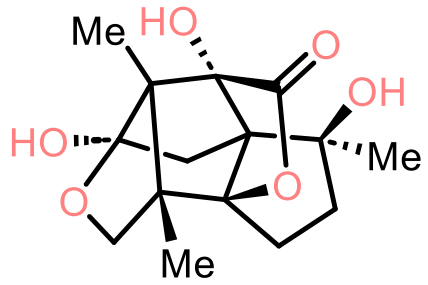
Total Syntheses of Illisimonin A



Illisimonin A

Reporter: Yifan Wang

Supervisor: Prof. Quan Cai

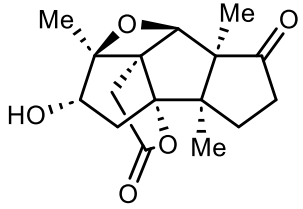
2026.3.13

Content

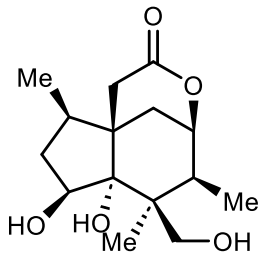
Content

Introduction

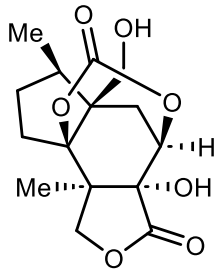
Representative illicium susquiterpenes



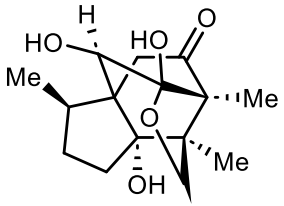
merrilactone A (**1**)



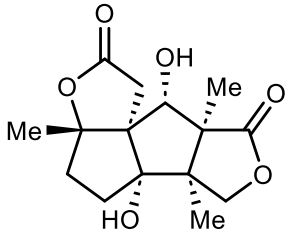
minwanensin (**2**)



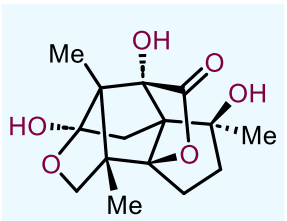
jiadifenolide (**3**)



11-O-debenzoyl tashironin (**4**)

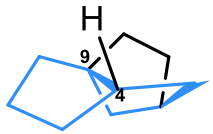


anislactone A (**5**)

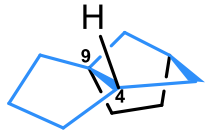


illisimonin A (**6**)

I. simonsii



1-22-cis fused:
0.00 kcal/mol



1-23-trans fused:
7.03 kcal/mol

MP2/6-31+G(d)

Bioactivity

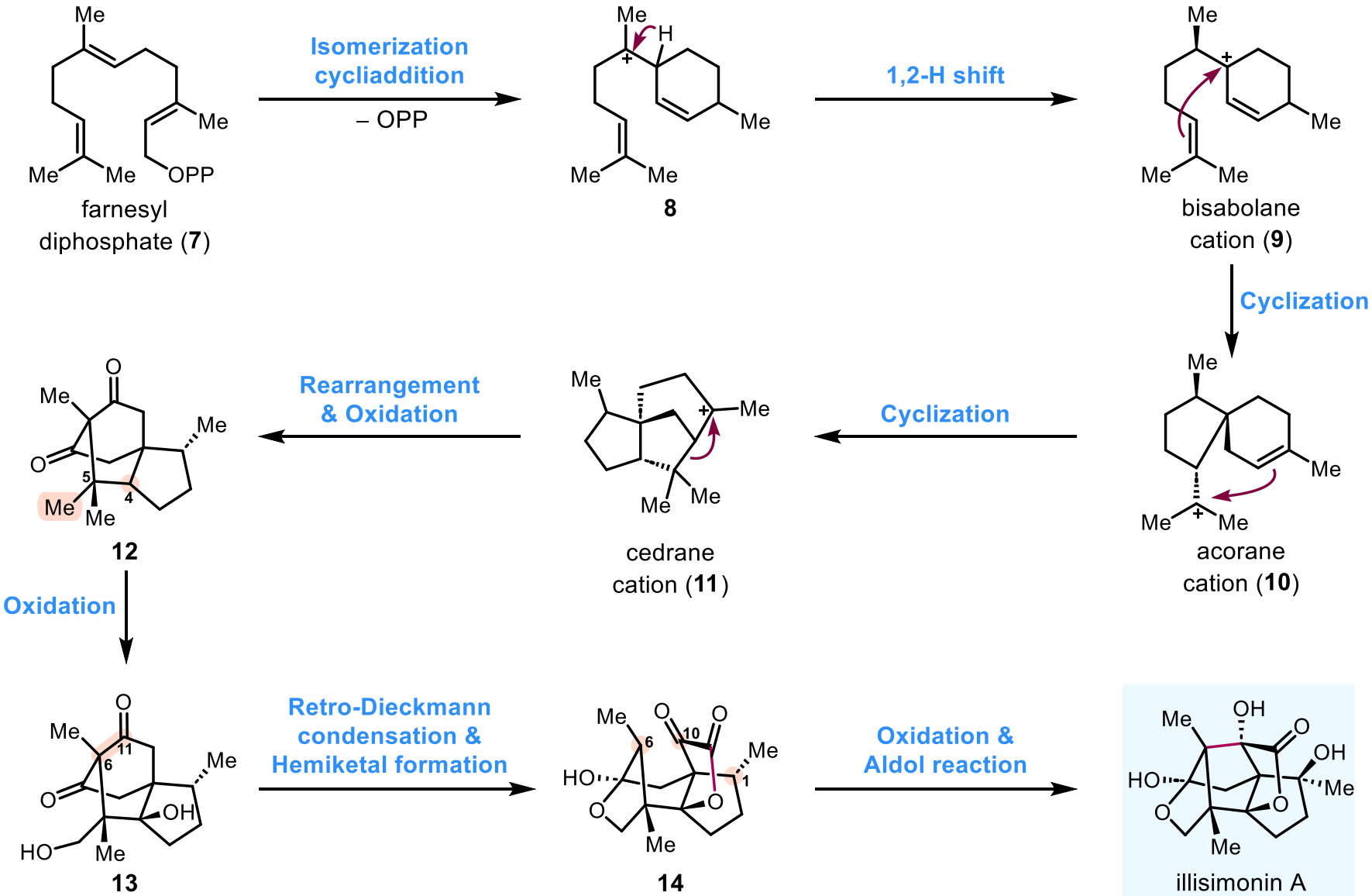
- ✓ Antimicrobial
- ✓ Neurotoxic (**1**)
- ✓ Neurotrophic (**2, 3, 4** ; facilitate neurite outgrowth)
- ✓ Neuroprotective effects (**4, 6**; against OGD-injury in SH-SY5Y; EC50 = 28.9 μM)

Structure features

- ✓ 5/5/5/5/5 pentacyclic skeleton
- ✓ 7 contiguous fully substituted stereocenters
- ✓ Several quaternary centers
- ✓ Trans-5/5-fused ring and norbornane substructure

Ma, S.; Li, M.; Lin, M.; Li, L.; Liu, Y.; Qiu, J.; Li, Y.; Wang, X.; Wang, R.; Xu, S.; Hou, Q.; Yu, S. *Org. Lett.* **2017**, *19*, 6160−6163.
Shenvia, R. A. *Nat. Prod. Rep*. **2016**, *33*, 535– 539.

Proposed biosynthetic pathway

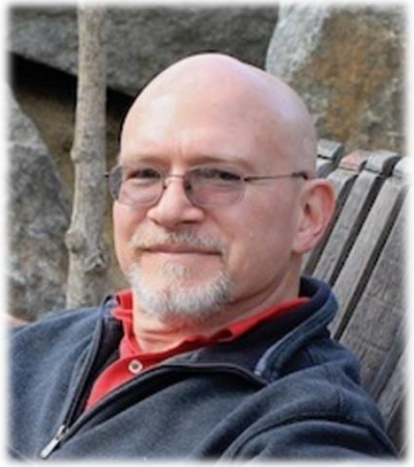


Ma, S.; Li, M.; Lin, M.; Li, L.; Liu, Y.; Qu, J.; Li, Y.; Wang, X.; Wang, R.; Xu, S.; Hou, Q.; Yu, S. *Org. Lett*. **2017**, *19*, 6160−6163.
Gong, X.; Huang, J.; Sun, X.; Chen, Z.; Yang, M. *Angew. Chem. Int. Ed*. **2023**, *62*, e202306367.

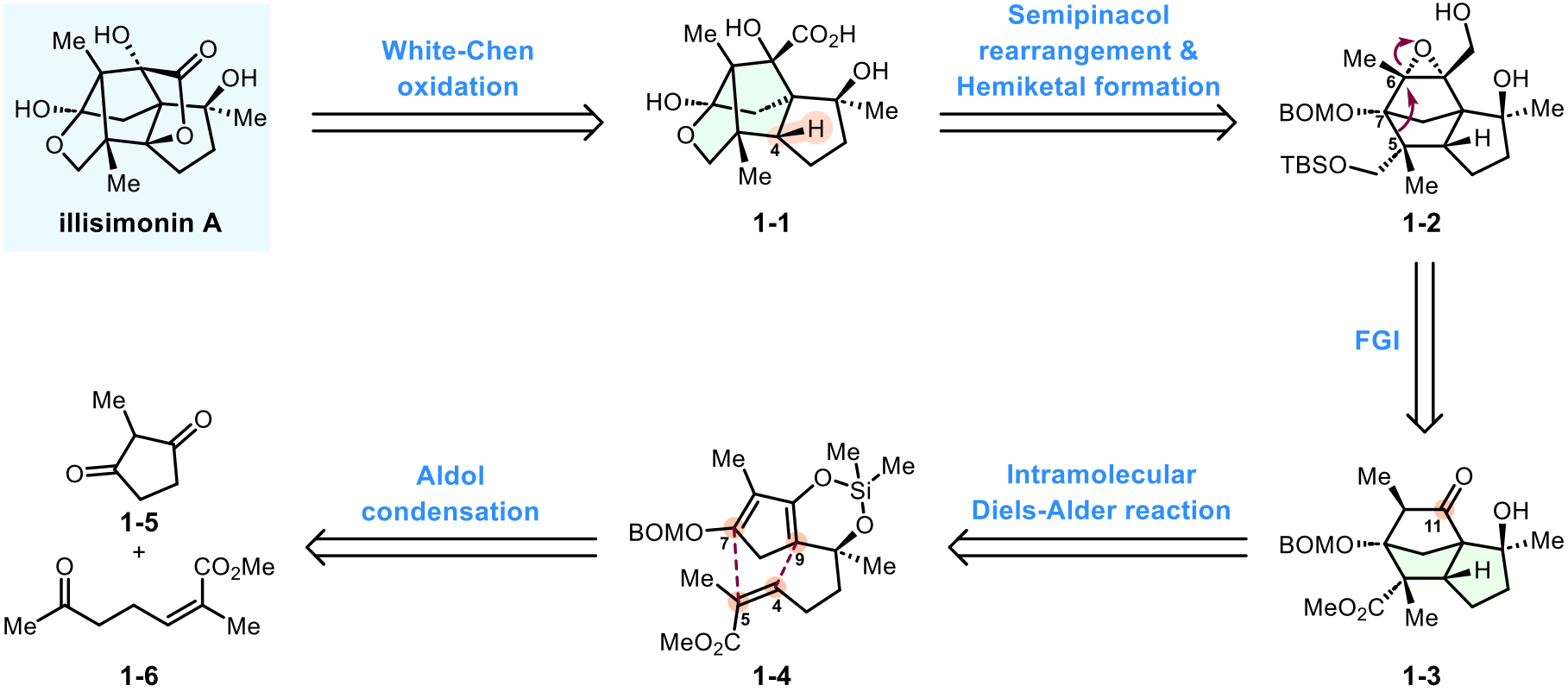
Content

Total Syntheses of Illisimonin A——Rychnovsky (2019)

Retrosynthetic Analysis



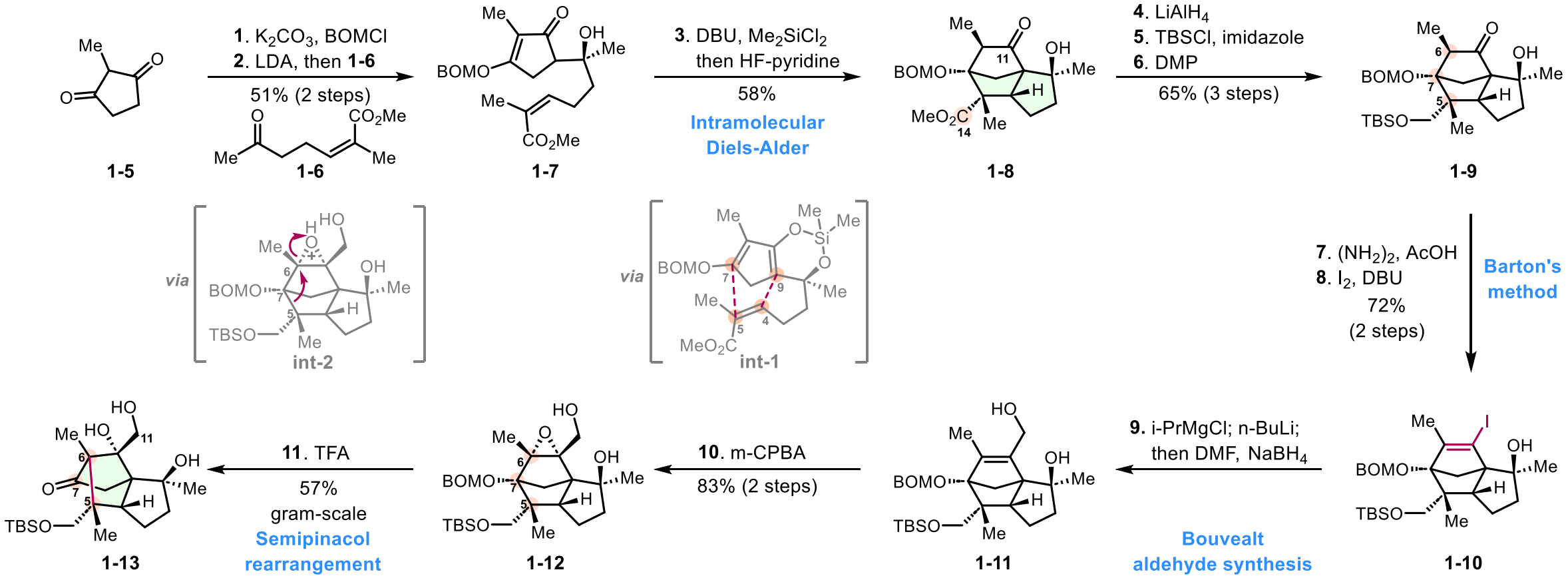
Scott D. Rychnovsky



Burns, A. S.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2019**, *141*, 13295−13300.

Total Syntheses of (±)-Illisimonin A——Rychnovsky (2019)

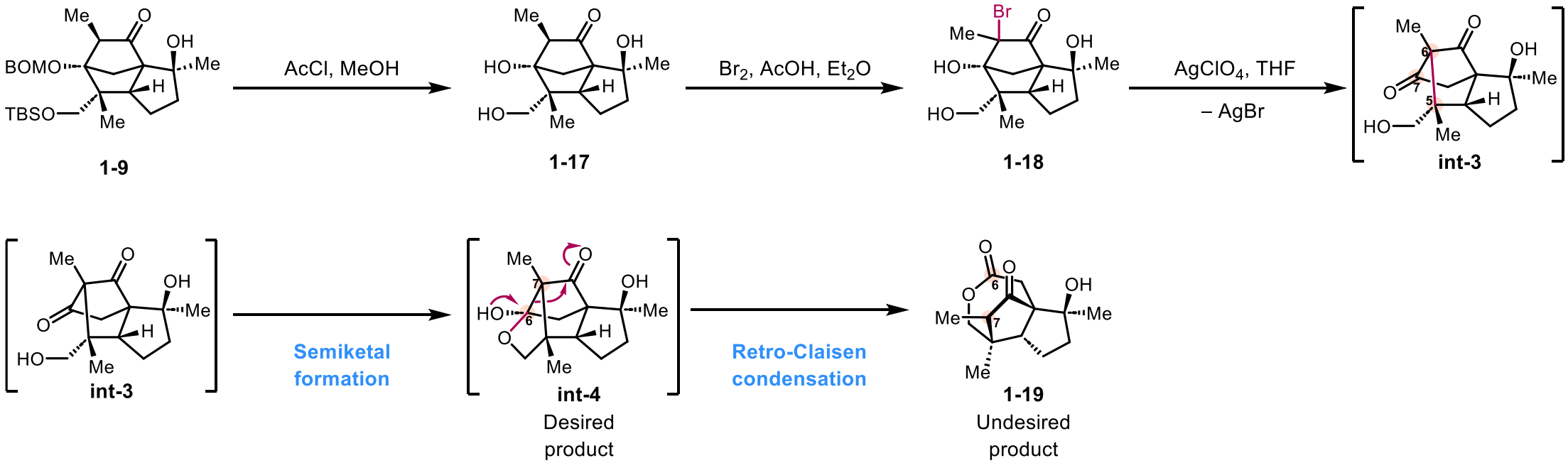
Construction of the 5/5/5 Skeleton



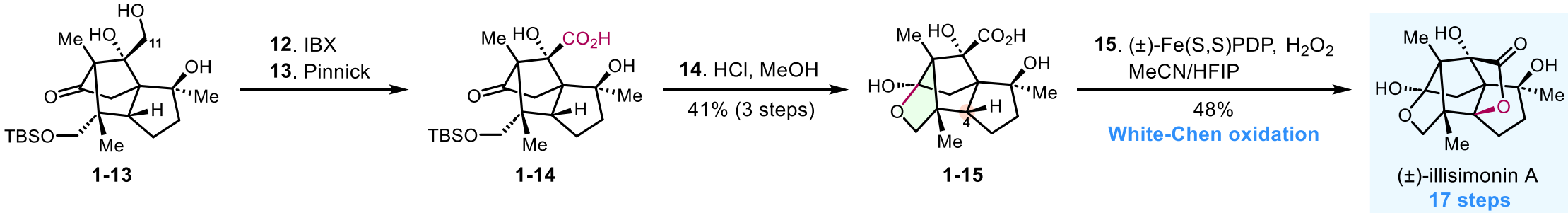
Burns, A. S.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2019**, *141*, 13295−13300.

Total Synthesis of (±)-Illisimonin A——Rychnovsky (2019)

Other Attempts at Construction of C5-C6 bond

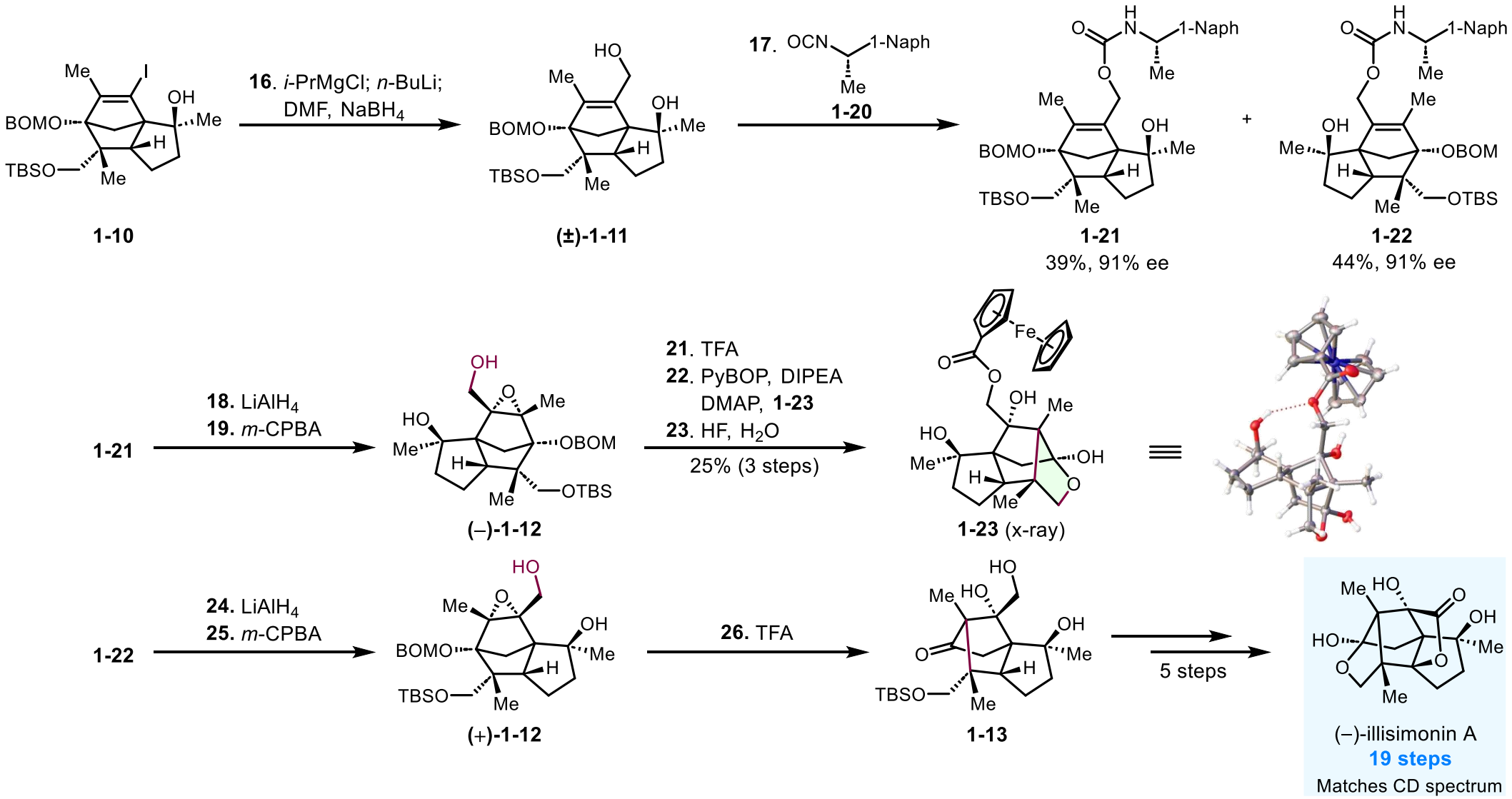


Total Synthesis of (±)-Illisimonin A



Burns, A. S.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2019**, *141*, 13295−13300.

Structure Revision of (−)-Illisimonin A——Rychnovsky (2019)



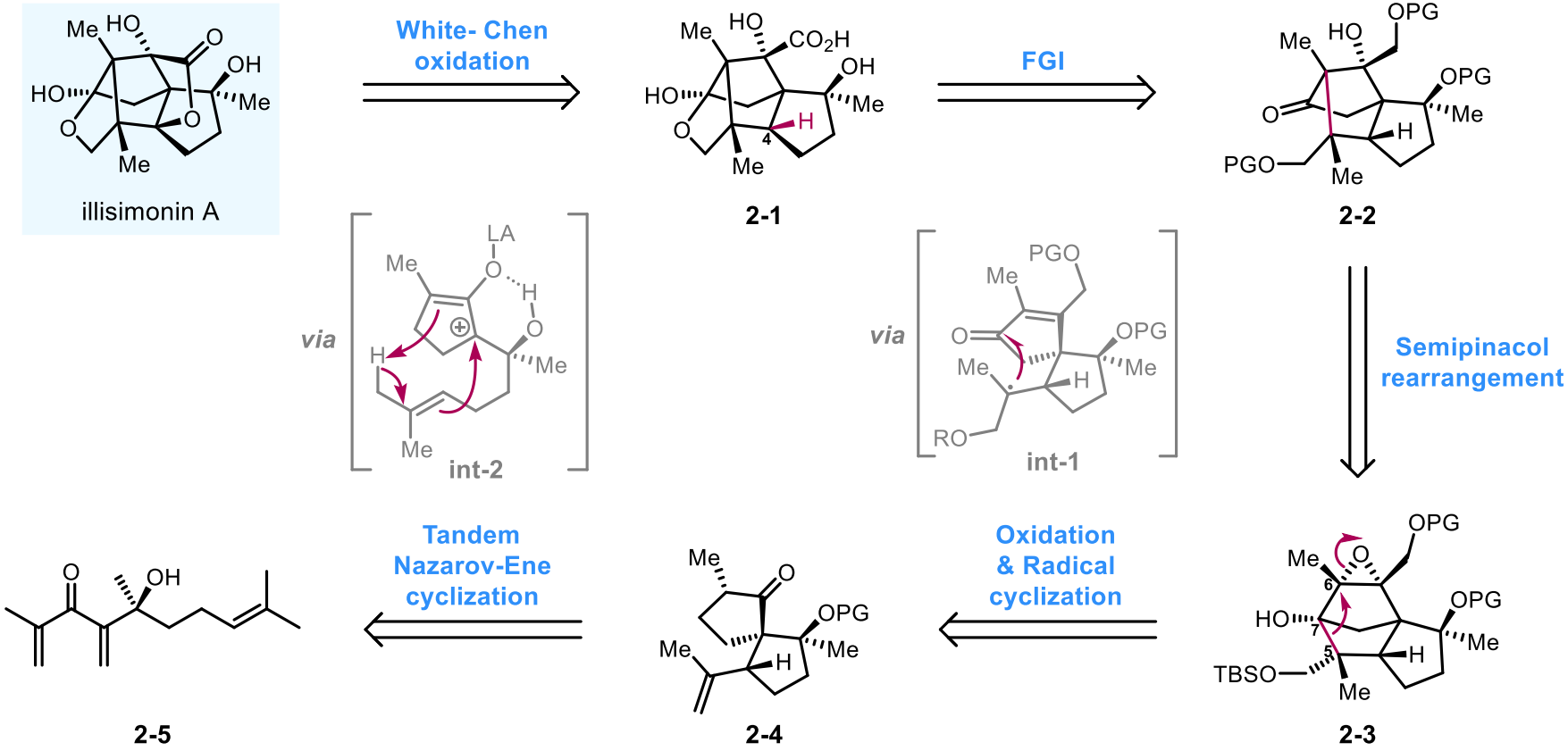
Burns, A. S.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2019**, *141*, 13295−13300.

Content

Total Syntheses of Illisimonin A——Kalesse (2023)

Retrosynthetic Analysis

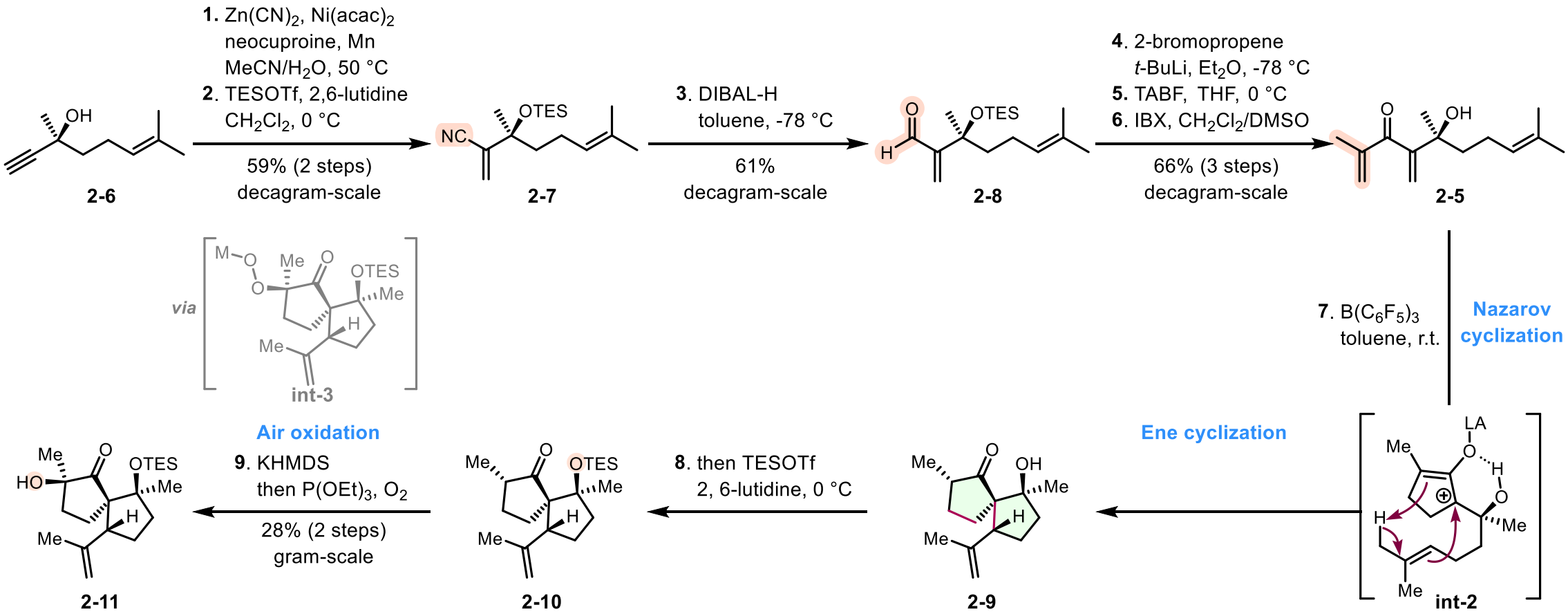
Markus Kalesse



Etling, C.; Tedesco, G.; Di Marco, A.; Kalesse, M. *J. Am. Chem. Soc.* **2023**, *145*, 7021−7029.

Total Syntheses of (−)-Illisimonin A——Kalesse (2023)

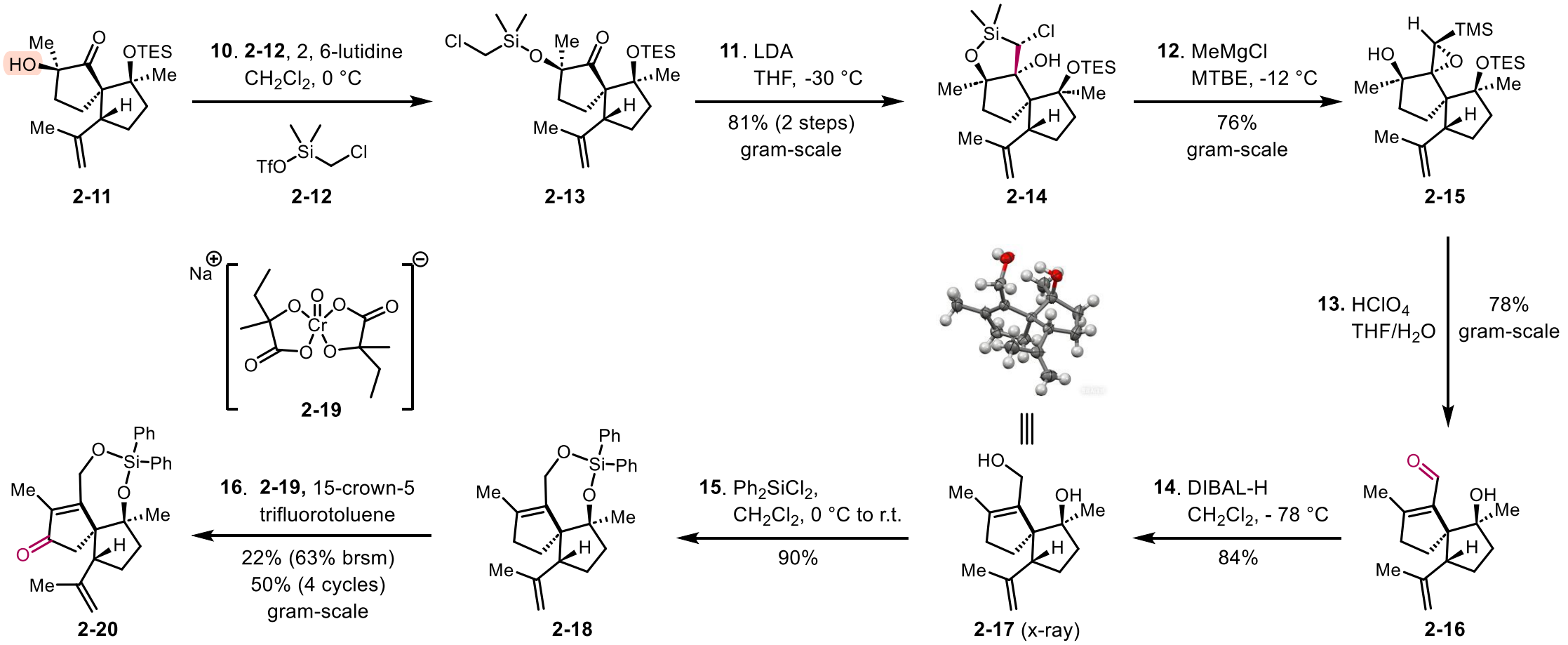
Construction of the Spirocyclic Framework



Etling, C.; Tedesco, G.; Di Marco, A.; Kalesse, M. *J. Am. Chem. Soc.* **2023**, *145*, 7021−7029.

Total Syntheses of (−)-Illisimonin A——Kalesse (2023)

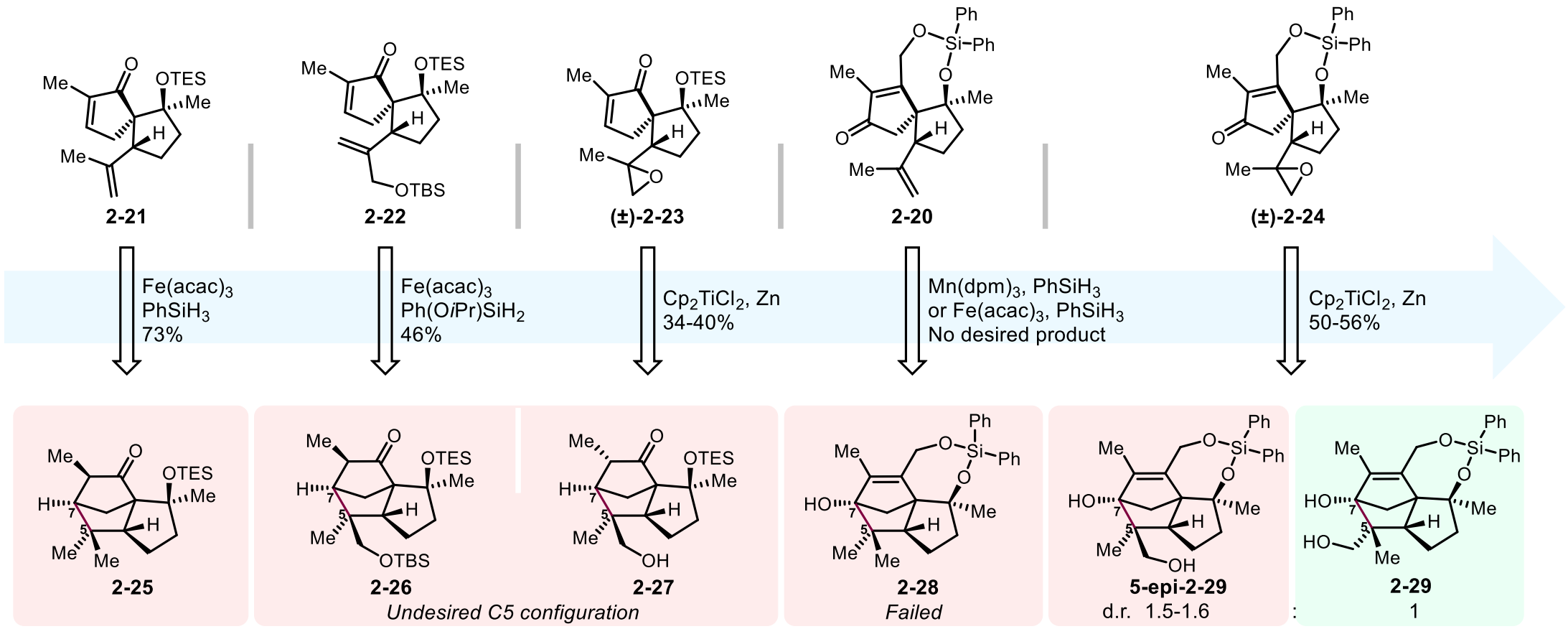
Preparation for Tricyclo[5.2.1.0^{1,5}]decane Synthesis



Etling, C.; Tedesco, G.; Di Marco, A.; Kalesse, M. *J. Am. Chem. Soc.* **2023**, *145*, 7021−7029.

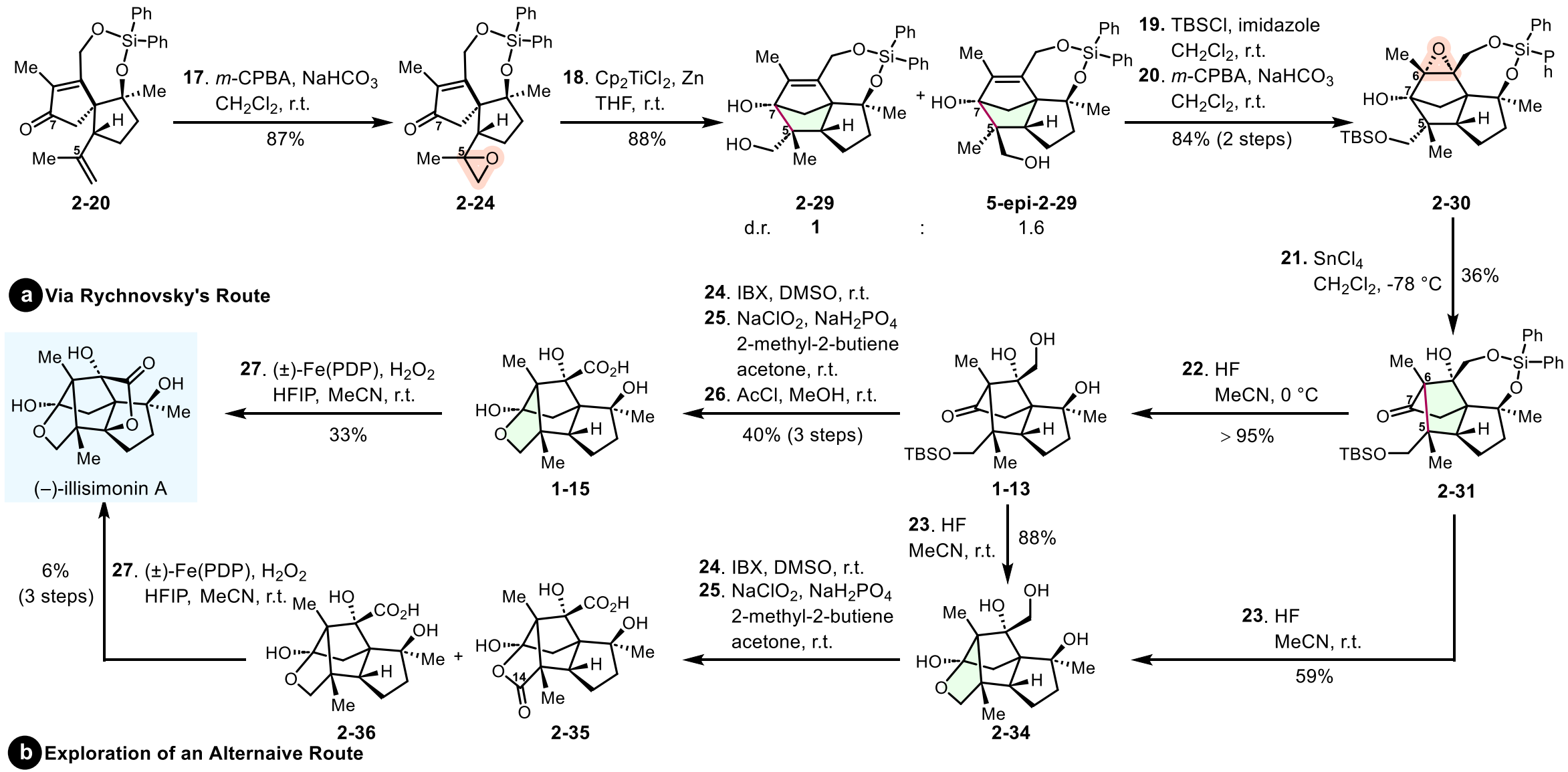
Total Syntheses of (−)-Illisimonin A——Kalesse (2023)

Evolution of C5-C7 Cyclization



Etling, C.; Tedesco, G.; Di Marco, A.; Kalesse, M. *J. Am. Chem. Soc.* **2023**, *145*, 7021−7029.

Total Syntheses of (−)-Illisimonin A——Kalesse (2023)



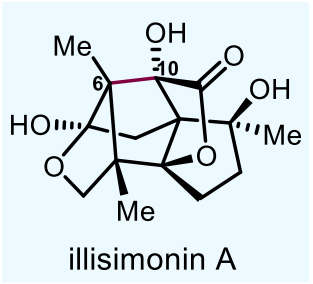
Etling, C.; Tedesco, G.; Di Marco, A.; Kalesse, M. *J. Am. Chem. Soc.* **2023**, *145*, 7021−7029.

Content

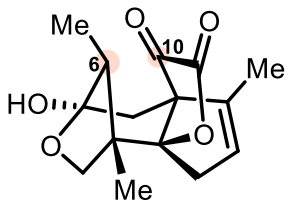
Total Syntheses of (±)-Illisimonin A——Ming Yang (2023)

Retrosynthetic Analysis

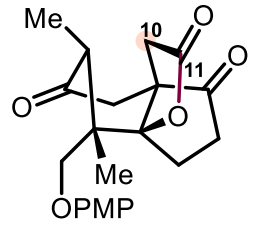
阳 铭



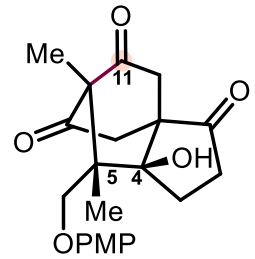
Oxidation &
Aldol condensation



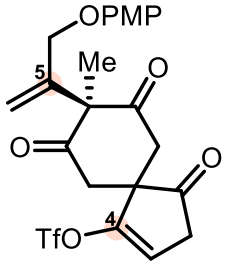
Hemiketal formation



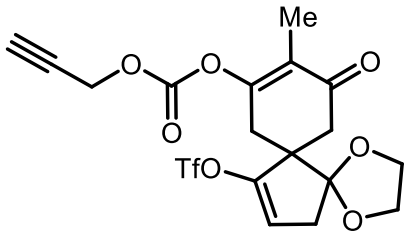
Retro-Dieckmann
condensation



Reductive
Heck reaction



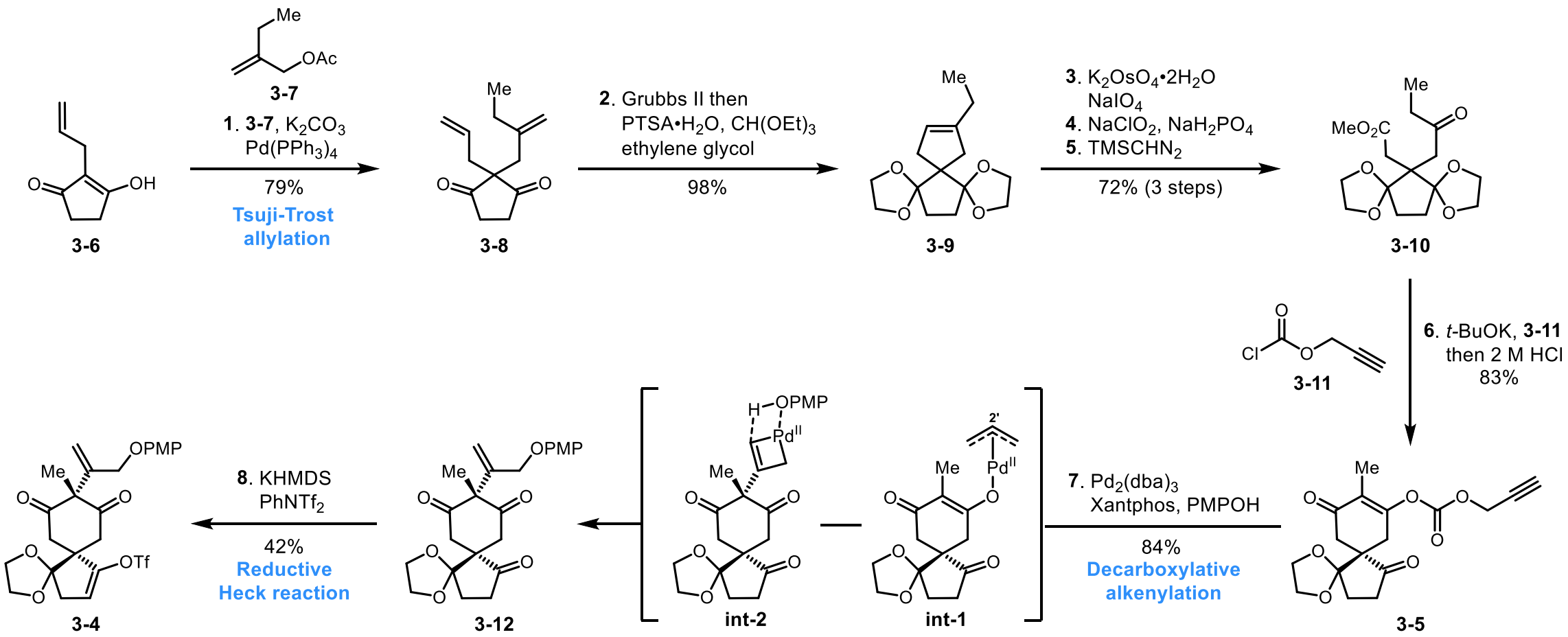
Pd-catalyzed
decarboxylative
alkenylation



Gong, X.; Huang, J.; Sun, X.; Chen, Z.; Yang, M. *Angew. Chem. Int. Ed.* **2023**, *62*, e202306367.

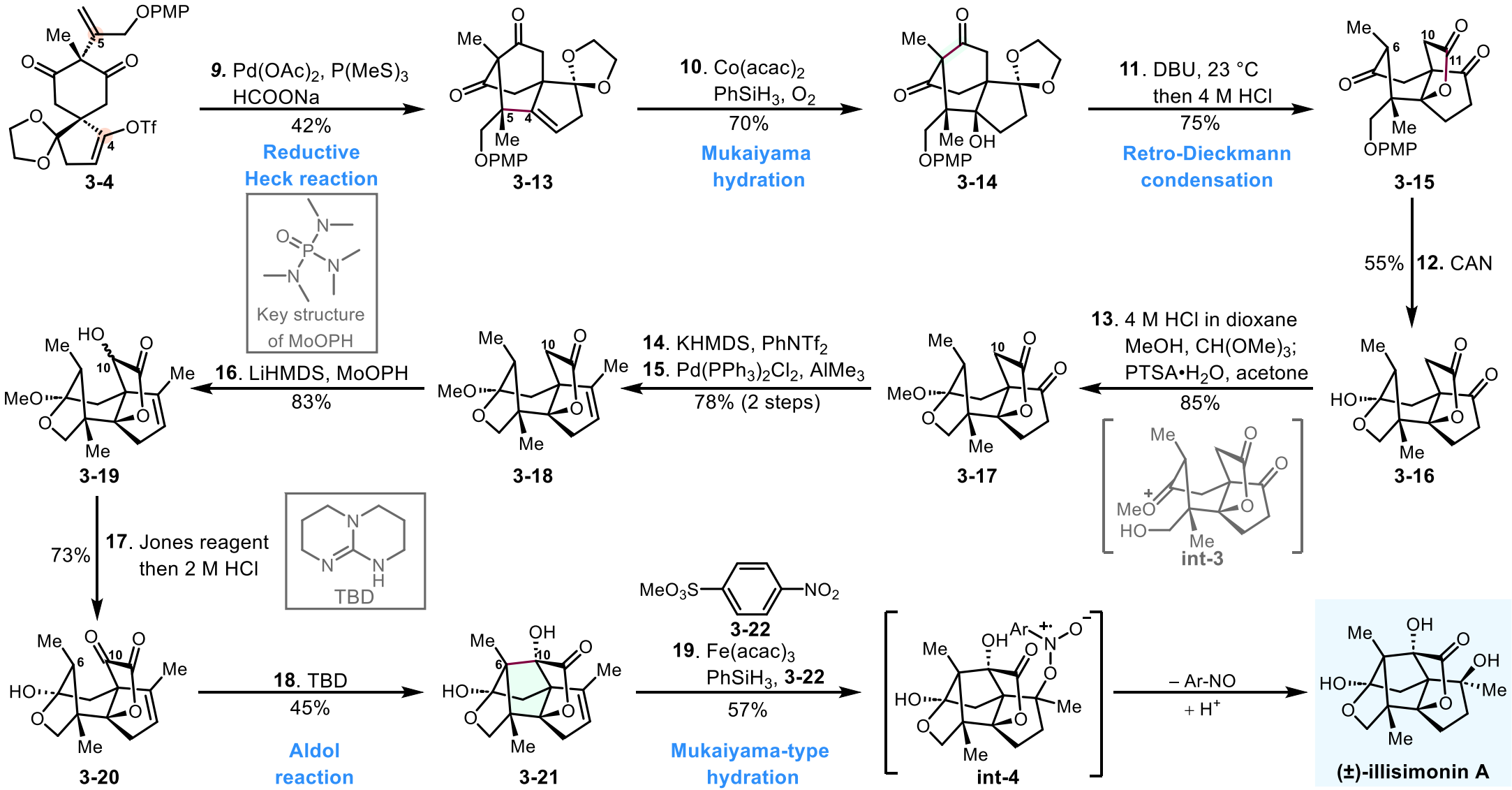
Total Syntheses of (±)-Illisimonin A——Ming Yang (2023)

Preparation of the Key Intermediate



Gong, X.; Huang, J.; Sun, X.; Chen, Z.; Yang, M. *Angew. Chem. Int. Ed.* **2023**, *62*, e202306367.

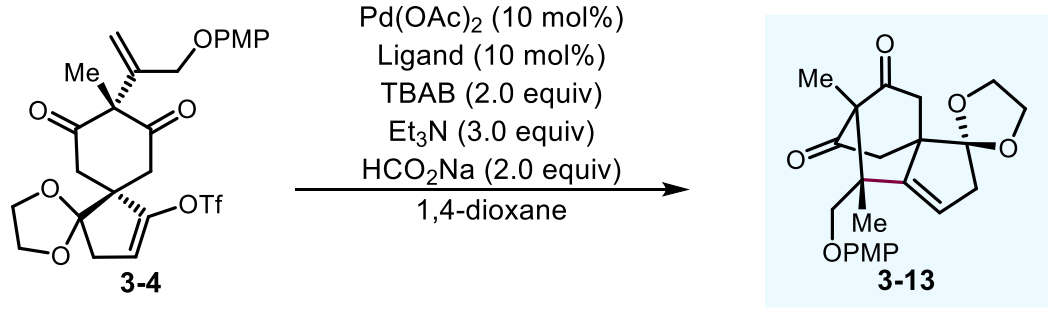
Total Syntheses of (±)-Illisimonin A——Ming Yang (2023)



Gong, X.; Huang, J.; Sun, X.; Chen, Z.; Yang, M. *Angew. Chem. Int. Ed.* **2023**, *62*, e202306367.

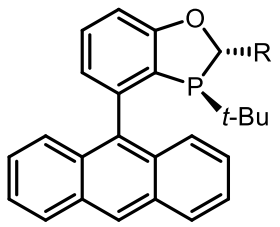
Total Syntheses of (±)-Illisimonin A——Ming Yang (2023)

Evolution of Asymmetric Synthesis of Illisimonin

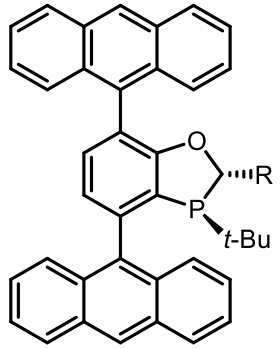


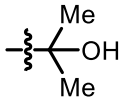
Entry	[Pd]	Ligand	Temp [°C]	Yield [%]	ee [%]
1	$Pd(OAc)_2$	**L1**	90	37	7
2	$Pd(OAc)_2$	**L2**	90	39	5
3	$Pd(OAc)_2$	**L3**	90	33	11
4	$Pd(OAc)_2$	**L4**	90	32	20
5	$Pd(OAc)_2$	**L5**	90	30	50
6	$Pd(OAc)_2$	**L6**	90	31	43
7	$Pd(OAc)_2$	**L7**	90	23	60
8	$Pd(OAc)_2$	**L8**	90	27	40

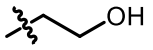
Entry	[Pd]	Ligand	Temp [°C]	Yield [%]	ee [%]
9[a]	$Pd_2(dba)_3$	**L7**	90	40	30
10[a]	$Pd_2(dba)_3$	**L7**	80	23	82
11[a]	$Pd_2(dba)_3$	**L7**	70	10	60

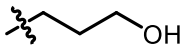


L1: R = Me
L2: R = i-Pr



L3: R = Me
L4: R = Et
L5: R = 

L6: R = CH_2OH
L7: R = 

L8: R = 

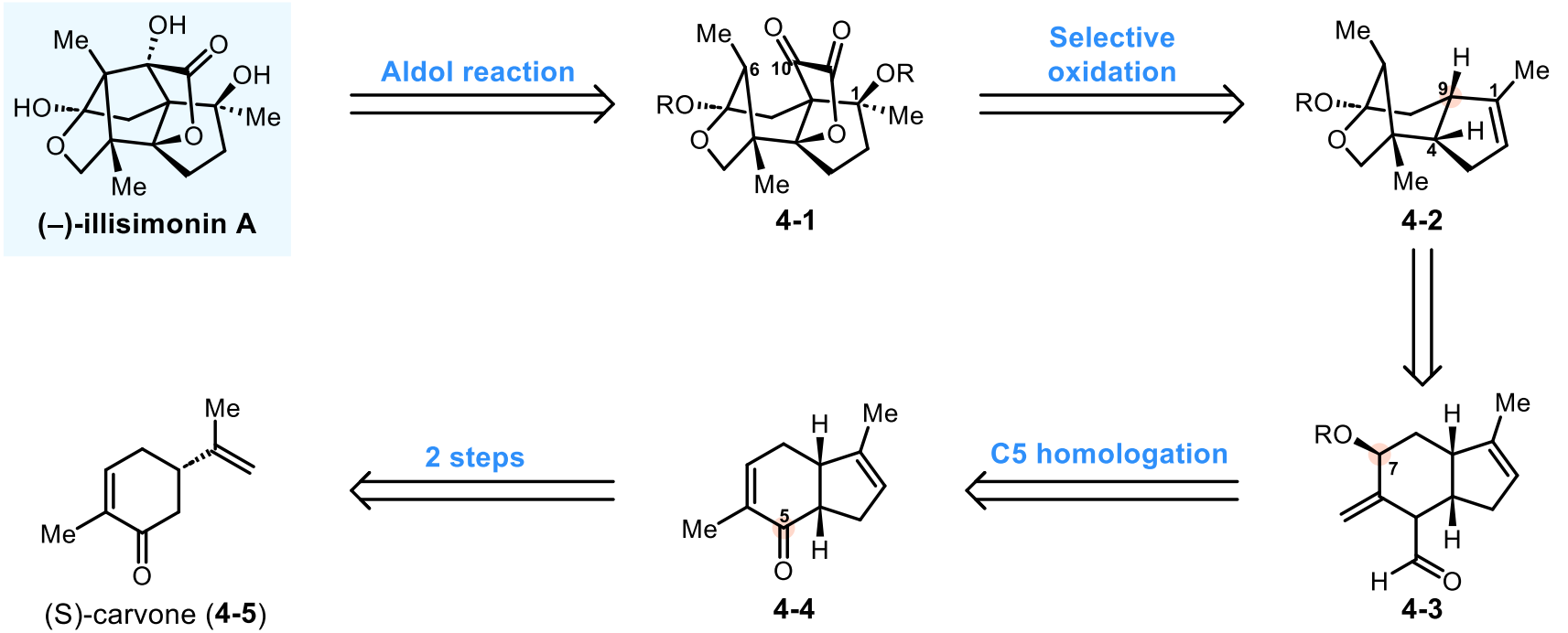
[a] Reaction conditions: $Pd_2(dba)_3$ (5 mol%) instead of $Pd(OAc)_2$ (10 mol%)

Gong, X.; Huang, J.; Sun, X.; Chen, Z.; Yang, M. *Angew. Chem. Int. Ed.* **2023**, *62*, e202306367.

Content

Total Syntheses of Illisimonin A——Mingji Dai (2025)

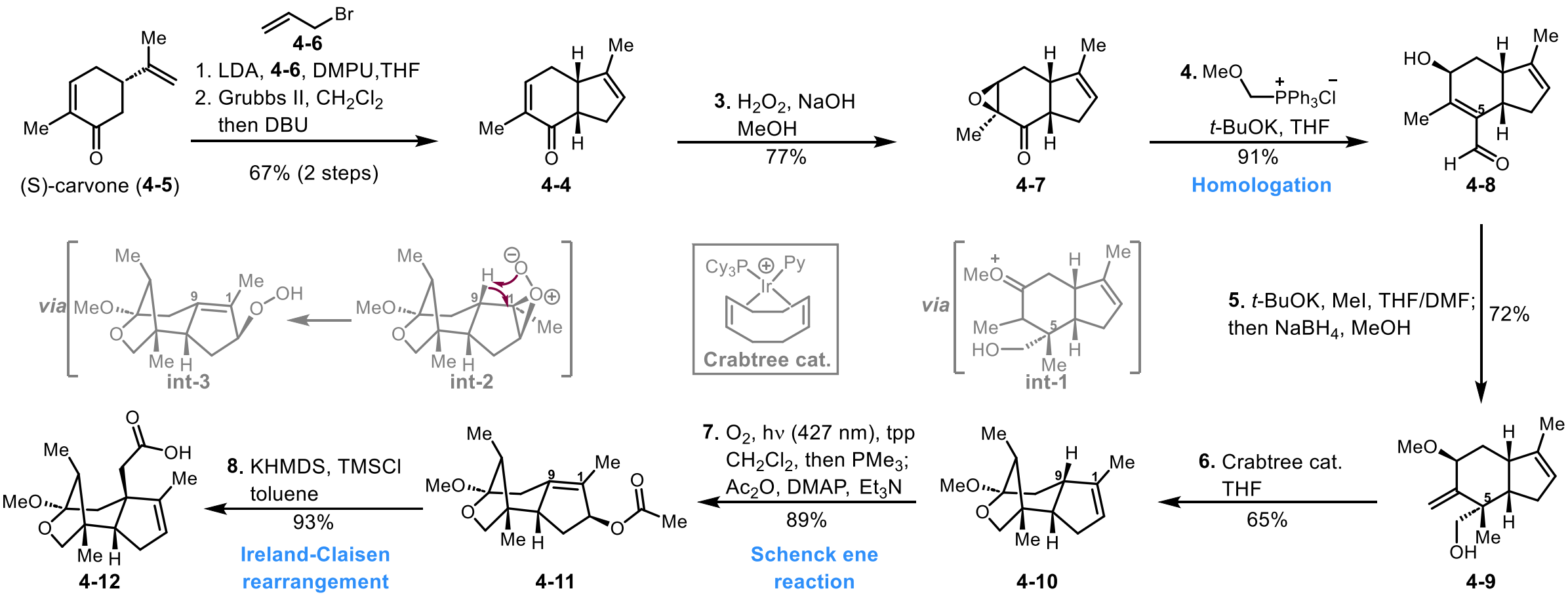
Retrosynthetic Analysis



代明骥

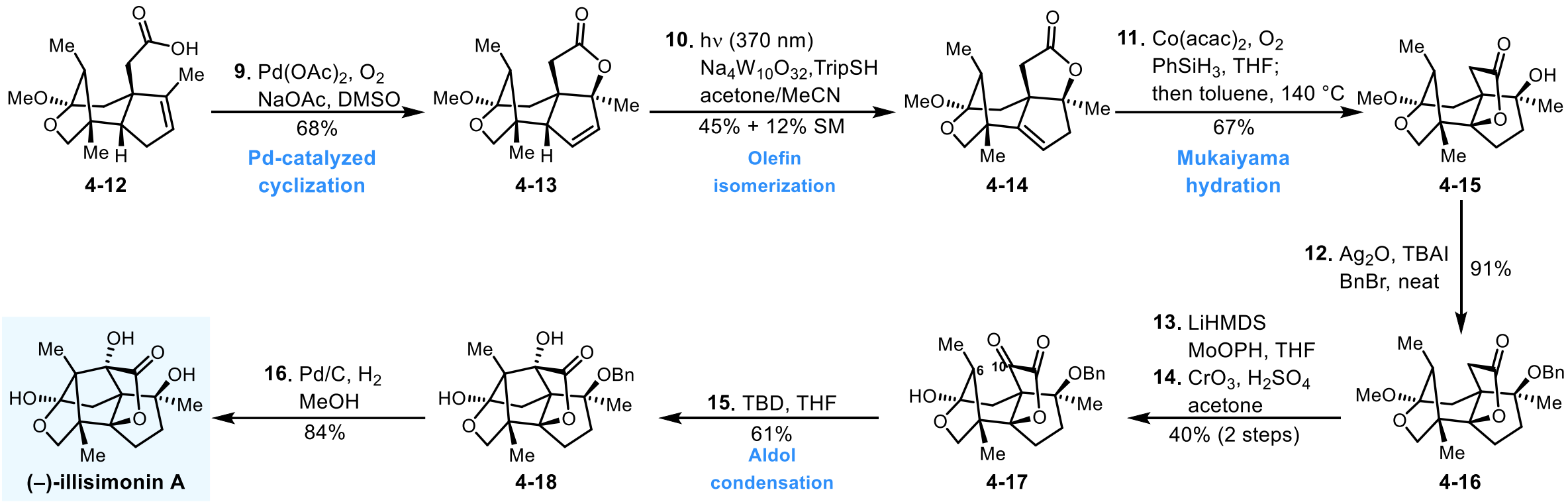
Xu, B.; Zhang, Z.; Dai, M. *J. Am. Chem. Soc.* **2025**, *147*, 17592−17597.

Total Syntheses of (−)-Illisimonin A——Mingji Dai (2025)



Xu, B.; Zhang, Z.; Dai, M. *J. Am. Chem. Soc.* **2025**, *147*, 17592−17597.

Total Syntheses of (−)-Illisimonin A——Mingji Dai (2025)



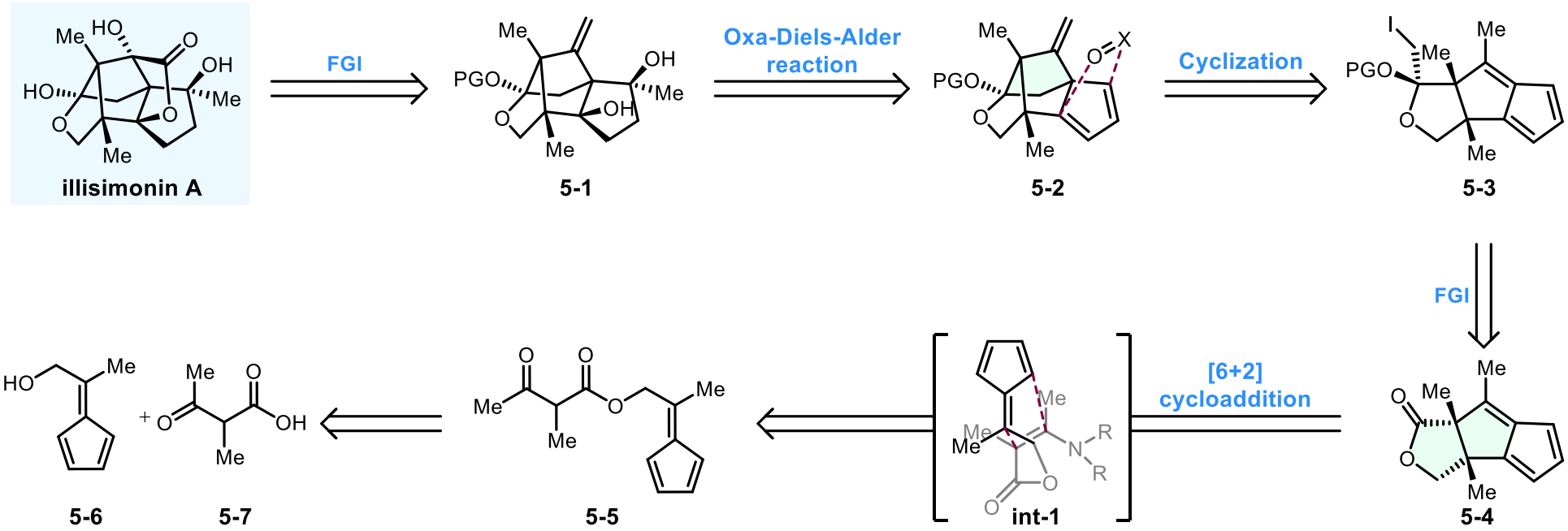
Xu, B.; Zhang, Z.; Dai, M. *J. Am. Chem. Soc.* **2025**, *147*, 17592−17597.

Content

Total Syntheses of (±)-Illisimonin A——Zhaohong Lu (2025)

Retrosynthetic Analysis

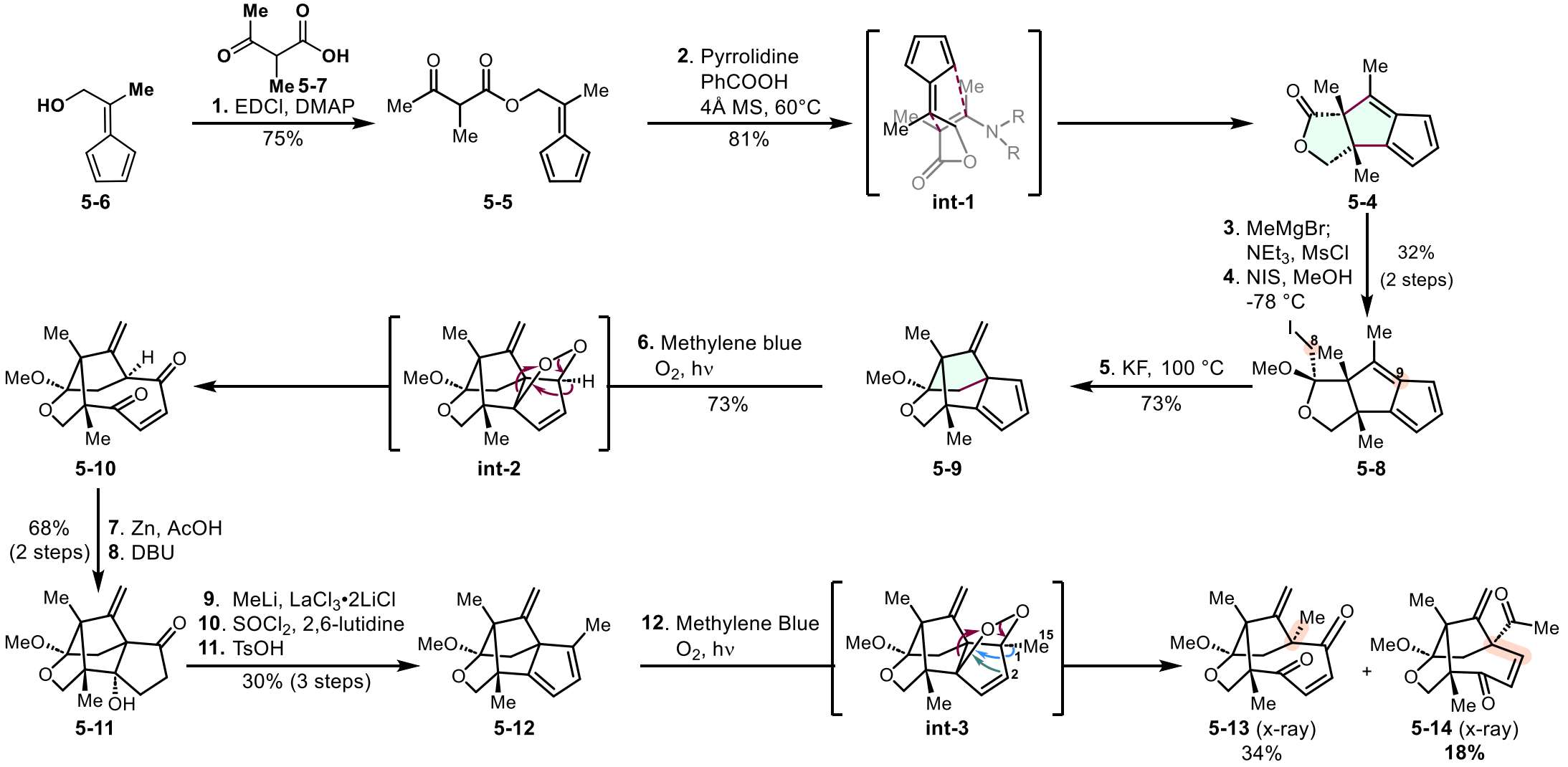
陆钊洪



Zhu, L.; Li, J.; Lu, Z. *J. Am. Chem. Soc.* **2025**, *147*, 23417−23421.

Total Syntheses of (±)-Illisimonin A——Zhaohong Lu (2025)

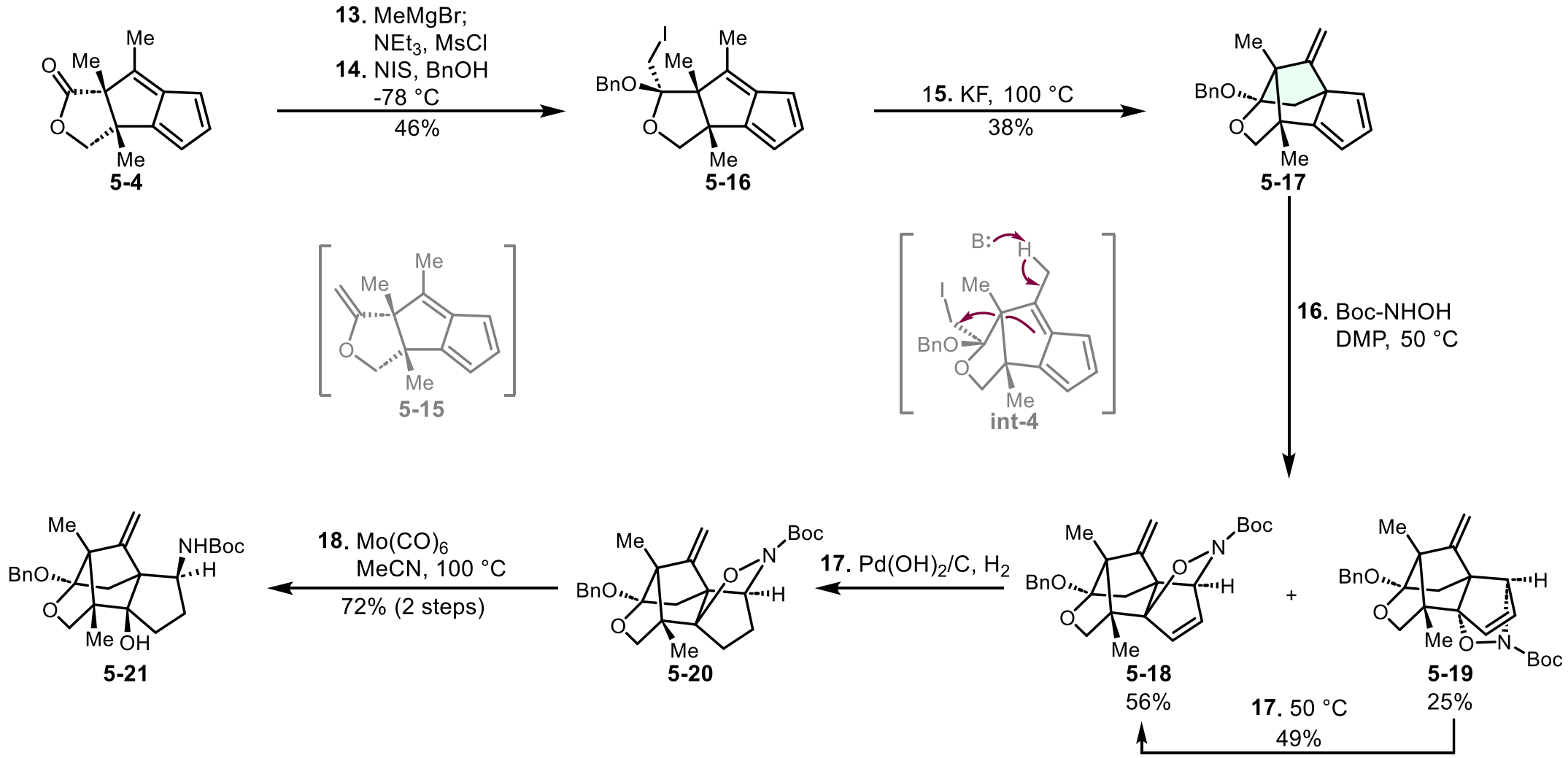
Construction of 5/5/5/5 Cage-Like Motif



Zhu, L.; Li, J.; Lu, Z. *J. Am. Chem. Soc.* **2025**, *147*, 23417−23421.

Total Syntheses of (±)-Illisimonin A——Zhaohong Lu (2025)

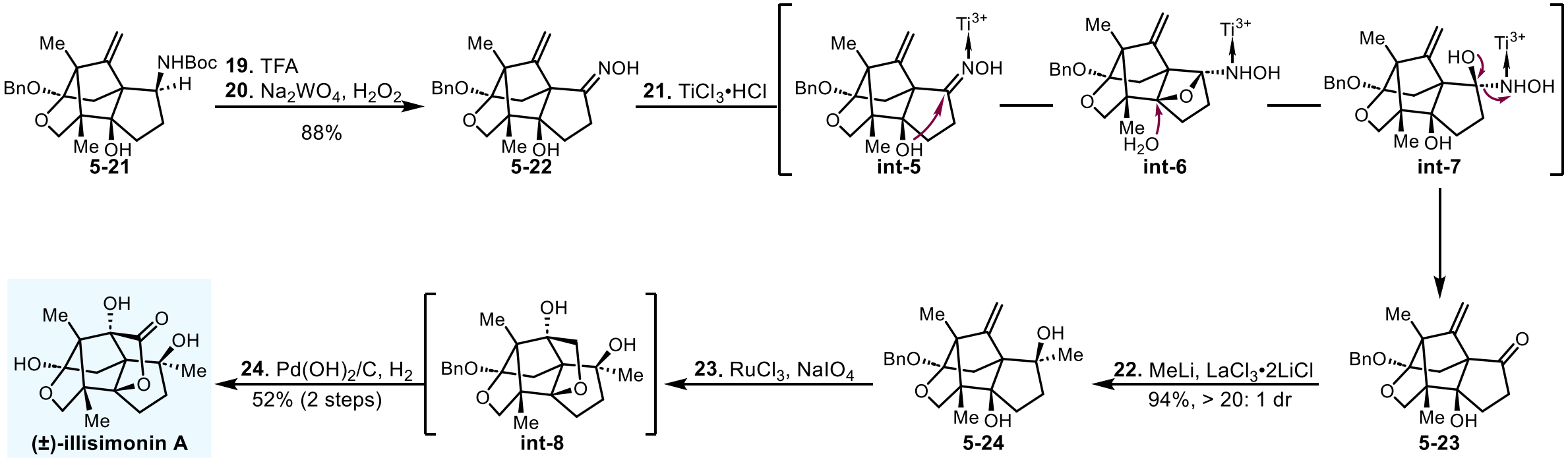
Construction of 5/5/5/5 Cage-Like Motif



Zhu, L.; Li, J.; Lu, Z. *J. Am. Chem. Soc.* **2025**, *147*, 23417−23421.

Total Syntheses of (±)-Illisimonin A——Zhaohong Lu (2025)

End Game



Zhu, L.; Li, J.; Lu, Z. *J. Am. Chem. Soc.* **2025**, *147*, 23417−23421.

Content

1. Introduction

2. Total Syntheses of Illisimonin A

   √ Rychnovsky, S. D. (2019)

   √ Kalesse, M. (2023)

   √ Ming Yang (2023)

   √ Mingji Dai (2025)

   √ Zhaohong Lu (2025)

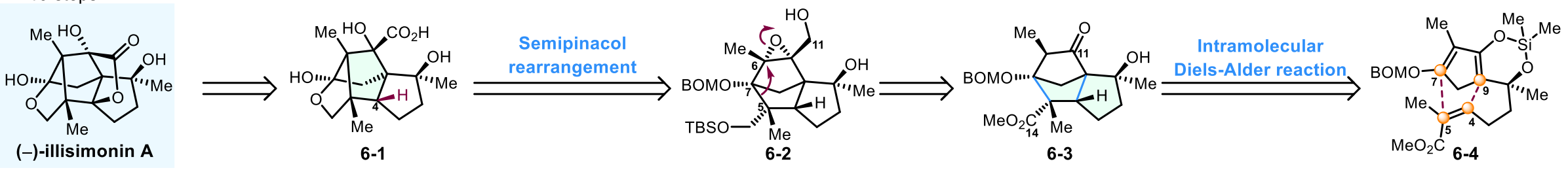
3. Summary

Summary

1. Structural Reorganization Strategy

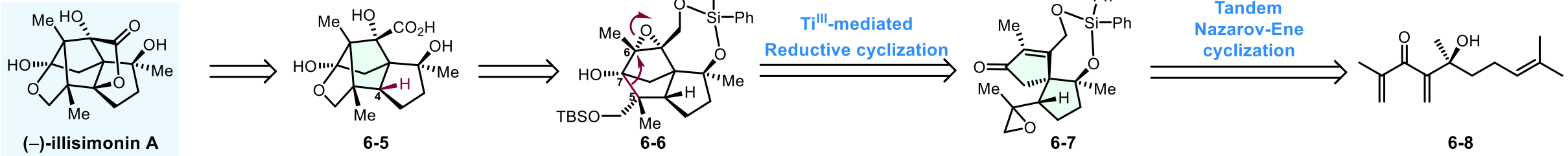
Rychnovsky

19 steps



Kalesse

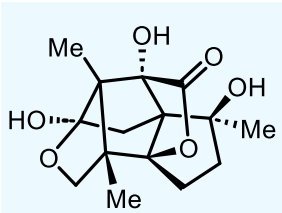
28 steps



Summary

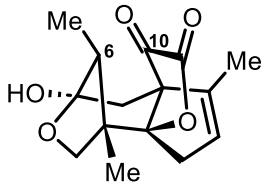
2. Annulation of Core Ring

Ming Yang
20 steps



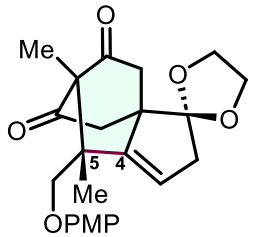
(±)-illisimonin A

Aldol reaction



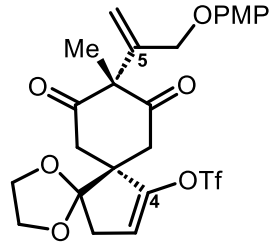
6-9

Retro-Dieckmann condensation



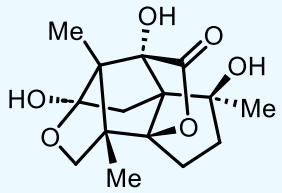
6-10

Reductive Heck reaction



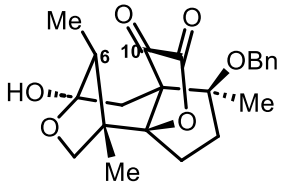
6-11

Mingji Dai
16 steps



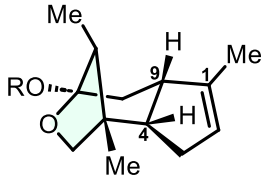
(–)-illisimonin A

Aldol reaction



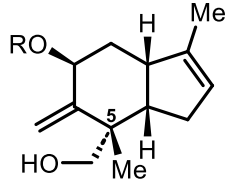
6-12

Selective oxidation



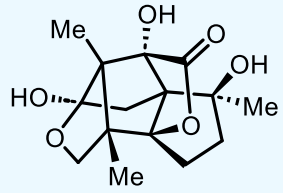
6-13

Hemiketal formation



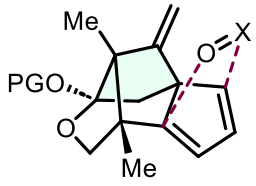
6-14

Zhaohong Lu
14 steps



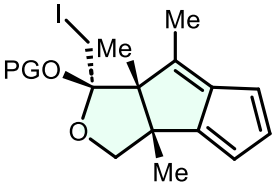
(±)-illisimonin A

Oxa-Diels-Alder reaction



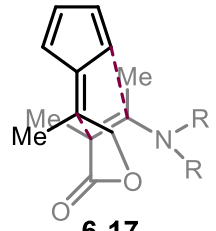
6-15

Cyclization



6-16

[6+2] cycloaddition



6-17

Thanks for your kind attention