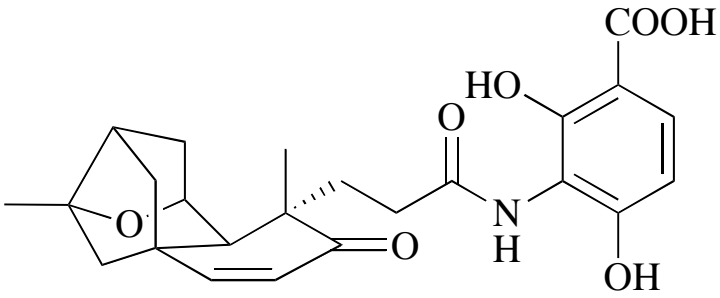
Total Synthesis of Platensimycin

Zhensheng Ding

October 19 2007



Nicolaou, K. C. *Angew. Chem. Int. Ed.,* **2006**, *45*, 7086-90

Nicolaou, K. C. *Angew. Chem. Int. Ed.,* **2007**, *46*, 3942-5

Nicolaou, K. C. *Angew. Chem. Int. Ed.,* **2007**, *46*, 4712-4

Nicolaou, K. C. *Chem. Commun.,* **2007**, 1922-3

Zou, Y.; Snider, B. *Org. Lett.,* **2007**, *9*, 1825-8

Heretsch, P.; Giannis, A. *Synthesis* **2007**, 2614-6

Ghosh, A. *Org. Lett.,* **2007**, *9*, 4013-6

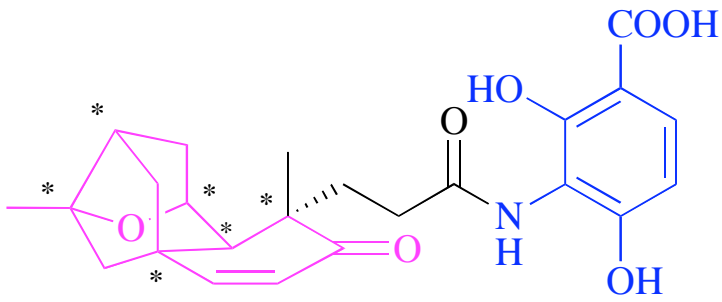
Kaliappan, K. P. and Ravikumar, V. *Org. Lett.,* **2007**, *9*, 2417-9

Li, P.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 9534 –5

Mulzer, J. *Angew. Chem. Int. Ed.* **2007**, *46*, 8074-5

Corey, E. J. *Org. Lett.,* **2007**, *xxxx*

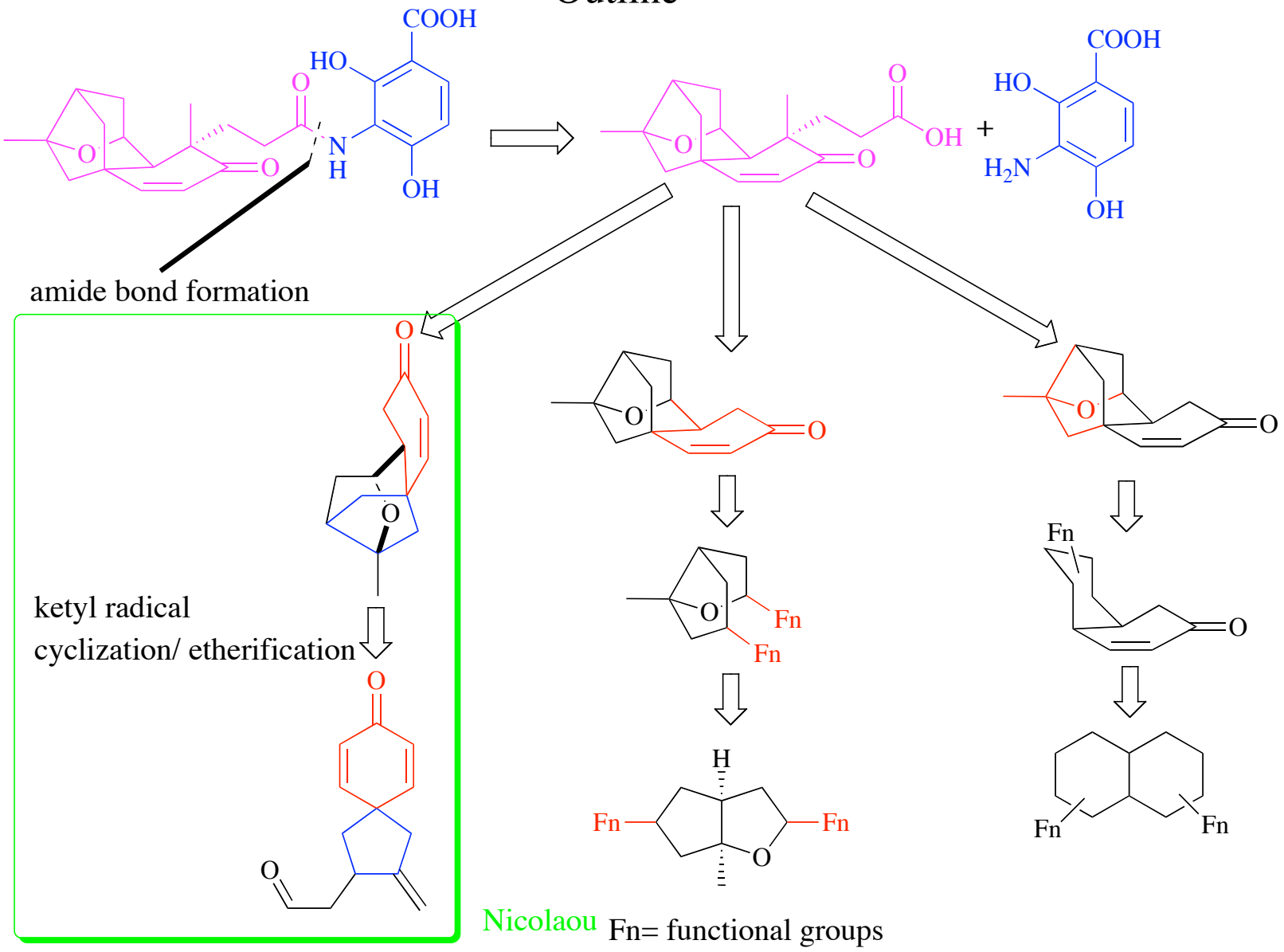
Super Drug: Platensimycin and Its Structure Features



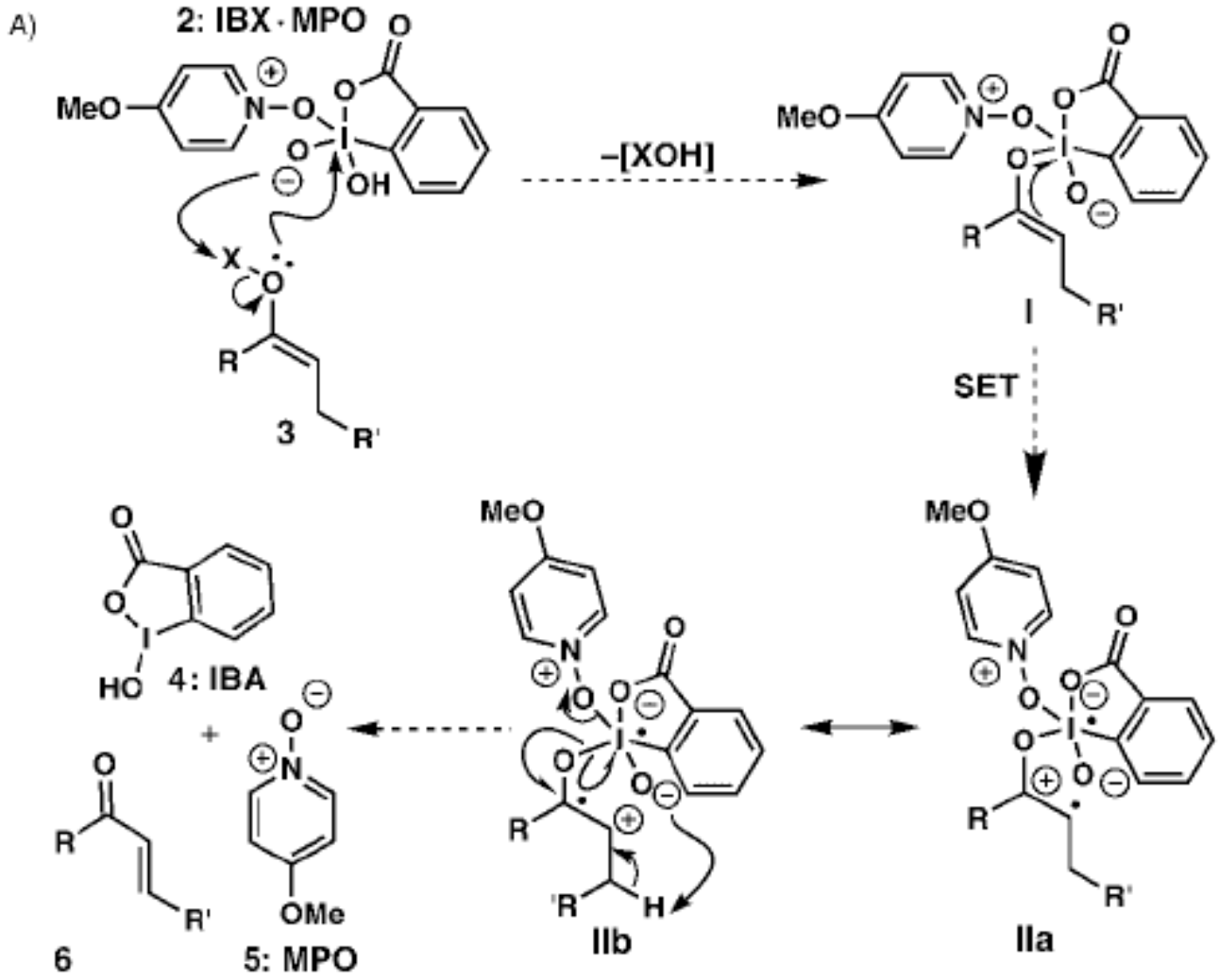
Tetracyclic motif
Cage-like
6 chiral centers
3 tertiary carbons
Ether linkage

Tetra-substituted resorcine
Amino acid

Outline


COOH
HO
O
N
H
OH
O
O
amide bond formation
O
OH
+
HO
COOH
H_2N
OH
ketyl radical
cyclization/ etherification
Fn
Fn
Fn
Fn
Fn
Fn
H
Nicolaou
Fn= functional groups

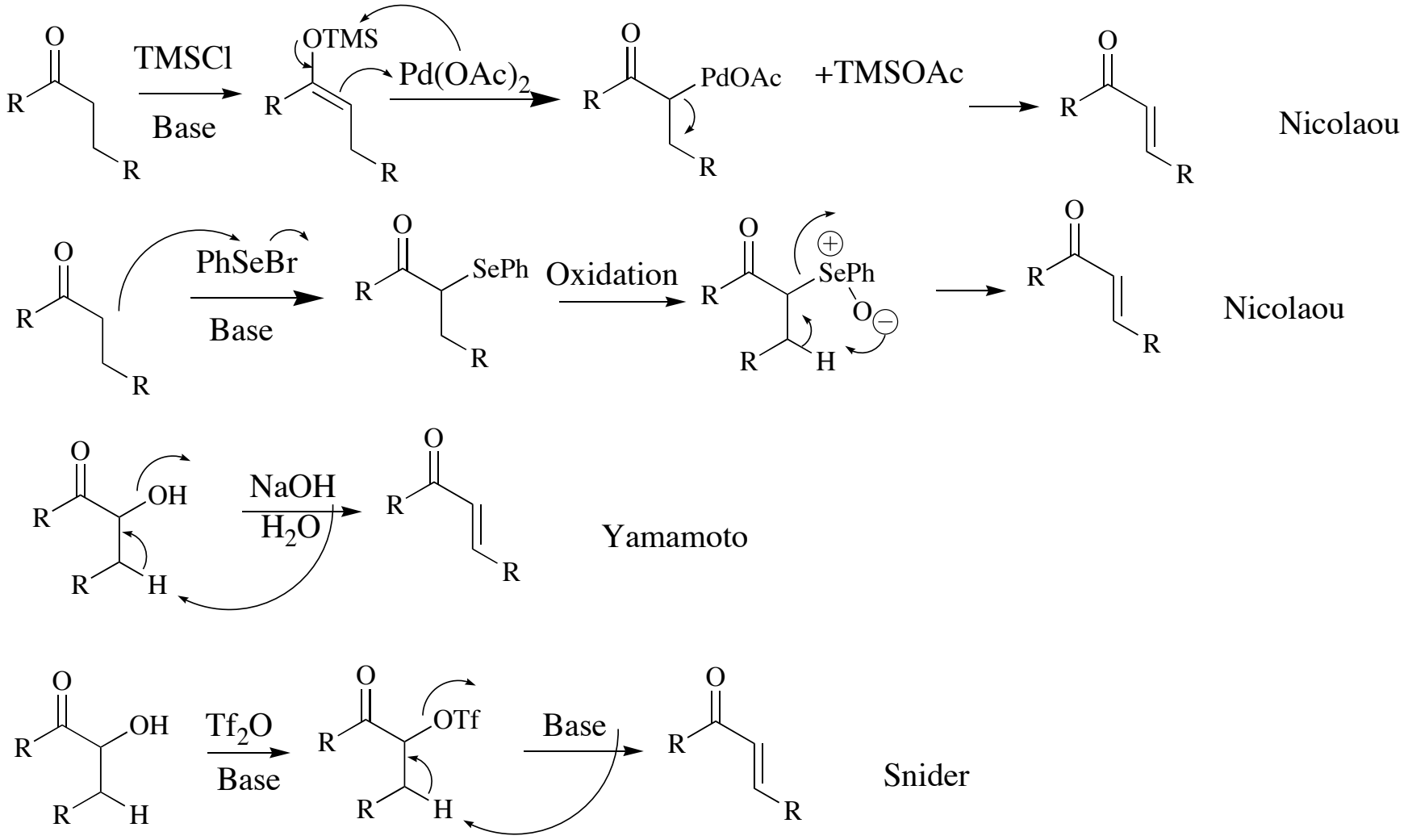
Summary: Enone Synthesis from Ketone



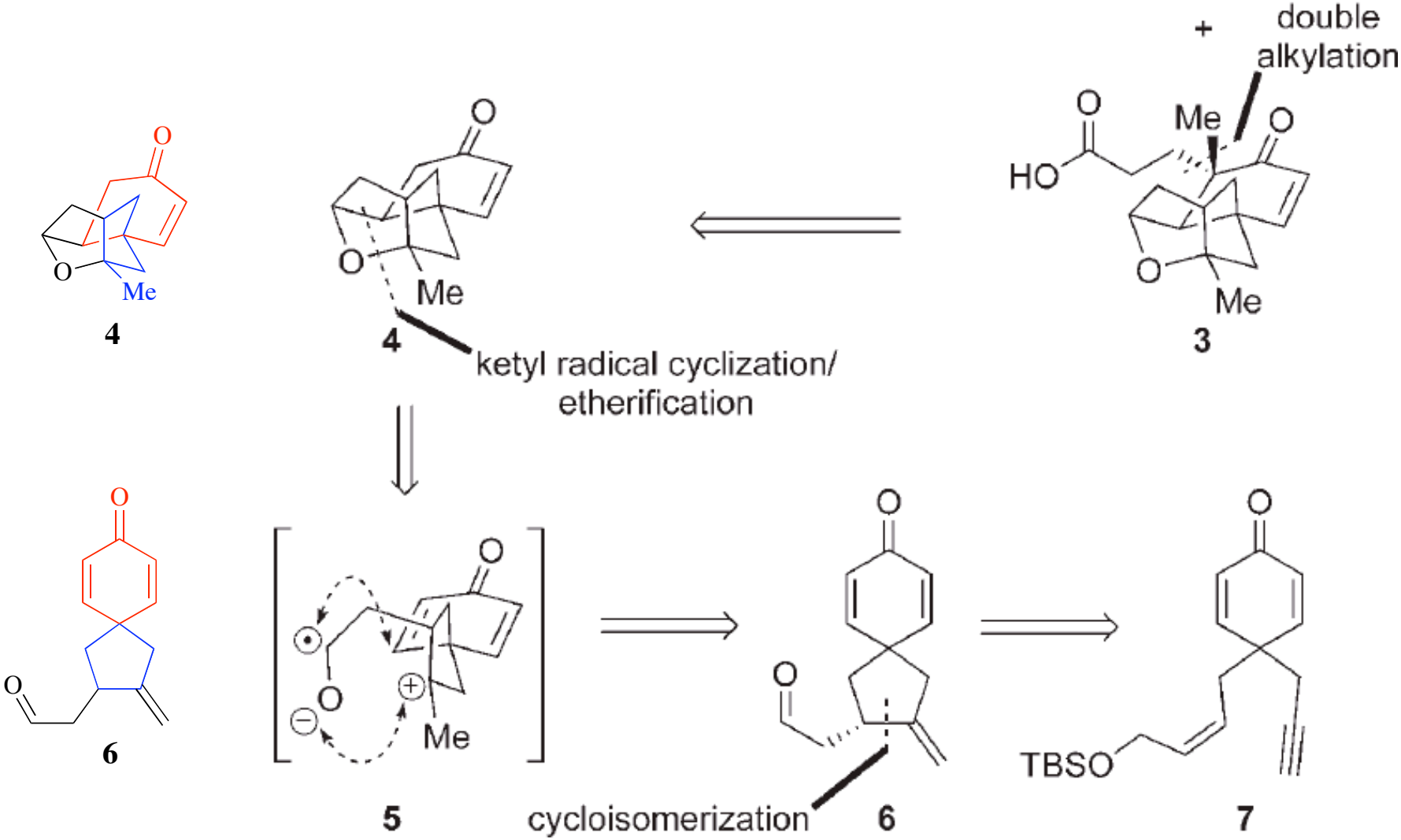
Nicolaou
Corey

Nicolaou, K. C.; *Angew. Chem., Int. Ed.* **2002**, *41*, 996-1000.

Summary: Enone Synthesis from Ketone

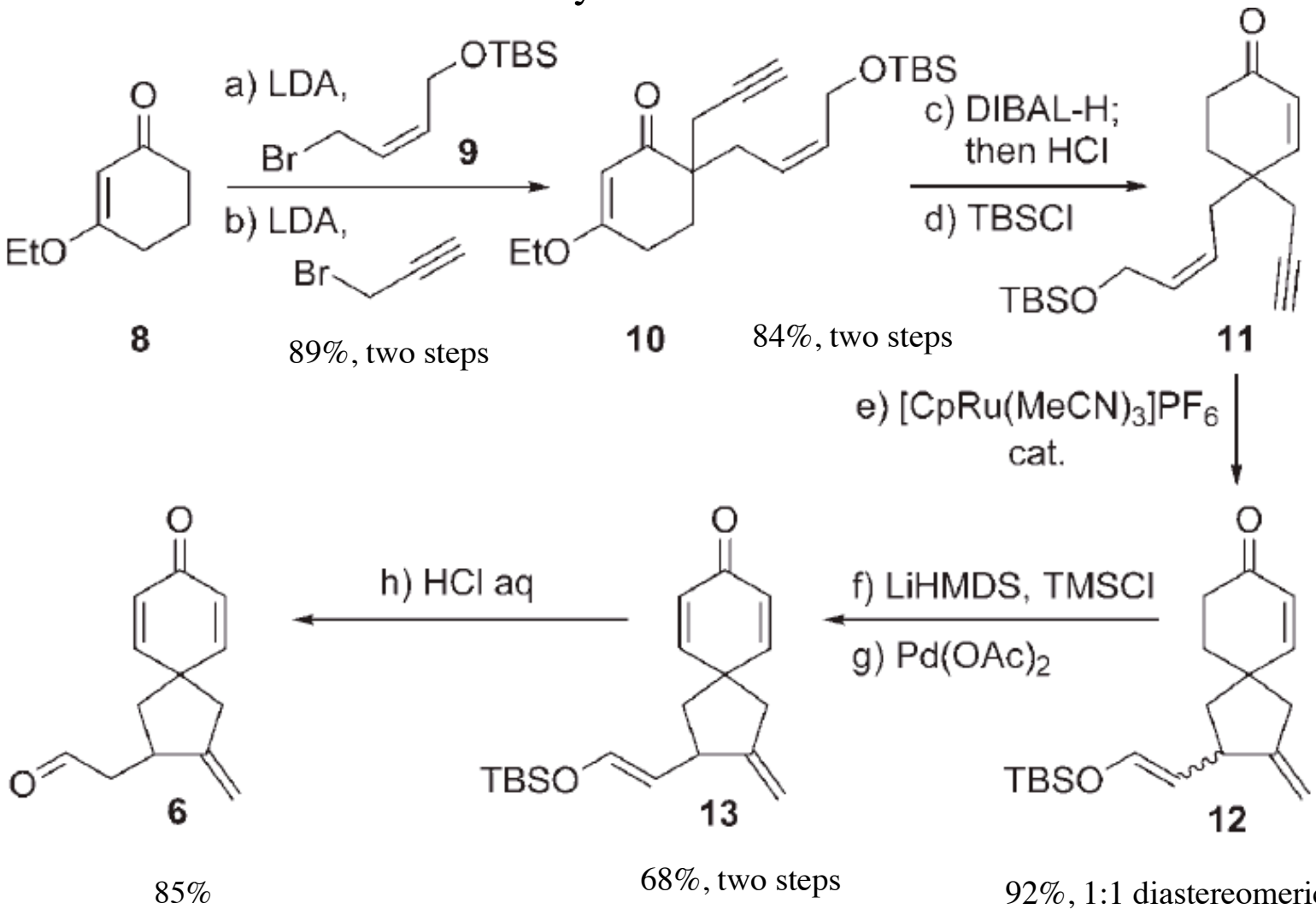


Nicolaou's Racemic Synthesis: Retrosynthesis



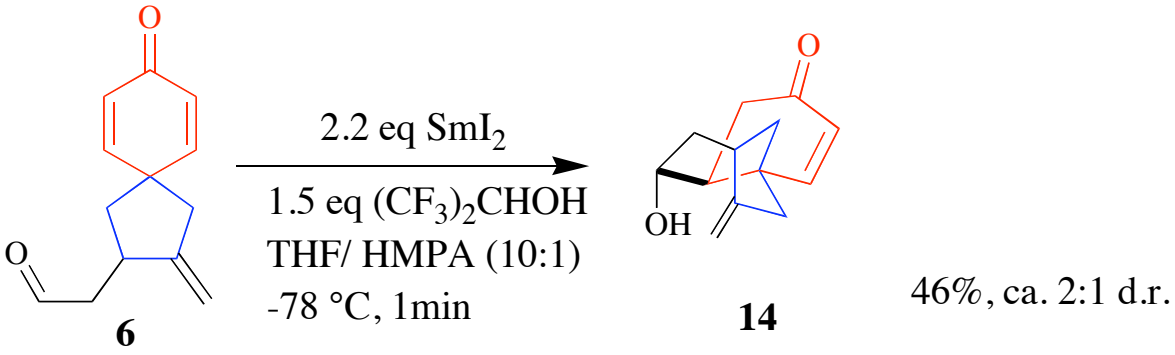
Nicolaou, K. C. *Angew. Chem. Int. Ed.*, **2006**, *45*, 7086-90

Synthesis

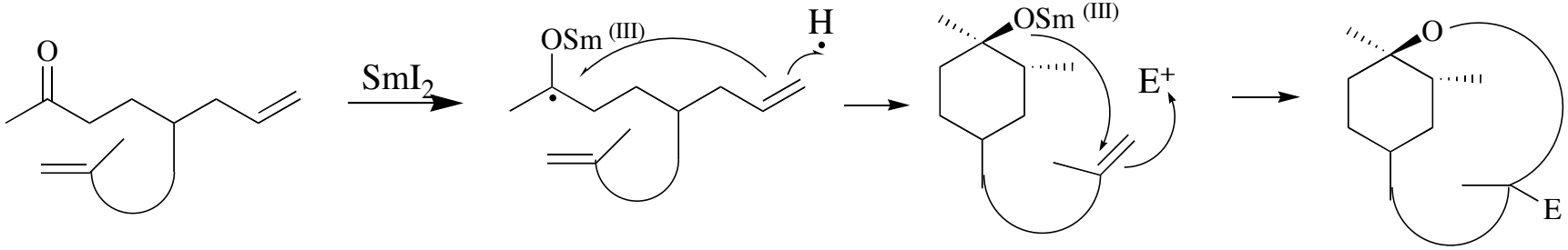


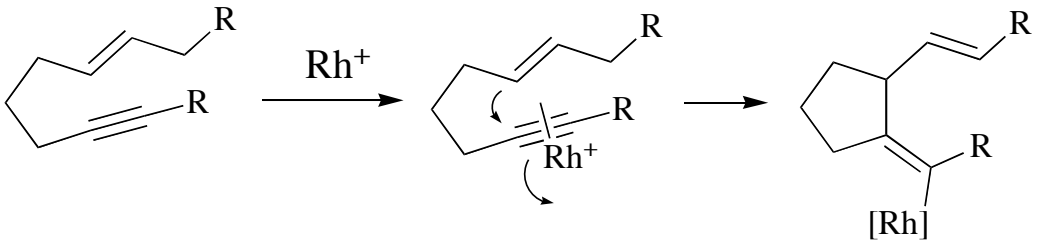
Nicolaou, K. C. *Angew. Chem. Int. Ed.,* **2006**, *45*, 7086-90

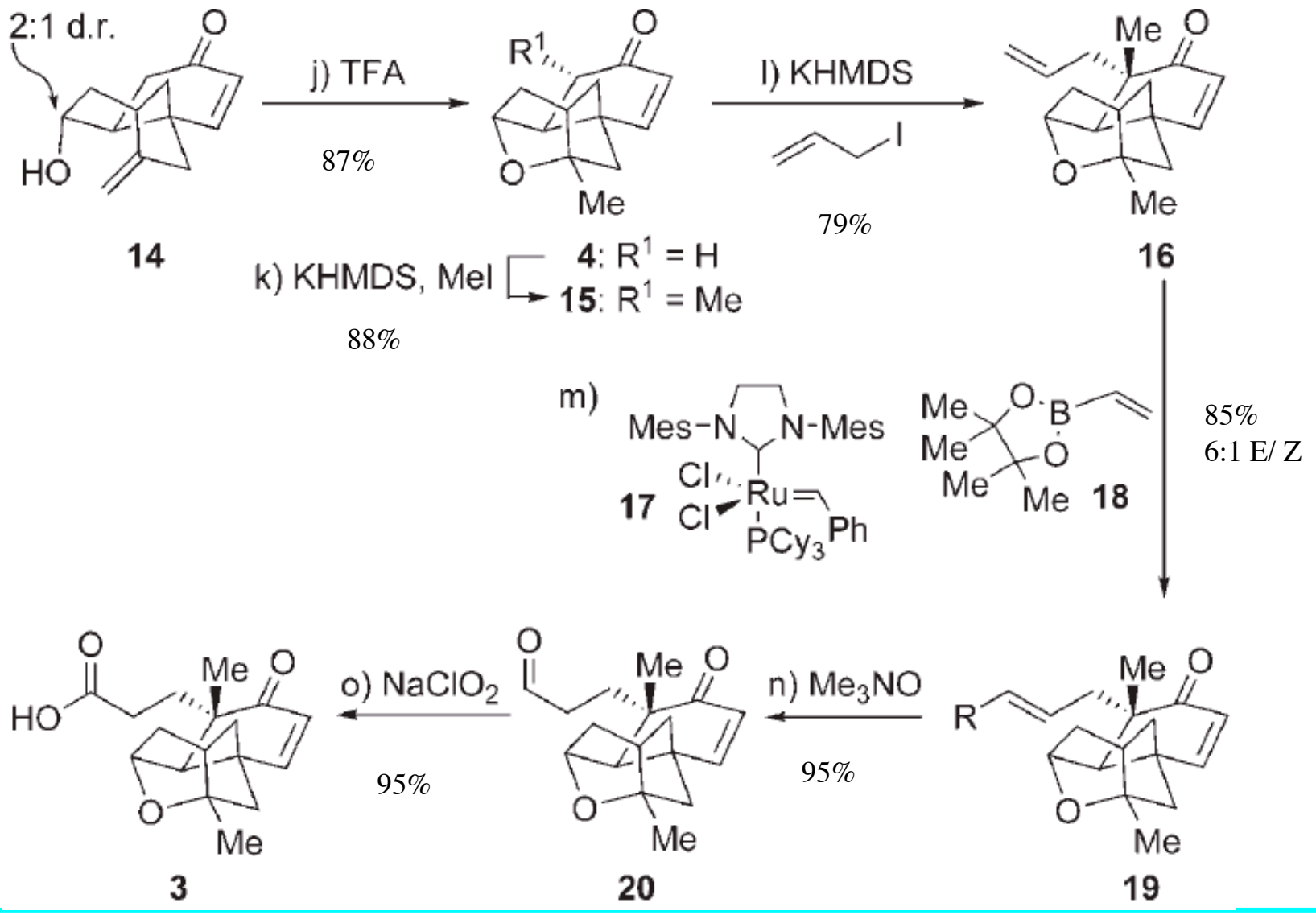
Synthesis



6 **14** 46%, ca. 2:1 d.r.

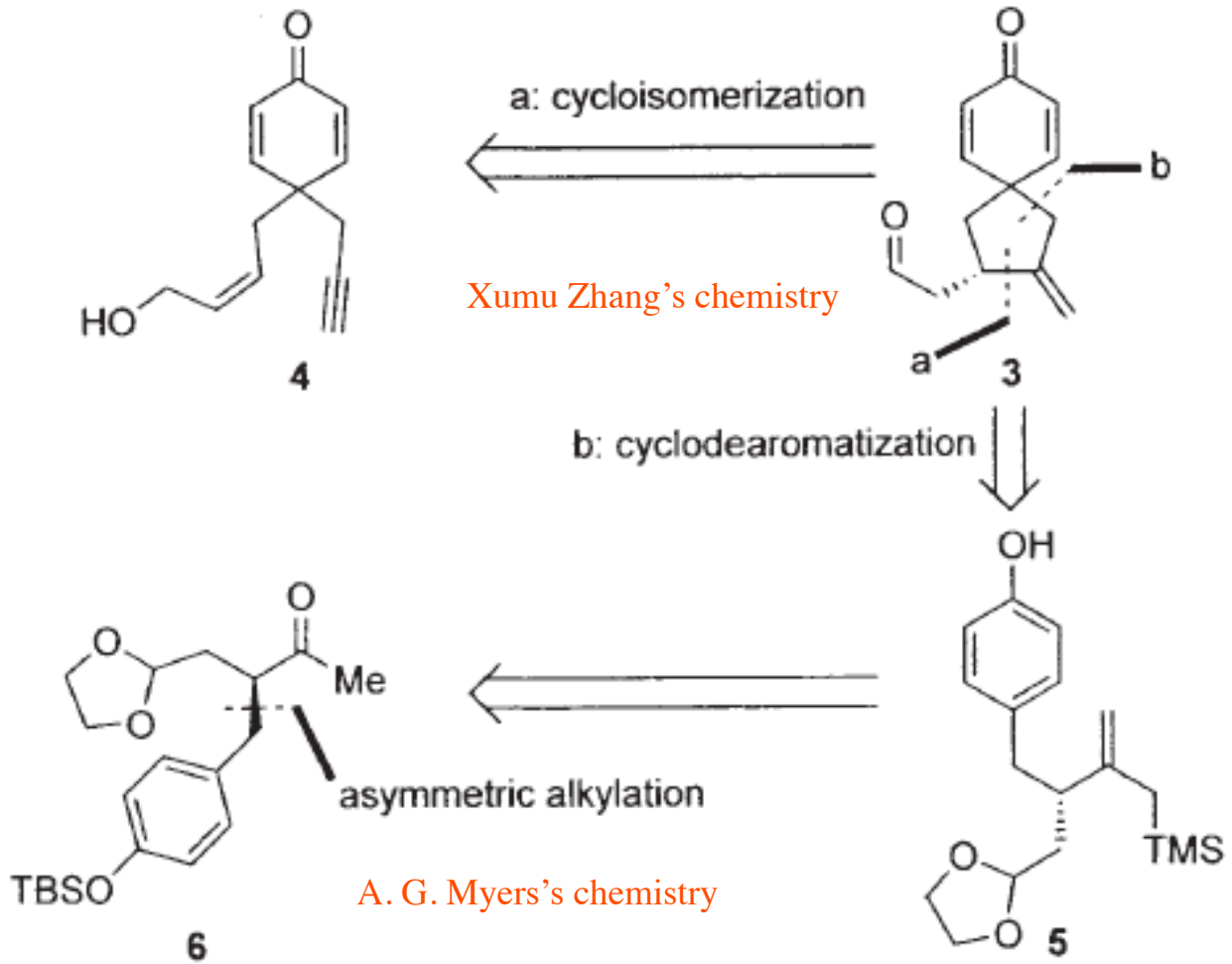






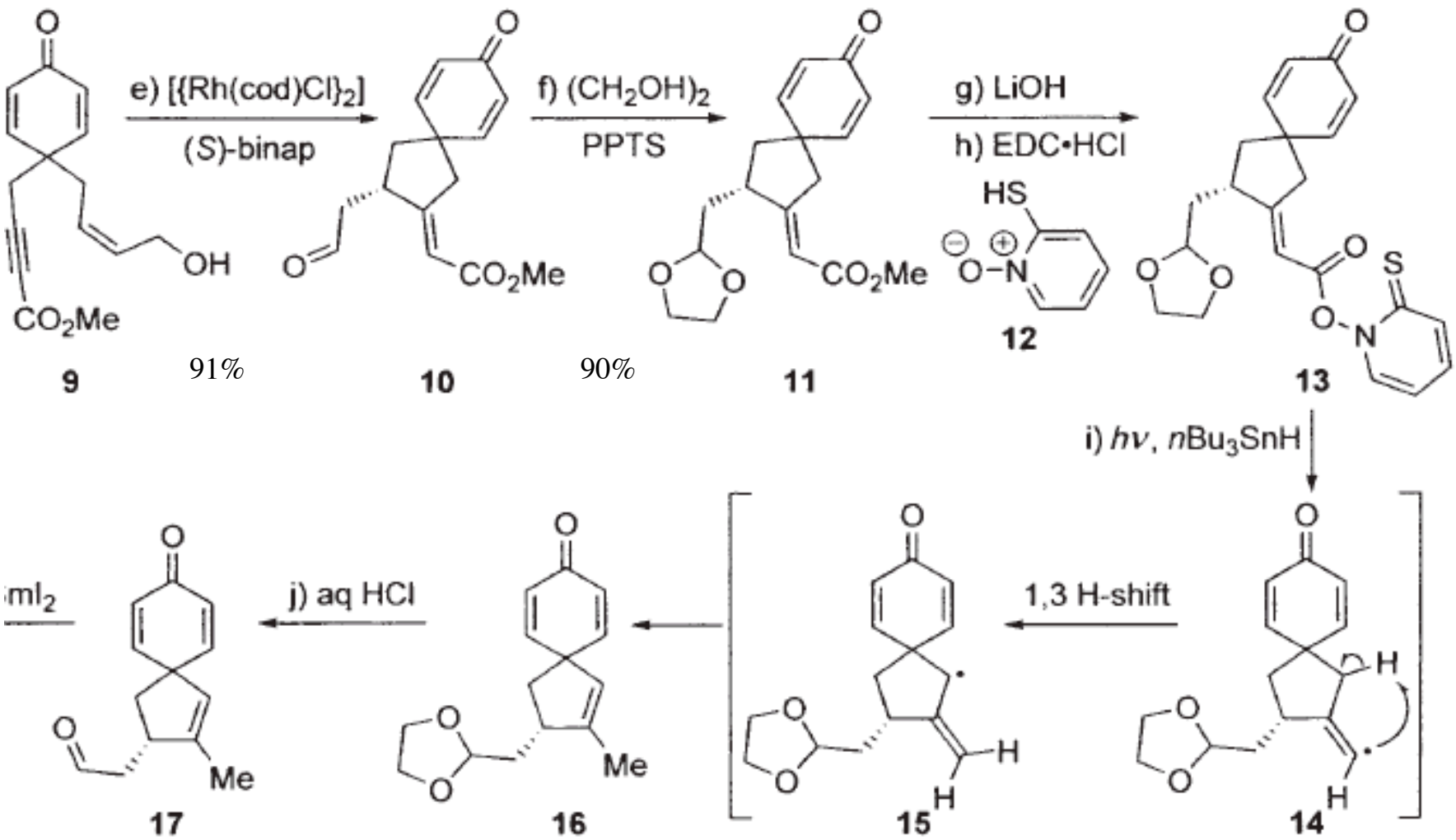
Nicolaou, K. C. *Angew. Chem. Int. Ed.,* **2006**, *45*, 7086-90

Nicolaou's Asymmetric Synthesis: Retrosynthesis



Nicolaou, K. C. *Angew. Chem. Int. Ed.*, **2007**, *46*, 3942-5

Nicolaou's Asymmetric Synthesis



Nicolaou, K. C. *Angew. Chem. Int. Ed.,* **2007**, *46*, 3942-5

Summary

Pathway a) was able to scale up; expensive and toxic reagents; multiple step.

$Cr(CO)_6$: $266/ 50g, toxic and carcinogen; BuLi: $107/ 800mL (2.5M), corrosive, highly sensitive to air

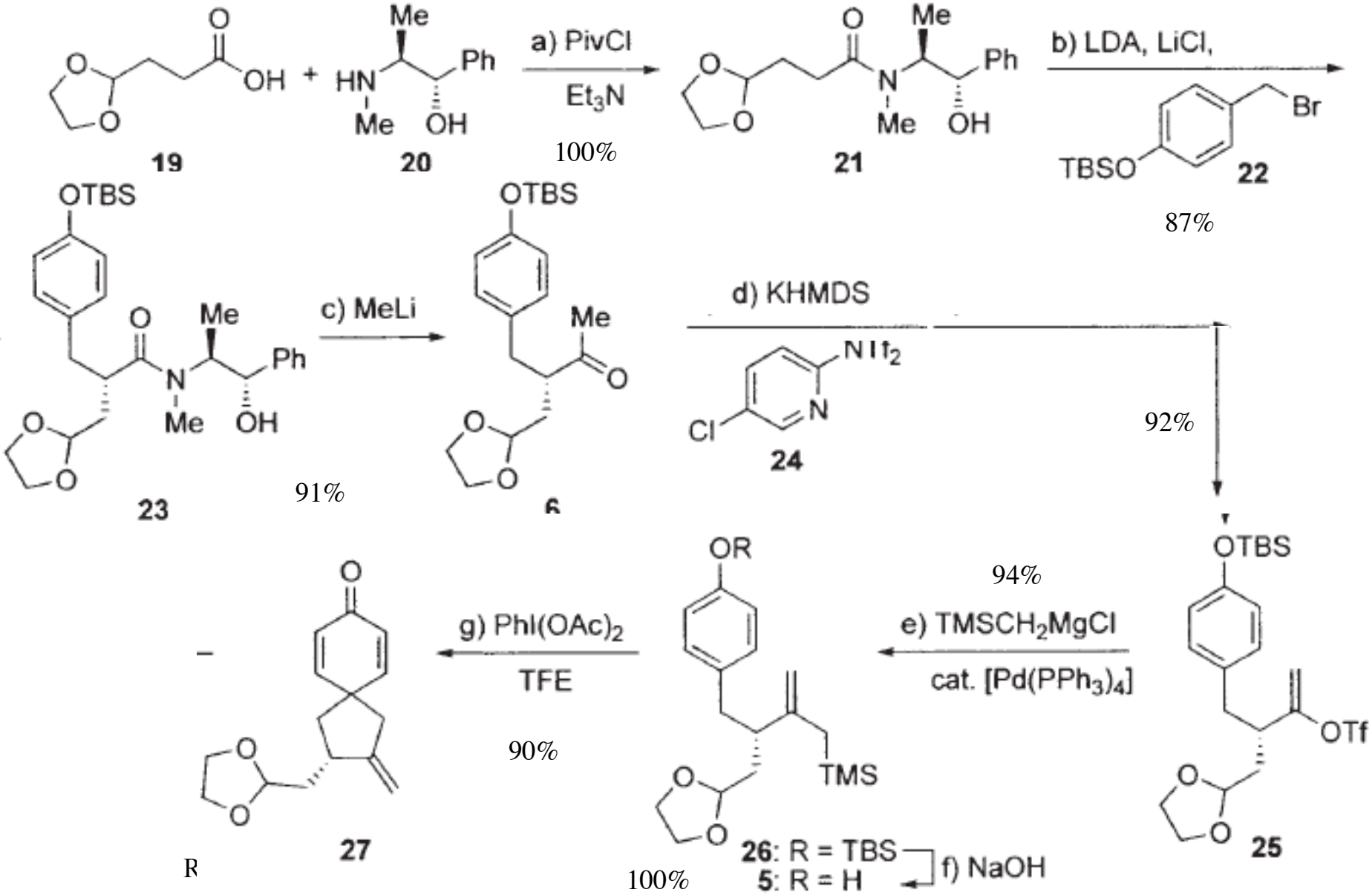
Pathway b) Moderate yield, one step synthesis; hard to purify, not suitable for old VAPOL synthesis.

Purpose: To find an efficient way to prepare both ligands with inexpensive starting materials.

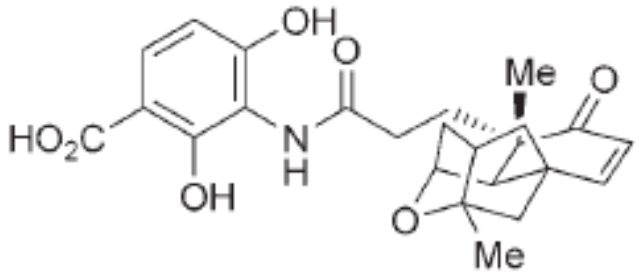
How to optimize pathway b) ?

1) Solvent---must be high bp, inert, easily removable;
2) Lower the reaction temperature (base);
3) None-toxic reagents;
4) More efficient

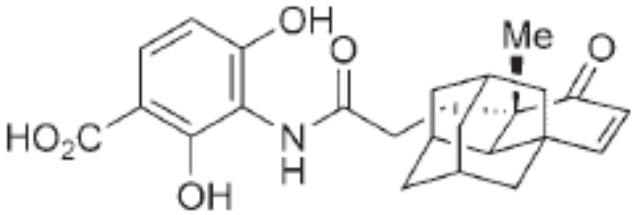
Nicolaou' s Asymmetric Synthesis: Another Pathway



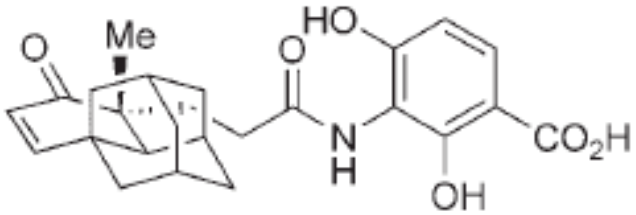
Nicolaou's Analogues Synthesis: Adamantaplatensimycin



(–)-**1**: platensimycin



(–)-**2**

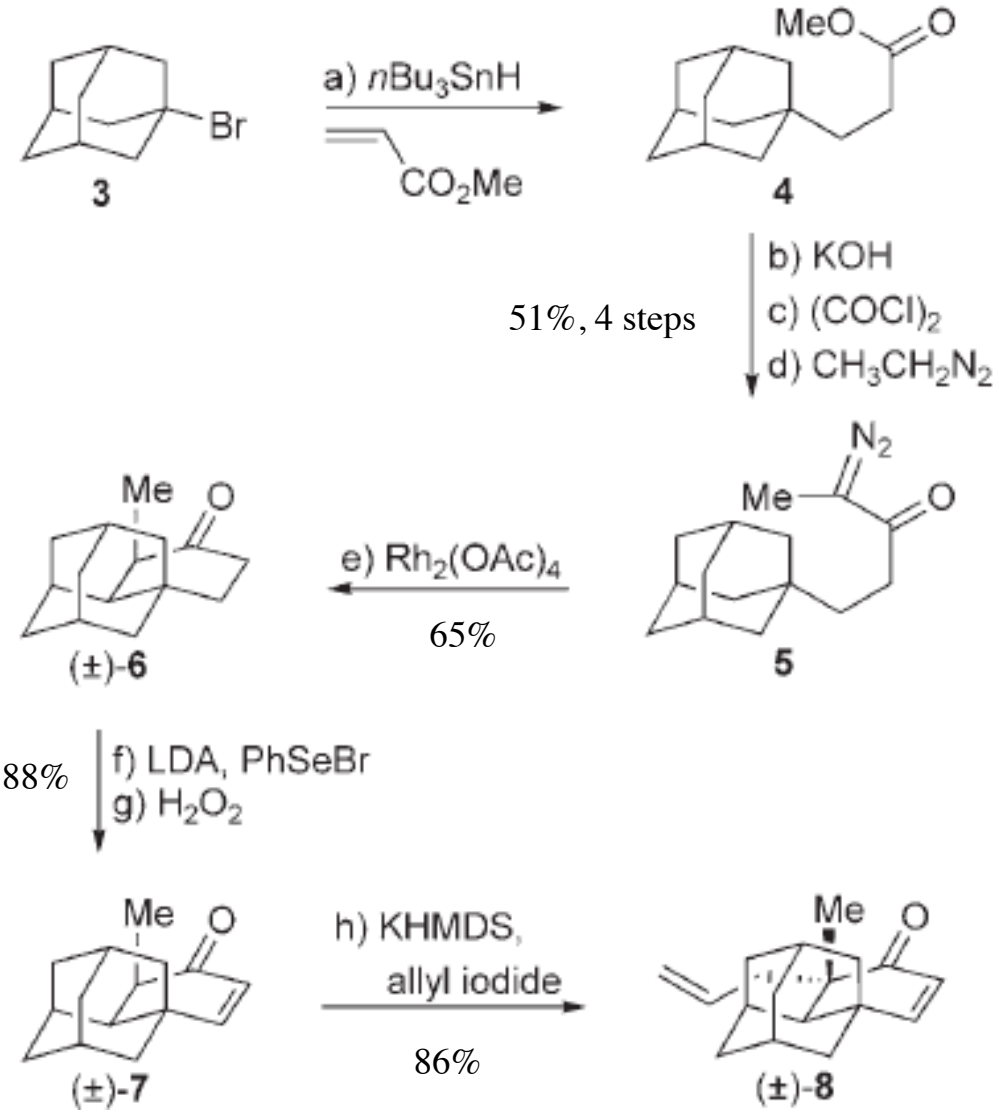


(+)-**2**

Table 1: Minimum inhibitory concentration values (μg mL^{-1}) of (–)-**2**, (+)-**2**, and (±)-**2** against methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecium* (VREF), and *E. coli*.[a]

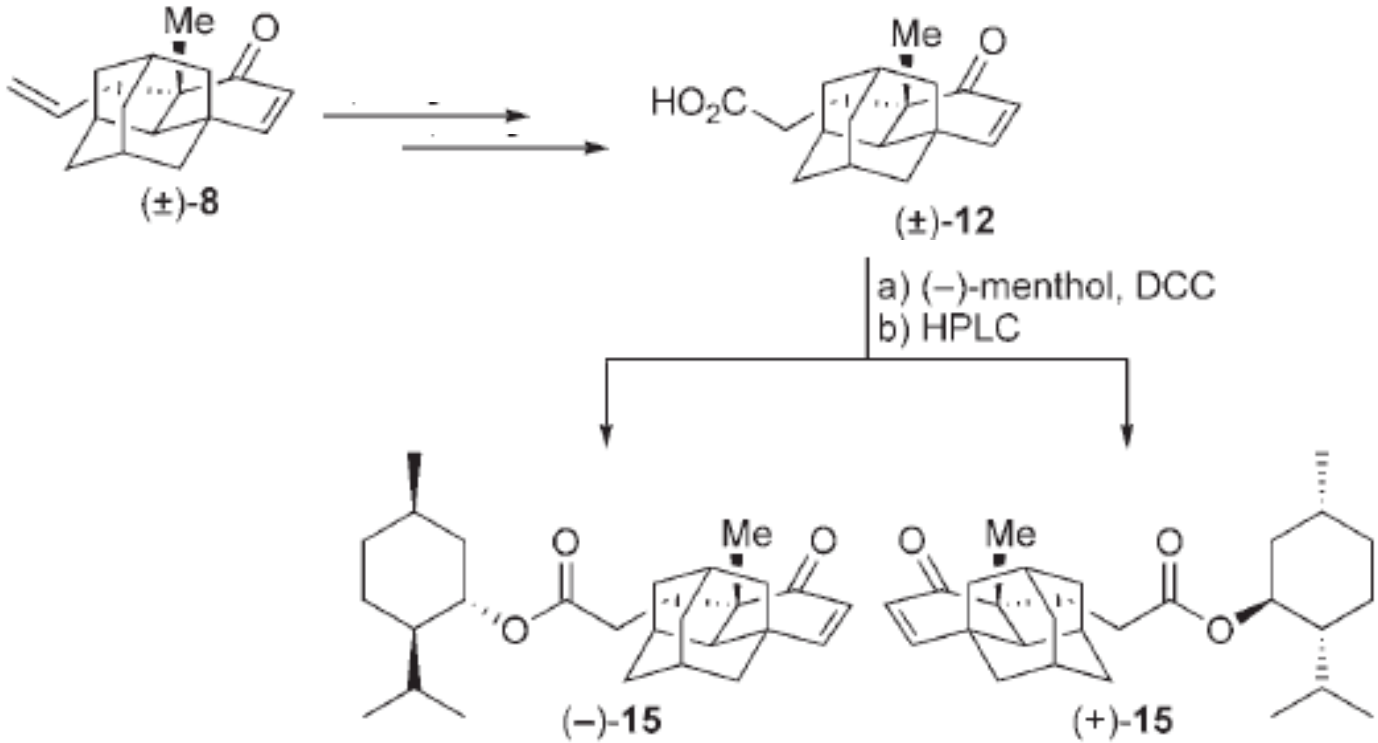
	(+)-**2**	(–)-**2**	(±)-**2**	(–)-**1**[b]	(±)-**1**[c]
MRSA	> 88	1.3–1.8	2.6–3.6	0.2–0.4	0.4–0.8
VREF	> 88	1.3–1.8	2.6–3.6	0.4–0.8	0.8–1.6
E. coli	> 88	> 88	> 88	> 88	> 88

Nicolaou's Analogues Synthesis: Adamantaplatensimycin

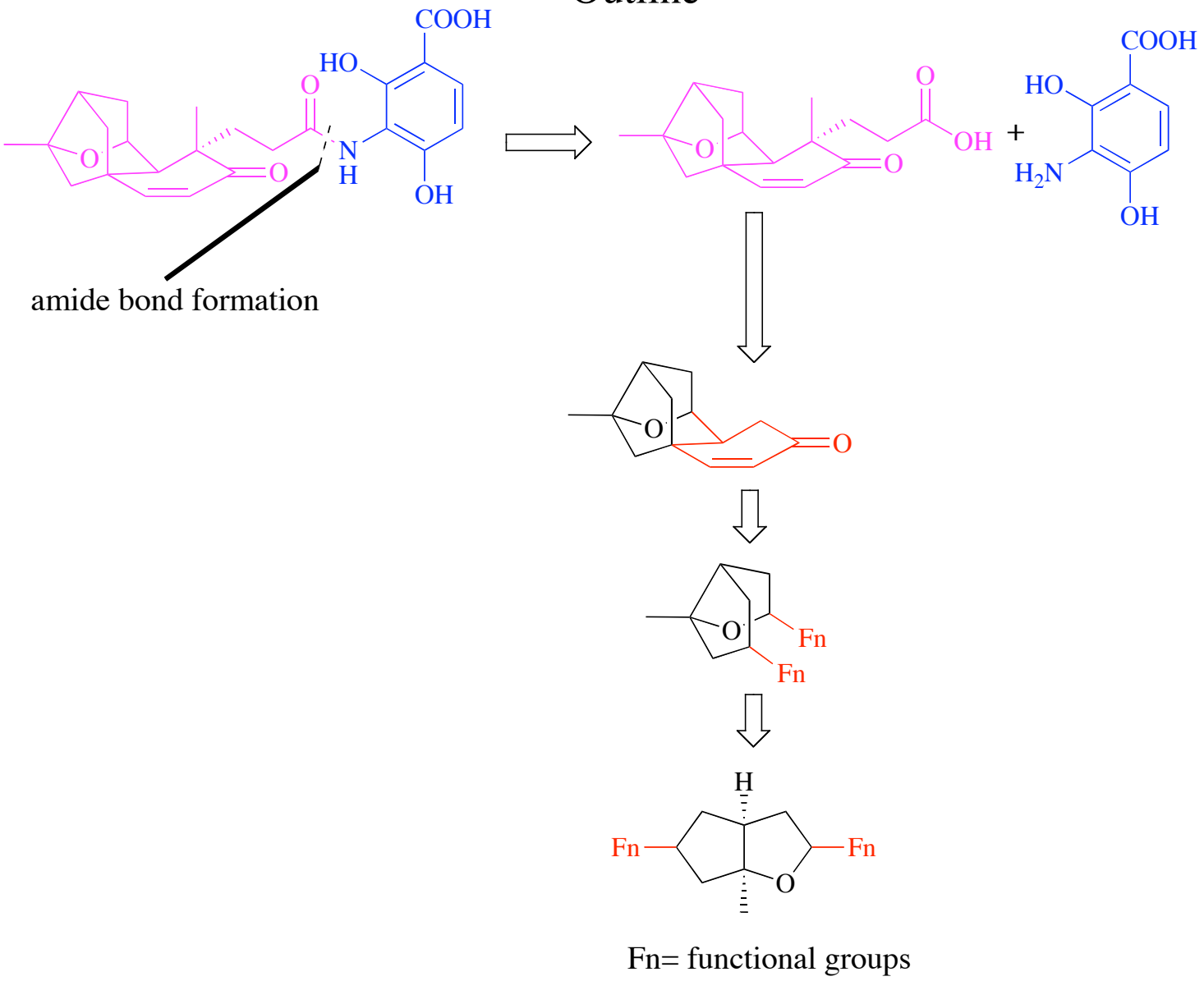


Nicolaou, K. C. *Angew. Chem. Int. Ed.,* **2007**, *46*, 4712-4

Resolution of **12**

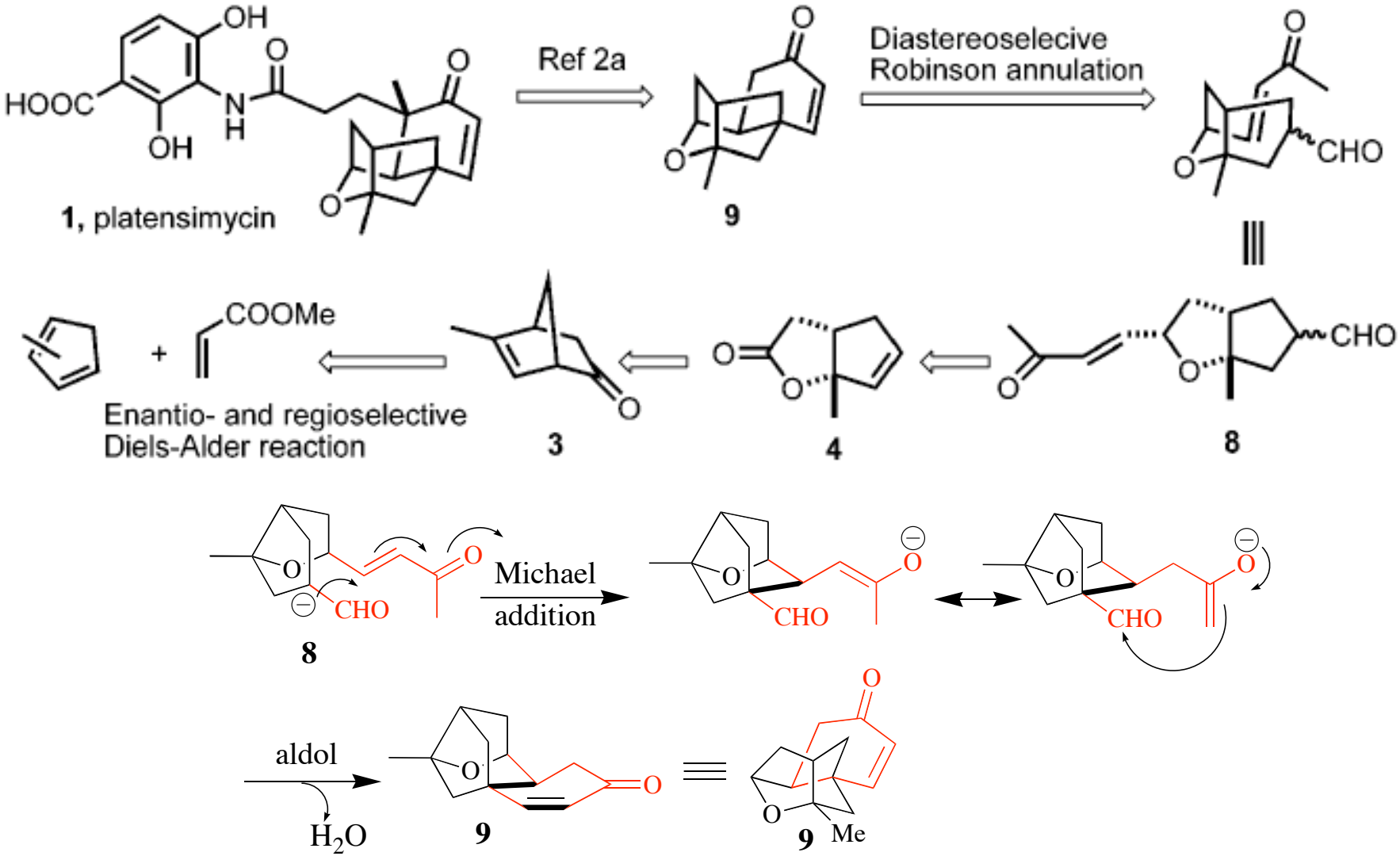


Outline

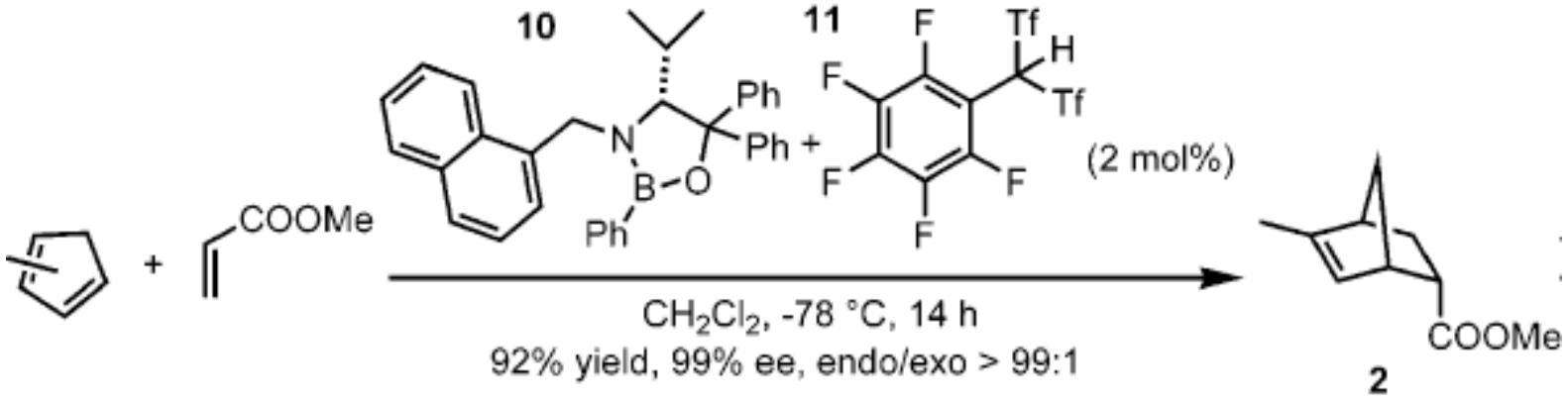


Fn= functional groups

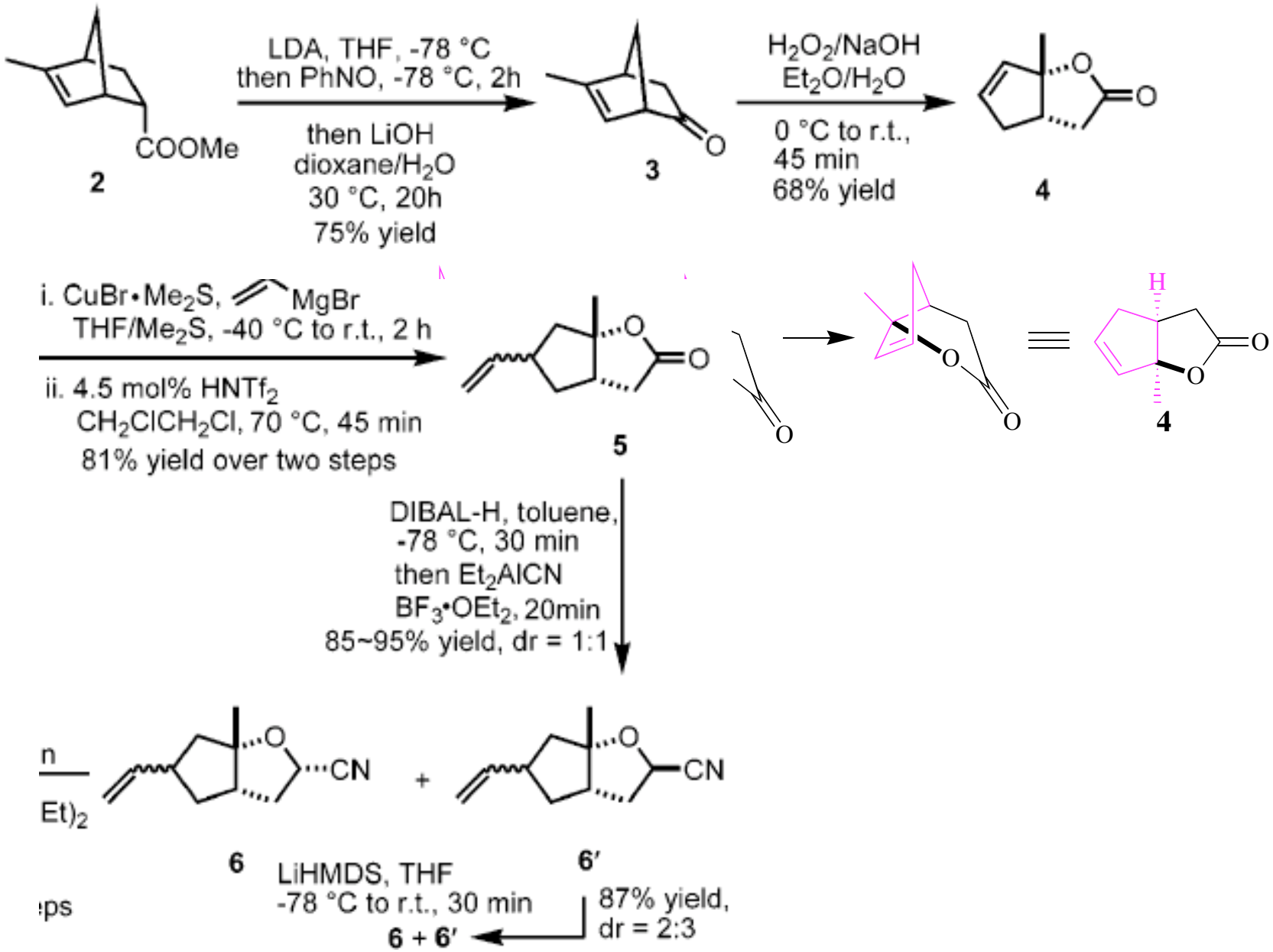
Yamamoto: Asymmetric DA-Robinson Annulation Sequence



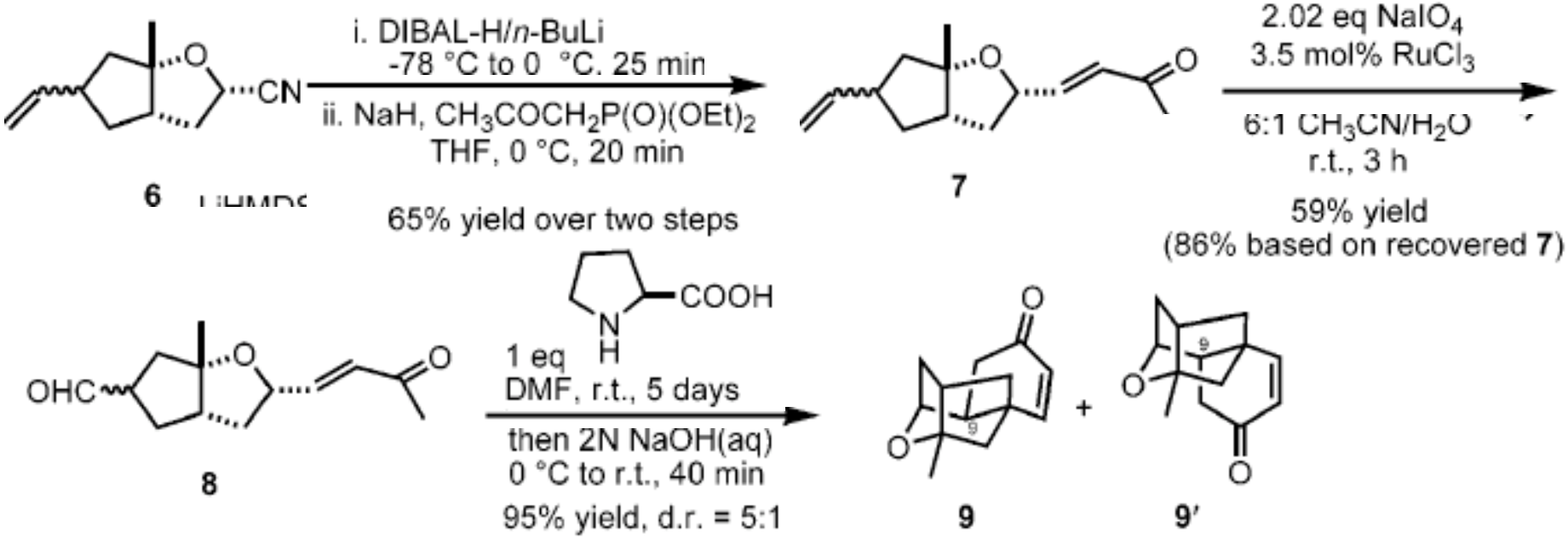
Yamamoto: Asymmetric DA-Robinson Annulation Sequence

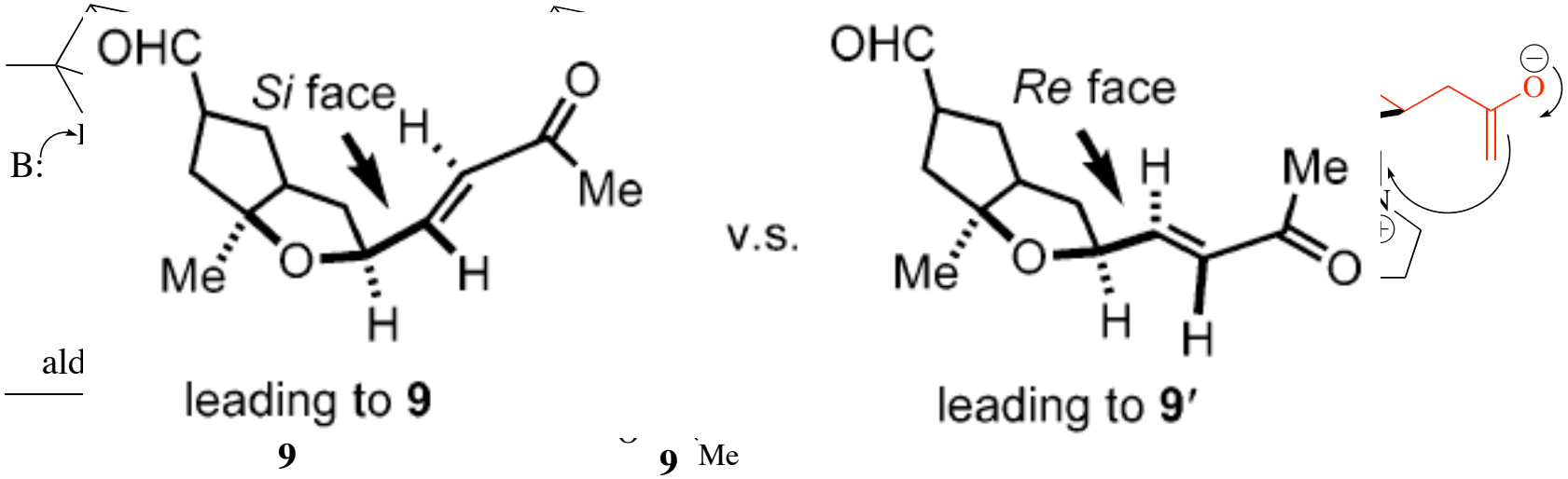


Yamamoto: Asymmetric DA-Robinson Annulation Sequence

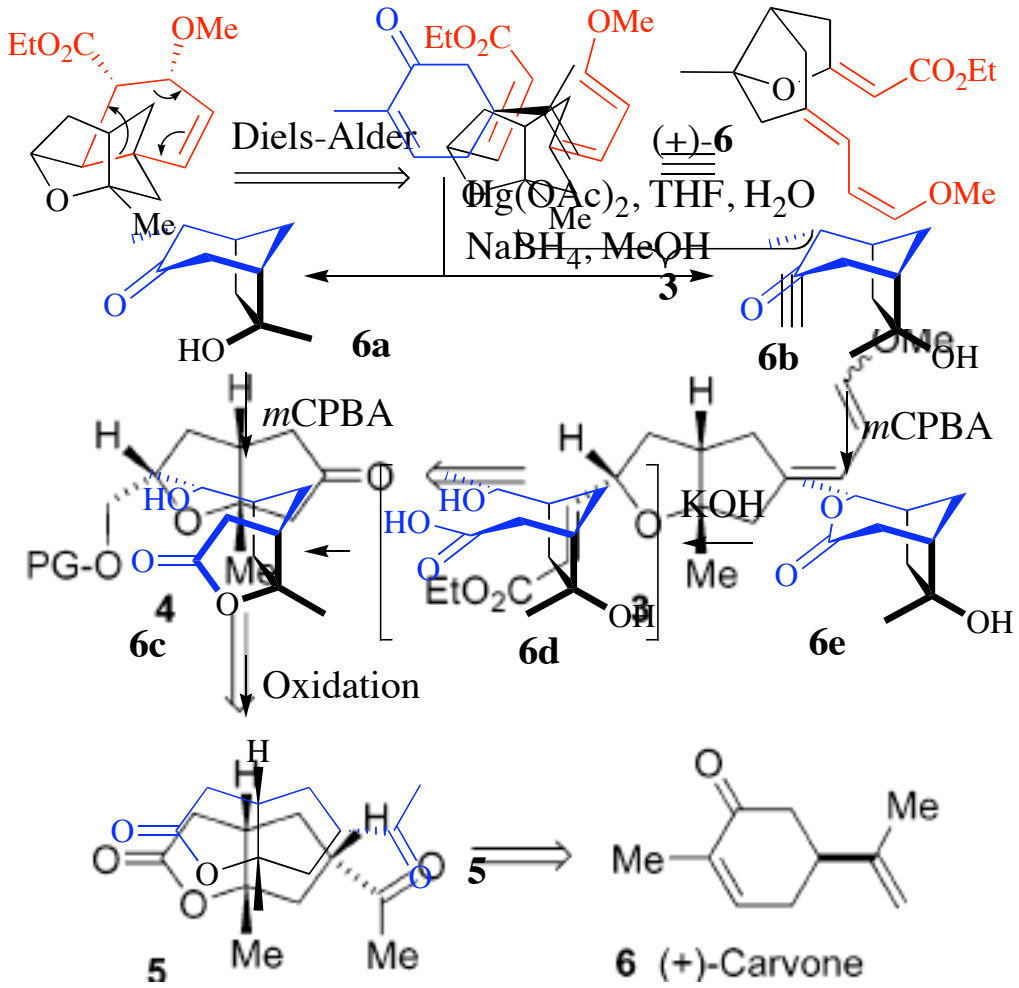


Yamamoto: Asymmetric DA-Robinson Annulation Sequence



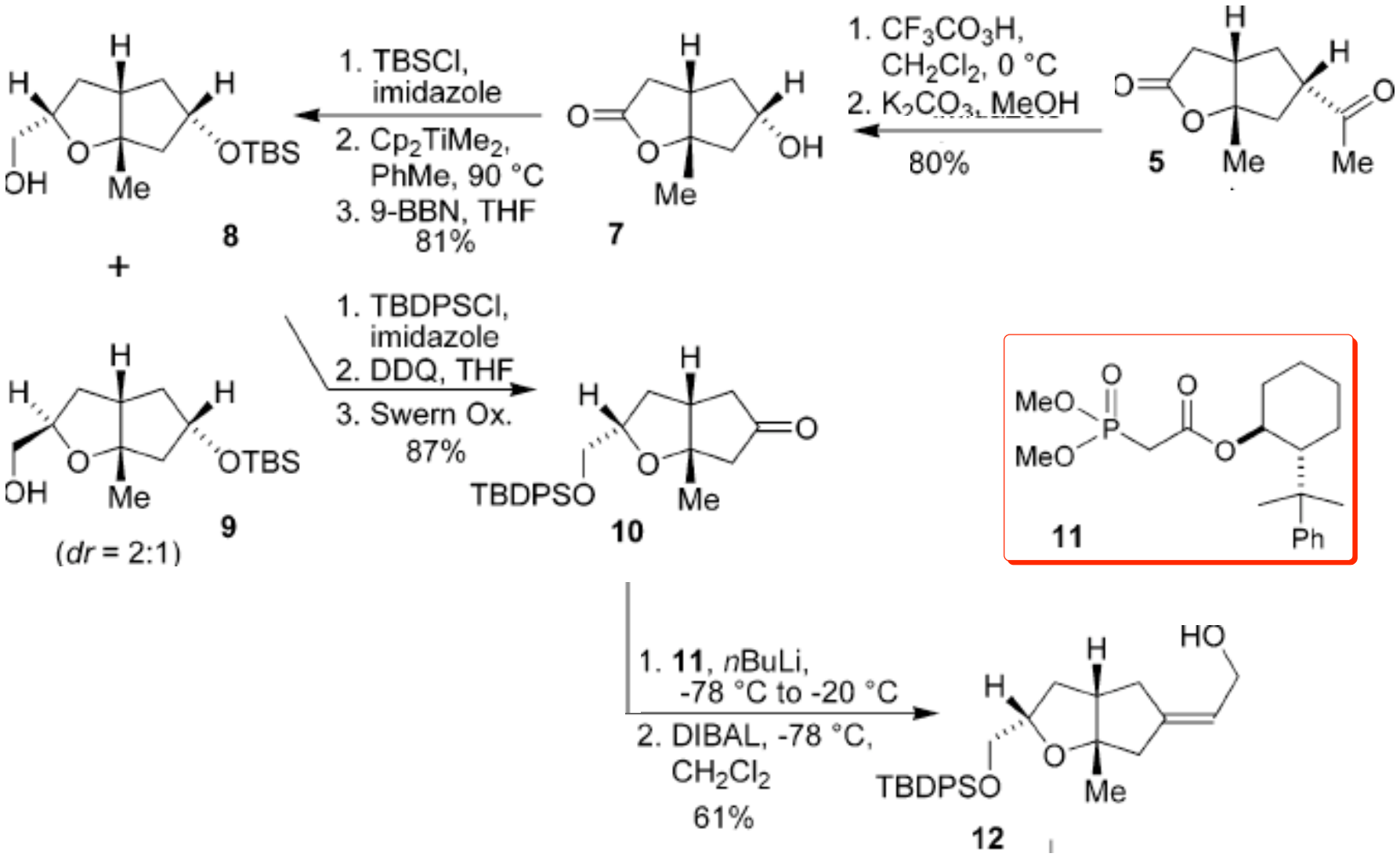


Ghosh: Intramolecular Diels-Alder Reaction Retrosynthesis

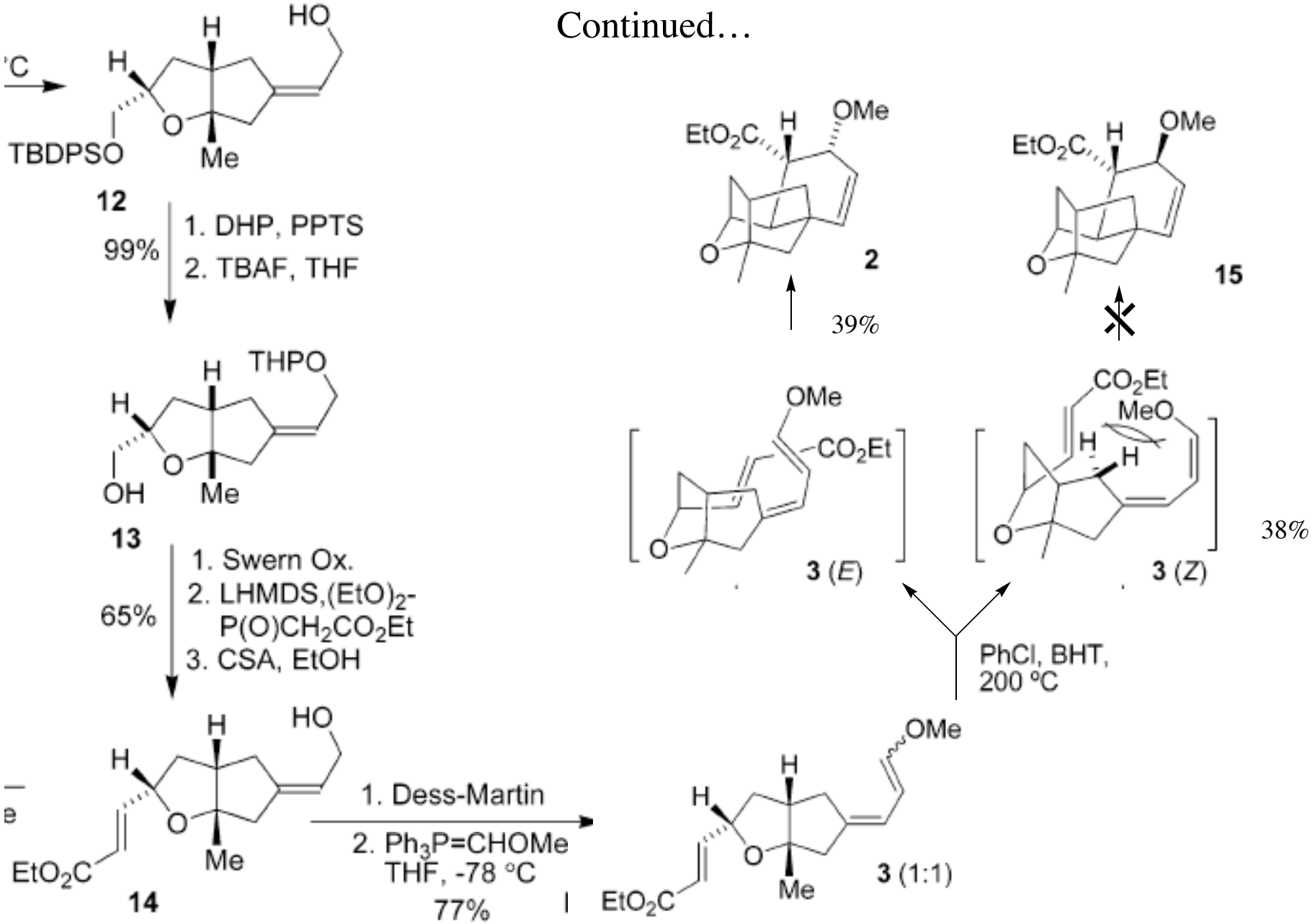


a) Srikrishna, A.; Hemamalini, P. *J. Org. Chem.* **1990**, *55*, 4883. (b) Weinges, K.; Reichert, H. *Synlett* **1991**, 785. (c) Weinges, K.; et al *Liebigs Ann. Chem.* **1993**, 403. (d) Weinges, K. et al *Chem. Ber.* **1994**, *127*, 549.

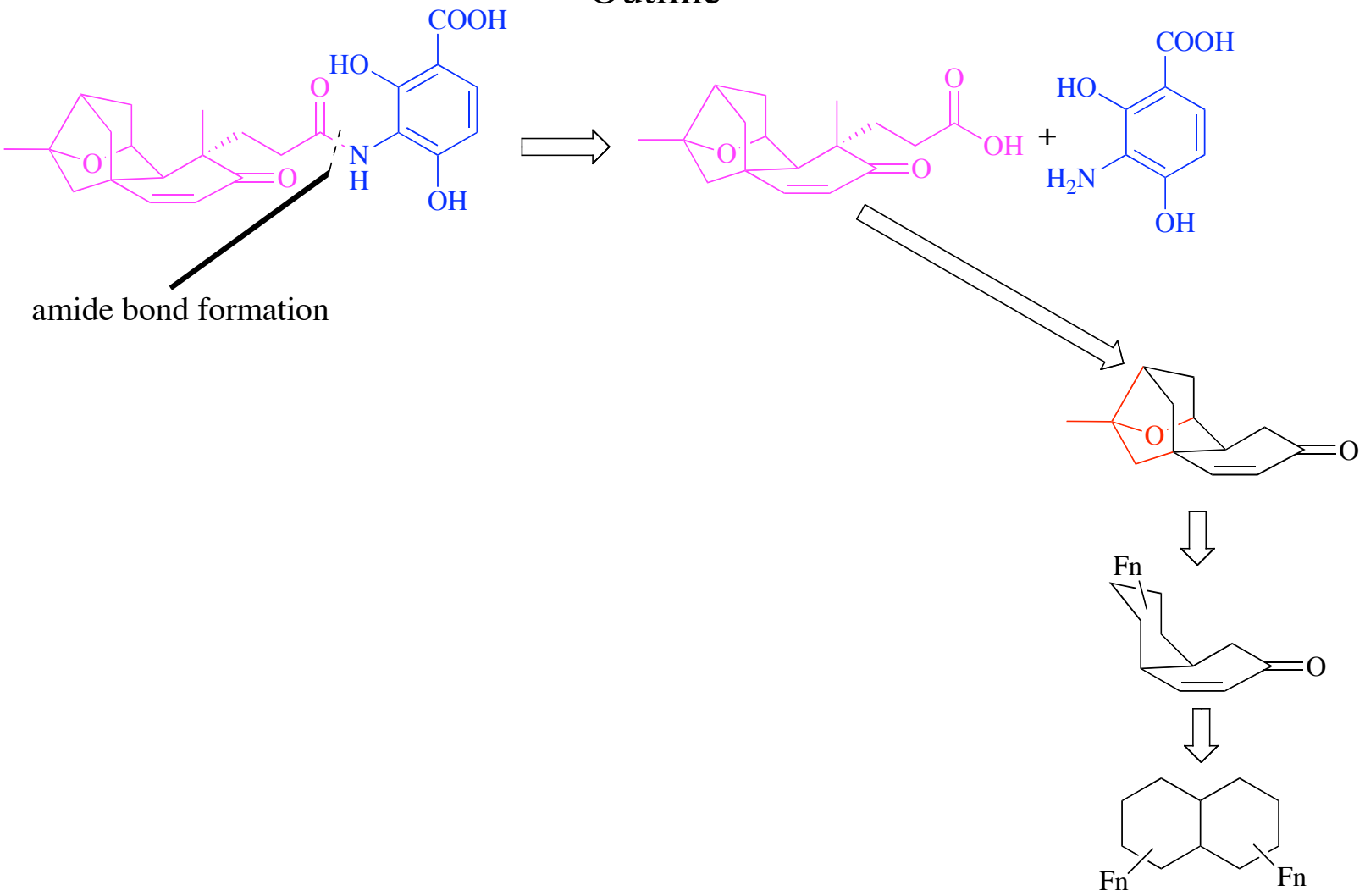
Ghosh: Intramolecular Diels-Alder Reaction



Continued…

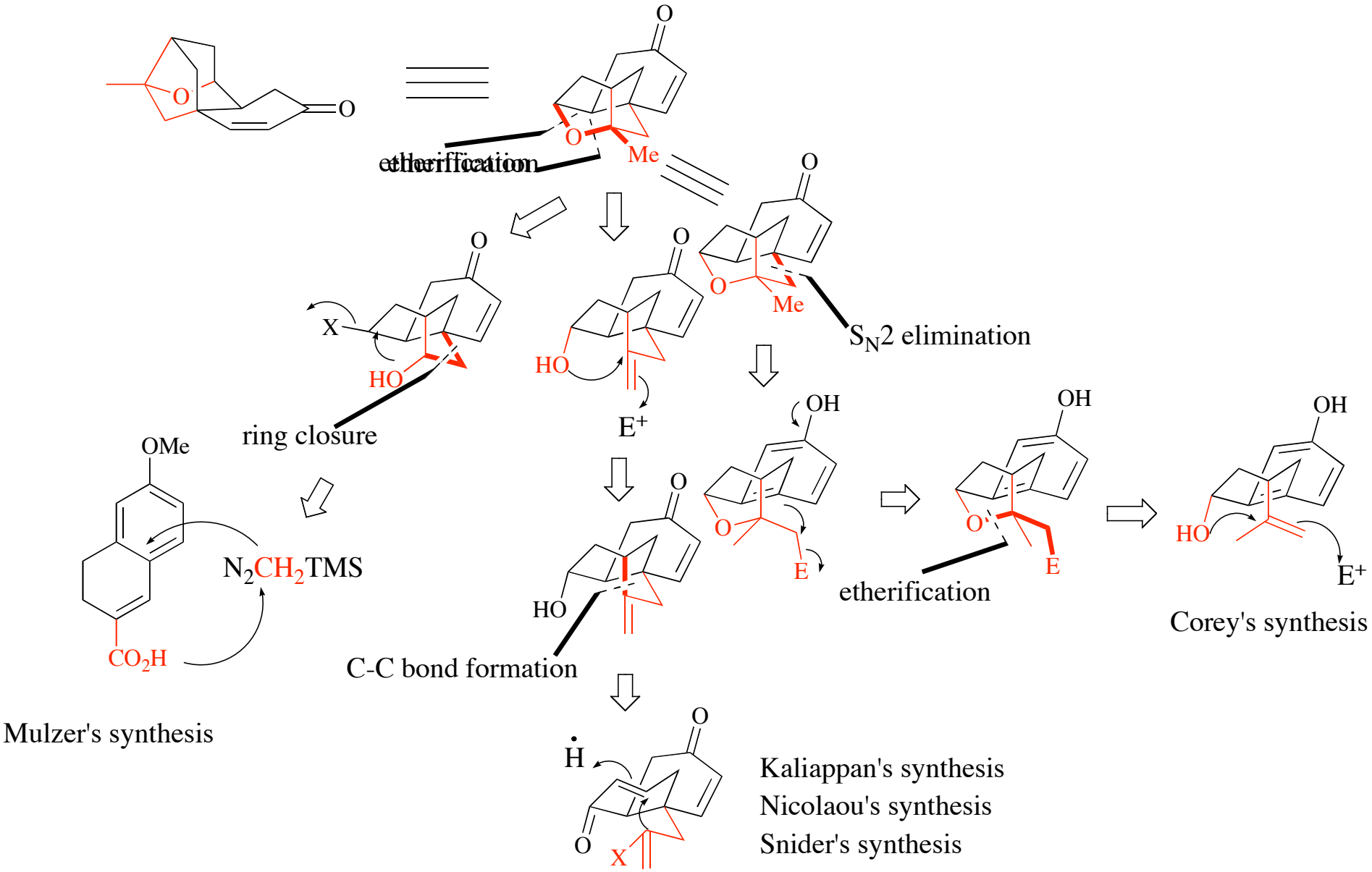

HO
H
H
O
TBDPSO
Me
12
99%
1. DHP, PPTS
2. TBAF, THF
THPO
OH
13
65%
1. Swern Ox.
2. LHMDS,(EtO)2-P(O)CH2CO2Et
3. CSA, EtOH
EtO2C
14
1. Dess-Martin
2. Ph3P=CHOMe
THF, -78 °C
77%
OMe
3 (1:1)
EtO2C
2
39%
15
CO2Et
MeO
3 (E)
3 (Z)
38%
PhCl, BHT,
200 °C

Outline

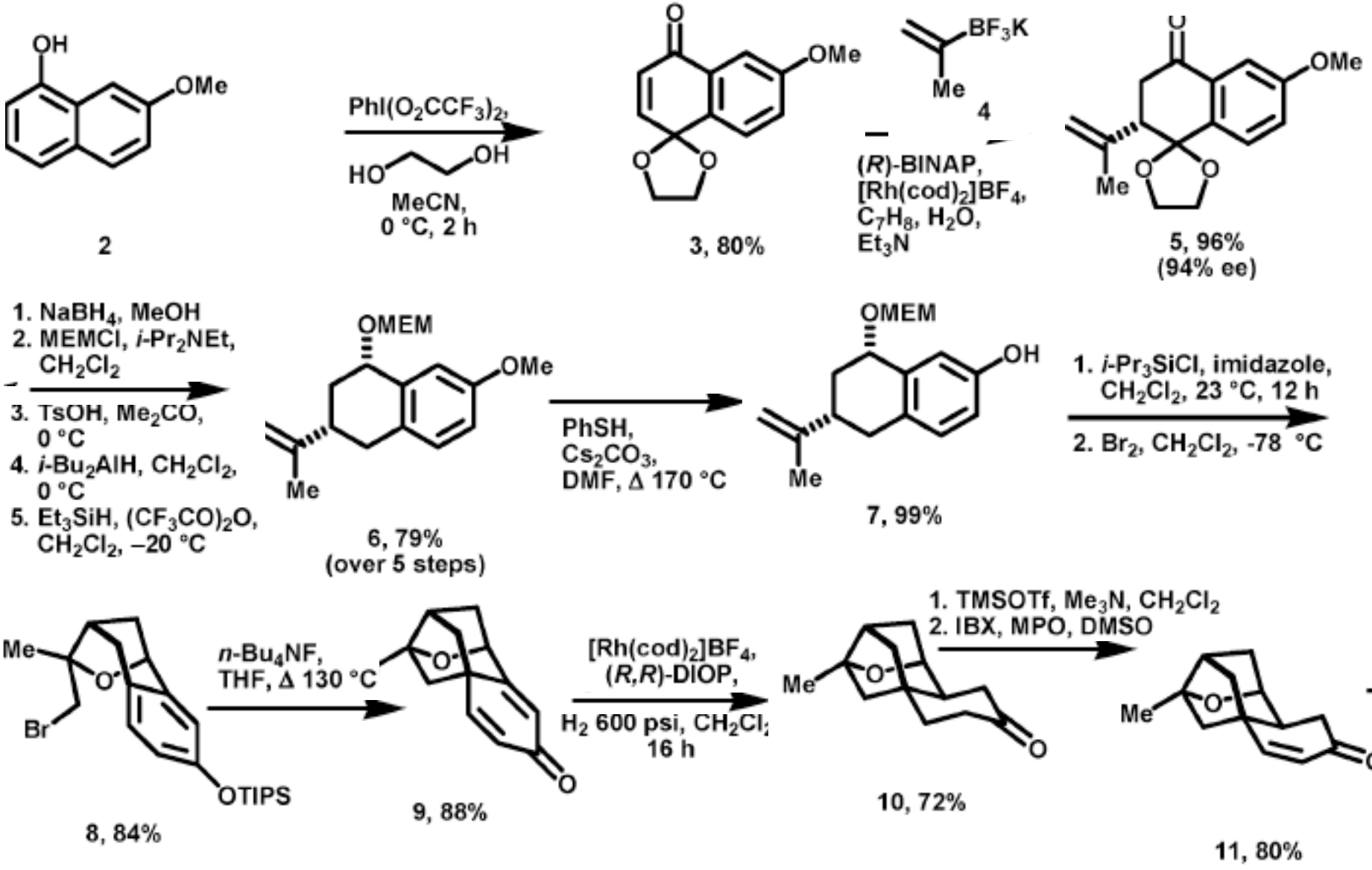


Fn= functional groups

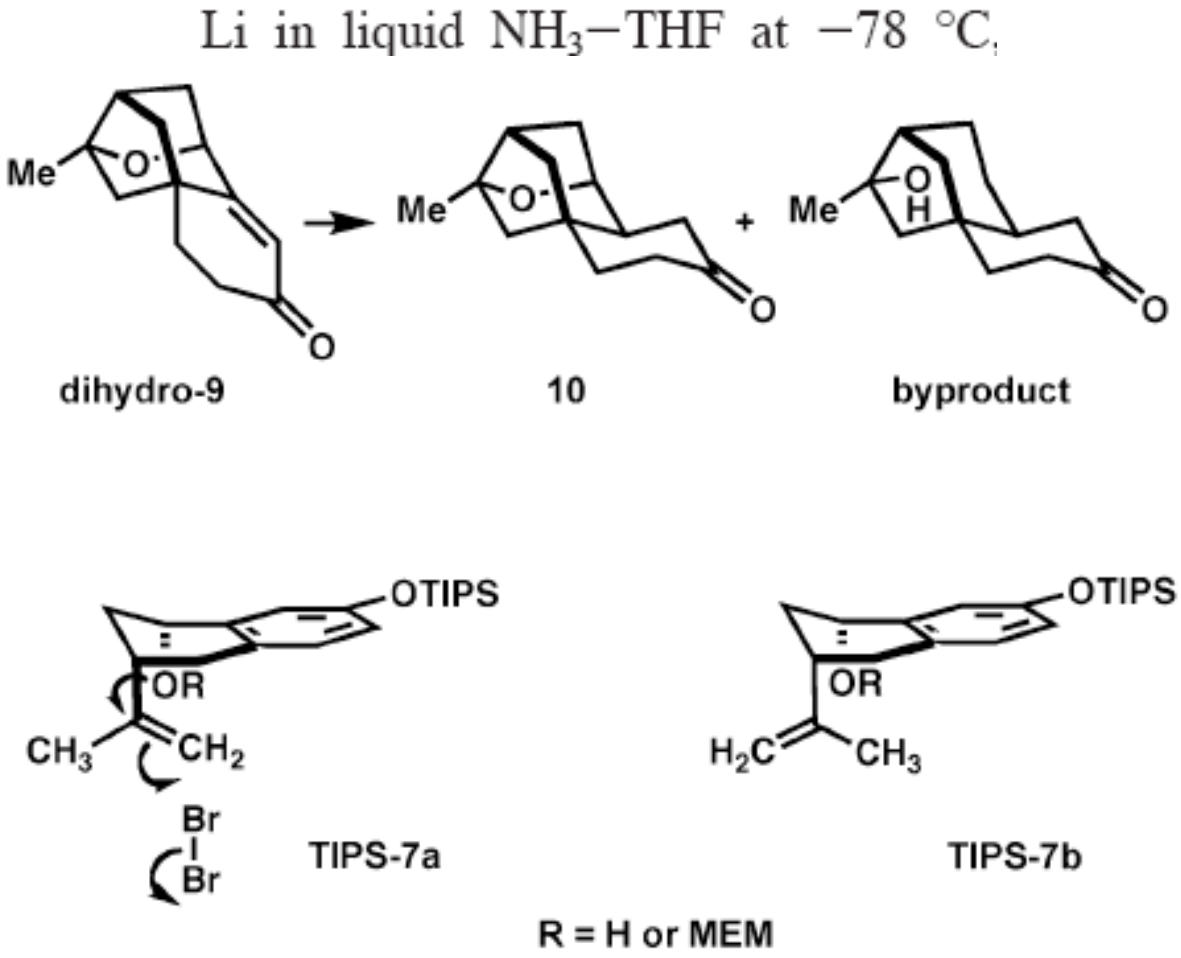
Retrosynthetic Analysis: Summary



Corey's Synthesis

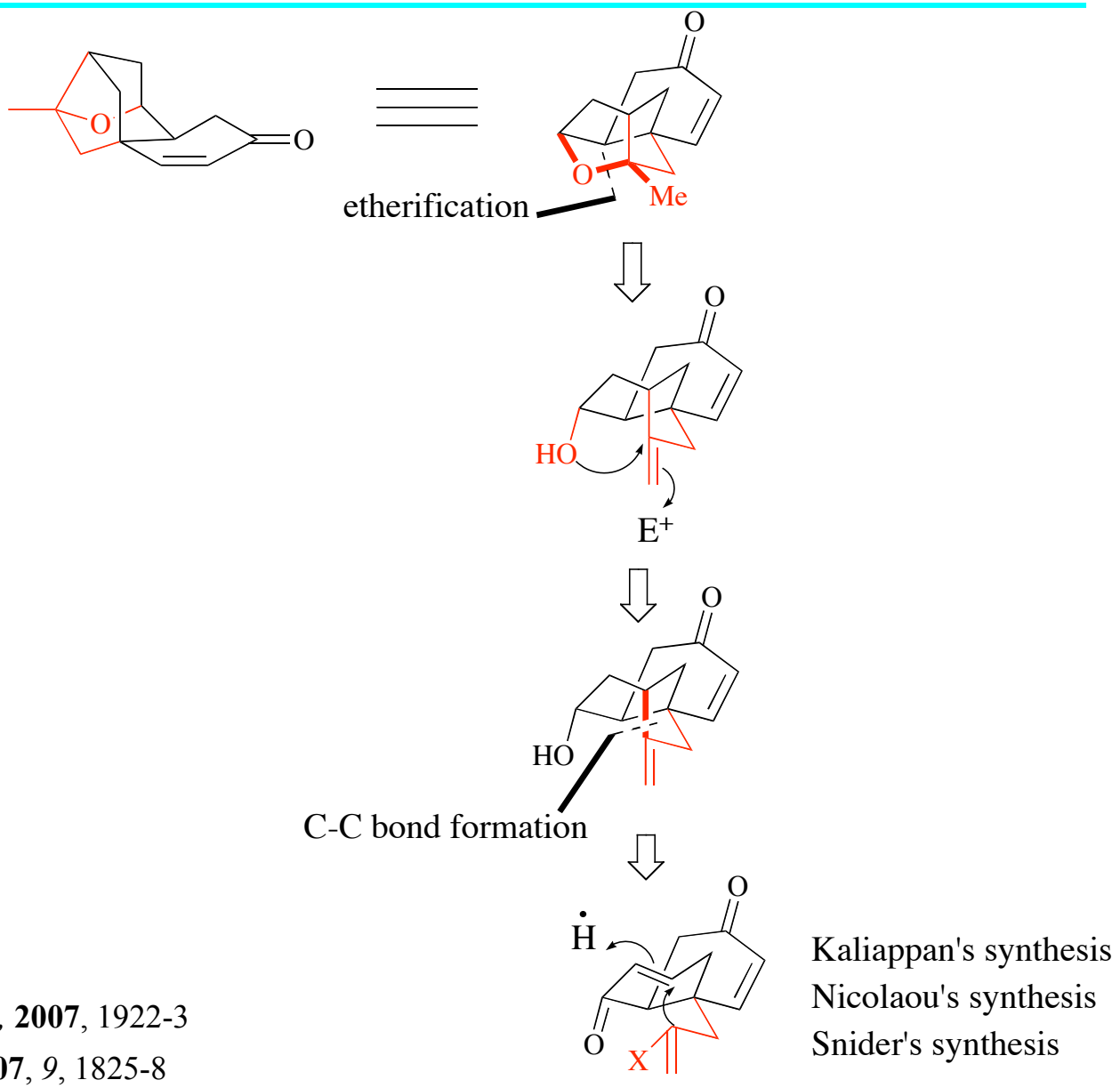


Corey's Synthesis



Corey, E. J. *Org. Lett.,* **2007**, *xxxx*

Caron-ring construction first



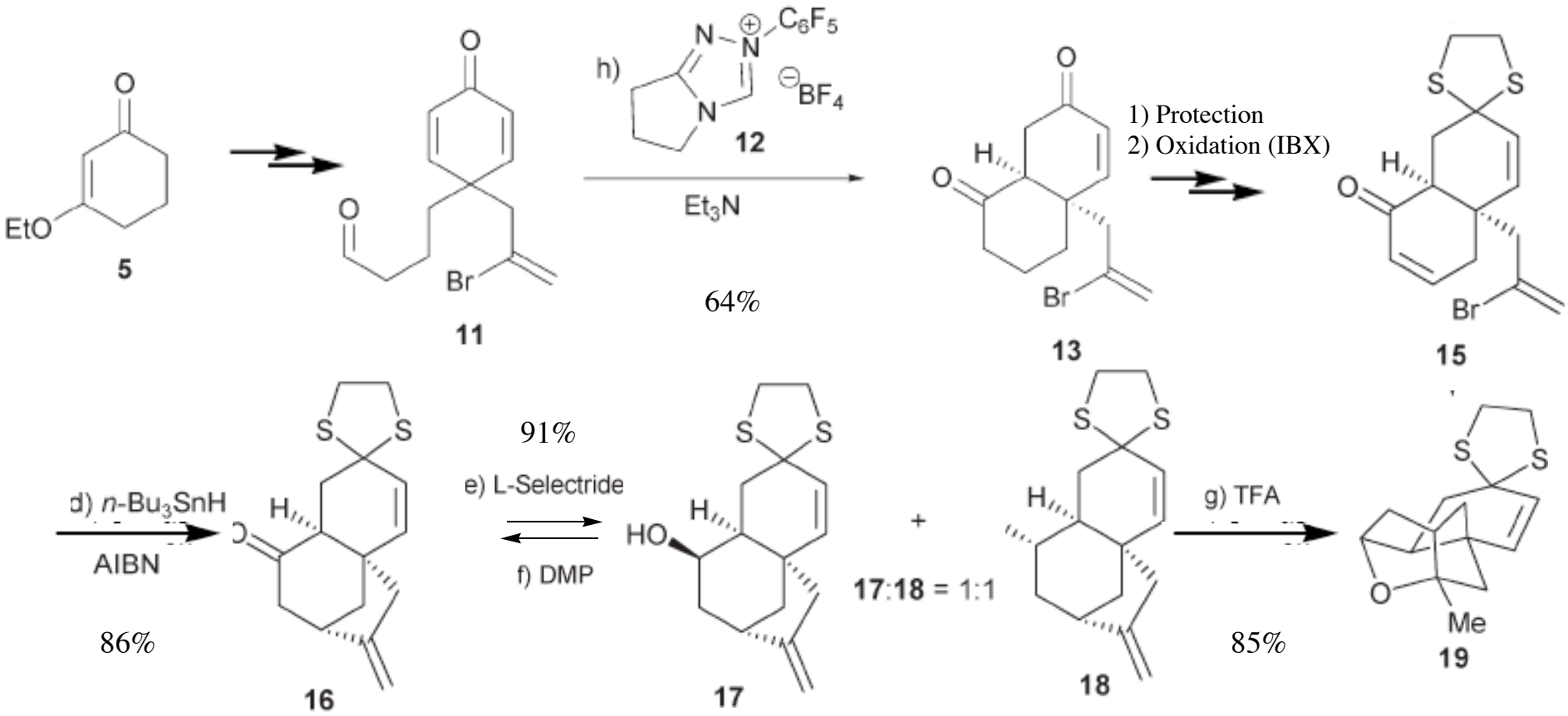
Kaliappan's synthesis
Nicolaou's synthesis
Snider's synthesis

Nicolaou, K. C. *Chem. Commun.,* **2007**, 1922-3

Zou, Y.; Snider, B. *Org. Lett.,* **2007**, *9*, 1825-8

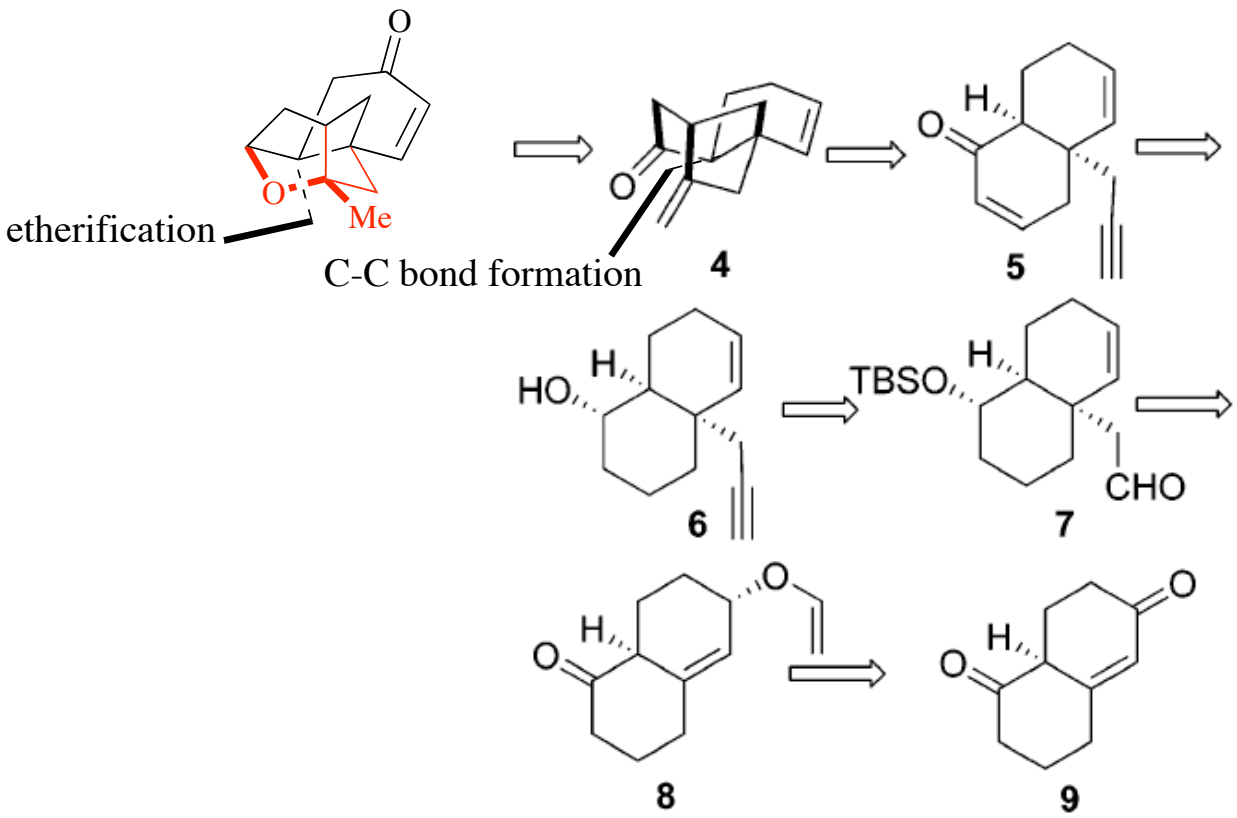
Kaliappan, K. P. and Ravikumar, V. *Org. Lett.,* **2007**, *9*, 2417-9

Nicolaou's Synthesis



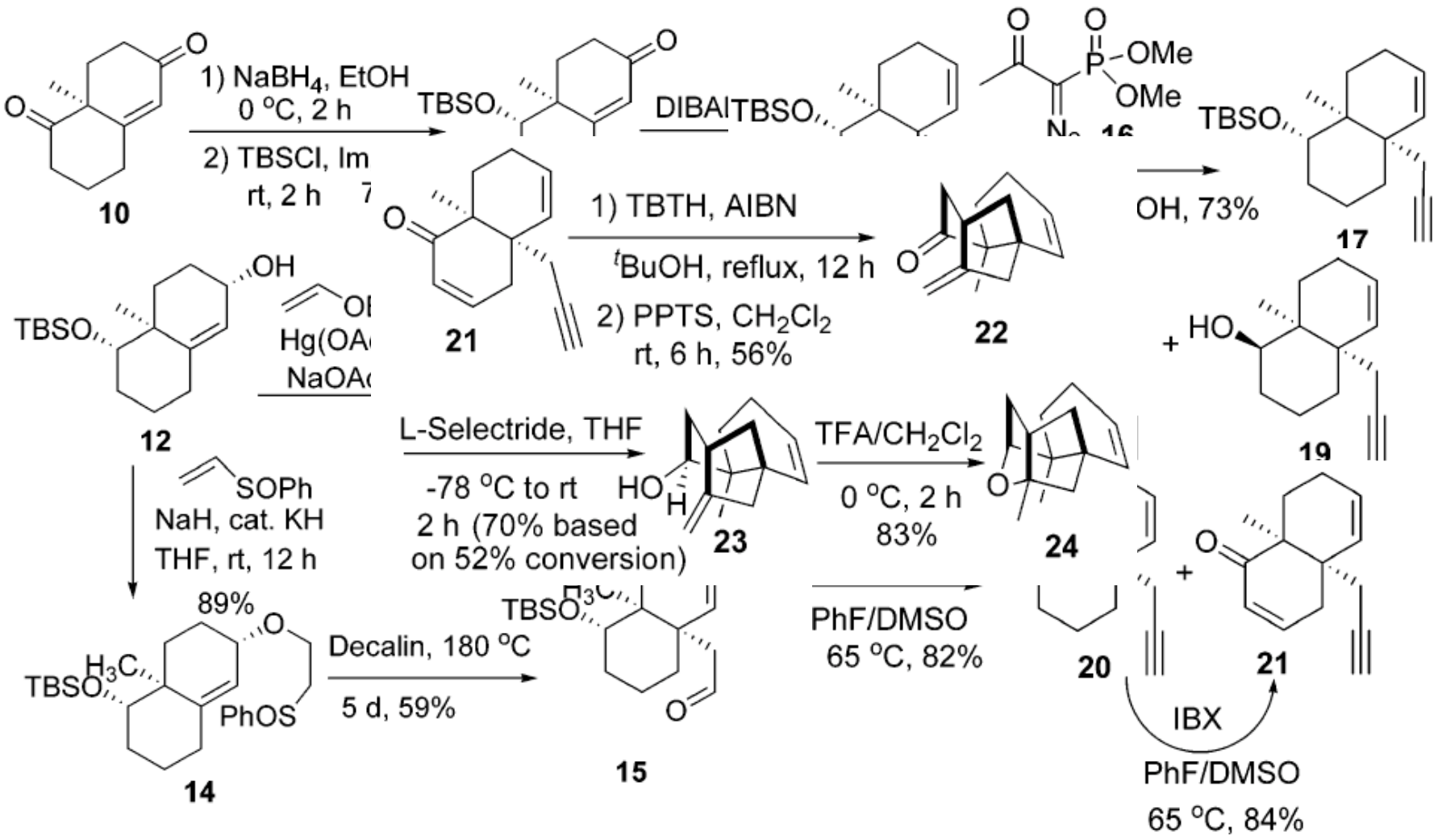
Nicolaou, K. C. *Chem. Commun.,* **2007**, 1922-3

Kaliappan's Retrosynthesis



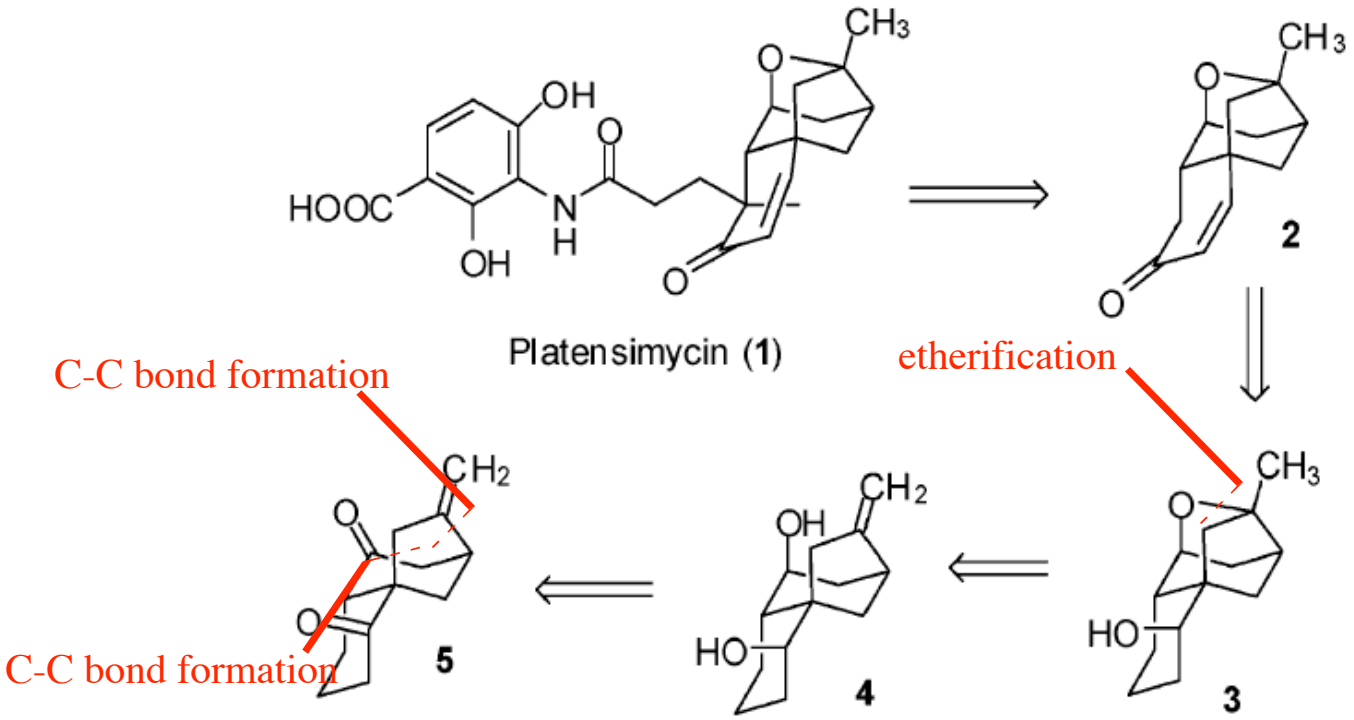
Kaliappan, K. P. and Ravikumar, V. *Org. Lett.,* **2007**, *9*, 2417-9

Kaliappan's Synthesis



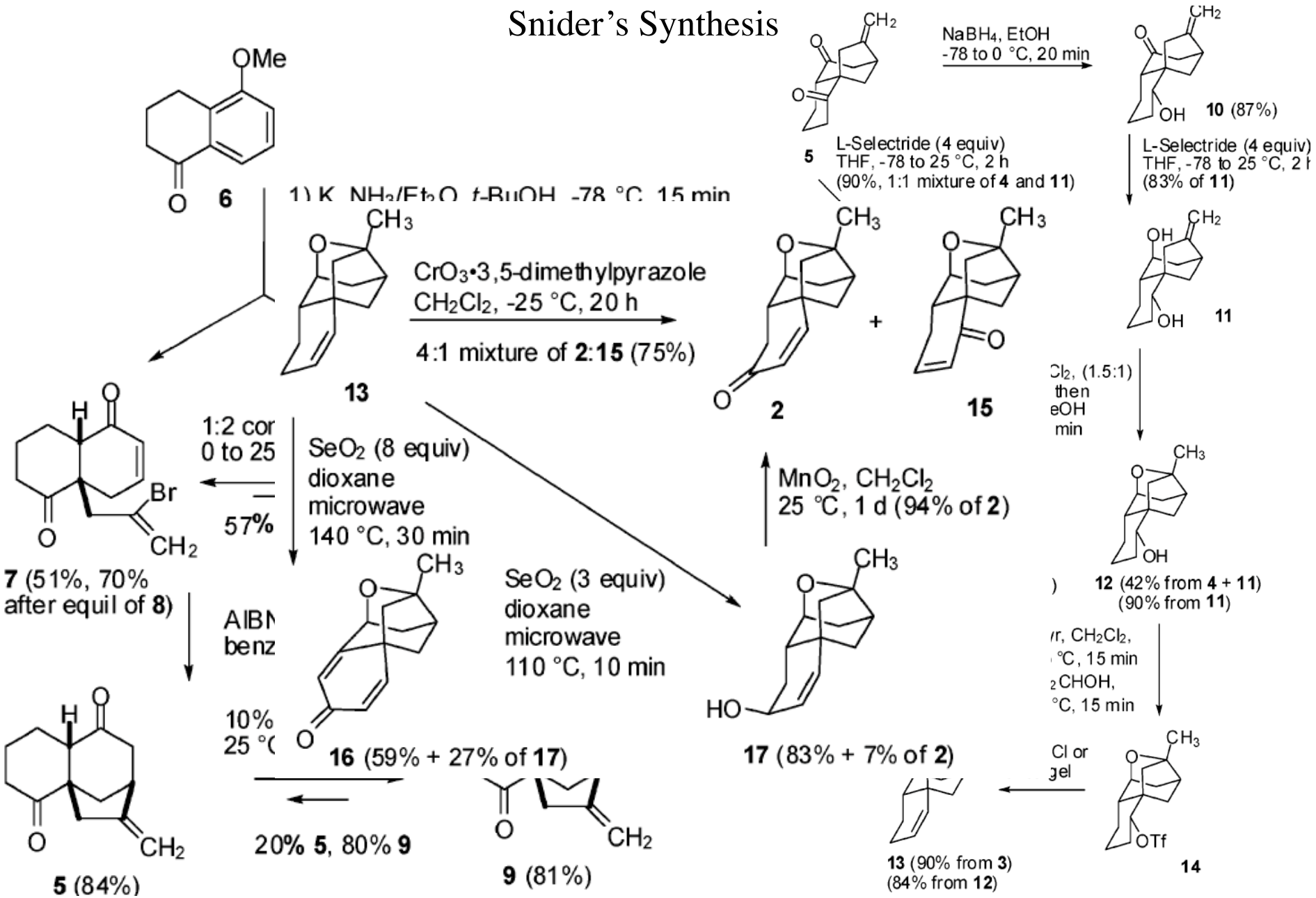
Kaliappan, K. P. and Ravikumar, V. *Org. Lett.,* **2007**, *9*, 2417-9

Snider's Retrosynthesis

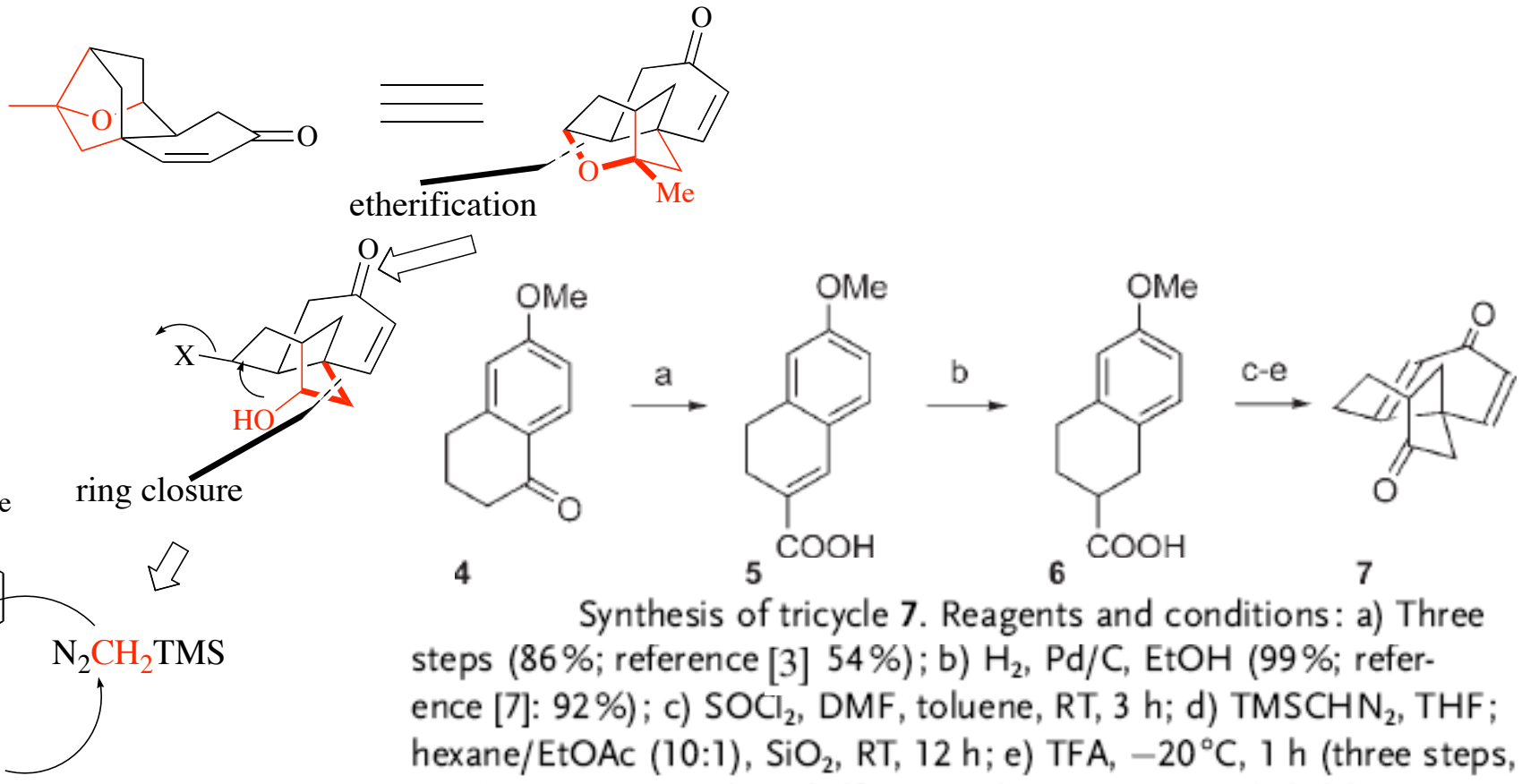


Zou, Y.; Snider, B. *Org. Lett.*, **2007**, *9*, 1825-8

Snider's Synthesis



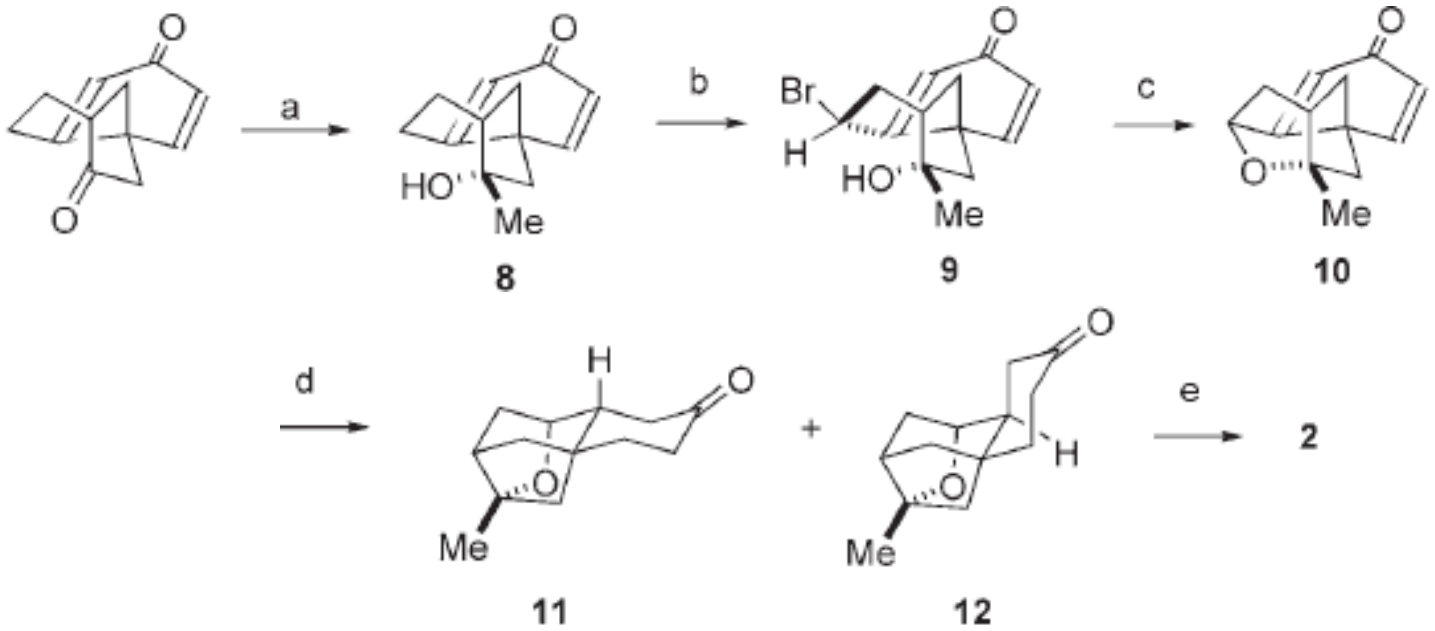
Mulzer's Synthesis



Synthesis of tricycle **7**. Reagents and conditions: a) Three steps (86%; reference [3] 54%); b) H_2, Pd/C, EtOH (99%; reference [7]: 92%); c) $SOCl_2$, DMF, toluene, RT, 3 h; d) $TMSCHN_2$, THF; hexane/EtOAc (10:1), SiO_2, RT, 12 h; e) TFA, −20°C, 1 h (three steps, 59%). DMF = *N*,*N*-dimethylformamide, TMS = trimethylsilyl, THF = tetrahydrofuran, TFA = trifluoroacetic acid.

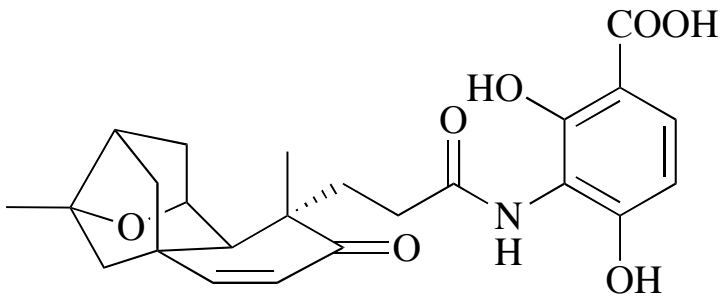
1) Mulzer, J. *Angew. Chem. Int. Ed.* **2007**, *46*, 8074-5
2) D. J. Beames, T. R. Klose, L. N. Mander, Aust. J. Chem. 1974, 27, 1269.
3) P. Anantha Reddy, G. S. Krishna Rao, Indian J. Chem. Sect. B 1981, 20, 100.

Mulzer's Synthesis



conditions: a) MeMgI, THF, −78 °C, 4 h (71% brsm); b) NBS, $(BzO)_2$, CCl_4, reflux, 90 min (75%); c) NaOMe, THF, 0 °C, 30 min (80%); d) cat. $[Ir(cod)Py(PCy_3)]PF_6$, H_2 (1 bar), CH_2Cl_2, over night, (78% brsm), **12**/**11** = 1.3:1; alternatively: Pd/C (5%), KOH, EtOH, H_2 (1 bar), 3 h (90%), **12**/**11** = 1:2; e) HIO_3·DMSO, DMSO, cyclohexene, 50 °C, 8 h (60%). brsm = based on recovered starting material, NBS = *N*-bromosuccinimide, Bz = benzoyl, cod = cyclooctadiene, Py = pyridine, Cy = cyclohexyl, DMSO = dimethyl sulfoxide.

Conclusions



1) Nicolaou's racemic: 10 steps, 11%;

2) Nicolaou's asymmetric: 16 steps, 5.6% using chrial catalysis; 11 steps, chiral auxiliary;

3) Snider's: 7 steps + equilibration + one step for conversion of a diasteromer, 32%;

4) Mulzer's: protecting-group-free; 5 steps from **7** (overall yield 20%);

5) Corey's: 14 steps, 25.6%; (calculated by meeeee!)

6) Kaliappan's: 13 steps, 5.6%; (calculated by meeeee!)

7) Yamamoto's: 8 steps + one step for conversion of a diasteromer, 18% (calculated by me! not sure!!!)

Mulzer, J. *Angew. Chem. Int. Ed.* **2007**, *46*, 8074-5


WOULD YOU BELIEVE IT'S AN AIR BAG ?