Total Synthesis of (–)-Histrionicotoxin through a Stereoselective Radical Translocation-Cyclization Reaction

Sato, M.; Azuma, H.; Daigaku, A.; Sato, S.; Takasu, K.; Okano, K.; Tokuyama, H. *Angew. Chem. Int. Ed.* **2017**, *56*, 1087.

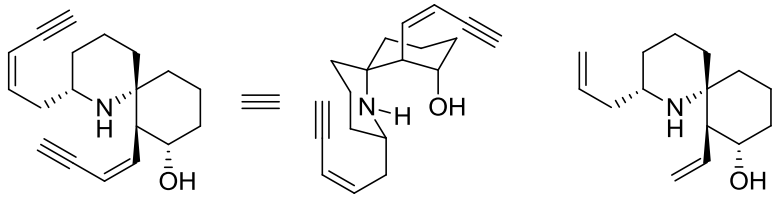
Histrionicotoxin (HTX) was isolated by Daly, Wiktop and coworkers from the poison-arrow frog Dendrobates histrionicus.

Posses activity as a noncompetitive blocker of nicotinic acetylcholine receptors.

HTX contains a 1-azaspiro[5.5]undecane core with two acid-labile *Z*- enyne side Chains.

Three total syntheses of optically active HTX and two total syntheses of racemic HTX have been reported previously.

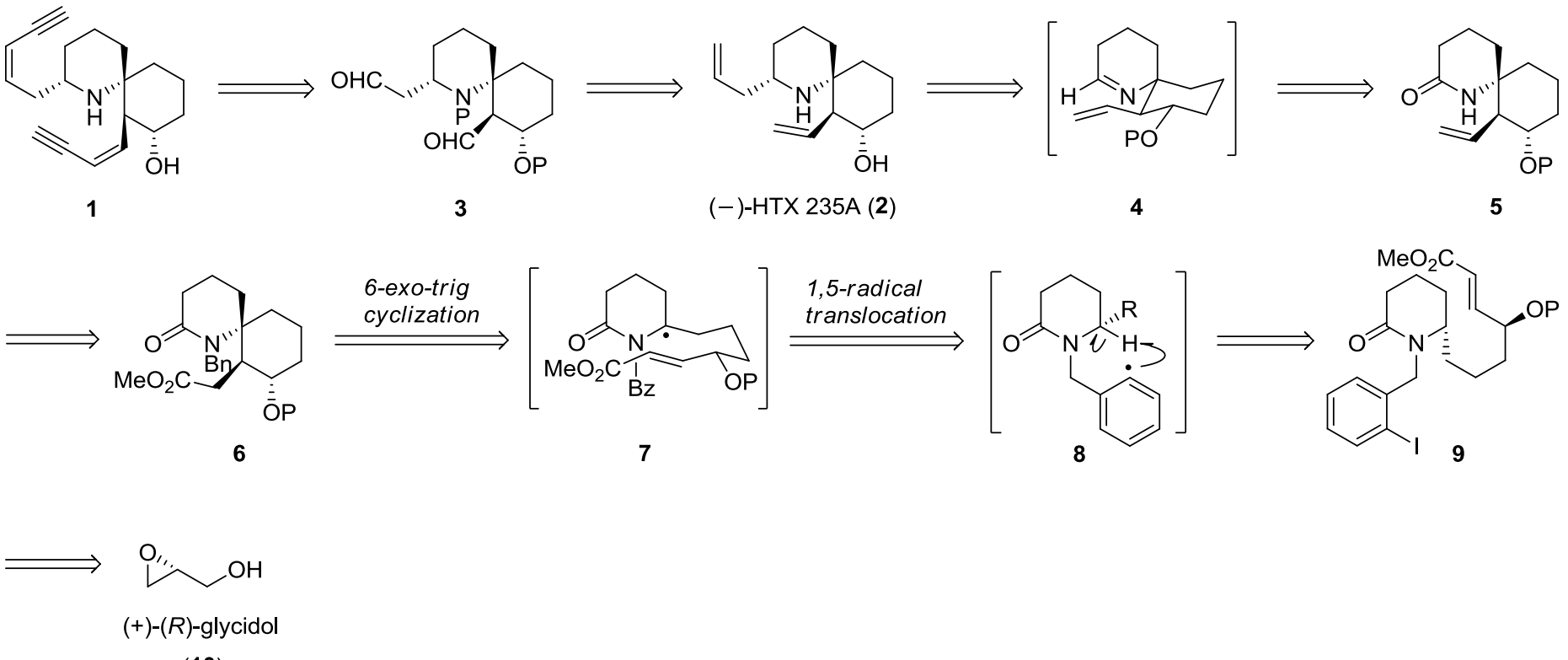
The current total synthesis is based on the construction of the 1-azaspiro[5,5]undecane core using a diastereoselective radical translocation-cyclization cascade



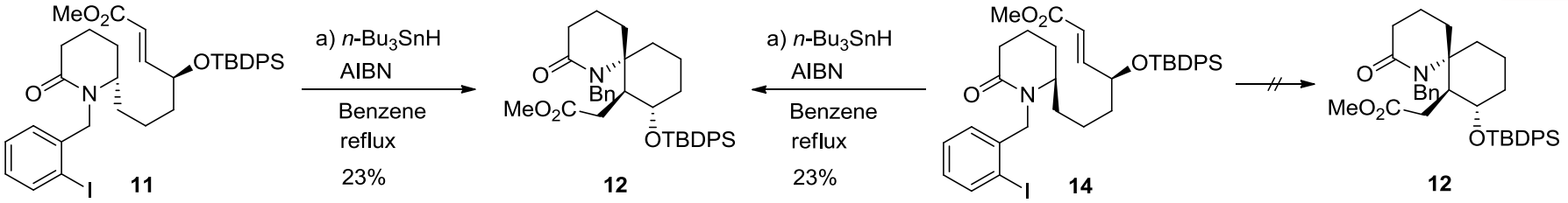
(−)-histrionicotoxin (HTX: **1**)

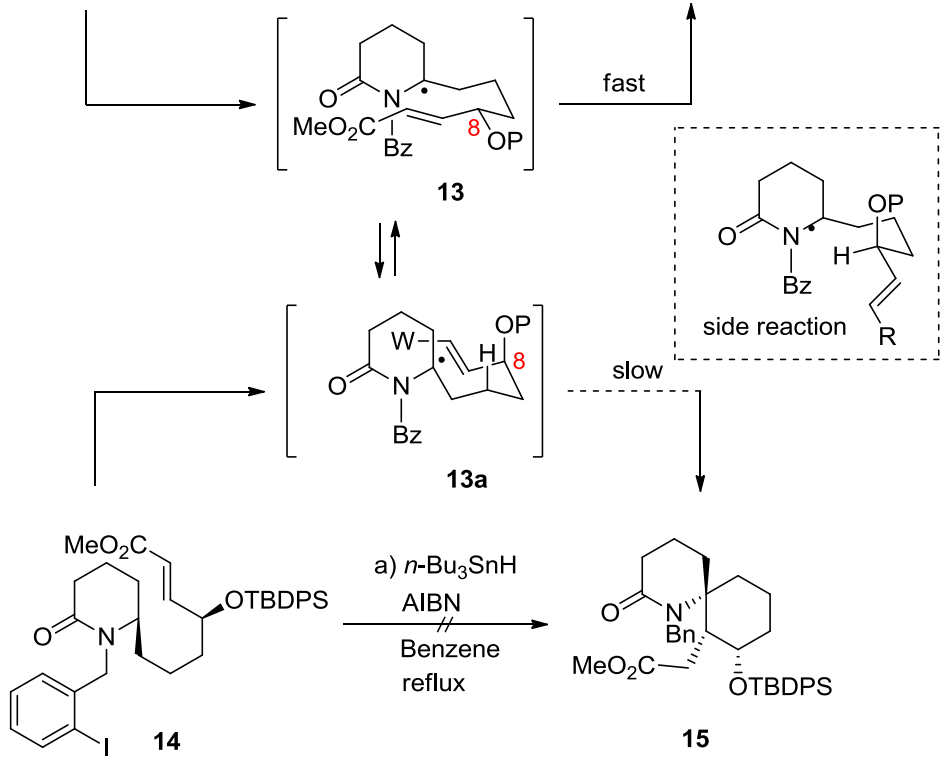
(−)-HTX 235A (**2**)

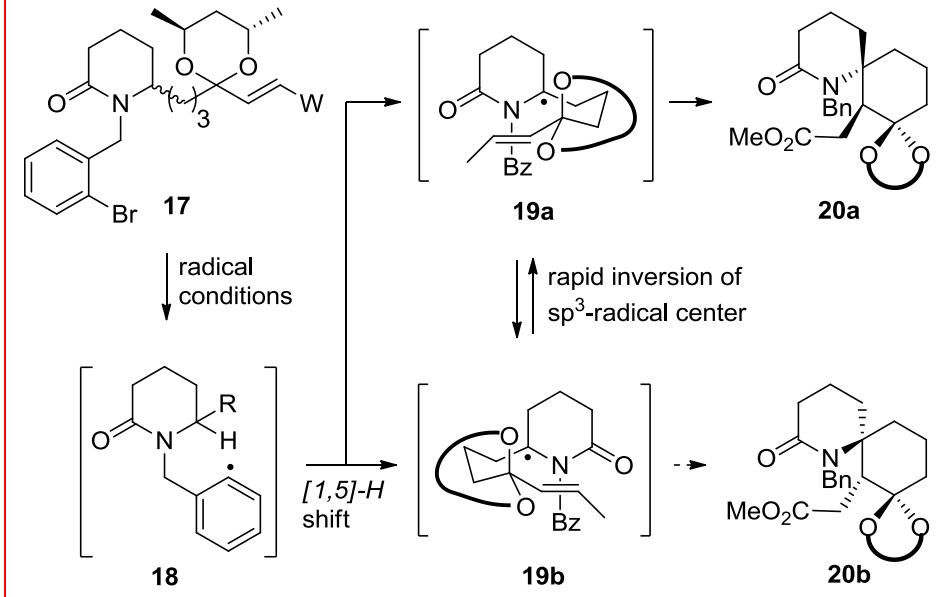
Retro-synthetic analysis



Synthetic approach and mechanistic explanation







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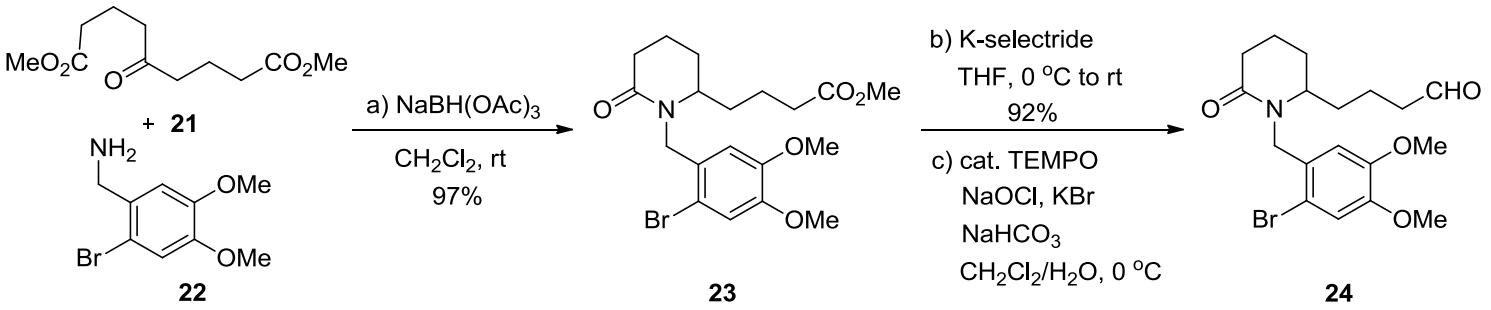
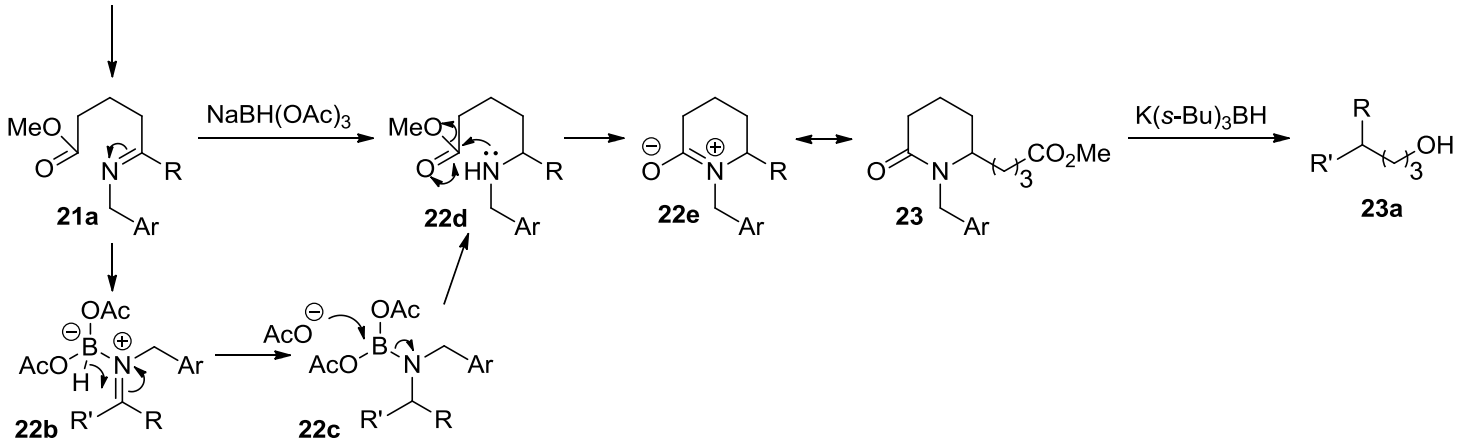
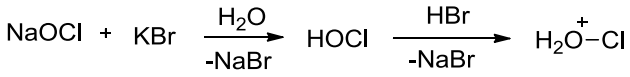
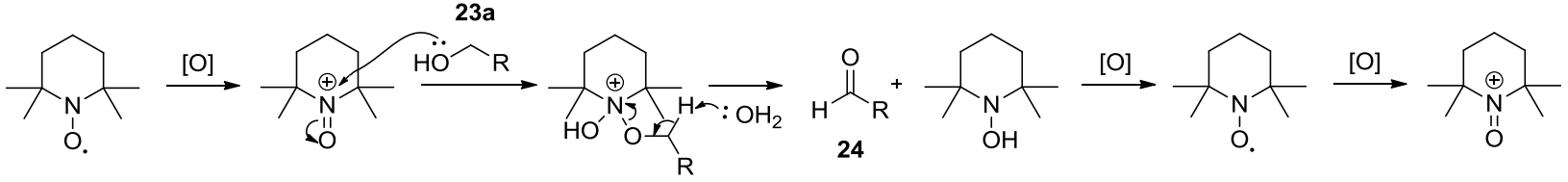




Alcohol to aldehyde





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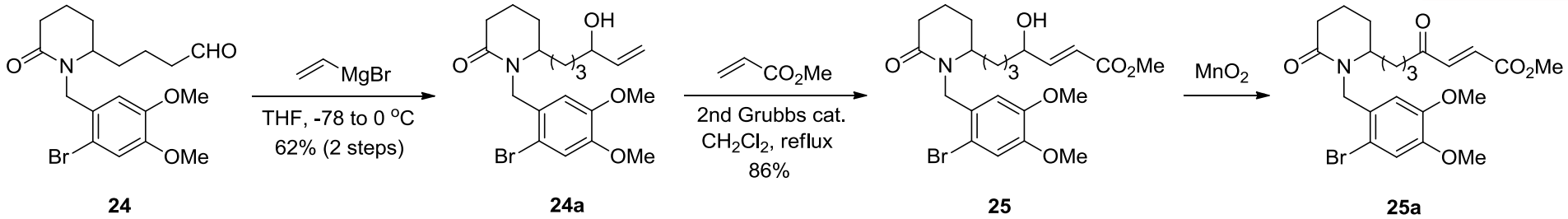
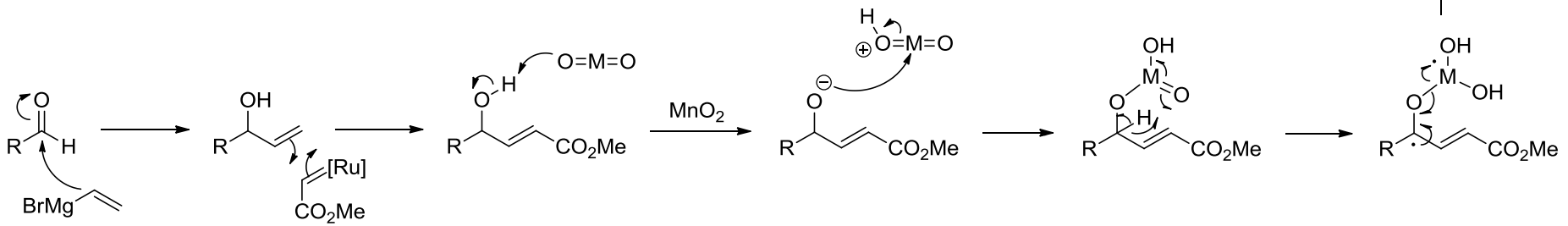
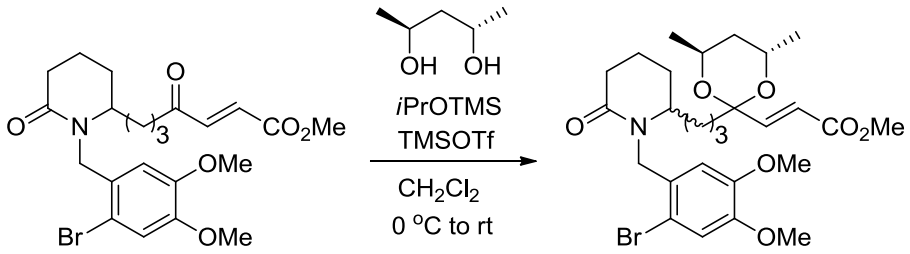


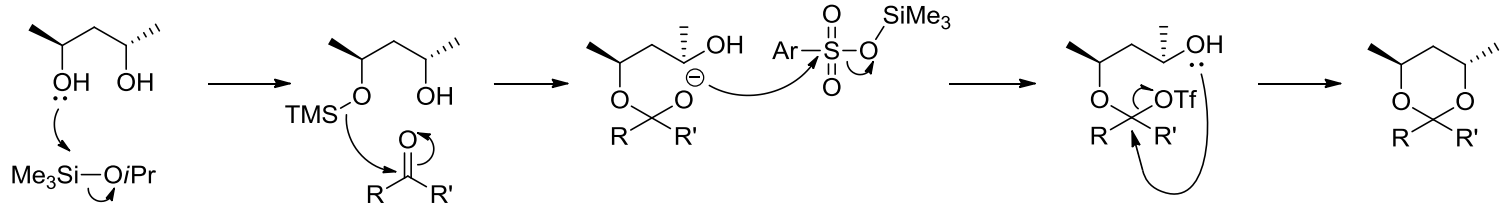
24 **24a** **25** **25a**





25a **26**

1:1 mixture of diastereomers



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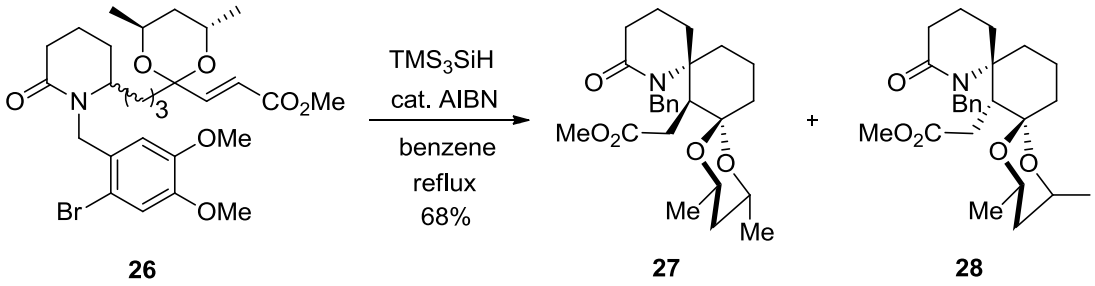
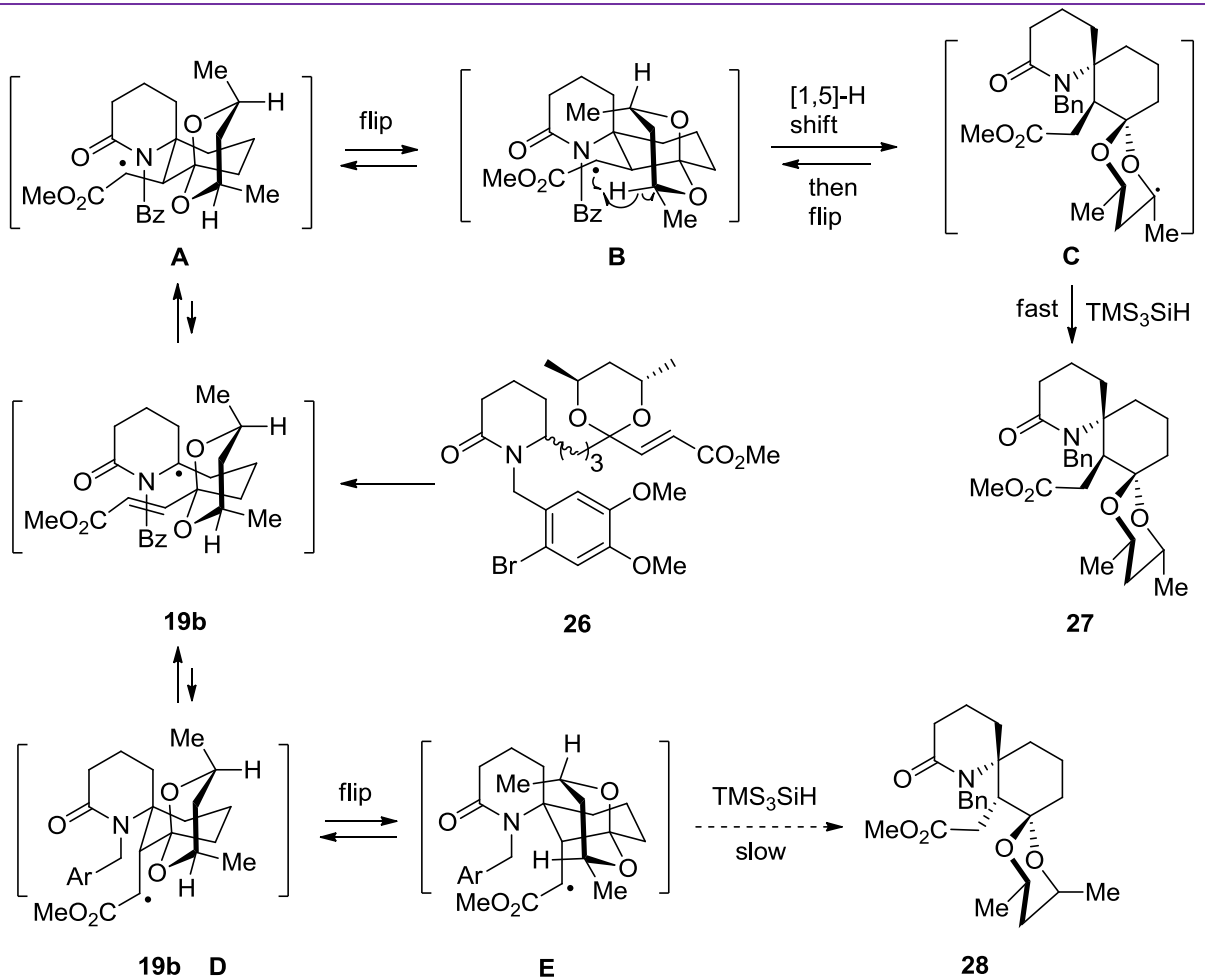
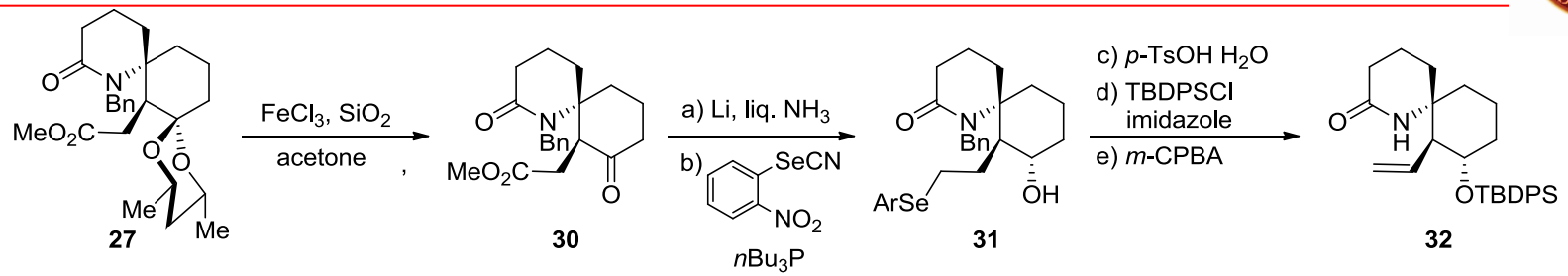
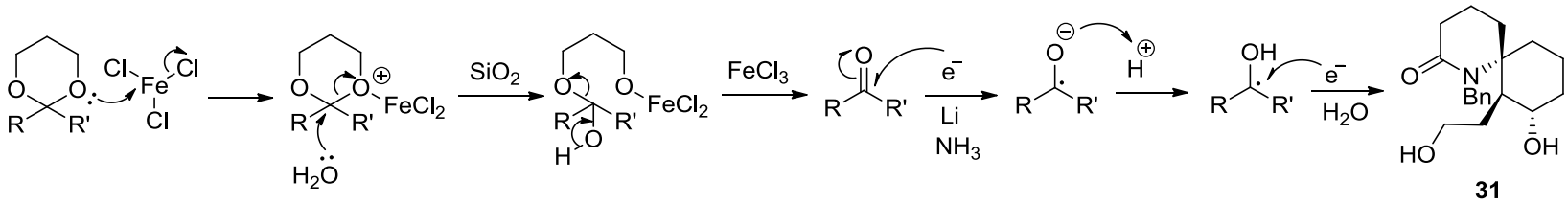
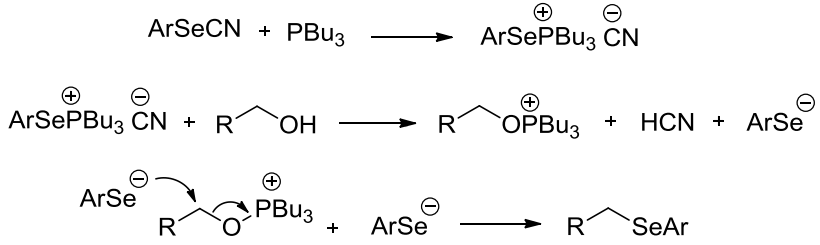

TMS3SiH
cat. AIBN
benzene
reflux
68%
26
27
28

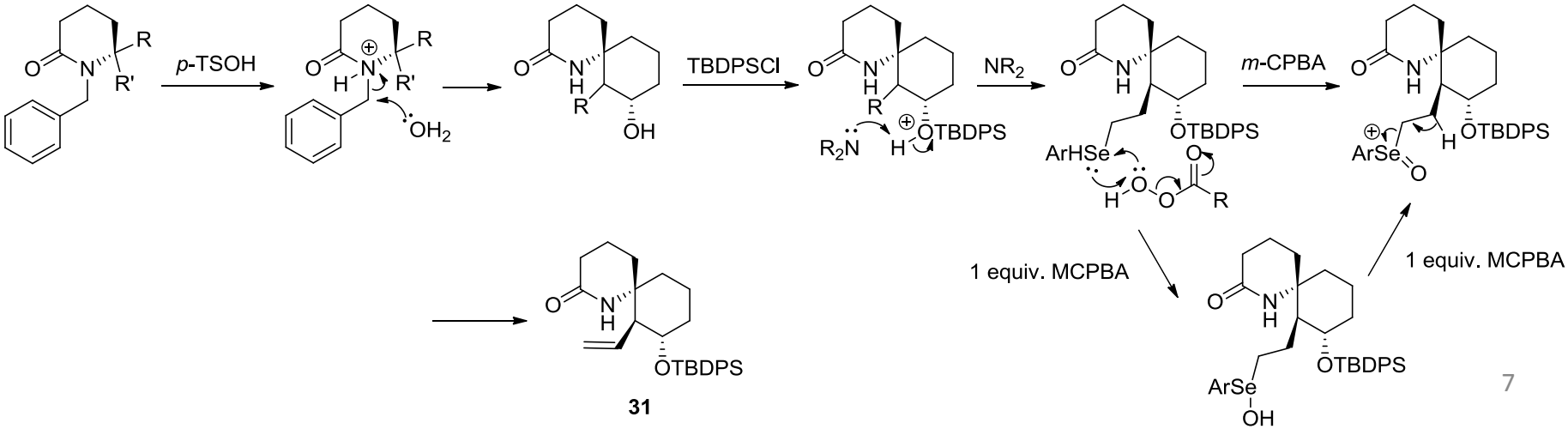

flip
[1,5]-H
shift
then
flip
fast
TMS3SiH
A
B
C
19b
26
27
19b D
E
28
slow

Contd.

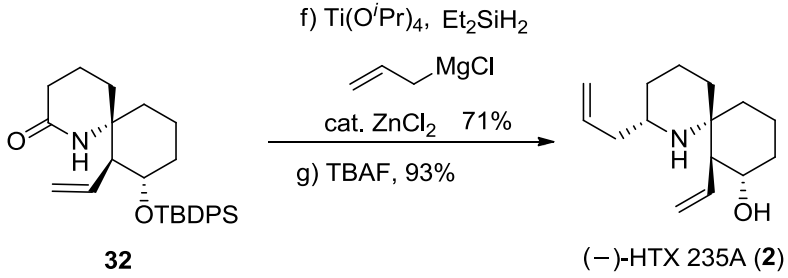

FeCl3, SiO2
acetone
a) Li, liq. NH3
b)
SeCN
NO2
nBu3P
c) p-TsOH H2O
d) TBDPSCl
imidazole
e) m-CPBA
27
30
31
32


SiO2
FeCl3
e−
Li
NH3
H2O
31

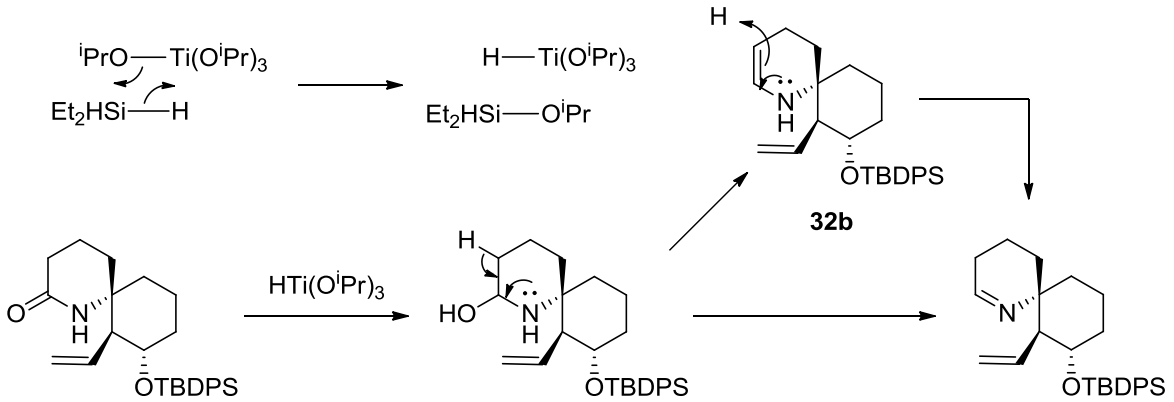

ArSeCN + PBu3
ArSePBu3 CN
ArSePBu3 CN + ROH
ROPBu3 + HCN + ArSe
ArSe + PBu3 + ArSe
SeAr


p-TSOH
TBDPSCl
NR2
m-CPBA
1 equiv. MCPBA
1 equiv. MCPBA
31

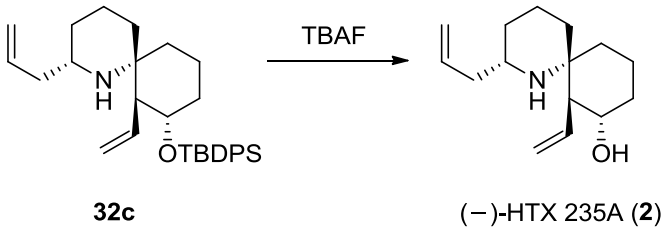
Contd.



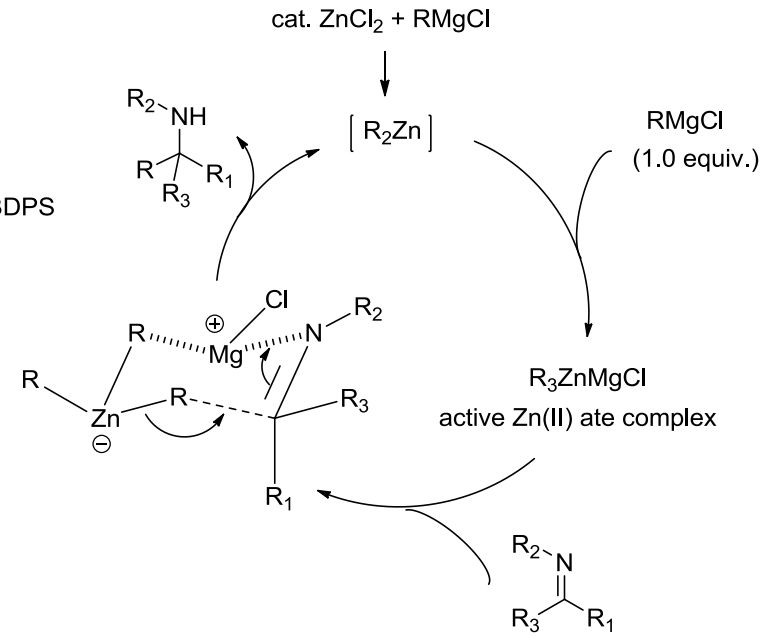
32 (−)-HTX 235A (**2**)



32 **32a** **32b** **32c**



32c (−)-HTX 235A (**2**)



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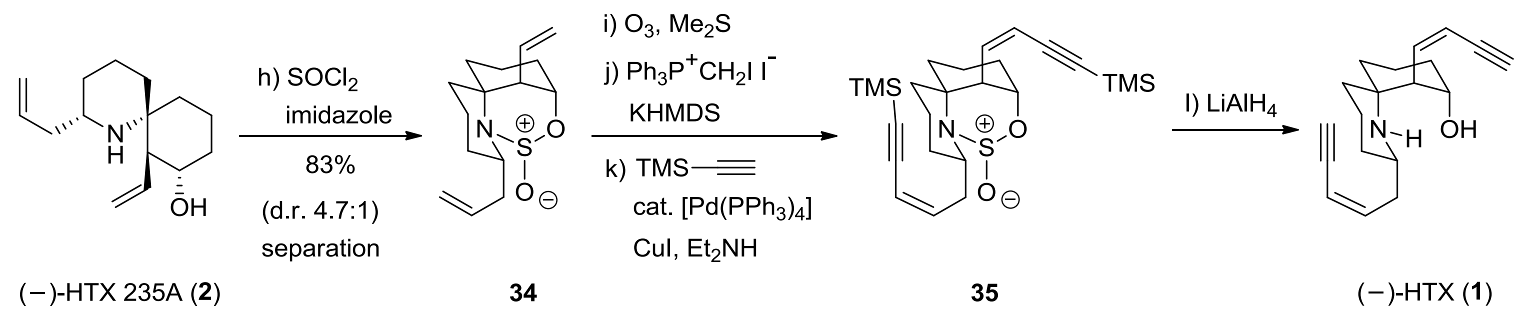
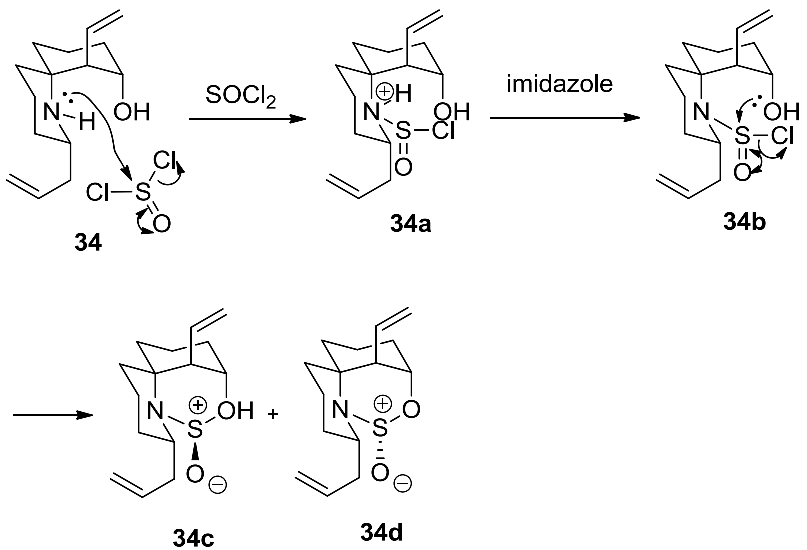
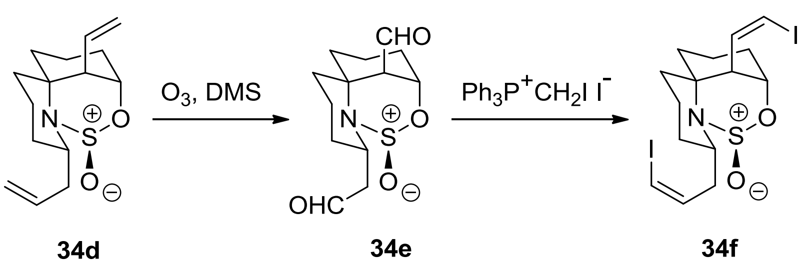


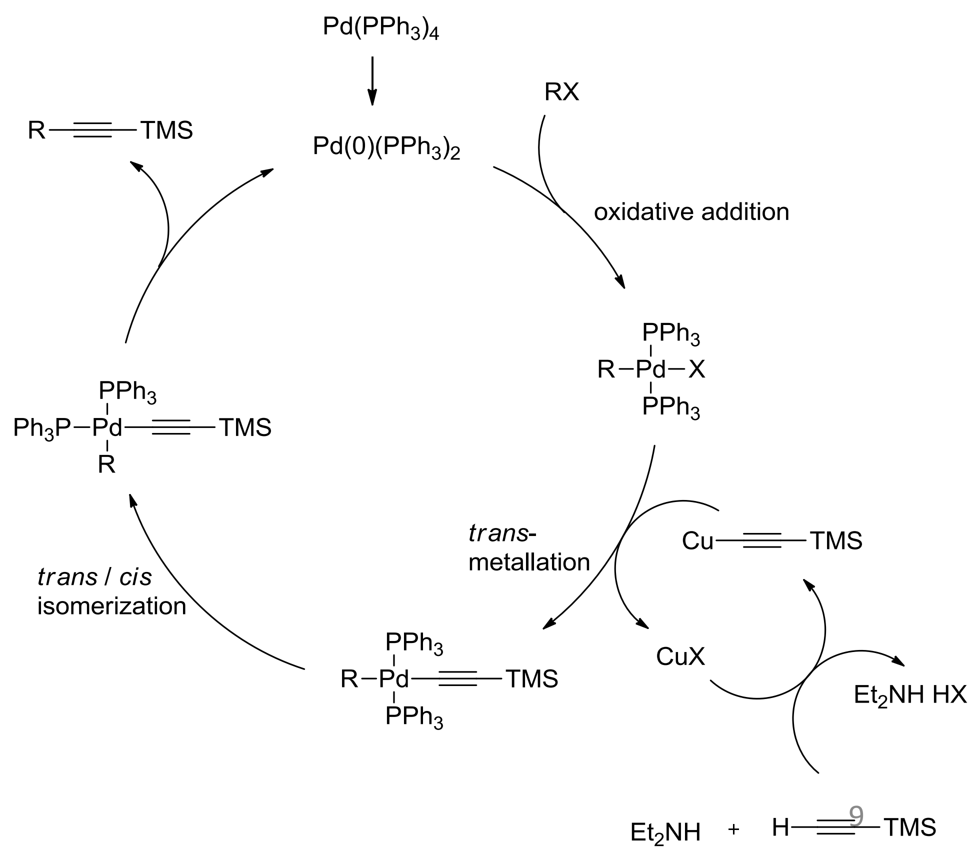
h) SOCl2
imidazole
83%
(d.r. 4.7:1)
separation
i) O3, Me2S
j) Ph3P+CH2I I-
KHMDS
k) TMS
cat. [Pd(PPh3)4]
CuI, Et2NH
TMS
TMS
l) LiAlH4
OH
(−)-HTX 235A (2)
34
35
(−)-HTX (1)



SOCl2
imidazole
34
34a
34b
34c
34d



O3, DMS
CHO
OHC
Ph3P+CH2I I-
34d
34e
34f



Pd(PPh3)4
Pd(0)(PPh3)2
RX
oxidative addition
R—TMS
trans-
metallation
trans / cis
isomerization
Cu—TMS
CuX
Et2NH HX
Et2NH + H—TMS