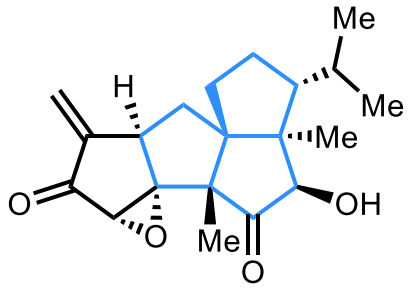
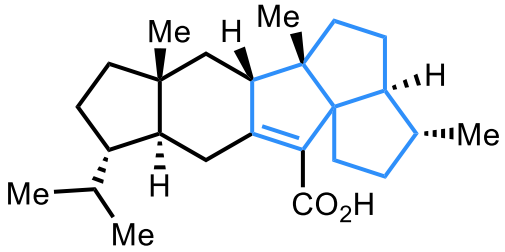
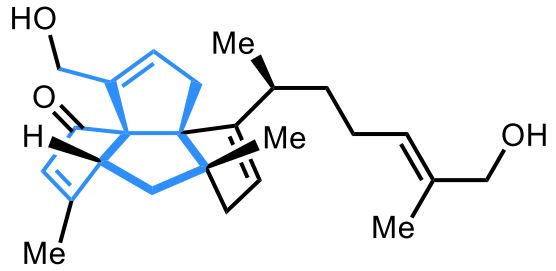
Concise Total Syntheses of Angular Triquinane Containing Terpenoids



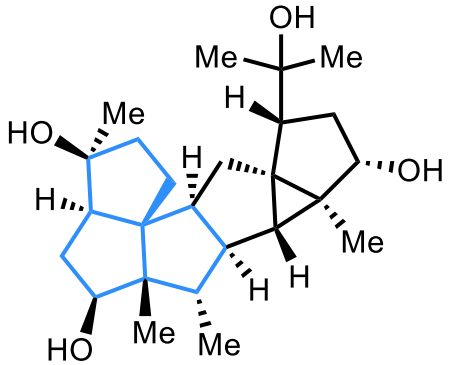
Crinipellin A



Retigeranic acid A



Bipolarolide D



Niduterpenoid B

Reporter: Yi Ma

Supervisor: Prof. Quan Cai

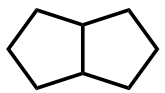
2024.10.25

Content

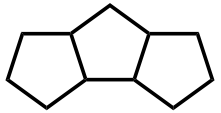
Content

1. Introduction

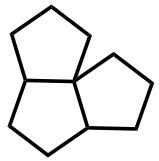
Polyquinane



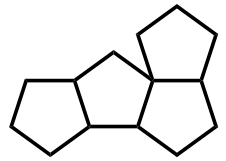
diquinane



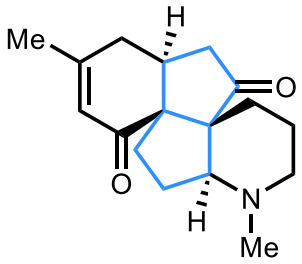
linear triquinane



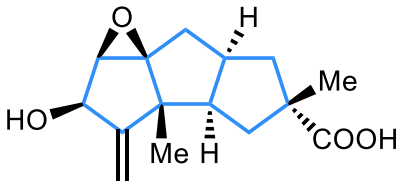
angular triquinane



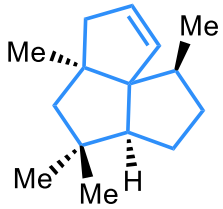
tetraquinane



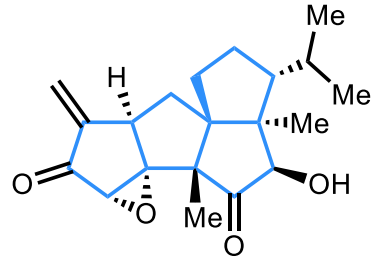
Lycojaponicumin C



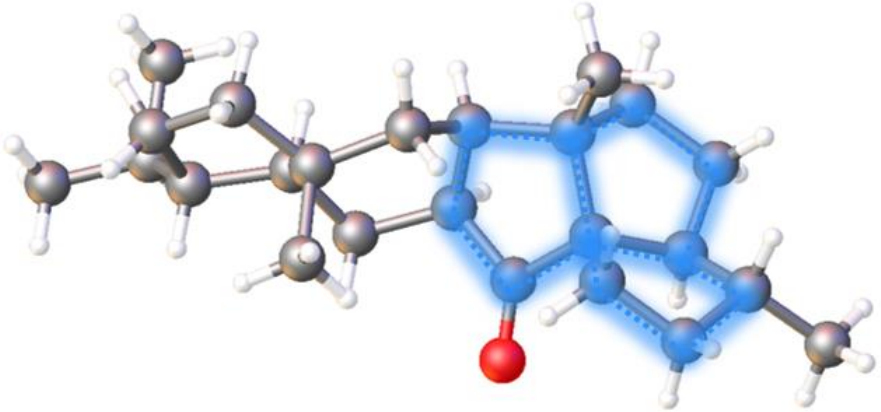
Hirsutic acid C



Silphinene



Crinipellin A



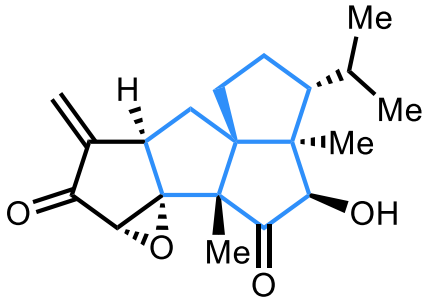
X-ray of **Retigeranic acid A**

- ✓ Highly twisted and congested ring system
- ✓ Multiple stereogenic centers
- ✓ Adjacent all-carbon quaternary centers

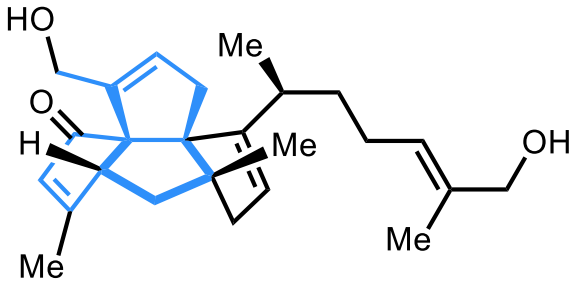
1. Introduction

Angular triquinane

Crinipellis



Crinipellin A

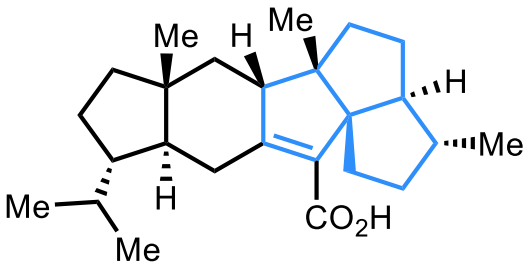


Bipolarolide D

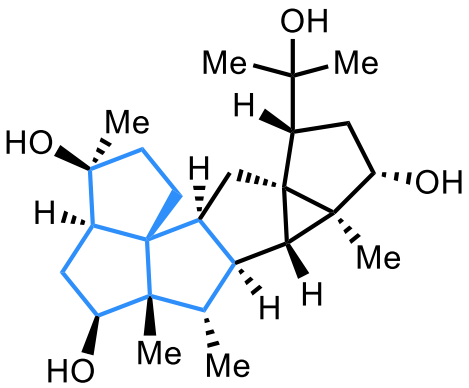
Fungus biolaris

Terpenoids

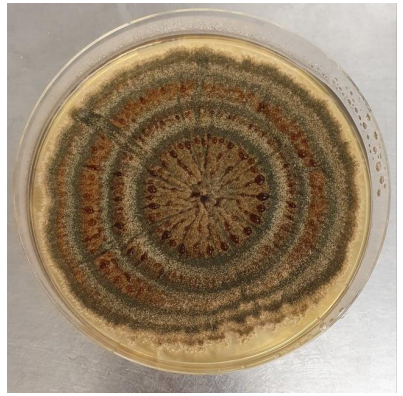
Lobaria retigera



Retigeranic acid A



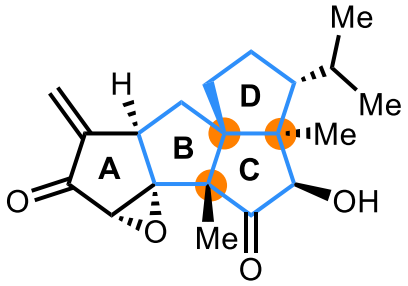
Niduterpenoid B



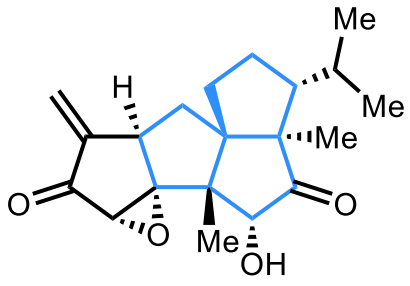
Aspergillus nidulans

Content

2. Diterpenoids Crinipellin A and B



Crinipellin A (**2-1**)



Crinipellin B (**2-2**)

from the fungus
Crinipellis stipitaria (Agaricales)

(伞菌目真菌) *Crinipellis*

Structure features

- ✓ Linear triquinane and angular triquinane
- ✓ Eight stereogenic centers
- ✓ Three adjacent all-carbon quaternary centers at bridgehead position
- ✓ Highly congested teracyclic ring system
- ✓ Multiple oxygenated and labile functional groups

Bioactivity

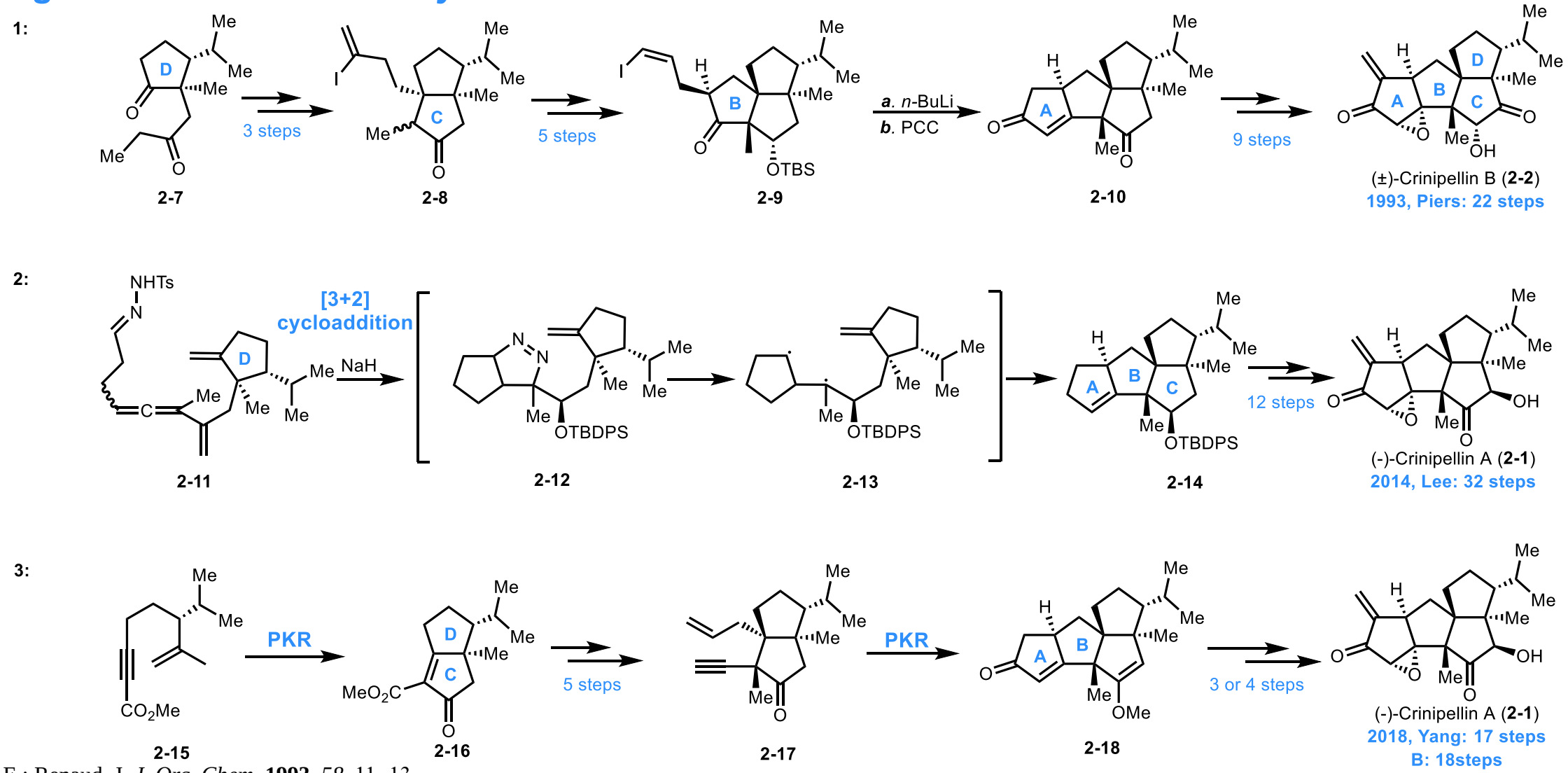
- ✓ Antibacterial and fibrinolytic activities

  MIC = 5 *u*g/ml to Sarcina lutea
- ✓ Potential protein covalent inhibitors

1) Kupka, J.; Anke, T.; Oberwinkler, F.; Schramm, G.; Steglich,W. *Pat. Antibiot.* **1979**, *32*, 130−135.
2) Gehringer, M.; Laufer, S. A. *J. Med. Chem.* **2019**, *62*, 5673-5724.

2. Diterpenoids Crinipellin A and B

Highlight of Previous Total Syntheses



3) Piers, E.; Renaud, J. *J. Org. Chem.* **1993**, *58*, 11−13.

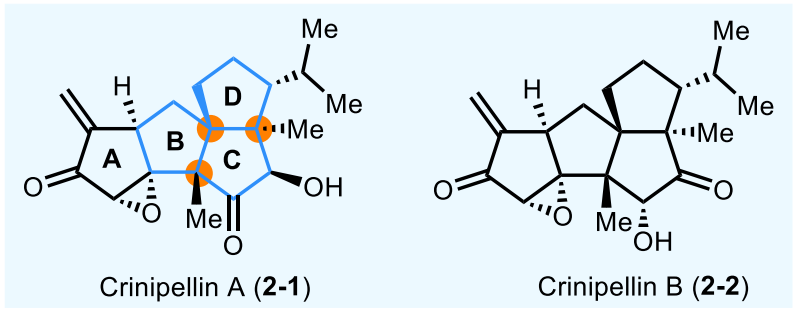
4) Kang, T.; Song, S. B.; Kim, W.-Y.; Kim, B. G.; Lee, H.-Y. *J. Am. Chem. Soc.* **2014**, *136*, 10274− 10276.

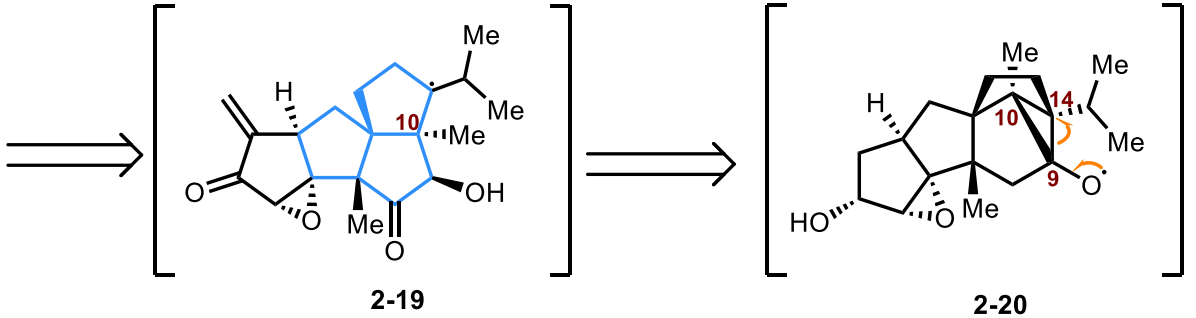
5) Huang, Z.; Huang, J.; Qu, Y.; Zhang, W.; Gong, J.; Yang, Z. *Angew. Chem., Int. Ed.* **2018**, *57*, 8744−8748.

2. Diterpenoids Crinipellin A and B ——Ding (2022)

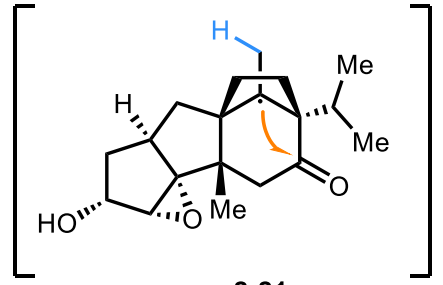
Retrosynthetic Analysis

Hanfeng Ding

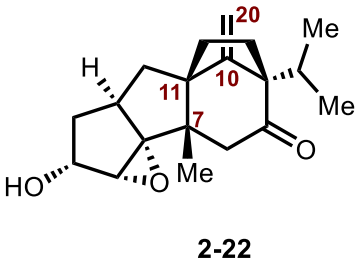




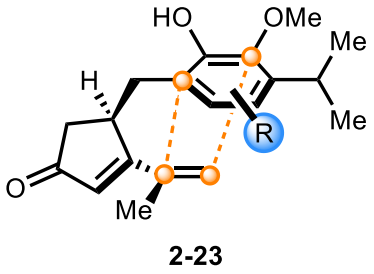
HAT-initiated Dowd-Beckwith rearrangement



HAT



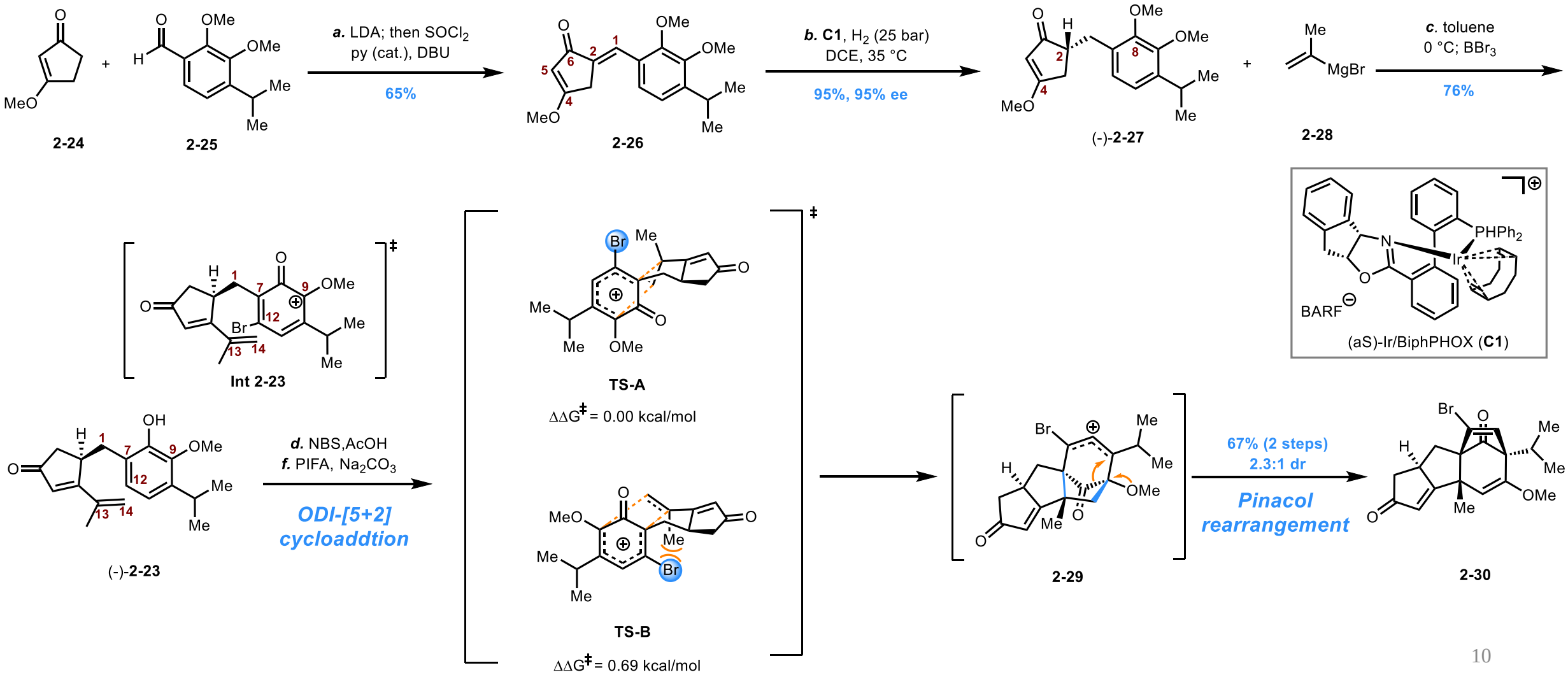
Diasterecontrolled ODI-[5+2] cascade



6) Zhao, Y.; Hu, J.; Chen, R.; Xiong, F.; Xie, H.; Ding, H. *J. Am. Chem. Soc.* **2022**, *144*, 2495-2500.

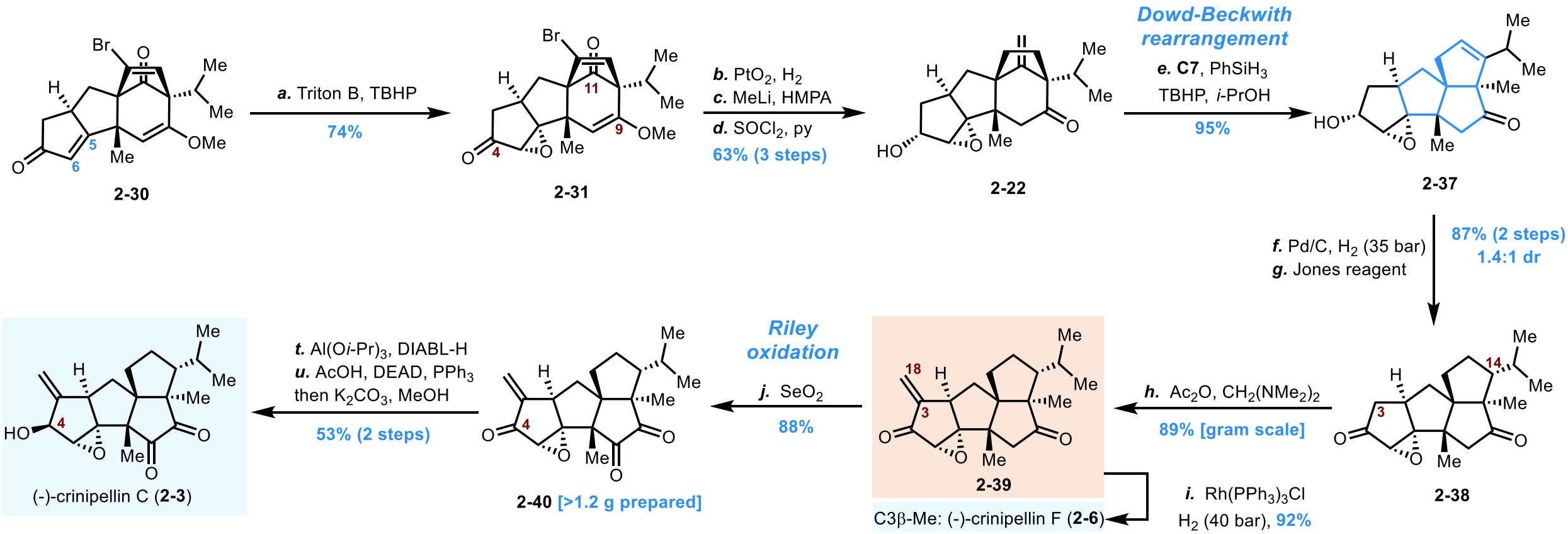
2. Diterpenoids Crinipellin A and B ——Ding (2022)

Construction of the 5/5/6/5 Tetracyclic Skeleton



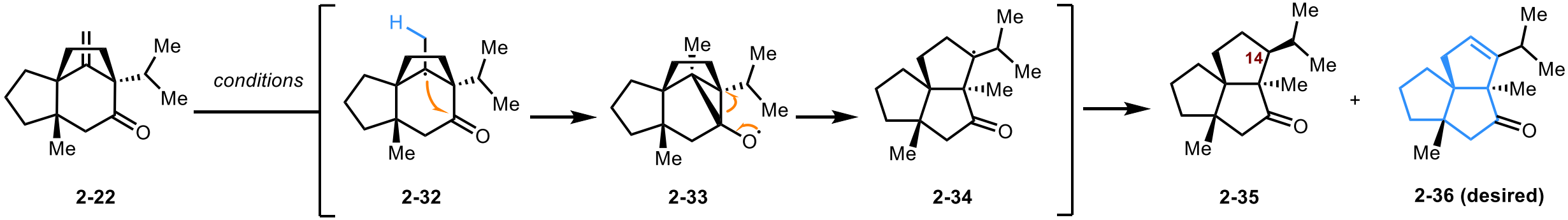
2. Diterpenoids Crinipellin A and B ——Ding (2022)

Divergent Total Syntheses of (-)-Crinipellins

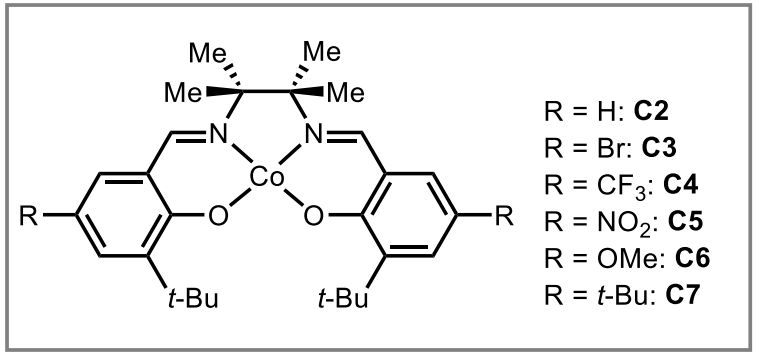


2. Diterpenoids Crinipellin A and B ——Ding (2022)

Optimization of the HAT-Initiated Dowd-Beckwith Rearrangement

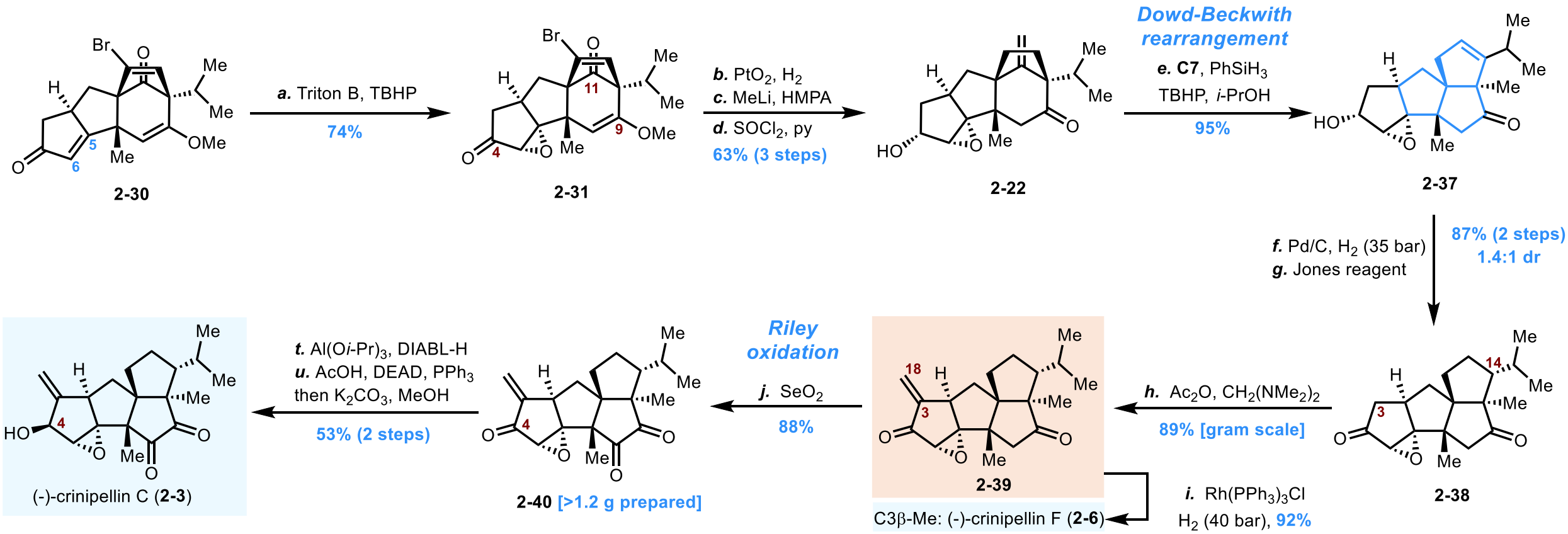


Entry	Conditions	Yield (%)	
		2-35	**2-36**
1	$Mn(dpm)_3$, $PhSiH_3$, TBHP, EtOH	84	<5
2	$Fe(acac)_3$, $Fe(acac)_2$, $PhSiH_3$, THF	40	33
3	$Co(acac)_2$, TMDSO, TBHP, *i*-PrOH	<5	45
4	**C2-C5**, $PhSiH_3$, TBHP, *i*-PrOH	<5	20-81
5	**C7**, $PhSiH_3$, TBHP, *i*-PrOH	11	83



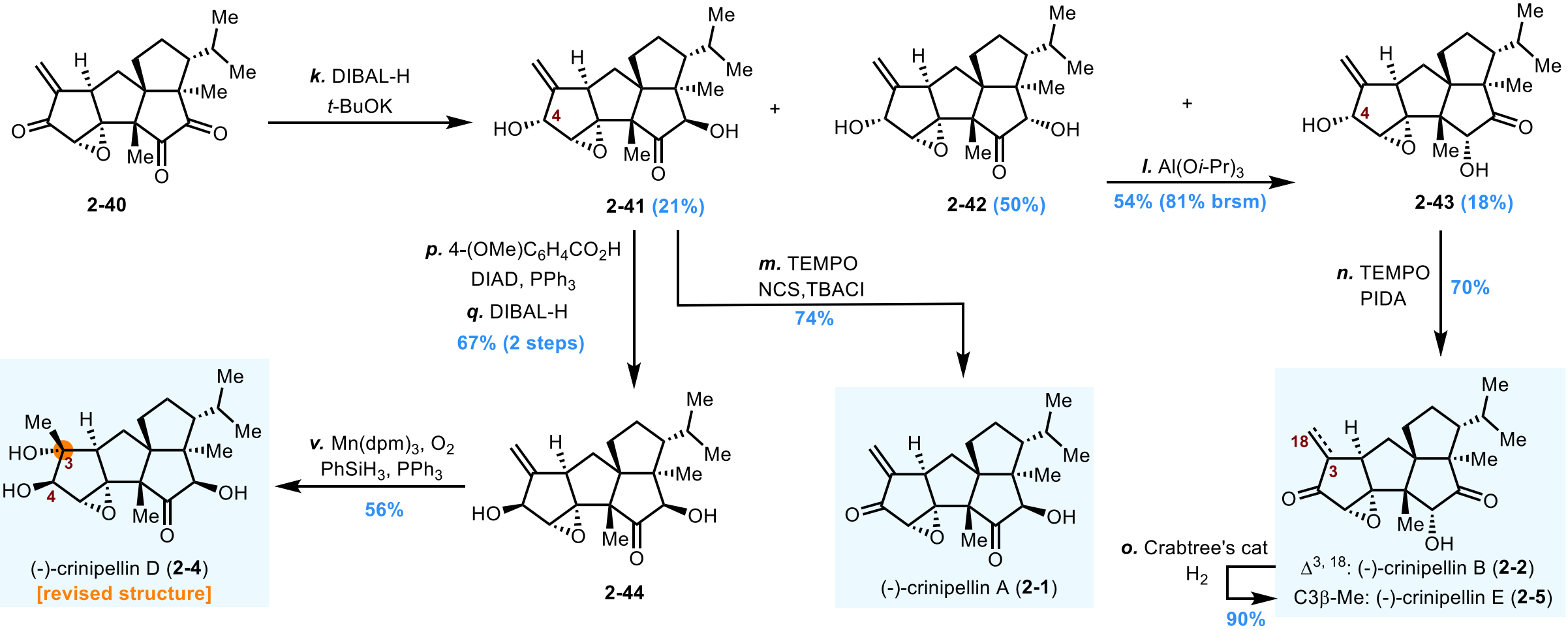
2. Diterpenoids Crinipellin A and B ——Ding (2022)

Divergent Total Syntheses of (-)-Crinipellins



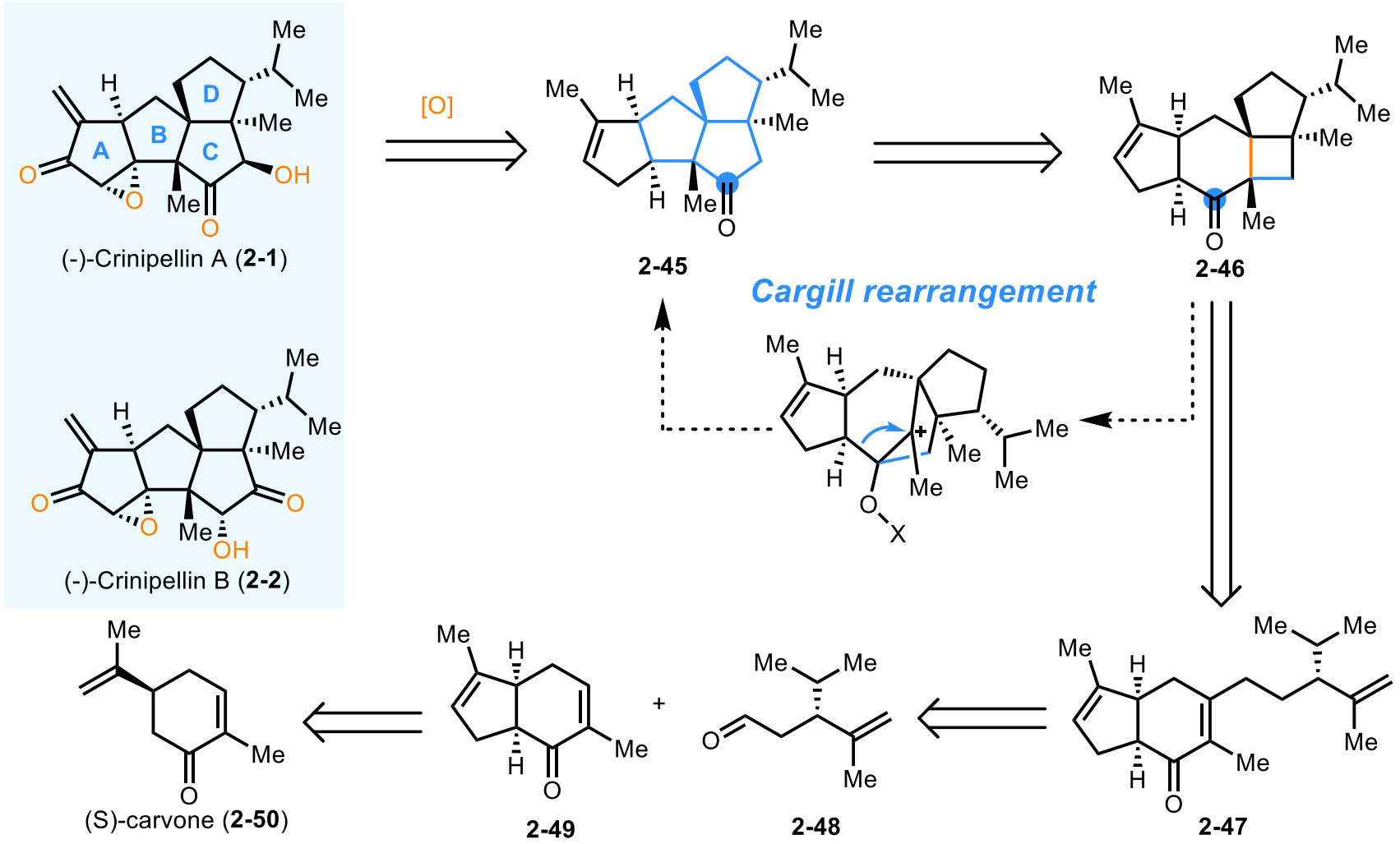
2. Diterpenoids Crinipellin A and B ——Ding (2022)

Divergent Total Syntheses of (-)-Crinipellins



2. Diterpenoids Crinipellin A and B ——Dai (2024)

Retrosynthetic Analysis

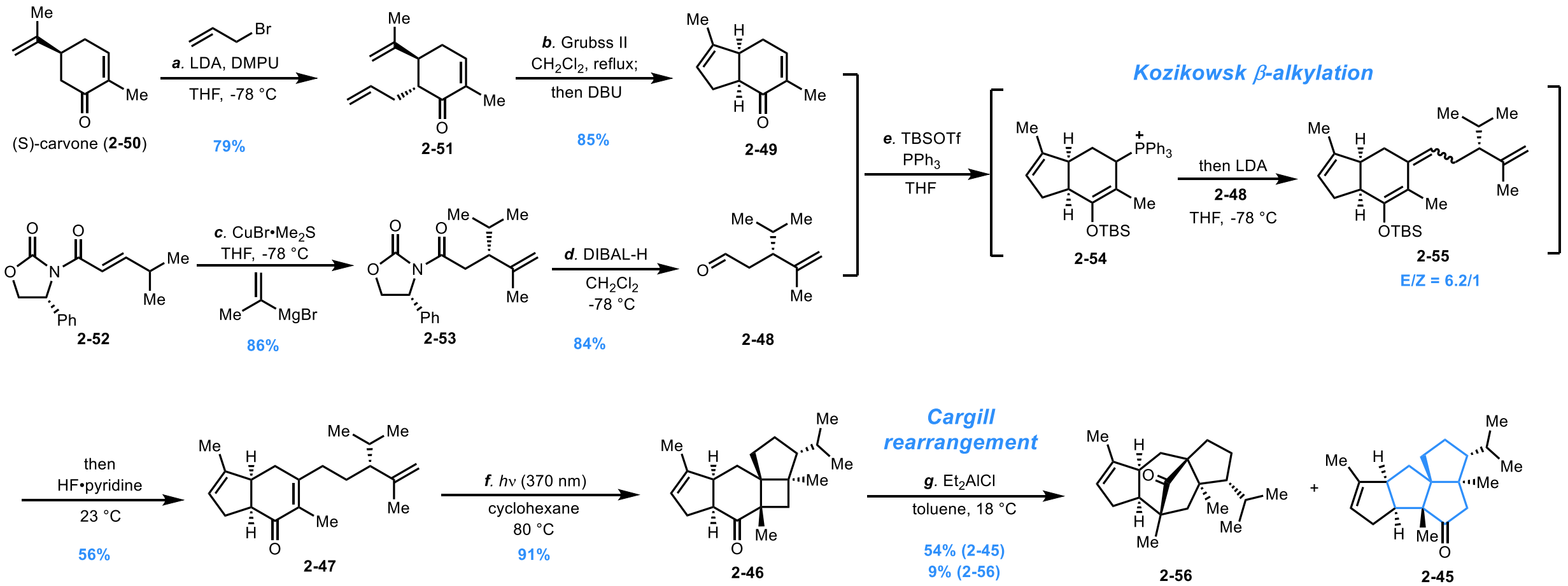


Mingji Dai

7) Xu, B.; Zhang, Z.; Tantillo, D. J.; Dai, M. *J. Am. Chem. Soc.* **2024**, *146*, 21250−21256

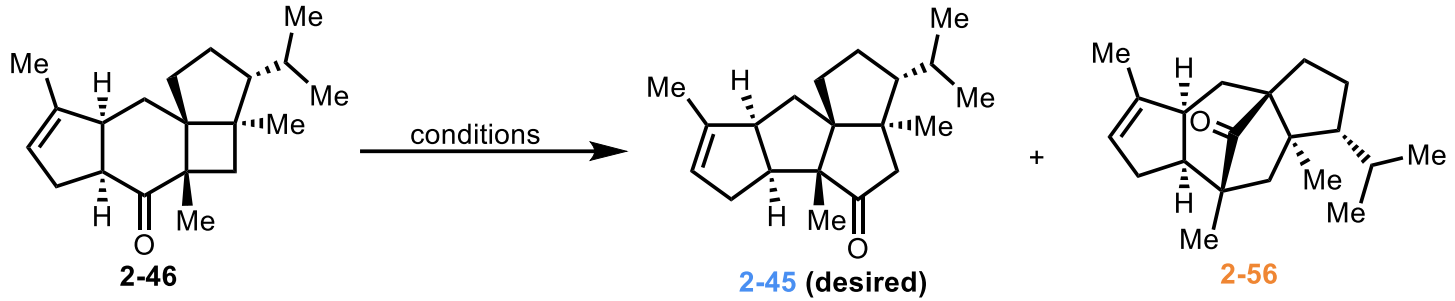
2. Diterpenoids Crinipellin A and B ——Dai (2024)

Construction of the Angular Triquinane Core



2. Diterpenoids Crinipellin A and B ——Dai (2024)

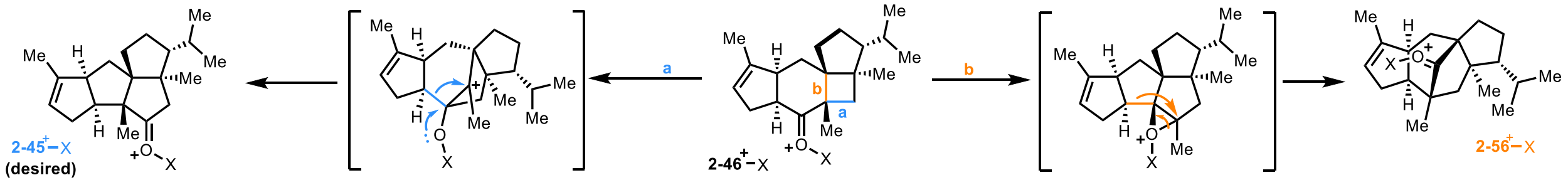
Cargill Rearrangement Optimization



Entry	Reaction conditions (equiv)	Results(**2-45**/**2-56**/**2-46**)/%
1	*p*-TsOH (1.0), PhH, 80 ℃	18/45/0
2	*p*-TsOH (1.0), LiCl, toluene, 23 ℃	0/0/85
3	Tf_2NH (1.0), CH_2Cl_2, 23 ℃	9/51/0
4	$Mg(ClO_4)_2$ (1.0), CH_2Cl_2, 23 ℃	0/0/91
5	$ZnCl_2$ (1.0), CH_2Cl_2, 23 ℃	0/79/0
6	$BF_3{\cdot}Et_2O$ (1.0), CH_2Cl_2, 23 ℃	7/59/0
7	$AlCl_3$ (1.0), CH_2Cl_2, 23 ℃	5/42/0
8	Me_2AlCl (1.0), CH_2Cl_2, 23 ℃	32/45/0
9	$EtAlCl_2$ (1.0), CH_2Cl_2, 23 ℃	28/46/0
10	Et_2AlCl (1.0), CH_2Cl_2, 23 ℃	35/23/0
11	Et_2AlCl (1.0), toluene, 23 ℃	65/16/0

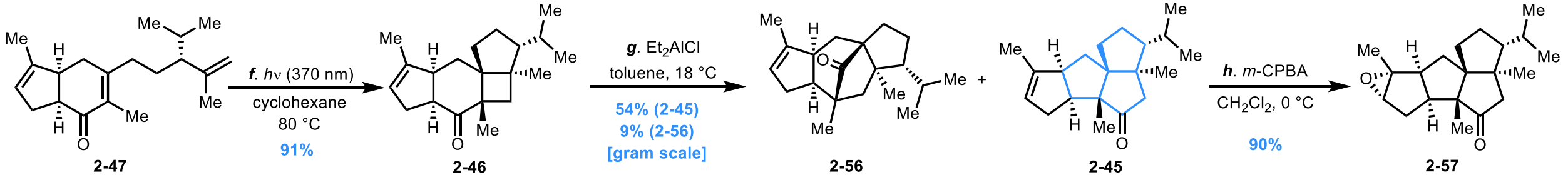
2. Diterpenoids Crinipellin A and B ——Dai (2024)

Computional Results of the Cargill Rearrangement



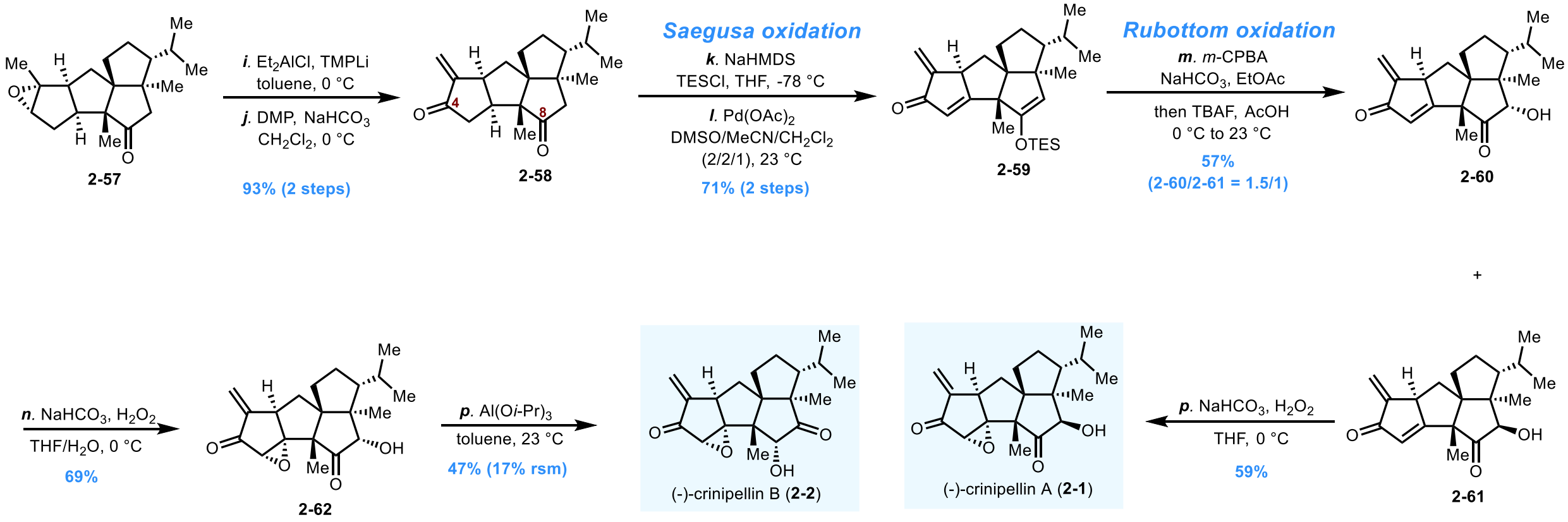
X = H	*intermediate*	*disfavored*	***favored by 2.9 kcal/mol***	*epoxonium*
X = $Al(Me)Cl_2$	*no intermediate*	*disfavored*	***favored by 0.8 kcal/mol***	*epoxonium*
X = $Al(Me)_2Cl$	*no intermediate*	***favored by 1.0 kcal/mol***	*disfavored*	*epoxonium*

Construction of the Angular Triquinane Core



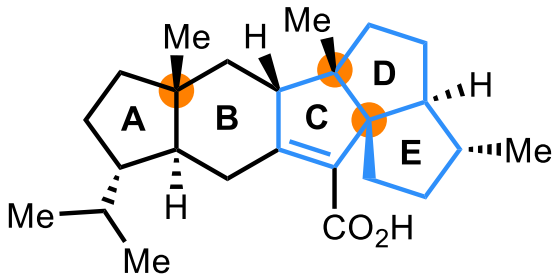
2. Diterpenoids Crinipellin A and B ——Dai (2024)

End Game



Content

3. Sesterterpenoid——Retigeranic Acid A



(-)-Retigeranic acid A

from lichens of the
Lobaria retigera group
in the Western Himalayas

（地衣）*Lobaria*

Structure features

- ✓ Trans-hydrindane fused angular triquinane
- ✓ Decorated with eight stereogenic centers
- ✓ Three quaternary centers at the bridgehead positions

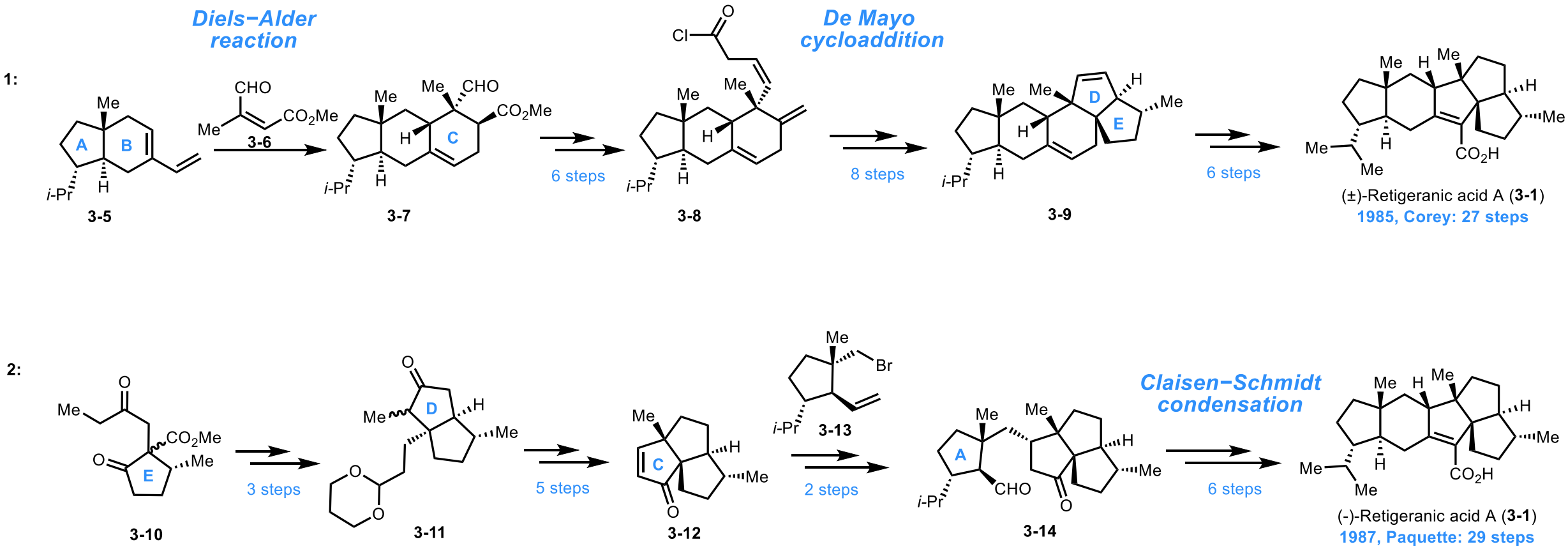
Bioactivity

- ✓ Biological activity of retigeranic acid A not been determined
- ✓ Its parent genus Lobaria can treating eczema and lung disorders

8) Rao, P.S.; Sarma, K. G.; Seshadri, T. R. *Curr. Sci.* **1965**, *34*, 9−11.
9) Calcott, M. J.; Ackerley, D. F.; Knight, A.; Keyzers, R. A.; Owen, J. G. *Chem. Soc. Rev.* **2018**, *47*, 1730−1760.

3. Sesterterpenoid——Retigeranic Acid A

Highlight of Previous Total Syntheses

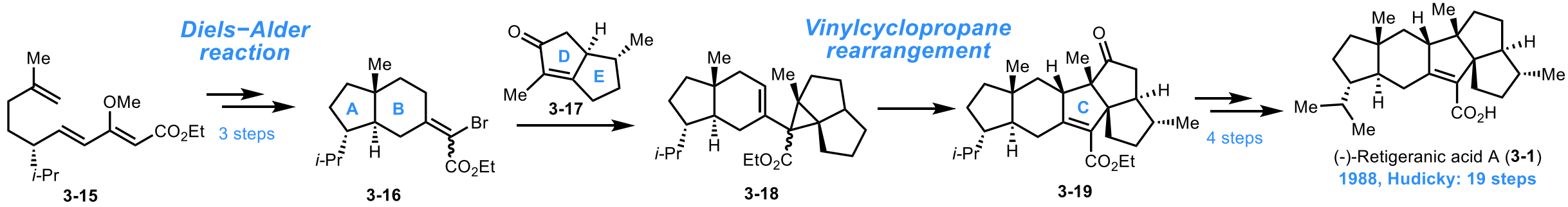


10) Corey, E. J.; Desai, M. C.; Engler, T. A. *J. Am. Chem. Soc.* **1985**, *107*, 4339−4341.
11) Paquette, L. A.; Wright, J.; Drtina, G. J.;Roberts, R. *J. Org.Chem.* **1987**, *52*, 2960−2962.

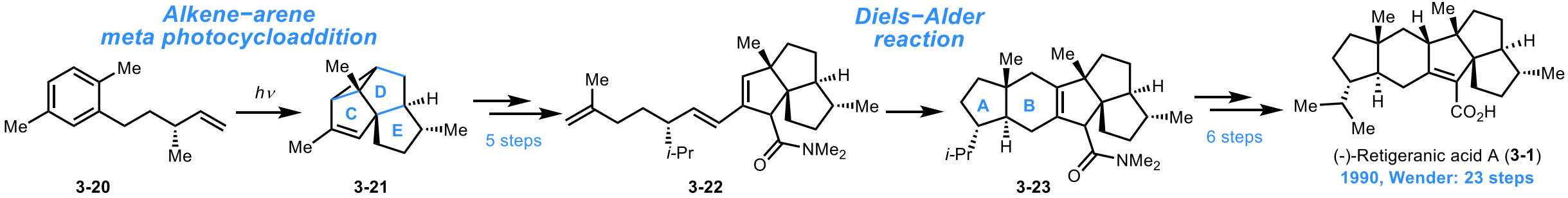
3. Sesterterpenoid——Retigeranic Acid A

Highlight of Previous Total Syntheses

3:



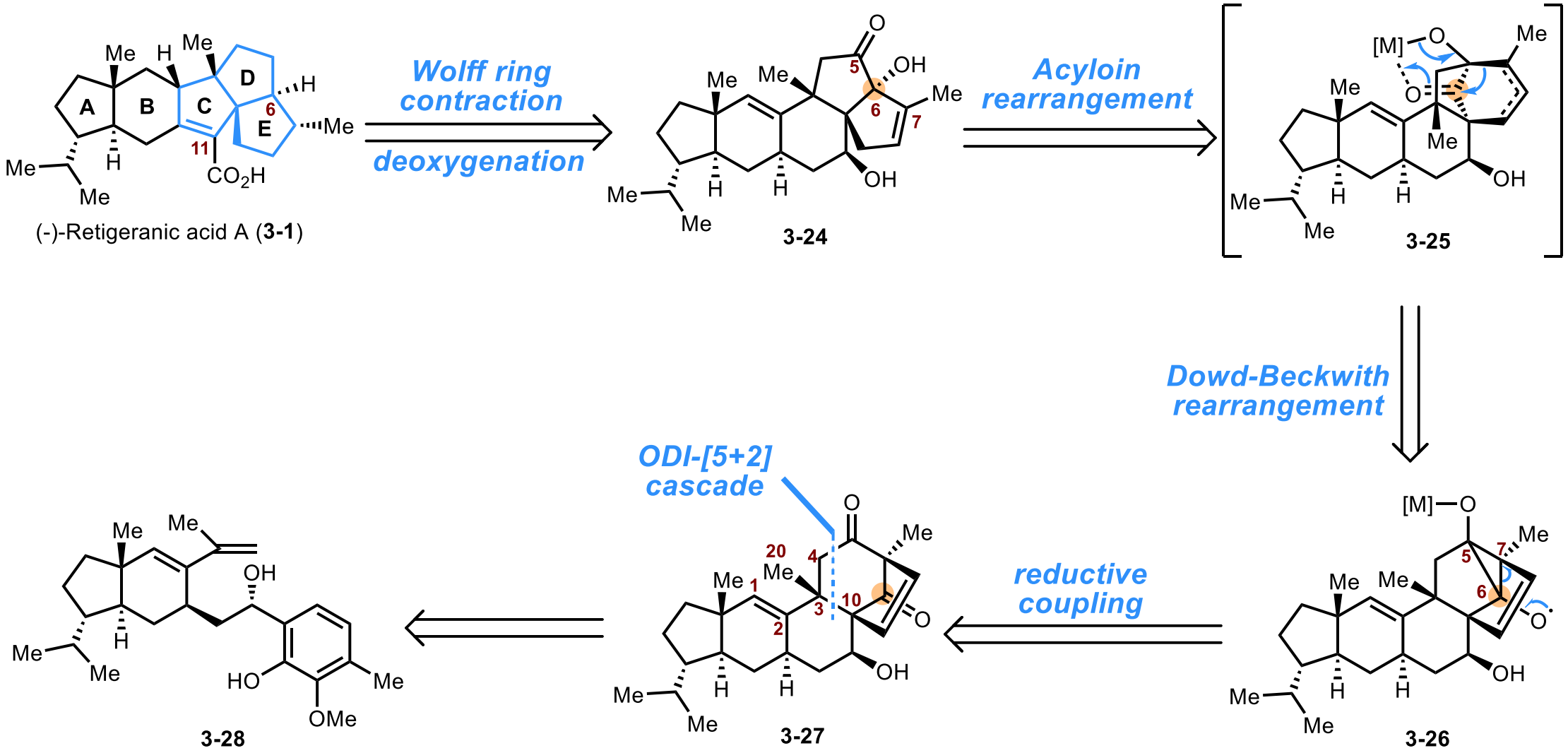
4:



12) Fleming, A.; Radesca, L *J. Am.Chem. Soc.* **1989**, *111*, 6691−6707.
13) Wender, P. A.; Singh, S. K.*Tetrahedron Lett.* **1990**, *31*, 2517−2520.

3. Sesterterpenoid Retigeranic Acid A——Ding (2023)

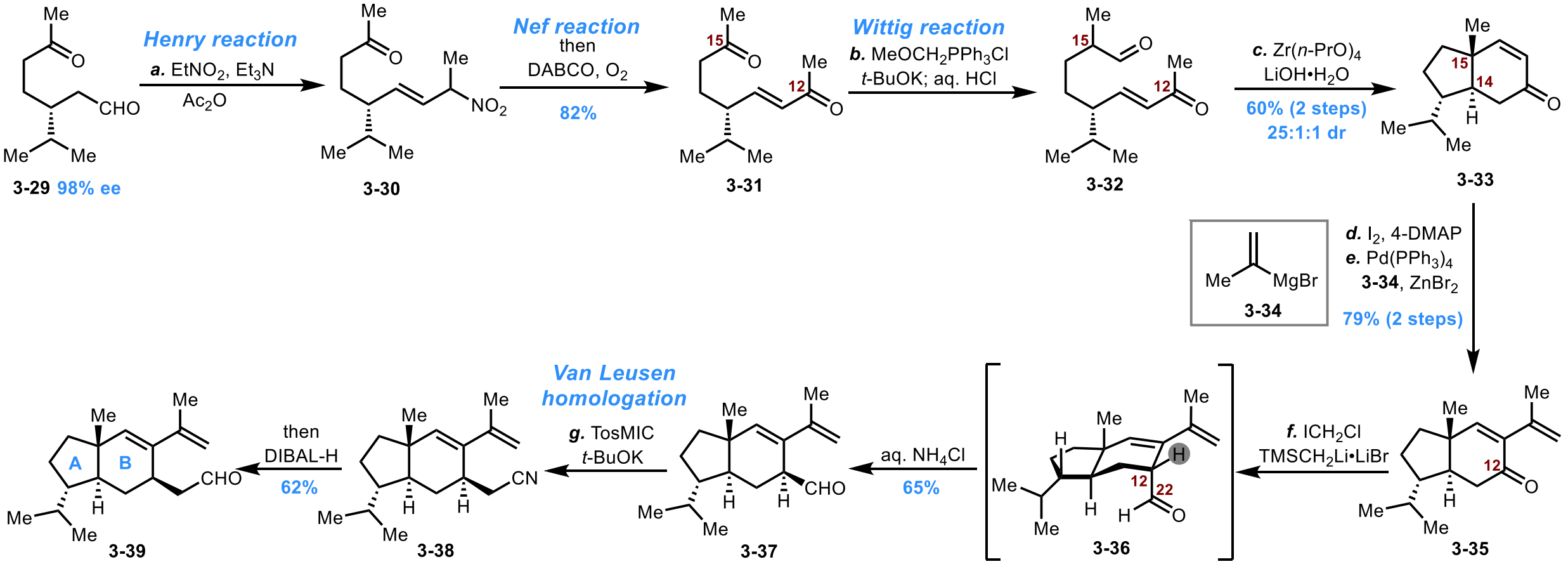
Retrosynthetic Analysis



14) Sun, D.; Chen, R.; Tang, D.; Xia, Q.; Zhao, Y.; Liu, C.-H.; Ding, H. *J. Am. Chem. Soc.* **2023**, *145*, 11927−11932

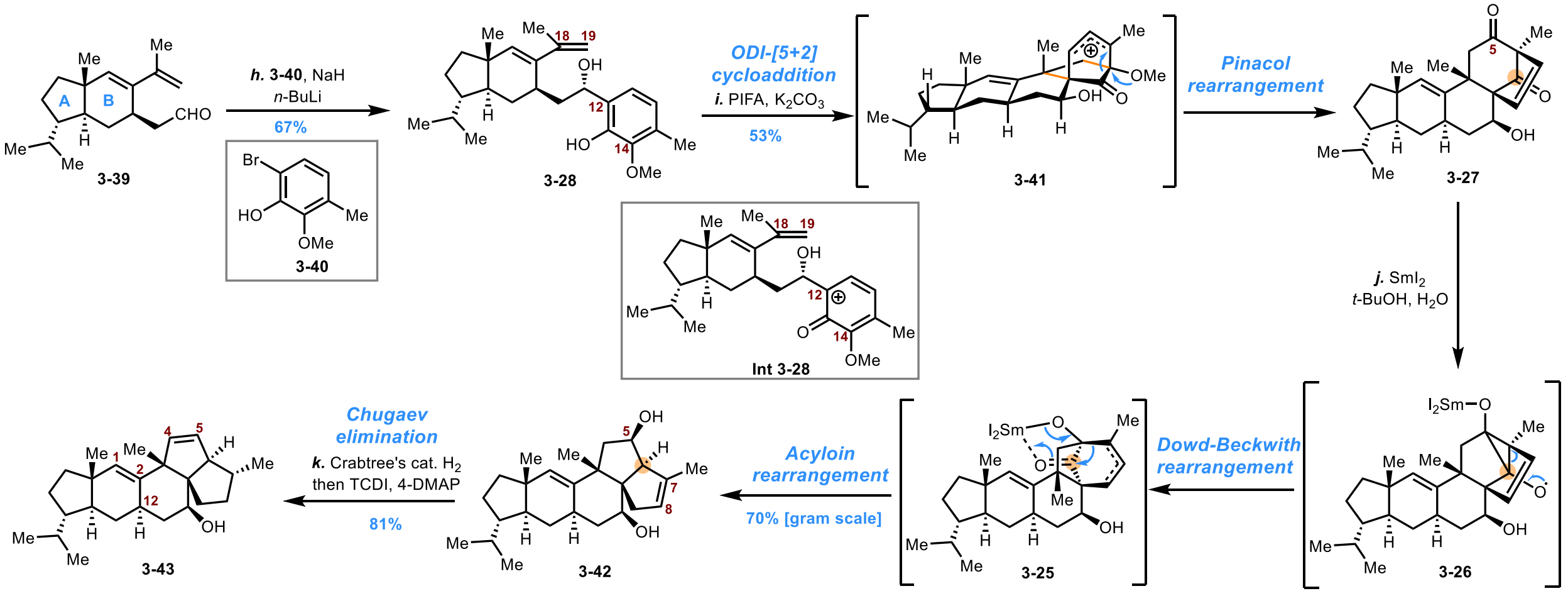
3. Sesterterpenoid Retigeranic Acid A——Ding (2023)

Construction of trans-Hydrindane Framework



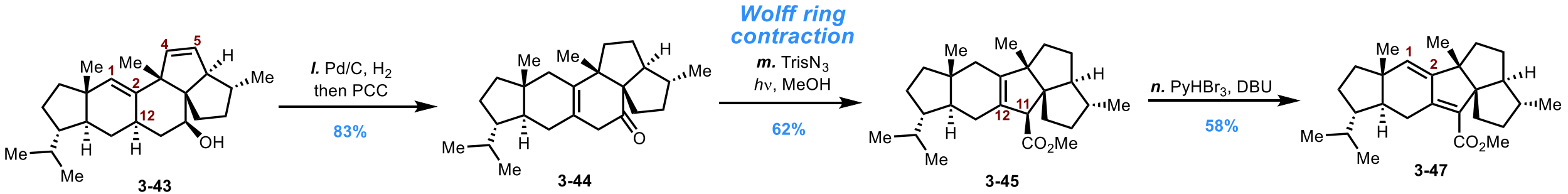
3. Sesterterpenoid Retigeranic Acid A——Ding (2023)

Construction of the Angular Triquinane



3. Sesterterpenoid Retigeranic Acid A——Ding (2023)

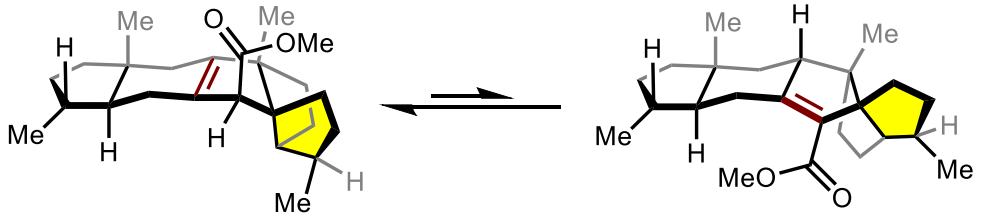
End Game



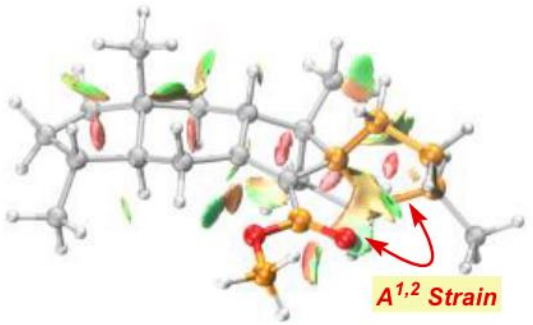
o. $Mn(dpm)_3$
$Ph(i\text{-}PrO)SiH_2$, TBHP
aq. KOH work up

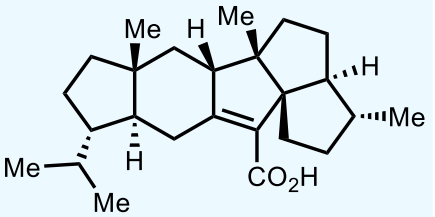
54%
4.4:1 dr at C2

Calculation of the Alkene Isomerization



3-45 (ΔG = 0 kcal/mol) ⇌ **3-46** (ΔG = 5.4 kcal/mol)

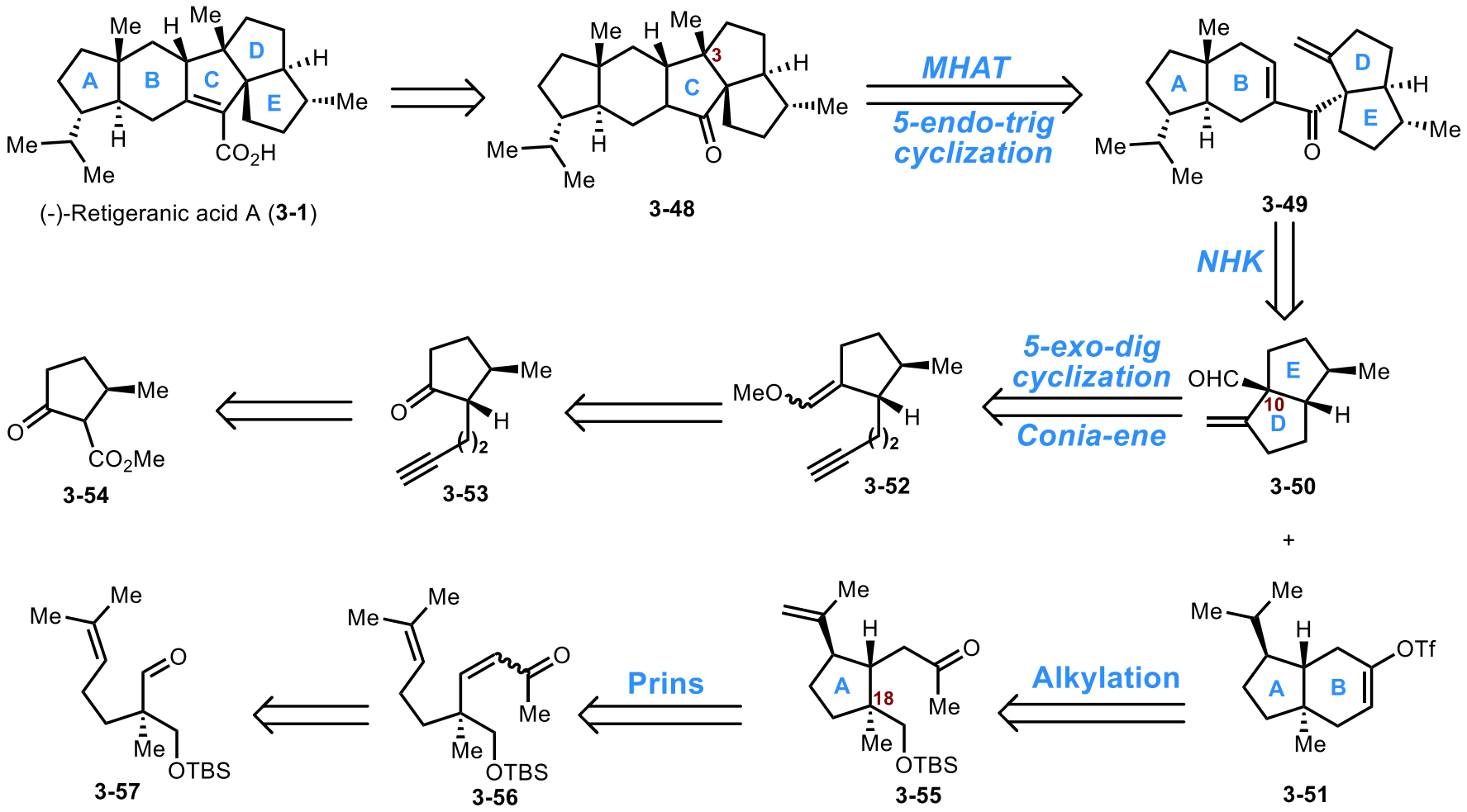




(-)-Retigeranic Acid A (**3-1**)

3. Sesterterpenoid Retigeranic Acid A——Chen (2023)

Retrosynthetic Analysis

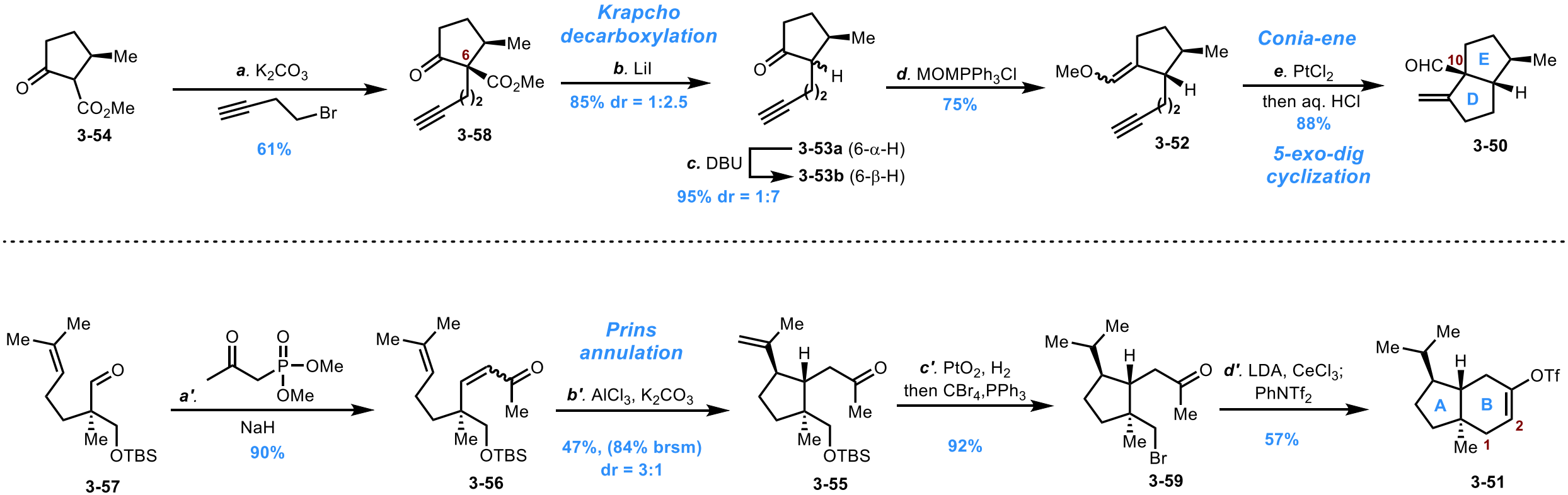


Xiaoming Chen

15) Chen, X.; Yao, W.; Zheng, H.; Wang, H.; Zhou, P.-P.; Zhu, D.-Y.; Wang, S.-H. *J. Am. Chem. Soc.* **2023**, *145*, 13549−13555

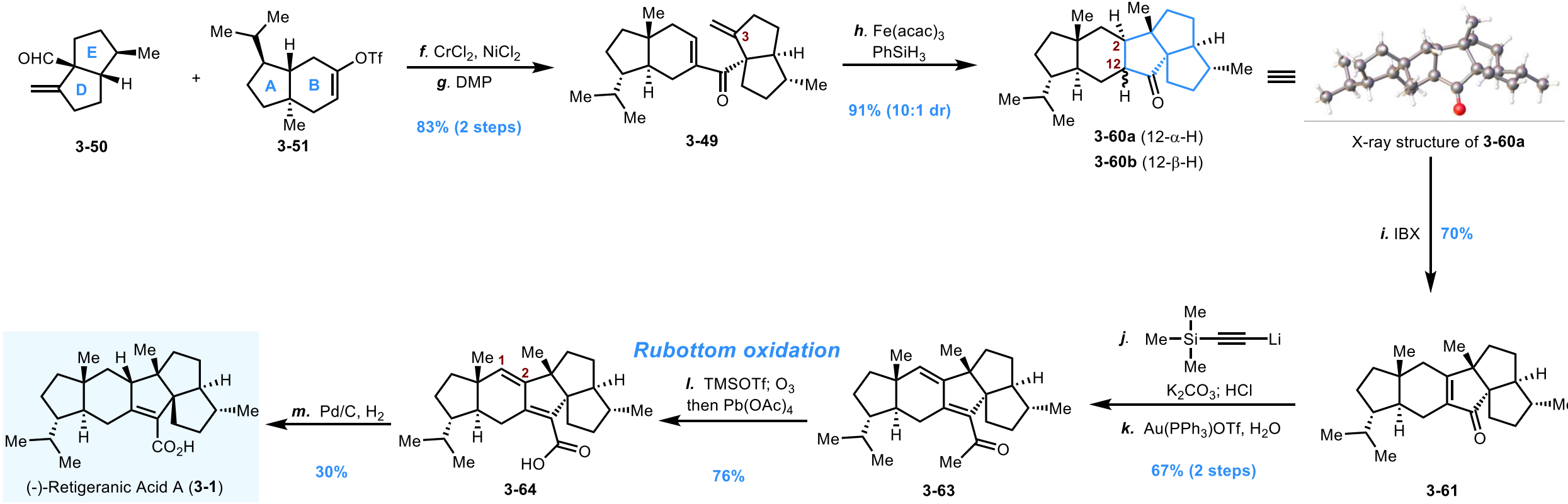
3. Sesterterpenoid Retigeranic Acid A——Chen (2023)

Preparation of Building Blocks



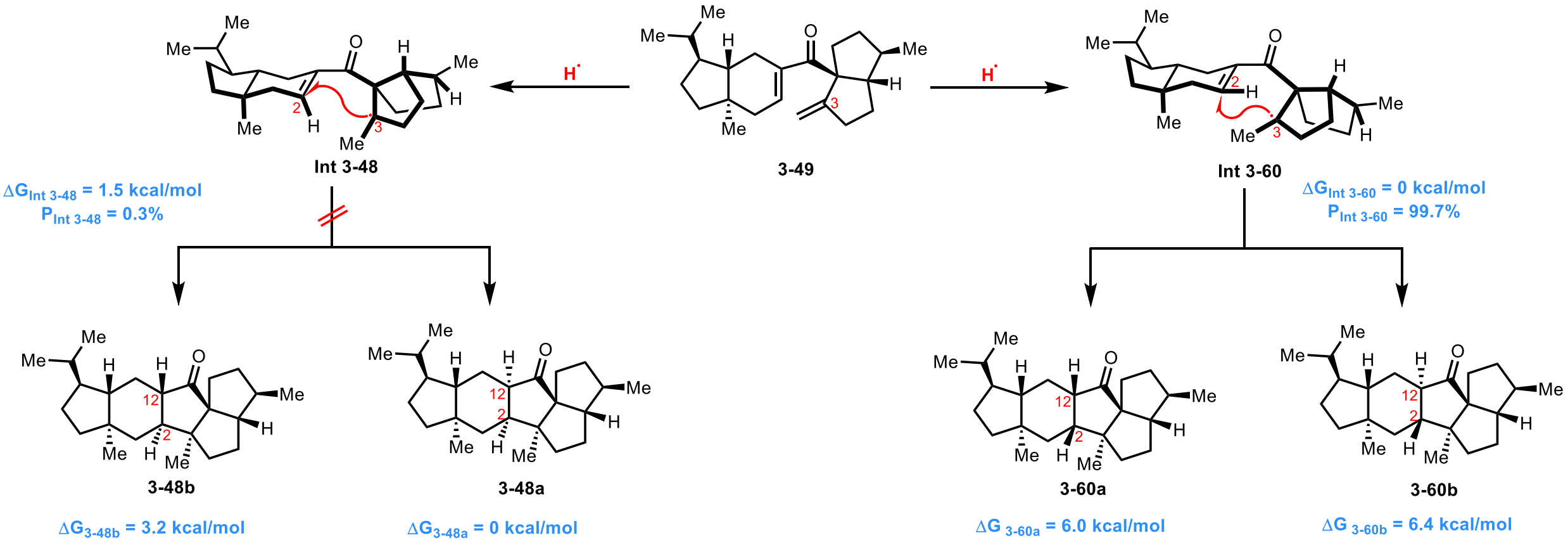
3. Sesterterpenoid Retigeranic Acid A——Chen (2023)

Total Synthesis of Retigeranic Acid A



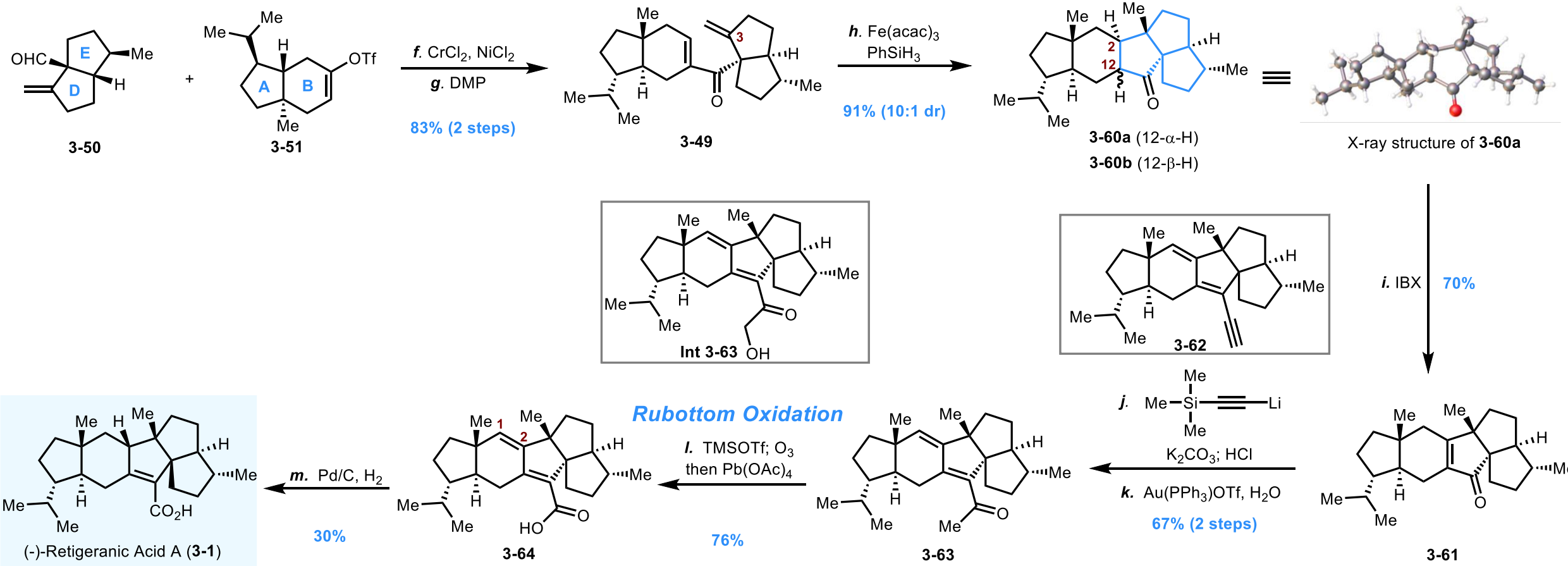
3. Sesterterpenoid Retigeranic Acid A——Chen (2023)

DFT Calculation for Generated 3-60a/b

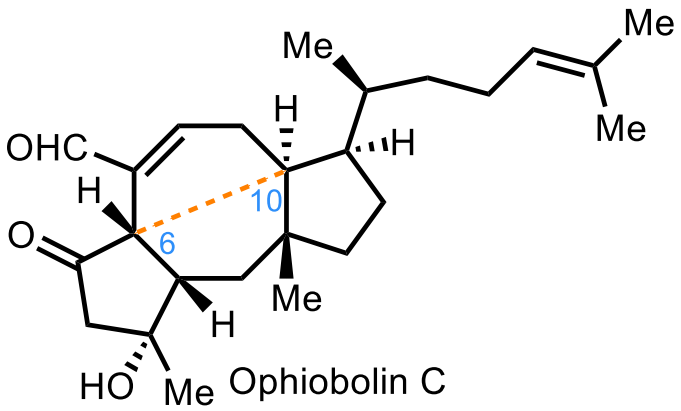


3. Sesterterpenoid Retigeranic Acid A——Chen (2023)

Total Synthesis of Retigeranic Acid A

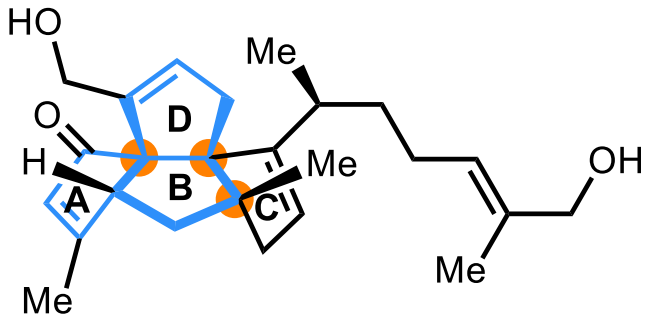


3. Sesterterpenoid Bipolarolide D



Ophiobolin C

biosynthesis
C6-C10 formation



Bipolarolide D (**3-2**)

Fungus biolaris

Structure features

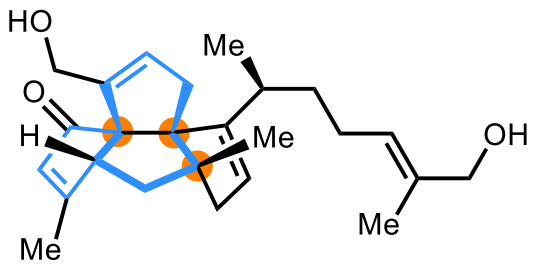
- ✓ 5/5/5/5 nonlinear fused rings
- ✓ Three consecutive all-carbon quaternary Centers
- ✓ A/B/C linear triquinane on a convex surface
- ✓ The A ring fully functionalized

16) Liu, M. T.; Sun, W. G.; Shen, L.; He, Y.; Liu, J. J.; Wang, J. P.;Hu, Z. X.; Zhang, Y. H. *Angew. Chem., Int. Ed.* **2019**, *58*, 12091−12095.

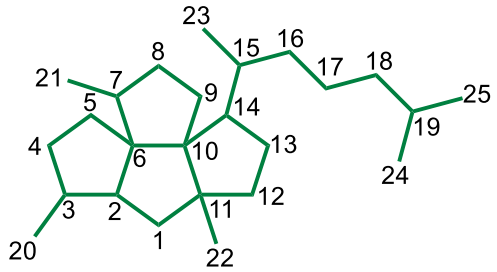
3. Sesterterpenoid Bipolarolide D——Lu (2024)

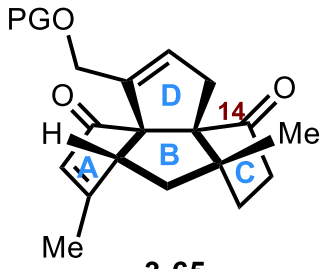
Retrosynthetic Analysis

Zhaohong Lu



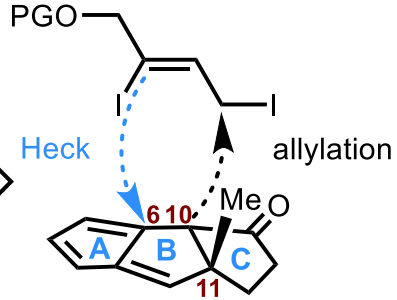
(-)-Bipolarolide D (**3-2**)



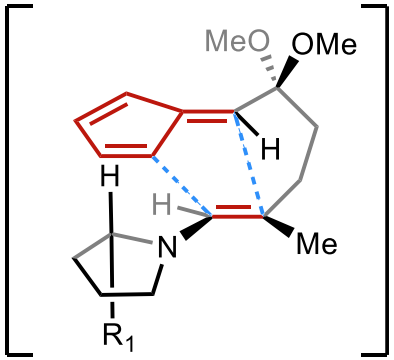


3-65

Pentafulvene-involved Heck cyclization

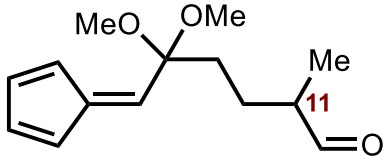


3-66



chiral enamine intermediate (**3-68**)

Enantioselective pentafulvene [6+2]

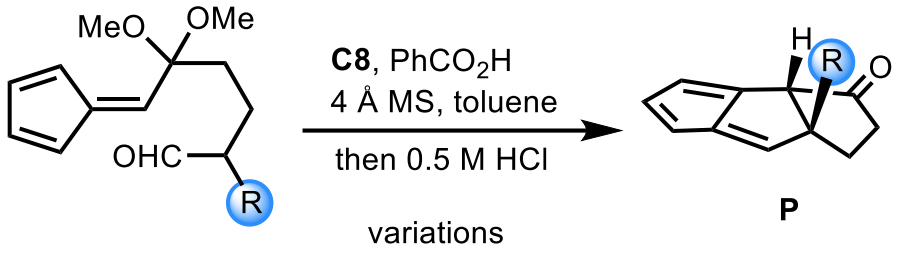


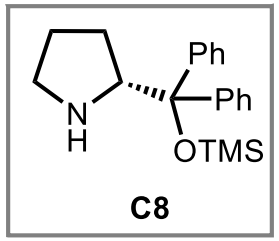
3-67

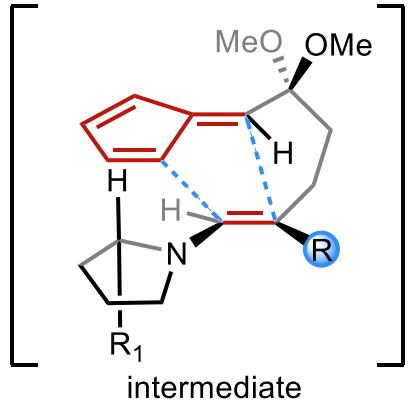
17) Sun, S.; Wei, Q.; Liu, Y.; Lu, Z.*J. Am. Chem. Soc.* **2024**, *146*, 14427−14432

3. Sesterterpenoid Bipolarolide D——Lu (2024)

Investigation of Asymmetric [6+2] Cycloaddtion





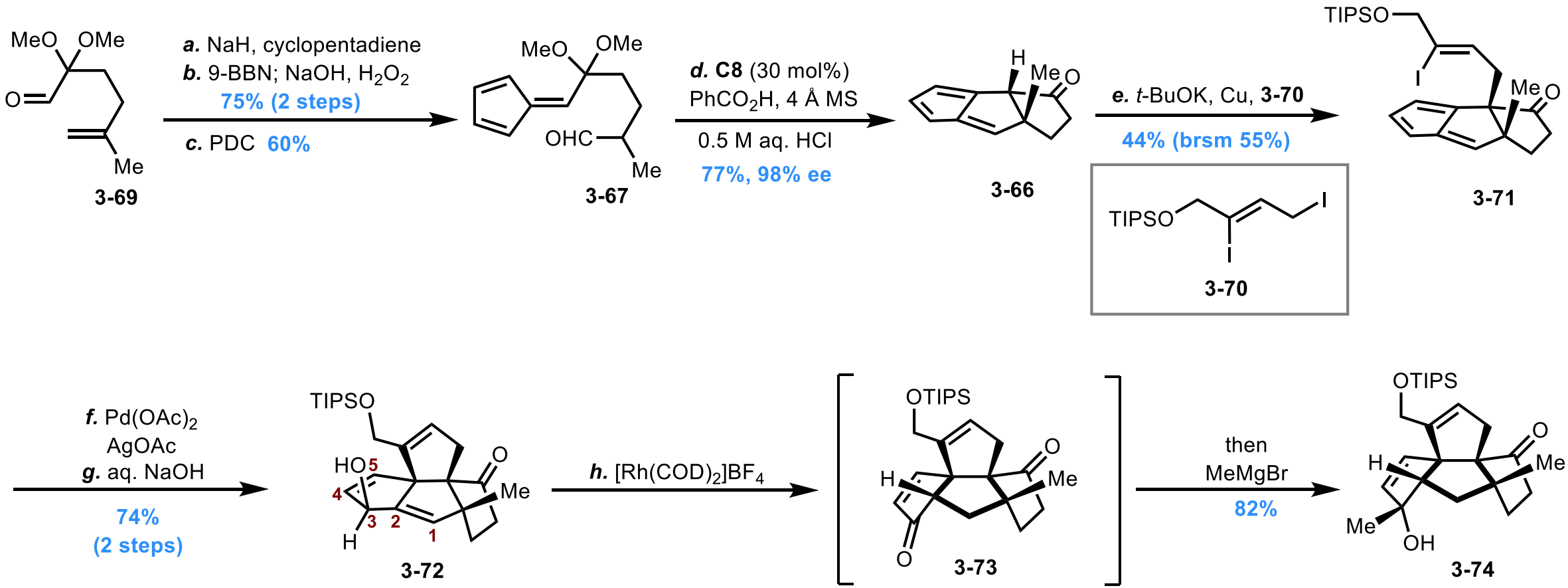


intermediate

Entry	R =	**C8**	$PhCO_2H$	T	**P**	Yield (%)	ee (%)
1	Me	10 mol%	20 mol%	rt	**3-66**	75	86
2	Me	10 mol%	20 mol%	-30 ℃	**3-66**	17	93
3	Me	20 mol%	20 mol%	-30 ℃	**3-66**	30	98
4	Me	30 mol%	15 mol%	-30 ℃	**3-66**	77	98
5	Me	30 mol%	20 mol%	-30 ℃	**3-66**	75	98
6	Me	30 mol%	30 mol%	-30 ℃	**3-66**	47	98
7	CH_2CH_2OBn	30 mol%	15 mol%	-30 ℃	**3-66a**	76	97

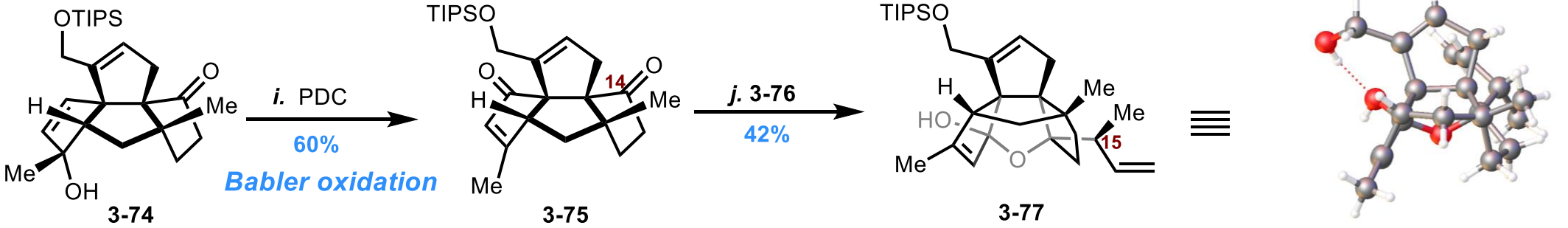
3. Sesterterpenoid Bipolarolide D——Lu (2024)

Construction of the Angular Triquinane

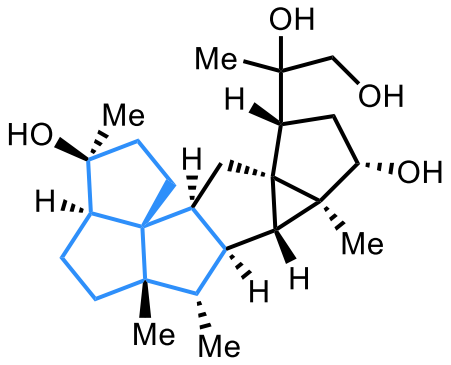


3. Sesterterpenoid Bipolarolide D——Lu (2024)

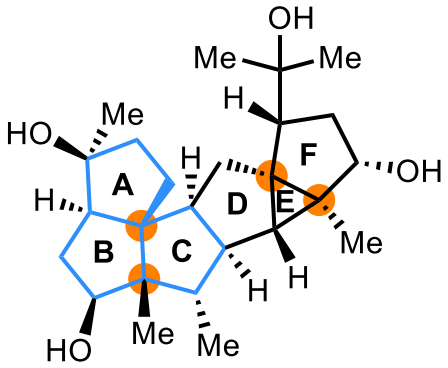
End Game



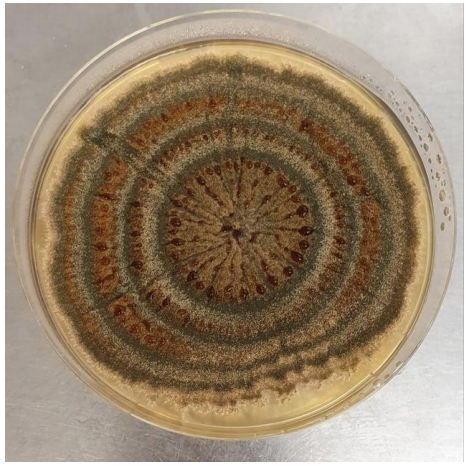
3. Sesterterpenoid Niduterpenoid B



Niduterpenoid A (**3-3**)



Niduterpenoid B (**3-4**)



(构巢曲霉)
Aspergillus nidulans

Stucture features

- ✓ Fused/angular tetraquinane
- ✓ Highly strained 3/5 bicyclic skeleton
- ✓ Thirteen contiguous stereocenters
- ✓ Four all-carbon quaternary centers

Bioactivity

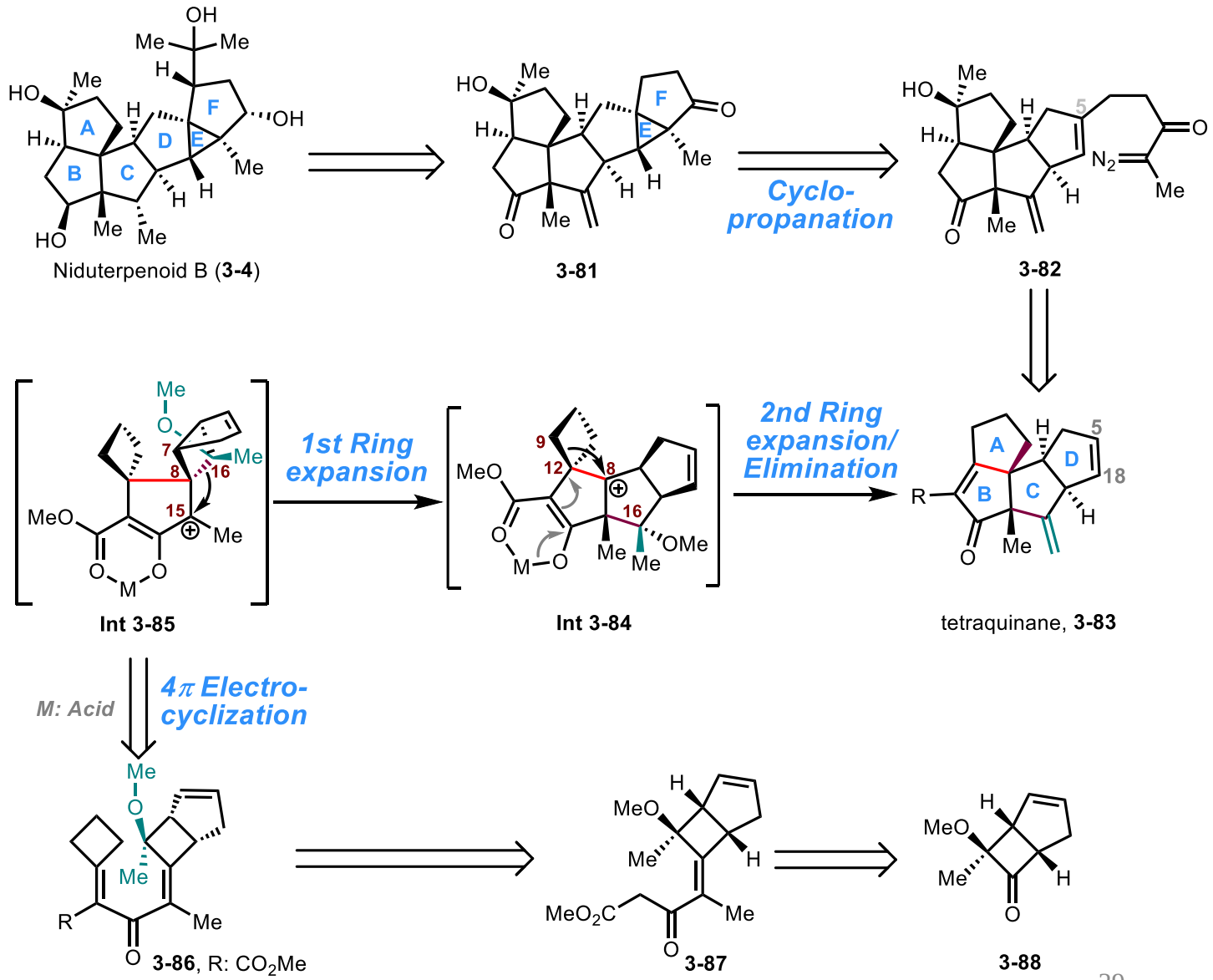
- ✓ Potential antagonists of ERα
  abolished 17-estradiol-induced proliferation of human breast tumor cell line MCF-7 (IC_{50} = 11.42 ± 0.85 μM)
  without exhibiting cytotoxic effects.

18) Li, Q.; Chen, C.; Wei, M.; Dai, C.; Cheng, L.; Tao, J.; Li, X. N.;Wang, J.; Sun, W.; Zhu, H.; Zhang, Y. *Org. Lett*. **2019**, *21*, 2290−2293.

3. Sesterterpenoid Niduterpenoid B——Tu(2024)

Retrosynthetic Analysis

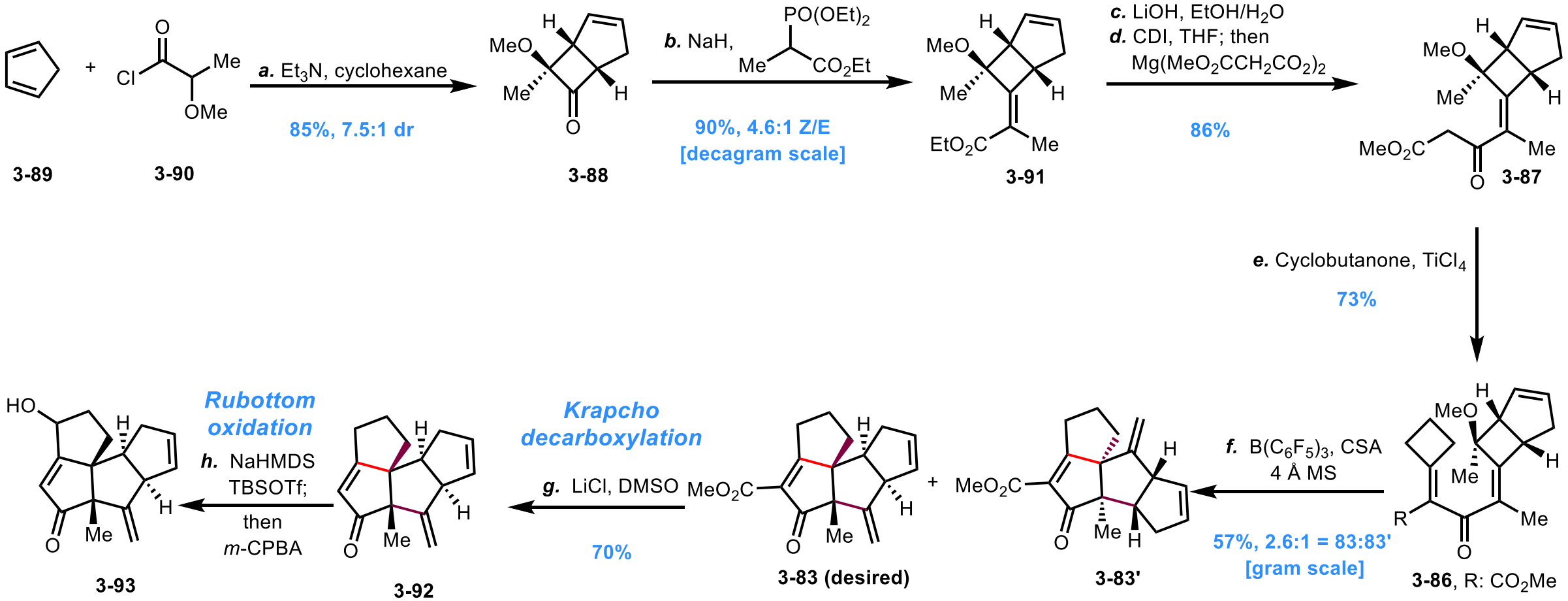
Yongqiang Tu



19) Xue, Y.; Hou, S. H.; Zhang, X.; Zhang, F. M.; Zhang, X. M.; Tu, Y. Q. *J. Am. Chem. Soc.* **2024**, *146*, 25445−25450

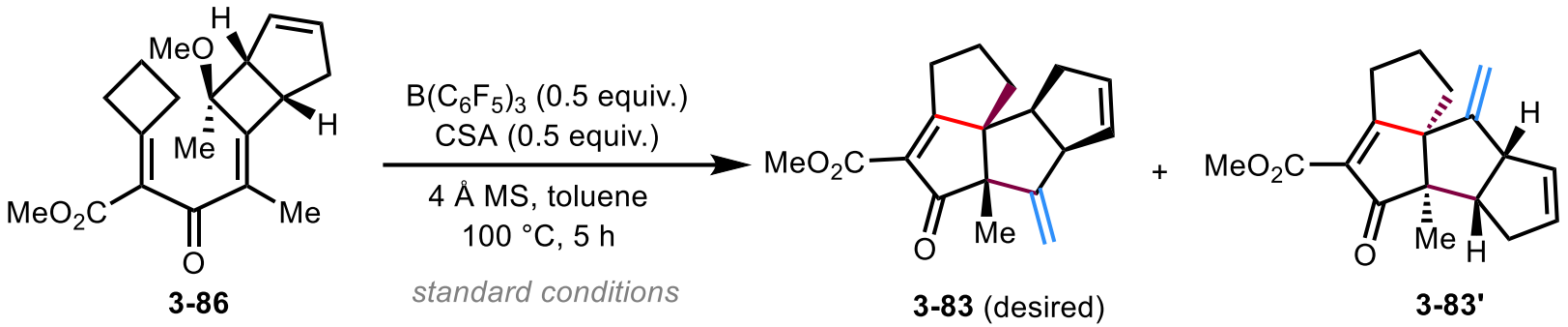
3. Sesterterpenoid Niduterpenoid B——Tu (2024)

Construction of the Angular Triquinane



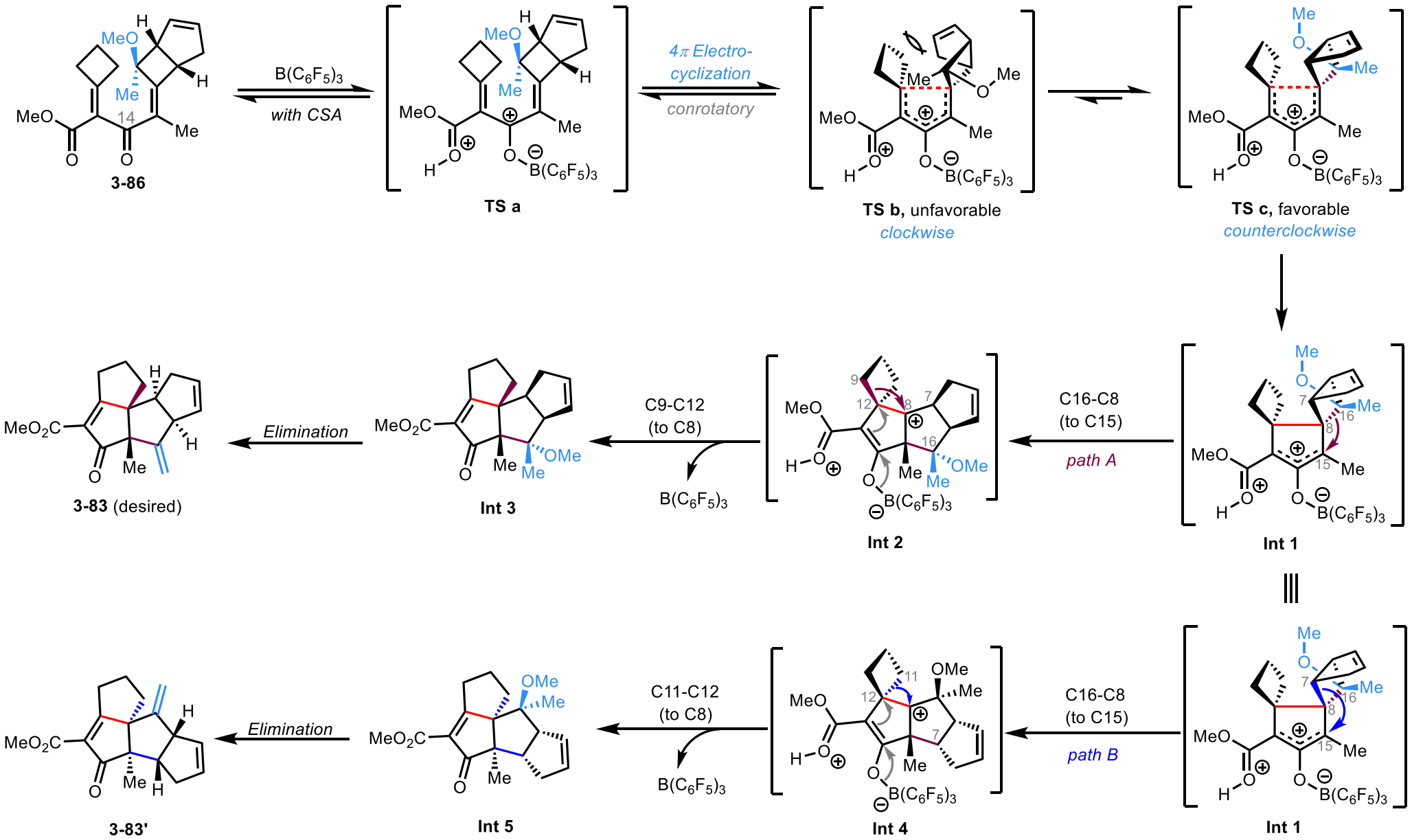
3. Sesterterpenoid Niduterpenoid B——Tu (2024)

Cascade Reaction Discovery and Optimization



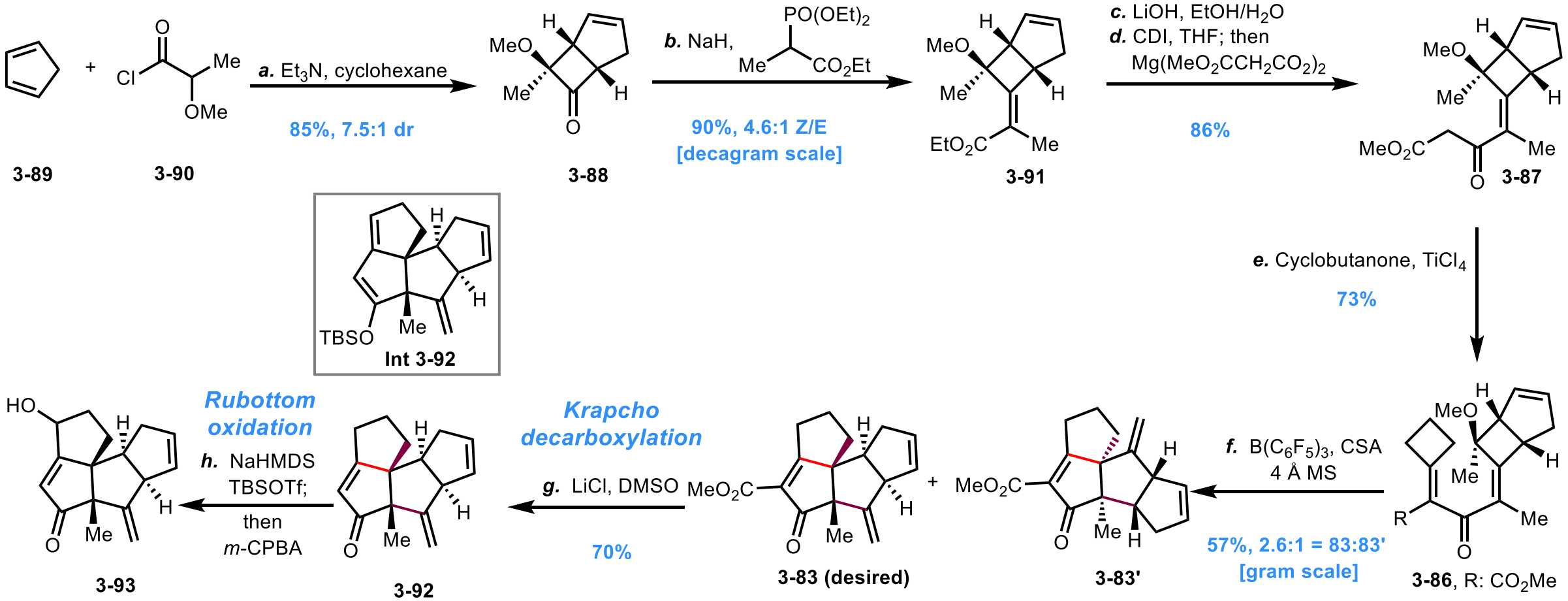
Entry	Variations from the "standard conditions"	Yield (%)	
		3-83	**3-83′**
1	none	36	14
2	3 g-scale of **86**	**41**	**16**
3	No $B(C_6F_5)_3$	0	0
4	CSA(1.0 equiv.), toluene, 120 ℃, 12 h	8	trace
5	No CSA	10	<5

3. Sesterterpenoid Niduterpenoid B——Tu (2024)



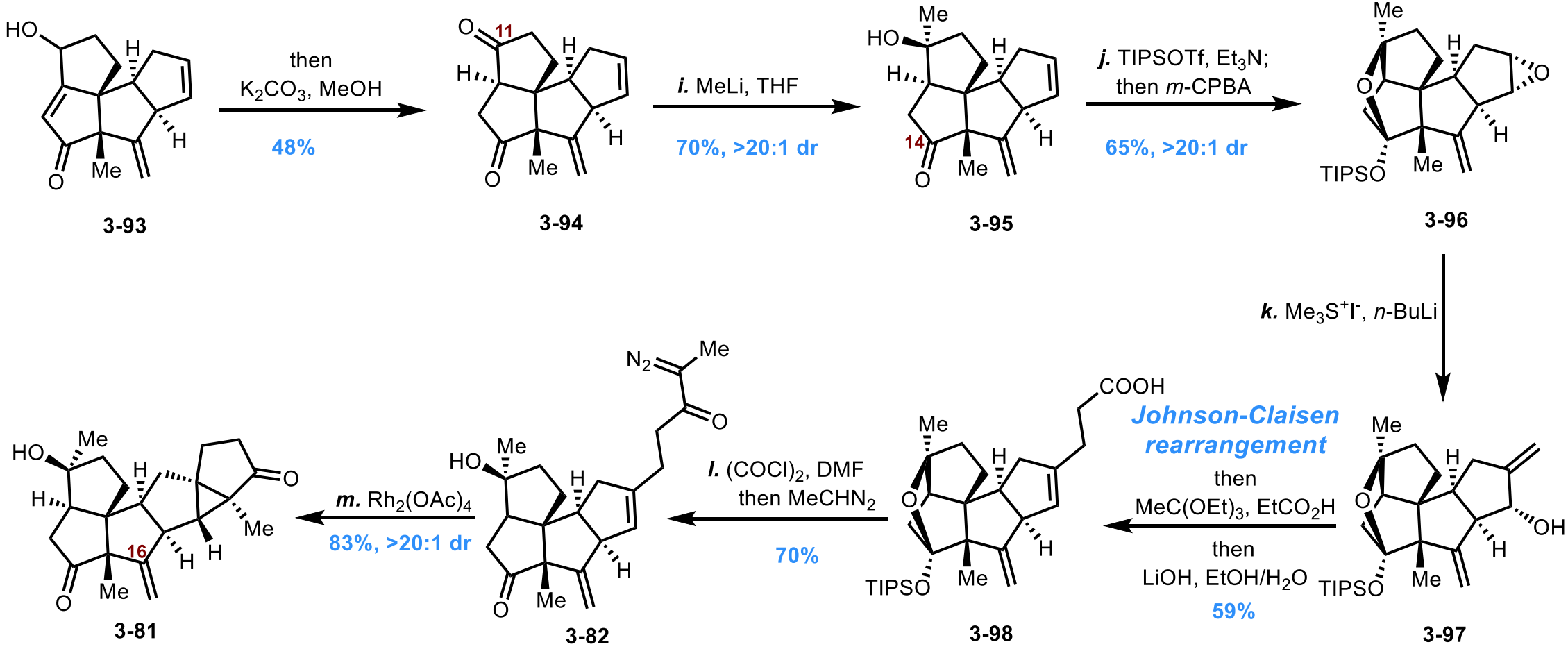
3. Sesterterpenoid Niduterpenoid B——Tu (2024)

Construction of the Angular Triquinane



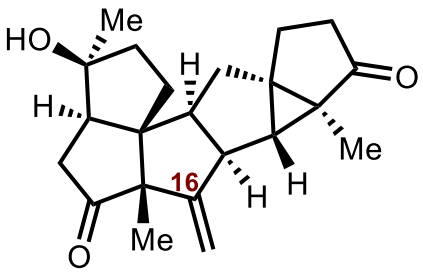
3. Sesterterpenoid Niduterpenoid B——Tu (2024)

Construction of the 3/5 bicyclic framework



3. Sesterterpenoid Niduterpenoid B——Tu(2024)

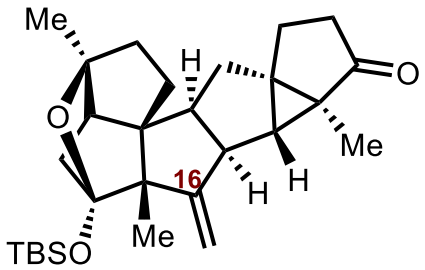
End Game



3-81

then TBSOTf, Et_3N

64%, >20:1 dr

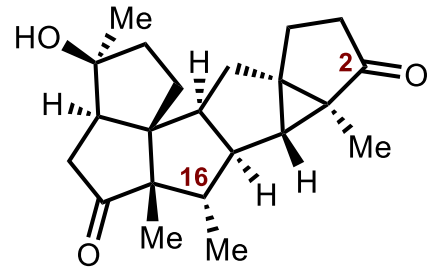


3-99

n. $Mn(dpm)_3$, TBHP
$Ph(i\text{-}PrO)SiH_2$, i-PrOH

then HF•pyridine

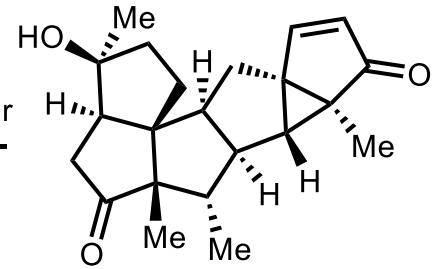
62%, 5.9:1 dr



3-100

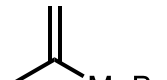
o. TBSOTf; then PhSeCl;
then H_2O_2

45%
76% >20:1 dr

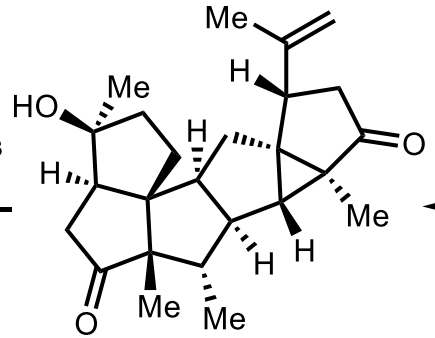


3-101

p.



$CuBr•Me_2S$

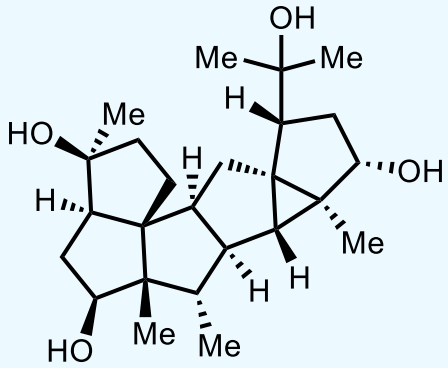


3-102

q. $Mn(dpm)_3$, $PhSiH_3$
O_2, EtOH

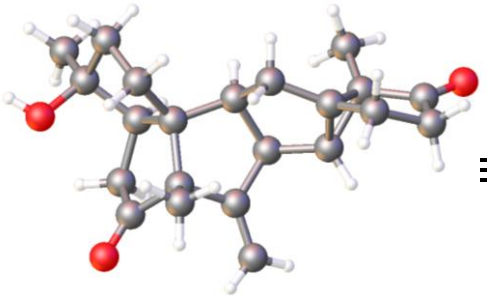
then $NaBH_4$

79%



Niduterpenoid B (**3-4**)

≡



x-ray of **3-4**

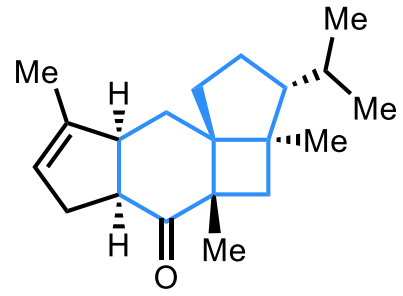
Content

3. Summary

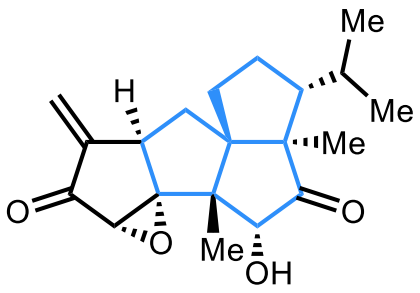
1. Structural Reorganization Strategy

Dai:

12&13 steps

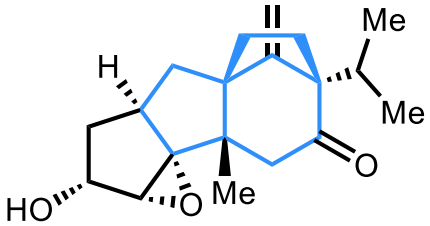


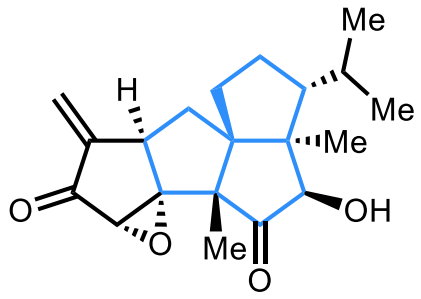
Cargill rearrangement



Crinipellin B

16 steps

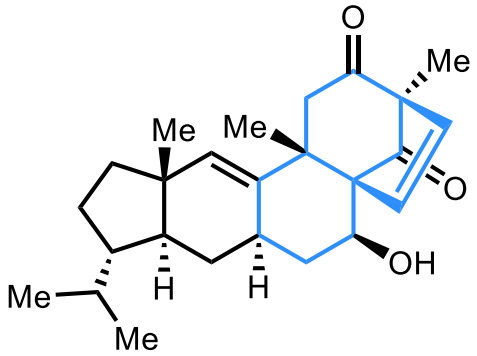




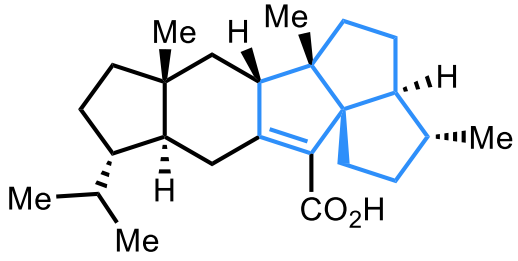
Crinipellin A

Ding:

15 steps



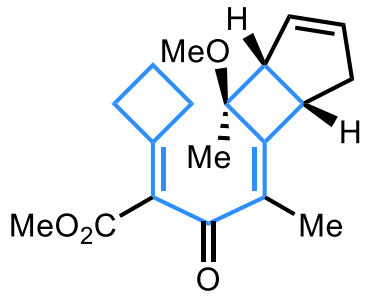
Dowd-Beckwith rearrangement



Retigeranic acid A

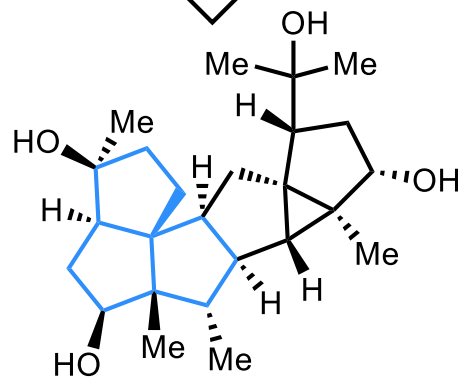
Tu:

17 steps



Double ring expansion

Nazarov annulation



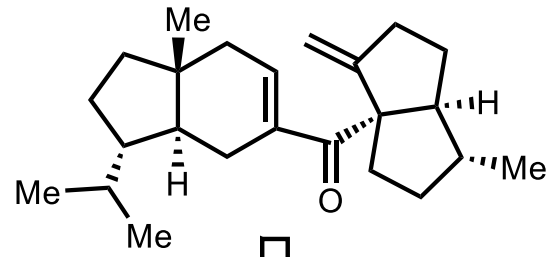
Niduterpenoid B

3. Summary

2. Annulation of Core Ring

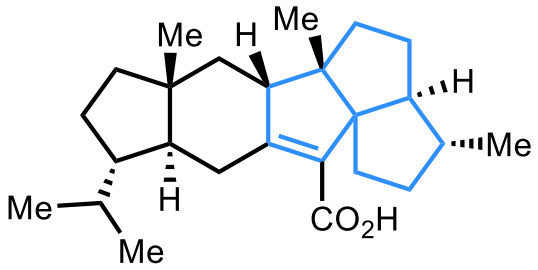
Chen:

16 steps



MHAT

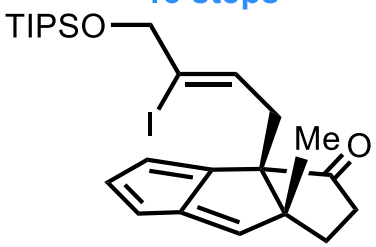
5-endo-trig annulation



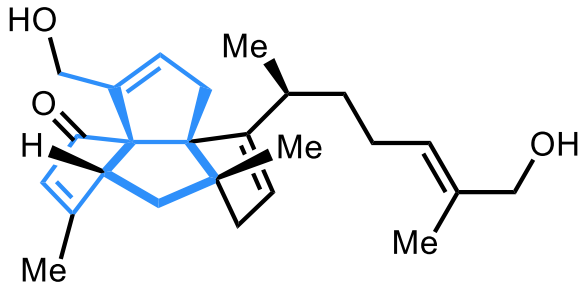
Retigeranic acid A

Lu:

13 steps



Heck cyclization



Bipolarolide D

Thanks for your kind attention