Literature Presentation
Renaud Group

January 22th 2015

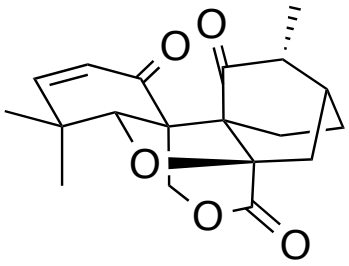
b
UNIVERSITÄT
BERN

Enantioselective Total Syntheses of (–)-Maoecrystal V

J. Am. Chem. Soc. **2014**, *136*, 17738–17749.
(DOI: 10.1021/ja510573v)

And

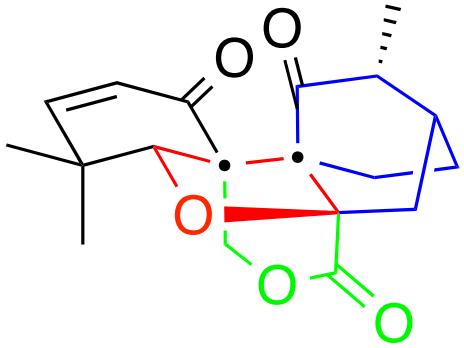
J. Am. Chem. Soc. **2014**, *136*, 17750–17756.
(DOI: 10.1021/ja5109694)



Julien

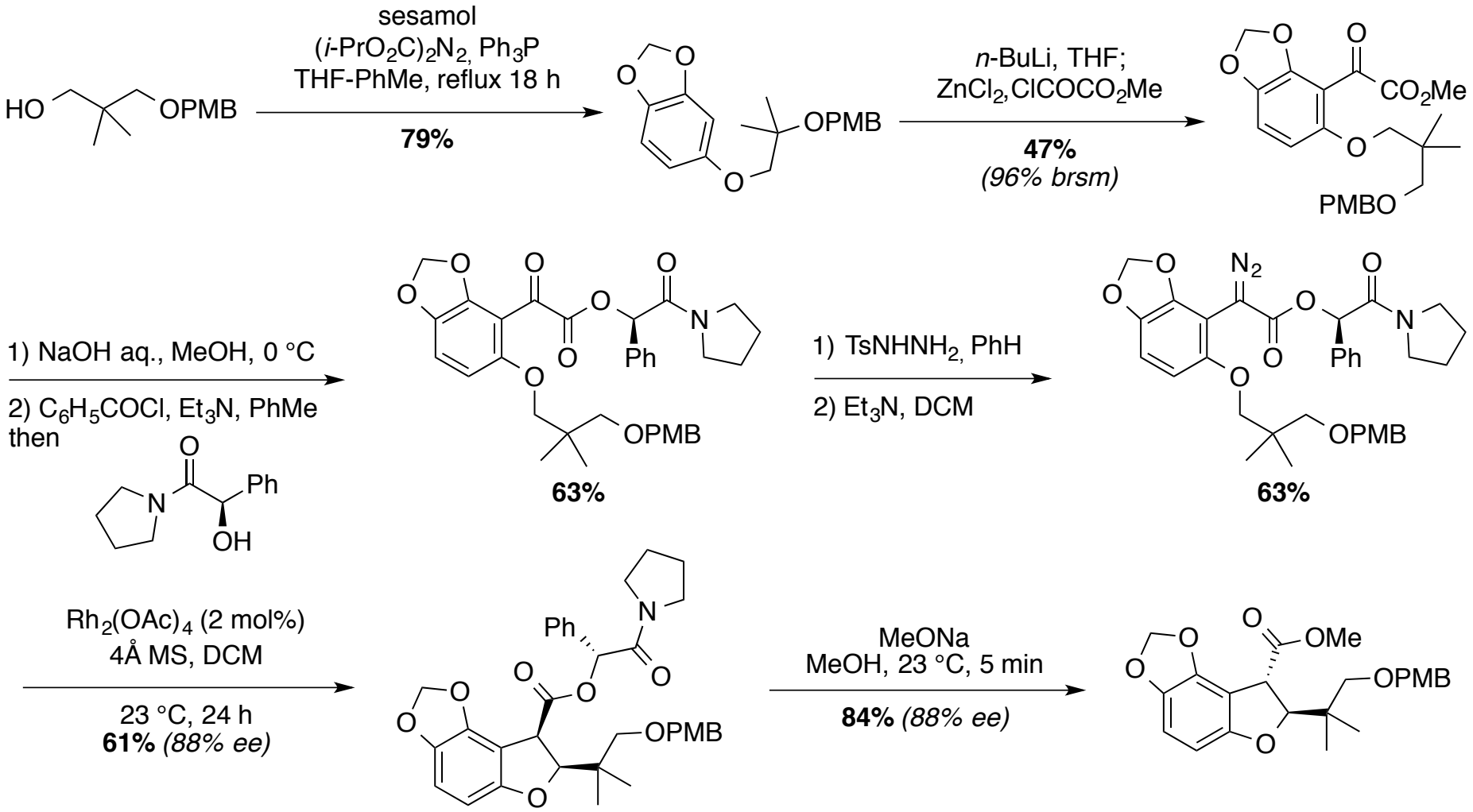
About Maoecrystal V

- Isolated from *Isodon eriocalyx* (Sun & co, 1994)
- Structure assignment *via* crystal X-ray diffraction (2004)
- 2 vicinal quaternary center, Strained cyclic ether, a spirolactone, a bicyclo[2.2.2]octane ring system and 6 stereogenic centers
- Cytotoxic activity against HeLa cells (IC_{50} = 60 nM)



Sheng-Hong Li; Jia Wang; Xue-Mei Niu; Yun-Heng Shen; Hong-Jie Zhang; Han-Dong Sun; Ma-Lin Li; Qin-E Tian; Yang, L.; Peng Cao, A.; Zheng, Q.-T. *Org. Lett.* **2004**, *6*, 4327–4330.
Sun, H.-D.; Huang, S.-X.; Han, Q.-B. *Nat. Prod. Rep.* **2006**, *23*, 673–698.

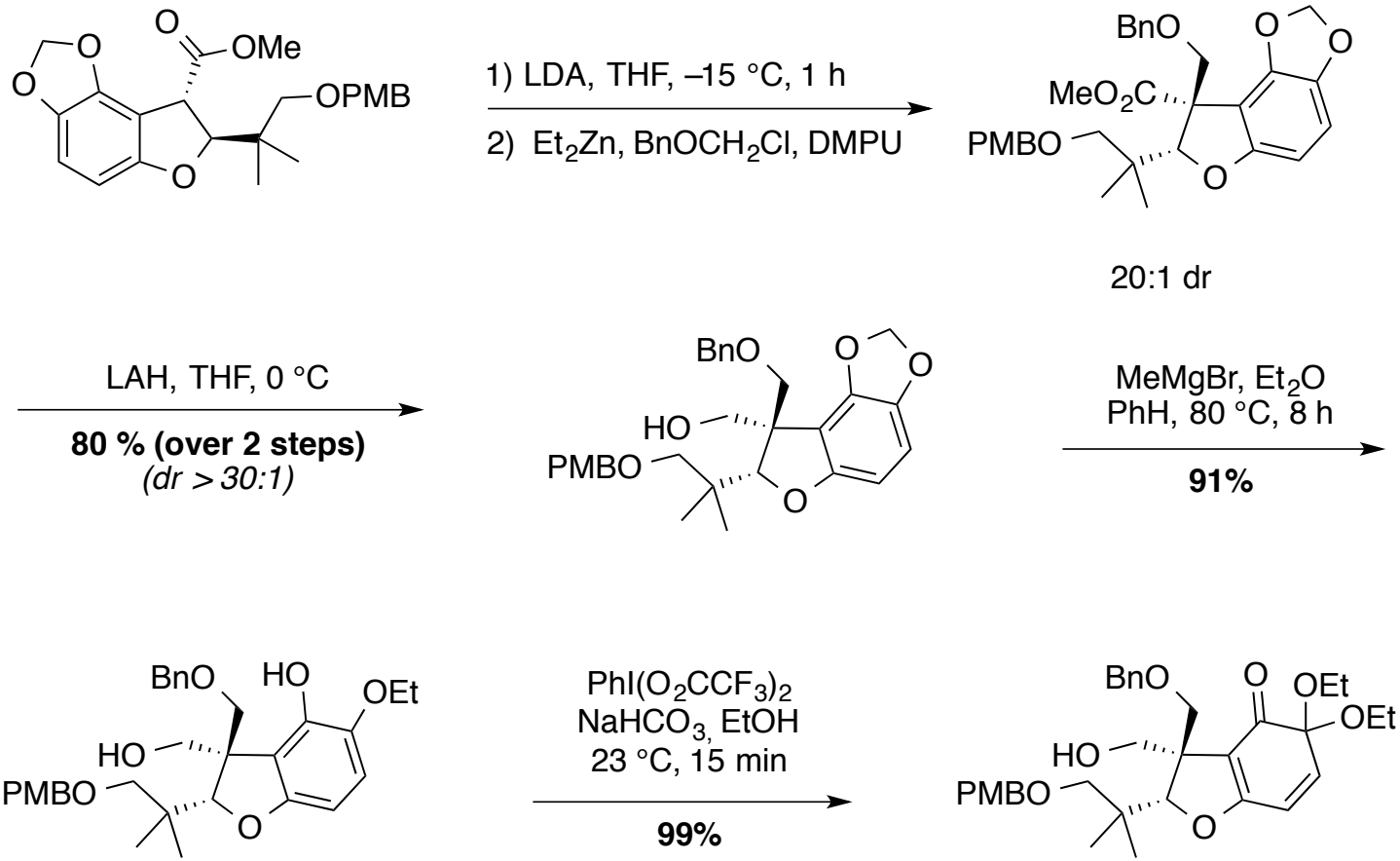
Zakarian/Davies' Synthesis



Lu, P.; Gu, Z.; Zakarian, A. *J. Am. Chem. Soc.* **2013**, *135*, 14552–14555.

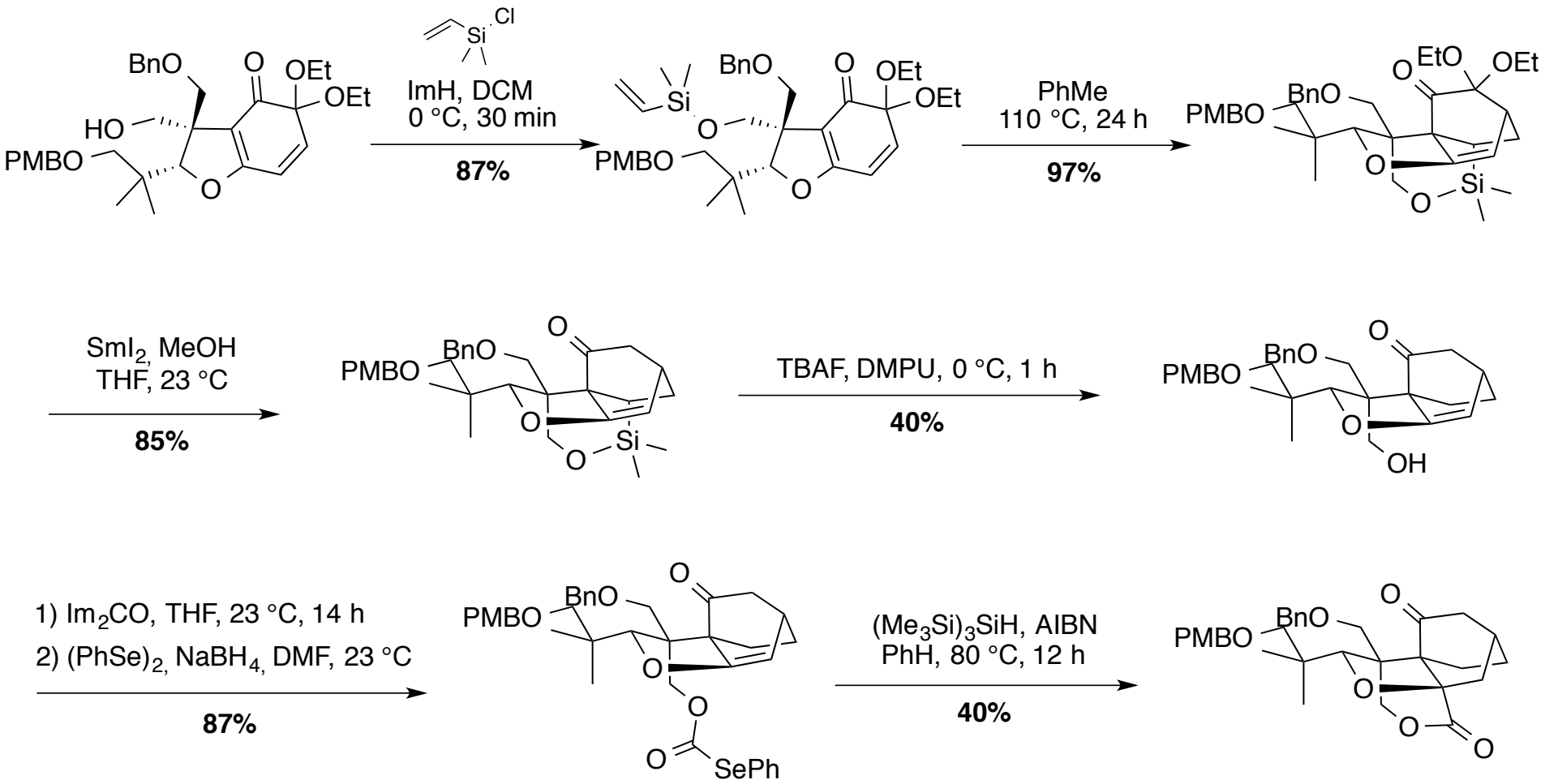
Lu, P.; Mailyan, A.; Gu, Z.; Guptill, D. M.; Wang, H.; Davies, H. M. L.; Zakarian, A. *J. Am. Chem. Soc.* **2014**, *136*, 17738–17749.

Zakarian/Davies' Synthesis



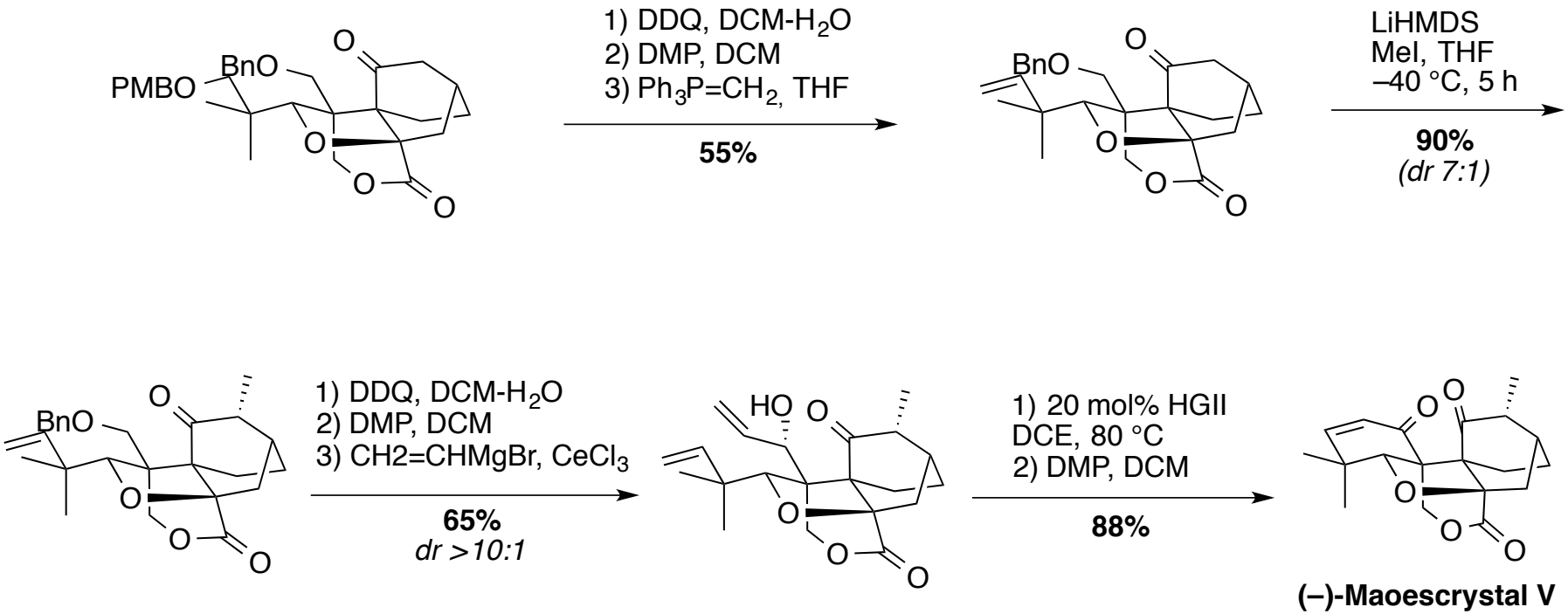
Lu, P.; Mailyan, A.; Gu, Z.; Guptill, D. M.; Wang, H.; Davies, H. M. L.; Zakarian, A. *J. Am. Chem. Soc.* **2014**, *136*, 17738–17749.

Zakarian/Davies' Synthesis



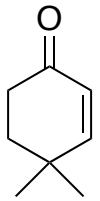
Lu, P.; Mailyan, A.; Gu, Z.; Guptill, D. M.; Wang, H.; Davies, H. M. L.; Zakarian, A. *J. Am. Chem. Soc.* **2014**, *136*, 17738–17749.

Zakarian's Synthesis



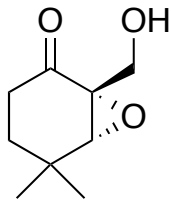
Lu, P.; Mailyan, A.; Gu, Z.; Guptill, D. M.; Wang, H.; Davies, H. M. L.; Zakarian, A. *J. Am. Chem. Soc.* **2014**, *136*, 17738–17749.

Thomson's Synthesis



1) CH_2O,sodium dodecyl sulfate
DMAP, H_2O

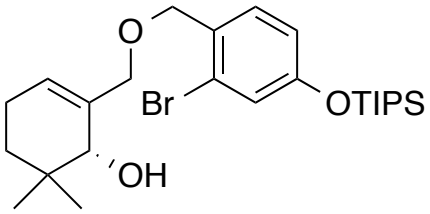
2) (–)-DIPT, $Ti(OiPr)_4$
*t*BuOOH, 4Å MS



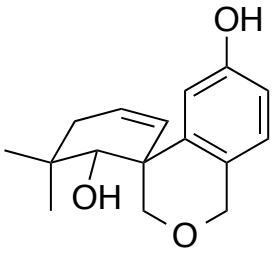
(53% over 2 steps)
Sharpless epoxidation
94% ee

3) TfOH, **10**
4) $NaBH_4$
5) I_2, Ph_3P, imidazole
6) Zn, NH_4Cl

(61% over 4 steps)

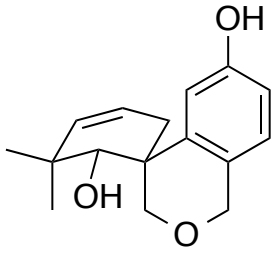


7) TESCl, imidazole (92%)
8) $Pd(PPh_3)_4$, PMP, 125 °C *then* TBAF

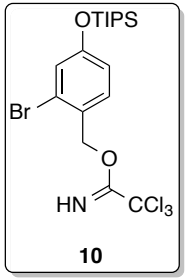


minor
13%

+



major
52%

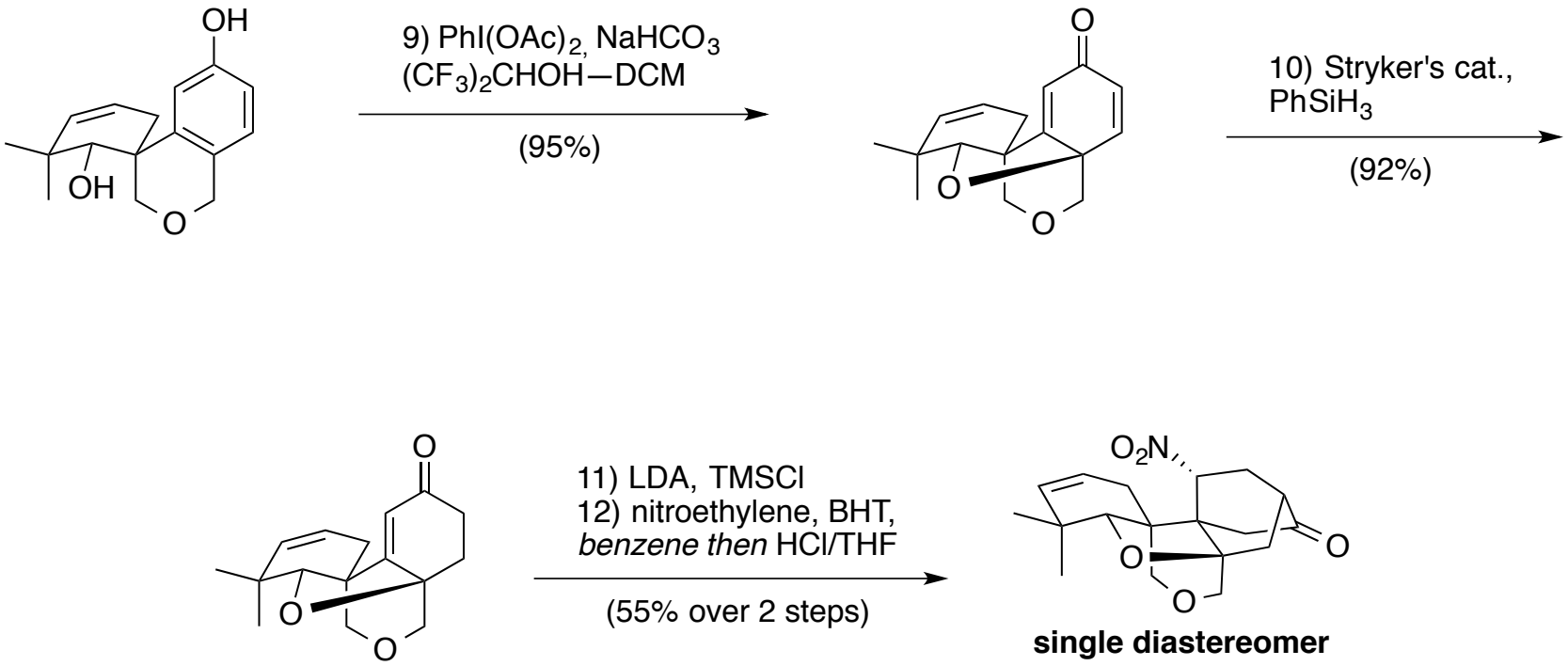


10

Zheng, C.; Dubovyk, I.; Lazarski, K. E.; Thomson, R. J. *J. Am. Chem. Soc.* **2014**, *136*, 17750–17756.

Thomson's Synthesis

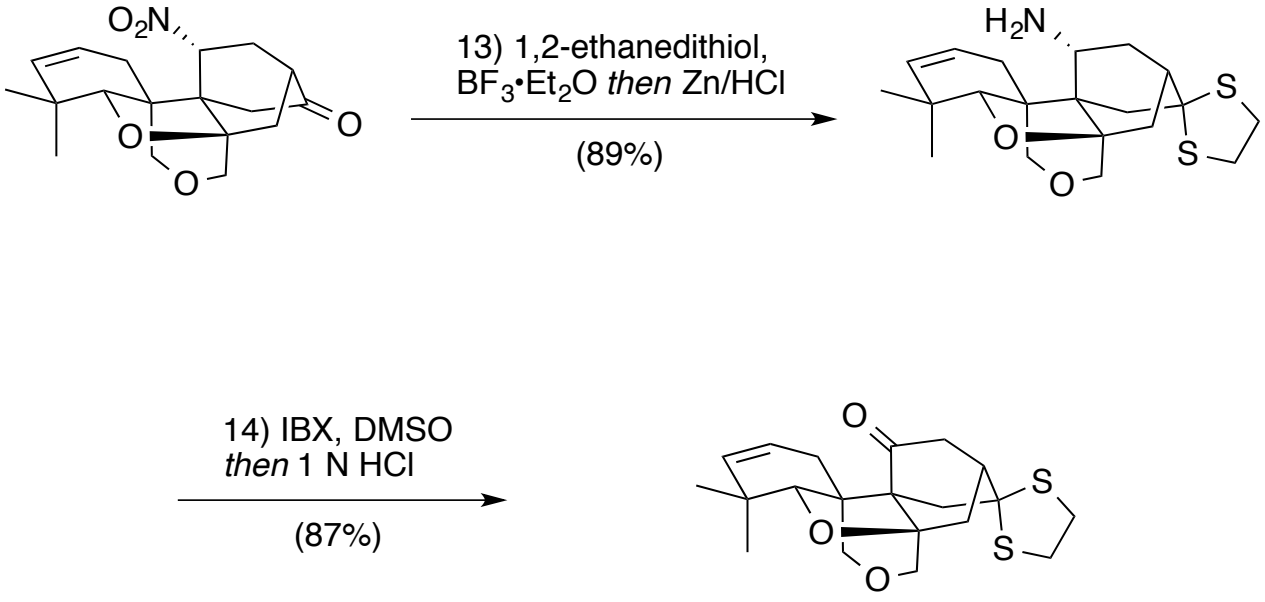
Stryker's cat. = $[(Ph_3P)CuH]_6$



single diastereomer

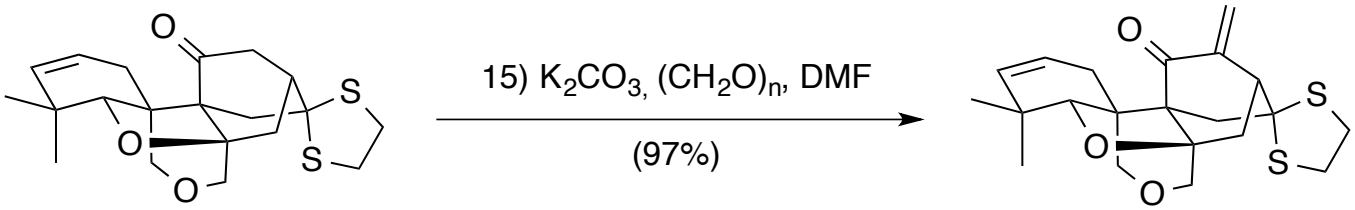
Zheng, C.; Dubovyk, I.; Lazarski, K. E.; Thomson, R. J. *J. Am. Chem. Soc.* **2014**, *136*, 17750–17756.

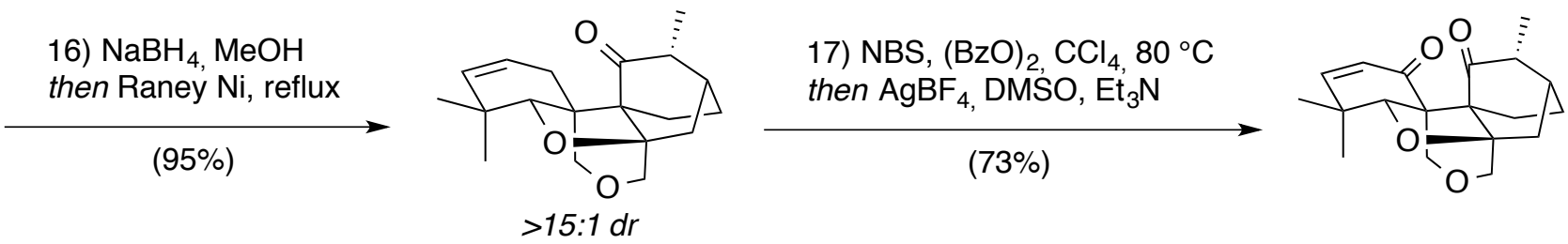
Thomson's Synthesis



Zheng, C.; Dubovyk, I.; Lazarski, K. E.; Thomson, R. J. *J. Am. Chem. Soc.* **2014**, *136*, 17750–17756.

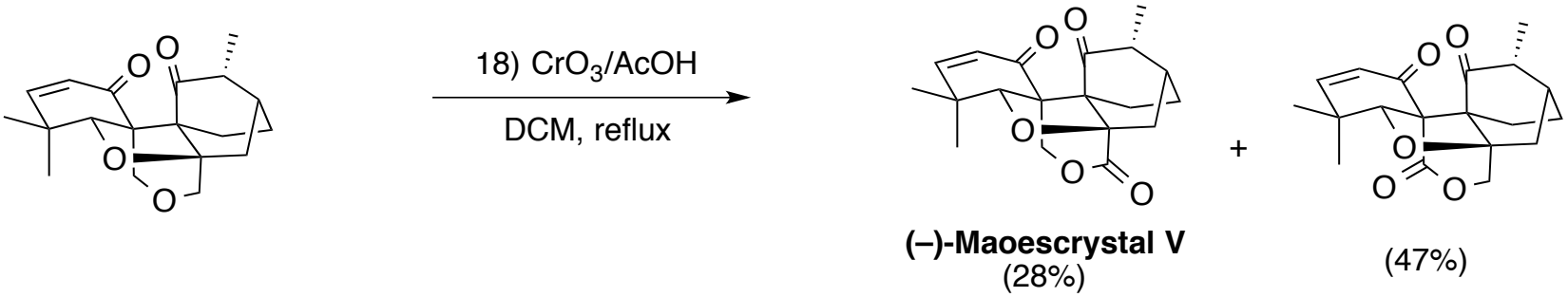
Thomson's Synthesis





Zheng, C.; Dubovyk, I.; Lazarski, K. E.; Thomson, R. J. *J. Am. Chem. Soc.* **2014**, *136*, 17750–17756.

Thomson's Synthesis



Zheng, C.; Dubovyk, I.; Lazarski, K. E.; Thomson, R. J. *J. Am. Chem. Soc.* **2014**, *136*, 17750–17756.

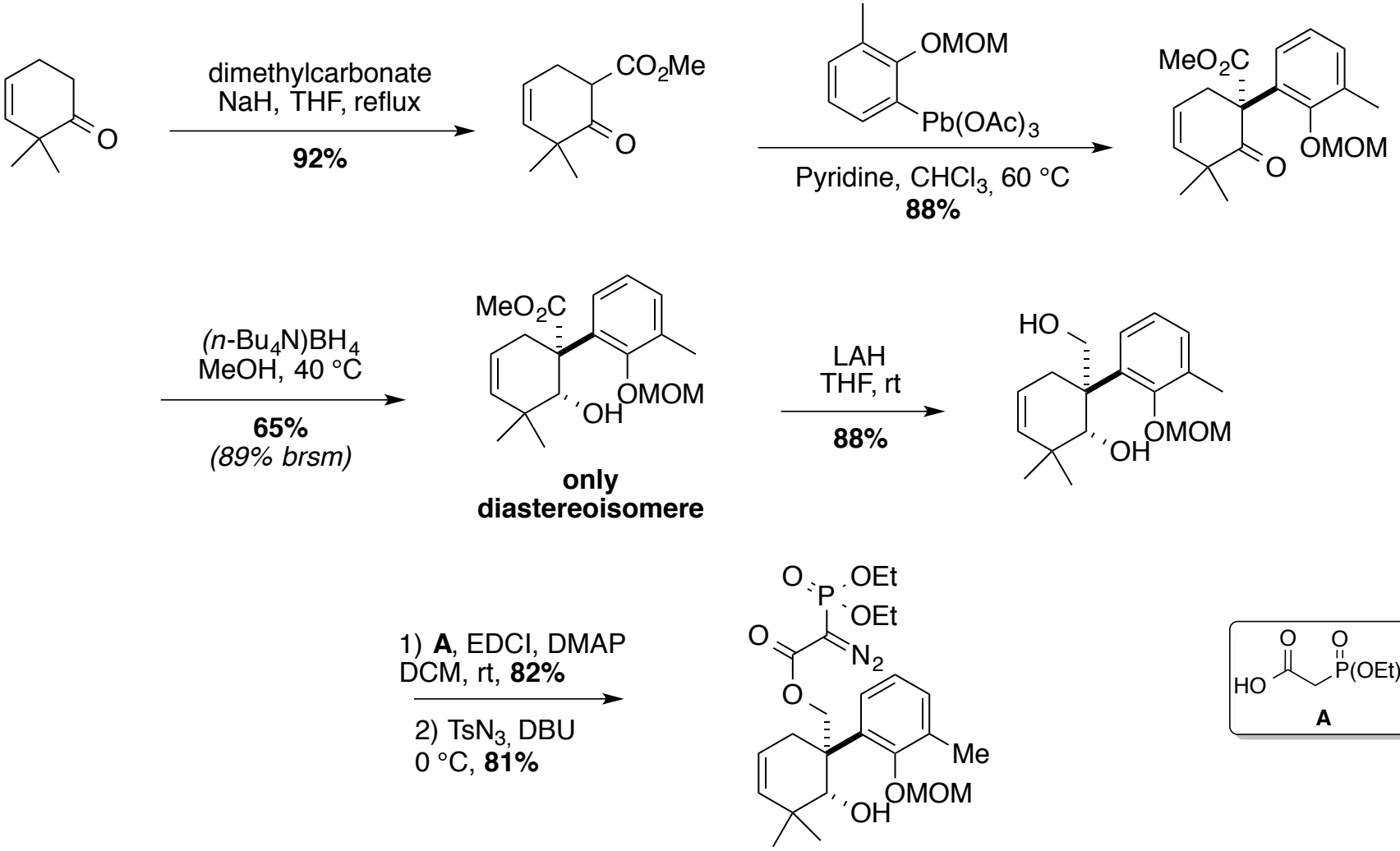
Conclusion

- Only 2 enantioselectives total syntheses
  - Zakarian (2014): 26 Steps, Overall Yield = 0.2%
  - Thomson (2014): 18 Steps, Overall Yield = 1%

- Key Steps:
  - Zakarian: Stereoselective Rh-catalyzed C-H functionalization and intramolecular Diels-Alder
  - Thomson: Heck spirocylization, oxidative cyclodearomatization, intermolecular Diels-Alder

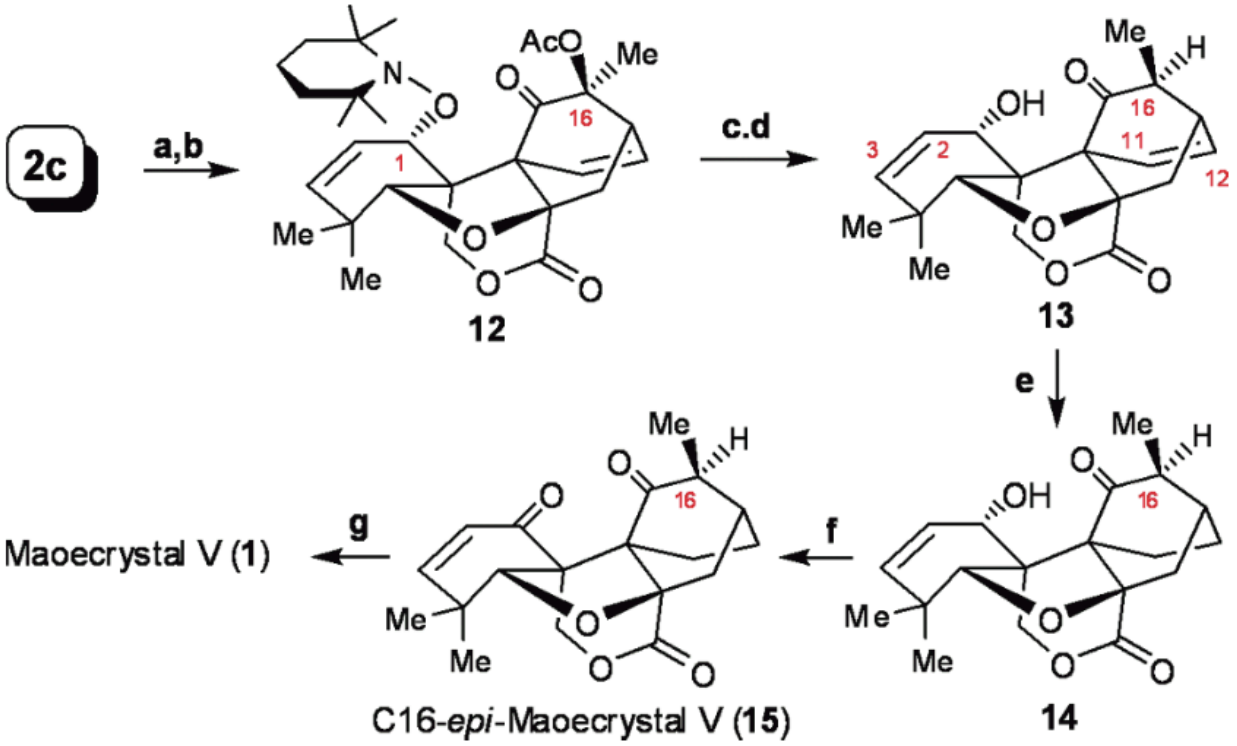
Thank's
for
your attention

Yang's Synthesis – Synthesis of the key intermediate



Gong, J.; Lin, G.; Sun, W.; Li, C.-C.; Yang, Z. *J. Am. Chem. Soc.* **2010**, *132*, 16745–16746.

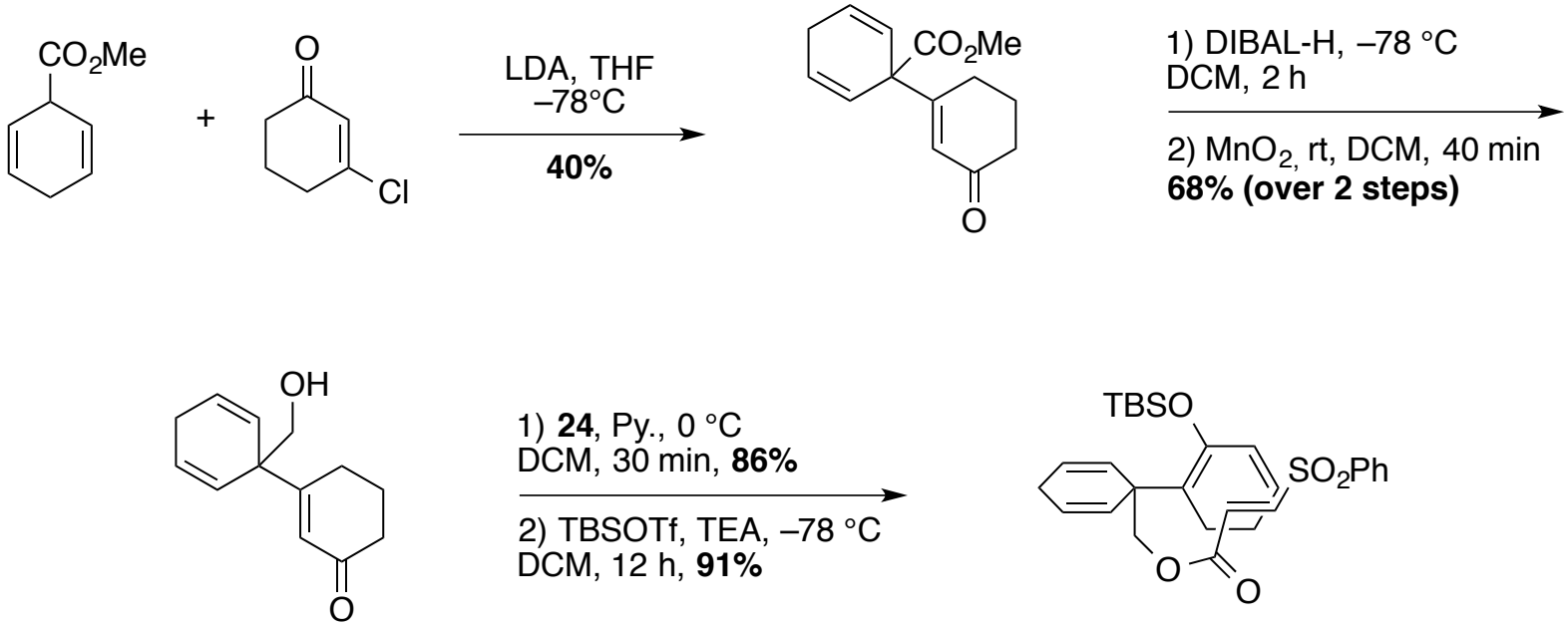
Yang's Synthesis – End of the Synthesis



[a] Reagent and conditions: (a) NBS, $(PhCO_2)_2$, CCl_4, reflux, 2 h, 90%; (b) Bu_3SnH, TEMPO, PhH, reflux, 2 h, 75%; (c) Zn, AcOH, THF, H_2O, 70 °C, 2 h, 85%; (d) SmI_2, THF, MeOH, rt, 10 min, 88%; (e) Lindlar cat. MeOH, THF, rt, 2 h, 92%; (f) DMP, CH_2Cl_2, rt, 1 h, 88%; (g) DBU, toluene, 100 °C, 1 h, 48% (90% brsm).

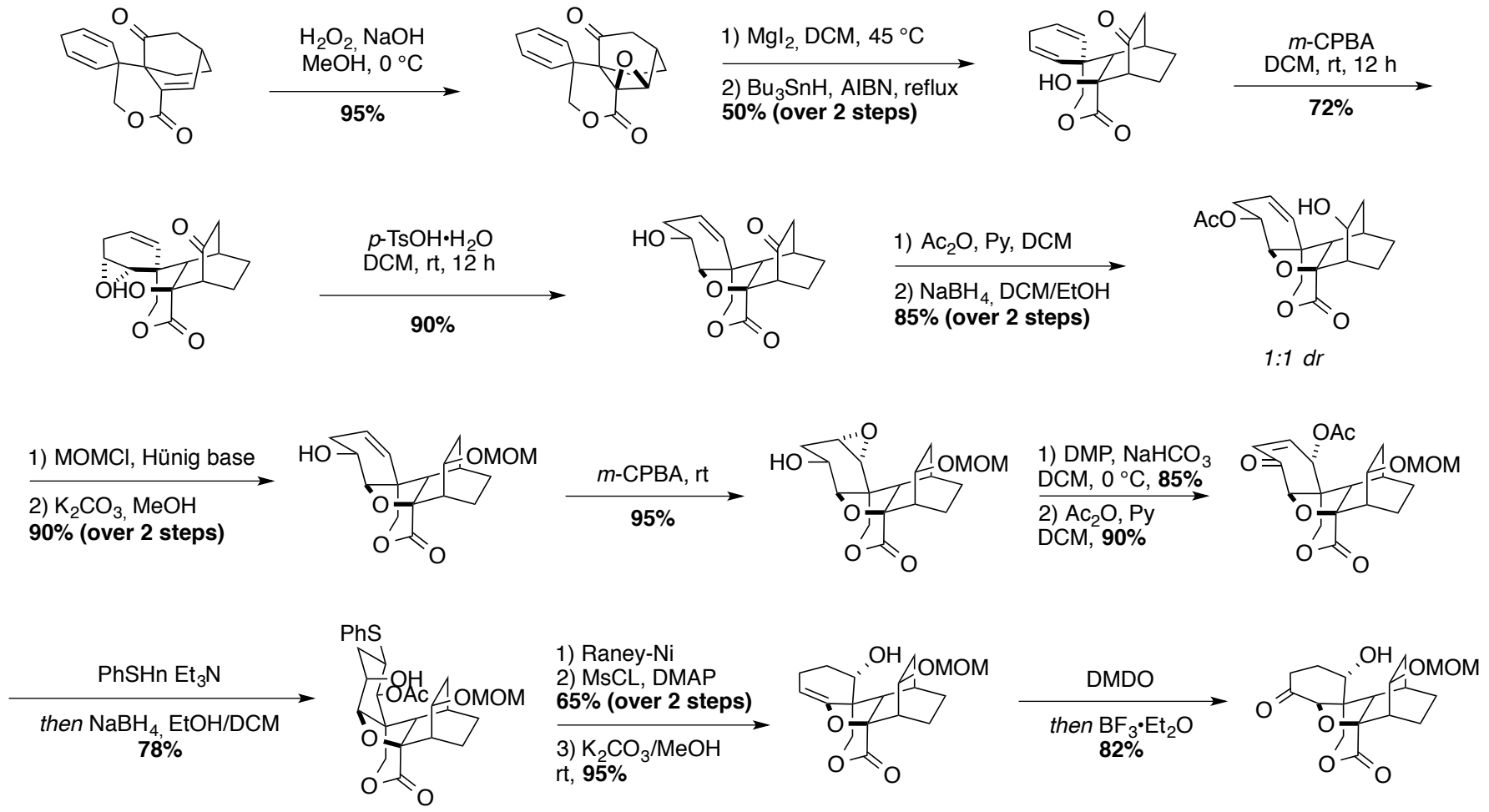
Gong, J.; Lin, G.; Sun, W.; Li, C.-C.; Yang, Z. *J. Am. Chem. Soc.* **2010**, *132*, 16745–16746.

Danishefsky's Synthesis – Synthesis of the key intermediate



Peng, F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2012**, *134*, 18860–18867.

Danishefsky's Synthesis – End of the Synthesis



Peng, F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2012**, *134*, 18860–18867.

Danishefsky's Synthesis – End of the Synthesis

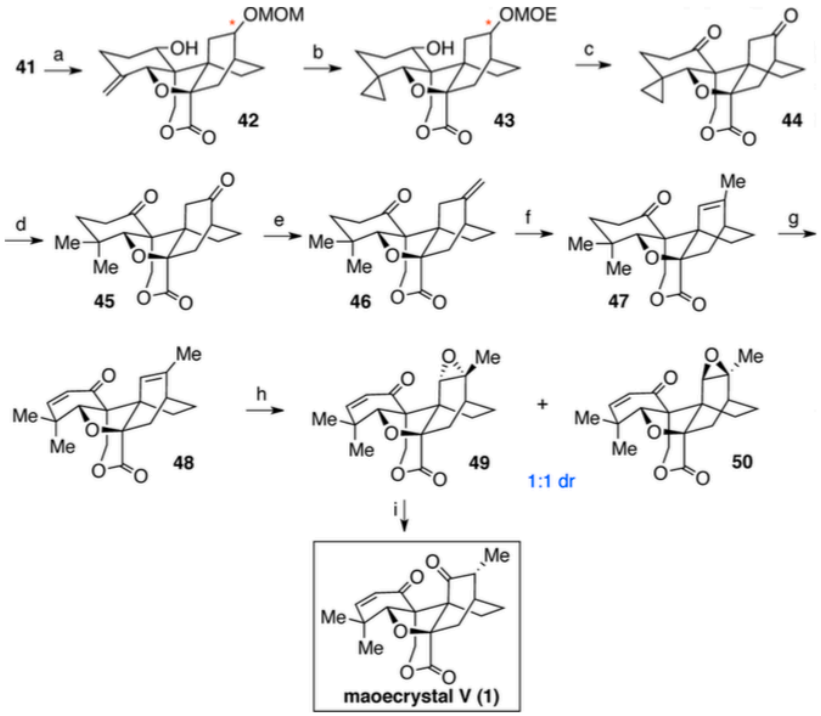


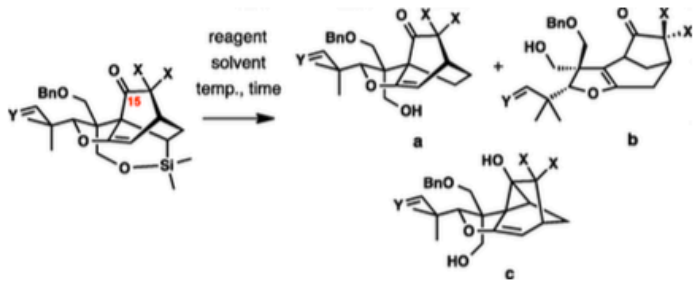
Figure 10. Completion of the synthesis of maoecrystal V (**1**). Key: (a) Lombardo reagent, DCM, room temperature, 85%; (b) CH_2I_2, Zn/Ag, Et_2O, 36 °C, 88%; (c) PCC, DCM, room temperature, 76%; (d) H_2, PtO_2, AcOH, 40%; (e) Lombardo reagent, DCM, 0 °C, 80%; (f) *p*-TsOH·H_2O, benzene, 76 °C, 85%; (g) LDA, TMSCl, THF, −78 °C, 90%; then $Pd(TFA)_2$, CH_3CN, 80%; (h) TFDO, CH_2Cl_2, −78 °C→0 °C, dr = 1:1, 90%; (i) BF_3·OEt_2, DCM, room temperature, 85%.

Peng, F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2012**, *134*, 18860–18867.

Zakarian's Sythesis

UNIVERSITÄT BERN

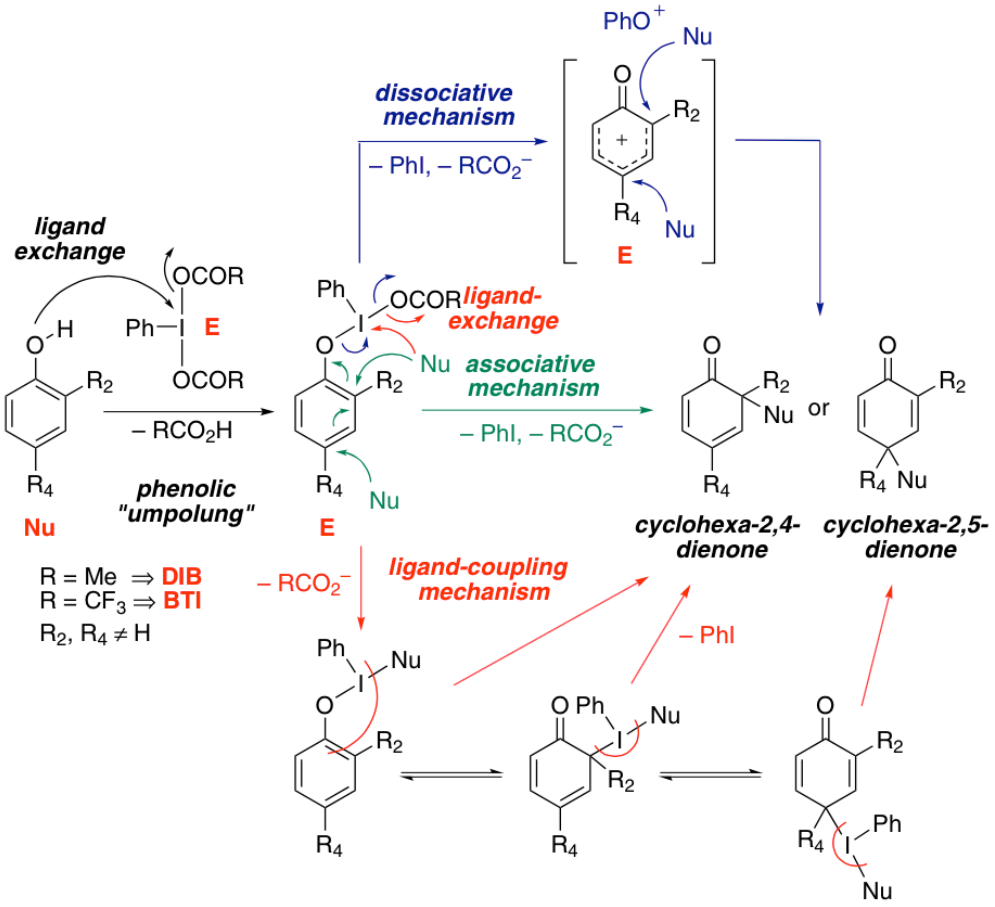
Table 4



entry	X	Y	reagent solvent	temp (°C), time (h)	a:b:c[a] (yield, a)
1	H	H, OBn	Bu_4NF, DMSO	0, 0.2	1.0:1.8:1 (20%)
2	H	H, OBn	Bu_4NF, DMSO	23, 0.2	0.9:1.5:1
3	H	H, OBn	Bu_4NF, DMF	−20, 2	1.5:1.3:1
4	H	H, OBn	Bu_4NF, DMF	0, 0.5	2.3:1.8:1
5	H	H, OBn	Bu_4NF, DMF	23, 0.3	1.9:1.6:1
6	H	H, OBn	Bu_4NF, DMF, (slow addition)	23, 3.2	1.6:1.3:1
7	H	H, OBn	Bu_4NF, NMP	0, 1.0	1.4:1.7:1
8	H	H, OBn	Bu_4NF, DMPU	0, 1.0	3.2:1.8:1
9	H	H, OBn	Bu_4NF, DMA	0, 0.5	2.4:1.7:1
10	H	H, OBn	Bu_4NF, DMSO−*t*-BuOH (4:1)	75, 1	0.3:1.2:1
11	H	H, OBn	Bu_4NF, AcOH, THF	0, 1.0	no reaction
12	H	H, OBn	CsF, *t*-BuOH	70, 15	no reaction
13	H	H, OBn	$Bu_4NPh_3SiF_2$, DMSO	50, 36	0:20:1
14	H	H, OBn	$Bu_4NPh_3SiF_2$, *t*-BuOH	50, 15	no reaction
15	OEt	CH_2	Bu_4NF, DMF	23, 0.2	0.8:5.1:1 (7%)
16	OEt	CH_2	Bu_4NF, THF	23, 0.5	no reaction
17	OEt	CH_2	Bu_4NF, MeCN	23, 0.2	0:3.4:1
18	H	CH_2	Bu_4NF, DMF	23, 0.5	1.1:3.6:1
19	H	H, OPMB	Bu_4NF, DMA	0, 1.0	2.9:2.2:1
20	H	H, OPMB	Bu_4NF, DMPU	0, 1.0	3.2:1.9:1 40–50%

Lu, P.; Mailyan, A.; Gu, Z.; Guptill, D. M.; Wang, H.; Davies, H. M. L.; Zakarian, A. *J. Am. Chem. Soc.* **2014**, *136*, 17738–17749.

Oxidative aromatization

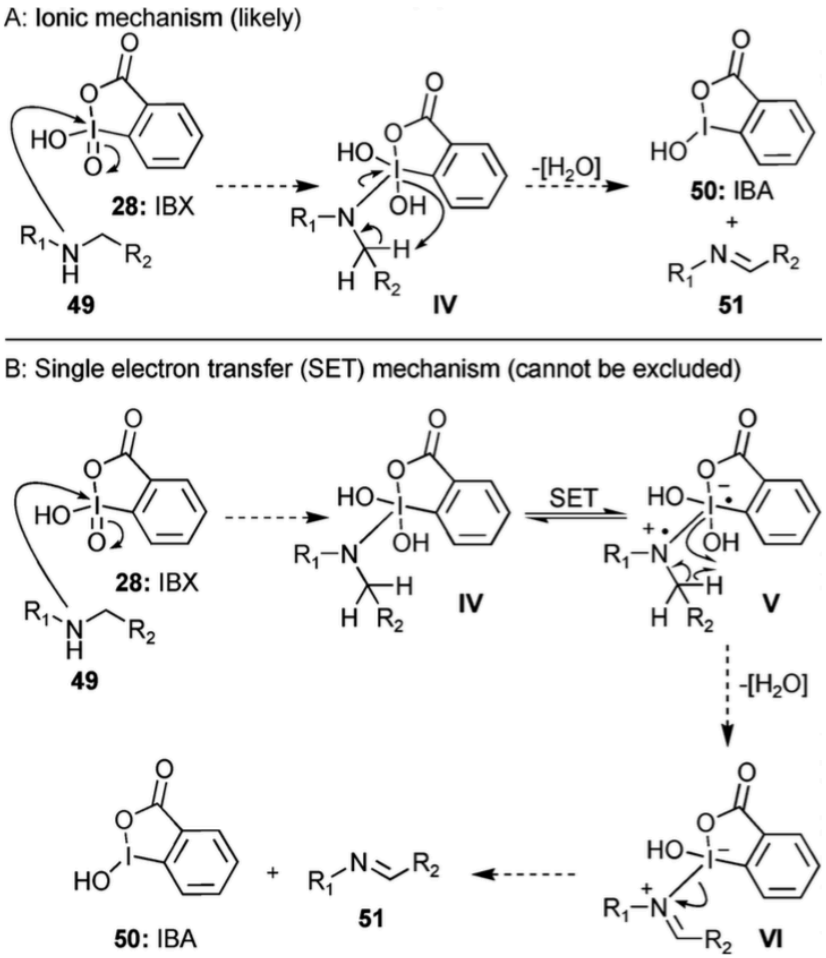


Scheme 4.

Pouységu, L.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 2235–2261.

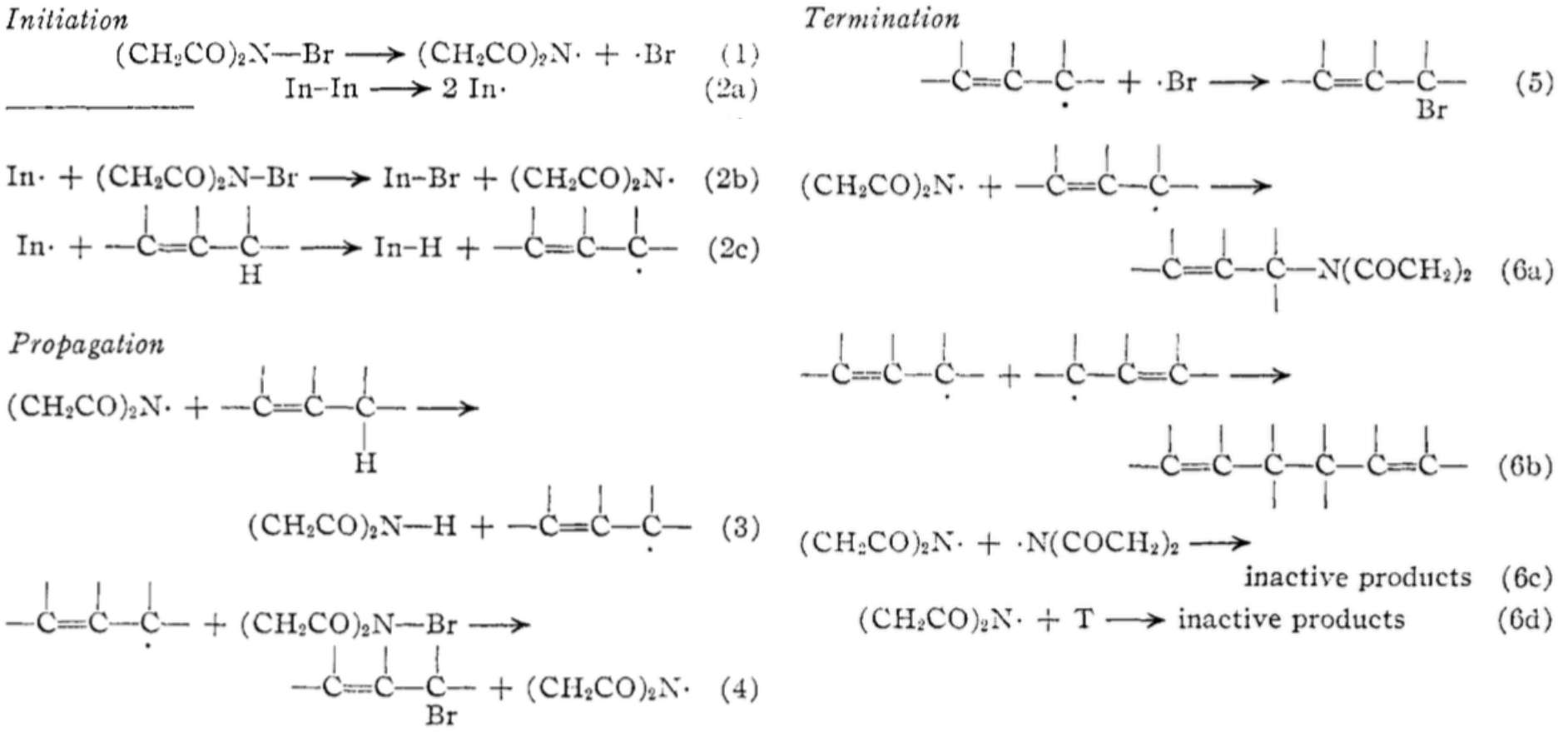
IBX oxidation

Scheme 3. Proposed (A) Ionic and (B) Single Electron Transfer (SET) Mechanisms for the Oxidation of Amines Mediated by IBX



Nicolaou, K. C.; Mathison, C. J. N.; Montagnon, T. *J. Am. Chem. Soc.* **2004**, *126*, 5192–5201.

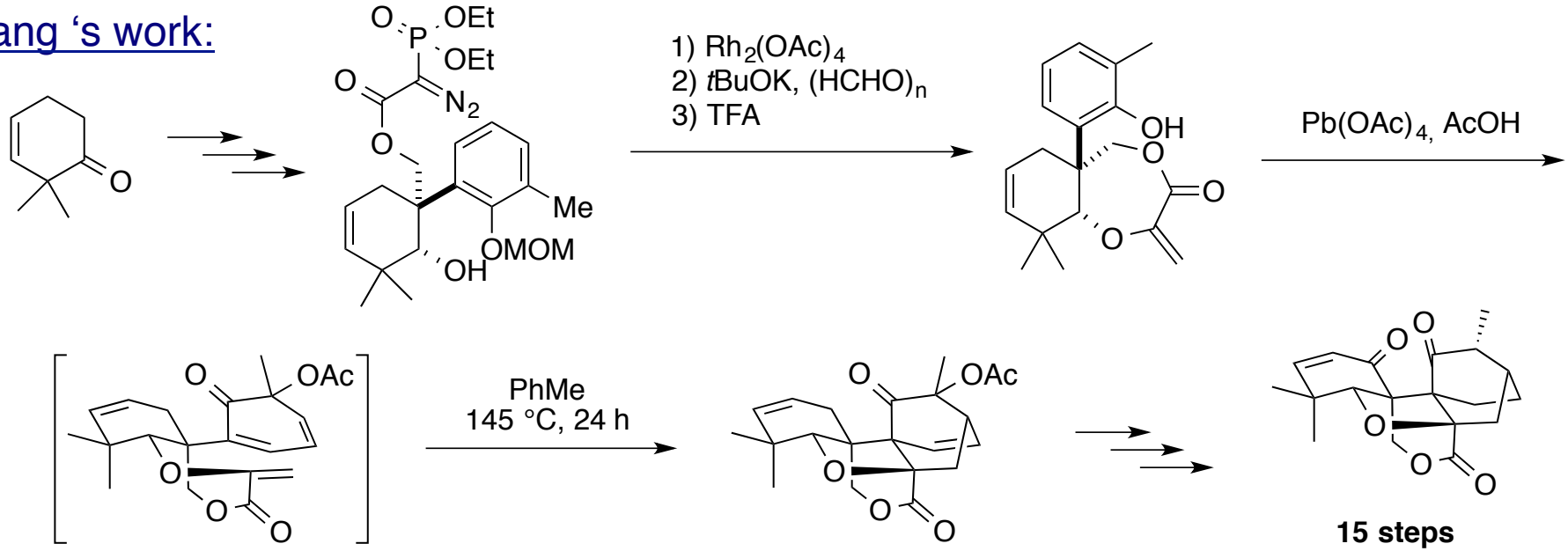
Allylic Bromination



Dauben, H. J., Jr; McCoy, L. L. *J. Am. Chem. Soc* **1959**, *81*, 4863–4873.

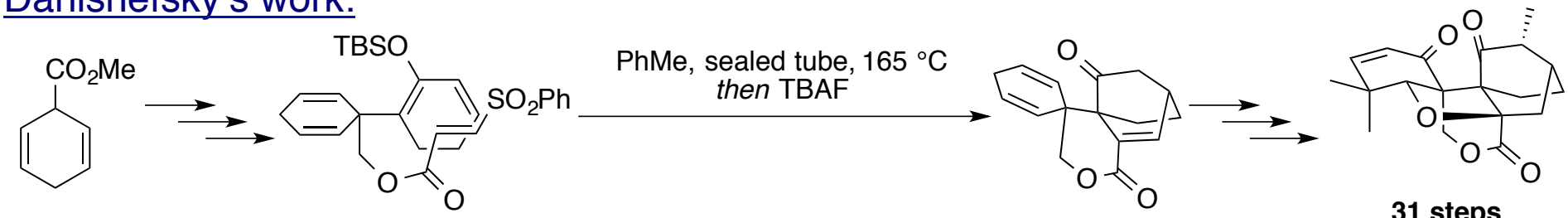
Previews Syntheses

Yang 's work:



15 steps
Overall Yield: 1%

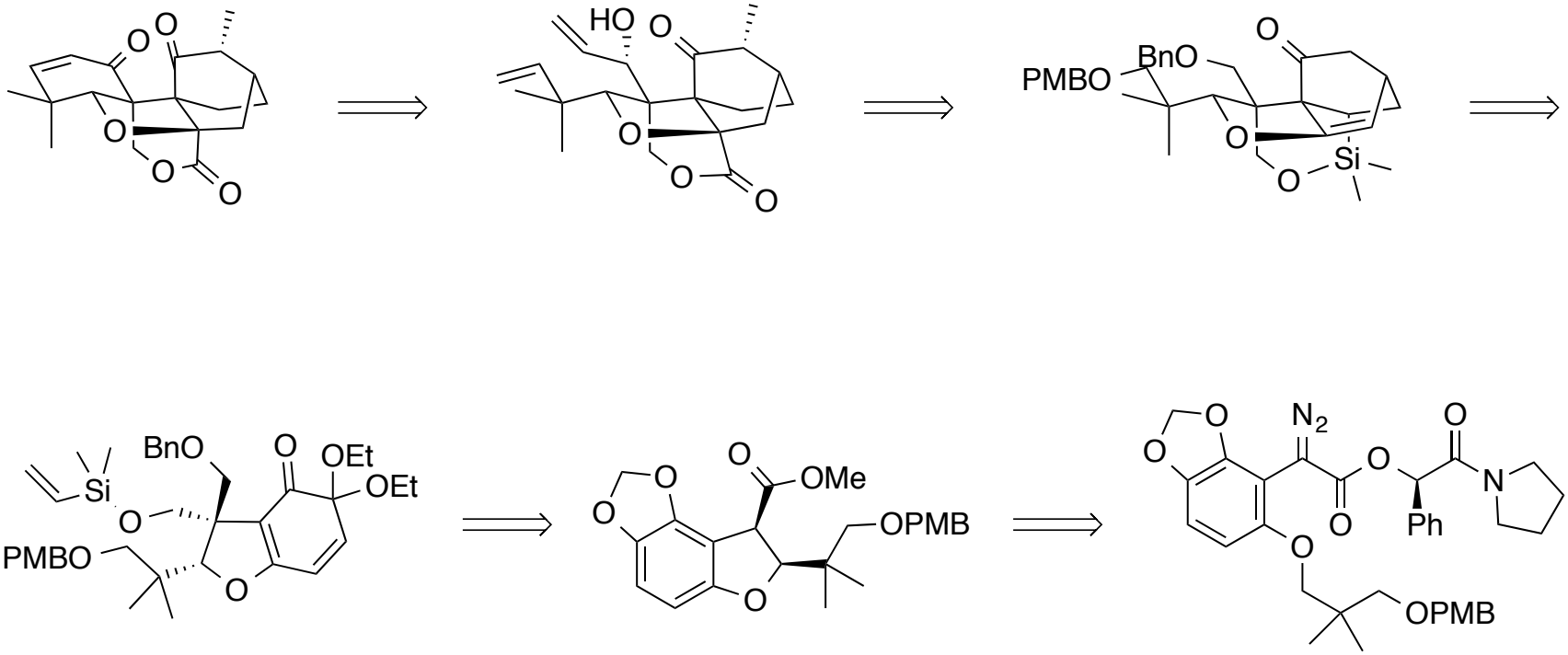
Danishefsky's work:



31 steps
overall Yield : 0.1%

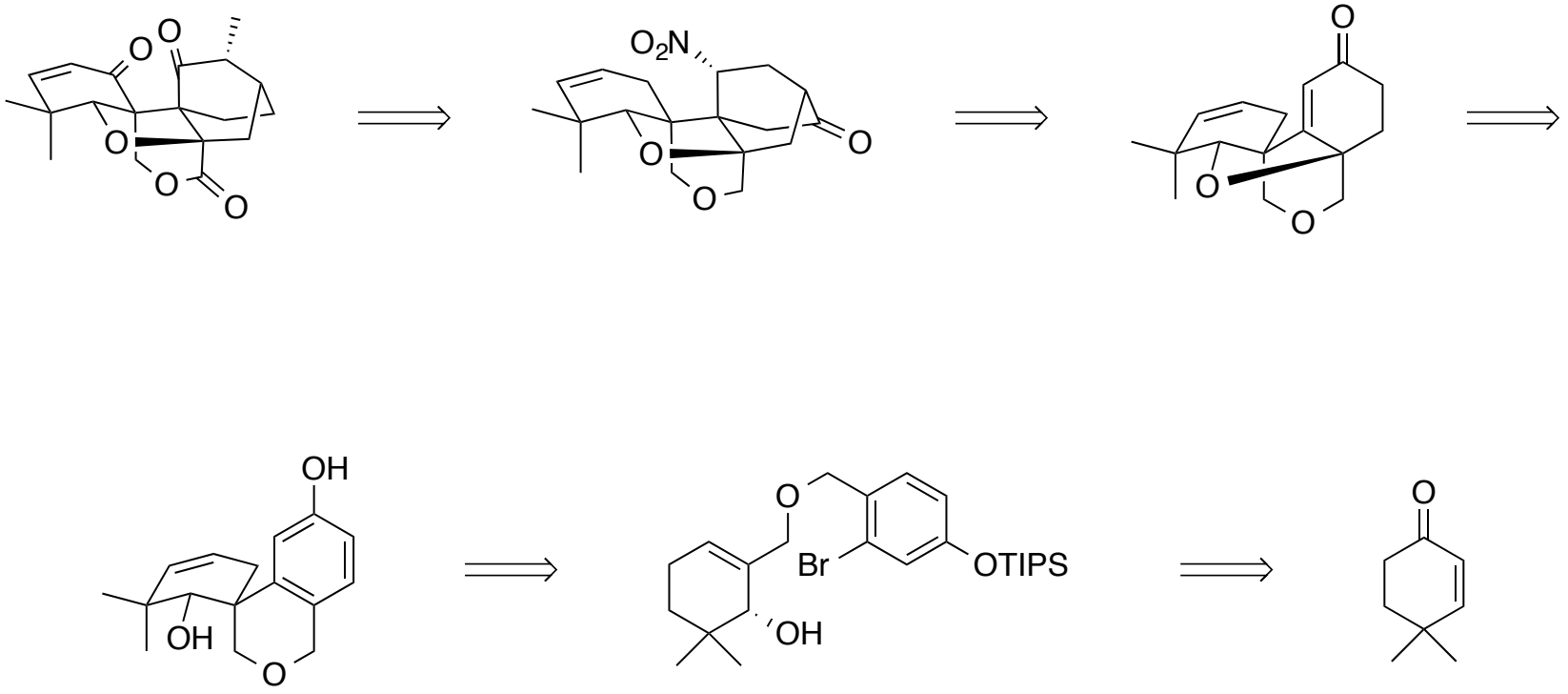
Gong, J.; Lin, G.; Sun, W.; Li, C.-C.; Yang, Z. *J. Am. Chem. Soc.* **2010**, *132*, 16745–16746.
Peng, F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2012**, *134*, 18860–18867.

Zakarian/Davies' Strategy



Lu, P.; Mailyan, A.; Gu, Z.; Guptill, D. M.; Wang, H.; Davies, H. M. L.; Zakarian, A. *J. Am. Chem. Soc.* **2014**, *136*, 17738–17749.

Thomson's Strategy



Zheng, C.; Dubovyk, I.; Lazarski, K. E.; Thomson, R. J. *J. Am. Chem. Soc.* **2014**, *136*, 17750–17756.