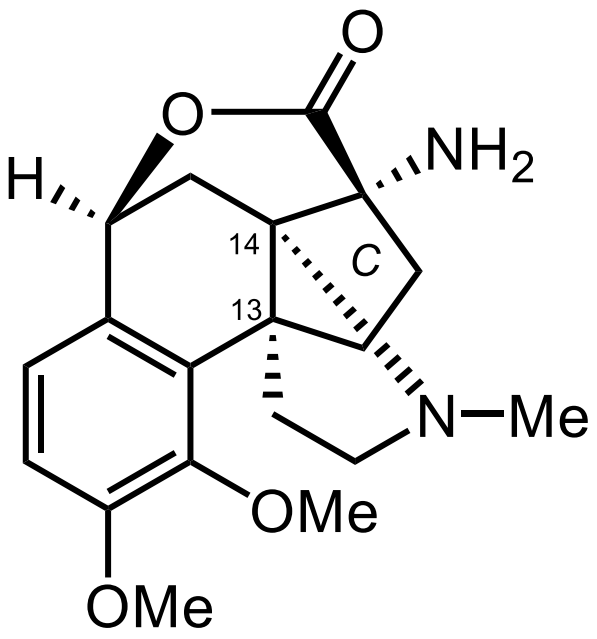
Enantioselective Total Synthesis of (+)-Stephadiamine through Bioinspired Aza-Benzilic Acid Type Rearrangement



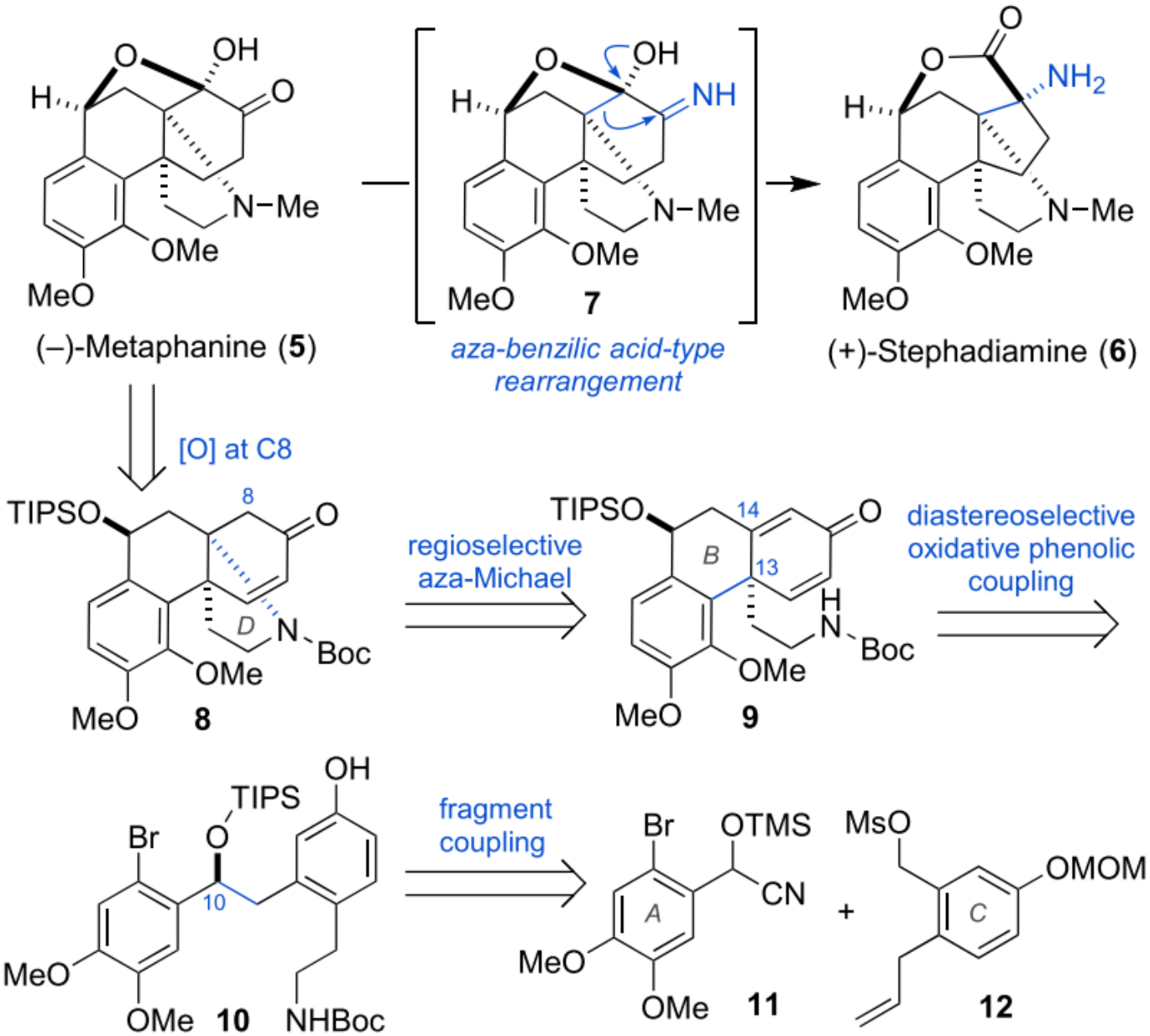
(+)-Stephadiamine

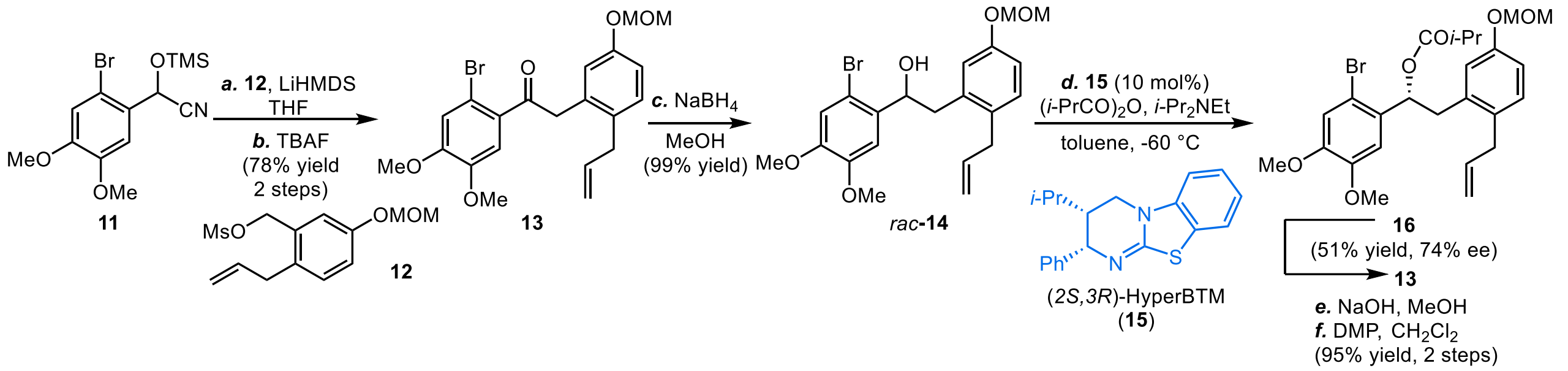
- First isolated by Ibuka and co-workers from Stephania Japonica.
- An aza[4,3,3]propellane scaffold with a five-membered C-ring, and four stereogenic centers, including an α-tertiary amine at C14 and an all-carbon quaternary stereogenic center at C13.
- The biological activity has not yet been investigated; More than 40 congeners identified to date show a wide range of biological activities, including antiviral, antimicrobial, and cytotoxic activities.

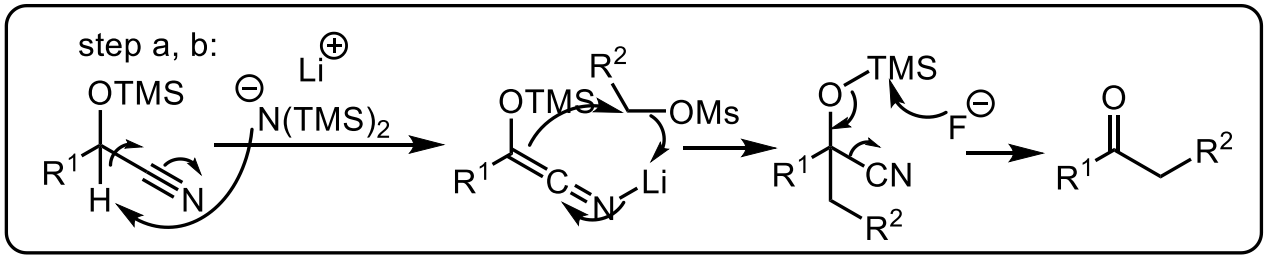
Ziyong Wang
Liu Research Group
Total Synthesis Presentation
3/24/2020

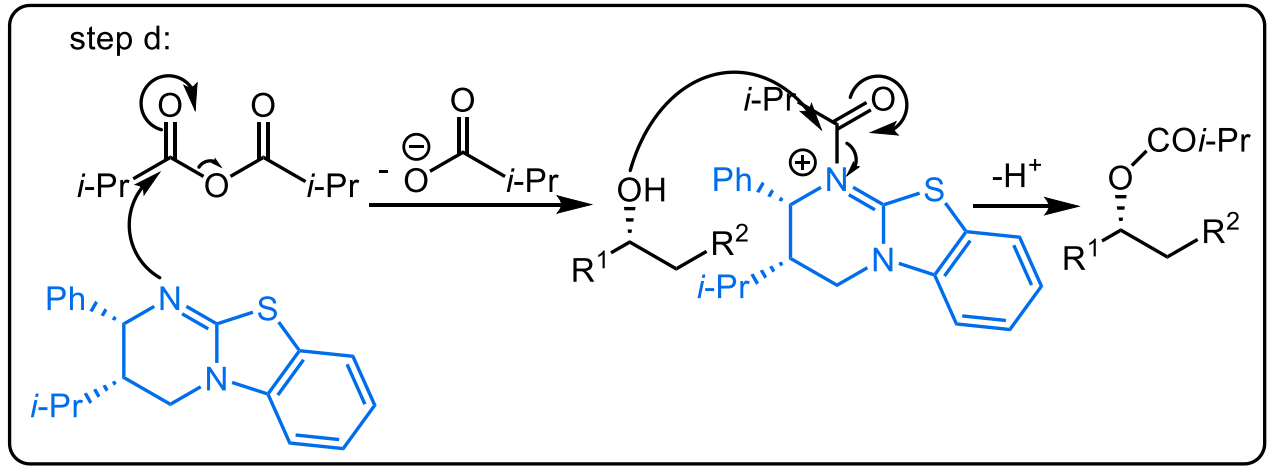
Odagi, M.; Matoba, T.; Hosoya, K.; Nagasawa, K., *J. Am. Chem. Soc.* **2021,** *143*, 2699-2704.

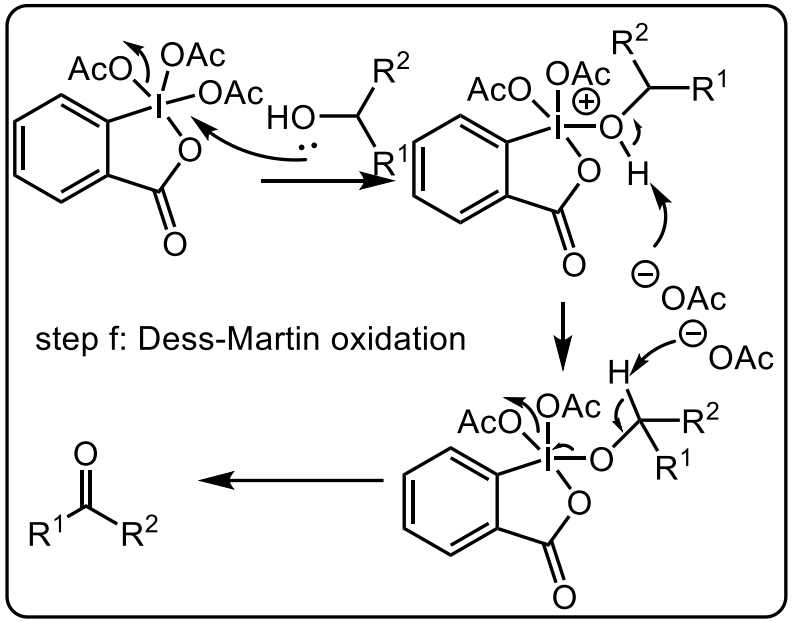
Retrosynthetic Analysis of (+)-Stephadiamine

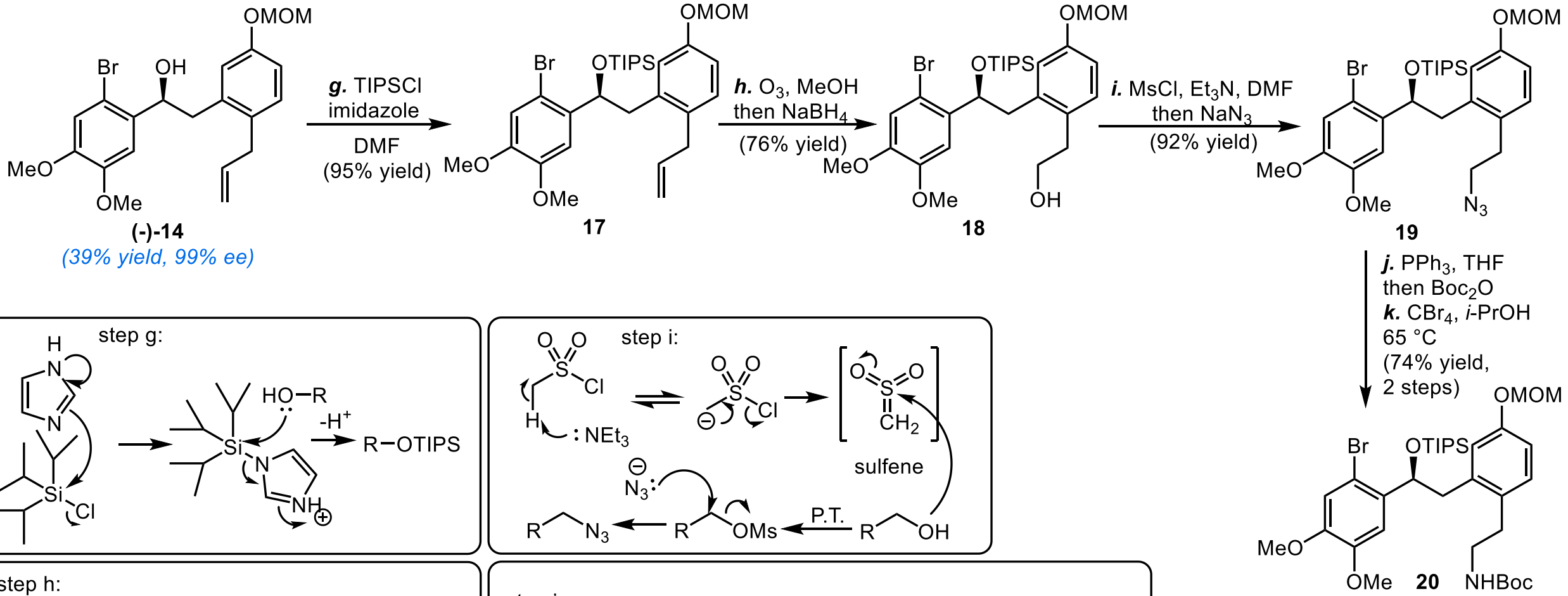



Br
OTMS
CN
MeO
OMe
11
a. 12, LiHMDS
THF
b. TBAF
(78% yield
2 steps)
MsO
OMOM
12
Br
O
OMOM
MeO
OMe
13
c. NaBH4
MeOH
(99% yield)
Br
OH
OMOM
MeO
OMe
rac-14
d. 15 (10 mol%)
(i-PrCO)2O, i-Pr2NEt
toluene, -60 °C
i-Pr
Ph
N
S
(2S,3R)-HyperBTM
(15)
CO i-Pr
16
(51% yield, 74% ee)
13
e. NaOH, MeOH
f. DMP, CH2Cl2
(95% yield, 2 steps)
+
(-)-14
(39% yield, 99% ee)


step a, b:
OTMS
Li
N(TMS)2
R1
H
N
R2
OMs
C
Li
TMS
F
CN
O

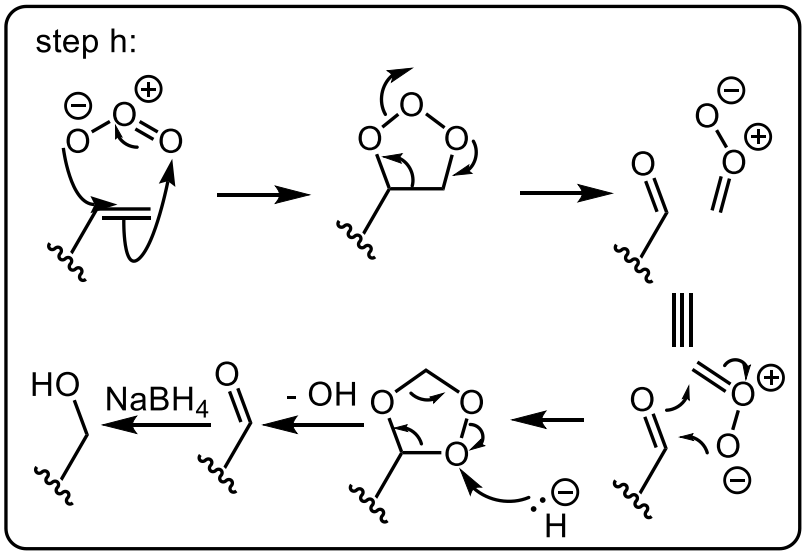

step d:
i-Pr
O
-
i-Pr
OH
Ph
N
S
i-Pr
R1
R2
-H+
CO i-Pr
i-Pr

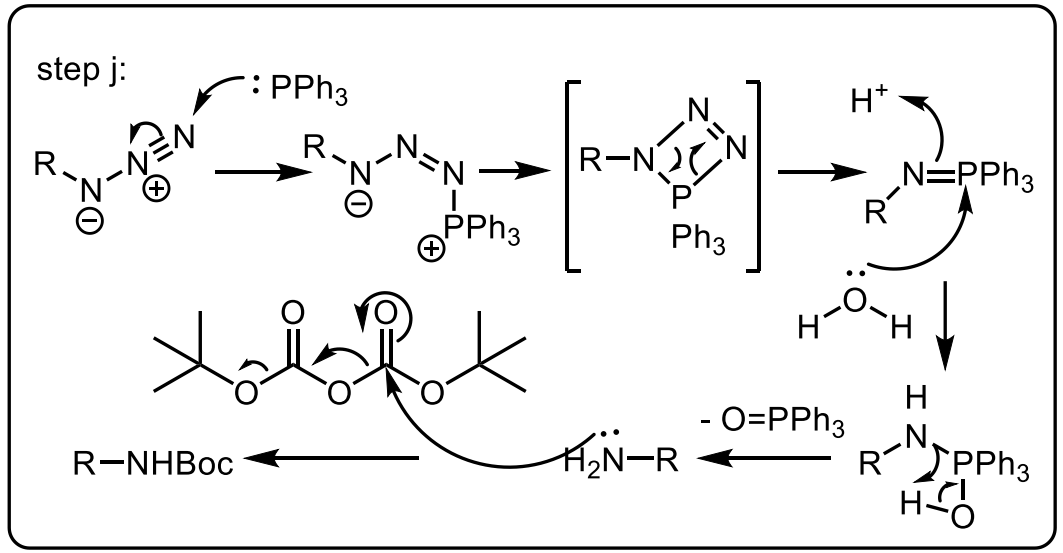

AcO
OAc
I
O
HO
R2
R1
H
step f: Dess-Martin oxidation

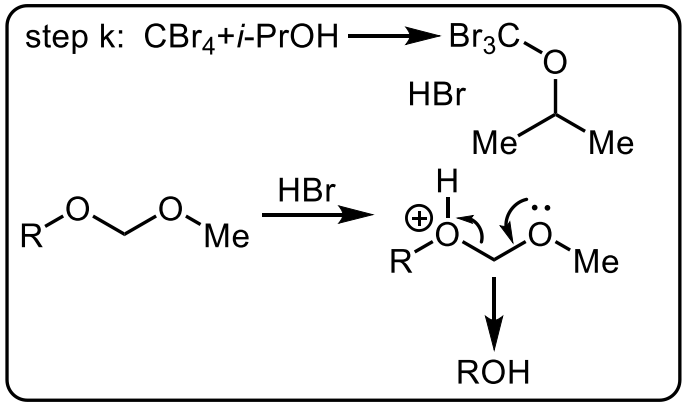

OMOM
Br
OH
MeO
OMe
(-)-14
(39% yield, 99% ee)
g. TIPSCl
imidazole
DMF
(95% yield)
OTIPS
17
h. O3, MeOH
then NaBH4
(76% yield)
18
i. MsCl, Et3N, DMF
then NaN3
(92% yield)
N3
19
j. PPh3, THF
then Boc2O
k. CBr4, i-PrOH
65 °C
(74% yield,
2 steps)
NHBoc
20

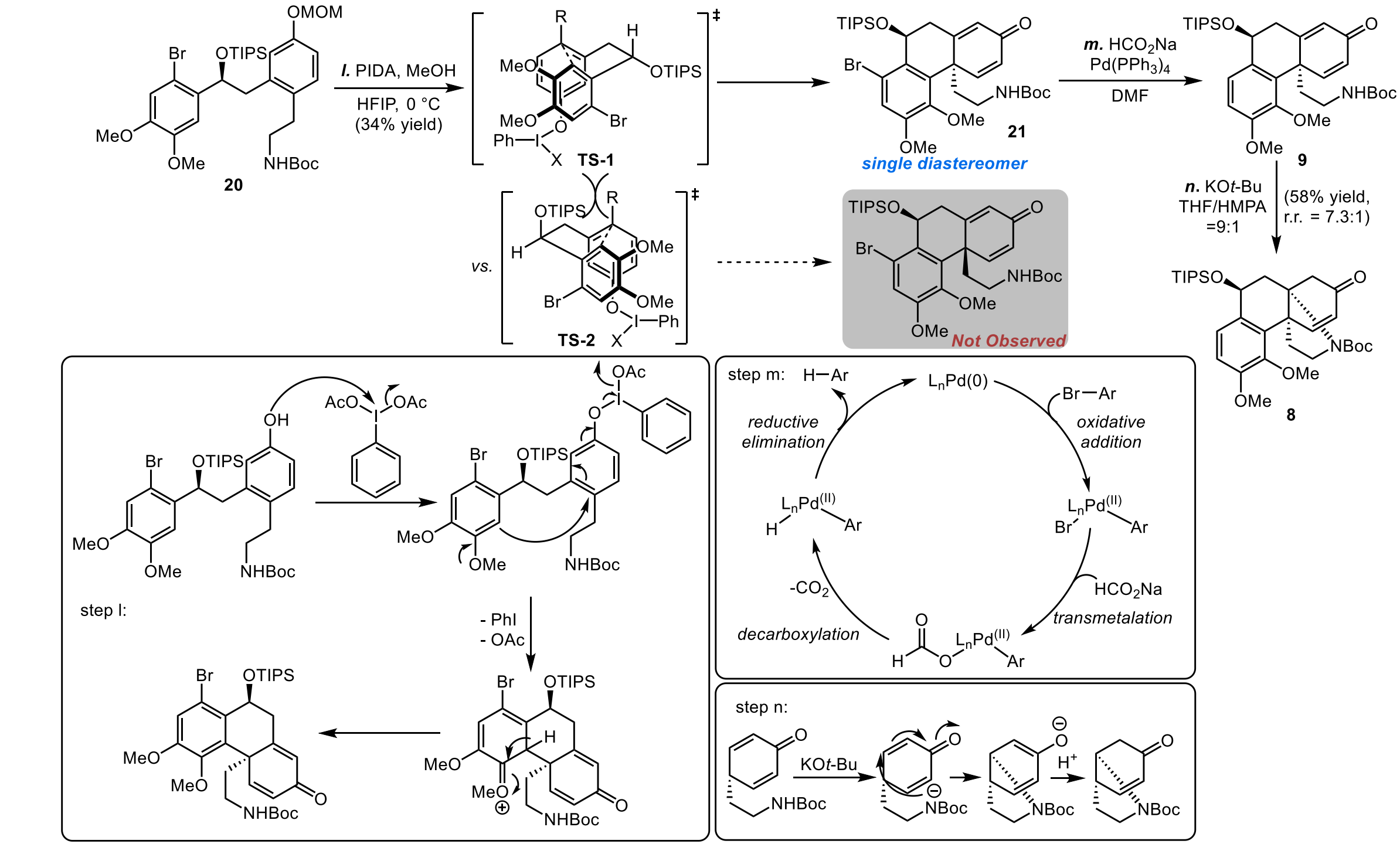
step g:
HO–R
-H+
R–OTIPS

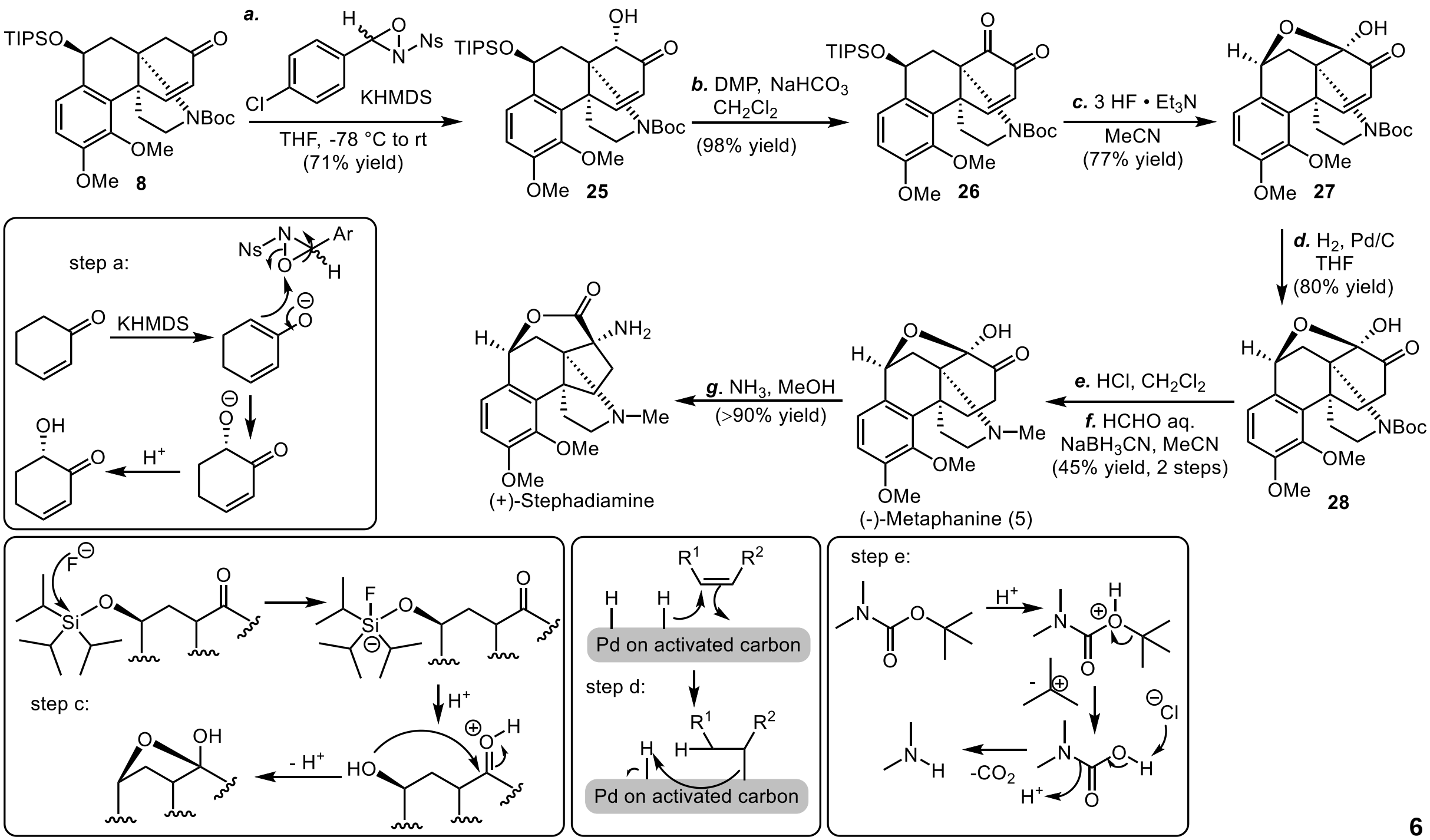
step i:
: NEt3
sulfene
P.T.

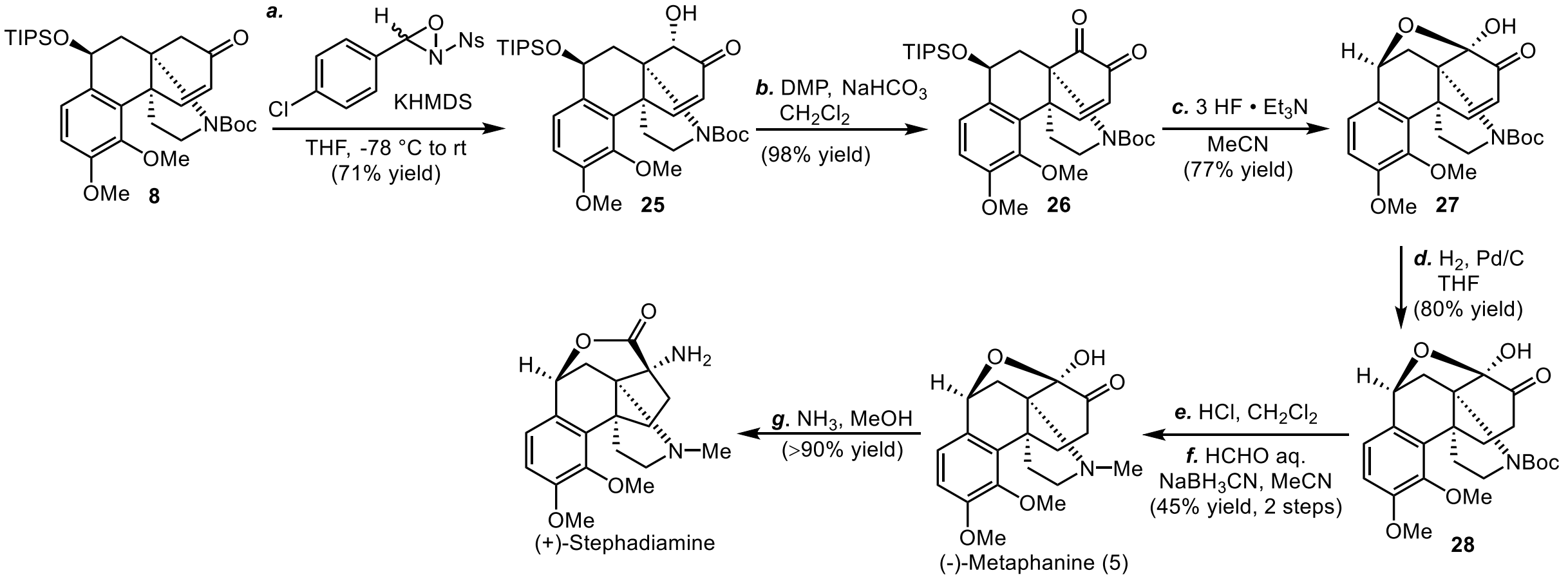

step h:
NaBH4
- OH


step j:
: PPh3
Ph3
- O=PPh3
R–NHBoc


step k: CBr4+i-PrOH
Br3C
HBr
HBr
ROH


20
I. PIDA, MeOH
HFIP, 0 °C
(34% yield)
TS-1
vs.
TS-2
21
single diastereomer
m. HCO2Na
Pd(PPh3)4
DMF
9
n. KOt-Bu
THF/HMPA
=9:1
(58% yield,
r.r. = 7.3:1)
8
Not Observed
step I:
- PhI
- OAc
step m:
reductive
elimination
oxidative
addition
transmetalation
decarboxylation
-CO2
step n:
KOt-Bu


a.
KHMDS
THF, -78 °C to rt
(71% yield)
b. DMP, NaHCO3
CH2Cl2
(98% yield)
c. 3 HF • Et3N
MeCN
(77% yield)
d. H2, Pd/C
THF
(80% yield)
e. HCl, CH2Cl2
f. HCHO aq.
NaBH3CN, MeCN
(45% yield, 2 steps)
g. NH3, MeOH
(>90% yield)
8
25
26
27
28
(+)-Stephadiamine
(-)-Metaphanine (5)
step a:
step c:
step d:
step e:
Pd on activated carbon
Pd on activated carbon


TIPSO
NBoc
OMe
OMe
8
a.
KHMDS
THF, -78 °C to rt
(71% yield)
25
b. DMP, NaHCO3
CH2Cl2
(98% yield)
26
c. 3 HF • Et3N
MeCN
(77% yield)
27
d. H2, Pd/C
THF
(80% yield)
28
e. HCl, CH2Cl2
f. HCHO aq.
NaBH3CN, MeCN
(45% yield, 2 steps)
(-)-Metaphanine (5)
g. NH3, MeOH
(>90% yield)
(+)-Stephadiamine
step f:
H+
NaBH3CN
step g:
NH3
MeOH
(+)-Stephadiamine