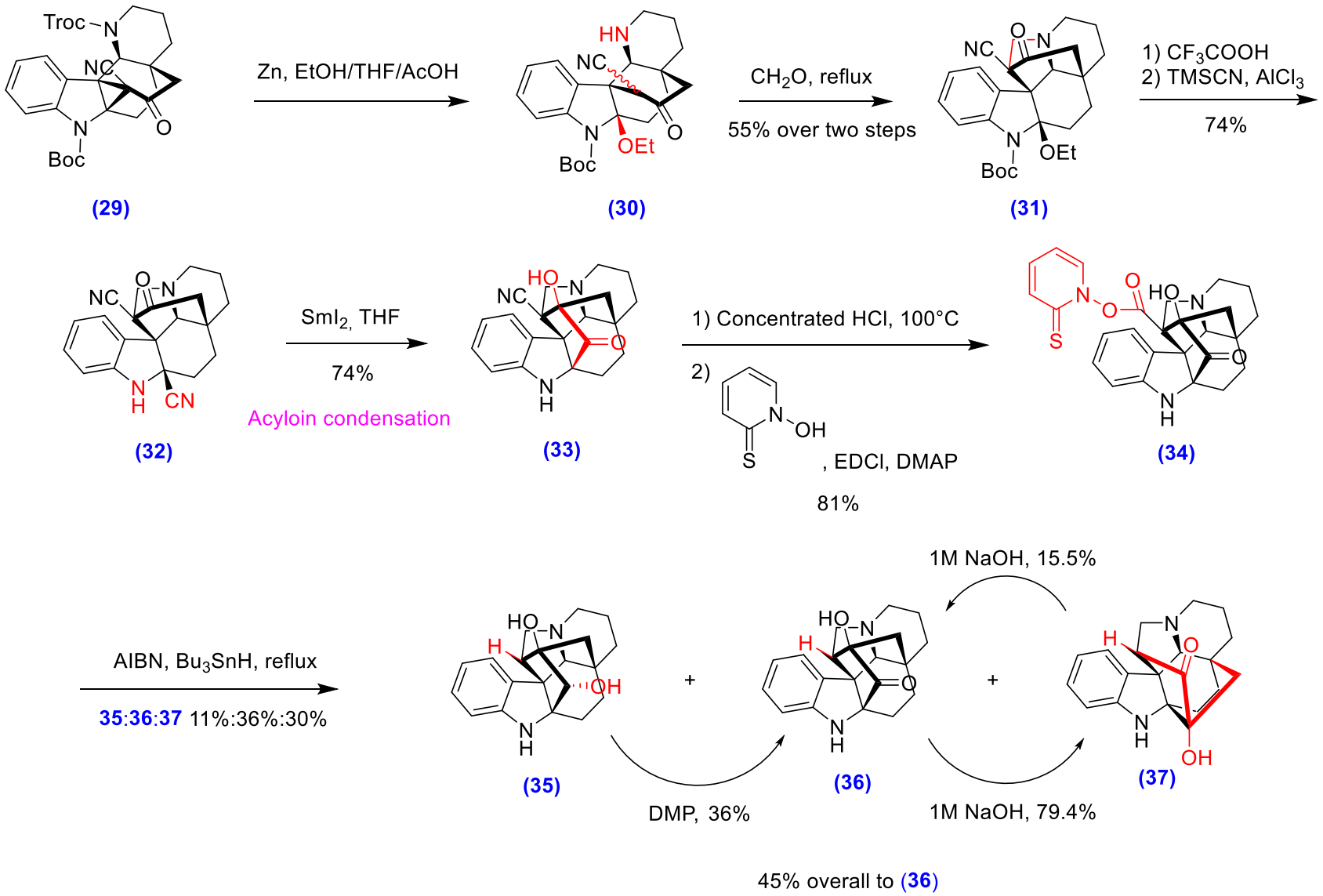


Entry	Catalyst	Solvent	T [°C]/t	Yield [%]	
				20	**30**
1	$[Rh(OAc)_2]$	DCM	25/3 h	trace	16
2	$Rh(C_3F_7CO_2)_2$	DCM	25/3 h	none	23
3	CuOTf	DCM	25/3 h	trace	22
4	$Cu(OTf)_2$	DCM	25/3 h	none	18
5	$Cu(TBS)_2$	DCE	80/2 h	none	15
6	$[Cu(acac)_2]$	DCE	80/2 h	10	15
7	$[Cu(tfacac)_2]$	DCE	80/2 h	17	12
8	$[Cu(hfacac)_2]$	DCE	80/2 h	22	13
9[b]	$[Cu(hfacac)_2]$	DCE	120/5 min	38	12
10	$[Cu(hfacac)_2]$	benzene	80/2 h	40	5
11	$[Cu(hfacac)_2]$	chlorobenzene	100/1 h	45	17
12	$[Cu(hfacac)_2]$	chlorobenzene	120/30 min	52	13
13	$[Cu(hfacac)_2]$	chlorobenzene	130/15 min	49	15
14	$[Cu(hfacac)_2]$	1,2-dichloro-benzene	150/10 min	34	13

[a] All reactions were performed with 20 mol% catalyst in 0.005 M concentration in freshly dried and argon-sparged solvent.[15] [b] Heating by microwave. acac = acetylacetonyl, hfacac = hexafluoroacetylacetone, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl, tfacac = trifluoroacetylacetone.

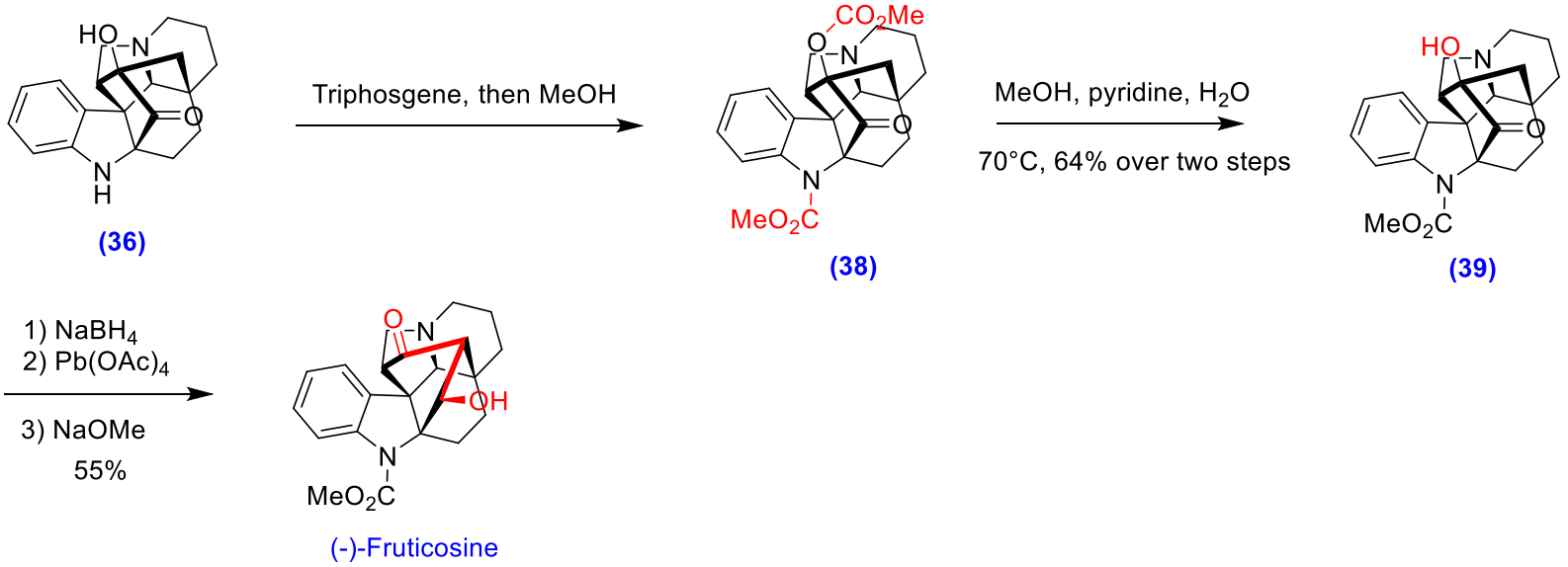
L. Leng, X. Zhou, Q. Liao, F. Wang, H. Song, D. Zhang, X.-Y. Liu, Y. Qin, *ACIE*, **2017**, *56,* 3703.

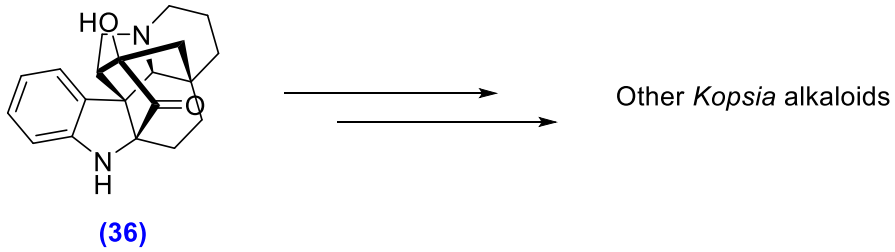
Total synthesis of (-)-*Fruticosine*



L. Leng, X. Zhou, Q. Liao, F. Wang, H. Song, D. Zhang, X.-Y. Liu, Y. Qin, *ACIE*, **2017**, *56,* 3703.

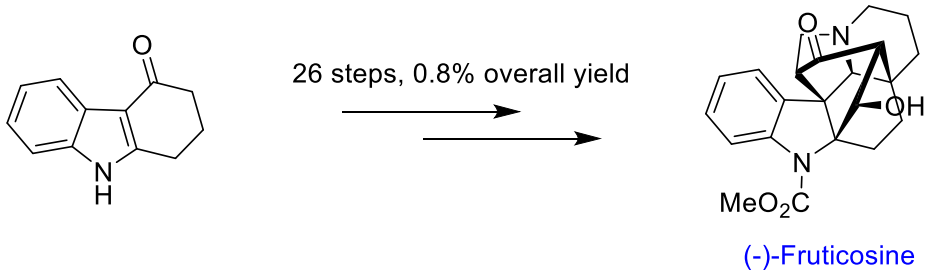
Total synthesis of (-)-*Fruticosine*





L. Leng, X. Zhou, Q. Liao, F. Wang, H. Song, D. Zhang, X.-Y. Liu, Y. Qin, *ACIE*, **2017**, *56,* 3703.

Total synthesis of (-)-*Fruticosine*



Key steps:

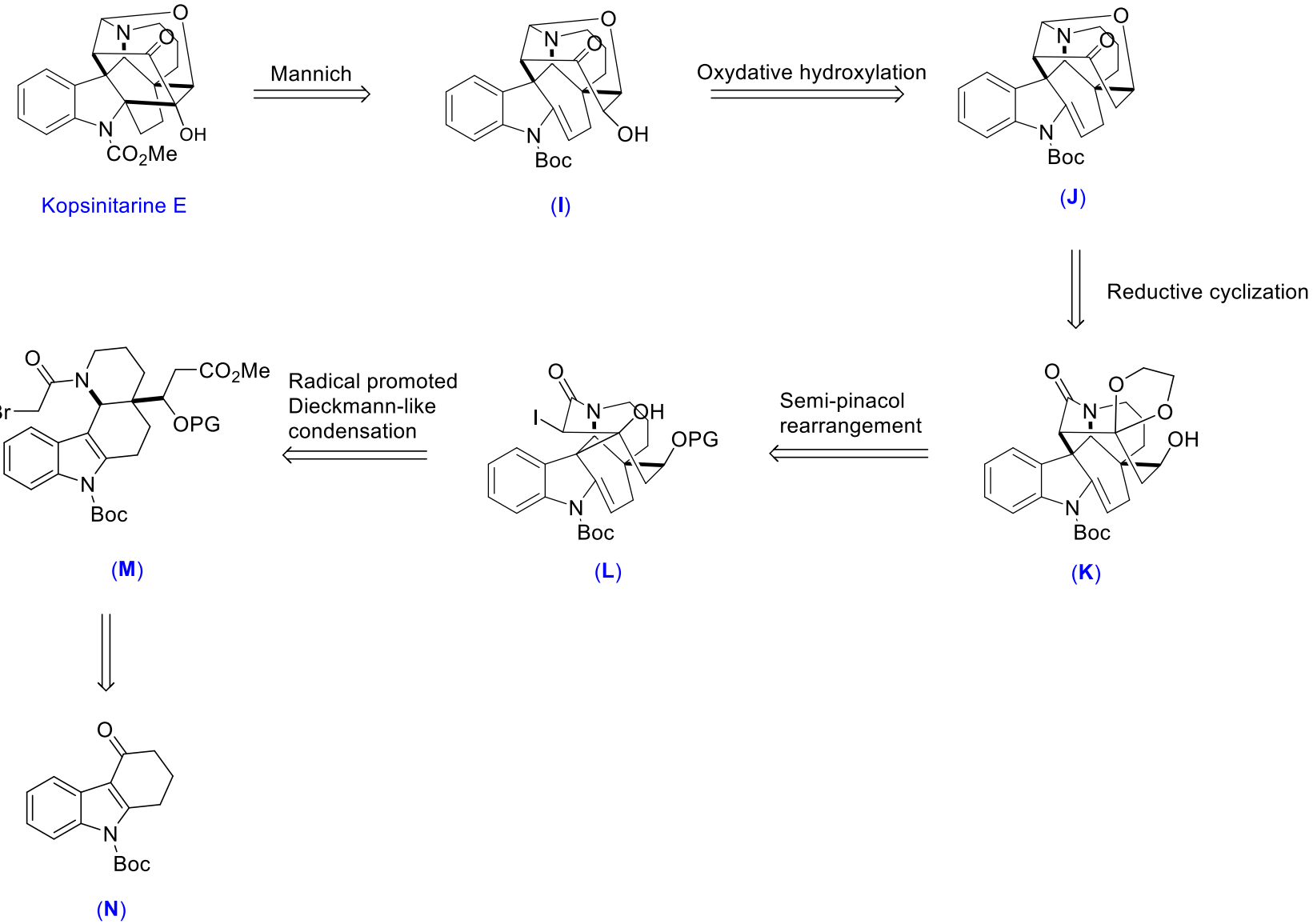
- Enantioselective Tsuji-Trost rearrangement to fix one all-carbon stereocenter
- Cyclopropanation to construct the upper ring
- SmI_2-mediated acyloin condensation to close the last ring

L. Leng, X. Zhou, Q. Liao, F. Wang, H. Song, D. Zhang, X.-Y. Liu, Y. Qin, *ACIE*, **2017**, *56,* 3703.

Outline

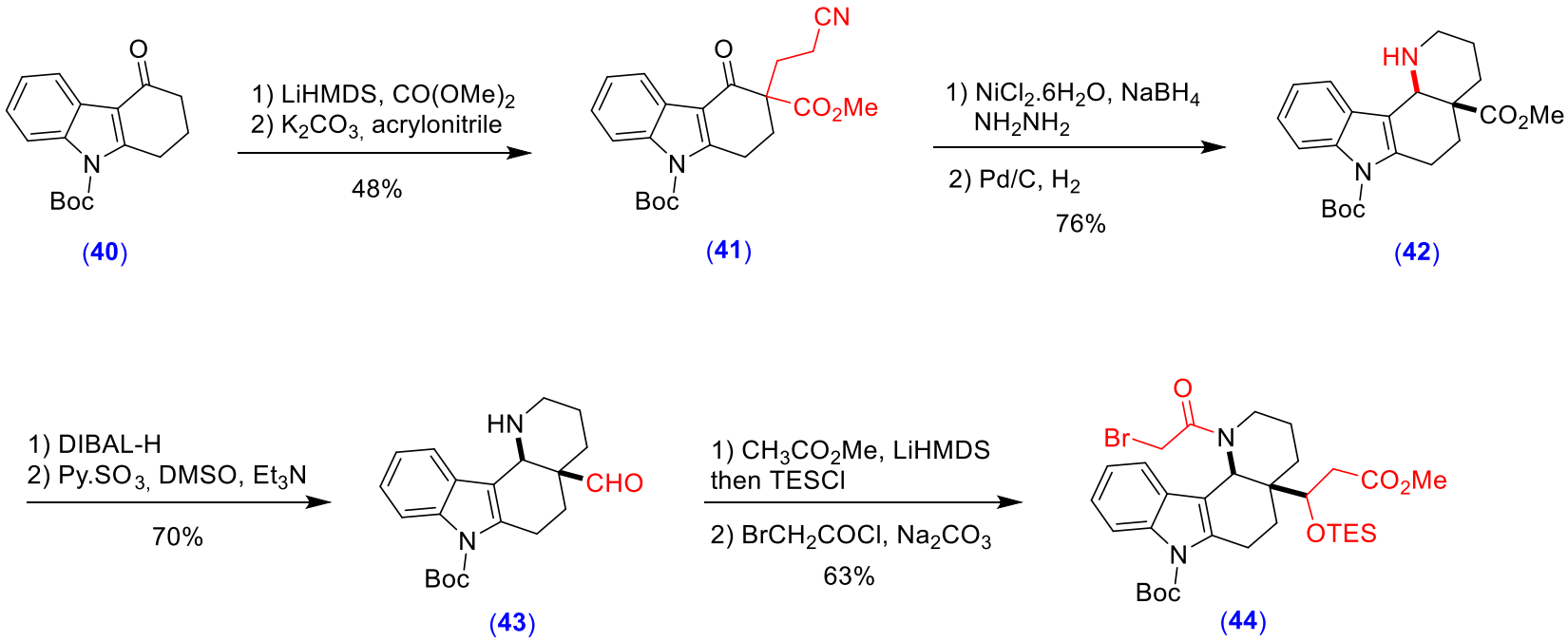
- 1. Introduction
- **2. Total synthesis of *Kopsia* alkaloids**
  - Total synthesis of kopsanone, 1983, Magnus
  - Total synthesis of (-)-kopsanone and (-)-kopsinine, 2011, MacMillan
  - Total synthesis of (-)-fruticosine, 2017, Qin
  - **Total synthesis of kopsinitarine E, 2020, Ma**
- 3. Summary

Retrosynthesis of *Kopsinitarine E*



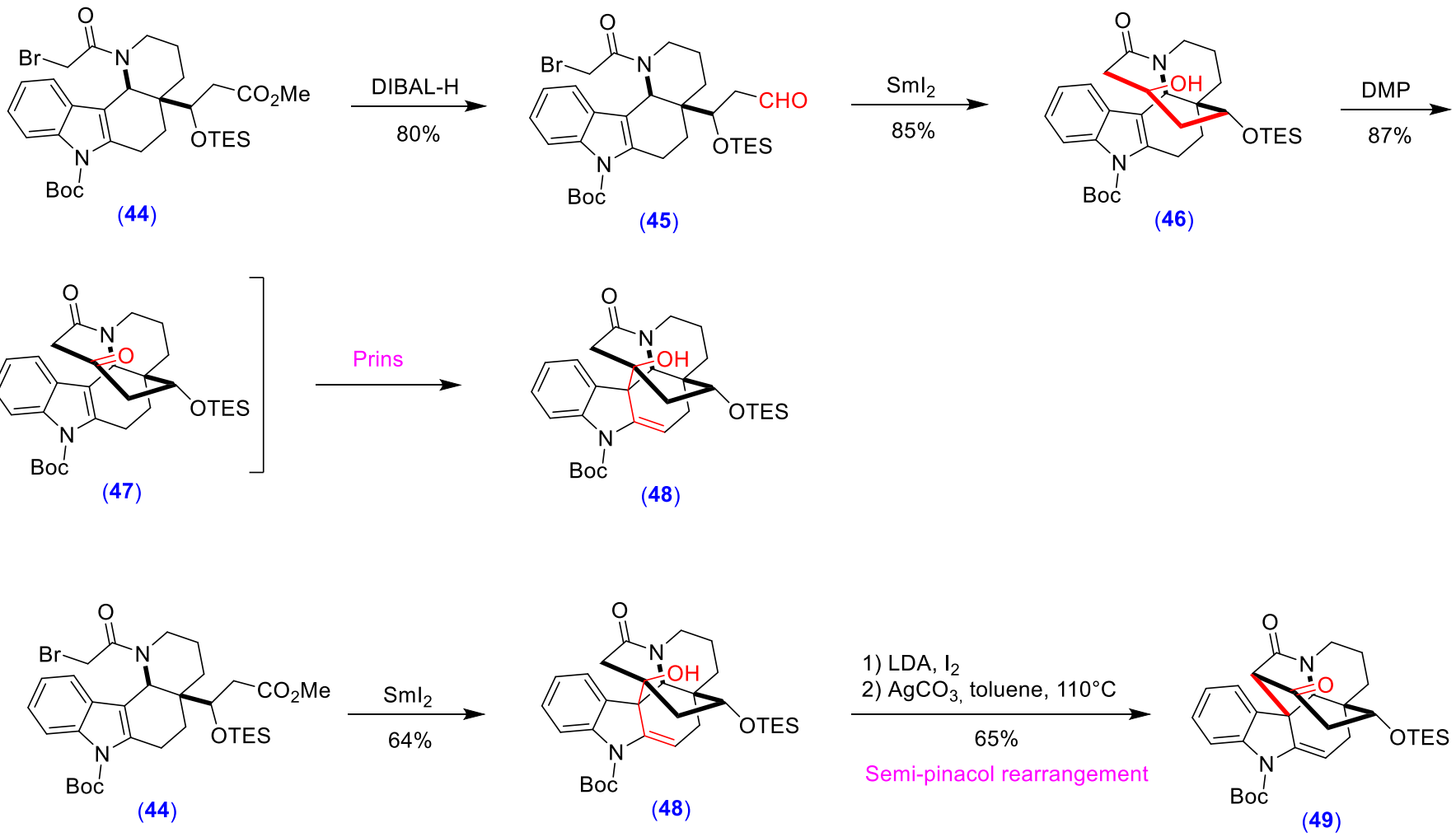
K. Nagaraju, D. Ni, D. Ma, *ACIE*, **2020**, *59,* 22039.

Total synthesis of *Kopsinitarine E*



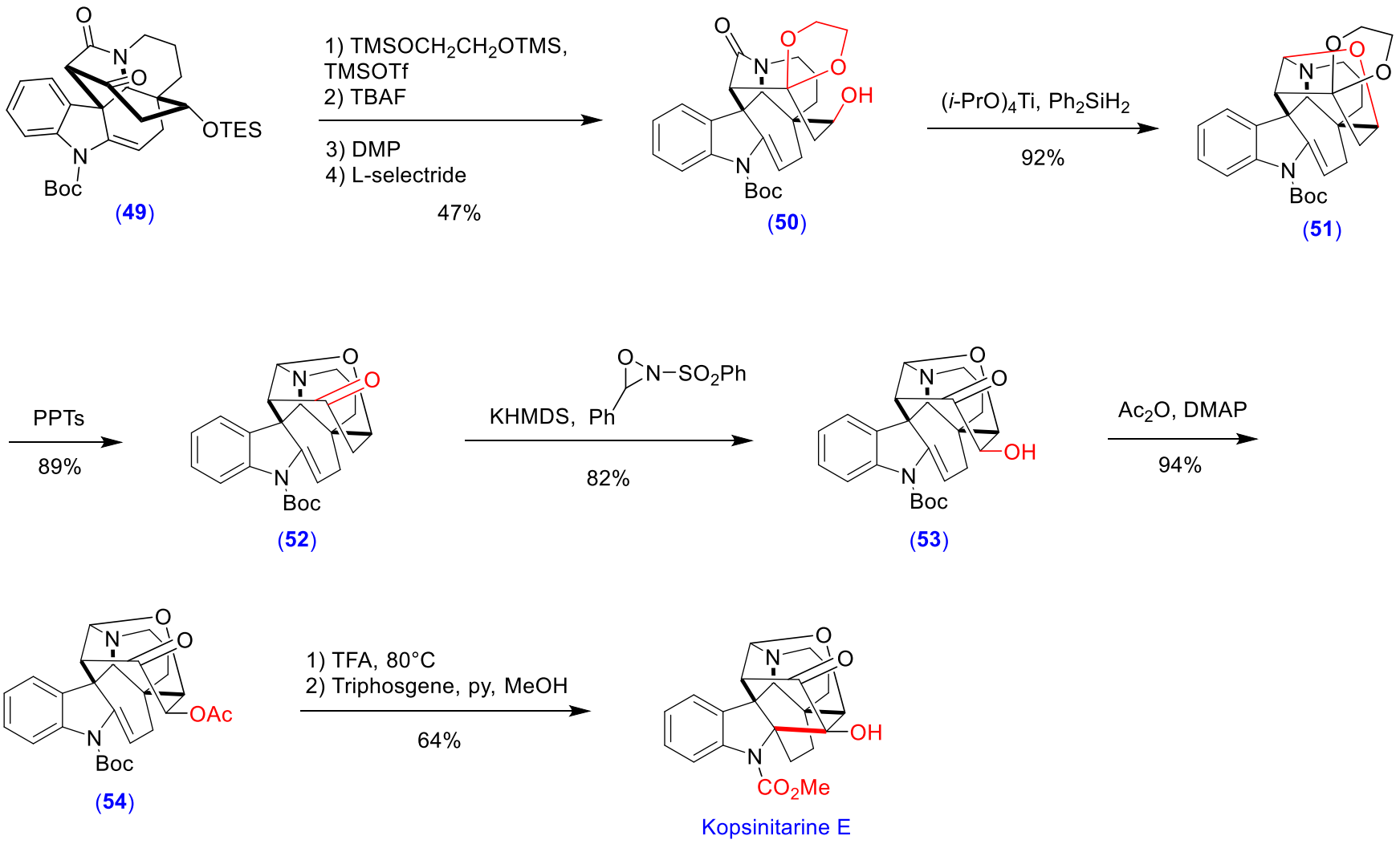
K. Nagaraju, D. Ni, D. Ma, *ACIE*, **2020**, *59,* 22039.

Total synthesis of *Kopsinitarine E*



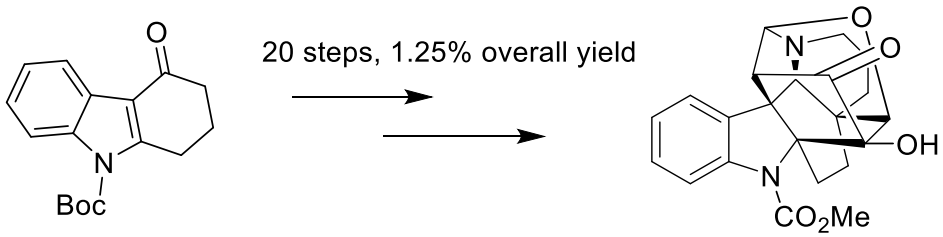
K. Nagaraju, D. Ni, D. Ma, *ACIE*, **2020**, *59,* 22039.

Total synthesis of *Kopsinitarine E*



K. Nagaraju, D. Ni, D. Ma, *ACIE*, **2020**, *59,* 22039.

Total synthesis of *Kopsinitarine E*



Kopsinitarine E

Key steps:

- SmI_2-mediated cyclization followed by a Prins-type cascade
- Semi-pinacol rearrangement to finish the core structure
- Titanium promoted reductive cyclization
- Intramolecular Mannich reaction

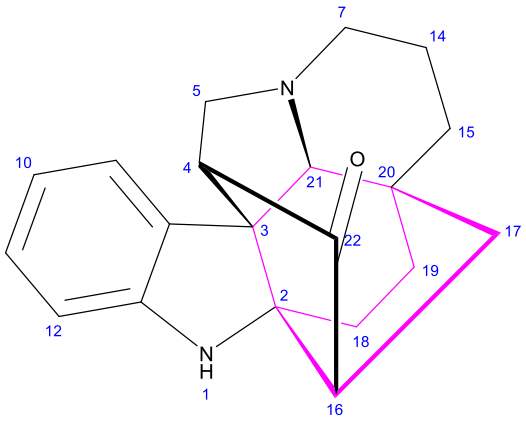
K. Nagaraju, D. Ni, D. Ma, *ACIE*, **2020**, *59,* 22039.

Outline

- 1. Introduction
- 2. Total synthesis of *Kopsia* alkaloids
  - Total synthesis of kopsanone, 1983, Magnus
  - Total synthesis of (-)-kopsanone and (-)-kopsinine, 2011, MacMillan
  - Total synthesis of (-)-fruticosine, 2017, Qin
  - Total synthesis of kopsinitarine E, 2020, Ma
- **3. Summary**

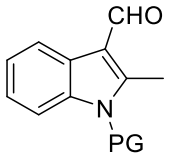
Summary

Kopsia alkaloids:

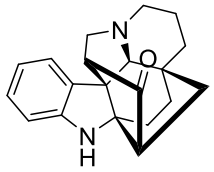


Key steps being the construction of C20-C16-C17-C2 bridge using Diels Alder (Magnus, MacMillan),
SmI_2-promoted acyloin condensation (Qin), Mannich (Ma).

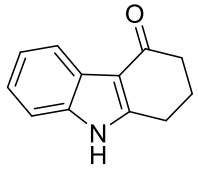
Few total syntheses in the literature.



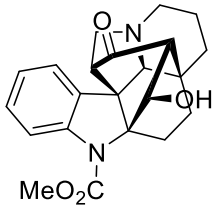
14 steps, 4.4% overall yield



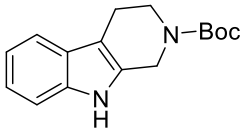
Kopsanone



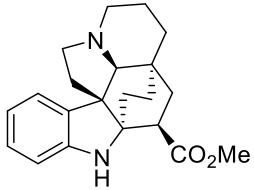
26 steps, 0.8% overall yield



(-)-Fruticosine

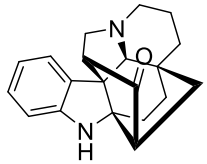


9 steps, 14% overall yield



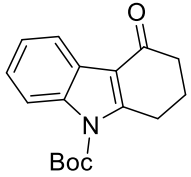
(-)-Kopsinine

2 steps, 74%

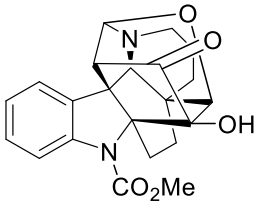


(-)-Kopsanone

(11 steps, 10% overall yield)



20 steps, 1.25% overall yield



Kopsinitarine E

Thanks for your attention !