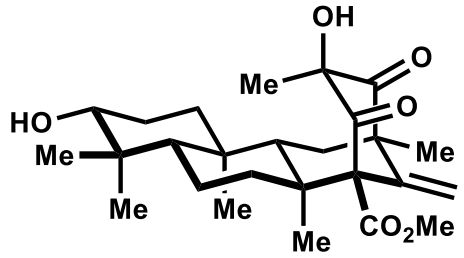
Total Synthesis of Berkeleyone A and its Derivatives



berkeleyone A

Reporter: Qitao Lu

Supervisor: Prof. Quan Cai

Content

- **Introduction**
- **Total Synthesis of Berkeleyone A and its Derivatives**
  - ✓ Maimone, T. J. (2016, **Berkeleyone A**)
  - ✓ Newhouse, T. R. (2017, **Berkeleyone A**)
  - ✓ Maimone, T. J. and Newhouse, T. R (2017, **Andrastin D** and **Terretonin L**)
  - ✓ 黎后华 (2021, **(−)-Berkeleyone A** and **Preaustinoids**)
  - ✓ 谢志翔 (2025, **Berkeleyone A**)
- **Summary**

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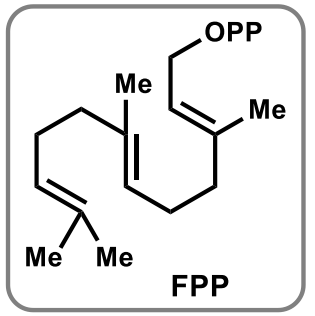
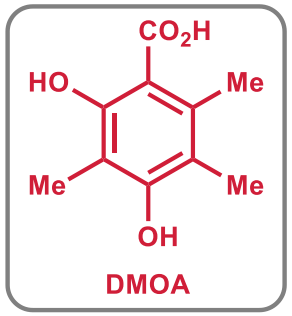
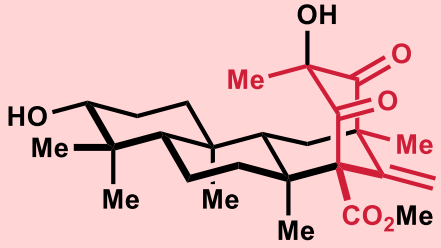
Introduction

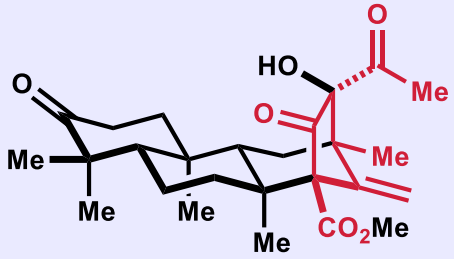
1. Representative (DMOA)-derived meroterpenoids



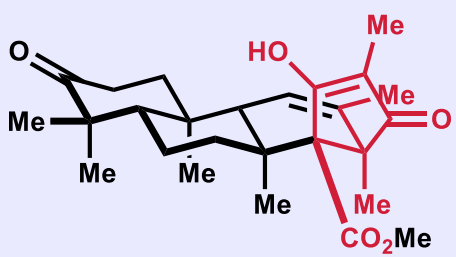




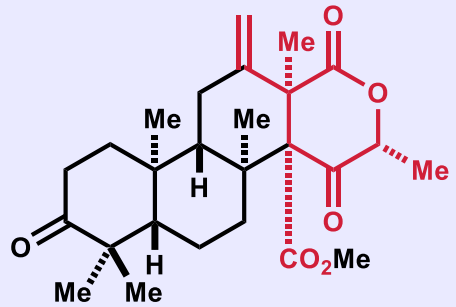
berkeleyone A



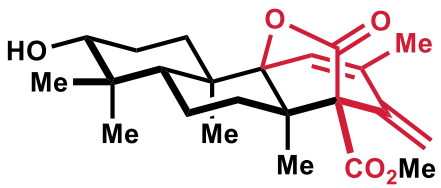
preaustinoid B



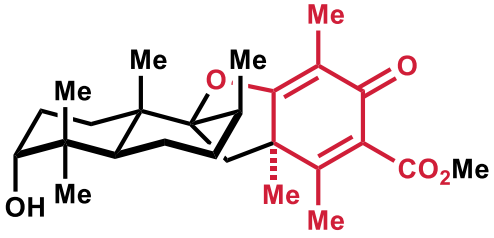
andrastin D



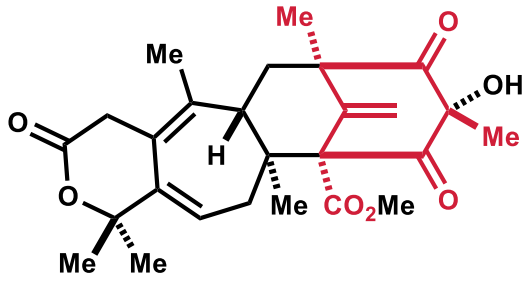
terretonin L



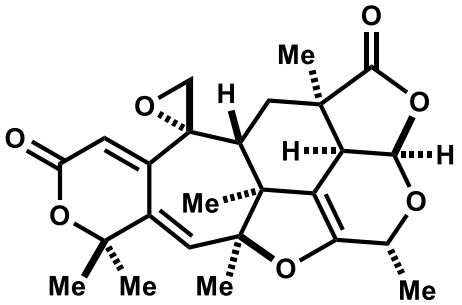
janthinoid A



simplicissin



berkeleydione

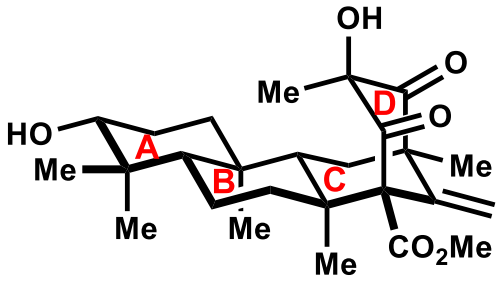


berkeleyacetal D

Springer, J. P.; Dorner, J. W.; Cole, R. J.; Cox, R. H. *J. Org. Chem.* **1979**, *44*, 4852.
Uchida, R.; Shiomi, K.; Inokoshi, J.; Sunazuka, T.; Tanaka, H.; Iwai, Y.; Takayanagi, H.; Omura, S. *J Antibiot.* **1996**, *49*, 418.
Stierle, D. B.; Stierle, A. A.; Hobbs, J. D.; Stokken, J.; Clardy, J. *Org. Lett.* **2004**, *6*, 1049.

Introduction

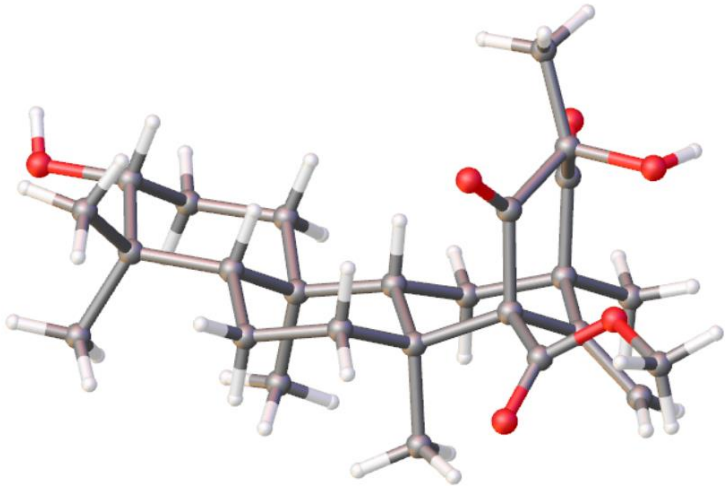
2. Berkeleyone A



berkeleyone A

from the Berkeley Pit Lake fungus
Penicillium rubrum (红色青霉菌)

Berkeley Pit



Structure features

- Dense tetracyclic framework
- Bicyclo[3.3.1]nonane core
- Three quaternary carbon centers within C-ring
- Highly oxidized D-ring without any hydrogen atom substituents

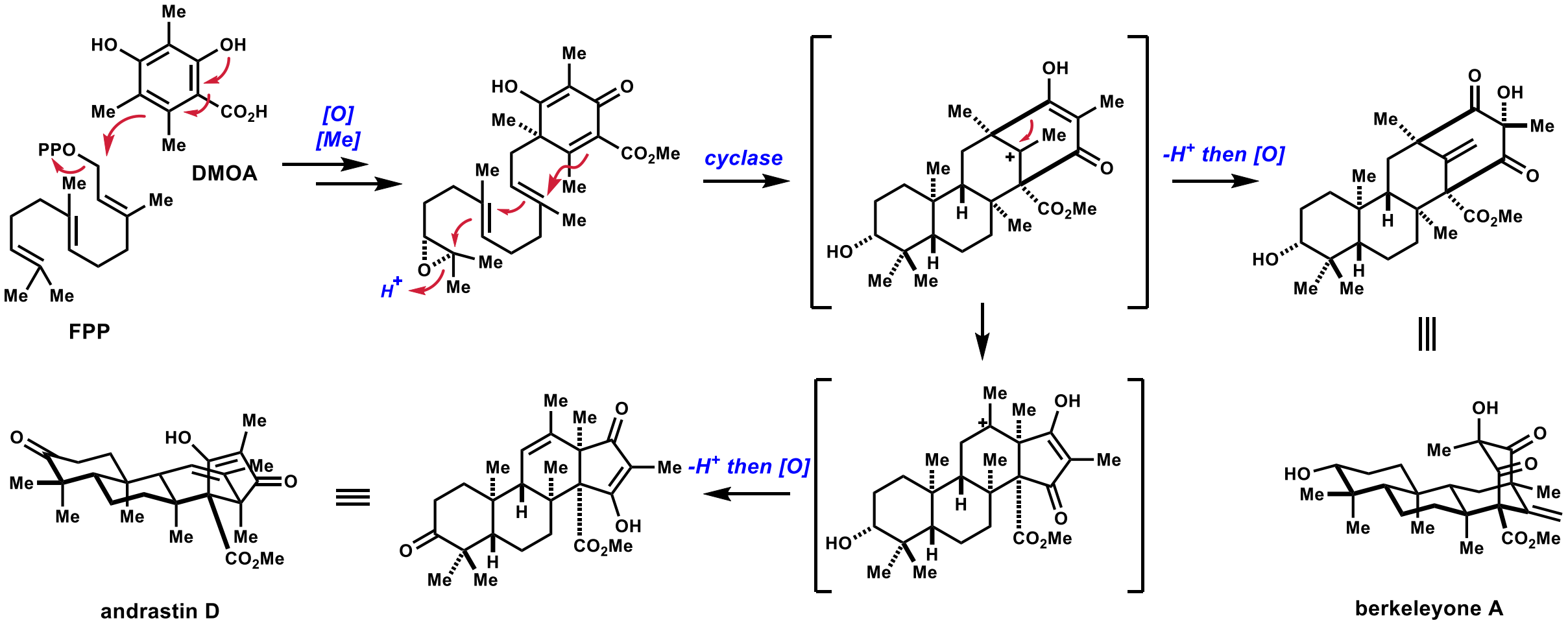
Bioactivity

- ✓ Inhibit caspase-1 (68% inhibition of caspase-1 activity in 100 μg/mL)
- ✓ An inhibitor of IL-1β production (IC50 = 2.7 μM)

Stierle, D. B.; Stierle, A. A.; Patacini, B.; McIntyre, K.; Girtsman, T.; Bolstad, E. *J. Nat. Prod.* **2011**, *74*, 2273.

Introduction

3. Simplified biosynthetic pathway



precursor to > 45 members
DMOA-derived meroterpenoid

precursor to > 50 members
DMOA-derived meroterpenoid

Matsuda, Y.; Abe, I. *Nat. Prod. Rep.* **2016**, *33*, 26.

Matsuda, Y.; Awakawa, T.; Mori, T.; Abe, I. *Curr. Opin. Chem. Biol.* **2016**, *31*, 1.

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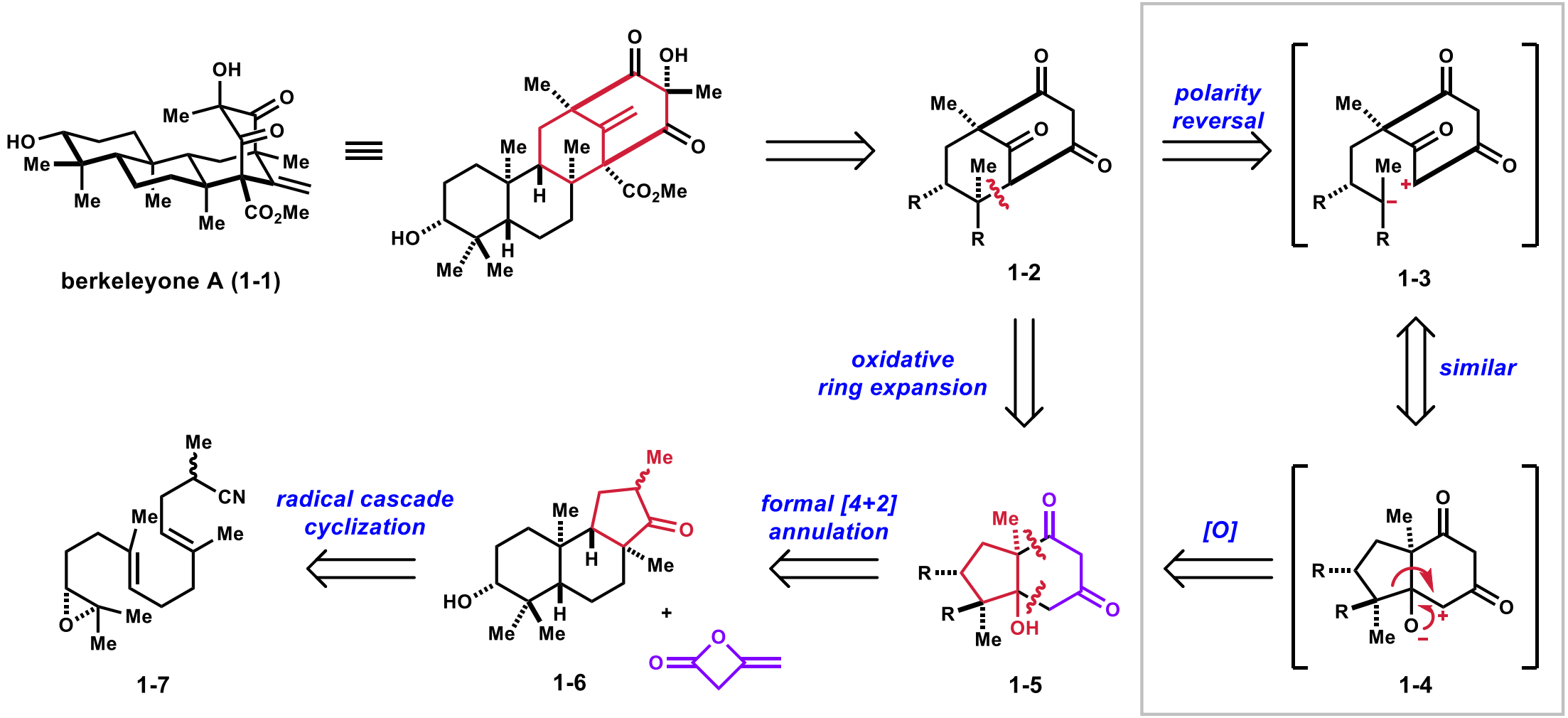
Total Synthesis of Berkeleyone A — *Maimone* (2016)

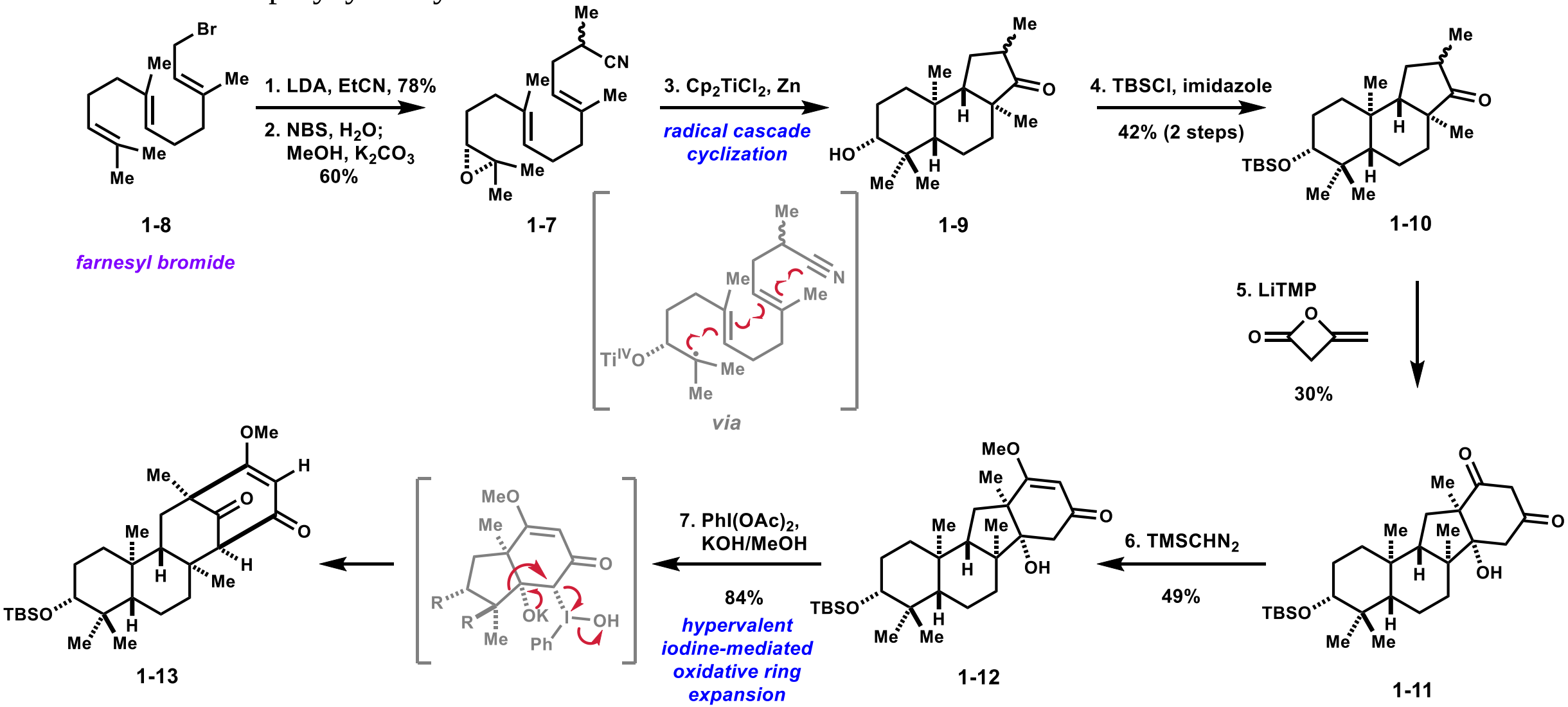
1. Retrosynthetic Analysis



Ting, C. P.; Maimone, T. J. *J. Am. Chem. Soc.* **2015**, *137*, 10516.
Ting, C. P.; Xu, G.; Zeng, X.; Maimone, T. J. *J. Am. Chem. Soc.* **2016**, *138*, 14868.

Total Synthesis of Berkeleyone A — *Maimone* (2016)

2. Construction of polycyclic system

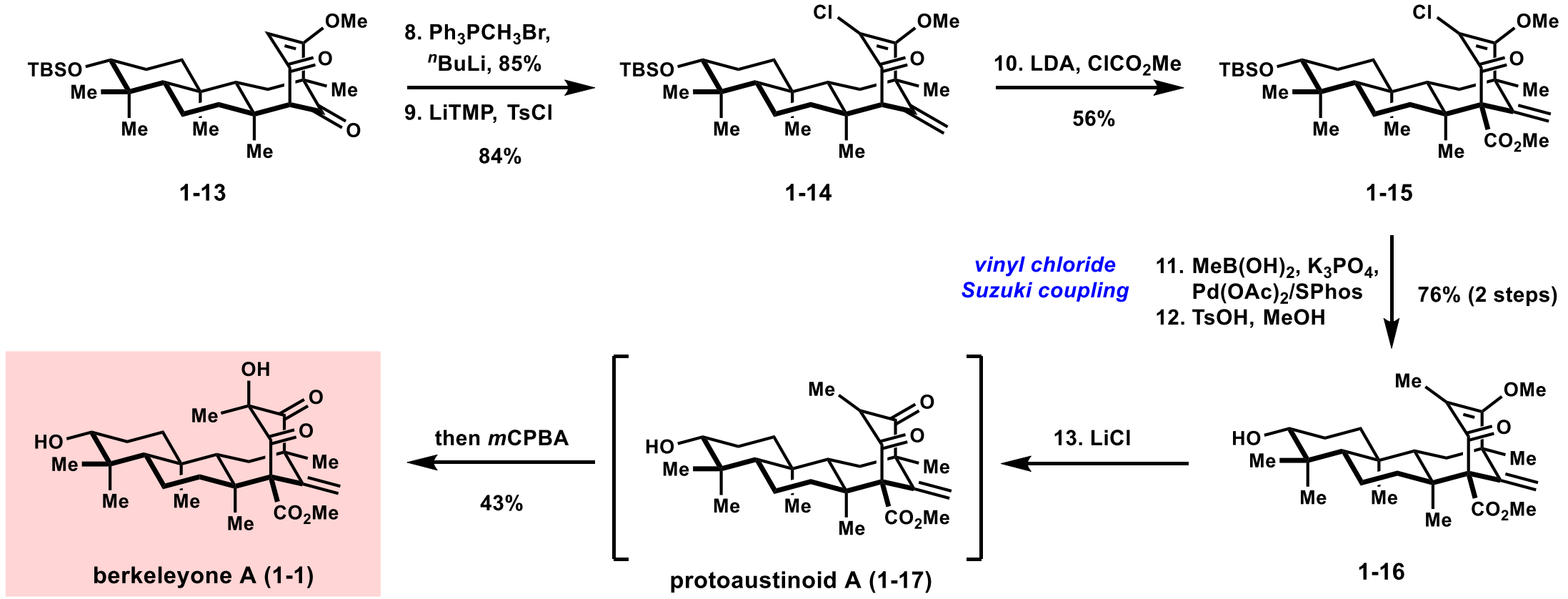


Fernández-Mateos, A.; Teijón, P. H.; Clemente, R. R.; González, R. R.; González, F. S. *Synlett* **2007**, *2007*, 2718.

Ting, C. P.; Xu, G.; Zeng, X.; Maimone, T. J. *J. Am. Chem. Soc.* **2016**, *138*, 14868.

Total Synthesis of Berkeleyone A — *Maimone* (2016)

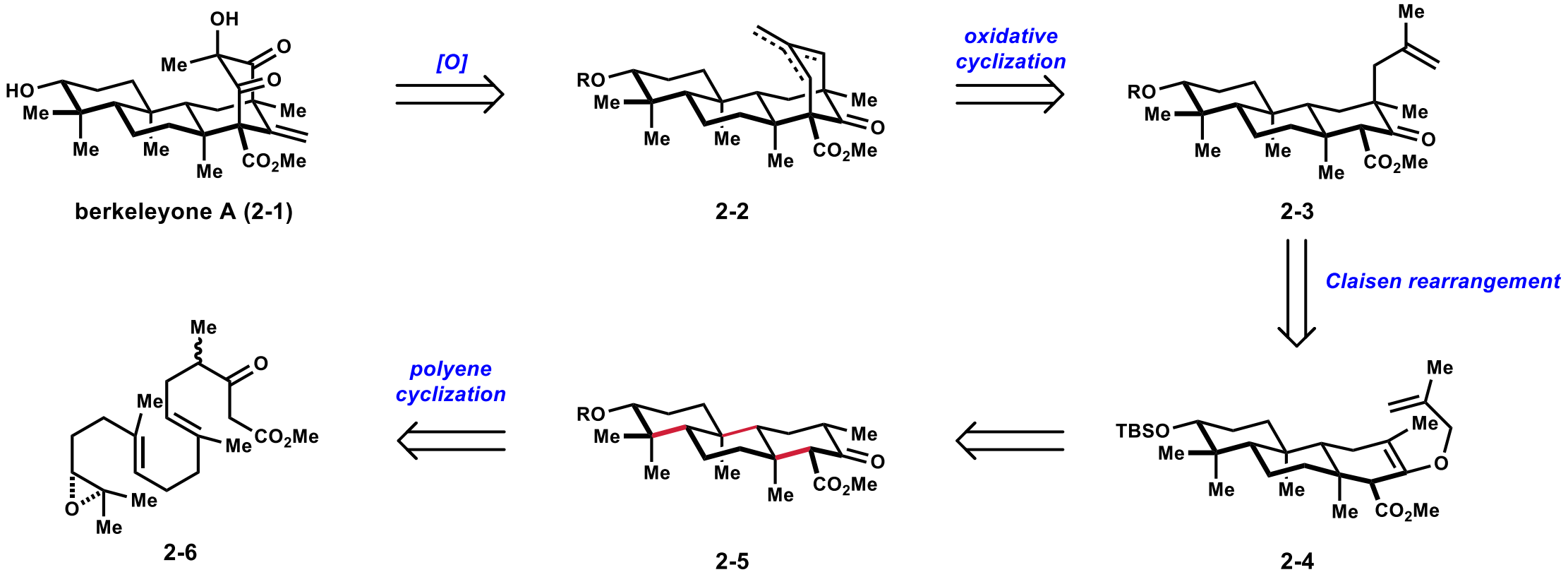
3. Synthesis of Berkeleyone A



Ting, C. P.; Xu, G.; Zeng, X.; Maimone, T. J. *J. Am. Chem. Soc.* **2016**, *138*, 14868.

Total Synthesis of Berkeleyone A — *Newhouse* (2017)

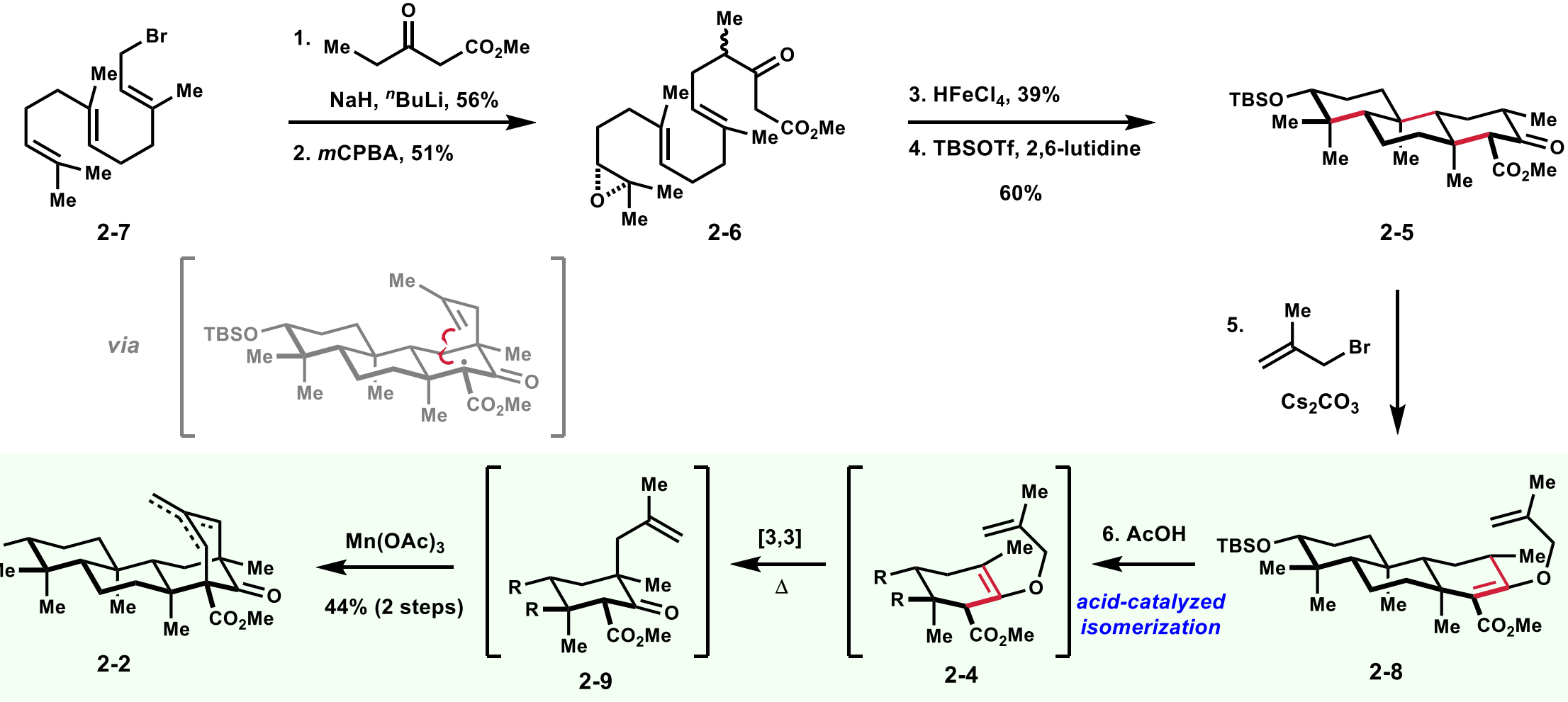
1. Retrosynthetic Analysis



Elkin, M.; Szewczyk, S. M.; Scruse, A. C.; Newhouse, T. R. *J. Am. Chem. Soc.* **2017**, *139*, 1790.

Total Synthesis of Berkeleyone A — *Newhouse* (2017)

2. Construction of polycyclic system

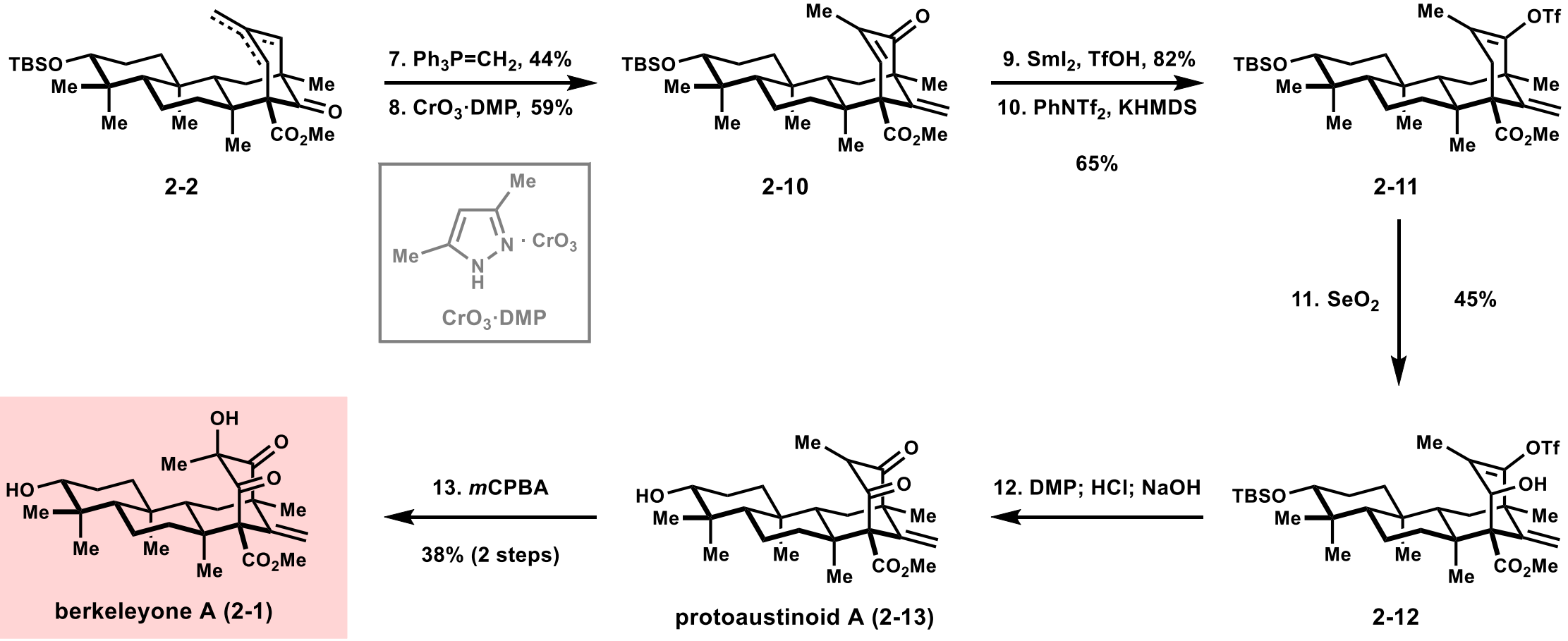


Snider, B. B. *Chem. Rev.* **1996**, *96*, 339.

Elkin, M.; Szewczyk, S. M.; Scruse, A. C.; Newhouse, T. R. *J. Am. Chem. Soc.* **2017**, *139*, 1790.

Total Synthesis of Berkeleyone A — *Newhouse* (2017)

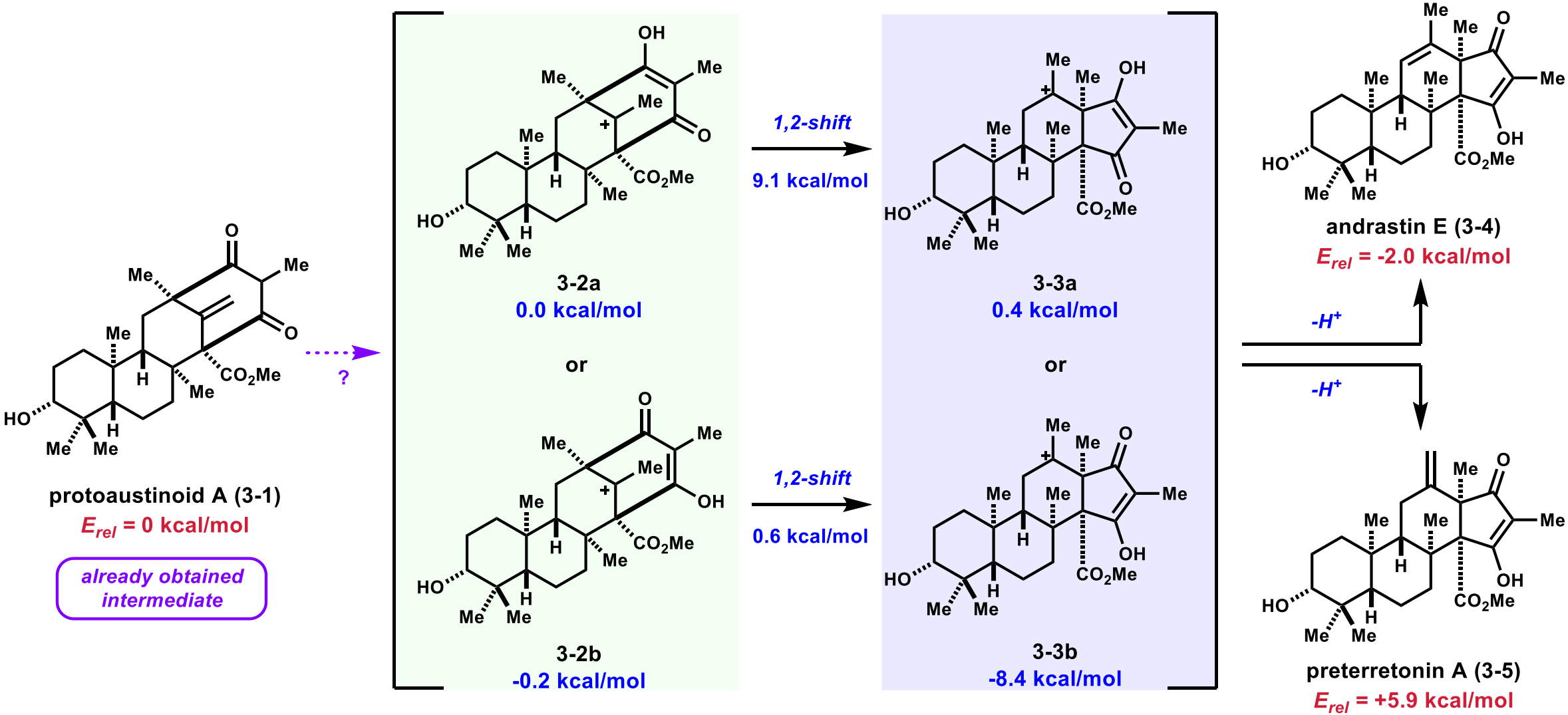
3. Synthesis of Berkeleyone A



Elkin, M.; Szewczyk, S. M.; Scruse, A. C.; Newhouse, T. R. *J. Am. Chem. Soc.* **2017**, *139*, 1790.

Total Synthesis of Andrastin D and Terretonin L — *Maimone* and *Newhouse* (2017)

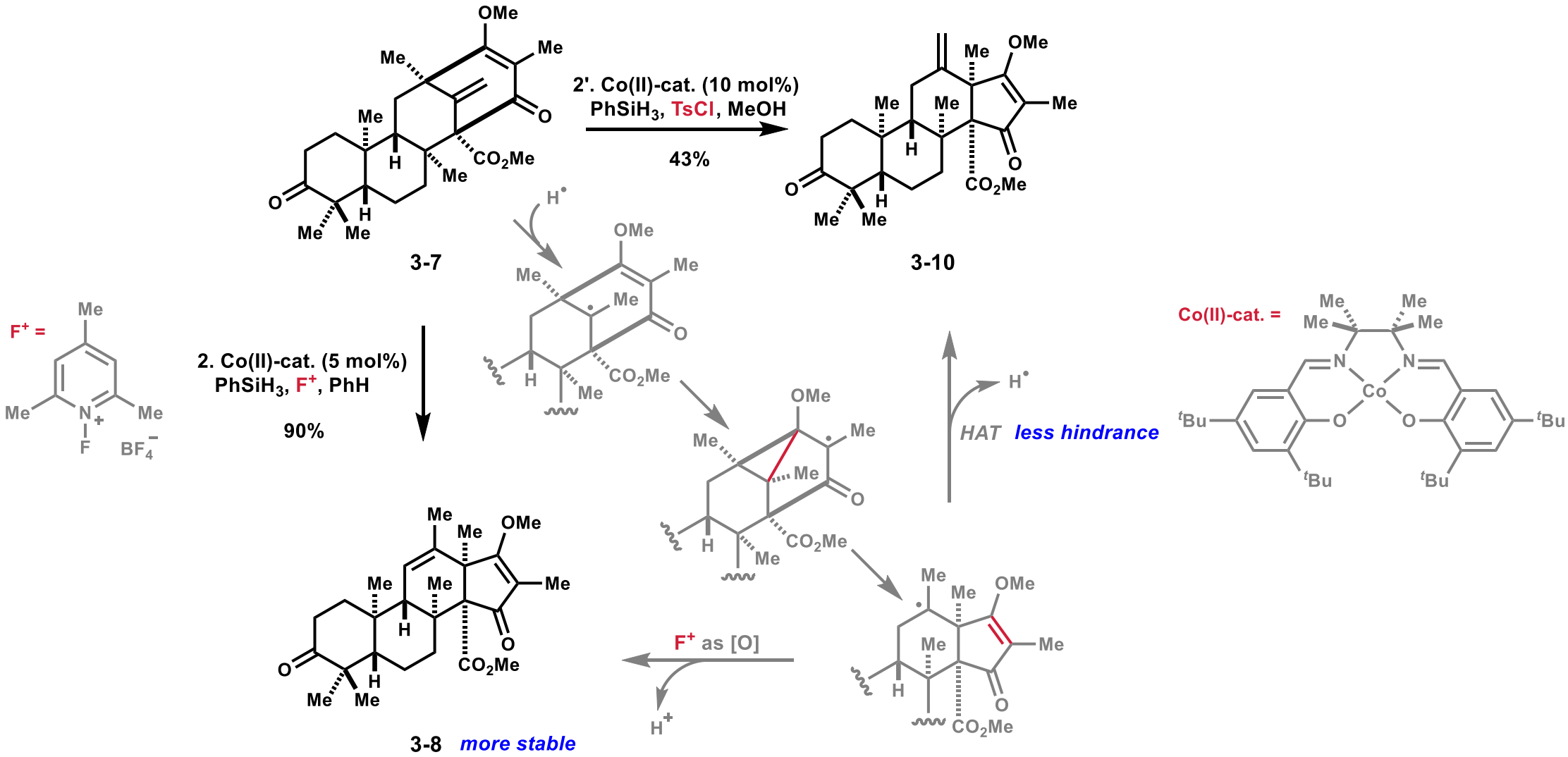
1. Synthetic design



Xu, G.; Elkin, M.; Tantillo, D. J.; Newhouse, T. R.; Maimone, T. J. *Angew. Chem., Int. Ed.* **2017**, *56*, 12498.

Total Synthesis of Andrastin D and Terretonin L — *Maimone* and *Newhouse* (2017)

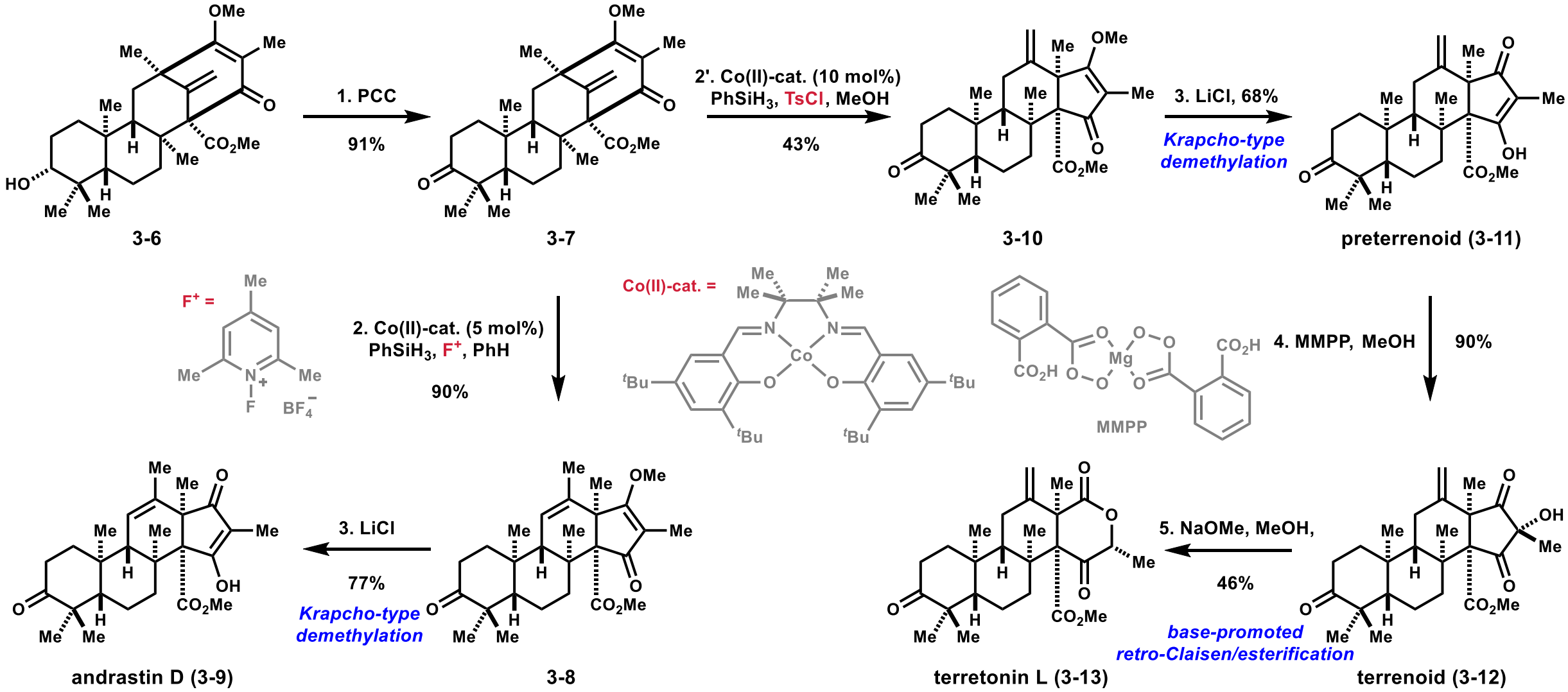
2. [1,2]-shift



Shigehisa, H.; Aoki, T.; Yamaguchi, S.; Shimizu, N.; Hiroya, K. *J. Am. Chem. Soc.* **2013**, *135*, 10306.
Gaspar, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 5758.

Total Synthesis of Andrastin D and Terretonin L — *Maimone* and *Newhouse* (2017)

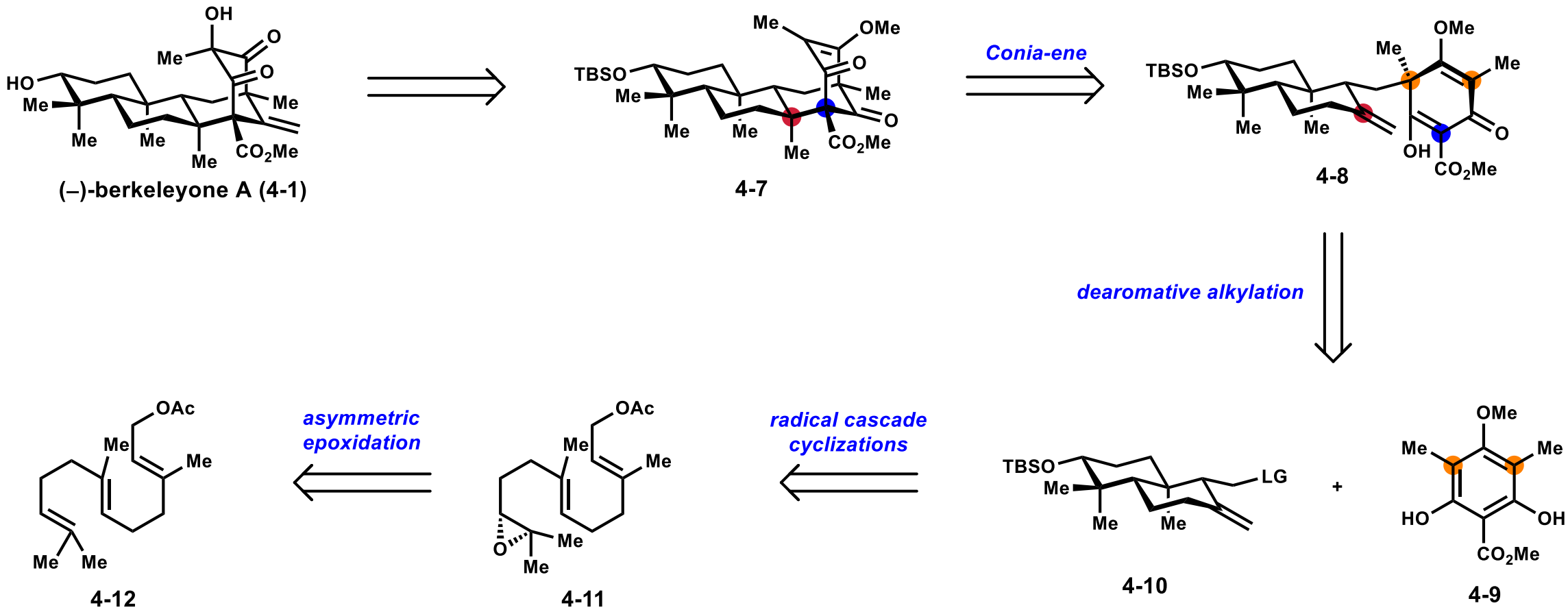
3. Syntheses of Andrastin D and Terretonin L



Xu, G.; Elkin, M.; Tantillo, D. J.; Newhouse, T. R.; Maimone, T. J. *Angew. Chem., Int. Ed.* **2017**, *56*, 12498.

Total Synthesis of (−)-Berkeleyone A and Preaustinoids — 黎后华 (2021)

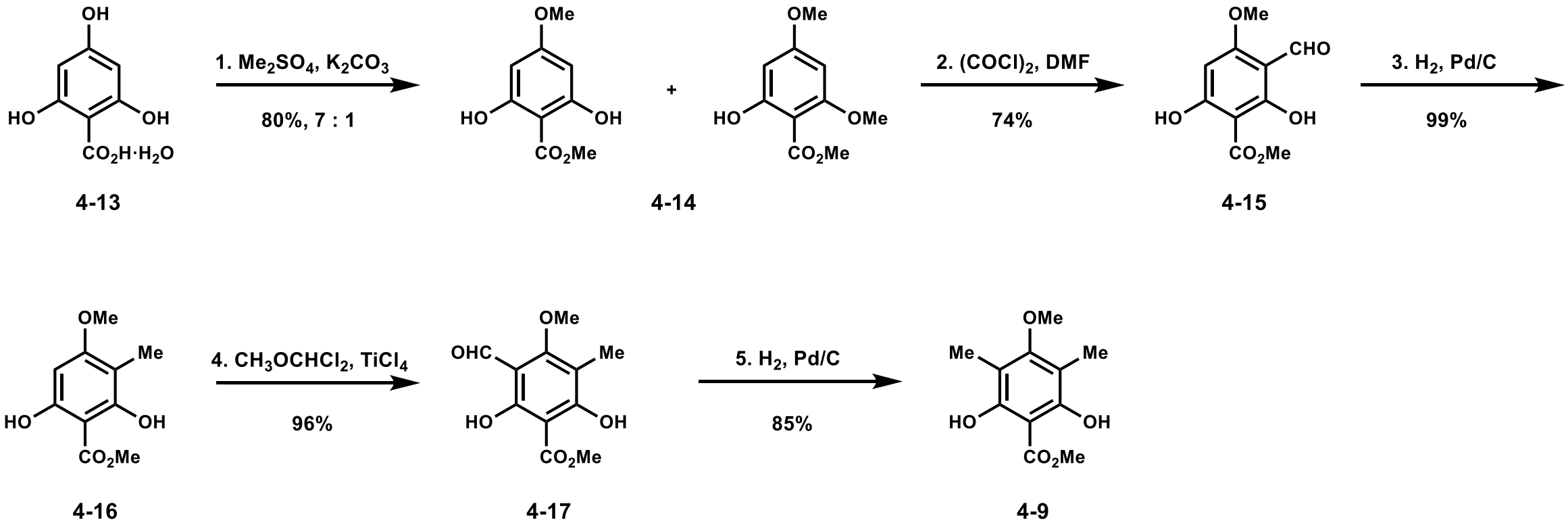
1. Retrosynthetic Analysis



Zhang, Y.; Ji, Y.; Franzoni, I.; Guo, C.; Jia, H.; Hong, B.; Li, H. *Angew. Chem., Int. Ed.* **2021**, *60*, 14869.

Total Synthesis of (−)-Berkeleyone A and Preaustinoids — 黎后华 (2021)

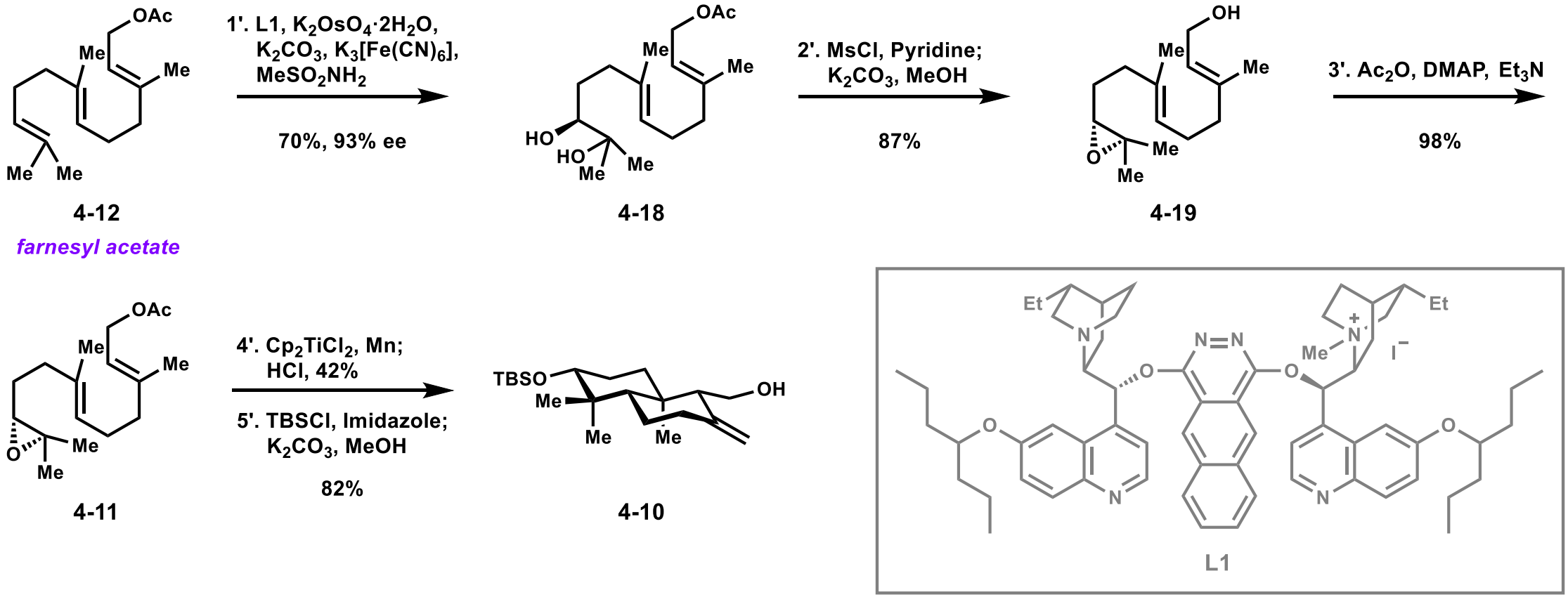
2. Synthesis of fragment **4-9**



Zhang, Y.; Ji, Y.; Franzoni, I.; Guo, C.; Jia, H.; Hong, B.; Li, H. *Angew. Chem., Int. Ed.* **2021**, *60*, 14869.

Total Synthesis of (−)-Berkeleyone A and Preaustinoids — 黎后华 (2021)

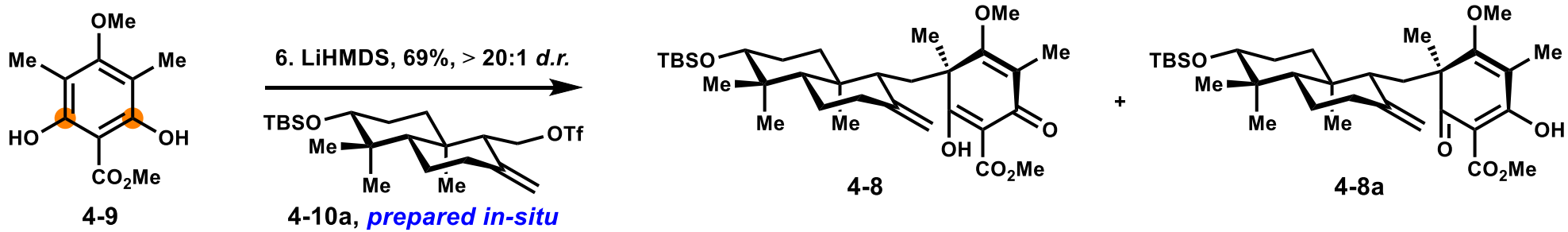
3. Synthesis of fragment **4-10**



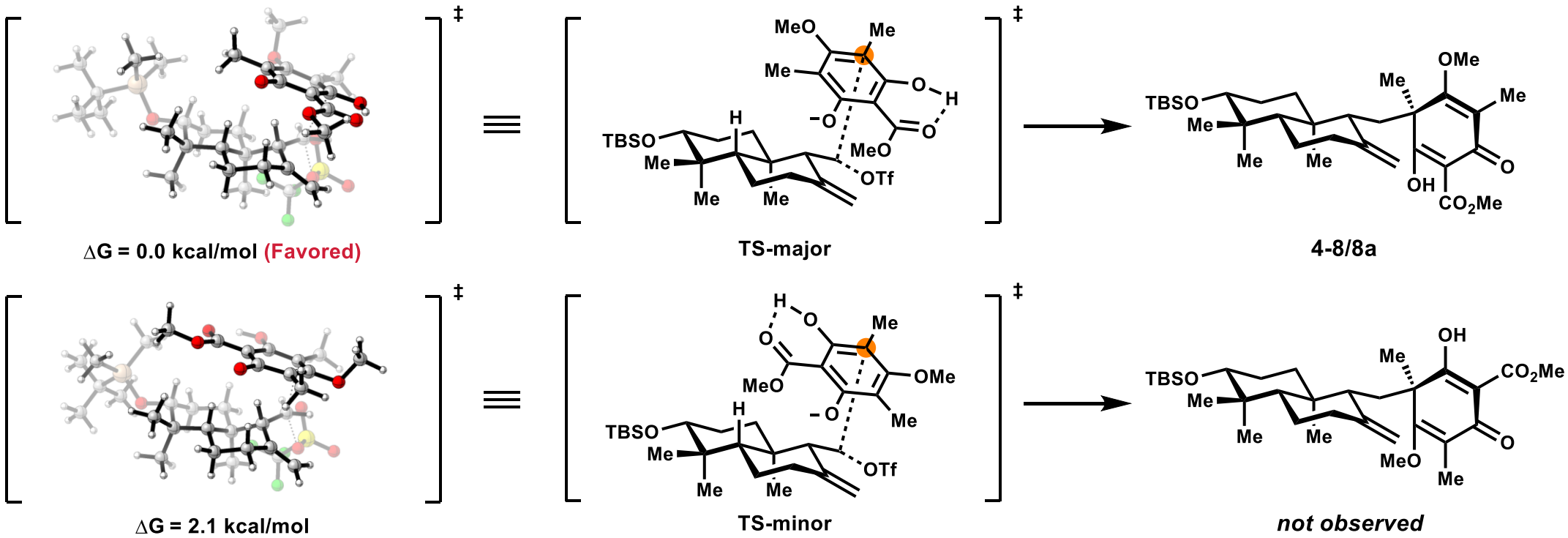
Zhang, Y.; Ji, Y.; Franzoni, I.; Guo, C.; Jia, H.; Hong, B.; Li, H. *Angew. Chem., Int. Ed.* **2021**, *60*, 14869.

Total Synthesis of (−)-Berkeleyone A and Preaustinoids — 黎后华 (2021)

4. Connect fragment **4-9** with fragment **4-10**



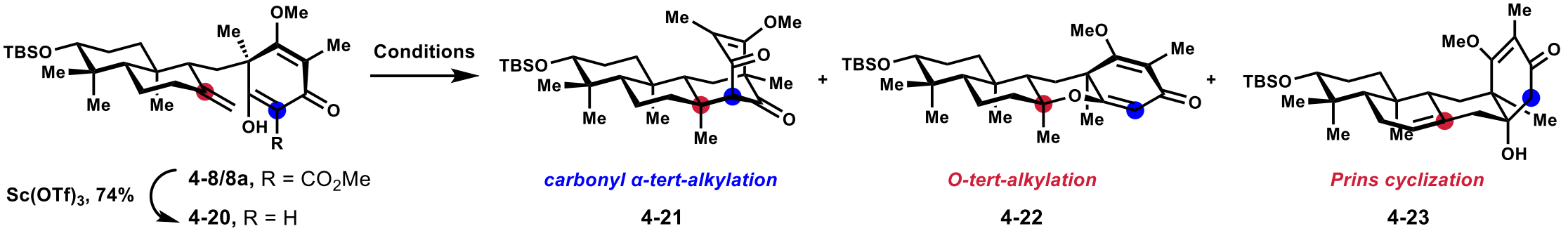
Diastereoselectivity rationale based on DFT calculations



Zhang, Y.; Ji, Y.; Franzoni, I.; Guo, C.; Jia, H.; Hong, B.; Li, H. *Angew. Chem., Int. Ed.* **2021**, *60*, 14869.

Total Synthesis of (−)-Berkeleyone A and Preaustinoids — 黎后华 (2021)

5. Construction of [3.3.1] bridged ring

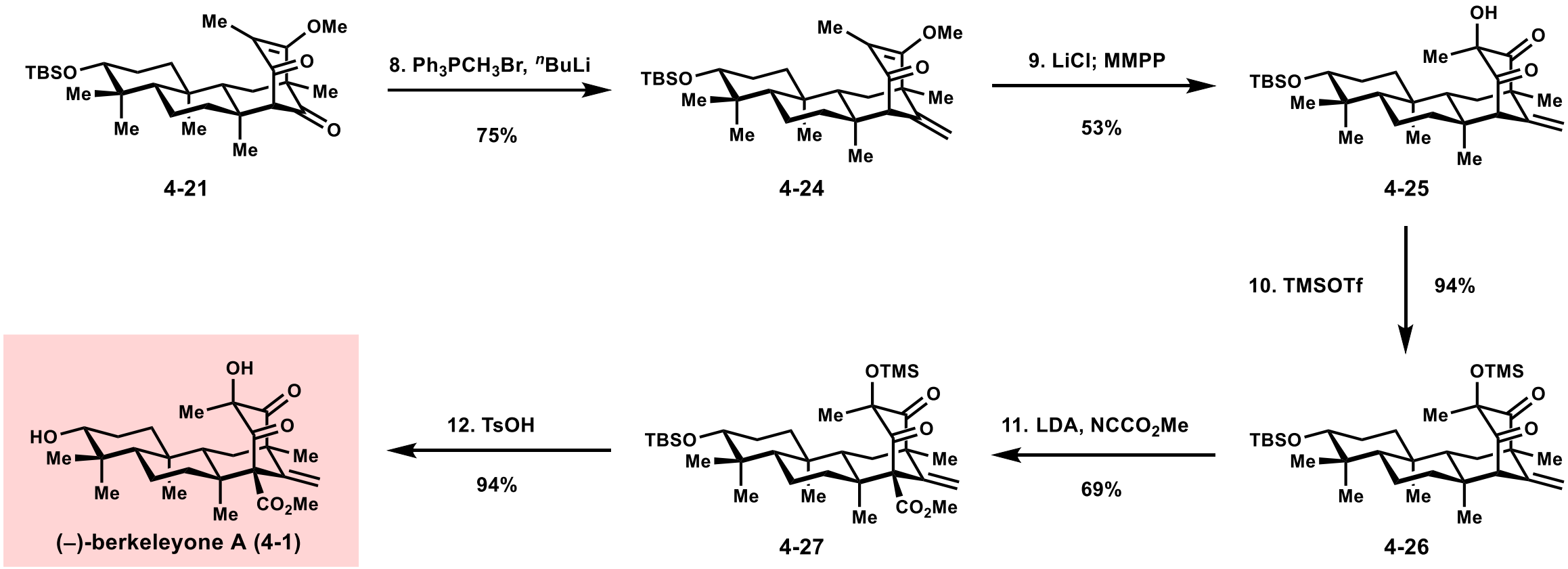


Entry	Conditions	21	22	23
1	**4-8/8a,** Brønsted acids (formic acid, TFA, p-TsOH, etc.)	100% consumption. unidentified decomposed side products		
2	**4-8/8a,** Lewis acids ($SnCl_4$, Et_2AlCl, $BF_3{\cdot}Et_2O$, etc.)			
3	**4-8/8a,** LED 390 nm, MeCN			
4	**4-8/8a,** $Mn(OAc)_3$, $Cu(OAc)_2$, AcOH			
5	**4-20,** Brønsted acids (formic acid, TFA, etc.)	0	–	–
6	**4-20,** $SnCl_4$, DCM, 23 °C	19%	27%	10%
7	**4-20,** $Sc(OTf)_3$, DCM, 23 °C	50%	13%	23%
8	**4-20,** Et_2AlCl, DCM, 23 °C	5%	–	67%
9	**4-8/8a,** $Sc(OTf)_3$, DMSO, 100 °C, then DCM, 23 °C	41%	6%	9%

Zhang, Y.; Ji, Y.; Franzoni, I.; Guo, C.; Jia, H.; Hong, B.; Li, H. *Angew. Chem., Int. Ed.* **2021**, *60*, 14869.

Total Synthesis of (−)-Berkeleyone A and Preaustinoids — 黎后华 (2021)

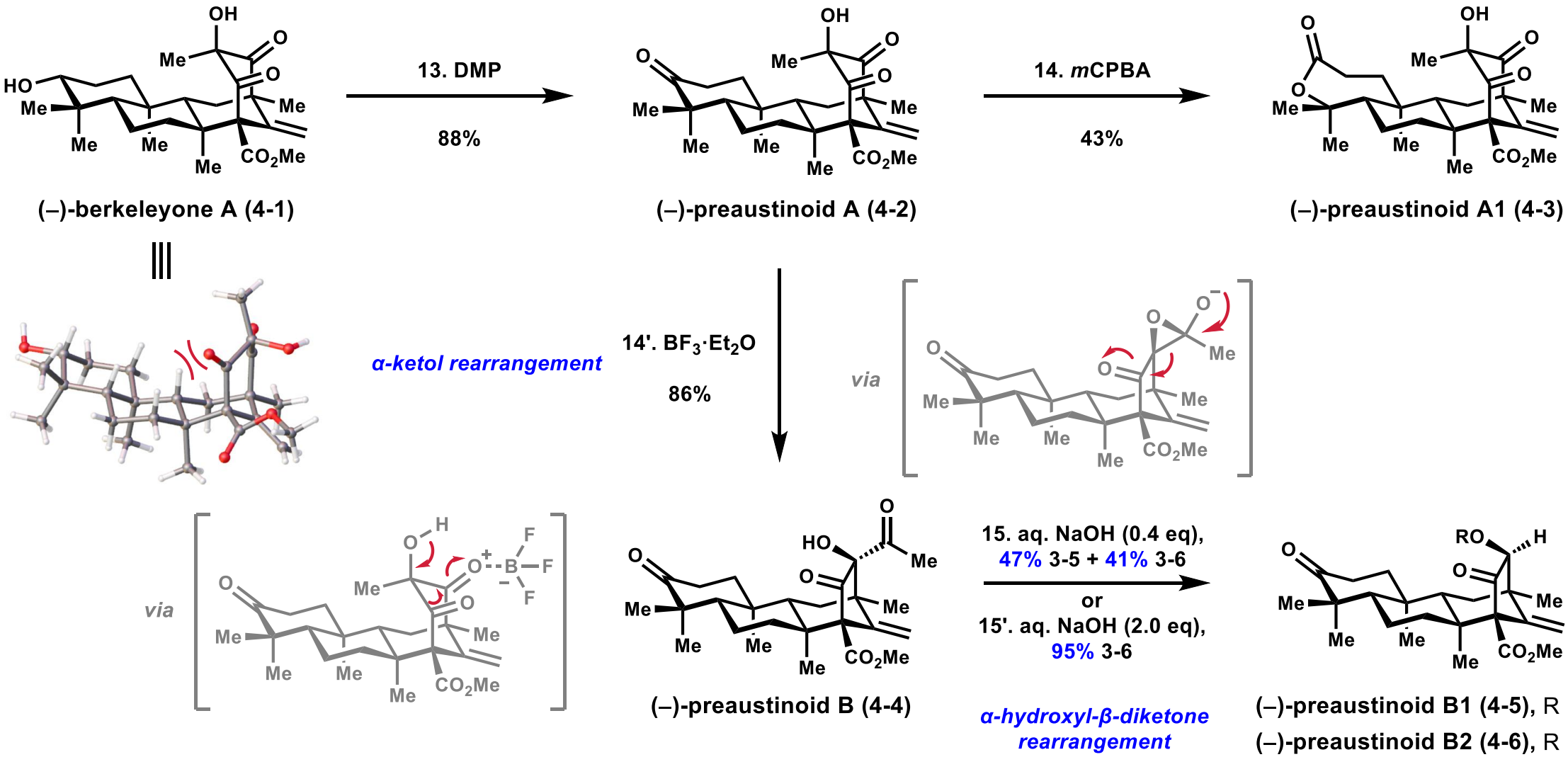
6. Synthesis of (−)-Berkeleyone A



Zhang, Y.; Ji, Y.; Franzoni, I.; Guo, C.; Jia, H.; Hong, B.; Li, H. *Angew. Chem., Int. Ed.* **2021**, *60*, 14869.

Total Synthesis of (−)-Berkeleyone A and Preaustinoids — 黎后华 (2021)

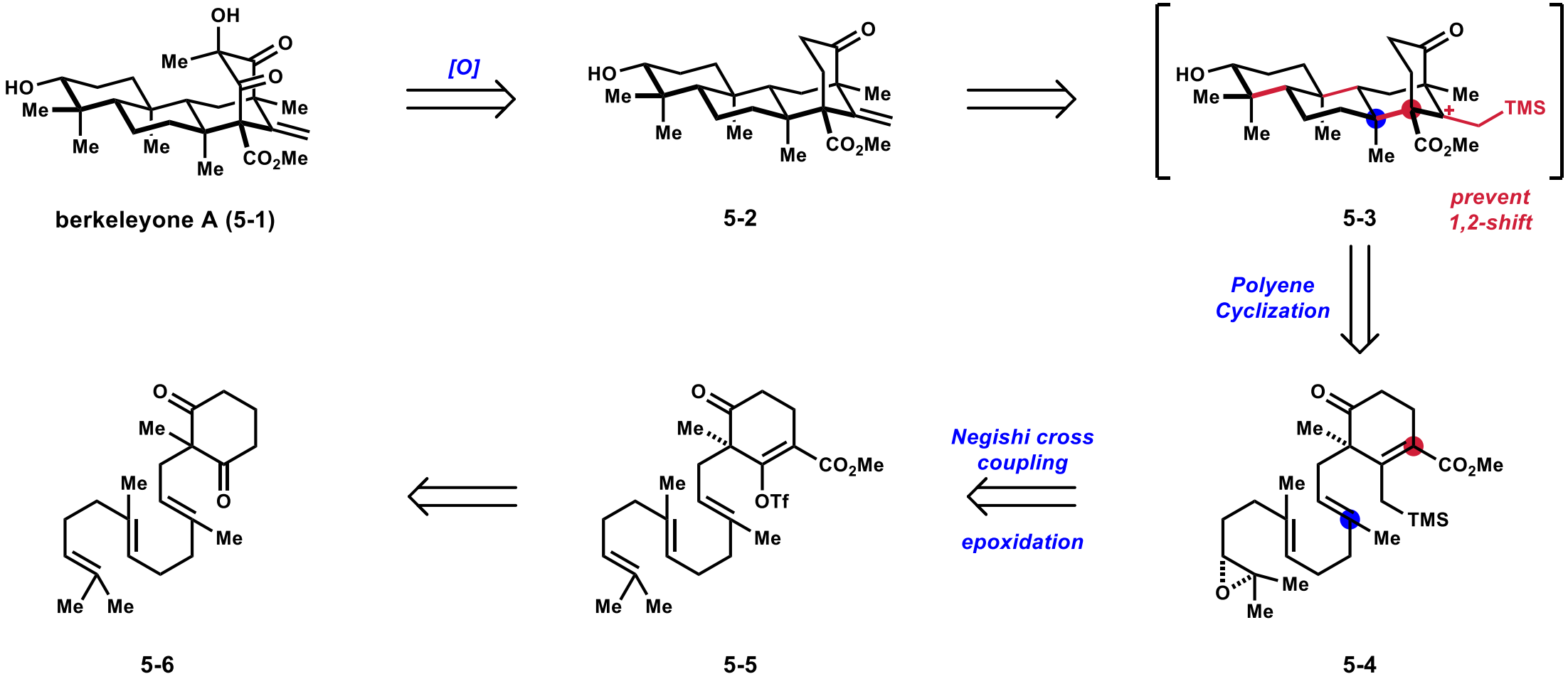
7. Synthesis of Preaustinoids



Zhang, Y.; Ji, Y.; Franzoni, I.; Guo, C.; Jia, H.; Hong, B.; Li, H. *Angew. Chem., Int. Ed.* **2021**, *60*, 14869.

Total Synthesis of Berkeleyone A — 谢志翔 (2025)

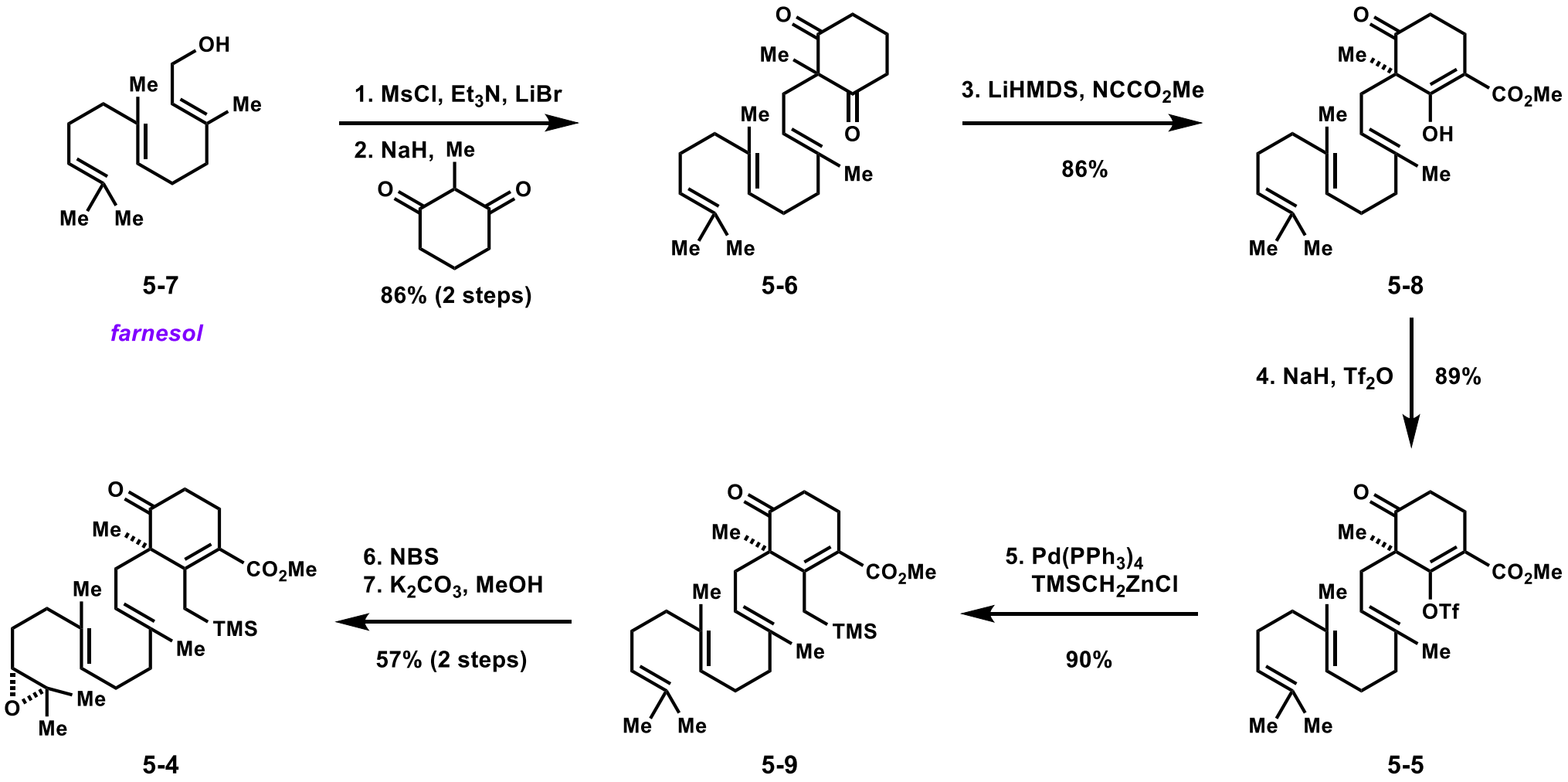
1. Retrosynthetic Analysis



Suzuki, K.; Yamakoshi, H.; Nakamura, S. *Chem.-Eur J.* **2015**, *21*, 17605.
Li, X.; Chang, Z.; Duan, S.; Xie, Z. *Angew. Chem., Int. Ed.* **2025**, *64*, e202416211.

Total Synthesis of Berkeleyone A — 谢志翔 (2025)

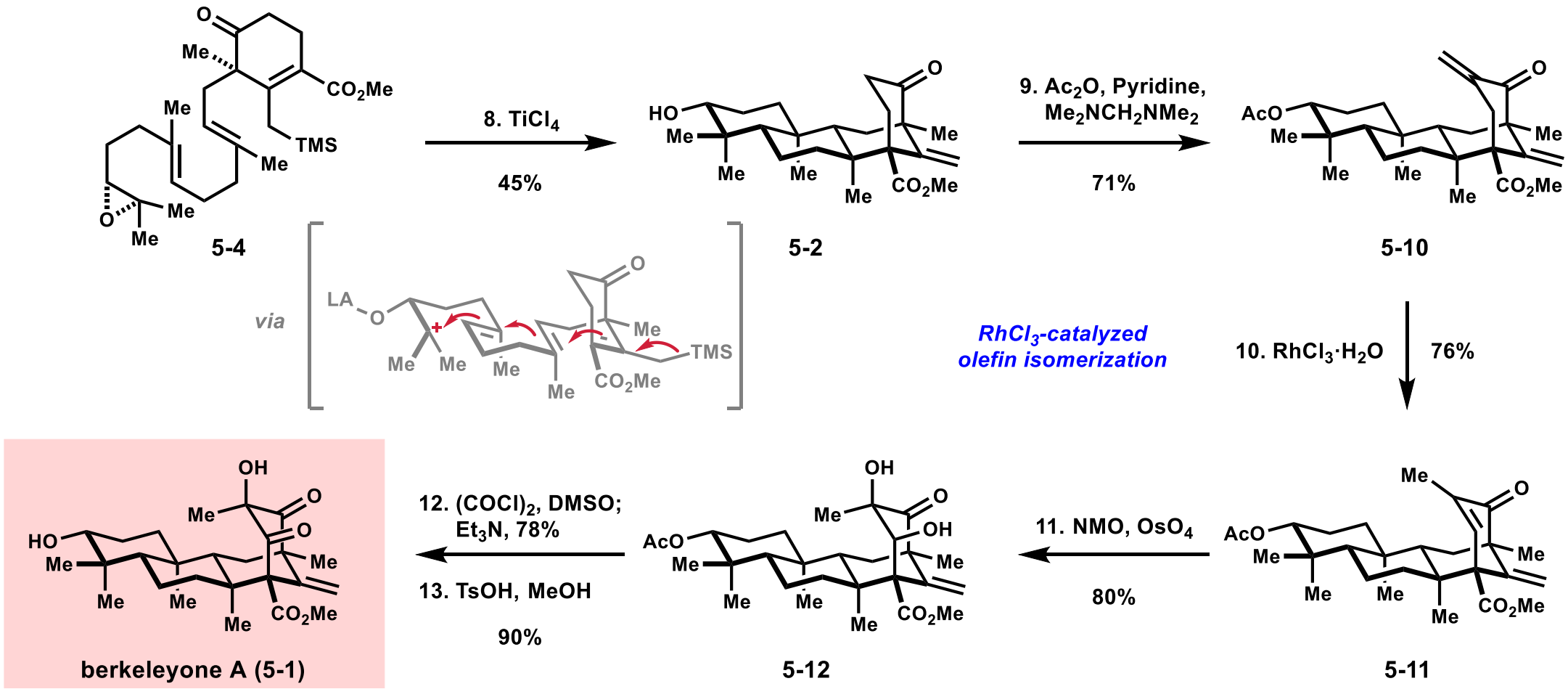
2. Synthesis of **5-4**



Li, X.; Chang, Z.; Duan, S.; Xie, Z. *Angew. Chem., Int. Ed.* **2025**, *64*, e202416211.

Total Synthesis of Berkeleyone A — 谢志翔 (2025)

3. Total Synthesis of Berkeleyone A



Li, X.; Chang, Z.; Duan, S.; Xie, Z. *Angew. Chem., Int. Ed.* **2025**, *64*, e202416211.

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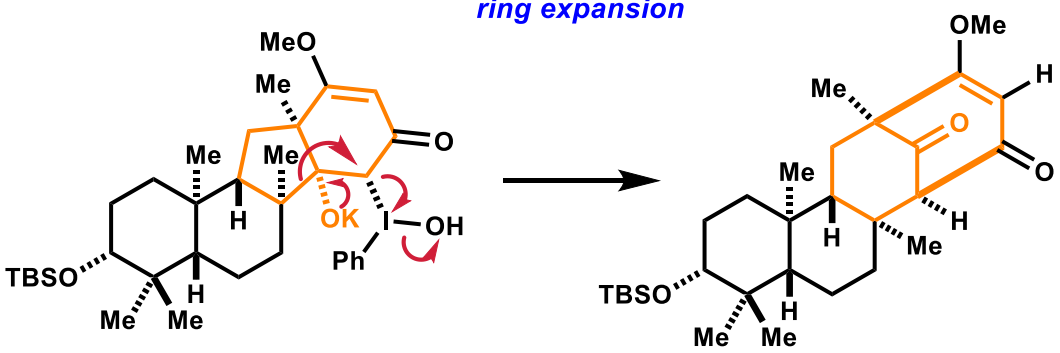
  - ✓ 谢志翔 (2025, **Berkeleyone A**)
- **Summary**

Summary

Maimone, T. J. (2016)

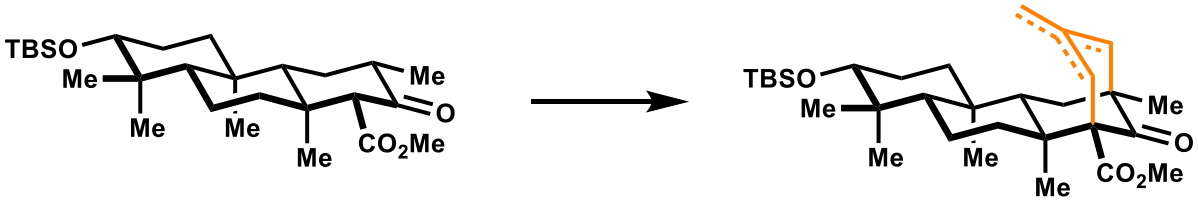
oxidative ring expansion



6/5-fused ring —*rear.*→ [3.3.1] bridged ring

Newhouse, T. R. (2017)

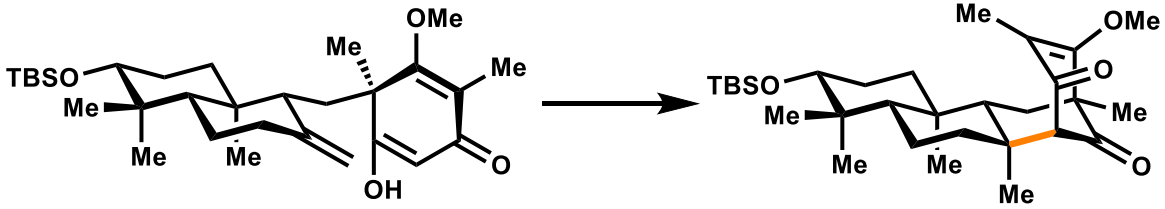
Claisen rearrangement/ oxidative cyclization



install a new ring between *α*-positions of the carbonyl group

黎后华 (2021)

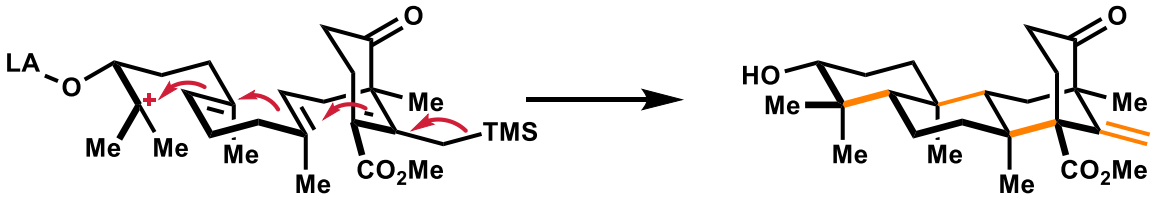
carbonyl α-tert-alkylation



connect a 6/6 fused ring with a highly oxidized ring

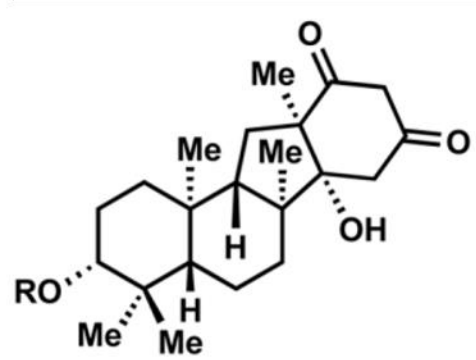
谢志翔 (2025)

polyene cyclization

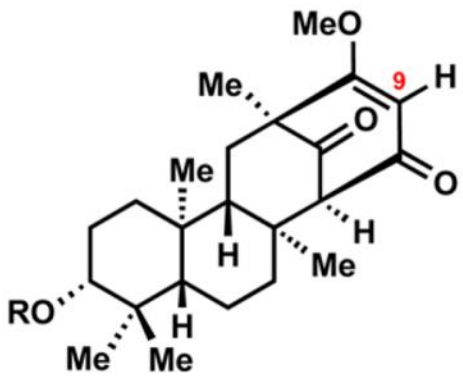


bioinspired Lewis acid-catalyzed polyene cyclization

Thanks for your kind attention



16

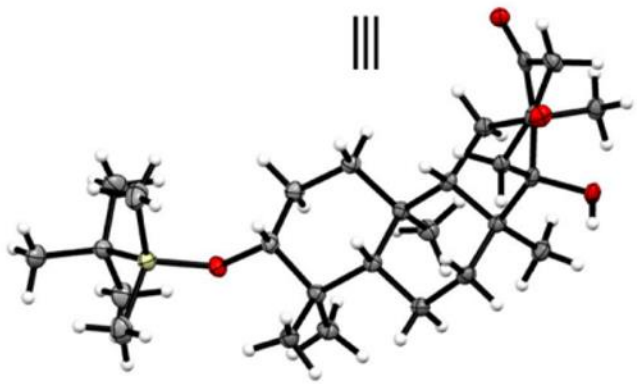


27

f. $TMSCHN_2$
49%

g. $PhI(OAc)_2$
KOH/MeOH
84%

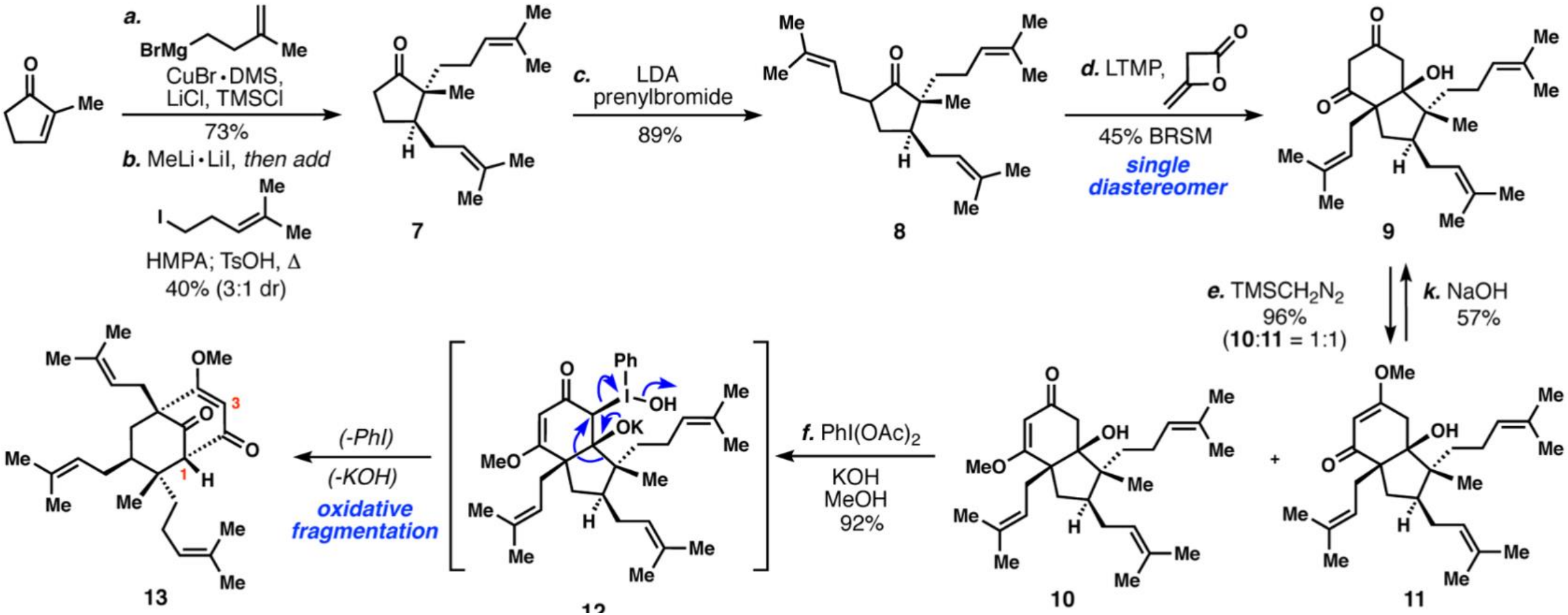
oxidative rearrangement

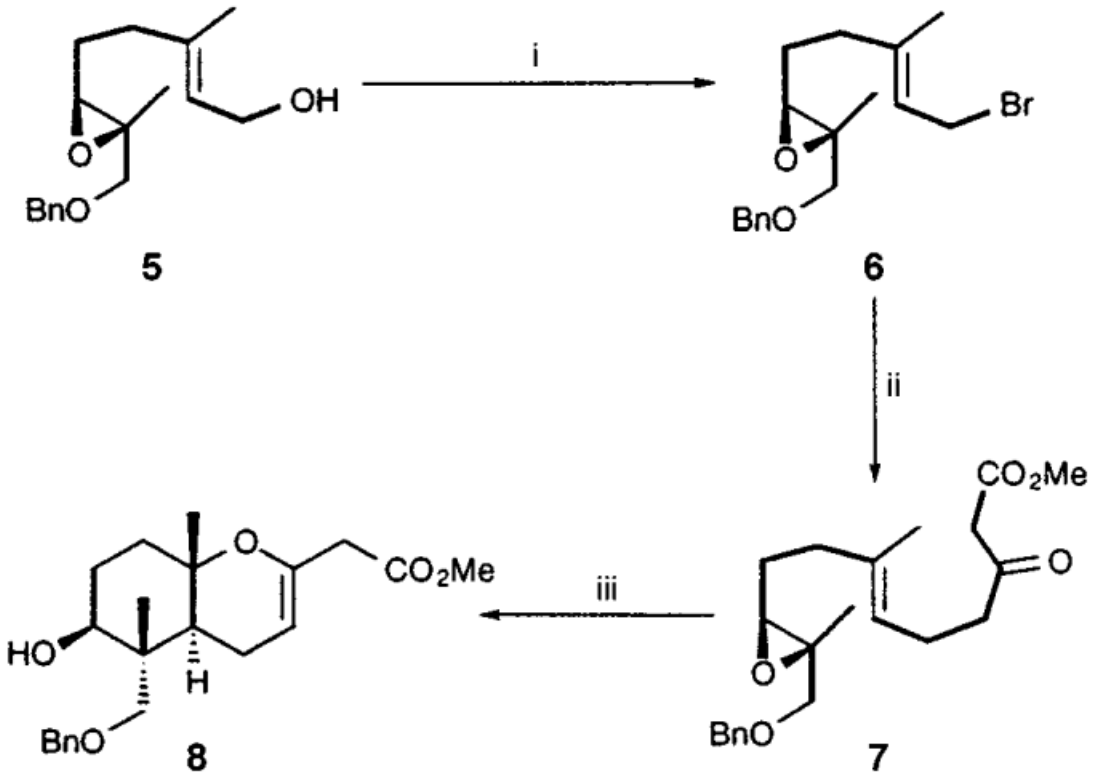


16 [X-ray]

Following *O*-methylation of the 1,3-diketone with trimethylsilyldiazomethane,[21] we

(21) A regioisomeric vinylogous ester was also formed in this reaction and accounted for the majority of the mass balance.

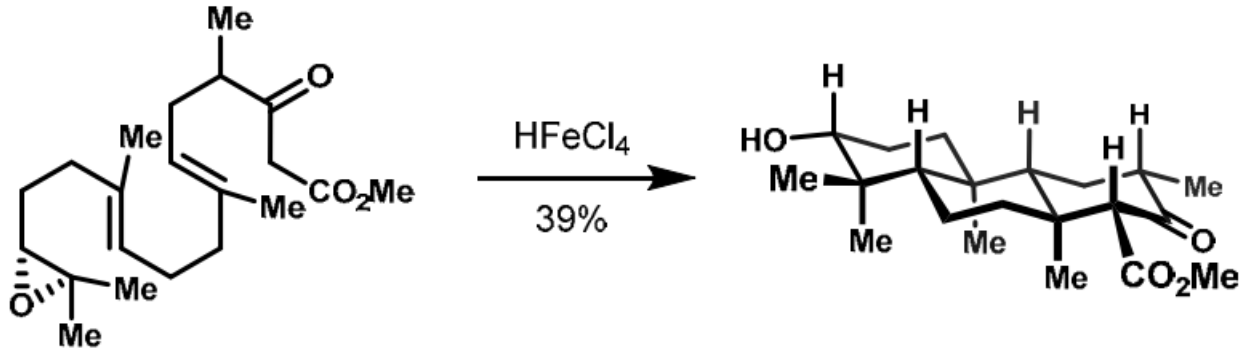

a.
BrMg
Me
CuBr•DMS,
LiCl, TMSCl
73%
b. MeLi•LiI, then add
I
Me
HMPA; TsOH, Δ
40% (3:1 dr)
7
c. LDA
prenylbromide
89%
8
d. LTMP,
45% BRSM
single
diastereomer
9
e. TMSCH2N2
96%
(10:11 = 1:1)
k. NaOH
57%
10
11
f. PhI(OAc)2
KOH
MeOH
92%
12
(-PhI)
(-KOH)
oxidative
fragmentation
13



yield. Upon treatment of β-keto ester **7** with $BF_3 \cdot OEt_2$ in CH_2Cl_2, epoxy-olefin cyclisation ensued but the oxabicycle **8** was formed exclusively.[10] To promote carbon over oxygen cyclisation, the carbonyl group had to be masked or removed and several possibilities were apparent from the literature. (i)

Unfortunately, polycyclization events that initiate with epoxide groups are most commonly conducted using Lewis-acids, whereas *β*-ketoester terminating groups generally require Brønsted-acids to facilitate carbon-based, rather than oxygen-based, nucleophilic attack by the *β*-ketoester.[16] Perhaps because of these opposing requirements, analysis of the literature indicates that, to the best of our knowledge, no such cyclization reactions have previously been reported, and instead multistep solutions are pursued.[16] Such a transformation, were it possible, would rapidly lead to the necessary tricycle **7** from readily available starting materials.

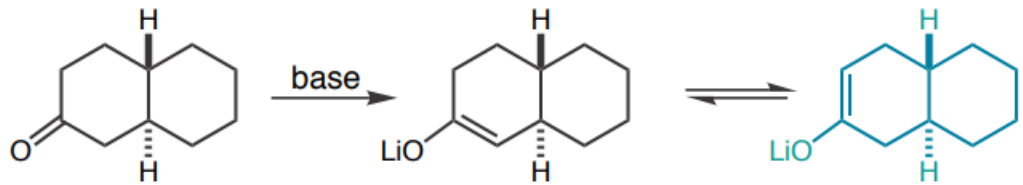
With the precursor **8** in hand, a broad examination of Lewis- and Brønsted-acid promoters was conducted, but our initial efforts were plagued by the formation of a range of undesired byproducts consistent with previous reports on similar cyclization reactions.[16] It was ultimately found that the yellow ether-solvated complex of $HFeCl_4$,[18] prepared in situ by treating a heterogeneous mixture of $FeCl_3$ in CH_2Cl_2 with anhydrous HCl in Et_2O, elicited the desired cyclization reaction to afford tricyclic compound **7** in 39% yield. This unique Brønsted acid with the noncoordinating $[FeCl_4]^-$ anion was found to be superior to either $FeCl_3$ or anhydrous HCl alone, in addition to the numerous other conditions explored. The majority of the berkeleyone scaffold, 3 carbon−carbon bonds and 6 stereogenic centers, is constructed in this key cyclization. To the best of our knowledge, this transformation is the first example of an epoxide-initiated, *β*-ketoester terminated polycyclization that provides the desired mode of cyclization at carbon.[16]



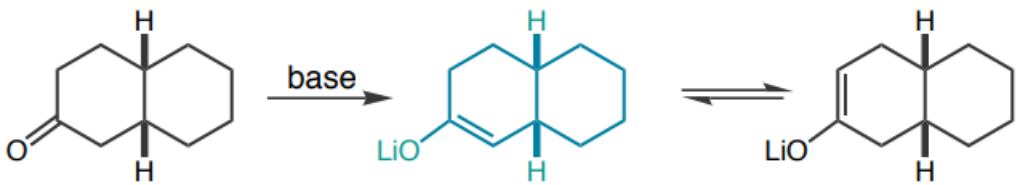
8 7

Tricycle 7: Anhydrous $FeCl_3$ (347 mg, 2.14 mmol, 1.6 equiv) was added to a round–bottomed flask with a stir bar. CH_2Cl_2 (145 mL, 0.01 M) was added to give a suspension, followed by anhydrous HCl as a solution in Et_2O (2.0 M, 0.70 mL, 1.4 mmol, 1.0 equiv) to yield a yellow, light-sensitive solution. The mixture was cooled to –78 °C using a dry–ice acetone bath and acyclic precursor **8** (477 mg, 1.36 mmol, 1.0 equiv) was added to form a deep purple solution. After the reaction was stirred at –78 °C for 30 minutes, the bath was removed and the reaction mixture was allowed to warm to ambient temperature and stirred for an additional 12 hours. The reaction was quenched by the addition of sat. aq. $NaHCO_3$ (50 mL) and diluted with EtOAc (200 mL). The organic and aqueous layers were separated and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure by rotary evaporation. The crude material thus obtained was purified by flash column chromatography (SiO_2, hexanes/EtOAc = 1:4 → 1:1) affording **7** (184 mg, 39%) as a pale-yellow foam.

Observation:
Relative enolate stability correlates to ring junction stereochemistry

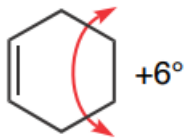


ratio: 13 : 87

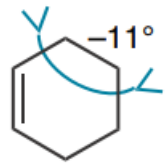


ratio: 70 : 30

House, *JOC* **1965**, *30*, 1341



For Φ_P

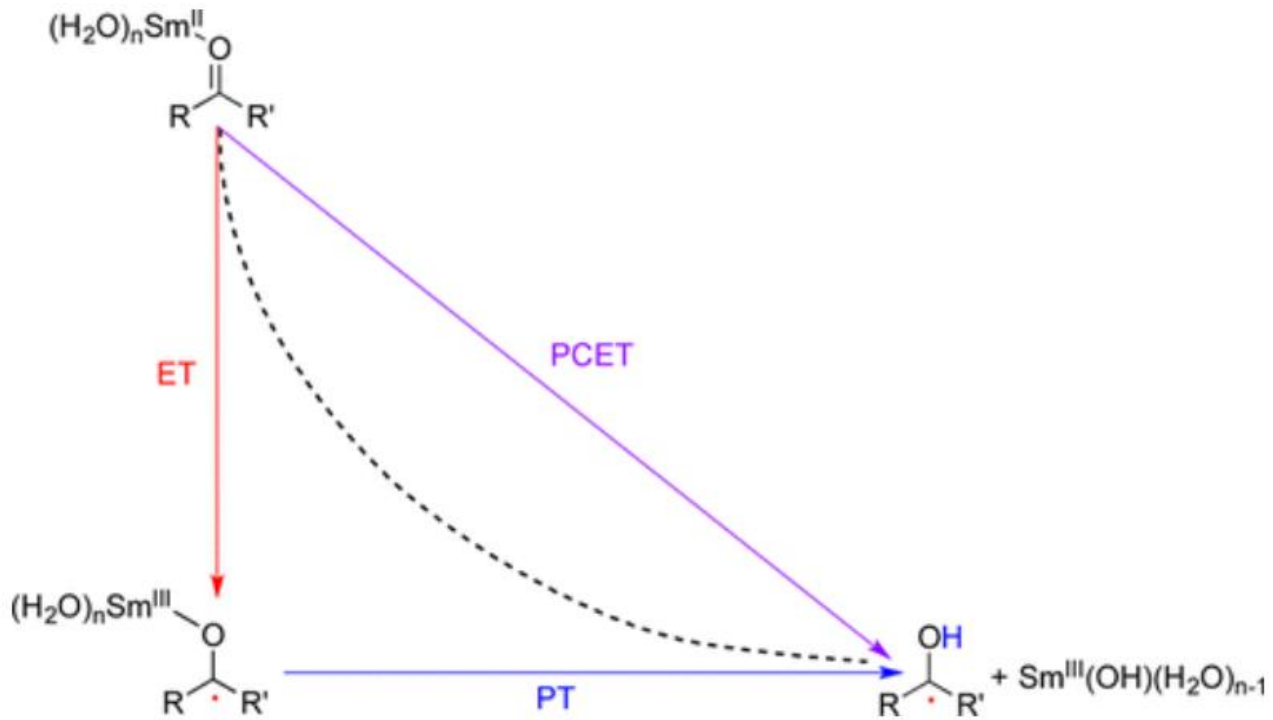


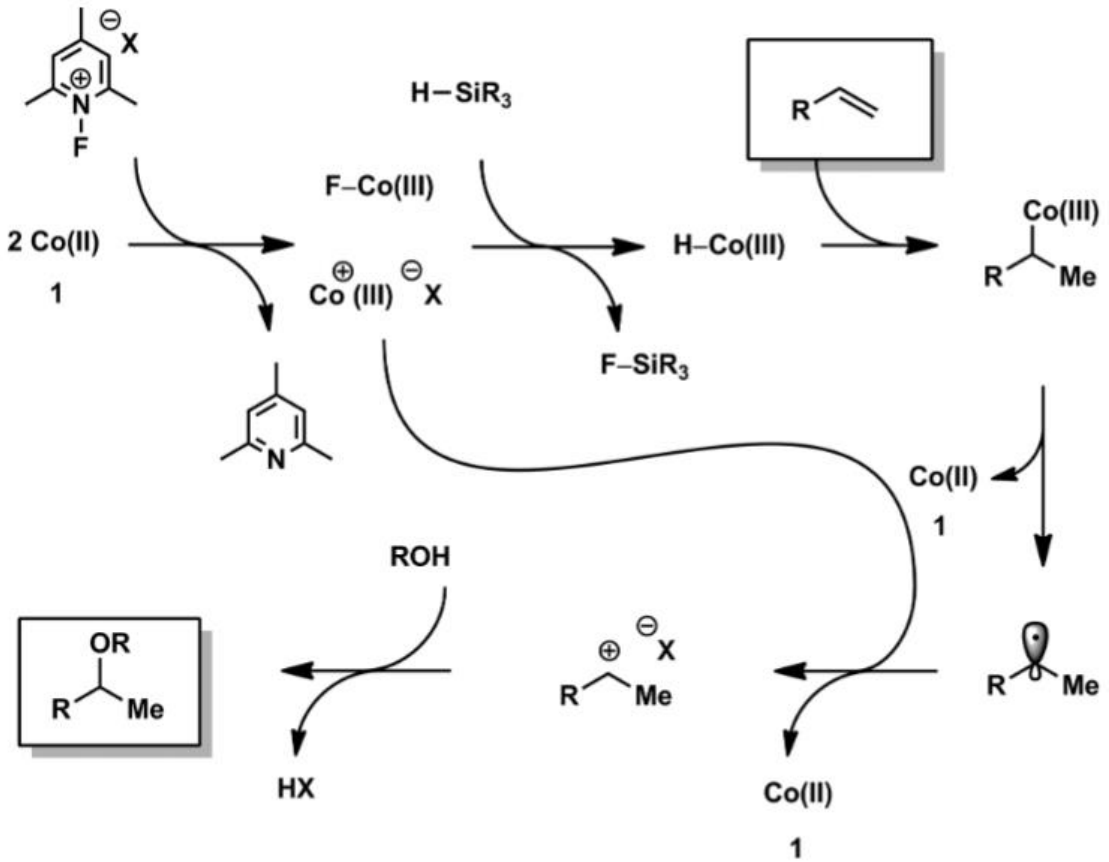
For Φ_M

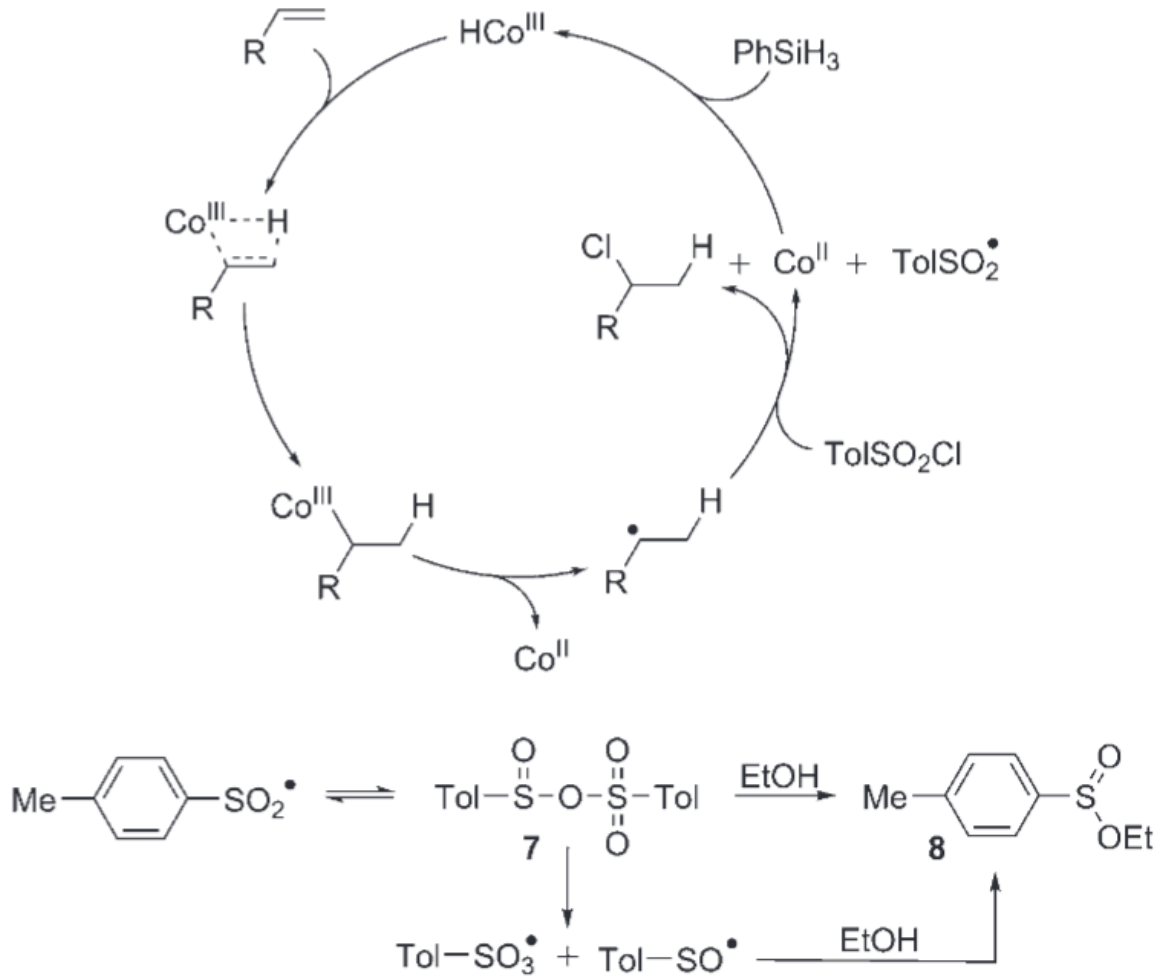
Preparation of the salt–free methylene triphenylphosphorane:[4] To a Schlenk flask equipped with a stir bar was added NaH (60% dispersion in mineral oil, 2.76 g, 69.0 mmol, 1.0 equiv), finely ground $MePPh_3Br$ (25.0 g, 70.0 mmol, 1.0 equiv) and toluene (125 mL, 0.55 M). The reaction vessel was sealed and sonicated for 30 minutes at 35 °C, resulting in a light yellow suspension. The reaction was stirred in a preheated oil bath at 90 °C for 16 hours. The bright yellow suspension was cooled to ambient temperature, at which point stirring was ceased and the solid material was allowed to settle to the bottom of the flask. The concentration was determined to be 0.39 M via color–endpoint titration in accordance with a known procedure,[5] as described below.

Titration of salt–free methylene triphenylphosphorane:[5] A flame–dried flask was charged with 0.25 mL of the bright yellow supernatant of the above mixture and cooled to 0 °C using an ice–water bath. A solution of benzaldehyde in toluene (0.98 M) was added dropwise via syringe over ~1 minute until the solution remained colorless.

Olefin SI-2: To a solution of ketone **6** (104 mg, 0.201 mmol, 1.0 equiv) in toluene (0.5 mL) in a sealed reaction vessel was added salt–free methylene triphenylphosphorane (0.39 M, 10 mL, 4.0 mmol, 20 equiv). The flask was sealed and the reaction stirred in a preheated oil bath at 90 °C for 24 hours, then cooled to ambient temperature. The reaction was diluted with hexanes (50 mL), and water (50 mL) was added. The aqueous and organic layers were separated, and the aqueous layer was extracted with hexanes (3 x 50 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL). The resulting solution was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure by rotary evaporation. The crude material thus obtained was purified by flash column chromatography (SiO_2, hexanes/CH_2Cl_2 = 9:1 → 7:3) to afford **SI-2** (46 mg, 44%) as a white foam.


(H2O)nSmII
O
R
R'
ET
PCET
(H2O)nSmIII
O
R
R'
PT
OH
R
R'
+ SmIII(OH)(H2O)n-1


2 Co(II)
1
F–Co(III)
H–SiR3
F–SiR3
H–Co(III)
Co(III)
Co(II)
1
ROH
HX
Co(II)
1


HCo(III)
PhSiH3
Co(III)–H
Co(II)
TolSO2•
TolSO2Cl
Co(III)
Co(II)
Me–SO2•
Tol–S(O)2–O–S(O)2–Tol
7
EtOH
8
Tol–SO3•
Tol–SO•
EtOH

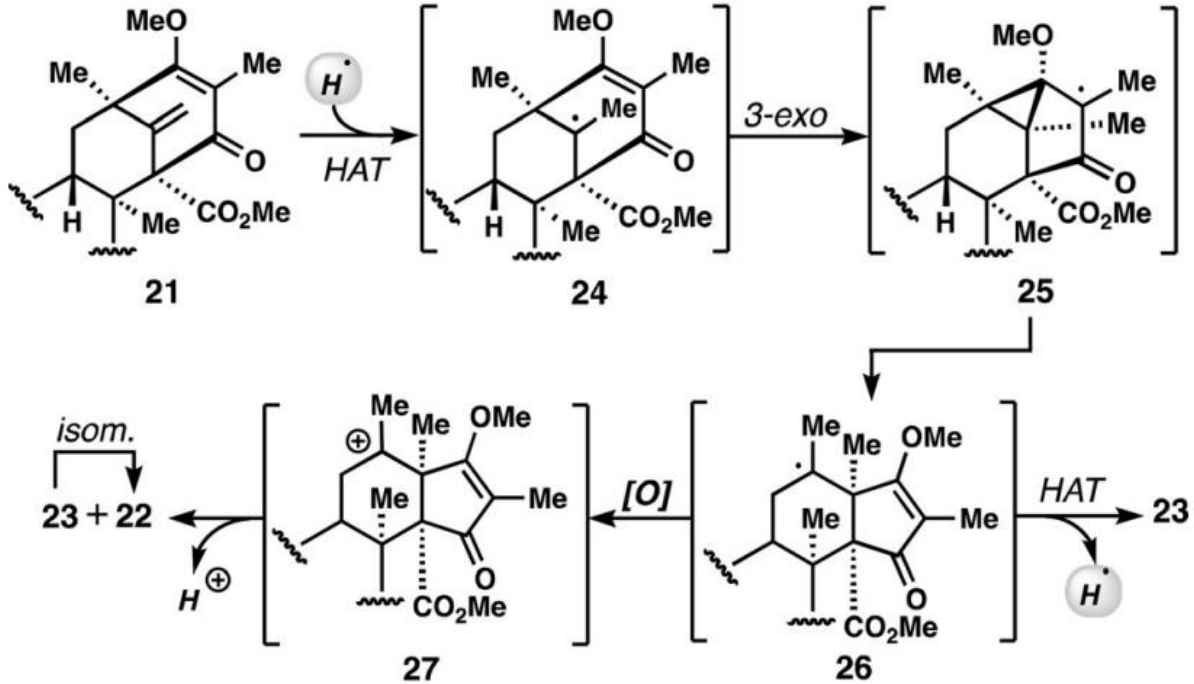


Figure 3. Abiotic radical-based HAT isomerization process.

[17] B. Gaspar, E. M. Carreira, *Angew. Chem. Int. Ed.* **2008**, *47*, 5758; *Angew. Chem.* **2008**, *120*, 5842.

[18] Similar results are obtained by replacing TsCl with *tert*-butyl hydroperoxide (TBHP). Presumably these reagents oxidize the Co^{II} precatalyst to Co^{III} which is required for the intial HAT.

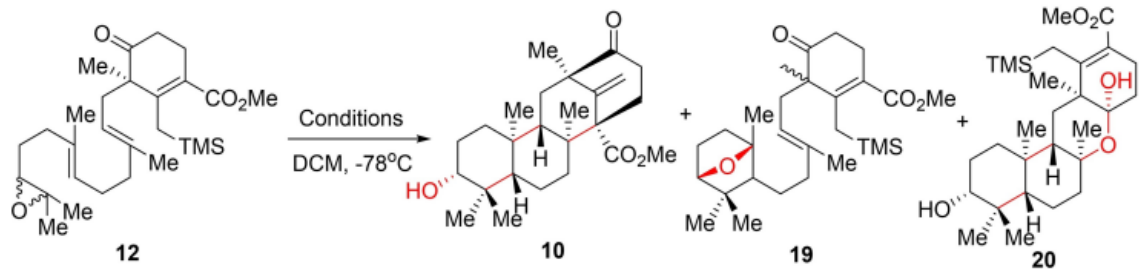
[19] S. W. M. Crossley, F. Barabé, R. A. Shenvi, *J. Am. Chem. Soc.* **2014**, *136*, 16788.

[20] DFT studies on a model system with a simplified A ring indicate that the radical rearrangment is both facile and significantly exergonic. The conversion of model radical **24** into **26** is downhill by 8 kcal mol^{-1} with activaton barriers of 11.6 kcal mol^{-1} for **24**→**25** and 4.9 kcal mol^{-1} for **25**→**26** (see the Supporting Information).

[21] CCDC 1570755 (**9**), 1570756 (**10**), and 1570754 (**22**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Manuscript received: June 2, 2017
Revised manuscript received: July 11, 2017
Accepted manuscript online: August 10, 2017
Version of record online: August 30, 2017

Table 1: Investigation of the epoxypolyene cyclization conditions.[a]



entry	Lewis acids	yield **10**[b]	yield **19**[b]	yield **20**[b]
1	$InCl_3$	trace	26%	11%
2	$SnCl_4$	trace	18%	10%
3	$FeCl_3$	trace	18%	21%
4	Et_2AlCl	14%	39%	21%
5	$EtAlCl_2$	25%	26%	9%
6	$AlCl_3$	34%	32%	6%
7	$TiCl_4$	45%	trace	11%

[a] Reaction conditions: Lewis acid (0.15 mmol) was added to a stirred solution of **12** (0.1 mmol) in dry DCM (1.0 mL) at −78 °C under an argon atmosphere, followed by stirring for 15 min. [b] Isolated yield. DCM = dichloromethane.