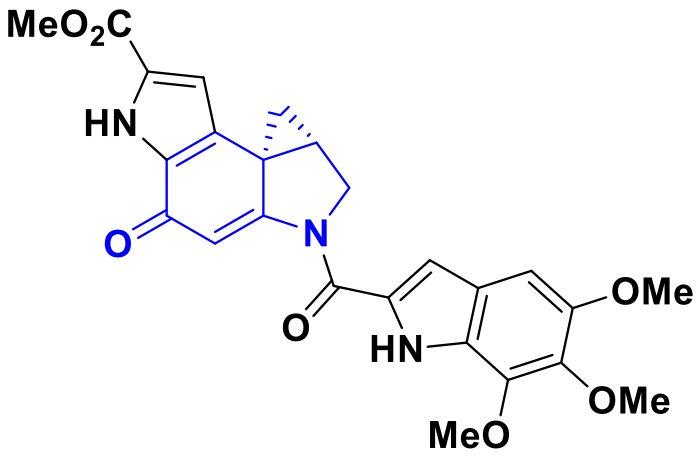
An Enantioselective Total Synthesis of (+)-Duocarmycin SA

Schmidt, M. A.; Simmons, E. M.; Wei, C. S.; Park, H.; Eastgate, M. D., *J. Org. Chem.* **2018, DOI:** 10.1021/acs.joc.8b00285
Bristol-Myers Squibb Company

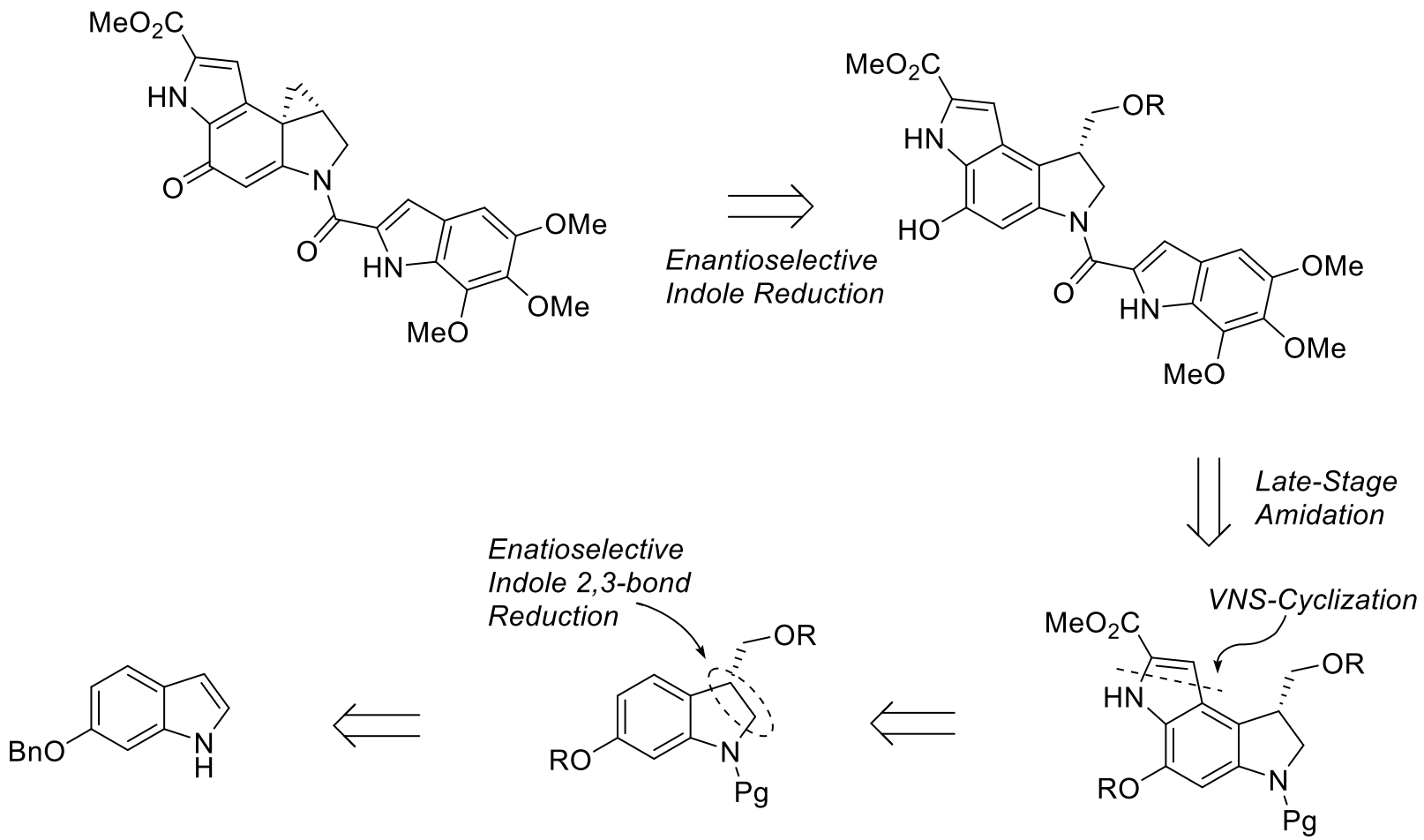
- Duocarmycins are a subset of potent antitumor antibiotics isolated from *Streptomyces* bacteria in the 1980s.
- Contains a 1,1a,2,3-tetrahydro-5*H*-cyclopropanindol-5-one that is responsible for cyctoxicity.
- (+)-Dyocarmycin SA is both the most potent and most stable of these compounds.
- Synthesis conducted over 17 steps with a 24.4% total yield, and is “flexible to allow analogous study but also concise and efficient to facilitate material throughput”

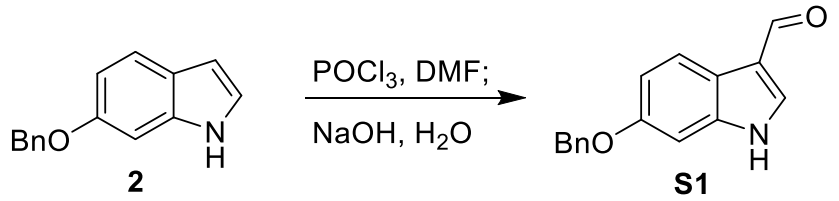


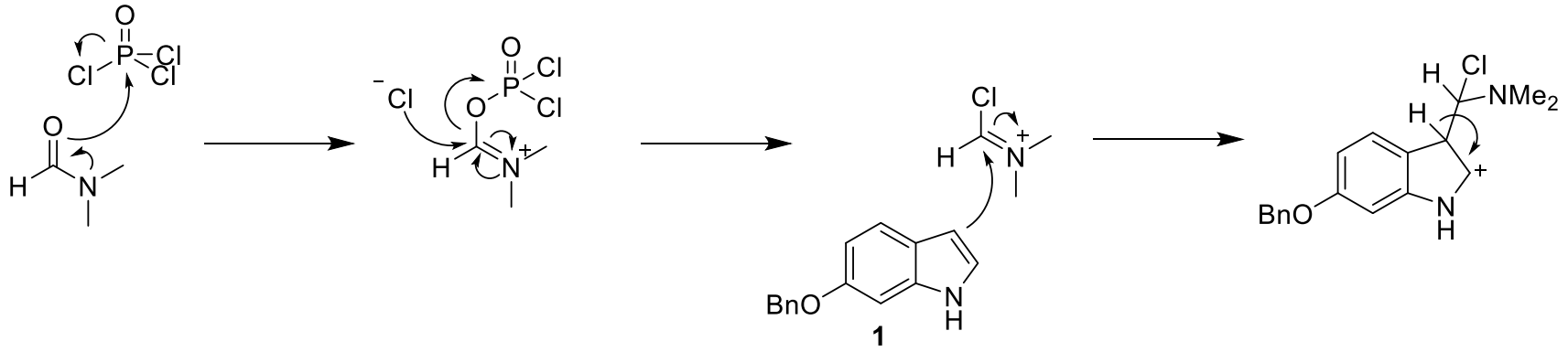
(+)-Duocarmycin SA

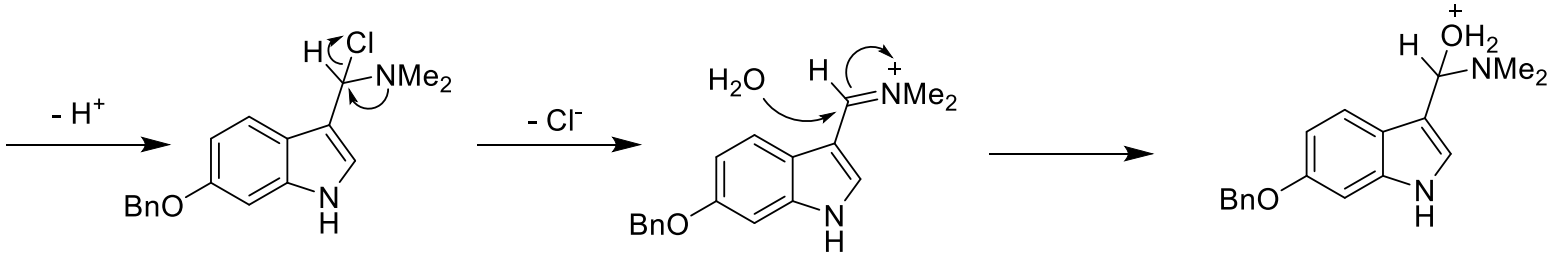
4 April 2018
Jeremy Armand

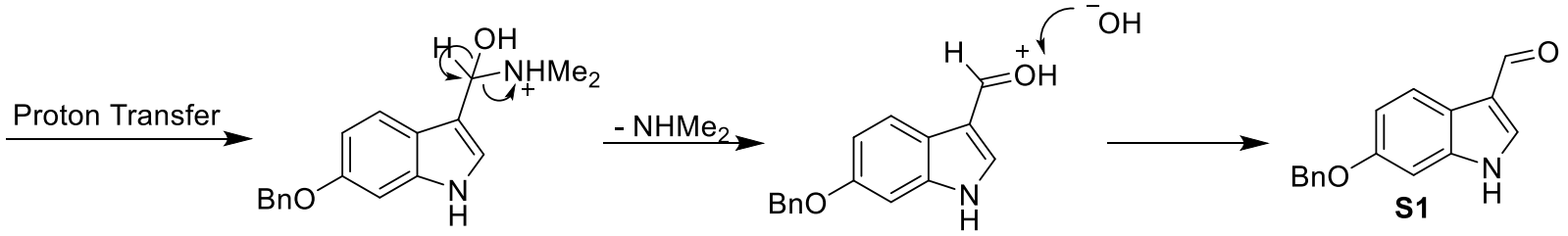
Retrosynthetic Analysis

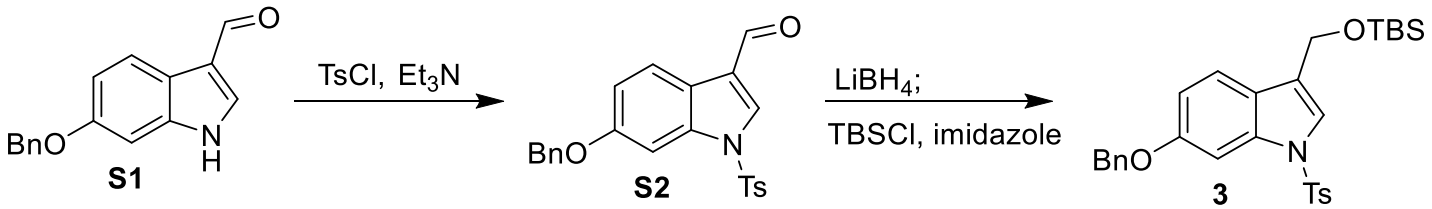



BnO
N
H
2
POCl3, DMF;
NaOH, H2O
O
BnO
N
H
S1

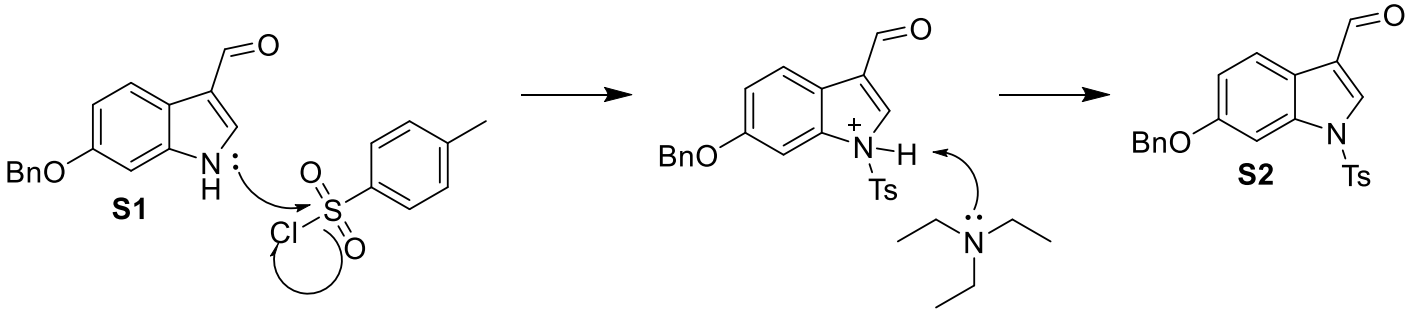

O
P
Cl
Cl
Cl
O
H
N
Cl
O
P
Cl
Cl
O
H
N
Cl
H
N
BnO
N
H
1
H
Cl
NMe2
H
BnO
N
H

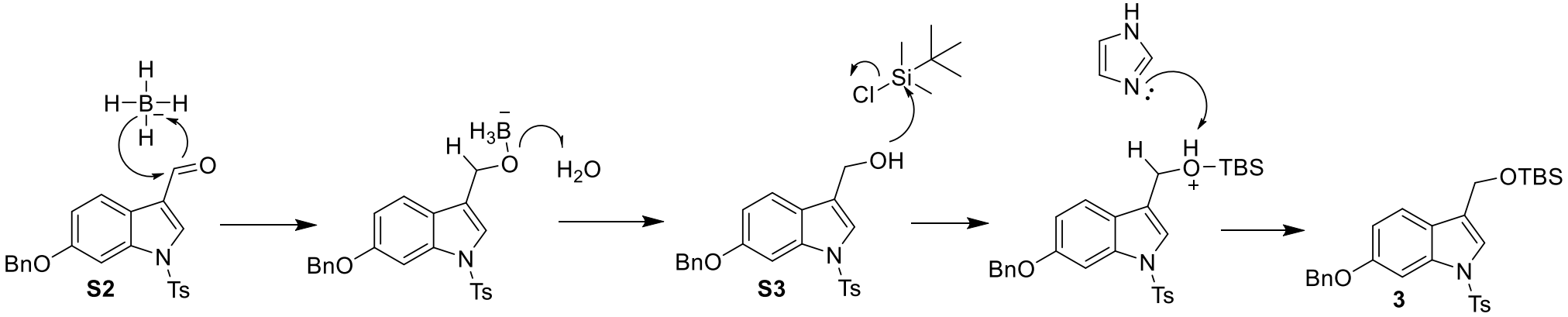

- H+
H
Cl
NMe2
BnO
N
H
- Cl-
H2O
H
NMe2
BnO
N
H
H
OH2
NMe2
BnO
N
H

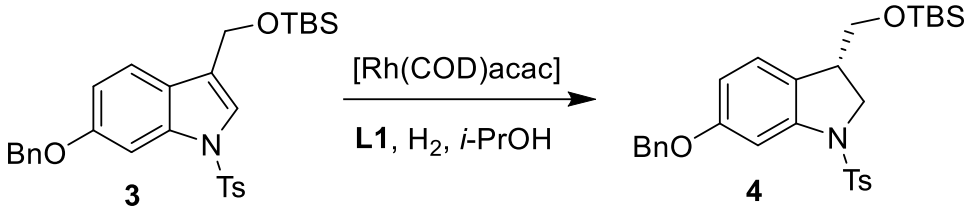

Proton Transfer
H
OH
NHMe2
BnO
N
H
- NHMe2
H
OH
OH
BnO
N
H
O
BnO
N
H
S1



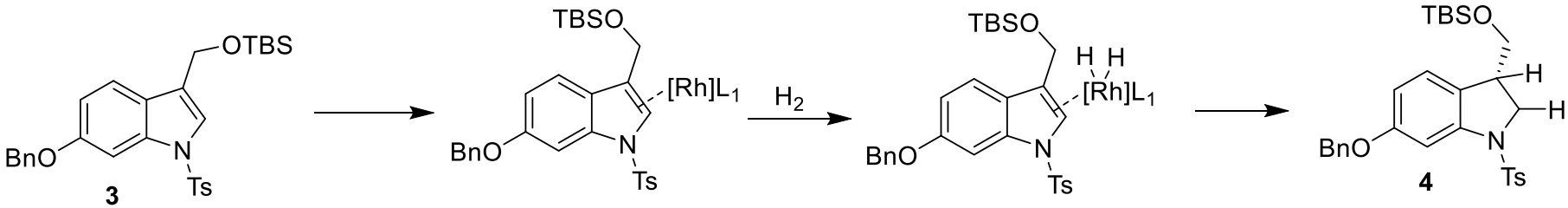
86% (four steps)

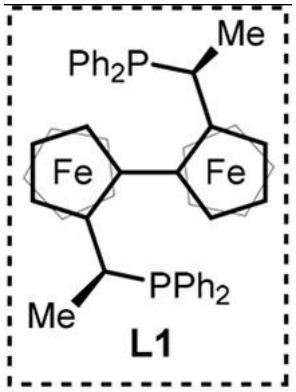


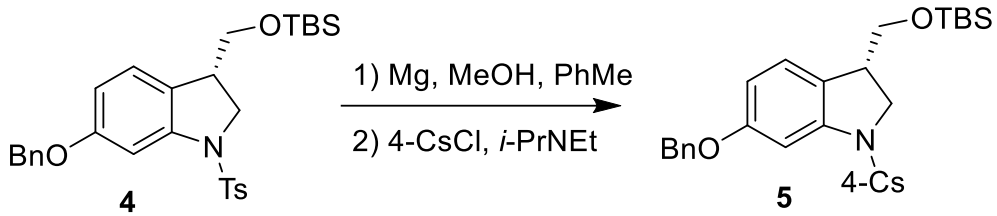



OTBS
BnO
N
Ts
3
[Rh(COD)acac]
L1, H2, i-PrOH
OTBS
BnO
N
Ts
4

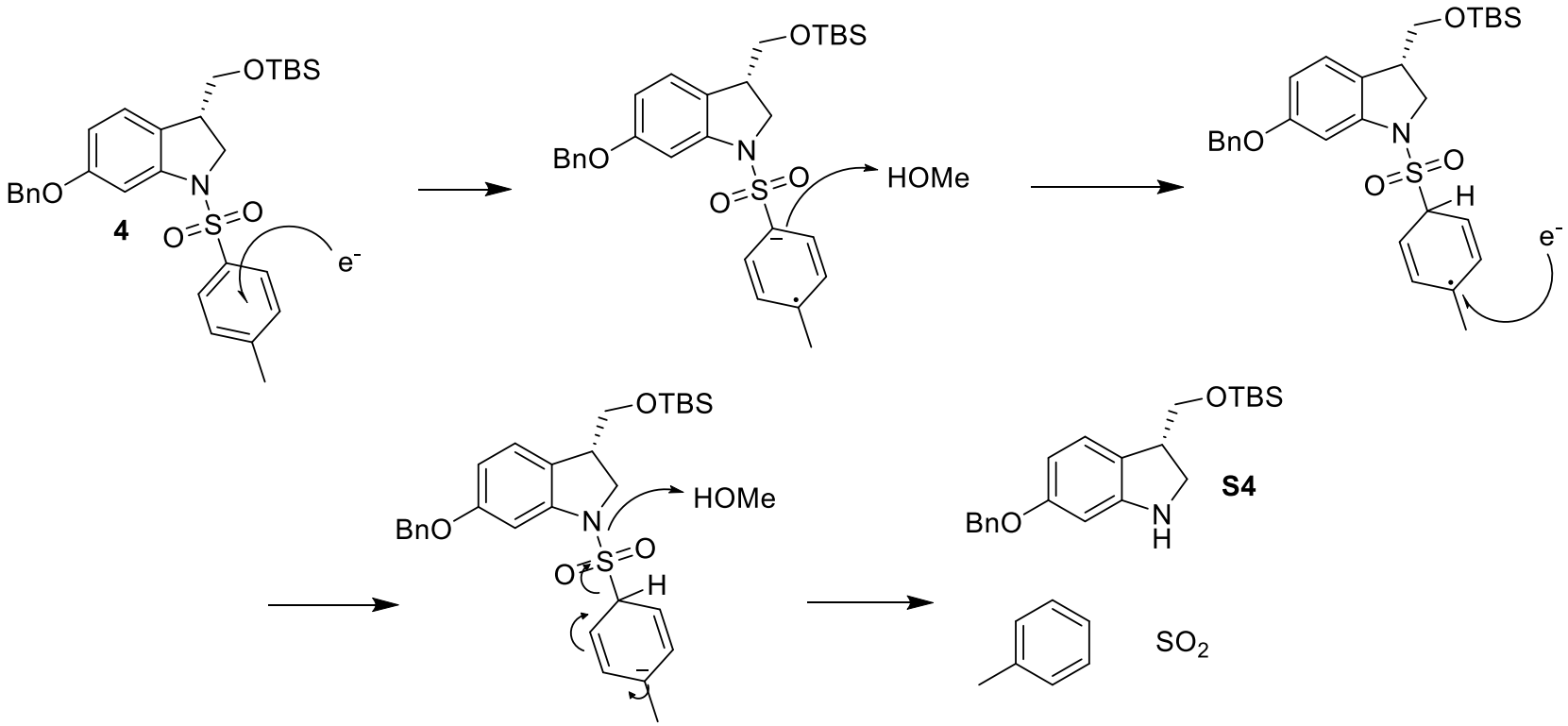
96%, 98.2% ee

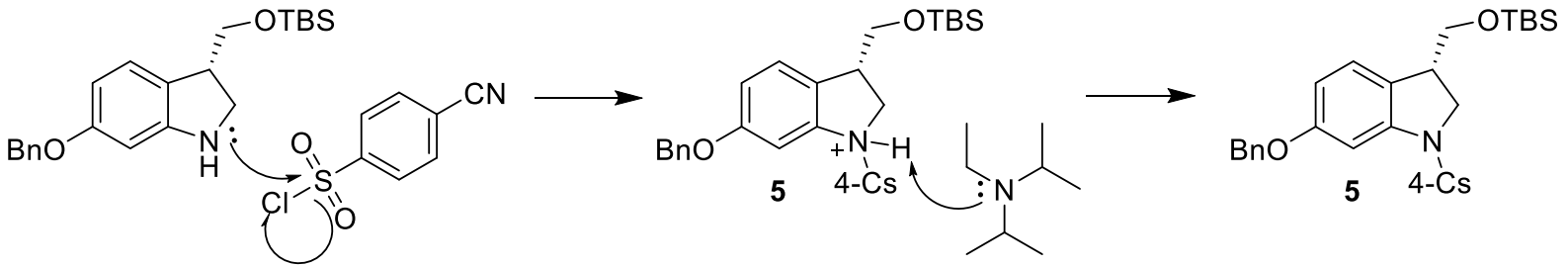

OTBS
BnO
N
Ts
3
TBSO
[Rh]L1
H2
TBSO
H H
[Rh]L1
TBSO
H
H
BnO
N
Ts
4

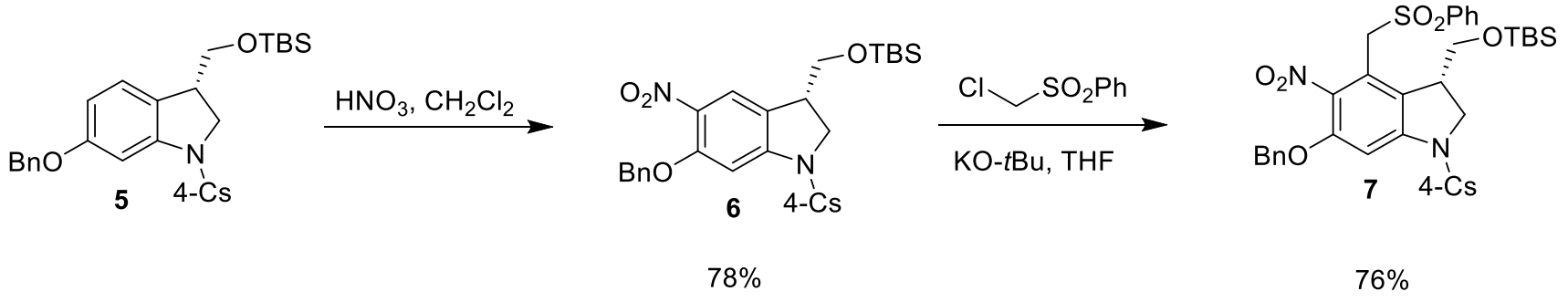

Ph2P
Me
Fe
Fe
Me
PPh2
L1

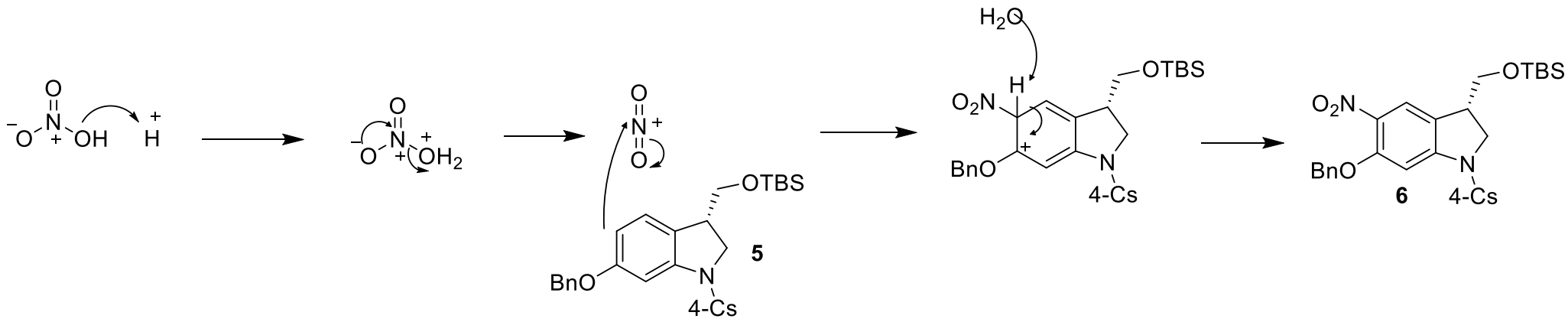

OTBS
BnO
N
Ts
4
1) Mg, MeOH, PhMe
2) 4-CsCl, i-PrNEt
OTBS
BnO
N
4-Cs
5

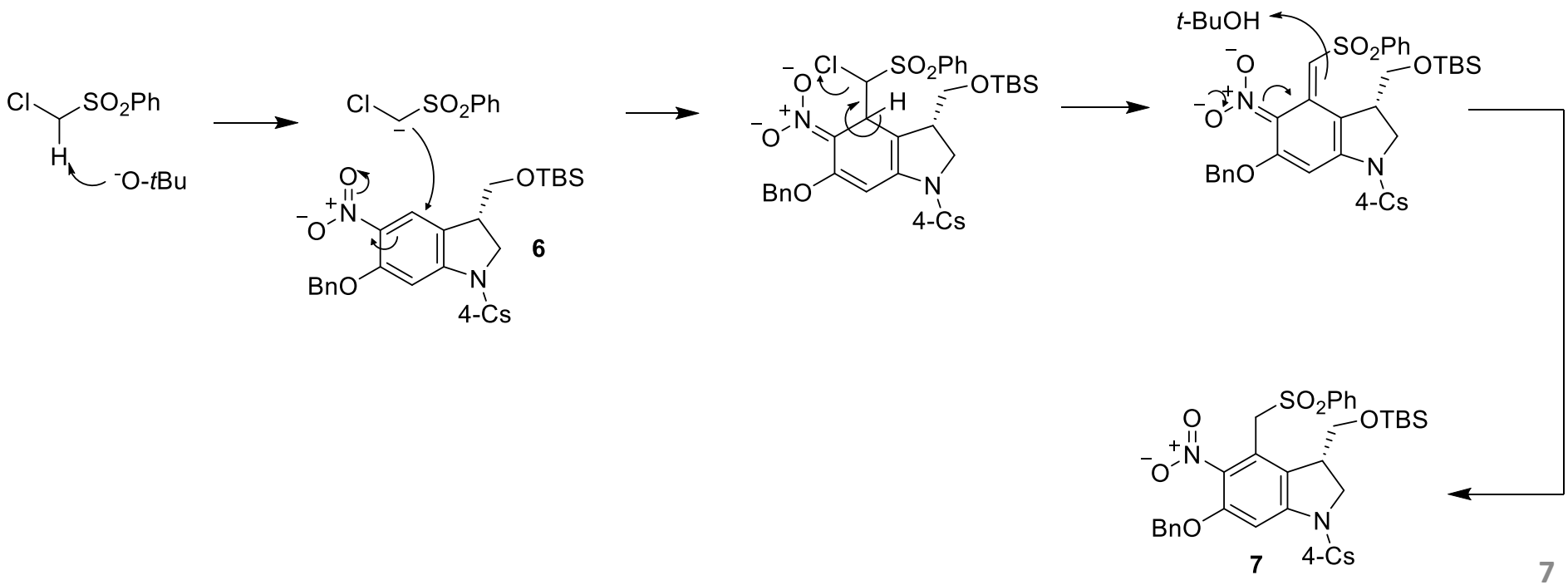
84% (2 steps)

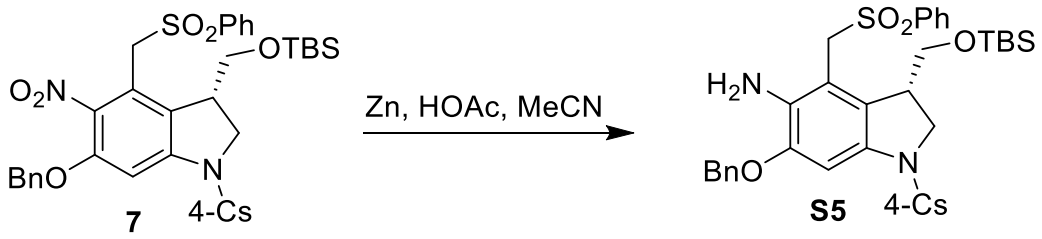

OTBS
BnO
N
4
O=S=O
e-
HOMe
H
S4
SO2

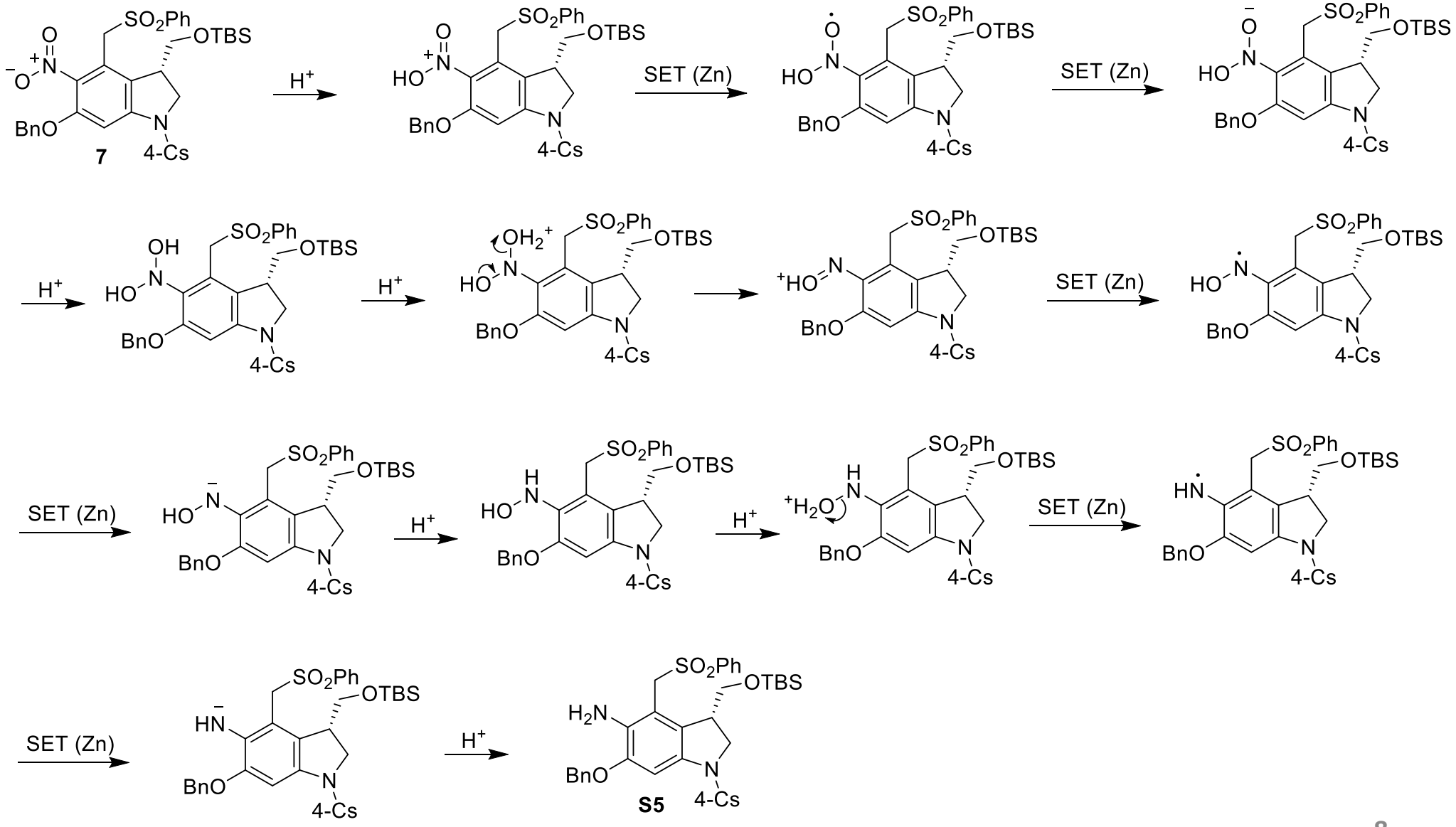

OTBS
BnO
N
H
CN
O
S
Cl
5
4-Cs
+N-H

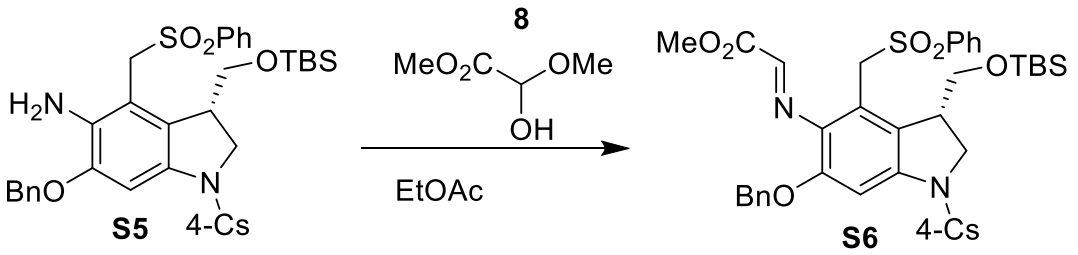

OTBS
BnO
N
4-Cs
5
HNO3, CH2Cl2
O2N
6
78%
Cl
SO2Ph
KO-tBu, THF
SO2Ph
7
76%

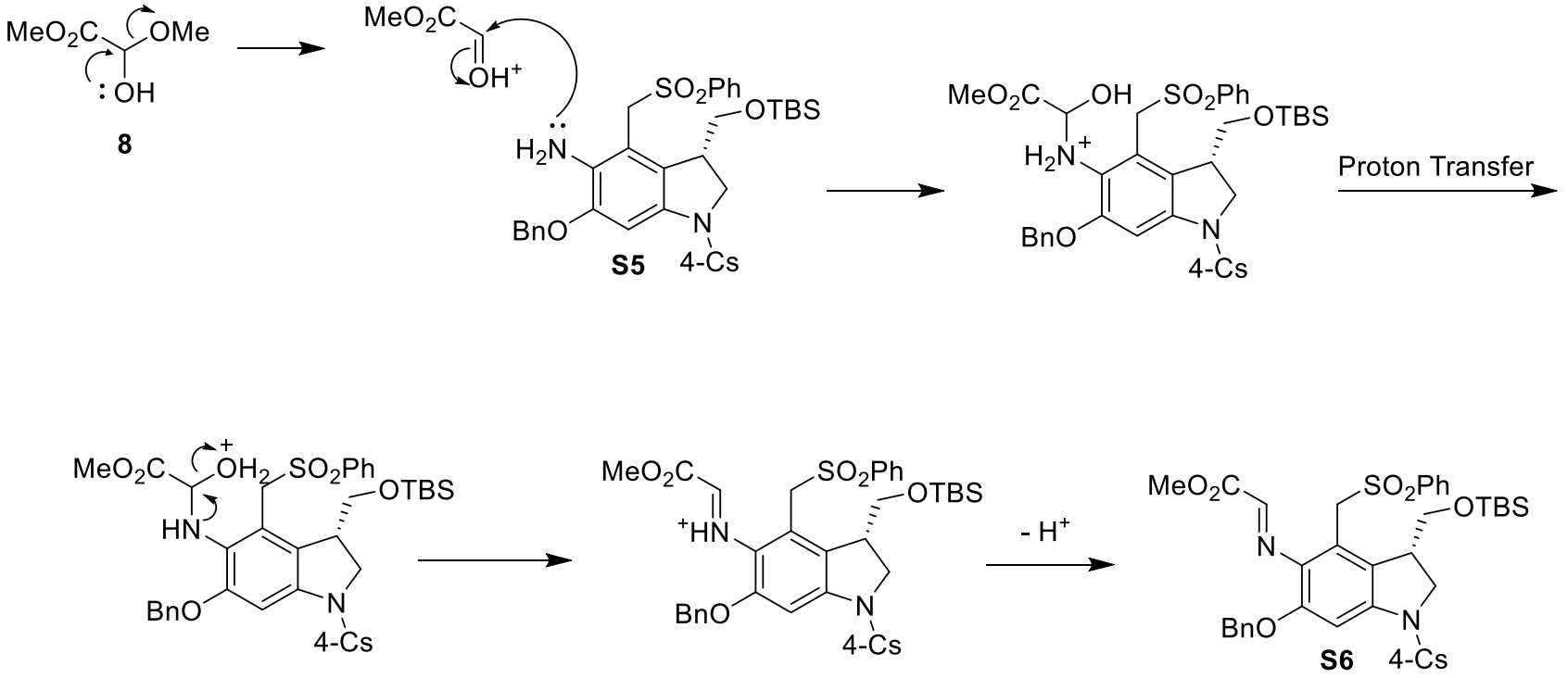

H2O
H
OTBS
O2N
BnO
N
4-Cs
5
6

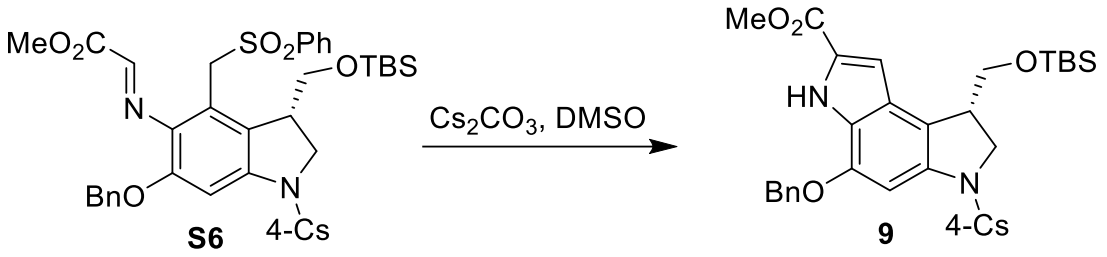

Cl
SO2Ph
H
-O-tBu
OTBS
BnO
N
4-Cs
6
t-BuOH
7

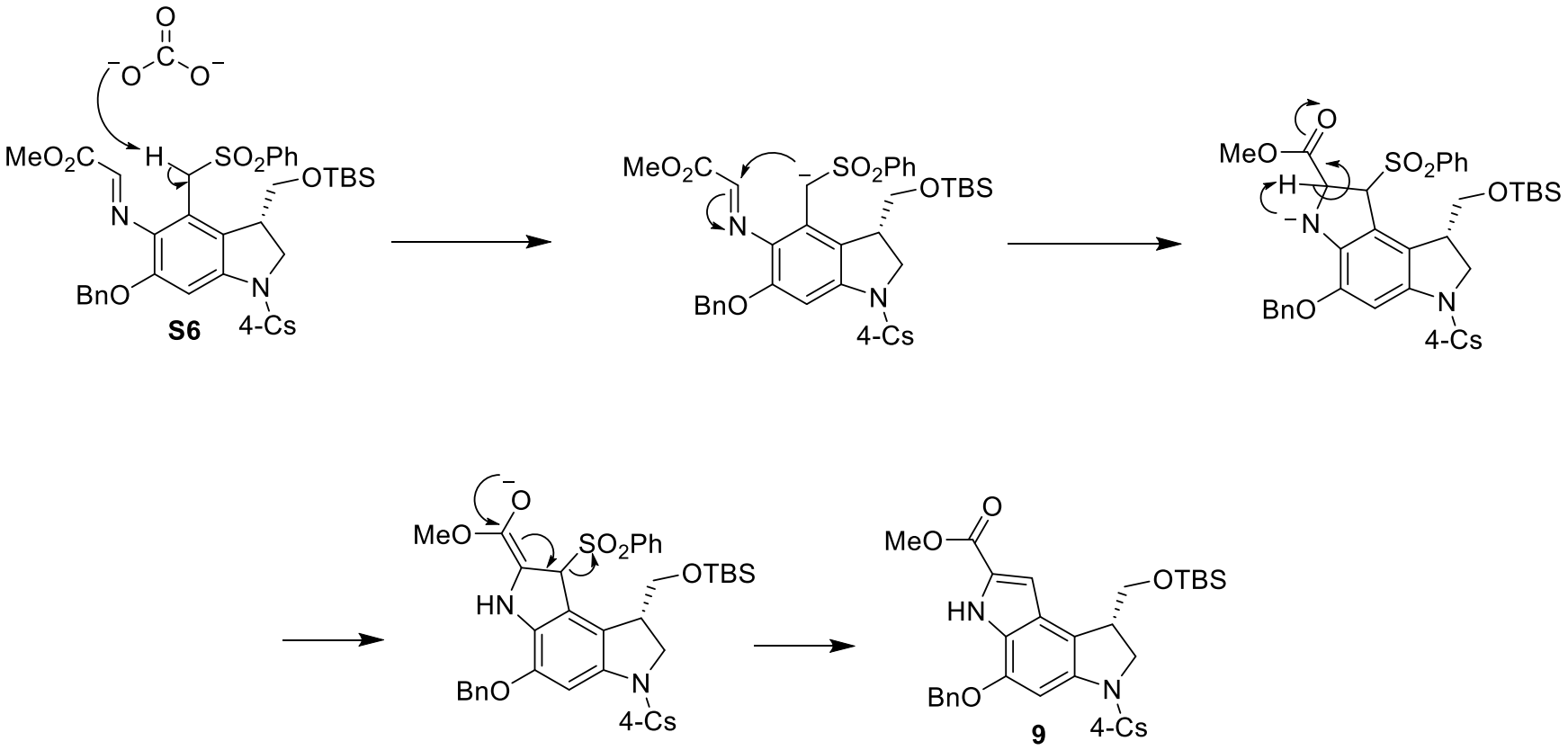

SO2Ph
OTBS
O2N
BnO
N
4-Cs
7
Zn, HOAc, MeCN
H2N
S5

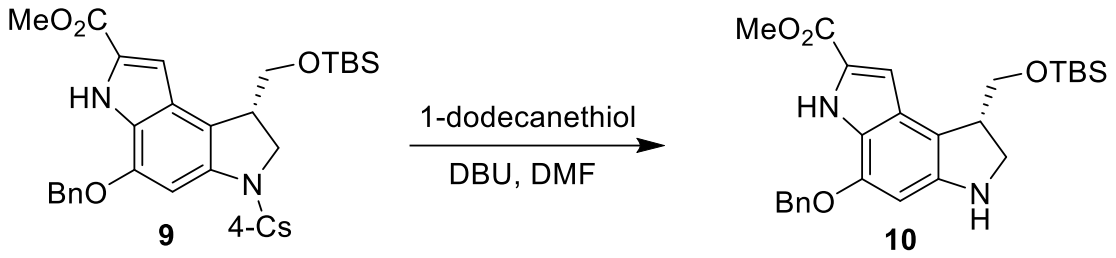

7
H+
SET (Zn)
OH
OH2+
+HO=N
HO-N
HN
+H2O
S5


8
SO2Ph
OTBS
H2N
MeO2C
OMe
OH
BnO
N
4-Cs
EtOAc
S5
S6

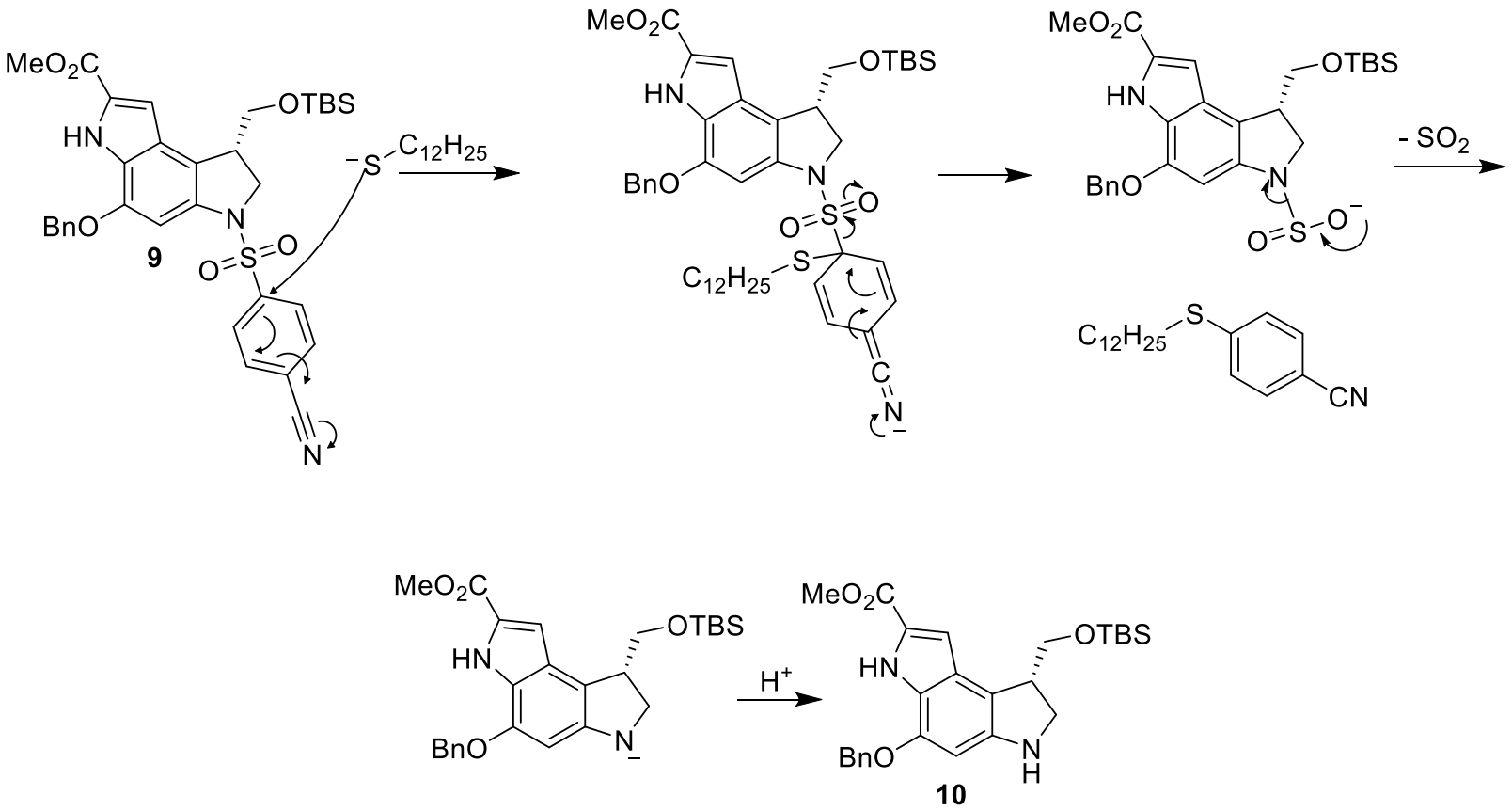

MeO2C
OMe
OH
8
OH+
SO2Ph
OTBS
H2N
BnO
N
4-Cs
S5
H2N+
Proton Transfer
HN
+HN
- H+
S6

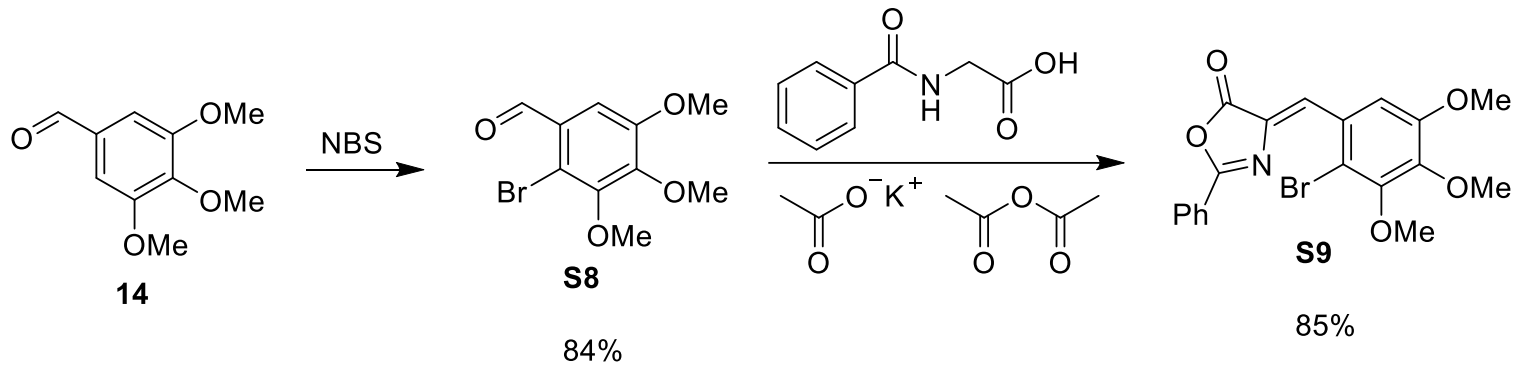

MeO2C
SO2Ph
OTBS
N
BnO
4-Cs
S6
Cs2CO3, DMSO
HN
9
73% (three steps)

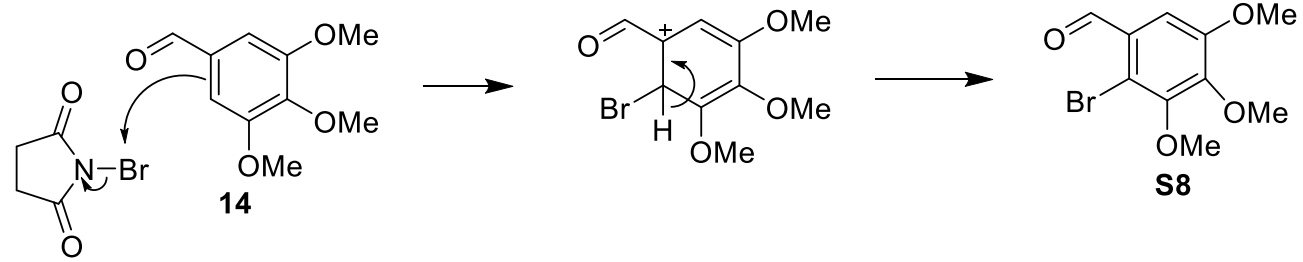

O
MeO2C
H
SO2Ph
OTBS
N
BnO
4-Cs
S6
MeO
HN
9

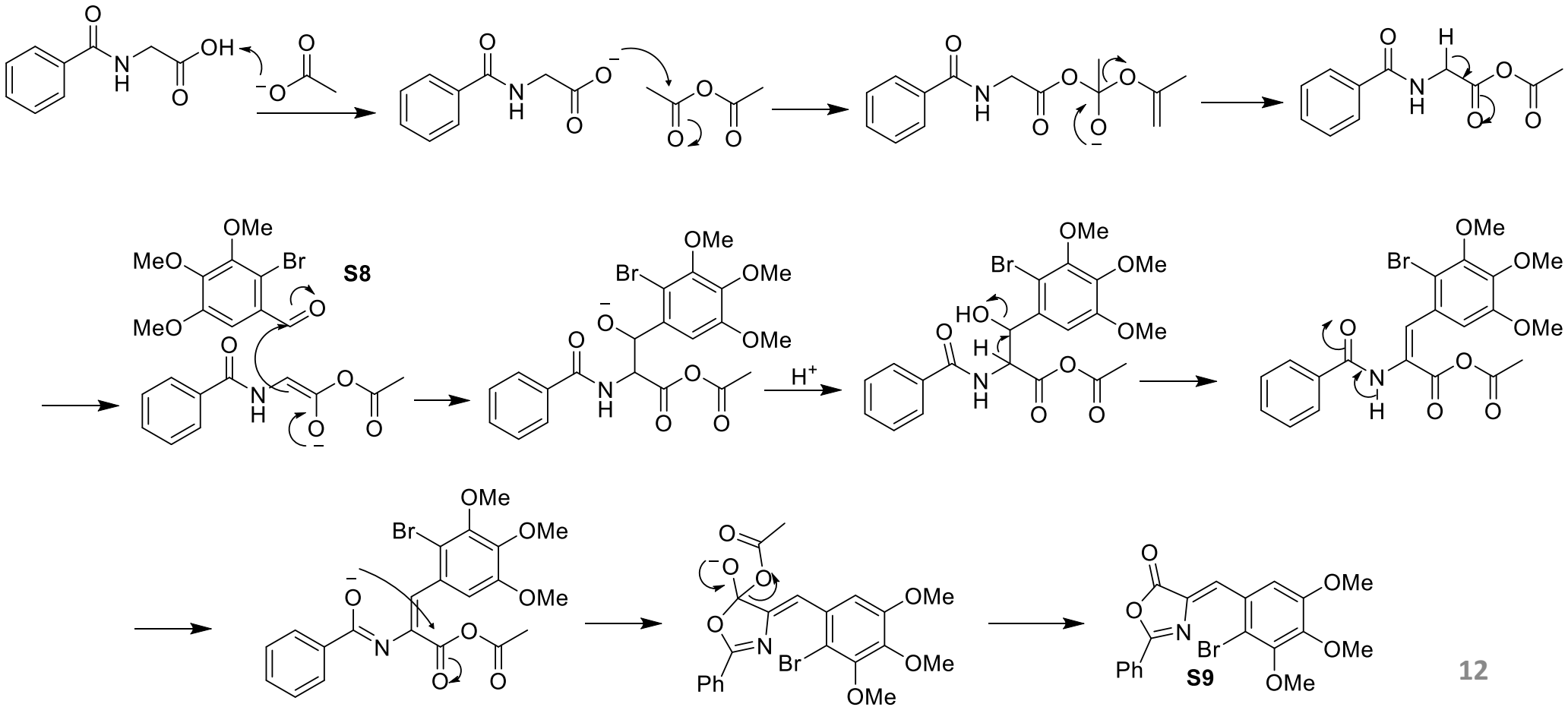

MeO2C
OTBS
HN
BnO
N
4-Cs
9
1-dodecanethiol
DBU, DMF
MeO2C
OTBS
HN
BnO
N
H
10

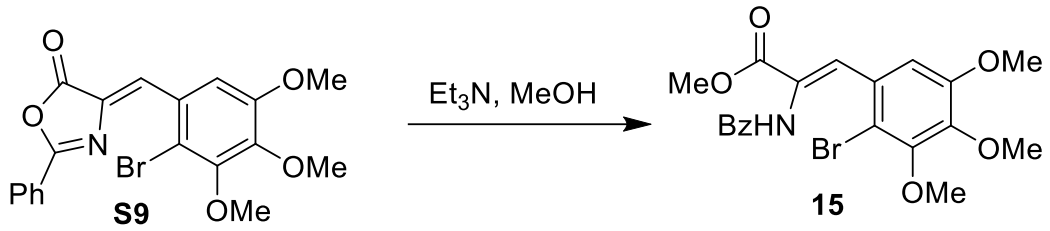
95%

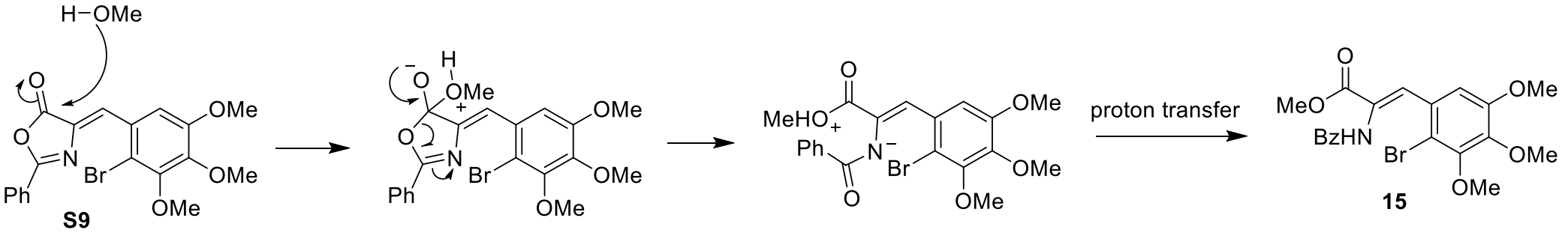

MeO2C
OTBS
HN
BnO
N
9
S
C12H25
O=S=O
N
MeO2C
OTBS
HN
BnO
N
O=S=O
S
C12H25
C
N
MeO2C
OTBS
HN
BnO
N
O=S-O
- SO2
C12H25
S
CN
MeO2C
OTBS
HN
BnO
N
H+
MeO2C
OTBS
HN
BnO
N
H
10

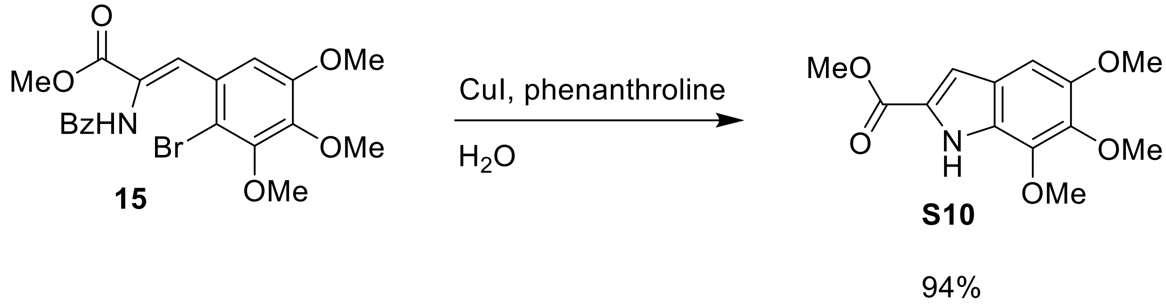

NBS
14
S8
84%
S9
85%

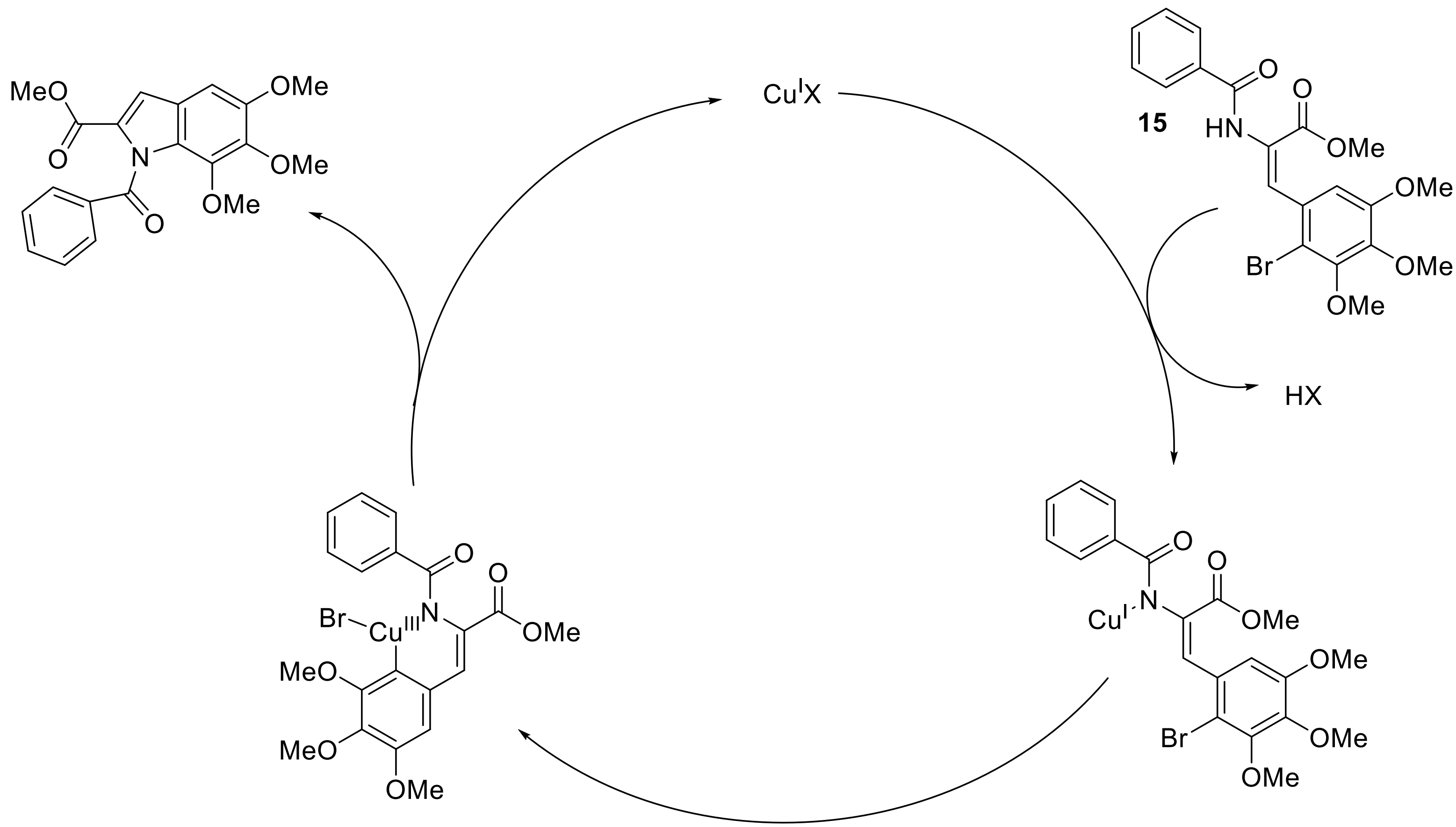

14
S8

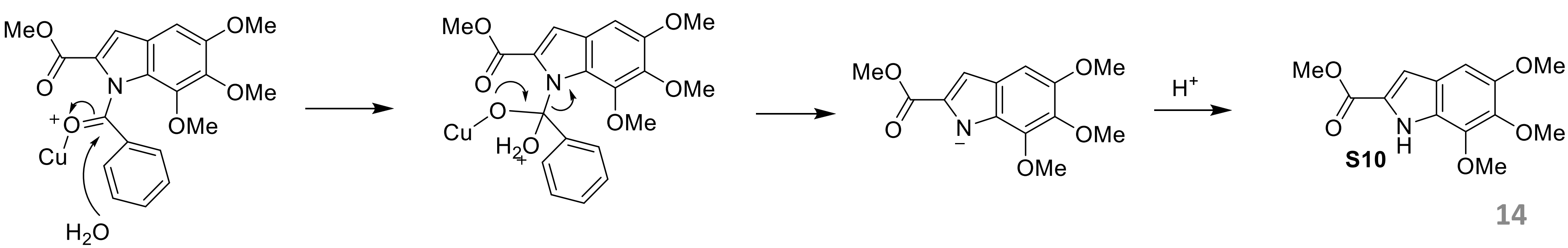

S8
H+
S9

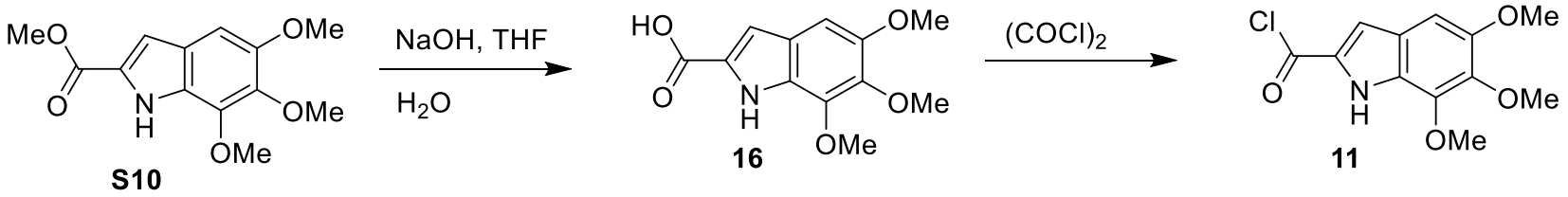

O
O
N
Br
Ph
OMe
OMe
OMe
S9
Et3N, MeOH
O
MeO
BzHN
Br
OMe
OMe
OMe
15
98%

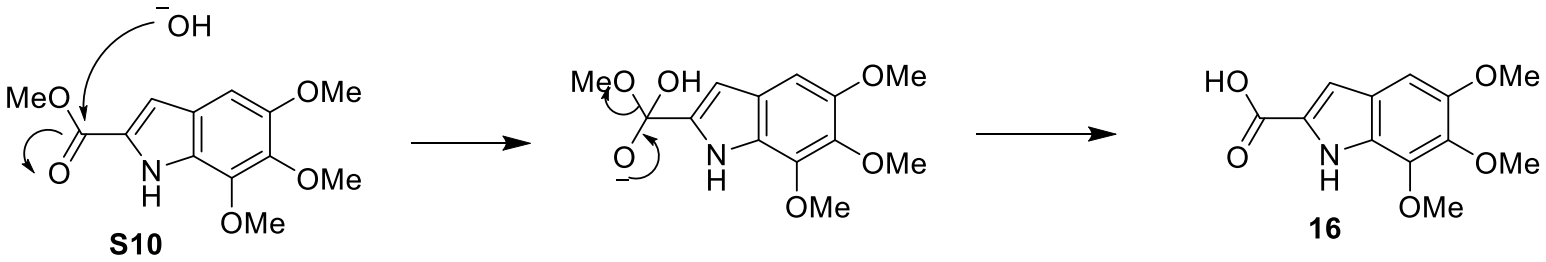

H−OMe
O
O
N
Br
Ph
OMe
OMe
OMe
S9
H
OMe
MeHO
Ph
N
O
proton transfer
MeO
BzHN
15

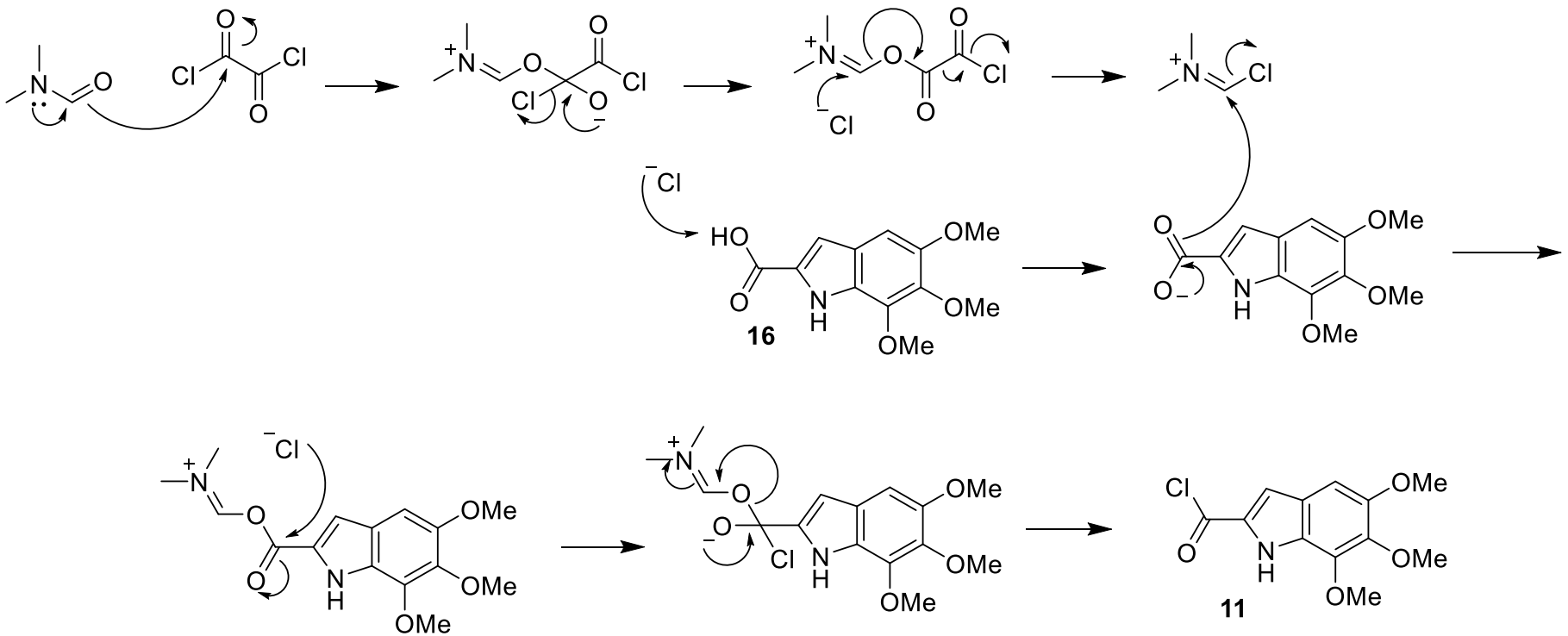

CuI, phenanthroline
H_2O
15
S10
94%

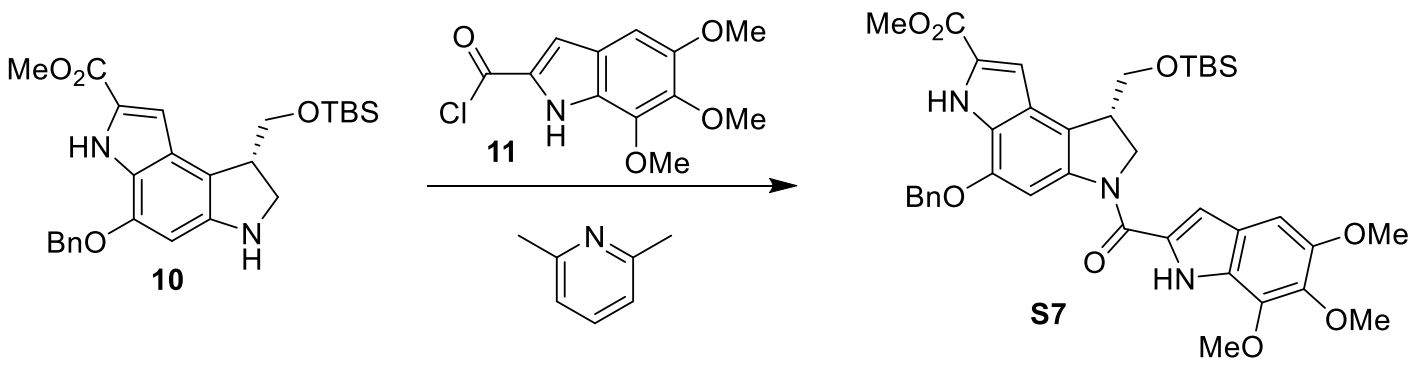

Cu^IX
15
HX

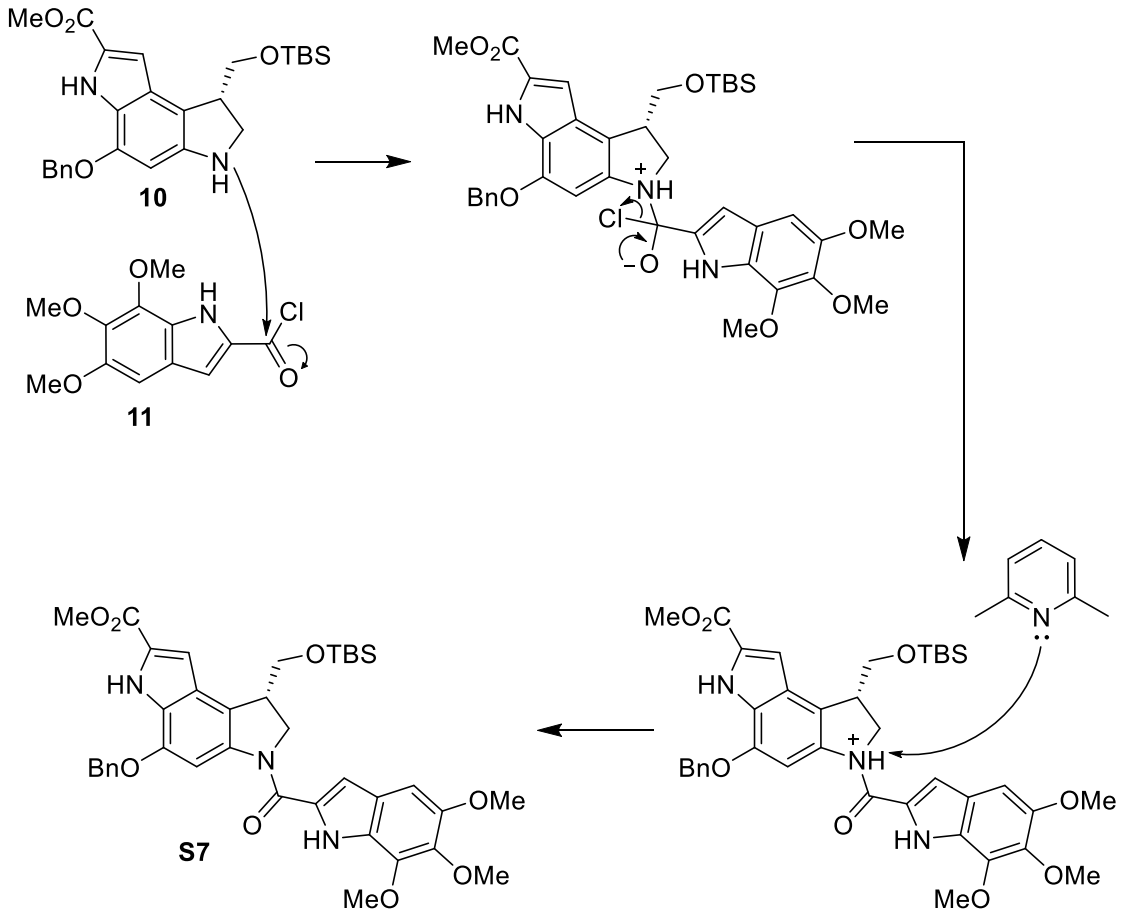

H_2O
H^+
S10

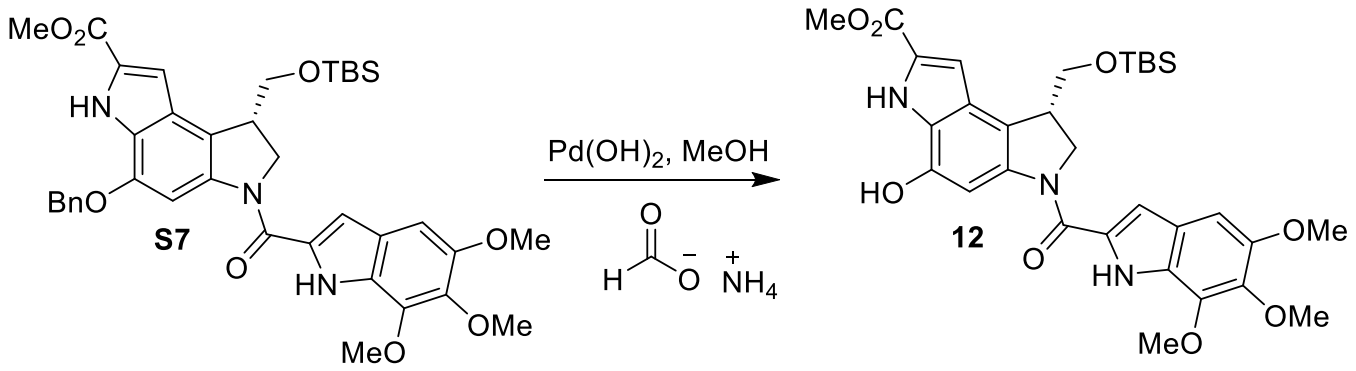

MeO
OMe
NaOH, THF
H2O
HO
(COCl)2
Cl
S10
16
11
87%
92%


OH
MeO
OMe
S10
16

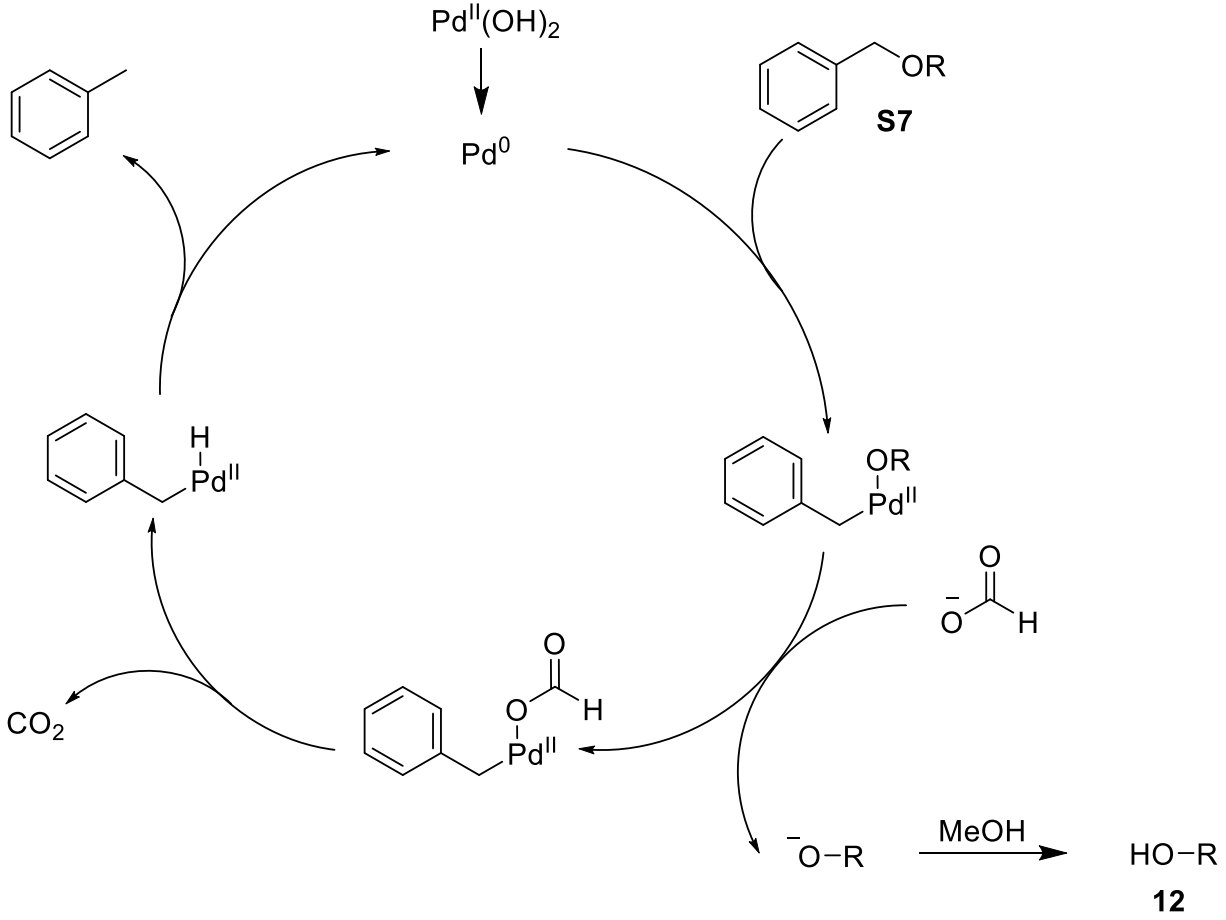

Cl
16
11

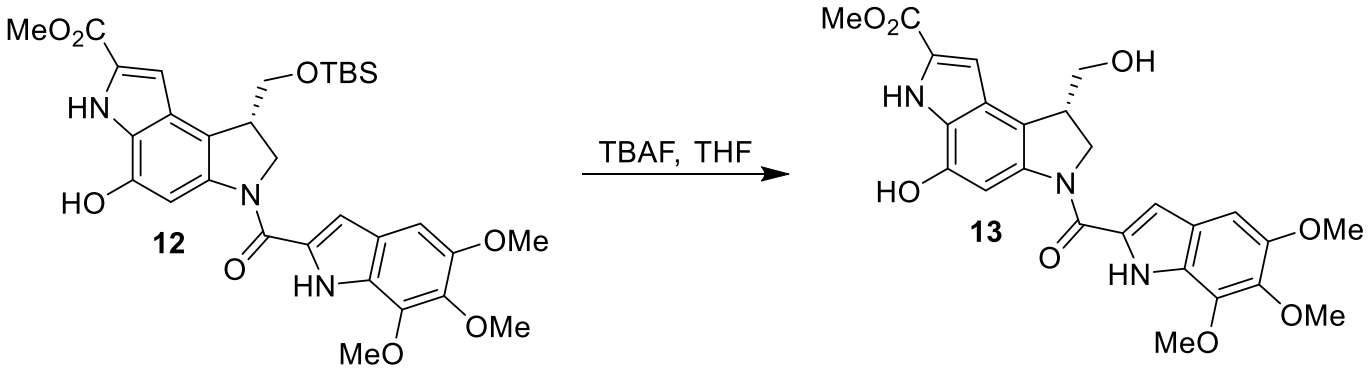

MeO2C
OTBS
HN
BnO
N
H
10
O
Cl
OMe
OMe
OMe
11
N
MeO2C
OTBS
HN
BnO
N
O
HN
OMe
OMe
MeO
S7


MeO2C
OTBS
HN
BnO
N
H
10
OMe
MeO
MeO
H
N
Cl
O
11
MeO2C
OTBS
HN
BnO
+
NH
Cl
–O
HN
OMe
OMe
MeO
N
MeO2C
OTBS
HN
BnO
+
NH
O
HN
OMe
OMe
MeO
MeO2C
OTBS
HN
BnO
N
O
HN
OMe
OMe
MeO
S7

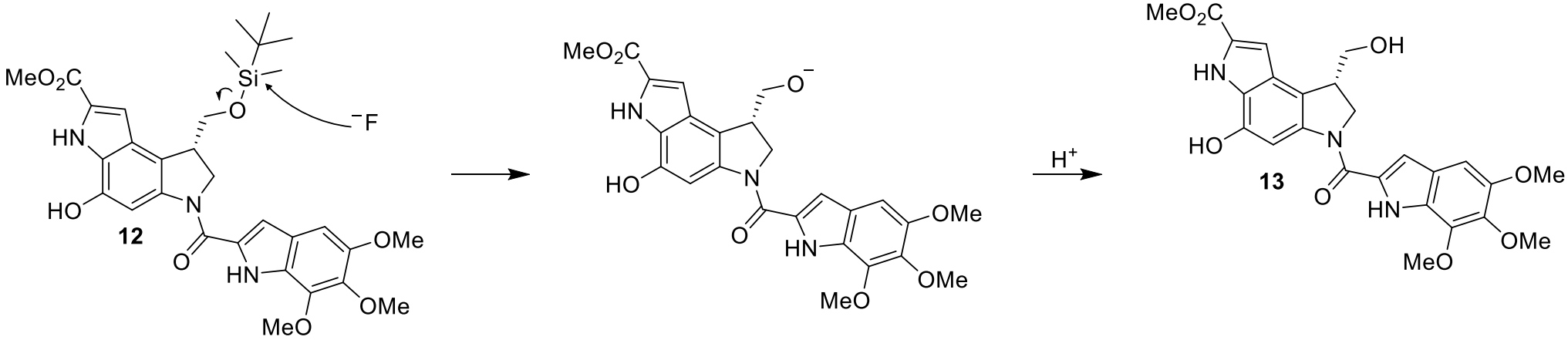

MeO2C
OTBS
HN
BnO
S7
N
O
HN
OMe
OMe
MeO
Pd(OH)2, MeOH
O
H
O
NH4
MeO2C
OTBS
HN
HO
12
N
O
HN
OMe
OMe
MeO

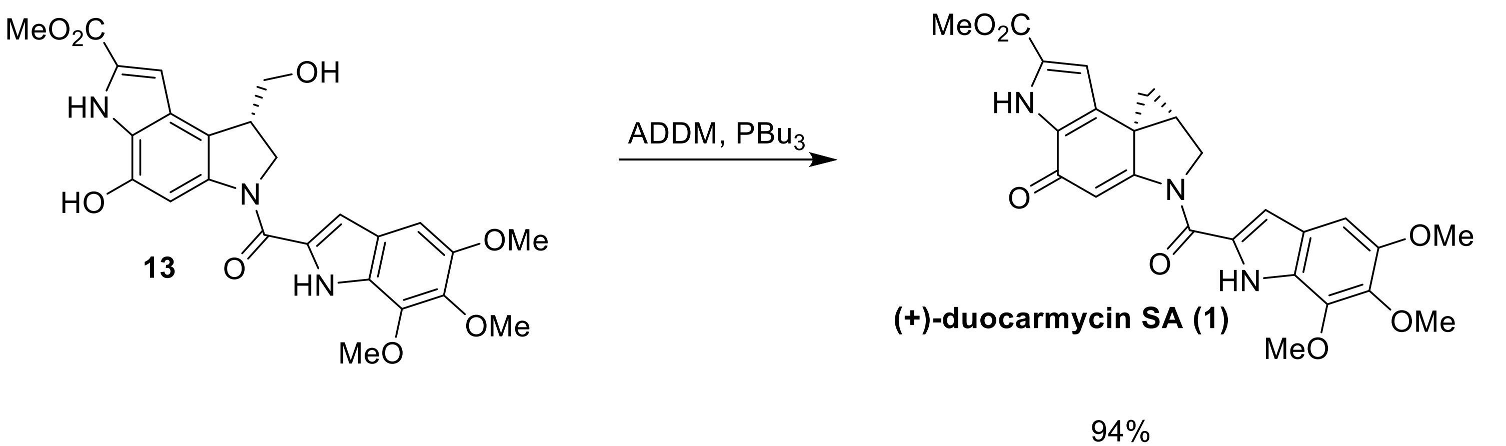
95% 2 steps

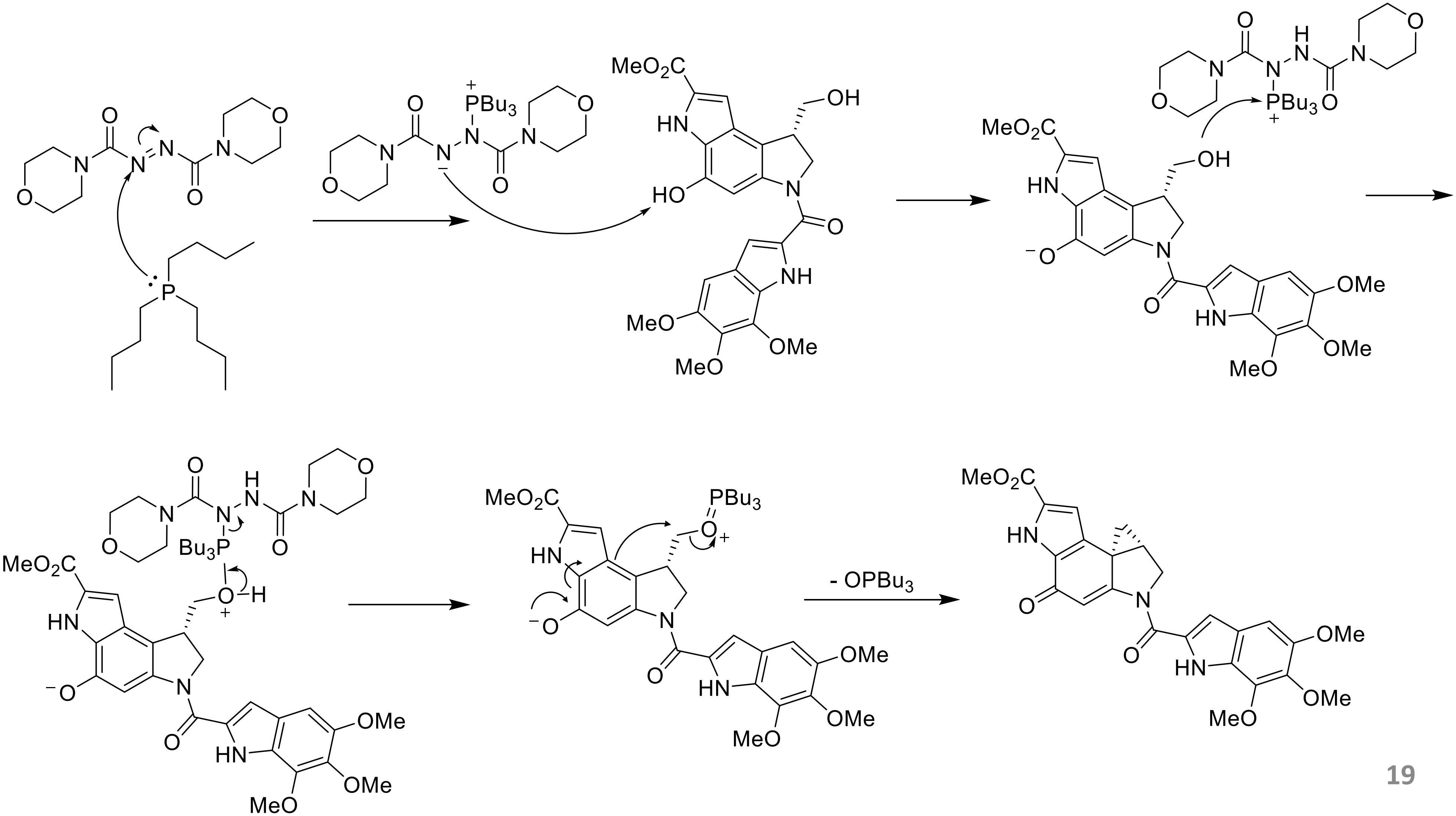

PdII(OH)2
Pd0
OR
S7
H
PdII
OR
PdII
O
O
H
O
H
PdII
CO2
−O−R
MeOH
HO−R
12


MeO2C
OTBS
HN
HO
12
N
O
HN
OMe
OMe
MeO
TBAF, THF
MeO2C
OH
HN
HO
13
N
O
HN
OMe
OMe
MeO

95%


MeO2C
Si
O
F
HN
HO
12
N
O
HN
OMe
OMe
MeO
MeO2C
O
HN
HO
N
O
HN
OMe
OMe
MeO
H+
MeO2C
OH
HN
HO
13
N
O
HN
OMe
OMe
MeO


MeO2C
OH
HN
HO
N
13
O
HN
OMe
MeO
OMe
ADDM, PBu3
(+)-duocarmycin SA (1)
94%


PBu3
- OPBu3