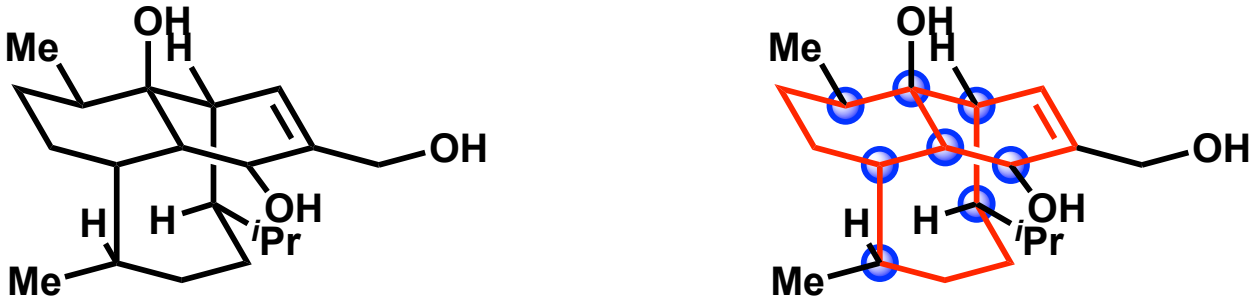
Total Synthesis of (-)-Vinigrol

2019. 12. 7. Literature Seminar
B4 Yuto Hikone

Contents

(-)-Vinigrol



Isolation: **from *Virgaria nigra* F-5408** [1)]

Structural features: **highly rigid 1,5-butanodecahydronaphthalene, 8 contiguous stereocenters**

Biological activity: **antihypertension, inhibition of platelet aggregation**
antagonist for tumor necrosis factor α (TNF-α) [2, 3)]

Total synthesis of Vinigrol

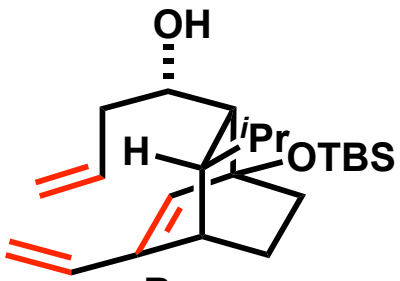
racemic: Baran (2009)[4)]**, Barrlault (2012)** [5)]**, Njardarson (2013)** [7)]

asymmetric: Kaliappan (formal synthesis, 2014) [6)]**, Luo (2019)** [8)]**, Li (2019)** [9)]

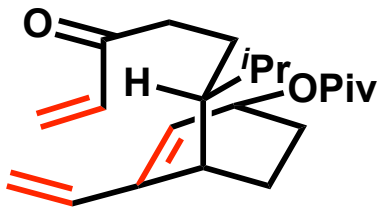
---

1) Uchida, I.; Ando, T.; Fukami, N.; Yoshida, K.; Hashimoto, M.; Tada, T.; Koda, S.; Morimoto, Y. *J. Org. Chem.* **1987**, 52, 5292−5293
2) Ando, T.; Tsurumi, Y.; Ohata, N.; Uchida, I.; Yoshida, K.; Okuhara, M. *J. Antibiot.* **1988**, 41, 25− 30
3) Norris, D. B.; Depledge, P.; Jackson, A. P. *PCT Int. Appl.* WO 9107953, **1991**.
4) Maimone, T. J.; Shi, J.; Ashida, S.; Baran, P. S. *J. Am. Chem. Soc.* **2009**, 131, 17066−17067
5) Poulin, J.; Grise-Bard, C. M.; Barriault, L. *Angew. Chem., Int. Ed.* **2012**, 51, 2111−2114
6) Betkekar, V. V.; Sayyad, A. A.; Kaliappan, K. P. *Org. Lett.* **2014**, 16, 5540−5543
7) Yang, Q.; Njardarson, J. T.; Draghici, C.; Li, F. *Angew. Chem., Int. Ed.* **2013**, 52, 8648−8651
8) Xuerong Yu, Lianghong Xiao, Zechun Wang, and Tuoping Luo. *J. Am. Chem. Soc.* **2019**. 141. 3440-3443
9) Long Min, Xiaohong LIn, and Chuang-Chuang Li. *J. Am. Chem. Soc.* **2019**. 141. 15773-15778

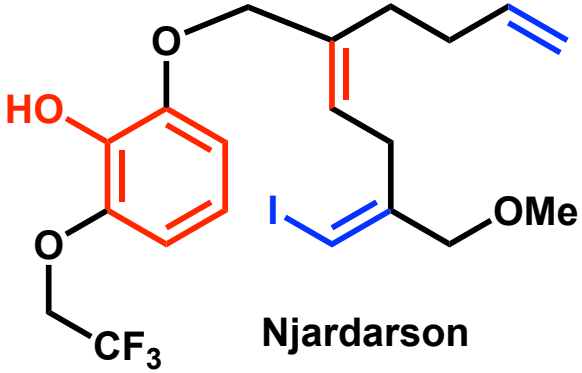
Synthetic Approach



Baran



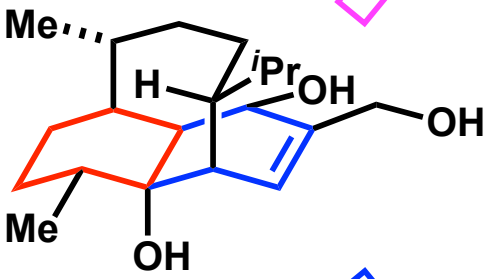
Barriault, Kaliappan



Njardarson

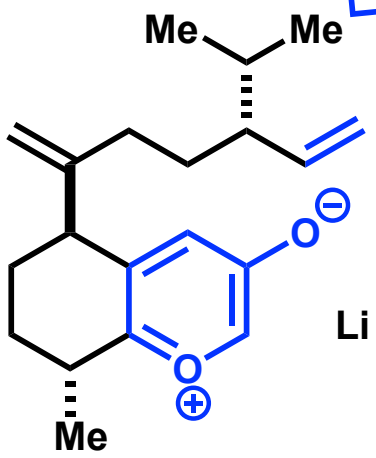
oxidative dearomatization/ intramolecular Diels Alder reaction and Heck reaction

intramolecular Diels Alder reaction



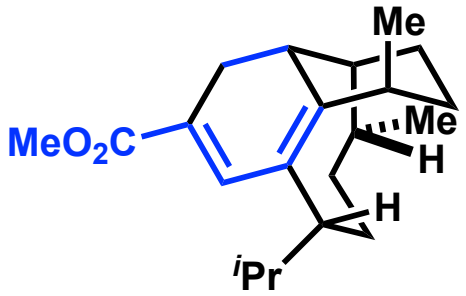
(-)-Vinigrol

type II [5+2] cycloaddition



Li

transannular Diels Alder reaction



Luo

Introduction of Prof. Li and Luo

Prof. Chuang-Chuang Li [1)]

2001 B.S. @China Agricultural University (Prof. Dao-quan Wang)
2006 Ph.D. @Peking University (Prof. Zhen Yang)
2008 Postdoctoral associate
@The Scripps Research Institute (Prof. Phil S. Baran)
2009-Associate professor
@Southern University of Science and Technology

Research interests:
total synthesis of biologically active and structually interesting natural products

Prof. Tuoping Luo [2)]

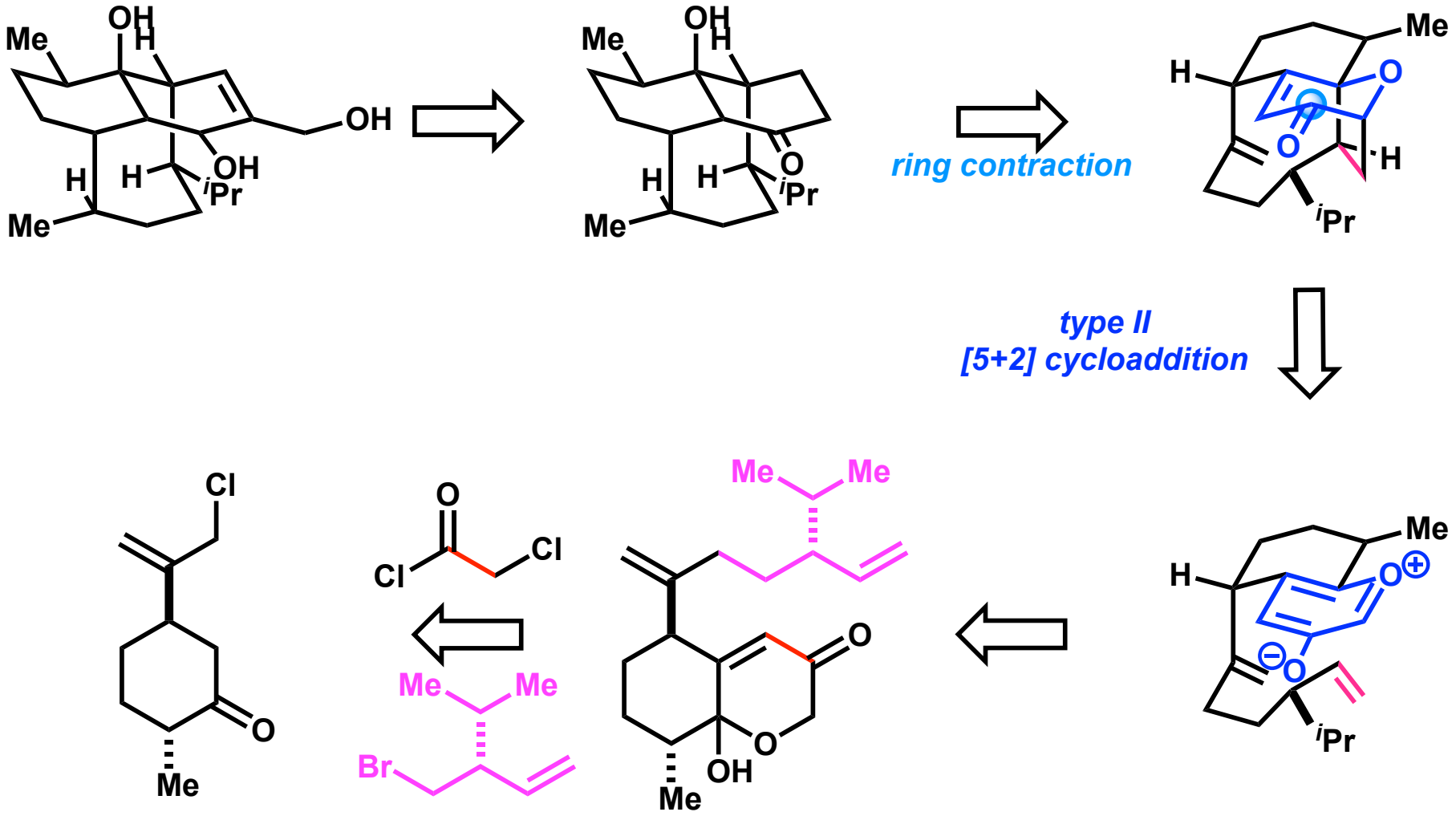
2005 B.S. @Peking University (Prof. Zhen Yang)
2011 Ph.D. @Harvard University (Prof. Stuart L. Schreiber)
2013 Postdoctoral fellow @H3 Biomedicine Inc. (Dr. John Yuan Wang)
2013-Principal investigator @Peking University
Provisional principal investigator
@Peking University-Tsinghua University Joint Center for Life Sciences

Research interests:
synthesis of natural products, organic reactions taking place in living cells

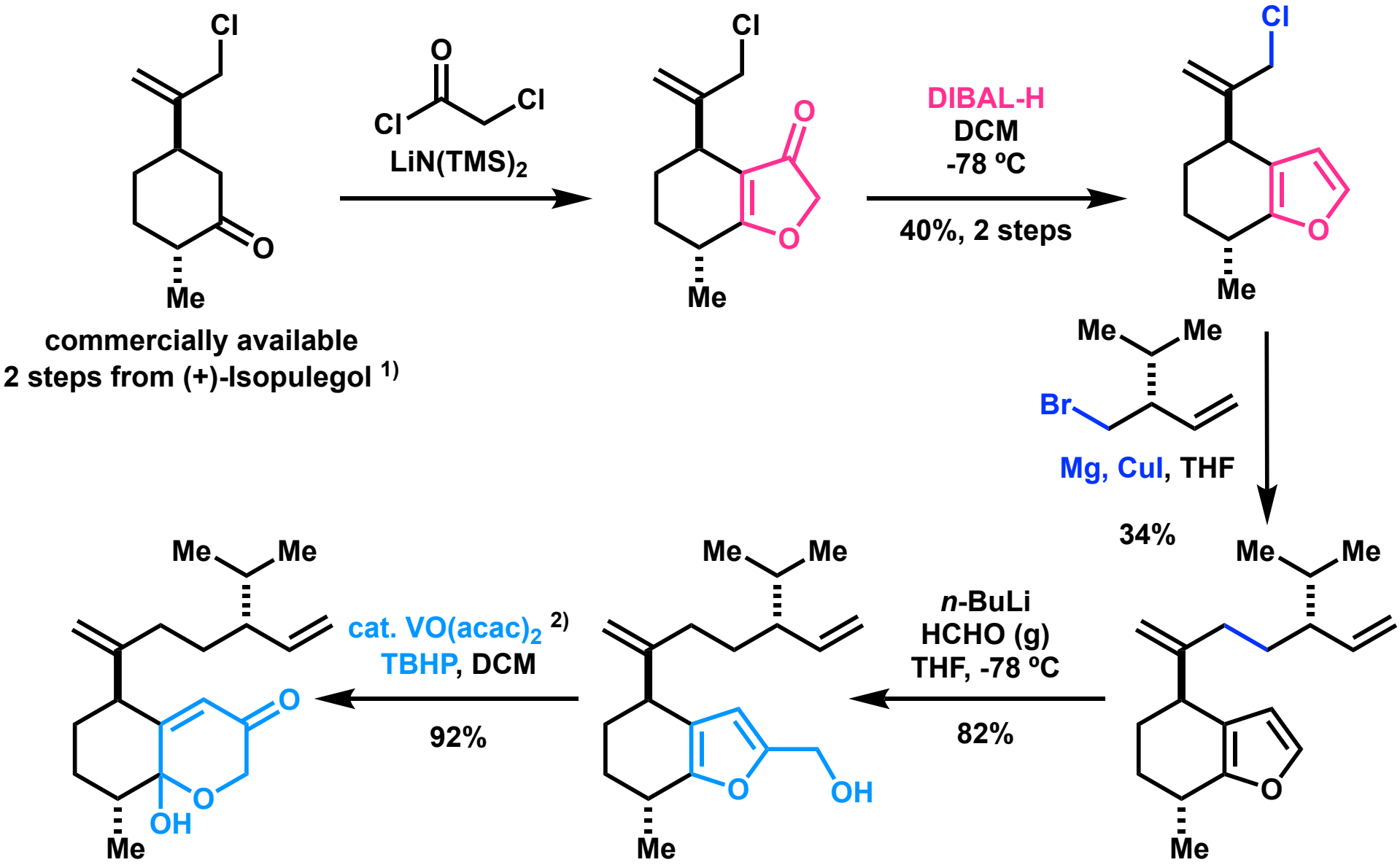
1) http://116.7.234.209/en/faculty_52/f/Li_ChuangChuang
2) http://www.chem.pku.edu.cn/luotp/index.htm

Contents

Retrosynthesis

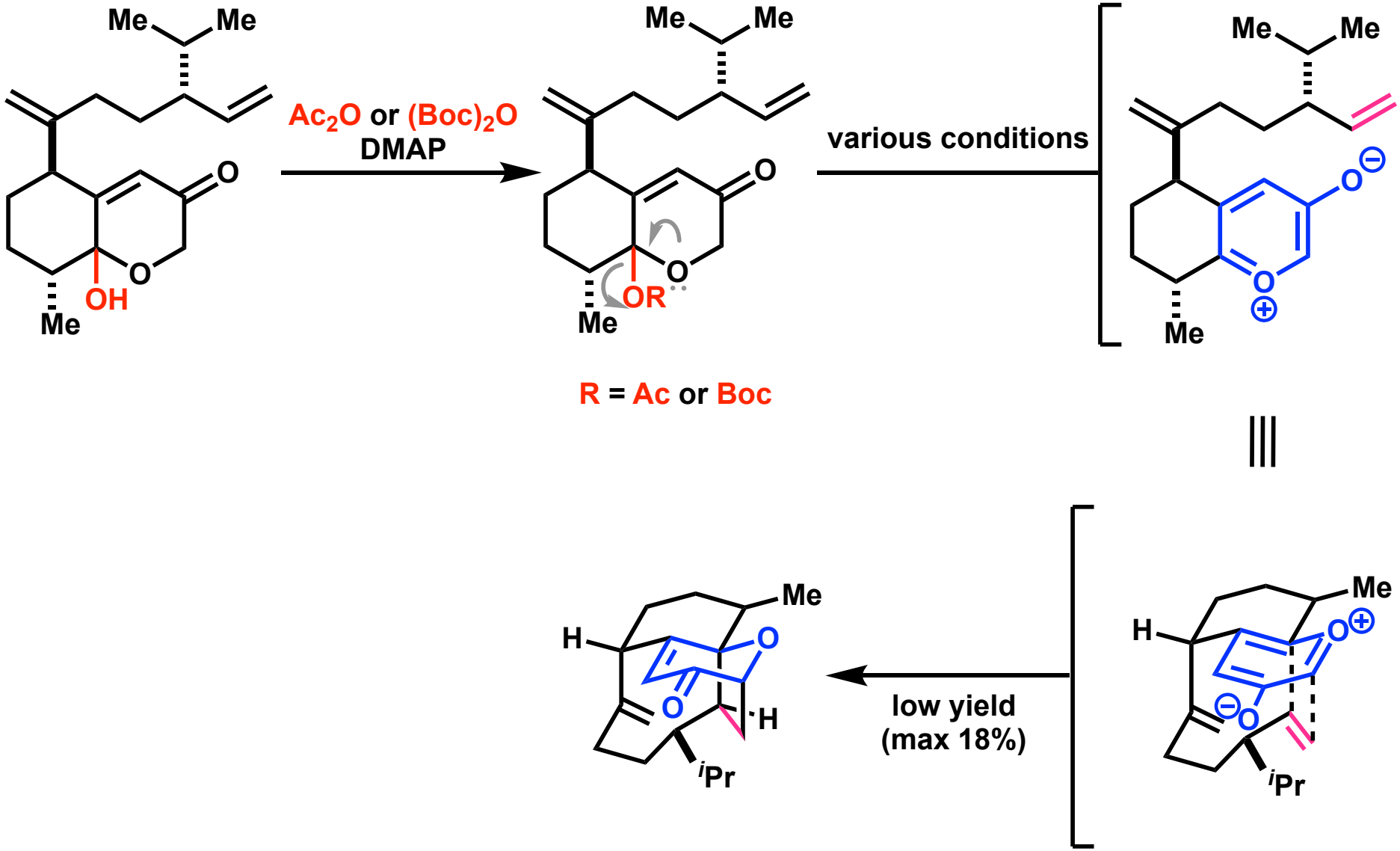


Synthesis of Dihydropyran for [5+2] Cycloaddition

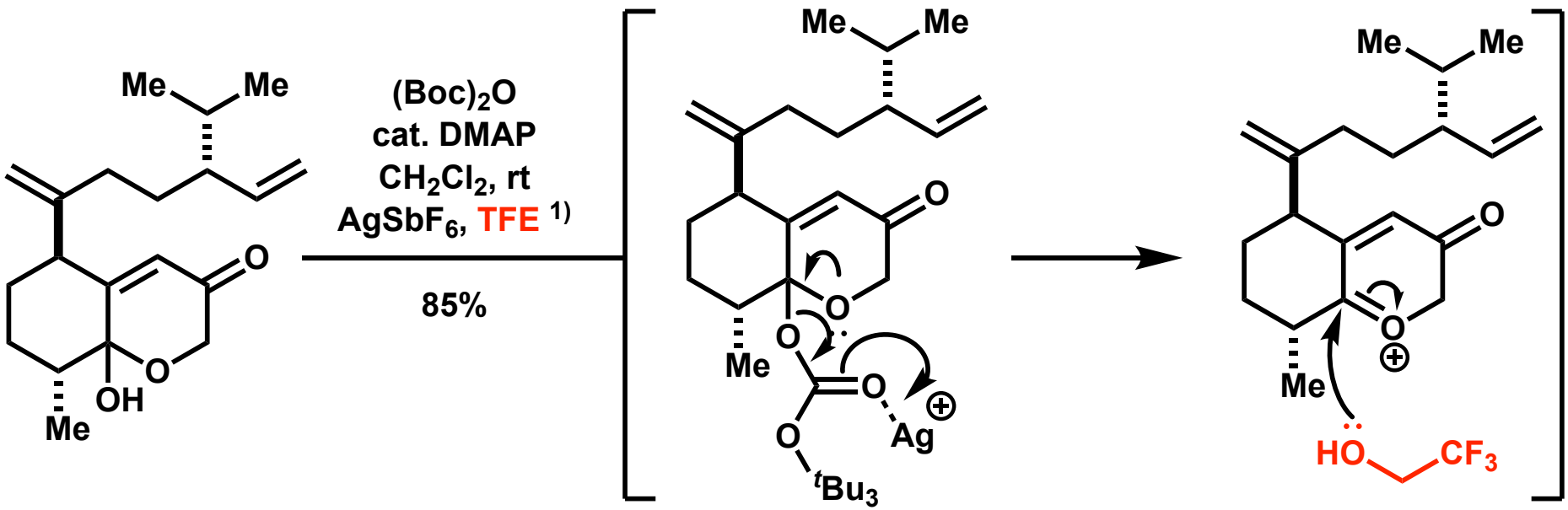


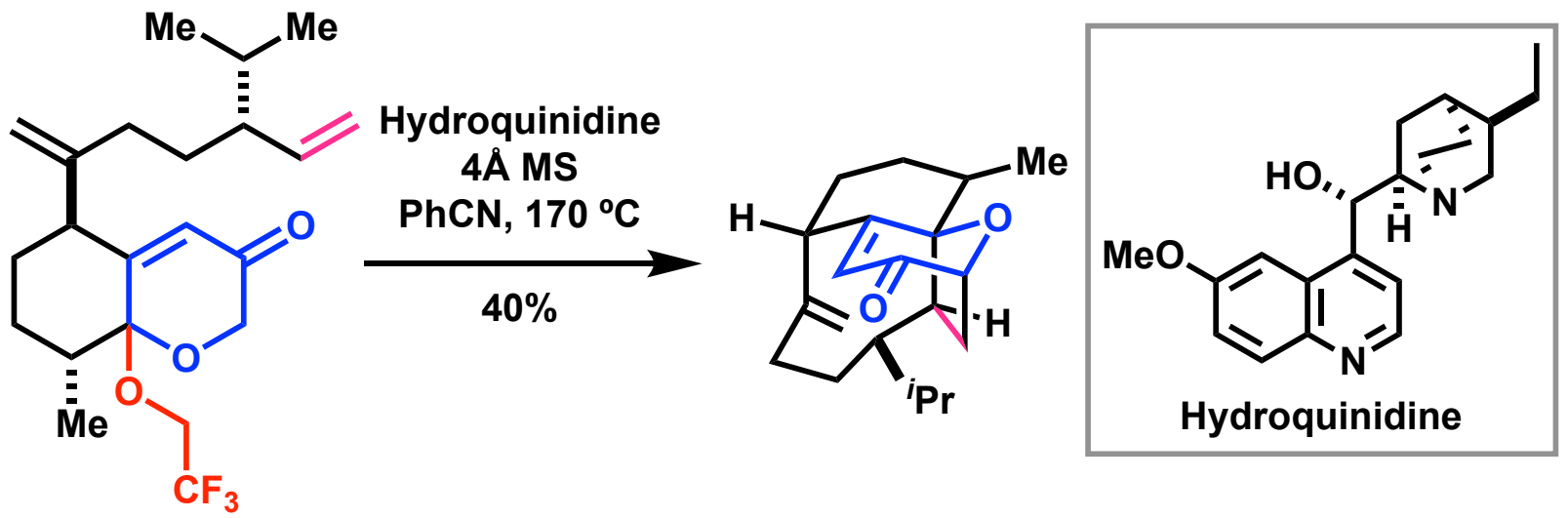
1) Shridhar G. Hegde, David Beckwith, Robert Doti, and Joseph Wolinsky. *J. Org. Chem.* **1985**, 50, 6, 894-896
2) A. K. Ghosh and Z. H. Chen, *Org. Lett.*, **2013**, 15, 5088–5091

Type II [5+2] Cycloaddition (1)



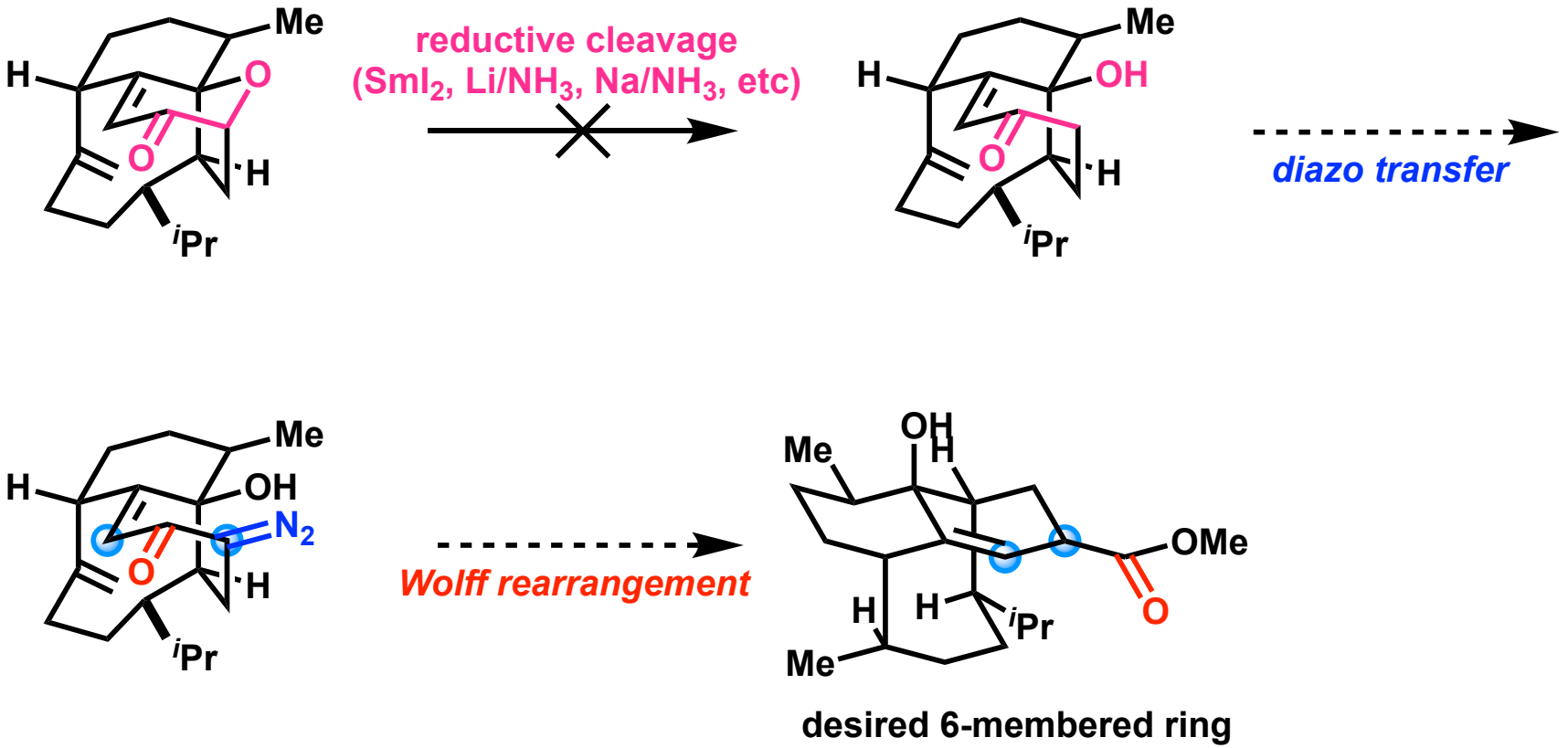
Type II [5+2] Cycloaddition (2)





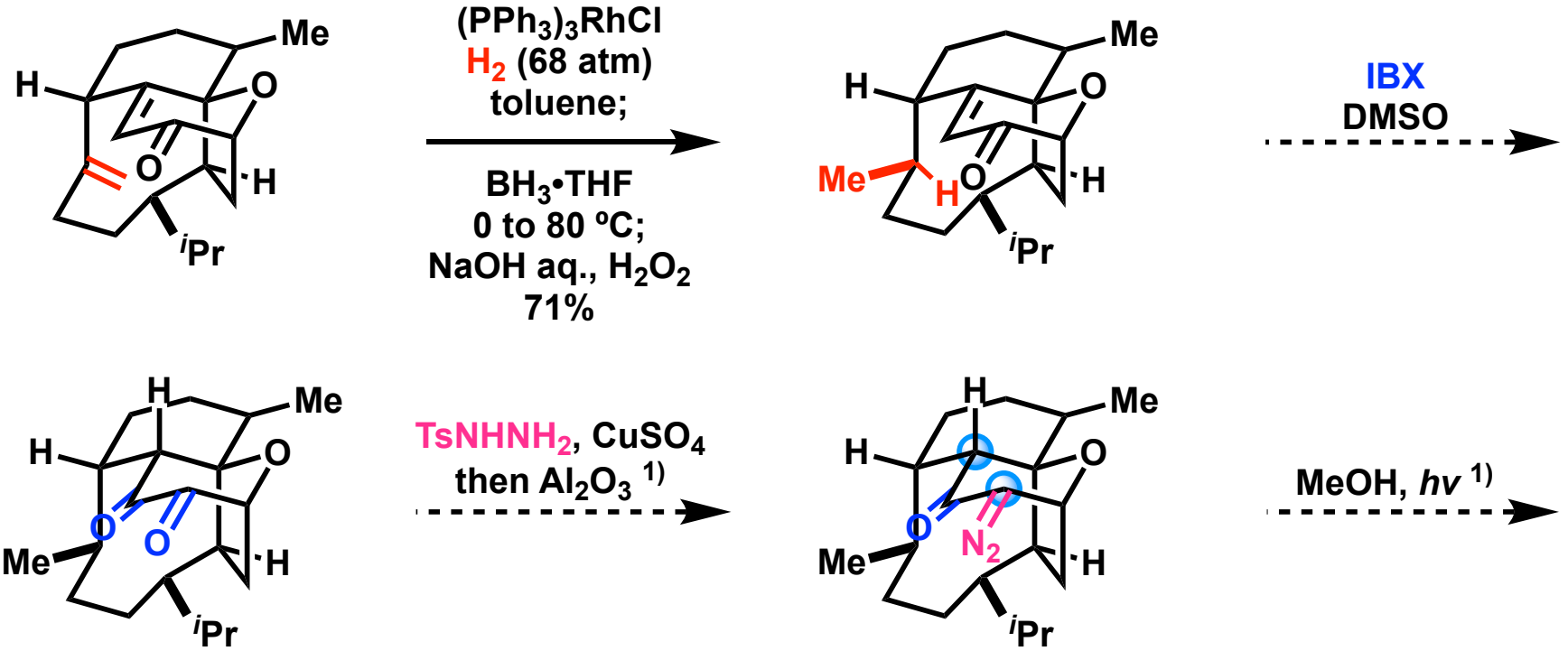
1) Liu, W.; Chen, Q.; Liang, J.; Du, Z.; Zhang, K.; Zheng, X.; O'Doherty, G. A.*Synlett* **2015**, 26, 1683−1686

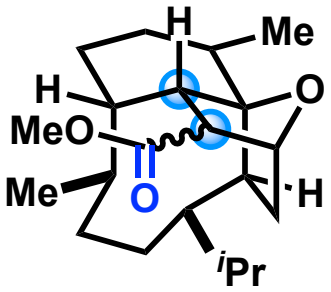
Attempted Ring Contraction



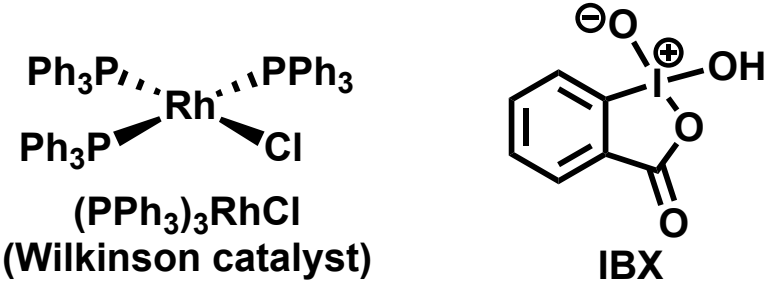
desired 6-membered ring

Another Plan of Ring Contraction



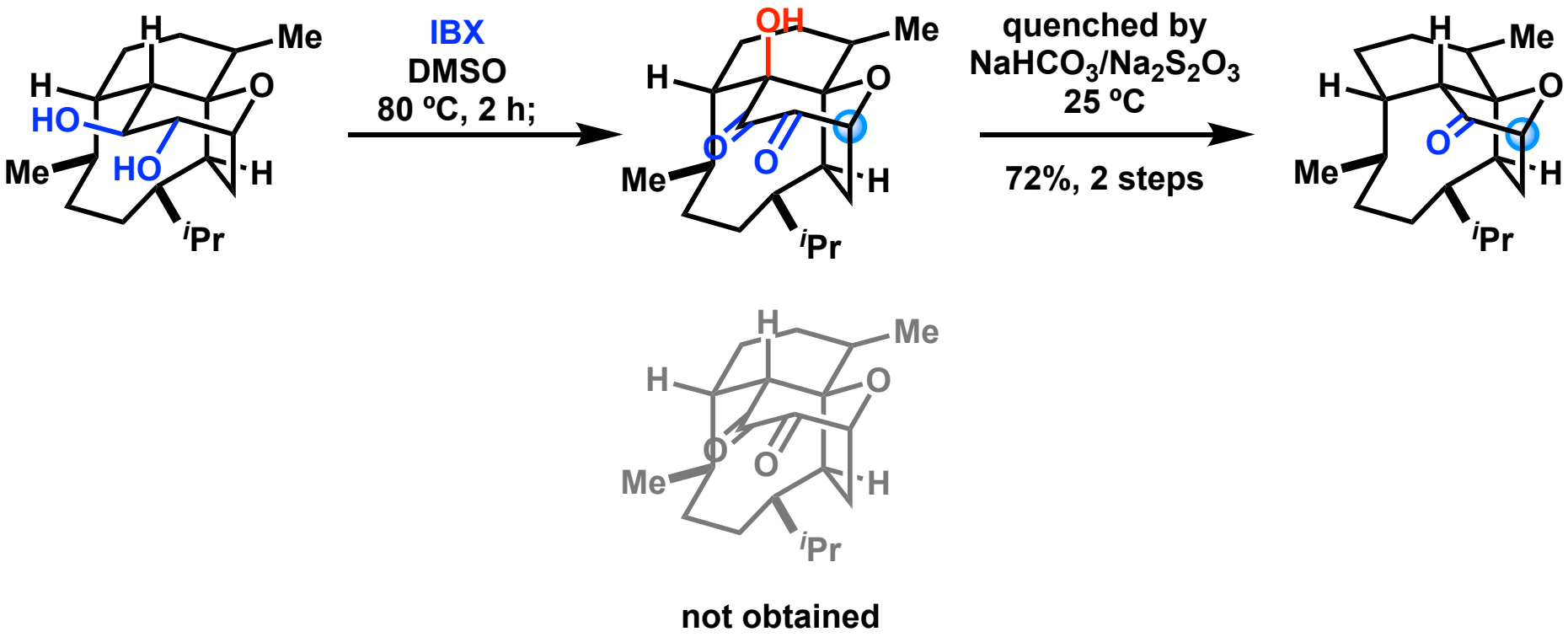


expected synthetic route based on the paper [2)]

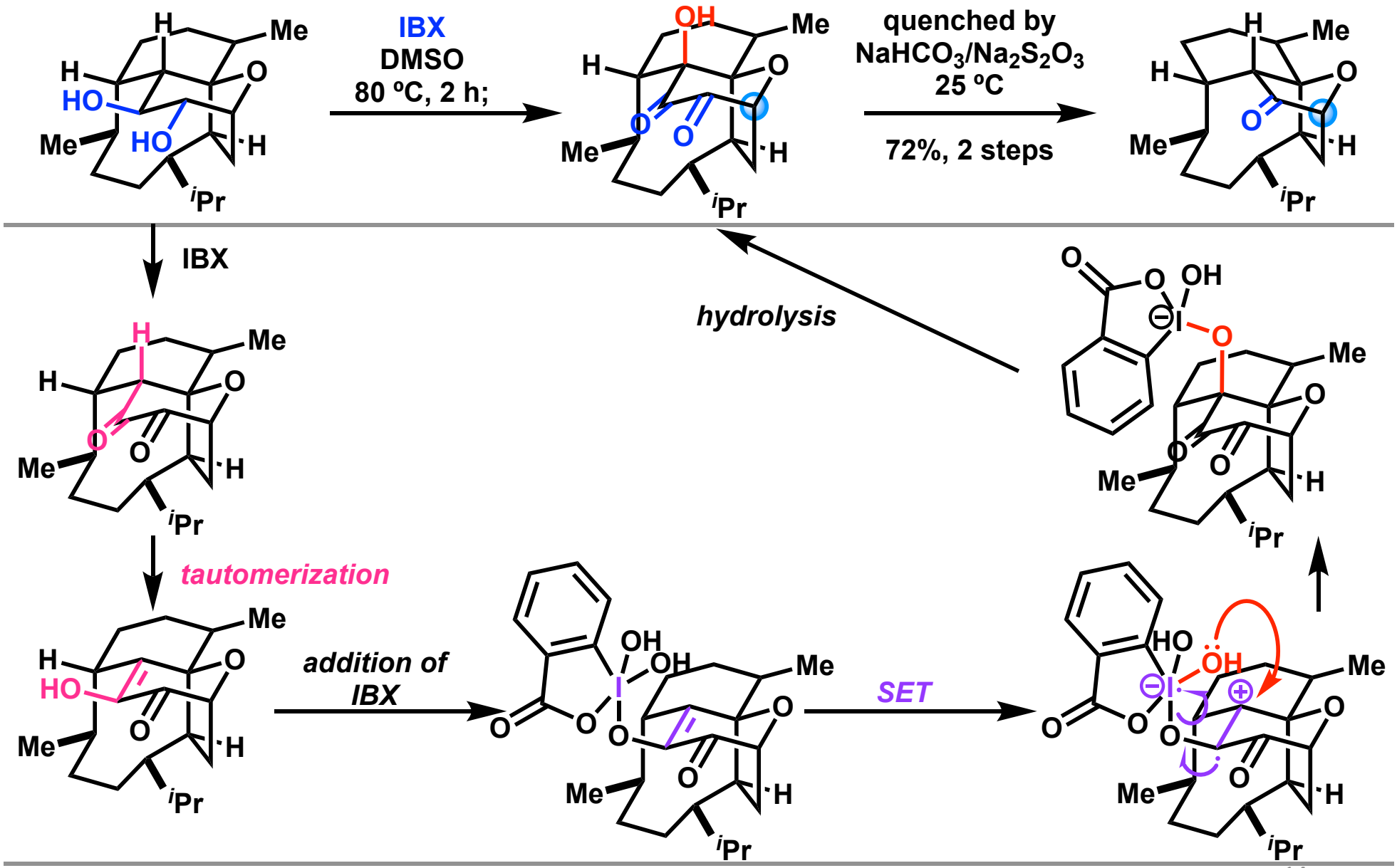


1) Wang, B.; Xie, Y. Z.; Yang, Q.; Zhang, G. Z.; Gu, Z. H. *Org. Lett.* **2016**, 18, 5388−5391.
2) Long Min, Xiaohong LIn, and Chuang-Chuang Li. *J. Am. Chem. Soc.* **2019**. 141. 15773-15778

Unexpected Oxidation and Ring Contraction (1)

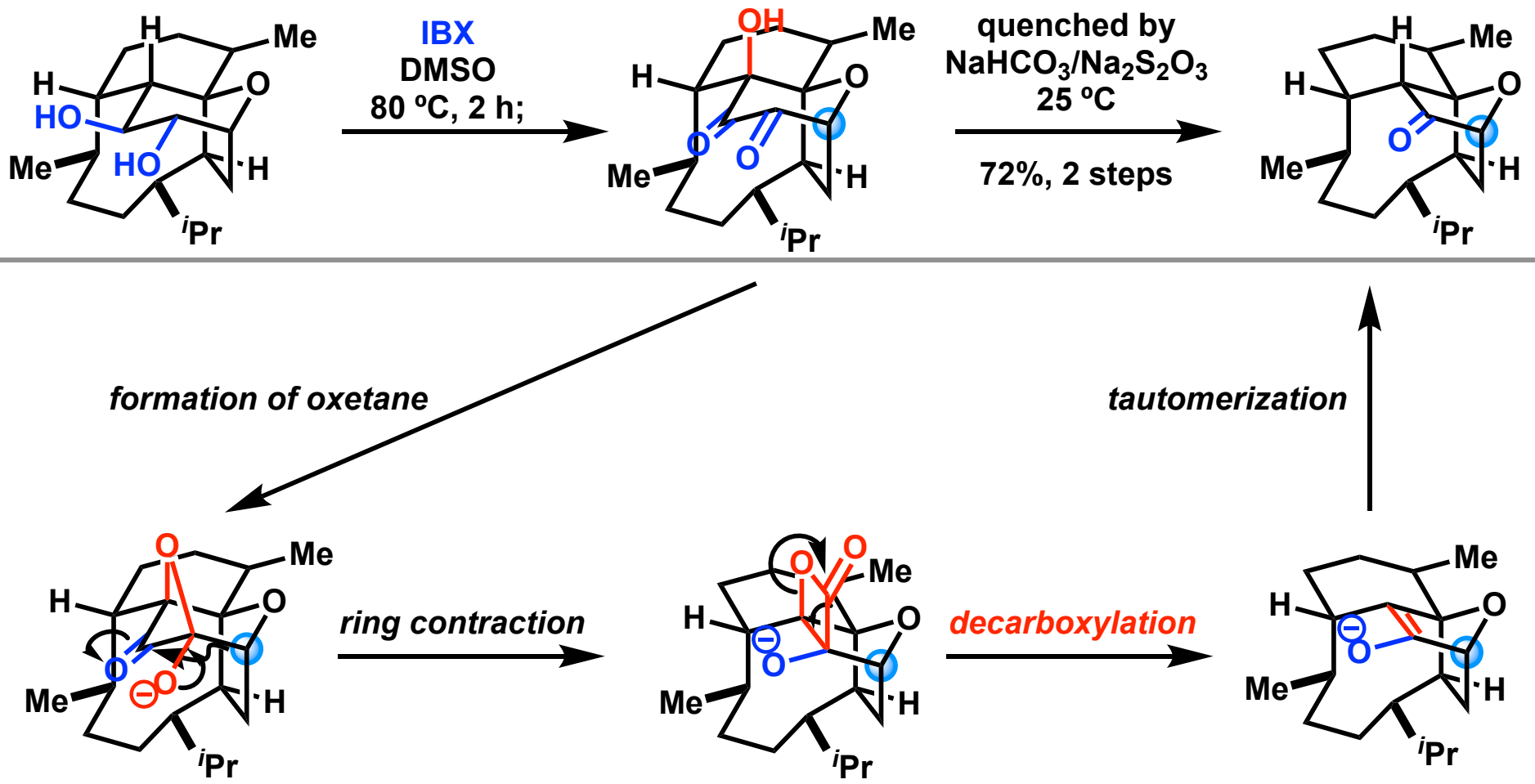


Unexpected Oxidation and Ring Contraction (2) [1)]

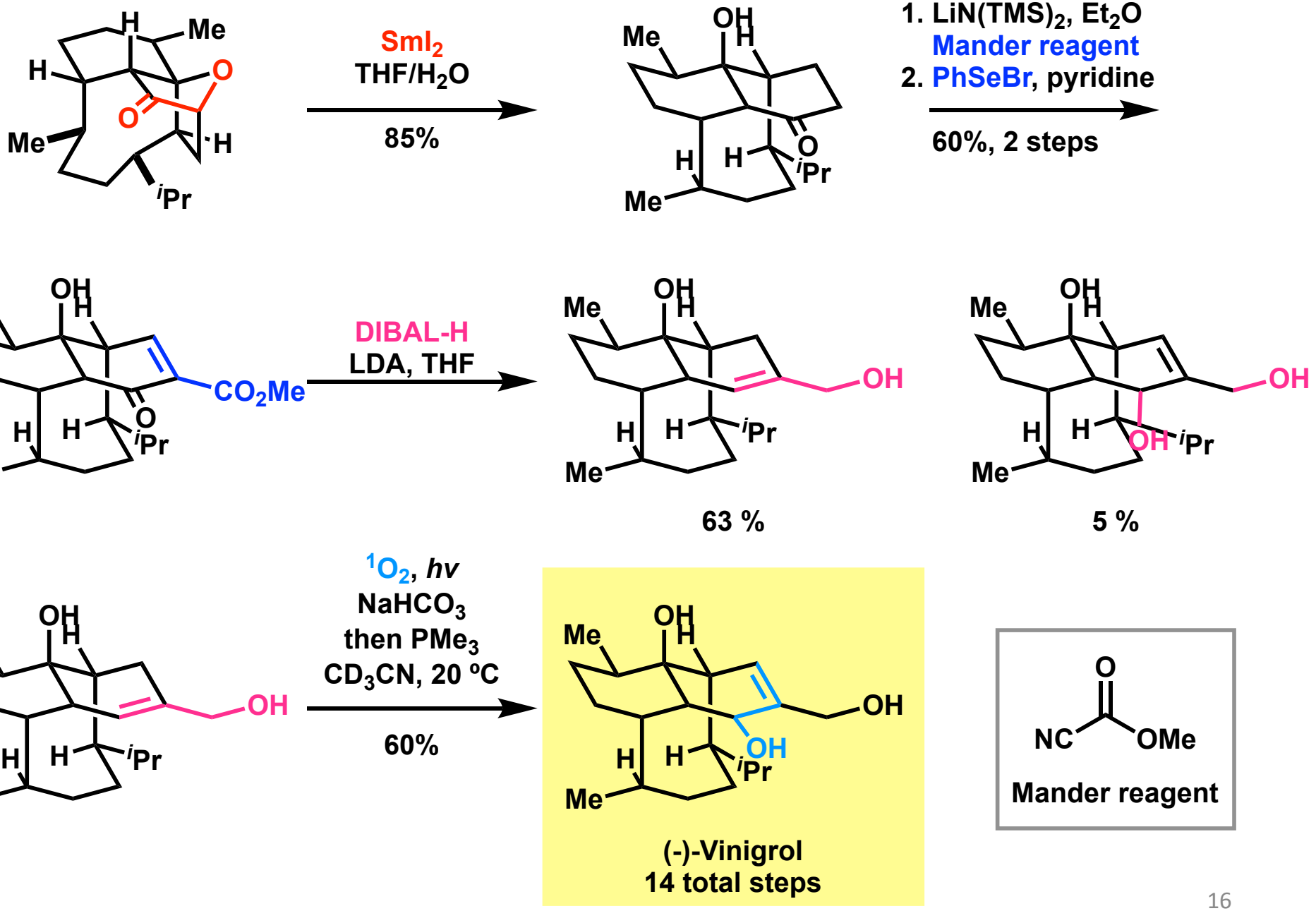


1) K. C. Nicolaou, Tamsyn Montagnon, and Phil S. Baran. *Angew. Chem. Int. Ed.* **2002**, 41, No. 6

Unexpected Oxidation and Ring Contraction (3)

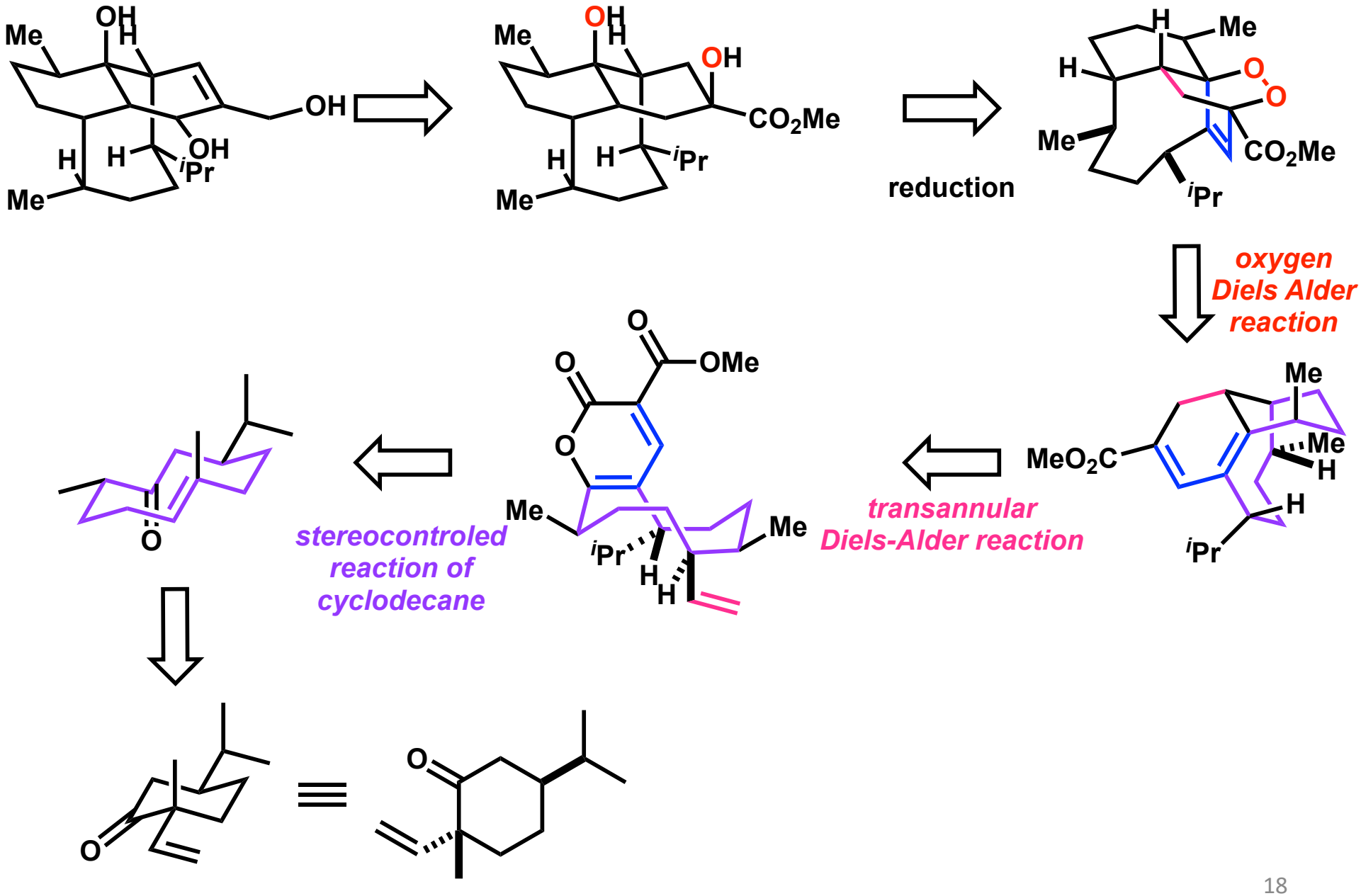


Total Synthesis of (-)-Vinigrol

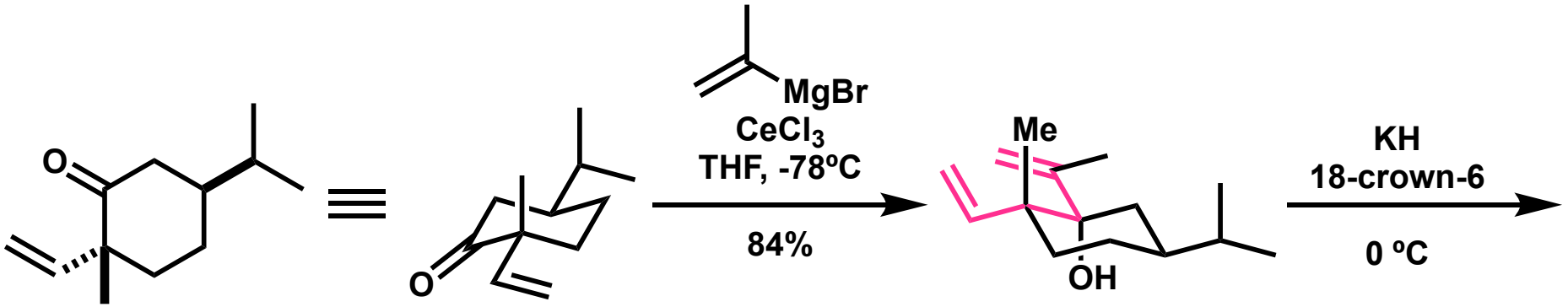


Contents

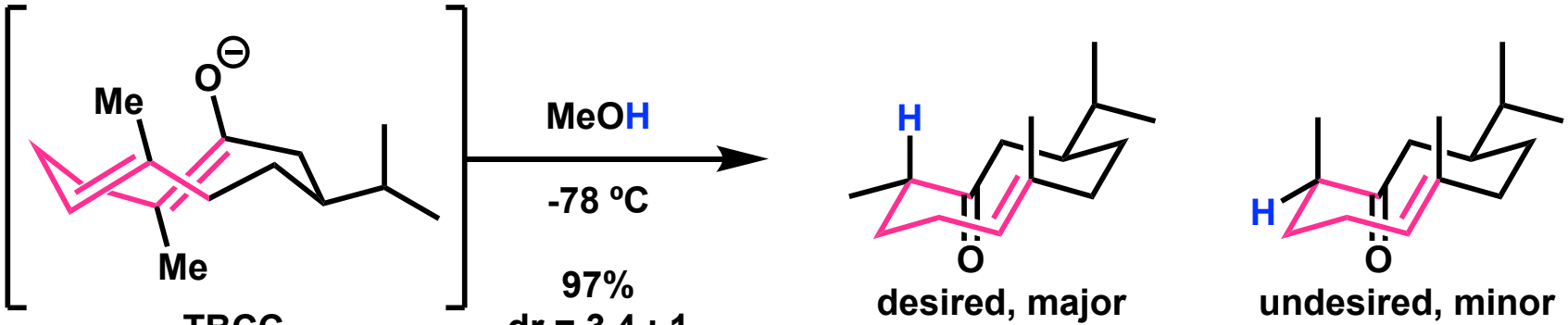
Retrosynthesis



Synthesis of Cyclodecene Containing (*E*)-Olefin



5 steps from
(*S*)-(-)-Limonene [1)]



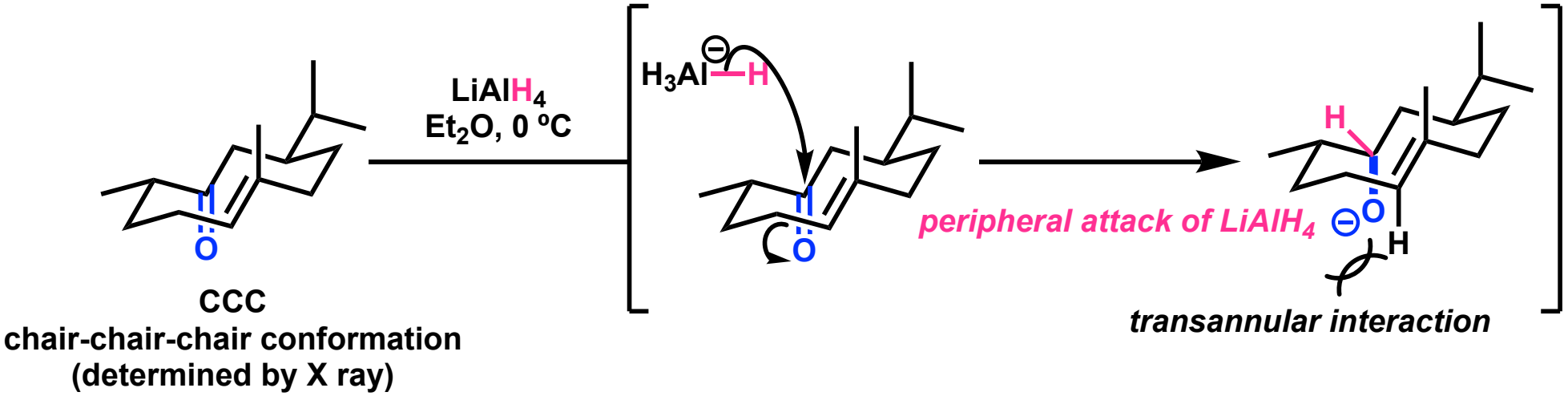
TBCC
twist-boat-chair-chair

peripheral protonation

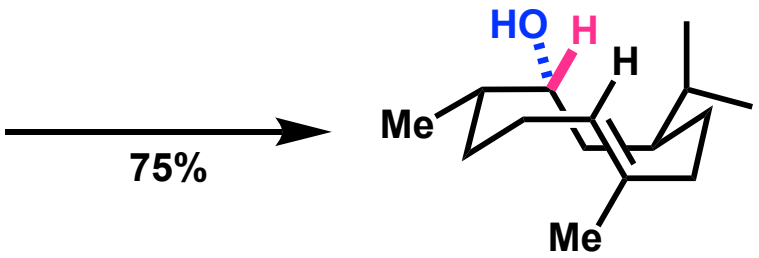
CCC
chair-chair-chair conformation
(determined by X ray)

1) Mehta, G.; Acharyulu, P. V. R. *J. Chem. Soc., Chem. Commun.* **1994**, 2759−2760

Reduction by $LiAlH_4$

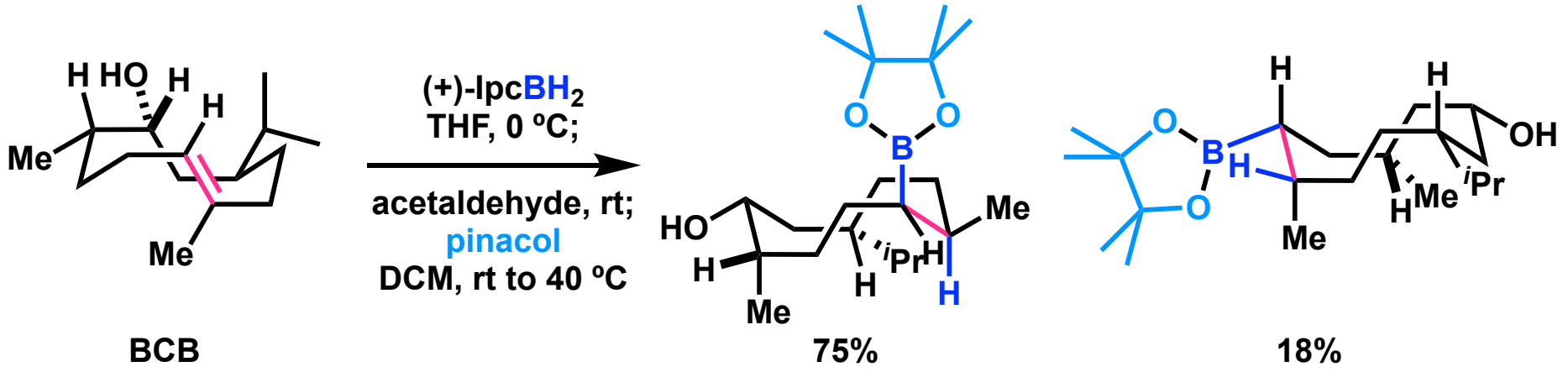


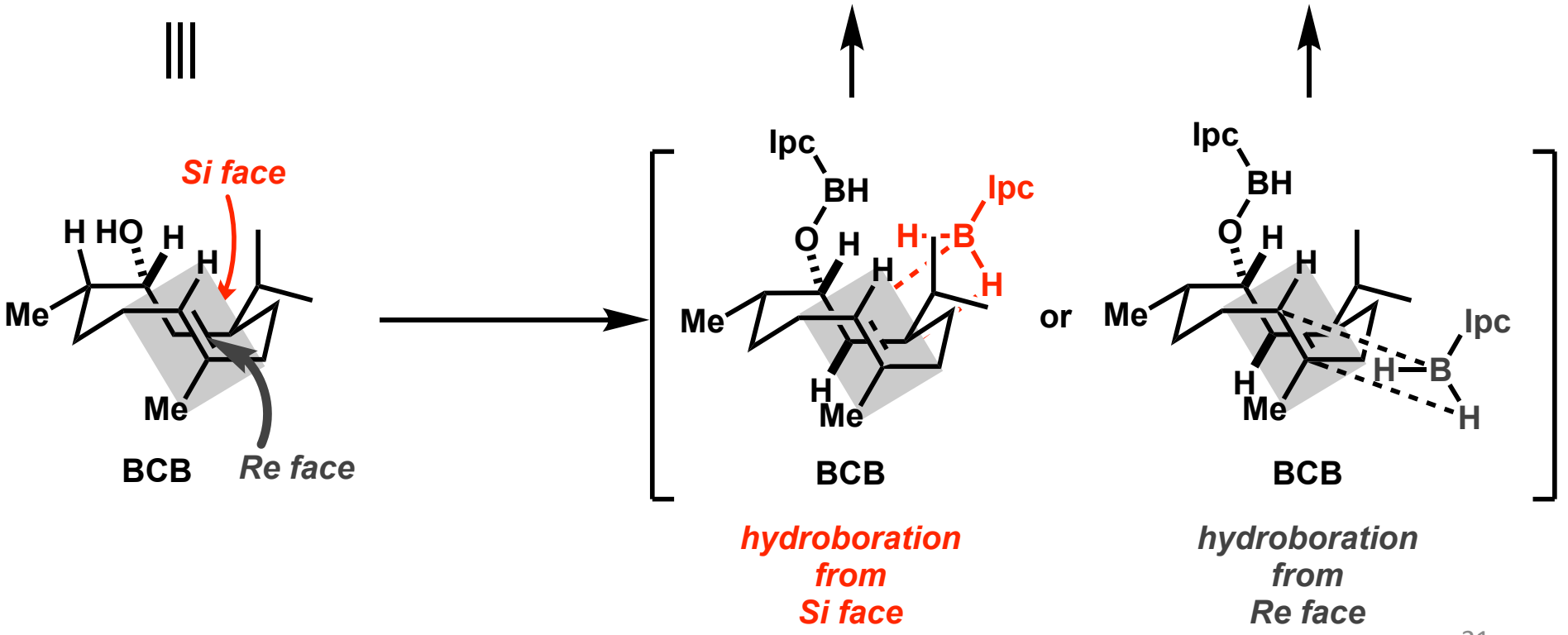
CCC
chair-chair-chair conformation
(determined by X ray)



BCB
boat-chair-boat conformation
(determined by X ray)

Hydroboration of (*E*)-Olefin





Hydroboration with Facial Selectivity (1)

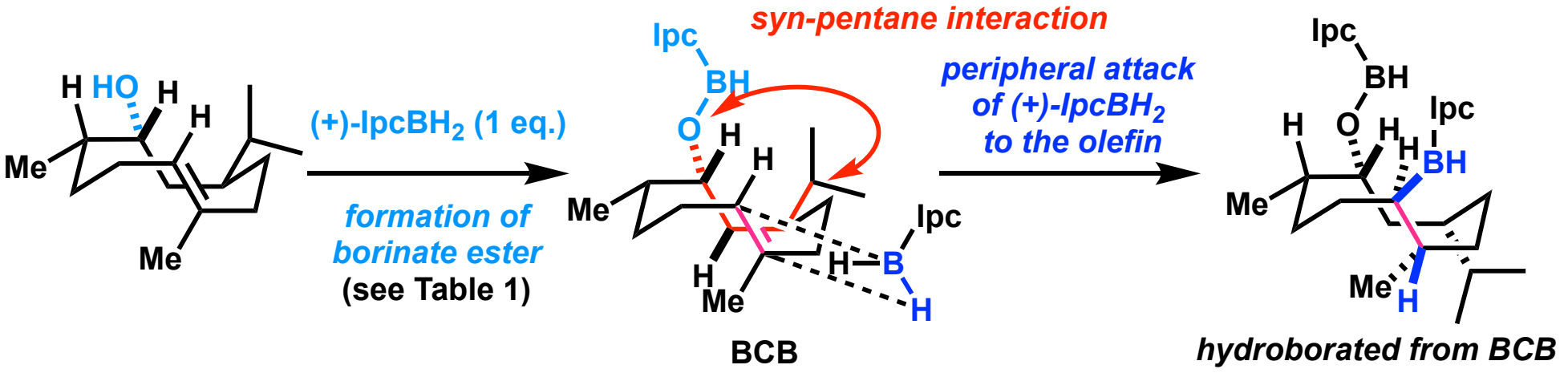
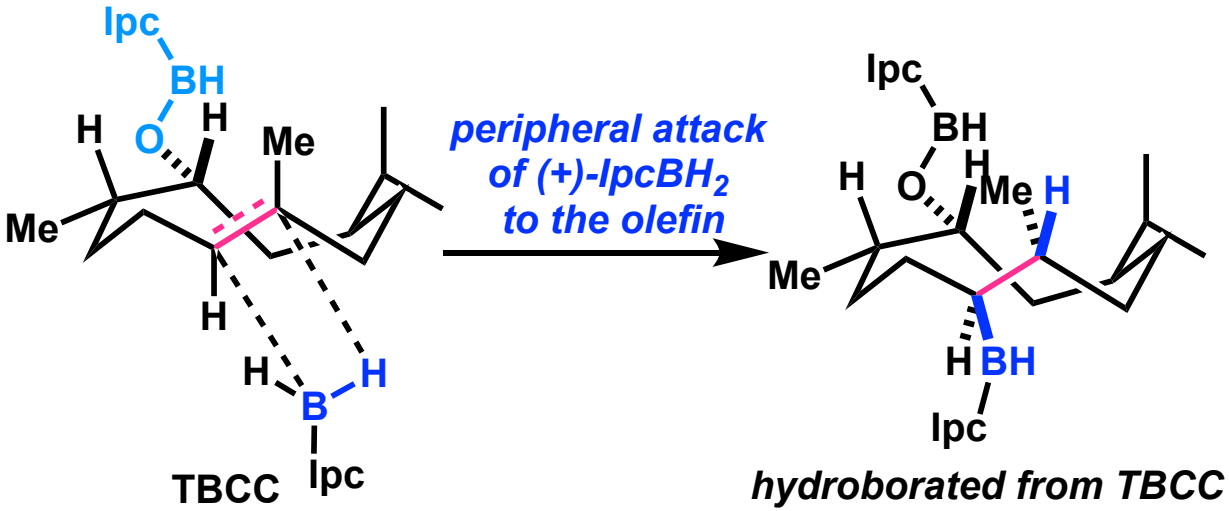
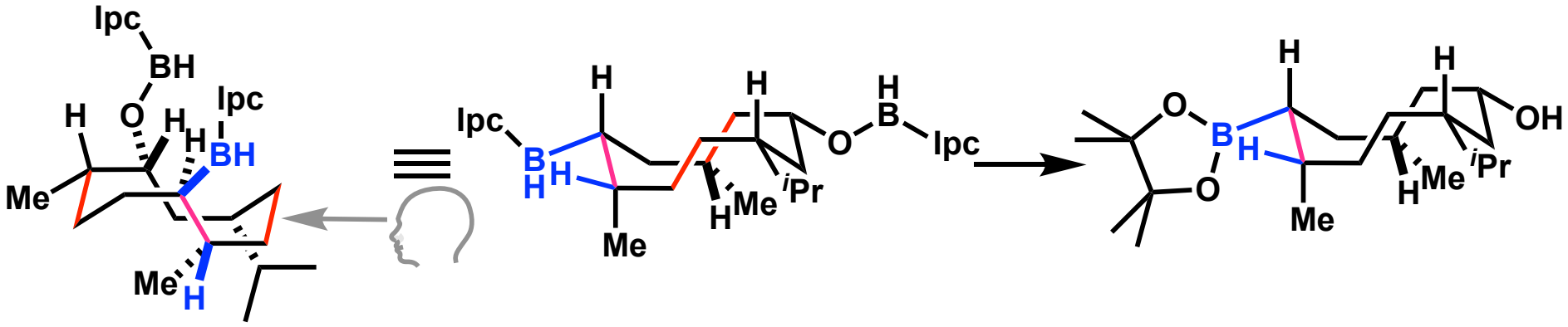


Table 1

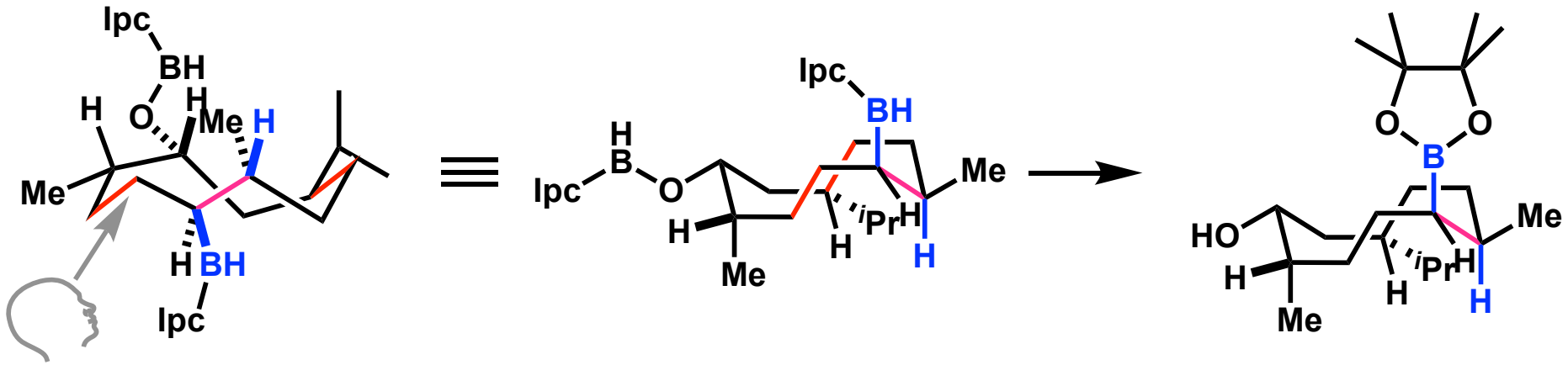
Eq. of (+)-IpcBH$_2$	result (major)
1.0	21% (brsm 35%)
1.5	48% (brsm 52%)
2.9	75%



Hydroboration with Facial Selectivity (2)

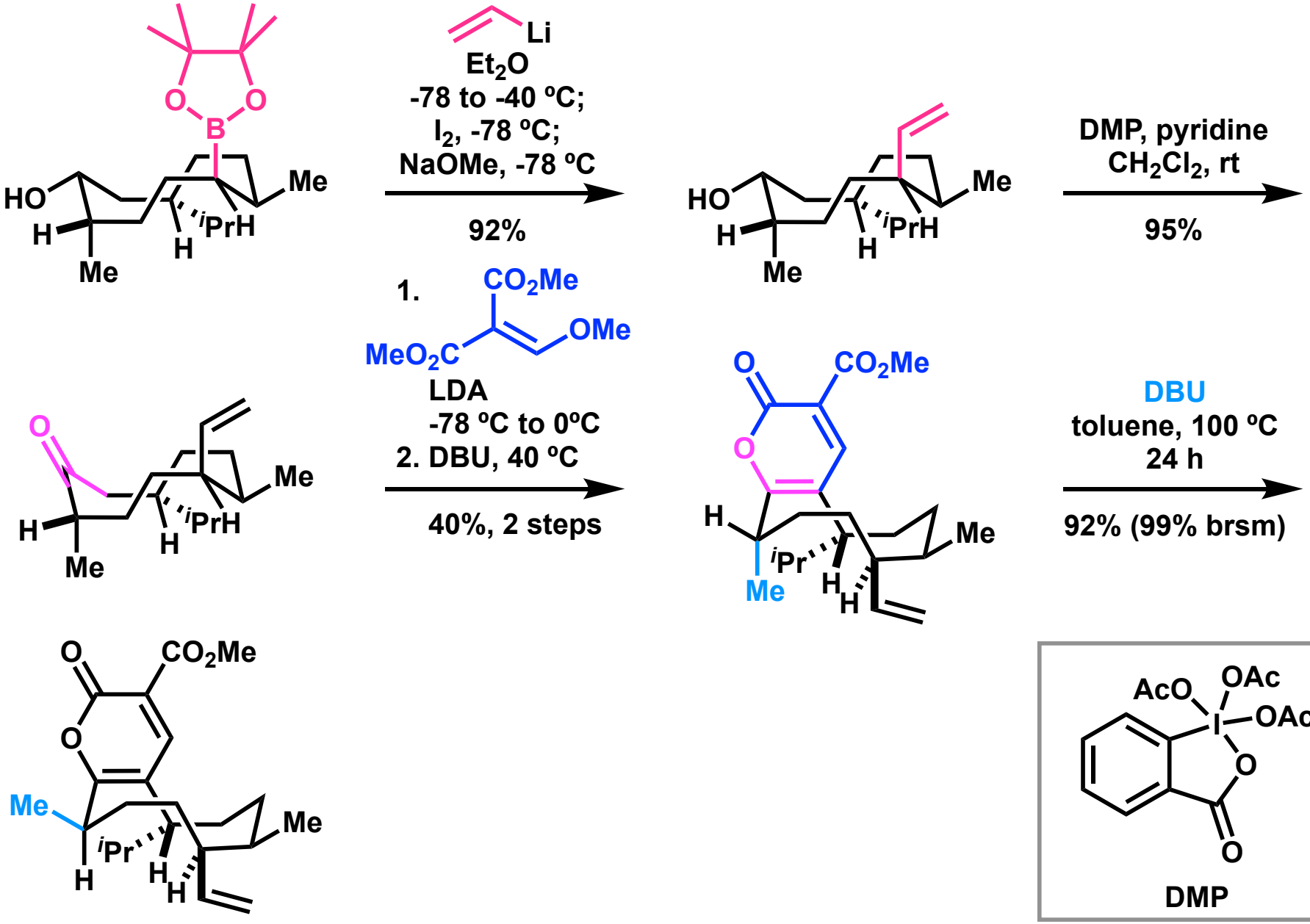


18% (minor)

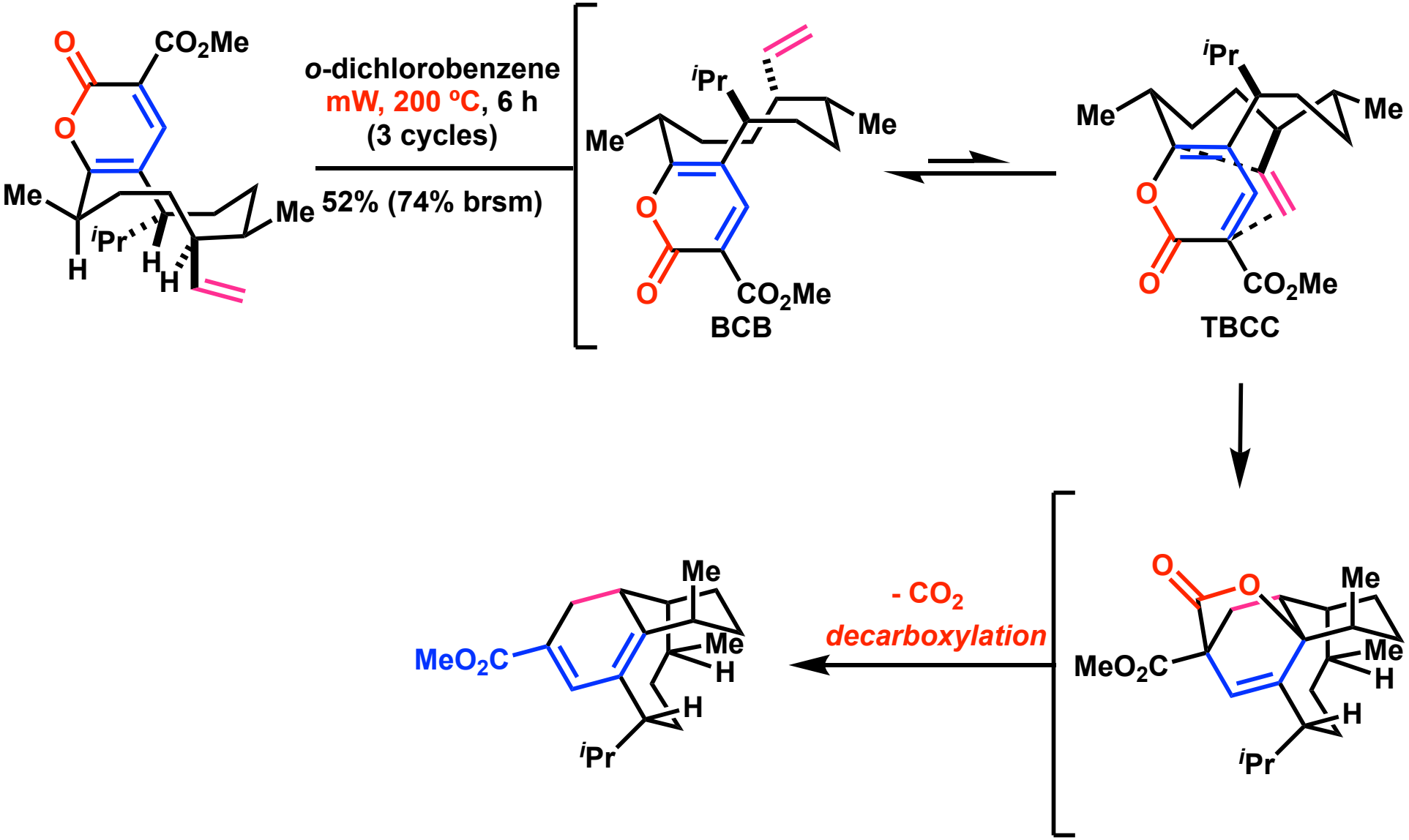


75% (major)

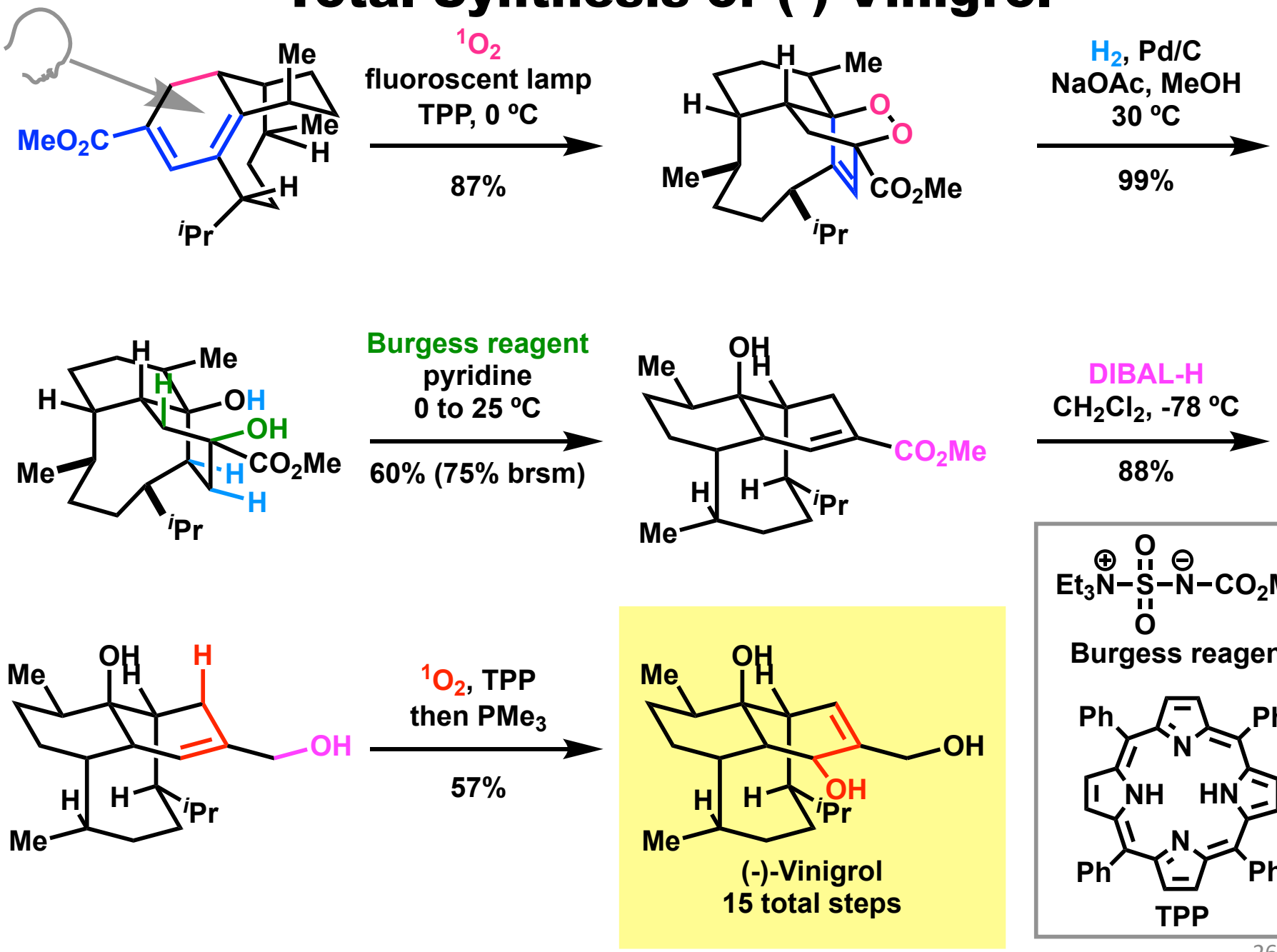
Synthesis of Pyrone



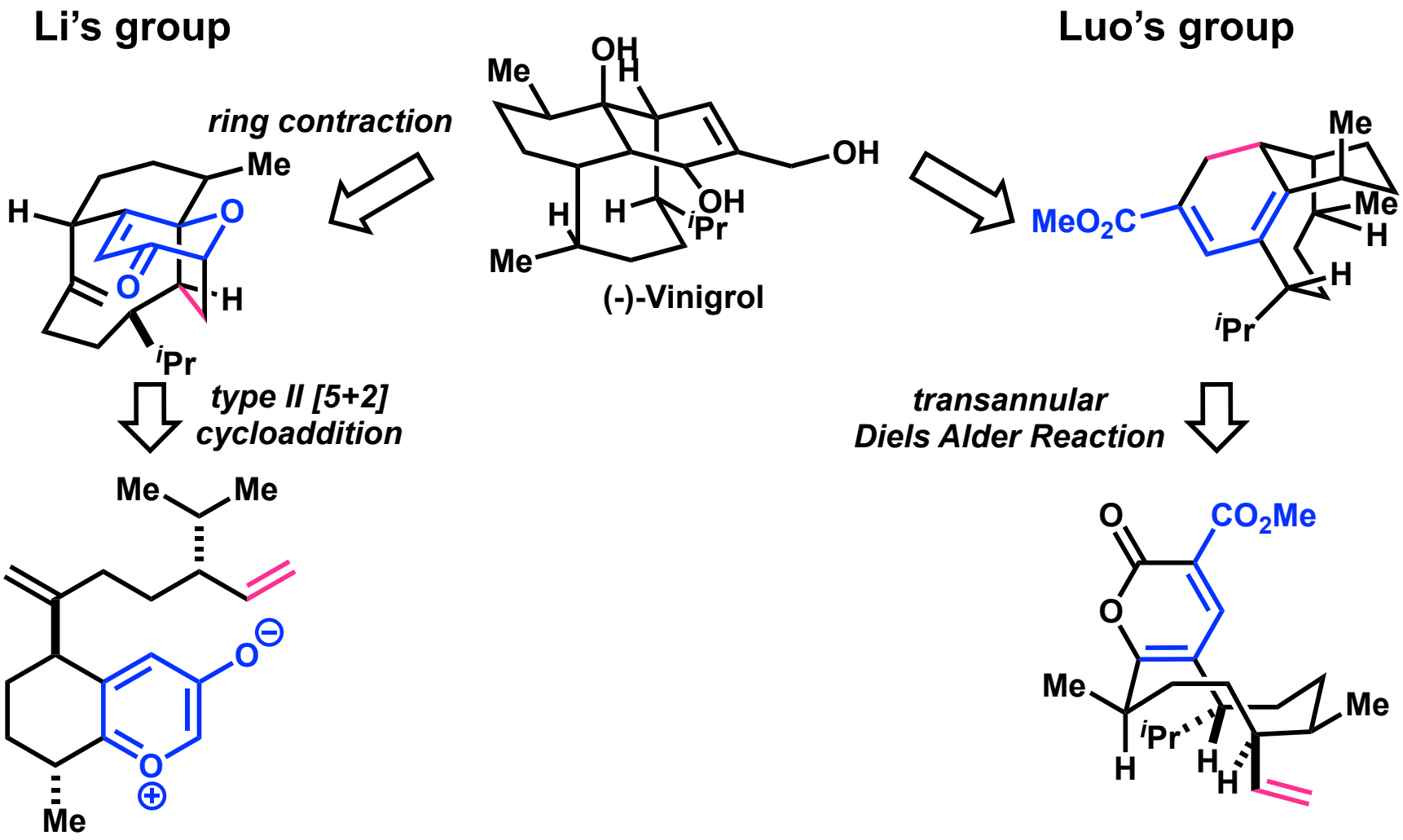
Transannular Diels Aider Reaction



Total Synthesis of (-)-Vinigrol



Summary

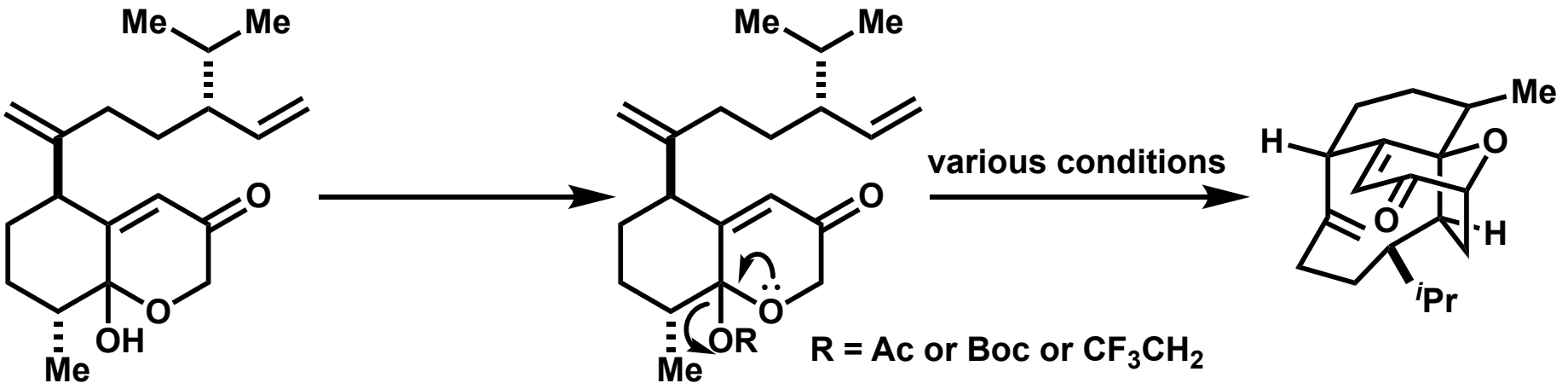


- Formation of highly strained 1,5-butanodecahydronaphtalene via type II [5+2] cycloaddition
- Making good use of unique ring contraction
- No protecting groups

- Sophisticated stereocontrol of cyclodecane
- Formation of bridge-head 6-6-8 tricyclic ring system via transannular Diels Alder reaction
- No protecting groups

Appendix

Conditions for Cycloaddition



R = Ac or Boc or CF_3CH_2

R = Ac or Boc

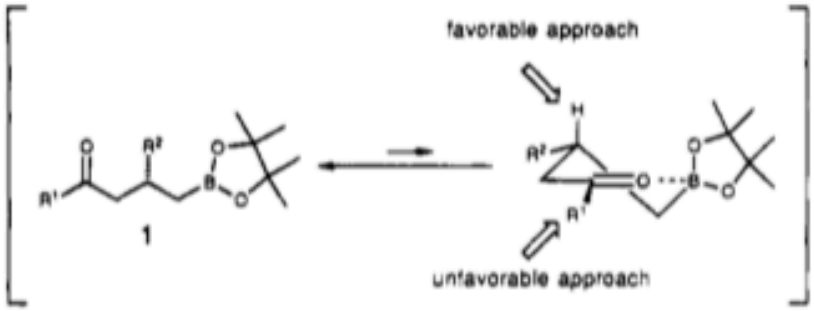
conditions	result (Ac / Boc)
$NaHCO_3$, MeCN, 80ºC, 15 h	decomp. / decomp.
$NaHCO_3$ (2 eq.), MeCN sealed tube, 160 ºC, 15 h	8% / 7%
TMP (2 eq.), MeCN sealed tube, 160 ºC, 15 h	3% / 18%
Pyrrolidine (4 eq.), MeCN sealed tube, 160 ºC, 15 h	decomp. / decomp.
DBU (2eq.), MeCN sealed tube, 160 ºC, 15 h	decomp. / decomp.

R = CF_3CH_2

conditions	result
Hydroquinidine (0.2 eq.) 4 Å MS, PhCN, 170 ºC, 20 h	40%
$NaHCO_3$ (2 eq.), MeCN sealed tube, 170 ºC, 15 h	10%
TMP (2 eq.), MeCN sealed tube, 160 ºC, 15 h	10%
Pyrrolidine (4 eq.), MeCN sealed tube, 170 ºC, 15 h	decomp. / decomp.
DBU (2eq.), MeCN sealed tube, 170 ºC, 15 h	decomp. / decomp.

Reduction of Ketone by BH_3•THF

Scheme I



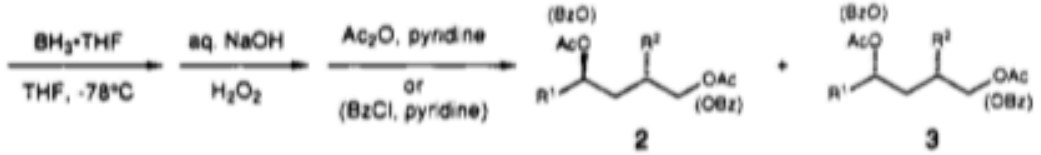
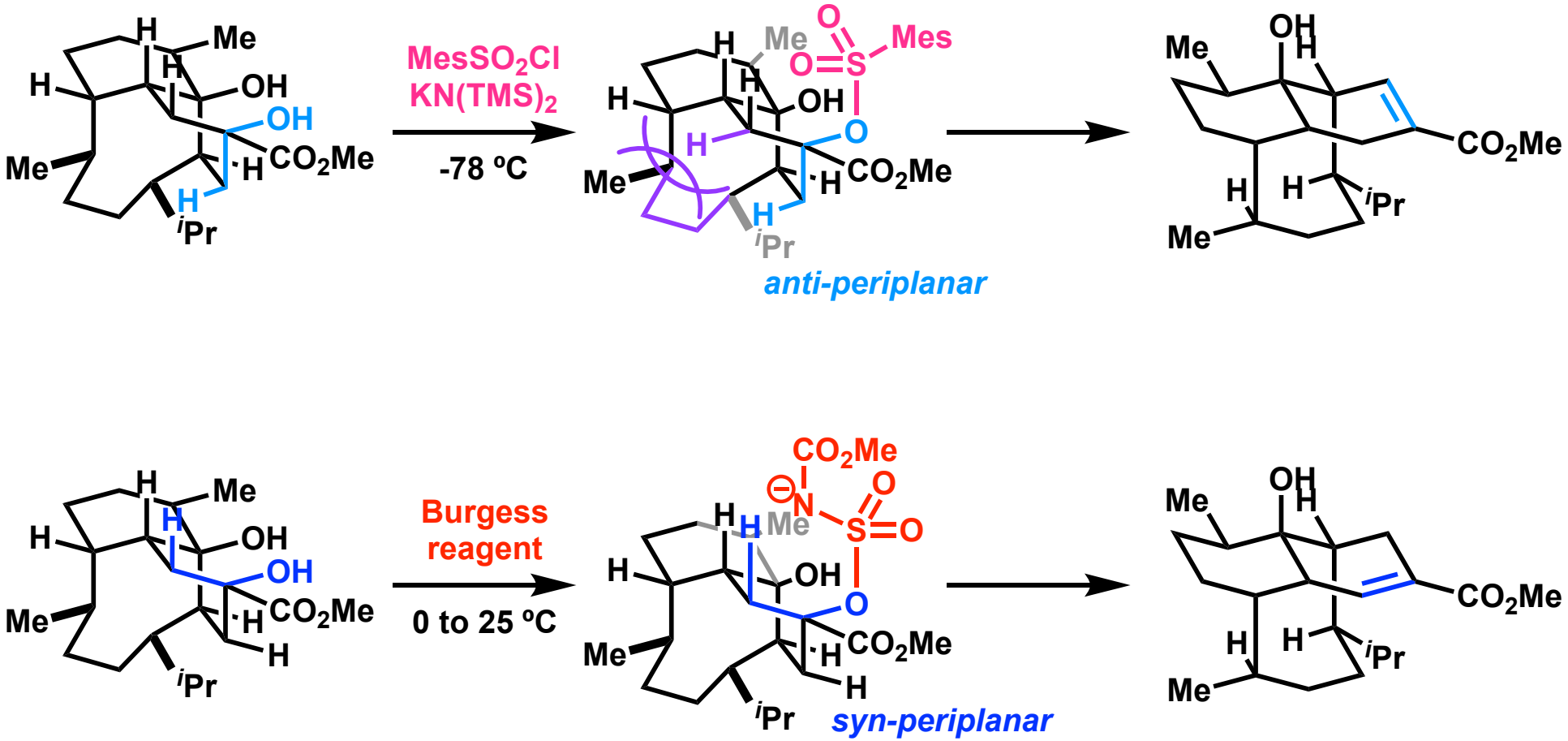


Table I. Results of the Diastereoselective BH_3·THF Reduction of Keto Boronates **1a–h**

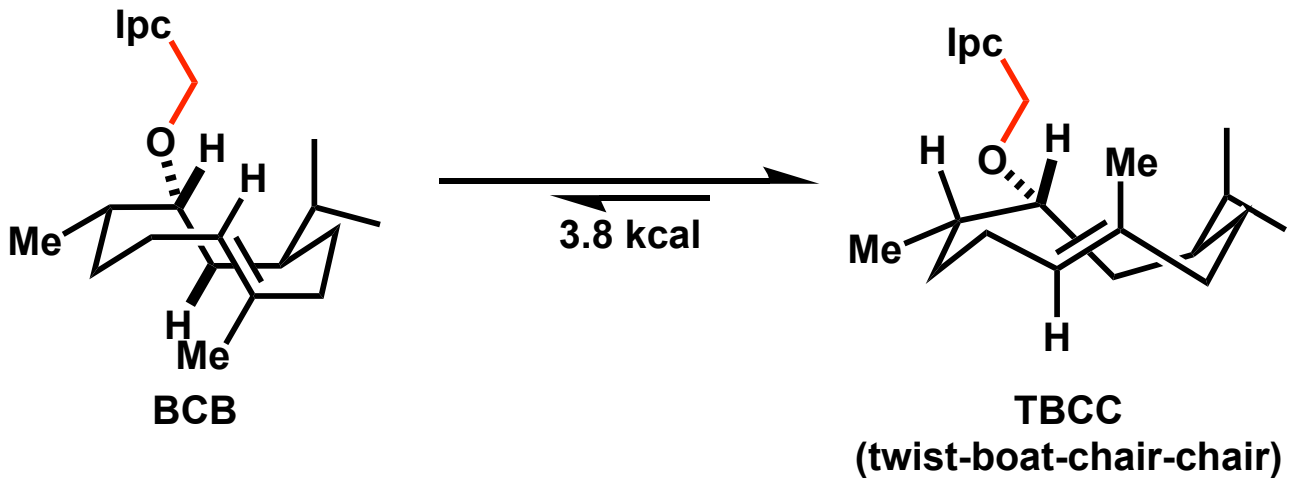
substrate	R^1	R^2	% isltd yield (2 + 3)[a]	diastereoselectivity (2:3)[b]
1a	Me	Me	71	34:1[c]
1b	Me	Et	84	22:1[d]
1c	Me	*i*-Pr	89	62:1
1d	Me	Ph	88[e]	24:1
1e	Et	Me	91	28:1[d]
1f	*i*-Pr	Me	92	>50:1[d]
1g	Ph	Me	86	20:1
1h	Pr	Me	88[f]	19:1

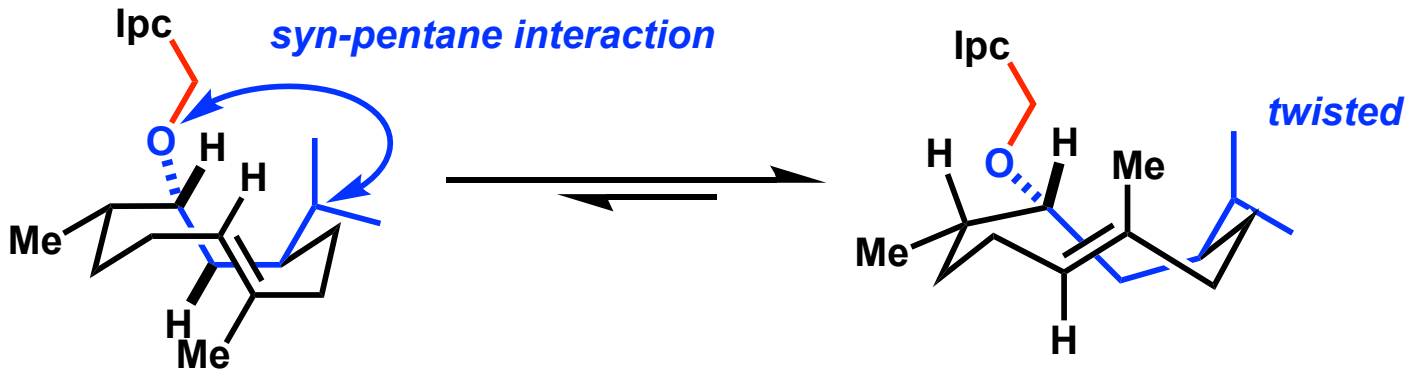
Gary A. Molander, Kevin L. Bobbitt, and Christopher K. Murray. *J. Am. Chem. Soc.,* **1992**, Vol. 114, No. 7,

Proposed Mechanism of regioselectivity



Computational Analysis of Conformation [1)]





1) Macro model was used. To calculate conformations, B(Borane) was replaced with C(Carbon).