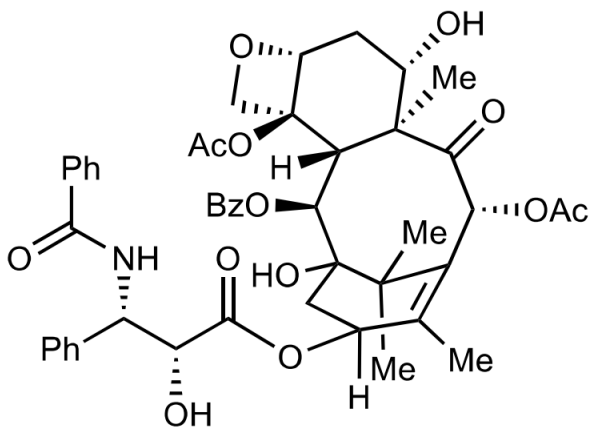
北京大学
PEKING UNIVERSITY

Taxane

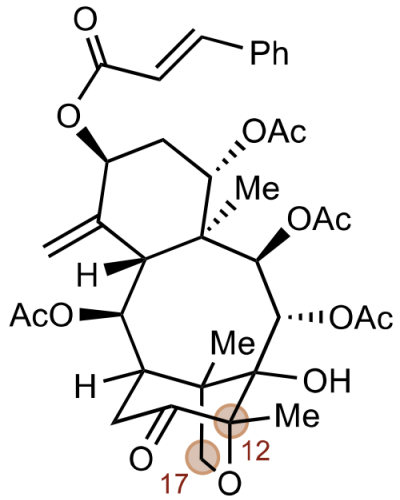
MaTianhao

2022.11.24

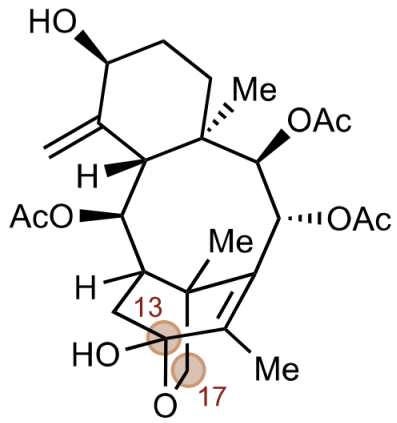
The separation and biological activity



taxol (**1**)
FDA-approved anticancer agent



taxagifine (**2**)
C17–C12 oxo-bridged

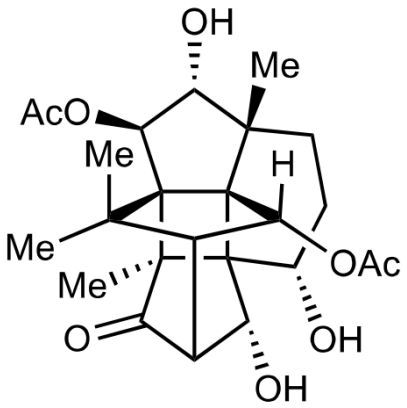


taxezopidine A (**3**)
C17–C13 oxo-bridged

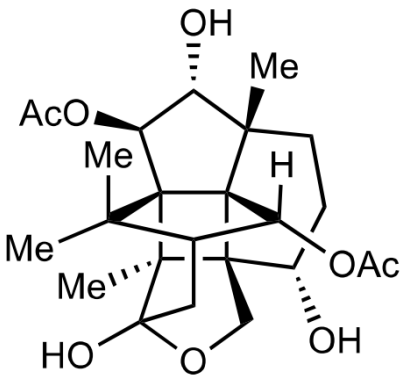
· In 1966, chemical invstigation resulted in a highly active agent, isolated by Wall and Wani in a yield of 0.014% and named it as taxol (1).
· Between the 1960s and 1970s, Japanese and American chemists isolated more than 20 taxanes from Japanese and European yews and most of them are derivatives of taxinine.
· 1974, Full clinical potential of taxol was recognized when the antitumor models changed to B16 melanoma against rapidly growing tumors and L1210 leukemia against solid tumors in 1974.

The Pacific yew *T. brevifolia*

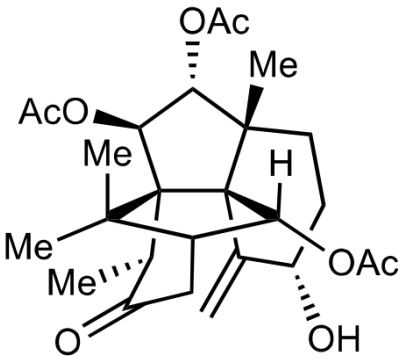
The separation and biological activity



canataxpropellane (**4**)



taxpropellane (**5**)



taxinine K (**6**)

·In 2007, A novel taxane canataxpropellane (4) with an unprecedented 5/5/4/6/6/6-membered hexacyclic skeleton containing [3.3.2]propellane was isolated from the needles of the Canadian yew, *Taxus canadensis*. by Kiyota group.

·It suffers from extremely inefficient sourcing from its natural producer, thus preventing biological and pharmaceutical investigations to this day

Canadian yew, *Taxus canadensis*

Richmond Sarpong

Macalester College, St. Paul, MN.

Bachelor of Arts Degree (Chemistry Major), May 1995 (Advisor Prof. Rebecca C. Hoye)

Princeton University, Princeton, NJ.

Master of Science Degree (Organic Chemistry), May 1997

Ph. D. in Organic Chemistry, May 2001 (Advisor Prof. Martin F. Semmelhack)

California Institute of Technology, Pasadena, CA

UNCF•Pfizer Postdoctoral Fellow, 2001–2004 (Advisor Prof. Brian M. Stoltz)

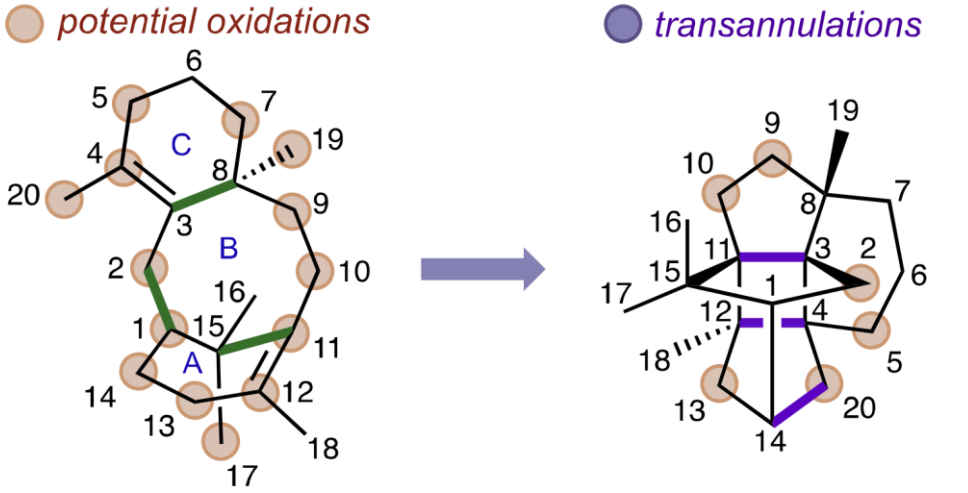
Professional Experience

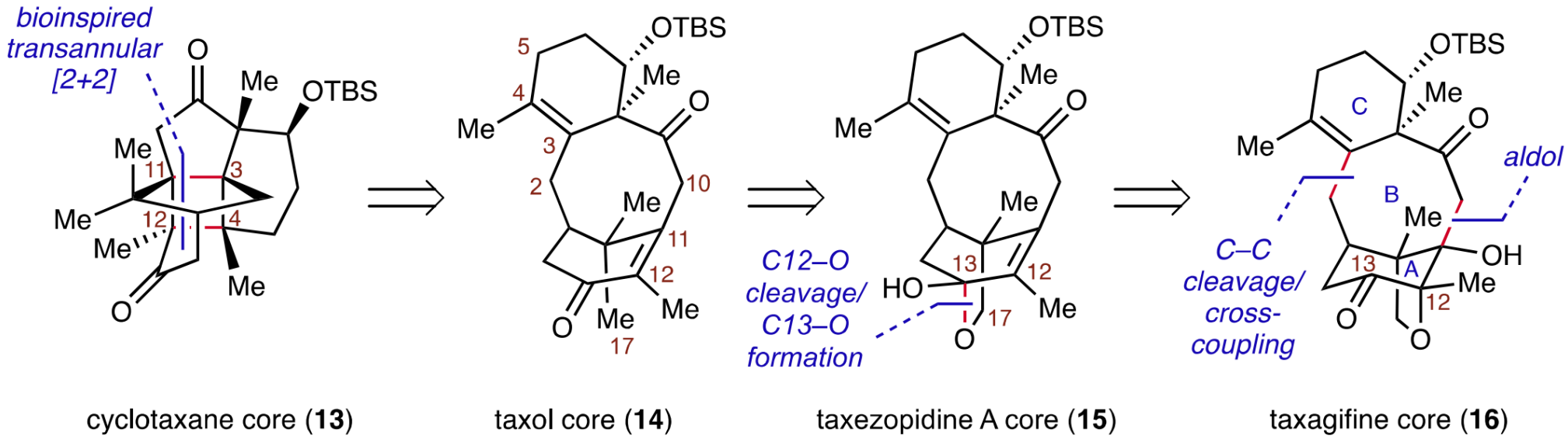
Assistant Professor, Department of Chemistry (July 2004–2010) UCB

Associate Professor, Department of Chemistry (July 2010–June 2014) UCB

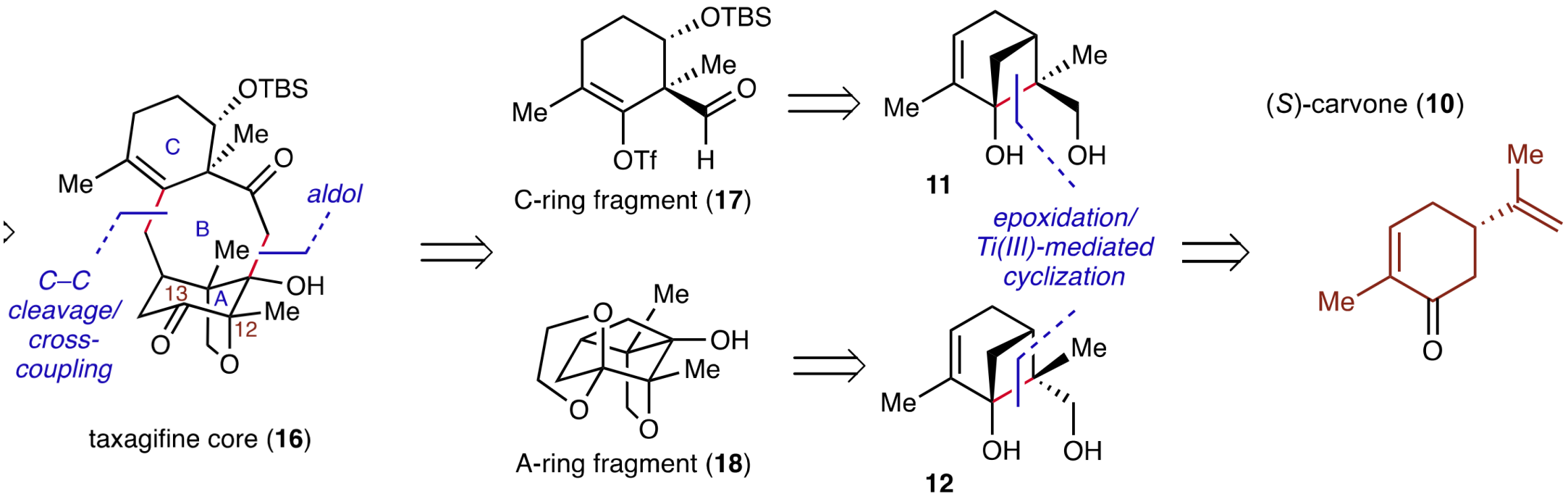
Full Professor, Department of Chemistry (July 2014–Present) UCB

Retrosynthetic Analysis

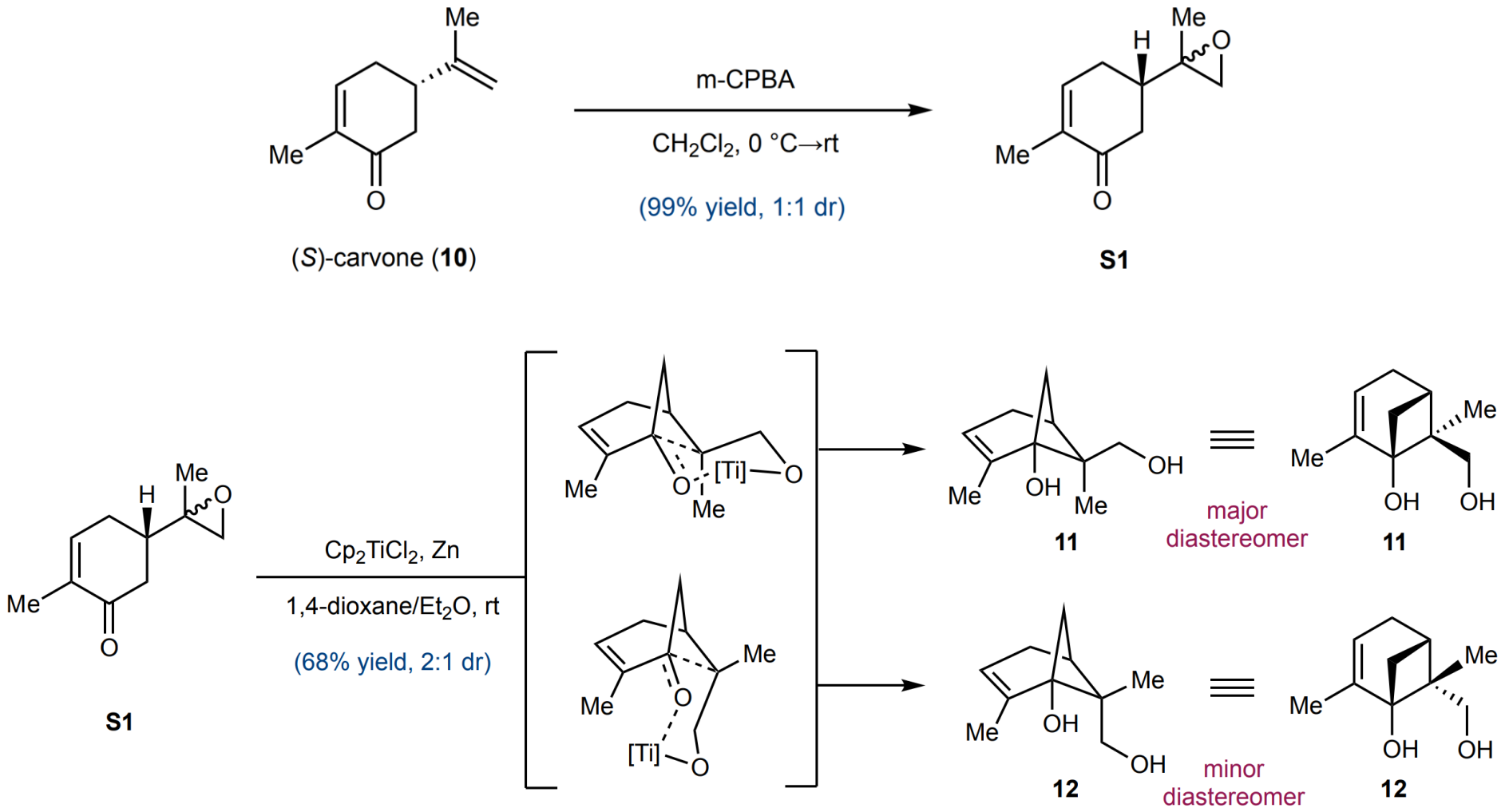




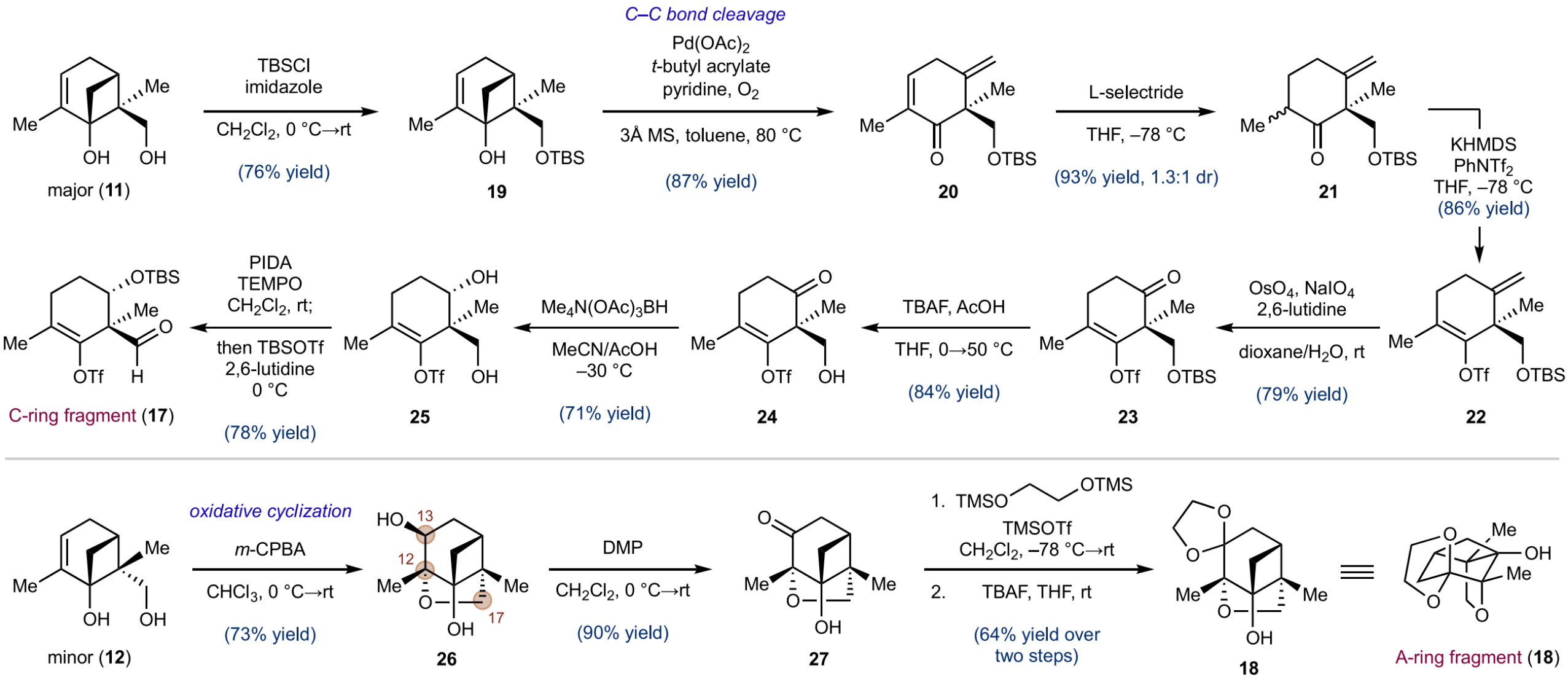
Retrosynthetic Analysis



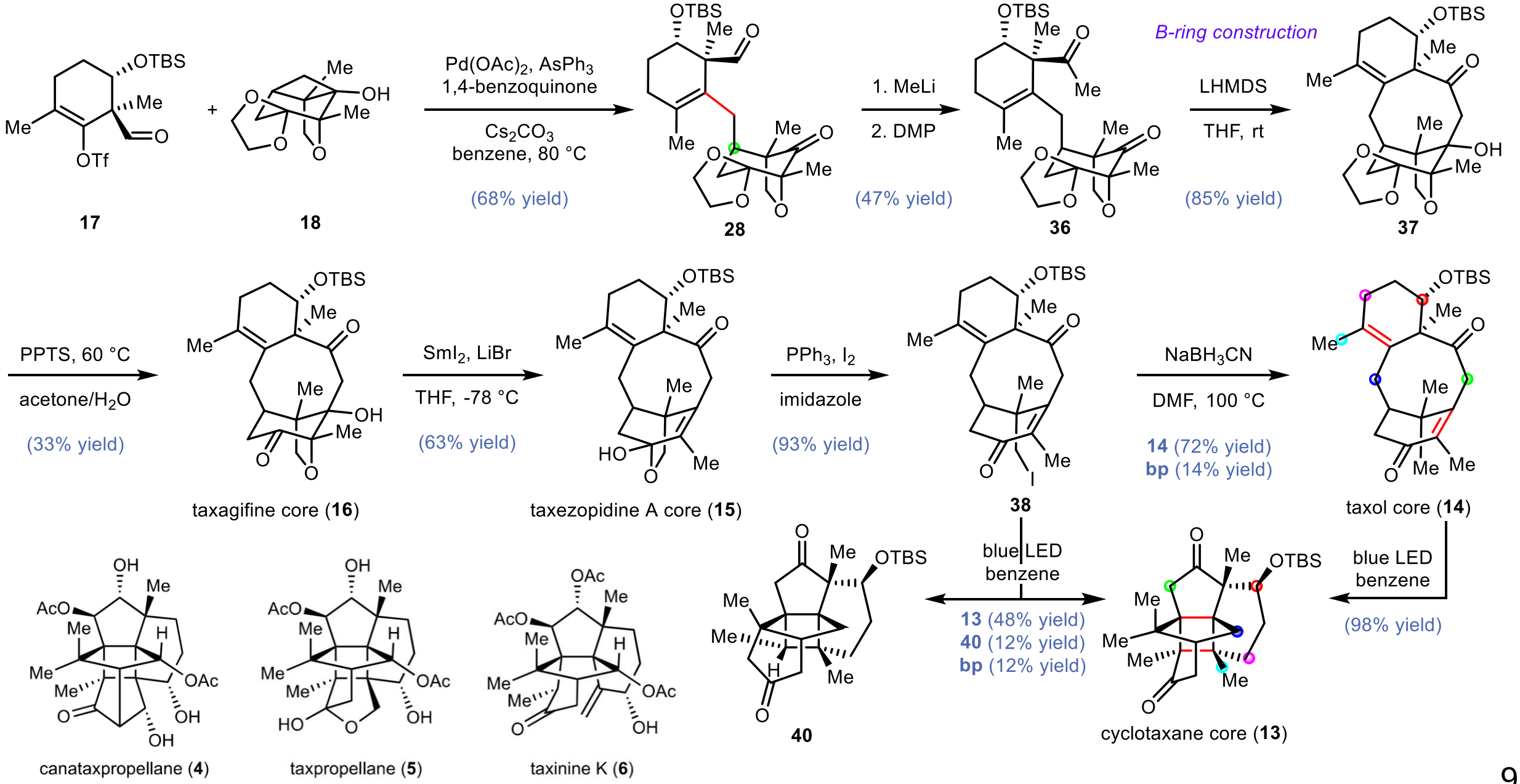
Synthesis


Me
Me
O
(S)-carvone (10)
m-CPBA
CH2Cl2, 0 °C→rt
(99% yield, 1:1 dr)
H
Me
O
Me
O
S1
Cp2TiCl2, Zn
1,4-dioxane/Et2O, rt
(68% yield, 2:1 dr)
[Ti]
11
major
diastereomer
12
minor
diastereomer
OH

Synthesis


major (11)
TBSCl
imidazole
CH2Cl2, 0 °C→rt
(76% yield)
19
C–C bond cleavage
Pd(OAc)2
t-butyl acrylate
pyridine, O2
3Å MS, toluene, 80 °C
(87% yield)
20
L-selectride
THF, –78 °C
(93% yield, 1.3:1 dr)
21
KHMDS
PhNTf2
THF, –78 °C
(86% yield)
22
OsO4, NaIO4
2,6-lutidine
dioxane/H2O, rt
(79% yield)
23
TBAF, AcOH
THF, 0→50 °C
(84% yield)
24
Me4N(OAc)3BH
MeCN/AcOH
–30 °C
(71% yield)
25
PIDA
TEMPO
CH2Cl2, rt;
then TBSOTf
2,6-lutidine
0 °C
(78% yield)
C-ring fragment (17)
minor (12)
oxidative cyclization
m-CPBA
CHCl3, 0 °C→rt
(73% yield)
26
DMP
CH2Cl2, 0 °C→rt
(90% yield)
27
1. TMSO OTMS
TMSOTf
CH2Cl2, –78 °C→rt
2. TBAF, THF, rt
(64% yield over two steps)
18
A-ring fragment (18)

Synthesis


17
18
Pd(OAc)2, AsPh3
1,4-benzoquinone
Cs2CO3
benzene, 80 °C
(68% yield)
28
1. MeLi
2. DMP
(47% yield)
36
B-ring construction
LHMDS
THF, rt
(85% yield)
37
PPTS, 60 °C
acetone/H2O
(33% yield)
taxagifine core (16)
SmI2, LiBr
THF, -78 °C
(63% yield)
taxezopidine A core (15)
PPh3, I2
imidazole
(93% yield)
38
NaBH3CN
DMF, 100 °C
14 (72% yield)
bp (14% yield)
taxol core (14)
blue LED
benzene
(98% yield)
blue LED
benzene
13 (48% yield)
40 (12% yield)
bp (12% yield)
40
cyclotaxane core (13)
canataxpropellane (4)
taxpropellane (5)
taxinine K (6)

Tanja Gaich

Studies of Molecular Biology (University of Salzburg), 1998-2000

Studies of Chemistry (University of Vienna), 1999-2005

PhD with Prof. J. Mulzer (University of Vienna), 2005-2009

FWF-Postdoctoral fellow with Prof. P. S. Baran (Scripps. La Jolla CA, USA), 2009-2010

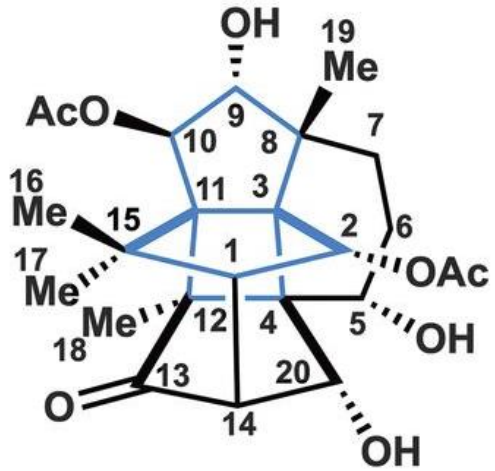
Professional Experience

Independent Researcher under supervision of Prof. M. Kalesse (Leibniz University Hannover), 2010-2015

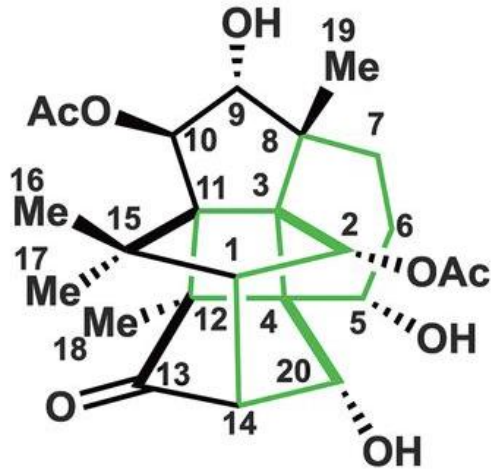
Full Professor of Organic Chemistry (University of Konstanz), 2015-present

Structural features

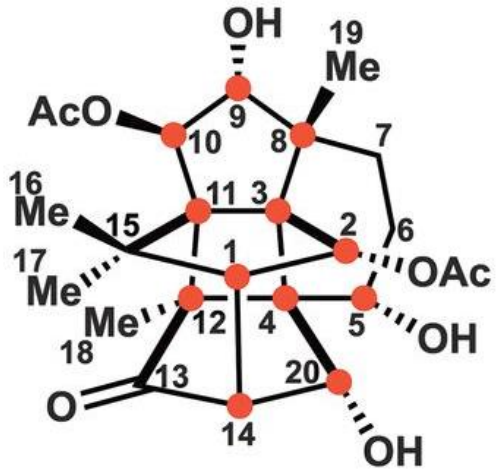
C Structure analysis



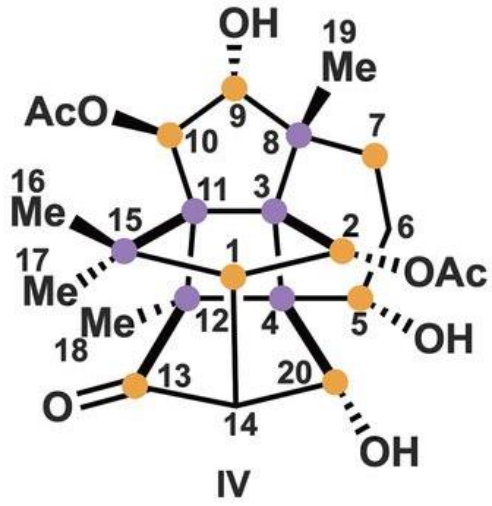
I



II



III

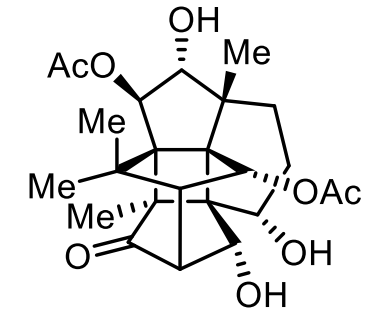


IV

Structural features

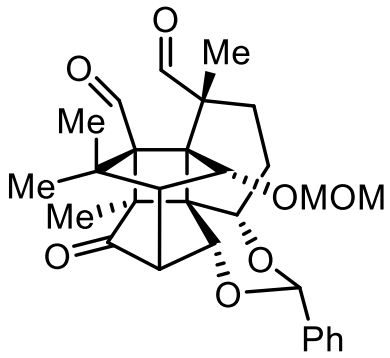
- [3.3.2]propellane (blue **I**)
- [4.4.2]propellane (green **II**)
- 12 contiguous stereocenters (red **III**)
- cyclobutane with all quaternary stereocenters (purple **IV**)
- 6 quaternary carbons (contiguous; purple **IV**)
- 5 quaternary stereocenters (contiguous 3; 4; 8; 11; 12 **IV**)
- 8 neopentyl positions (yellow **IV**)
- only 2 non-neopentyl positions (6; 14 **IV**)
- densly functionalized & highly oxidized

Retrosynthetic Analysis



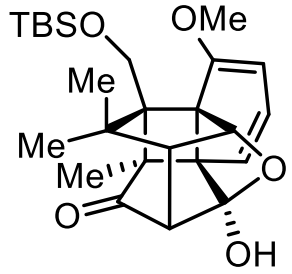
canataxpropellane (**41**)

pinacol couping



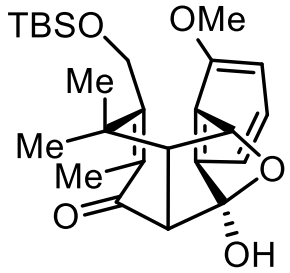
42

B-ring functionalization



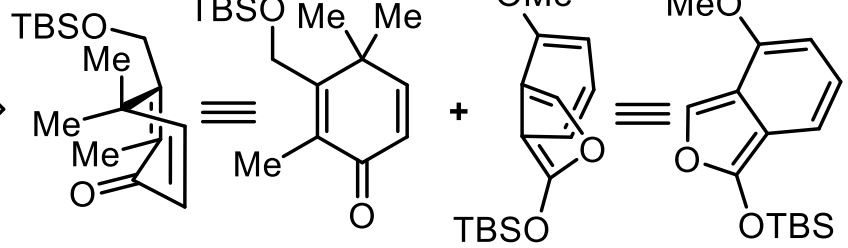
43

2+2 cycloadditon



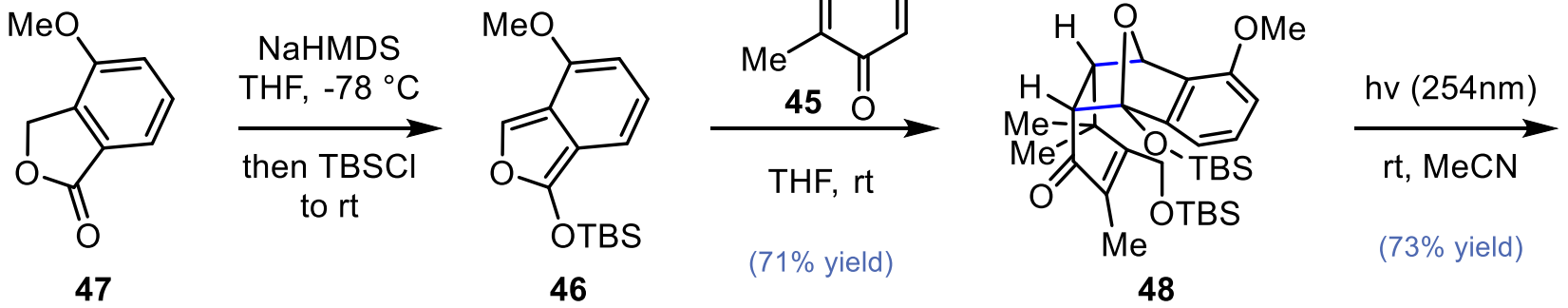
44

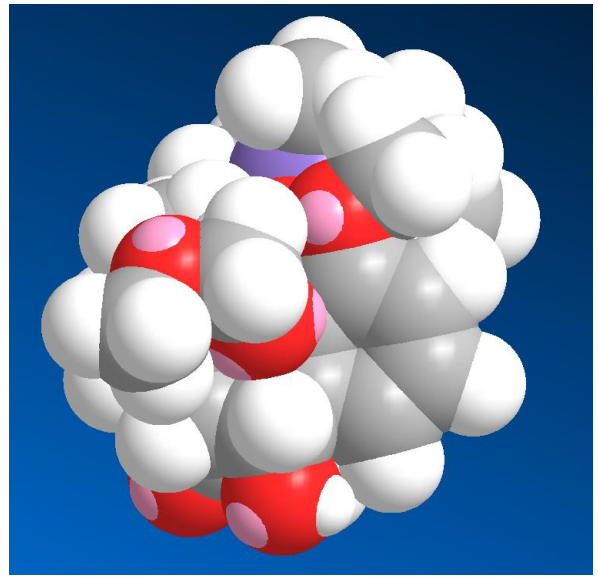
Diels-Alder reaction



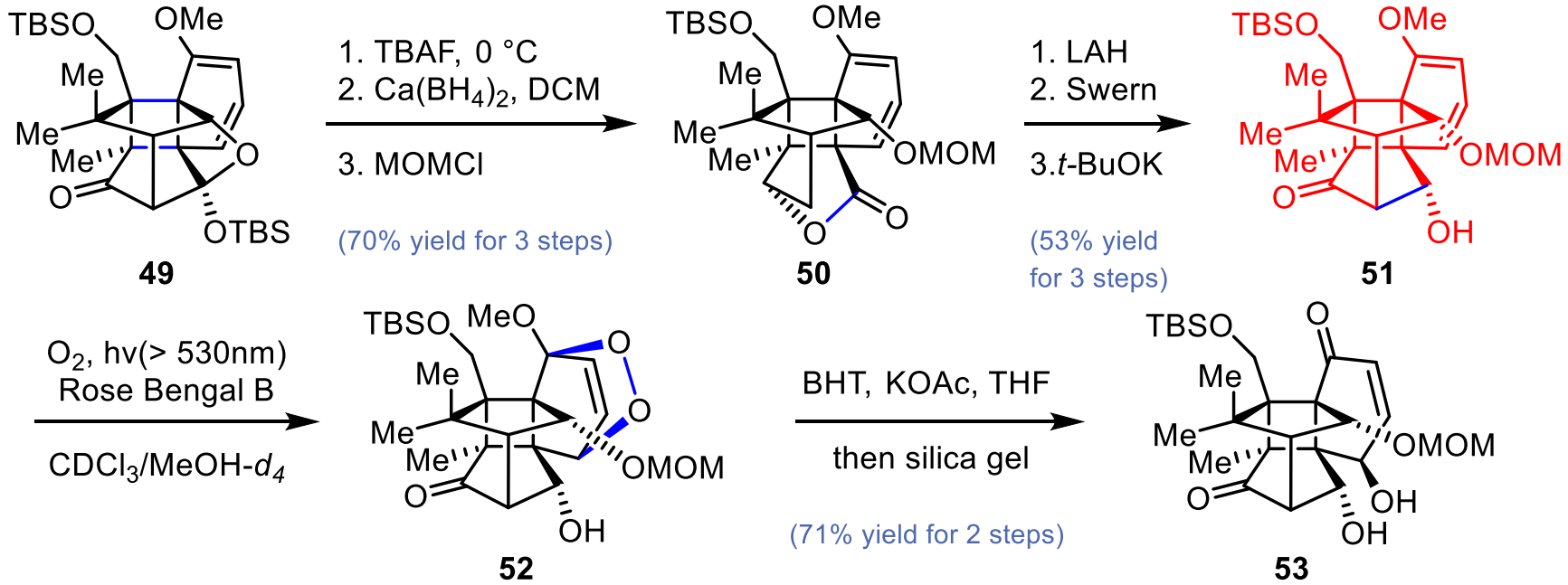
45 **46**

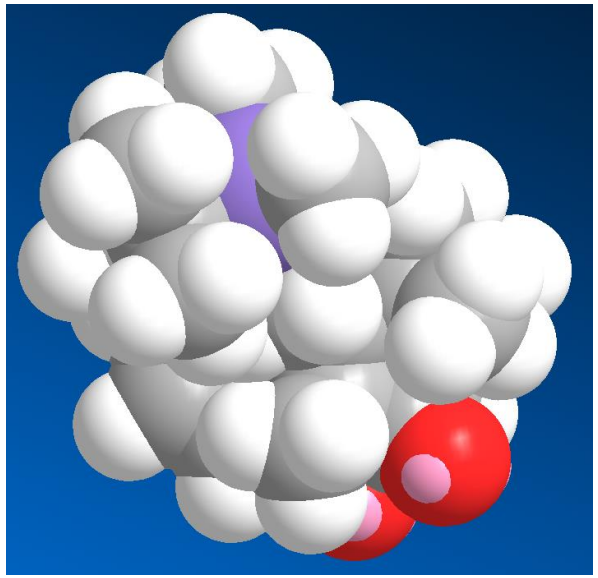
Synthesis





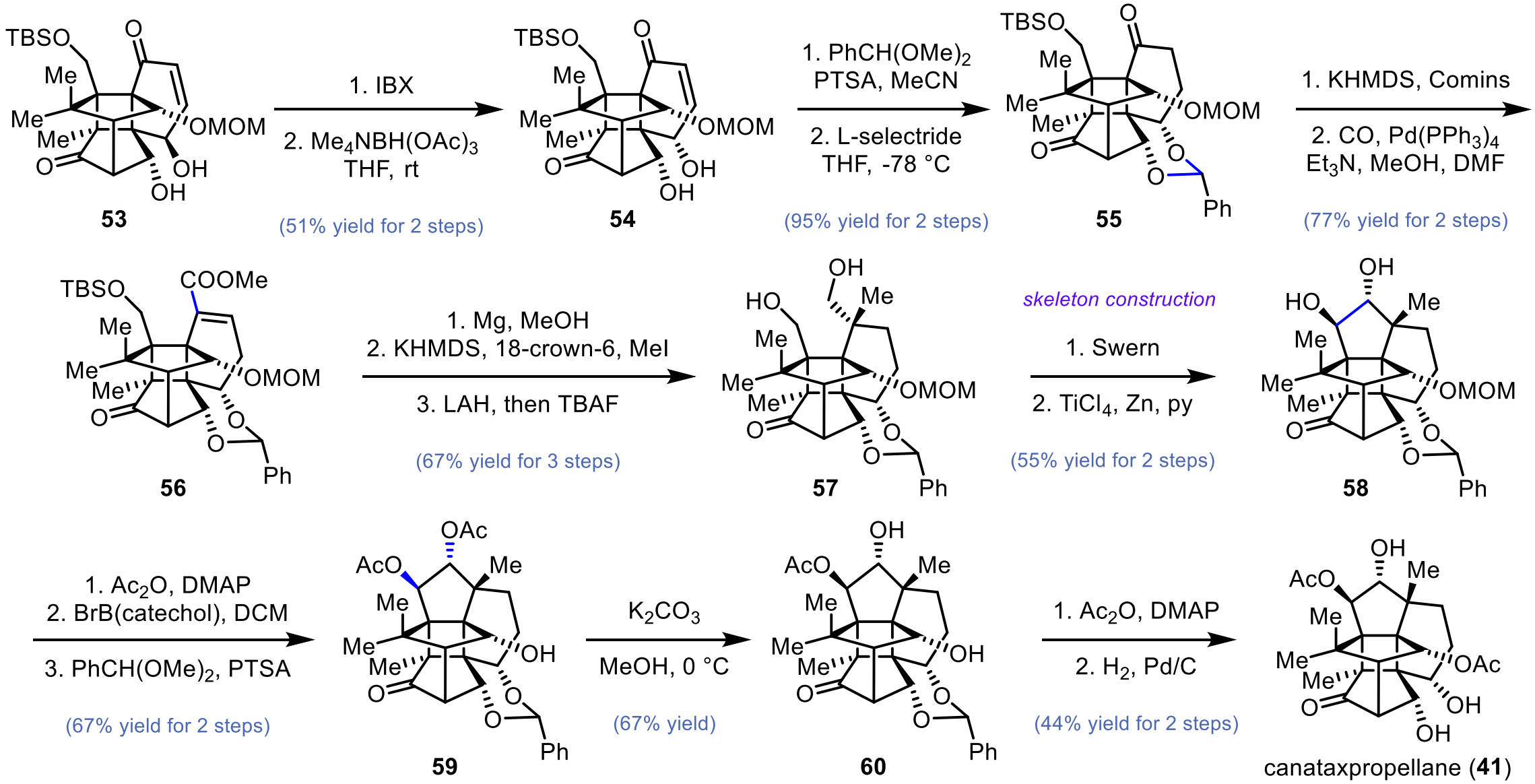
51 exo face (see from right)



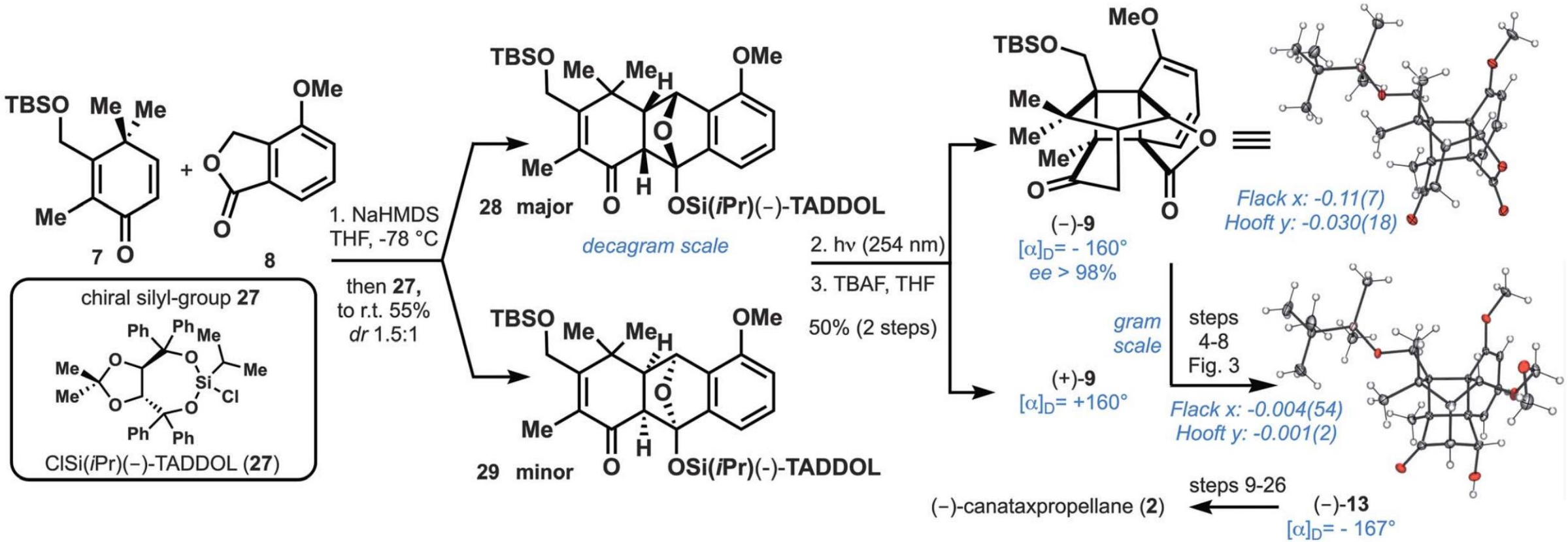


51 endo face (see from left)

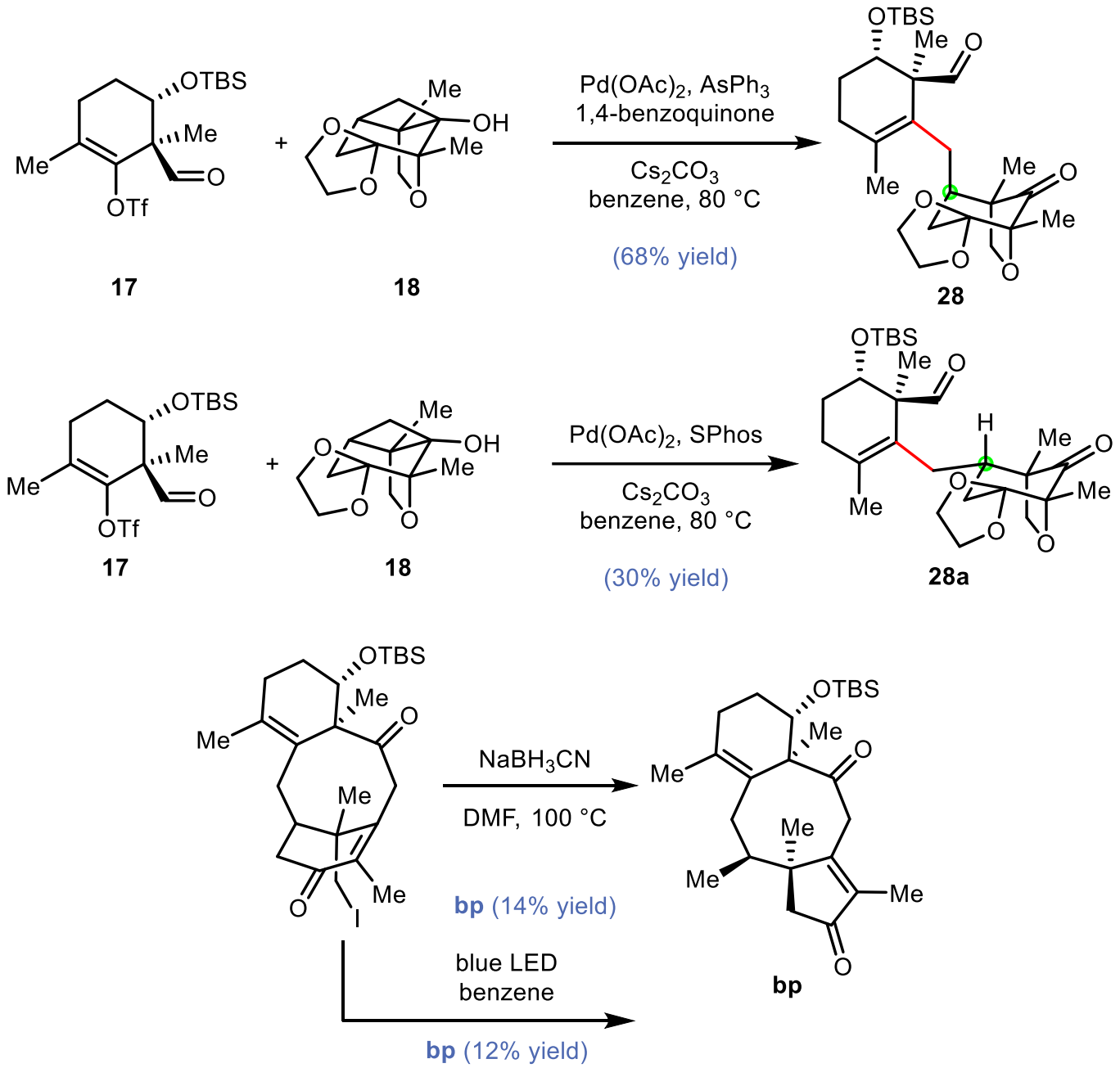
Synthesis

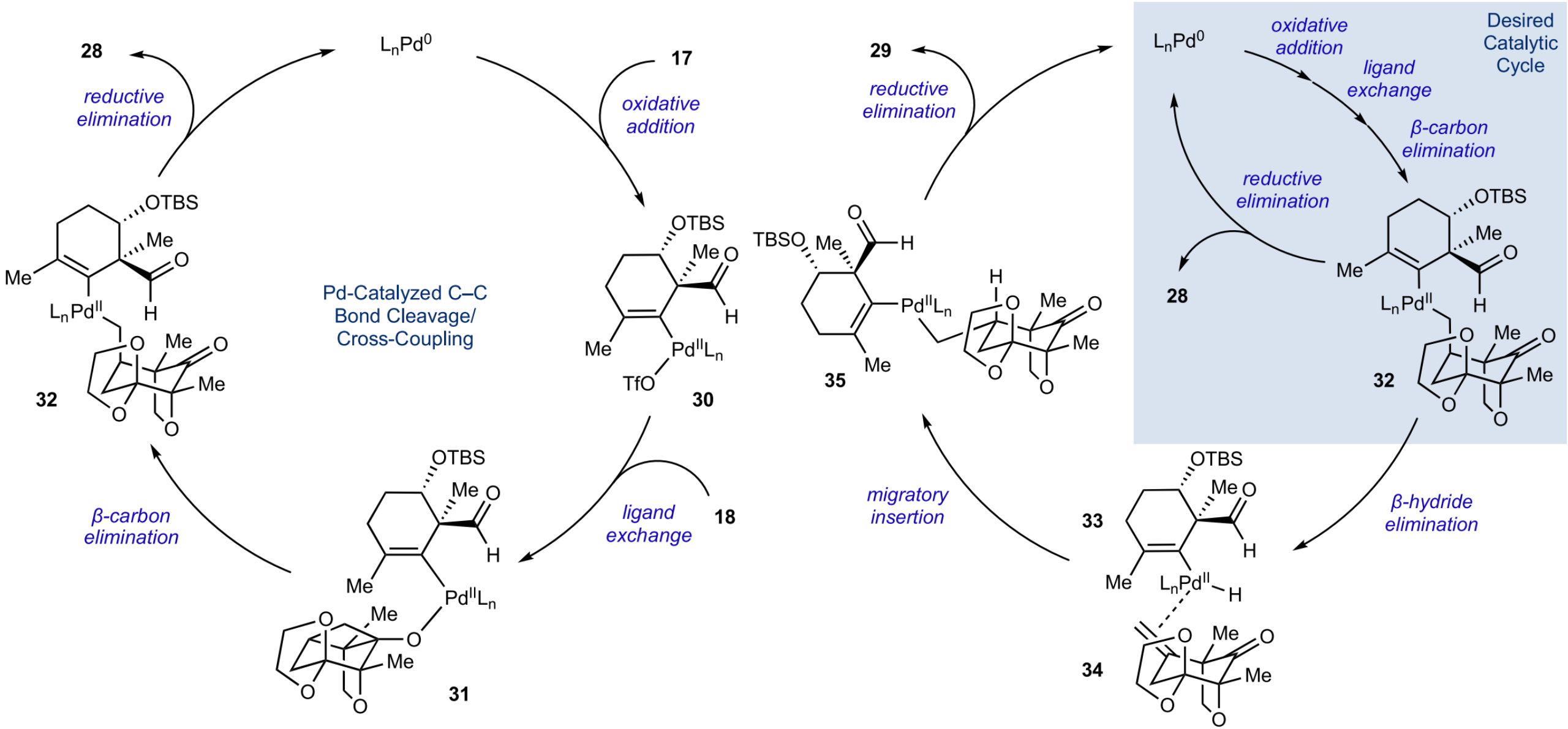

TBSO
Me
Me
Me
O
OMOM
O
OH
OH
53
1. IBX
2. Me4NBH(OAc)3
THF, rt
(51% yield for 2 steps)
54
1. PhCH(OMe)2
PTSA, MeCN
2. L-selectride
THF, -78 °C
(95% yield for 2 steps)
55
1. KHMDS, Comins
2. CO, Pd(PPh3)4
Et3N, MeOH, DMF
(77% yield for 2 steps)
COOMe
56
1. Mg, MeOH
2. KHMDS, 18-crown-6, MeI
3. LAH, then TBAF
(67% yield for 3 steps)
HO
57
skeleton construction
1. Swern
2. TiCl4, Zn, py
(55% yield for 2 steps)
58
1. Ac2O, DMAP
2. BrB(catechol), DCM
3. PhCH(OMe)2, PTSA
(67% yield for 2 steps)
OAc
AcO
59
K2CO3
MeOH, 0 °C
(67% yield)
60
1. Ac2O, DMAP
2. H2, Pd/C
(44% yield for 2 steps)
canataxpropellane (41)

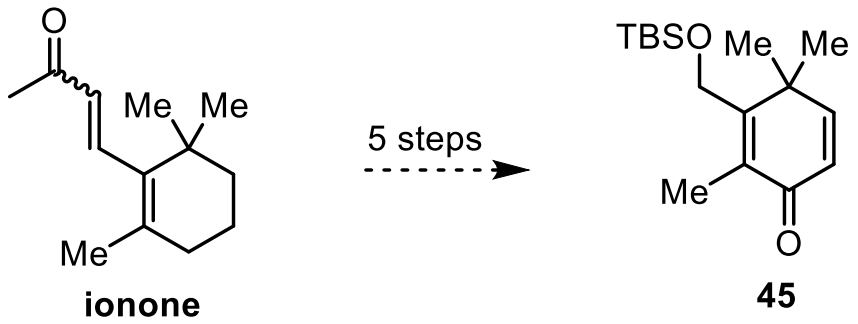
Asymmetric Synthesis

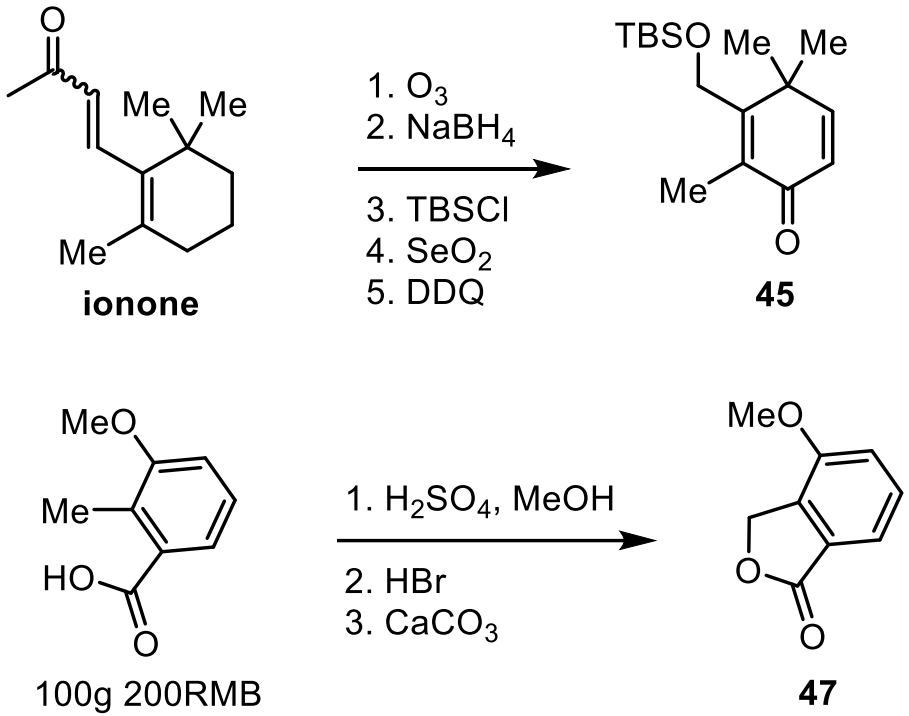


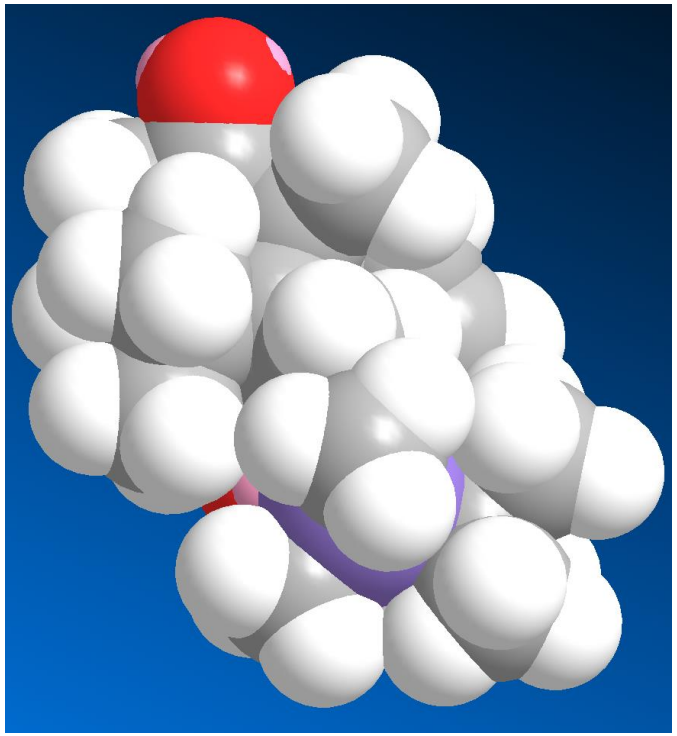
Discussion


OTBS
Me
Me
O
OTf
17
+
Me
OH
Me
O
O
O
18
Pd(OAc)2, AsPh3
1,4-benzoquinone
Cs2CO3
benzene, 80 °C
(68% yield)
OTBS
Me
O
Me
Me
O
Me
O
O
28
OTBS
Me
Me
O
OTf
17
+
Me
OH
Me
O
O
O
18
Pd(OAc)2, SPhos
Cs2CO3
benzene, 80 °C
(30% yield)
OTBS
Me
O
H
Me
O
Me
Me
O
O
28a
OTBS
Me
Me
O
Me
Me
I
NaBH3CN
DMF, 100 °C
bp (14% yield)
blue LED
benzene
bp (12% yield)
OTBS
Me
Me
O
Me
Me
Me
O
bp

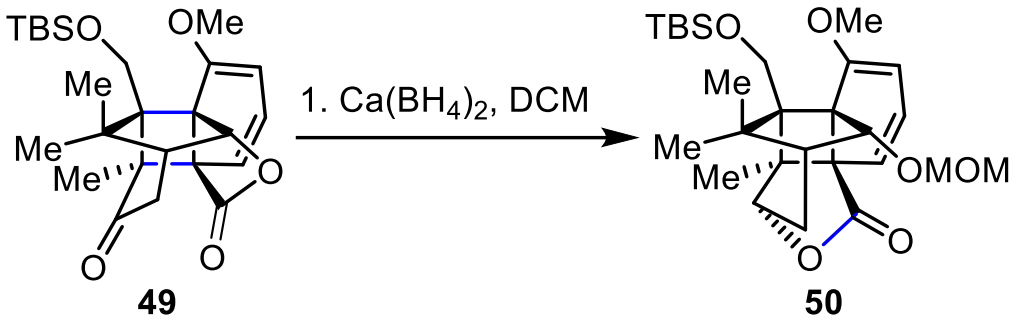

Pd-Catalyzed C–C
Bond Cleavage/
Cross-Coupling
L_nPd^0
oxidative addition
17
ligand exchange
18
β-carbon elimination
reductive elimination
28
29
migratory insertion
β-hydride elimination
30
31
32
33
34
35
TfO
TBSO
OTBS
Me
H
O
$Pd^{II}L_n$
Desired Catalytic Cycle
oxidative addition
ligand exchange
β-carbon elimination
reductive elimination

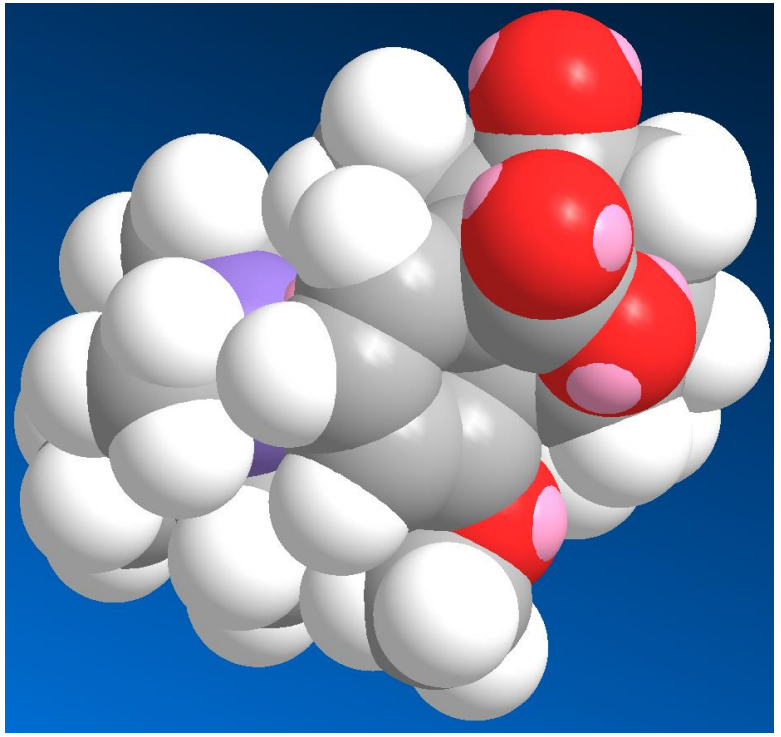

O
Me
Me
Me
ionone
5 steps
TBSO
Me
Me
Me
O
45
MeO
Me
HO
O
100g 200RMB
3 steps
MeO
O
O
47


O
Me
Me
Me
ionone
1. O_3
2. $NaBH_4$
3. TBSCl
4. SeO_2
5. DDQ
TBSO
Me
Me
Me
O
45
MeO
Me
HO
O
100g 200RMB
1. H_2SO_4, MeOH
2. HBr
3. $CaCO_3$
MeO
O
O
47



49 re-face





49 si-face

1. Atomic radius： $Li^+ < Na^+ < Ca^{2+}$
   Electric charge： $Ca^{2+} < Na^+, Li^+$
   Ability of polarize the borohydride anion
   $Li^+ > Ca^{2+} > Na^+$
2. Ability of coordinating with the carbonyl oxygen
   $Li^+ > Ca^{2+} > Na^+$

Ability of reduction： $LiBH_4 > Ca(BH4)_2 > NaBH_4$

H. C. Brown, *et al. J. Org. Chem.* **1982**, *47*, 4702–4708.


Thanksgiving Day