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Communication

Total Synthesis Provides Strong Evidence: Xestocyclamine A is the Enantiomer of Ingenamine

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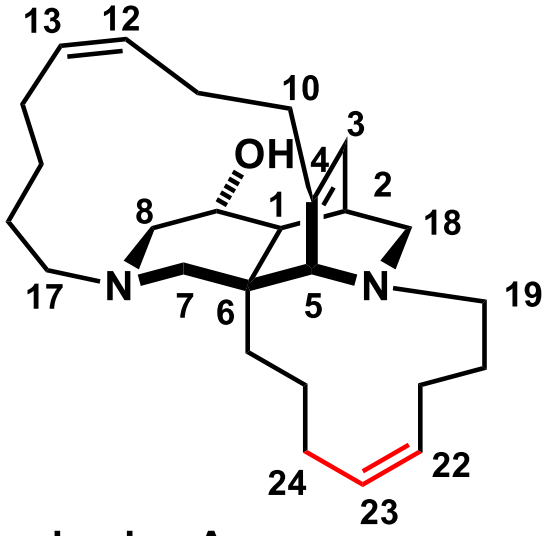
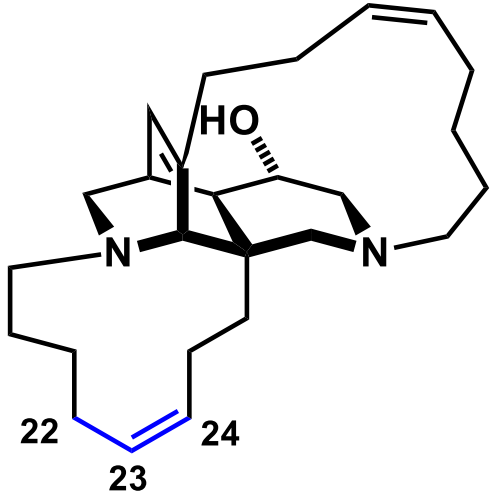
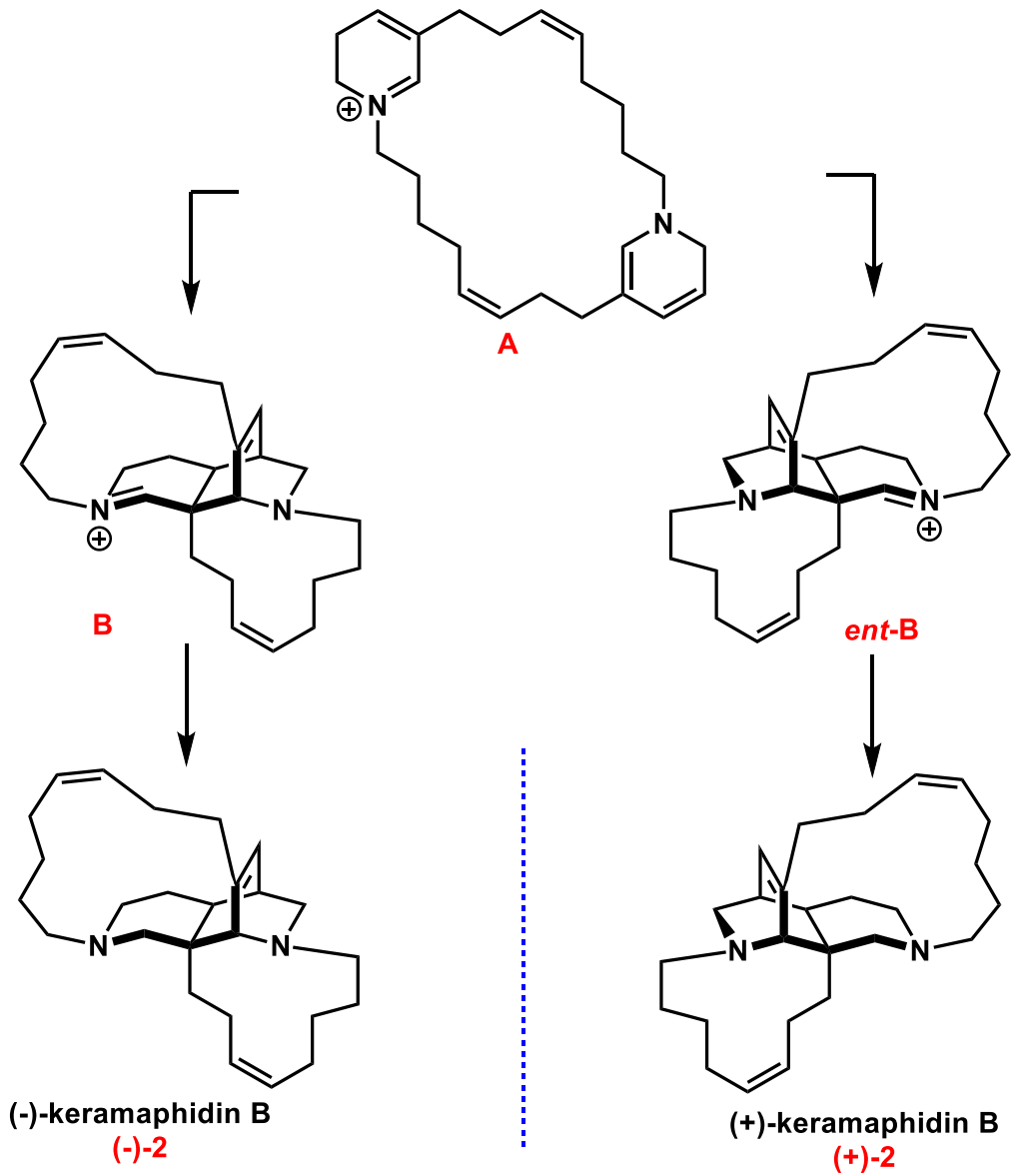


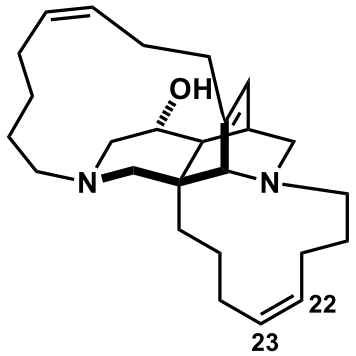
Xestocyclamine A
originally proposed structure



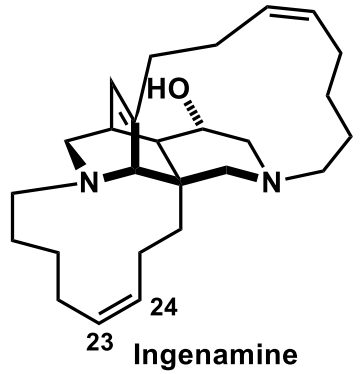
Ingenamine A

Scheme 1. Biosynthetic Reasoning and Structures of Some Alkylpyridine-Derived Alkaloids



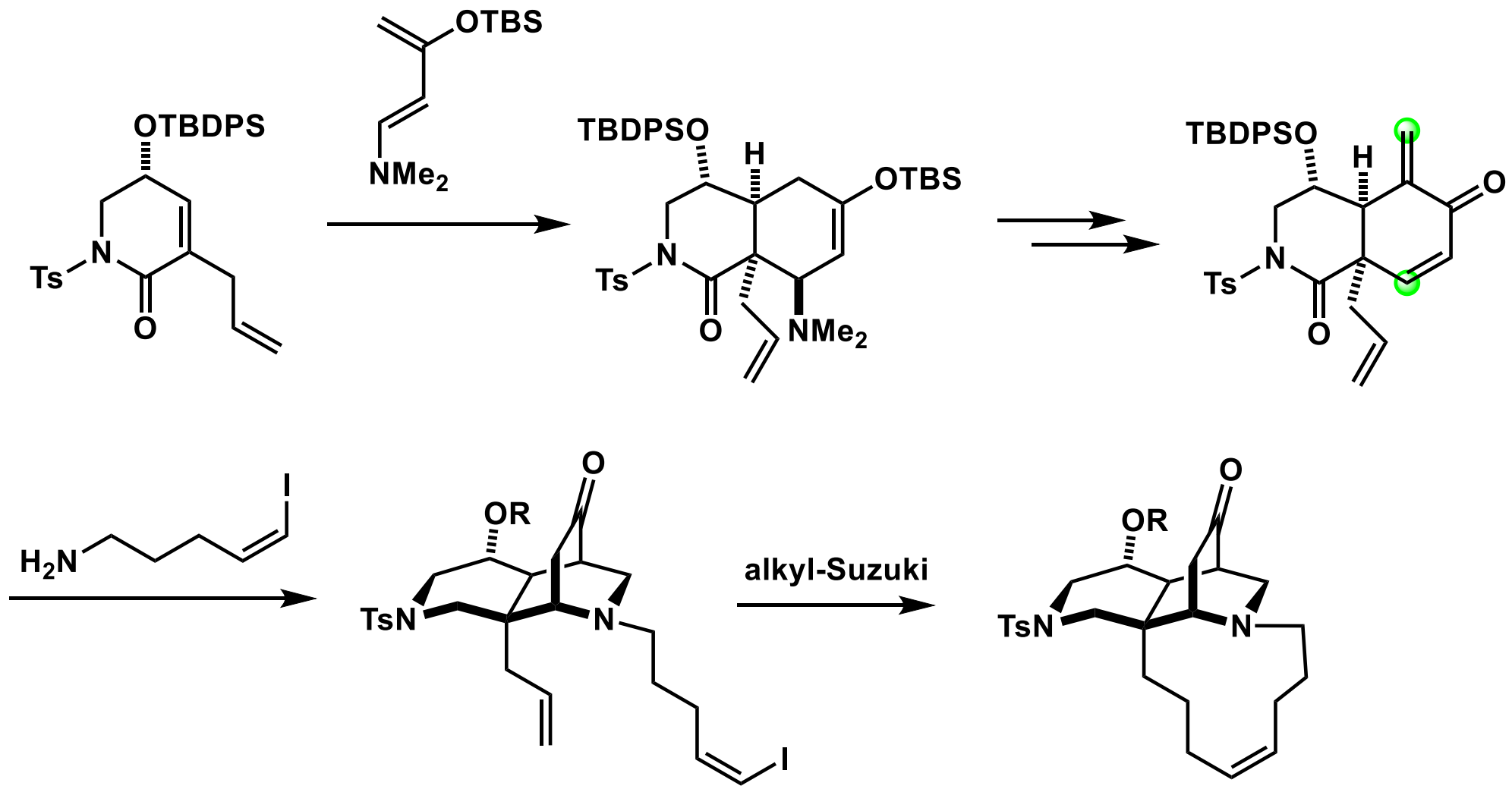


Xestocyclamine A
(-)-1
as originally assigned

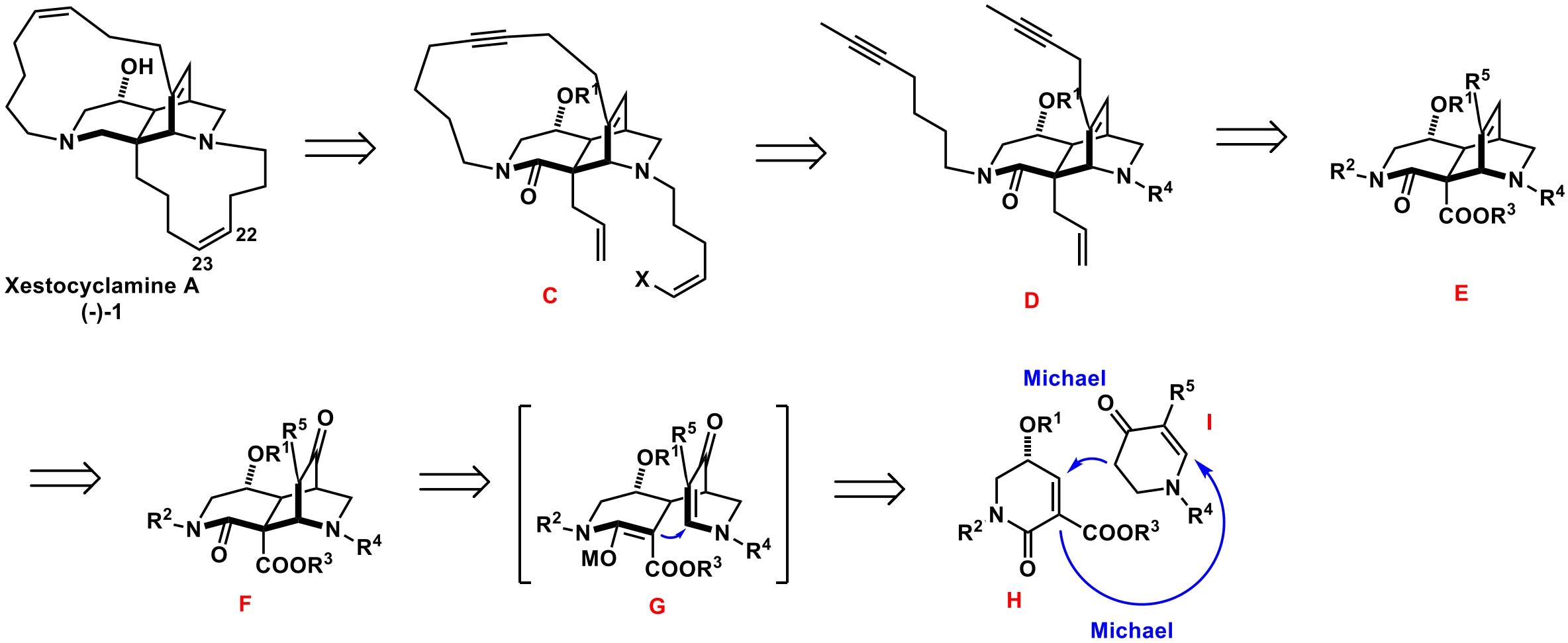


Ingenamine
(+)-3

Scheme 2. Major Literature Precedent: The Danishefsky Model Study



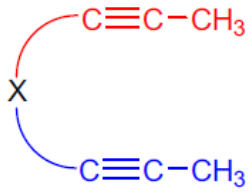
Scheme 3. Retrosynthetic Analysis

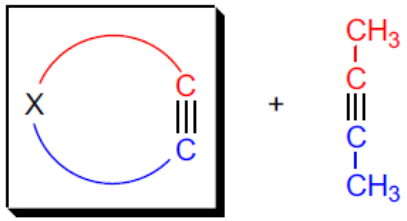


alkyne metathesis

a) $R^1-C\equiv C-R^1$ + $R^2-C\equiv C-R^2$ ⇌ (or) $(t\text{-BuO})_3W\equiv C-t\text{-Bu}$ ⇌ 2 $R^1-C\equiv C-R^2$

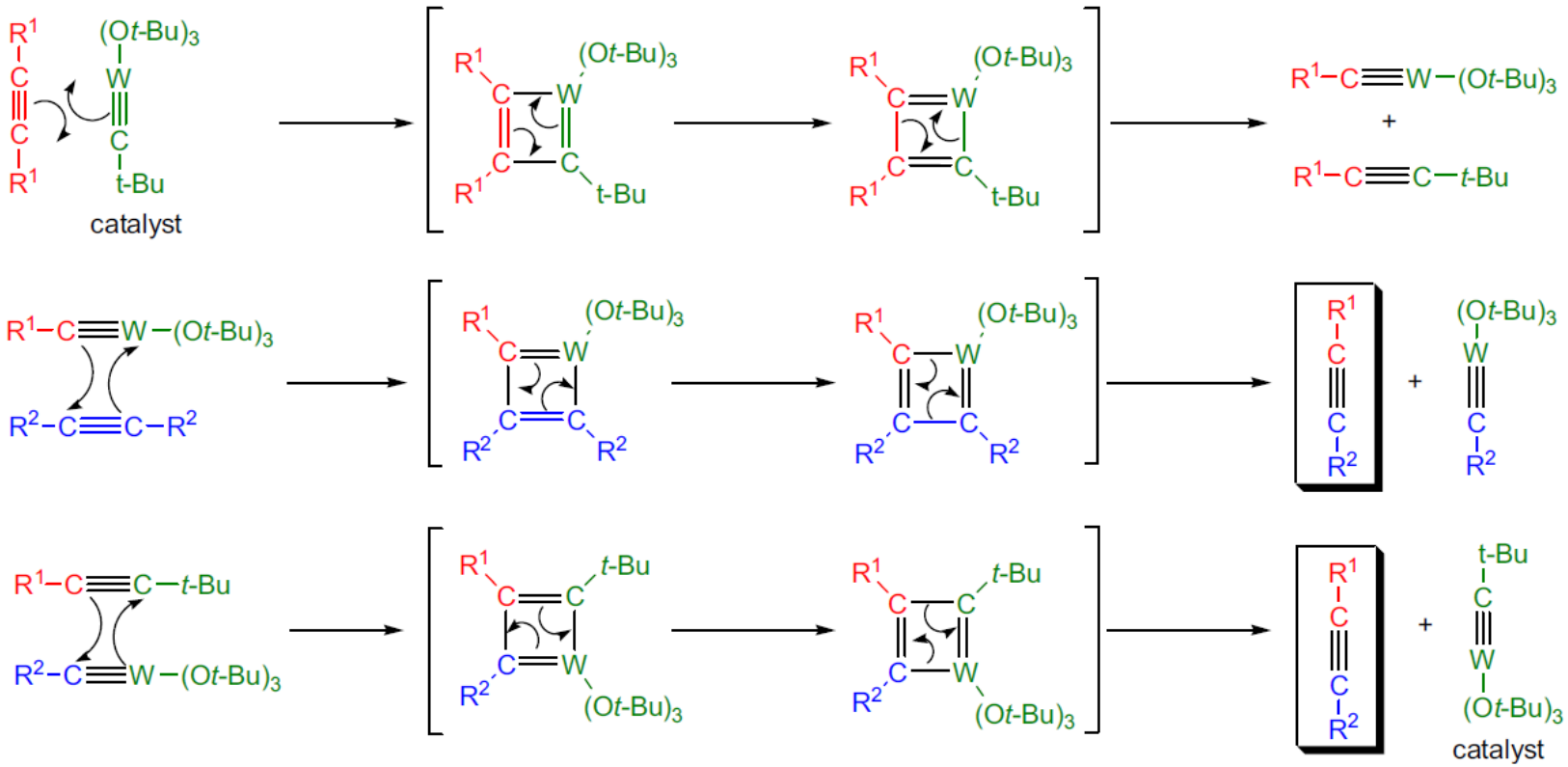
Alkyne cross metathesis

b) 

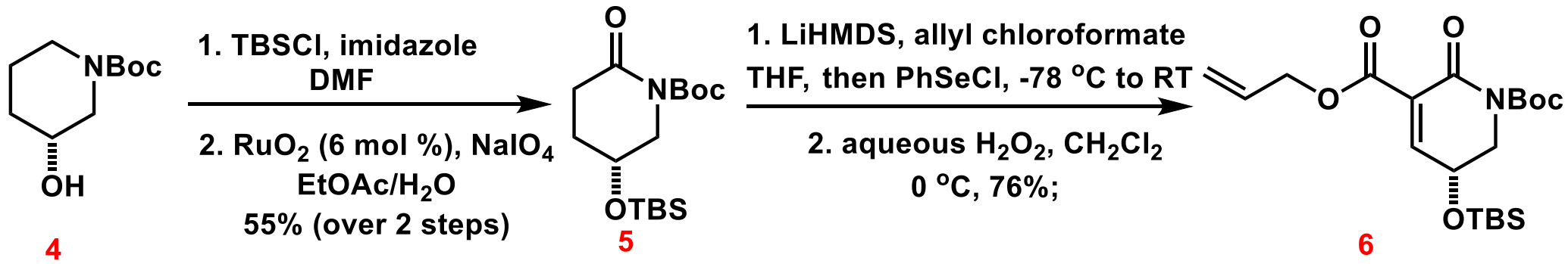
$(t\text{-BuO})_3W\equiv C-t\text{-Bu}$ →


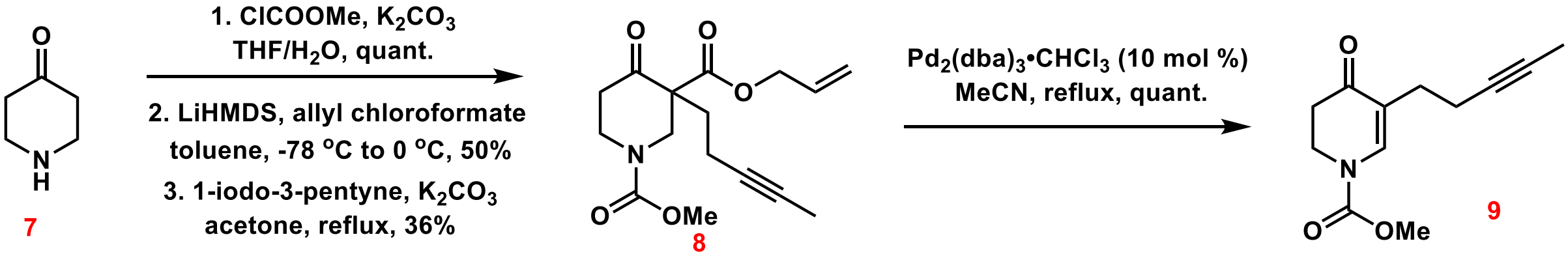
+

RCAM
Ring-closing alkyne metathesis

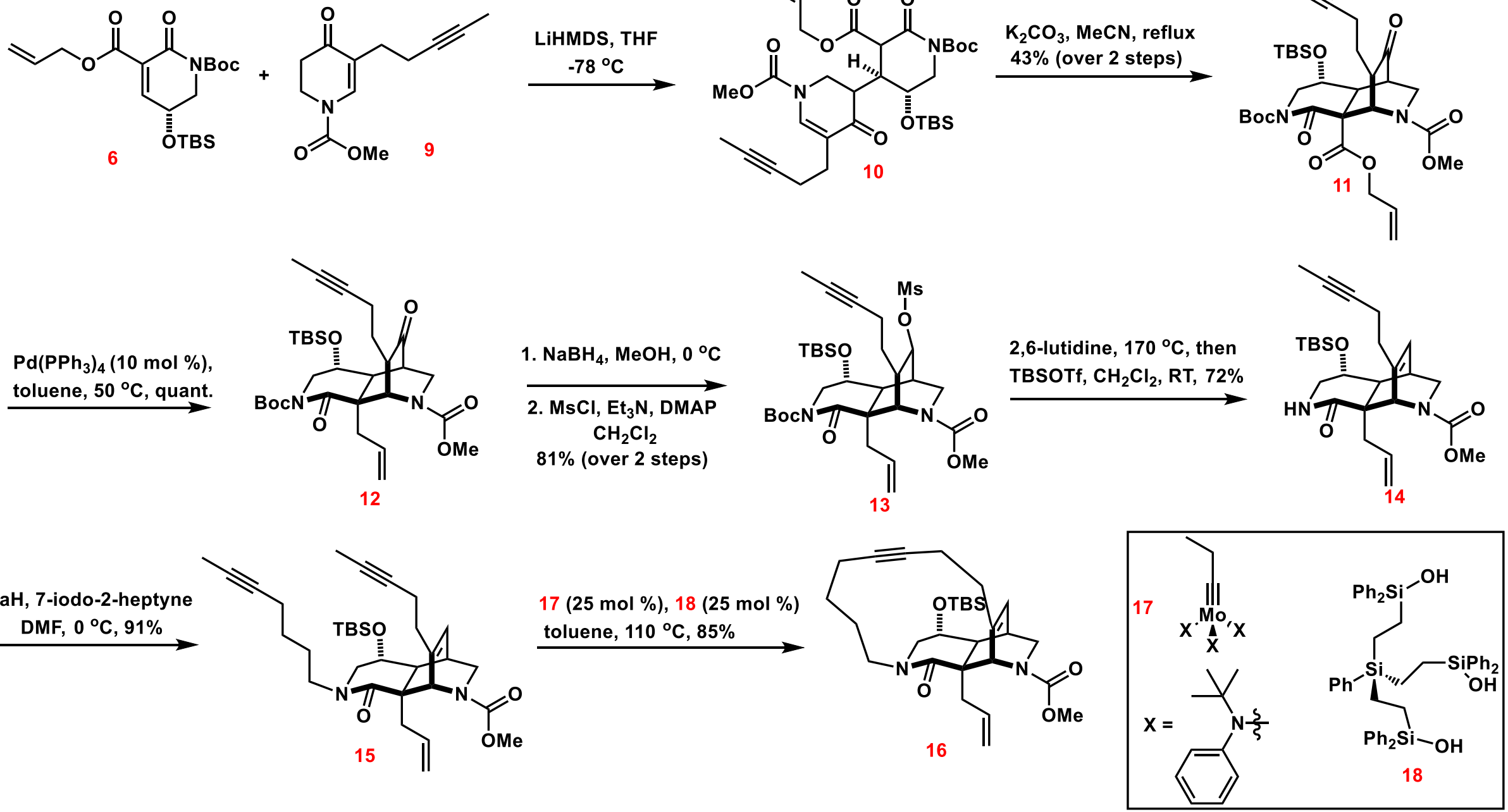


Scheme 4

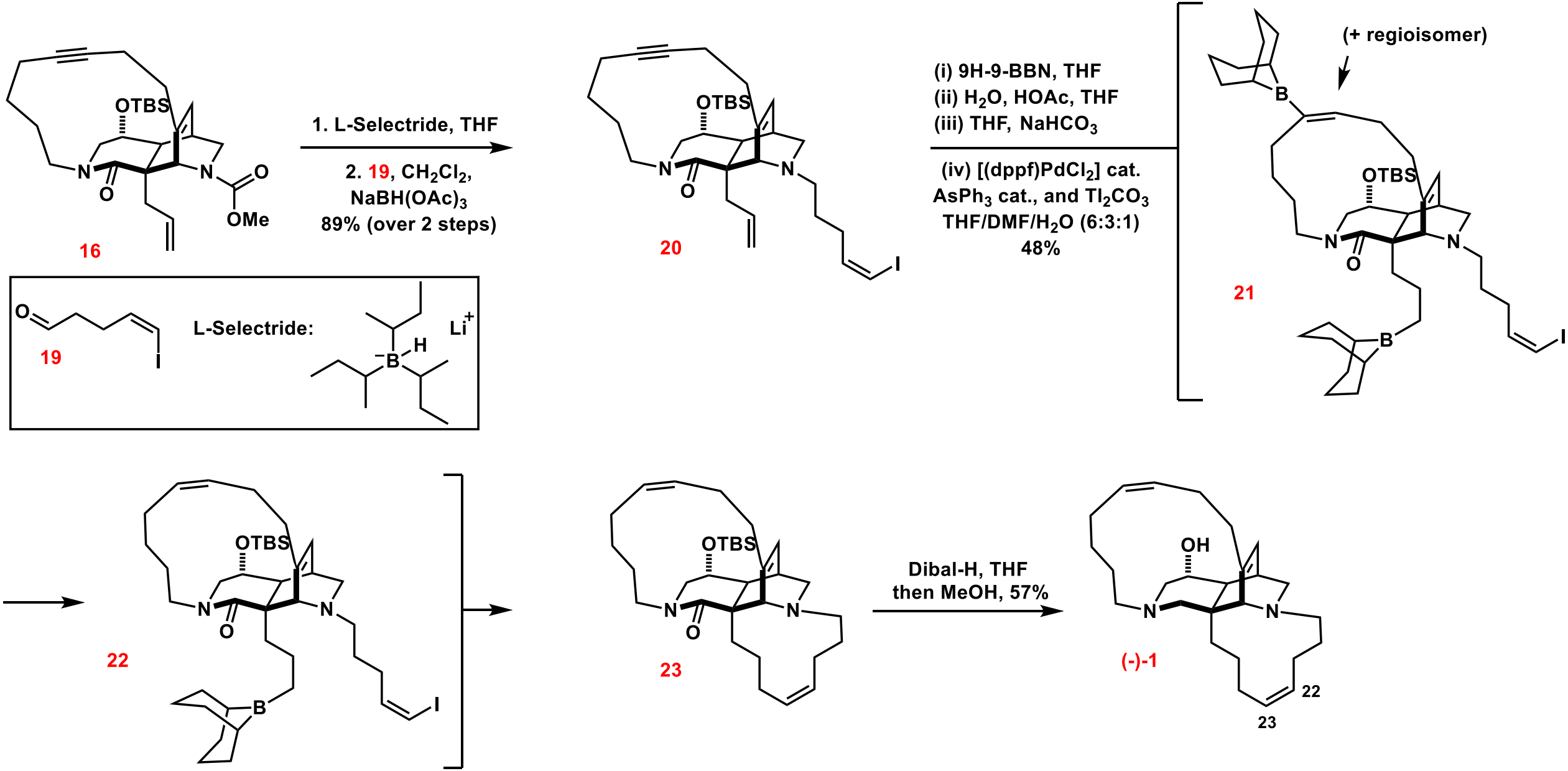

NBoc
OH
4
1. TBSCl, imidazole
DMF
2. RuO2 (6 mol %), NaIO4
EtOAc/H2O
55% (over 2 steps)
O
NBoc
OTBS
5
1. LiHMDS, allyl chloroformate
THF, then PhSeCl, -78 °C to RT
2. aqueous H2O2, CH2Cl2
0 °C, 76%;
O
O
O
NBoc
OTBS
6


O
N
H
7
1. ClCOOMe, K2CO3
THF/H2O, quant.
2. LiHMDS, allyl chloroformate
toluene, -78 °C to 0 °C, 50%
3. 1-iodo-3-pentyne, K2CO3
acetone, reflux, 36%
O
O
O
N
O
OMe
8
Pd2(dba)3•CHCl3 (10 mol %)
MeCN, reflux, quant.
O
N
O
OMe
9

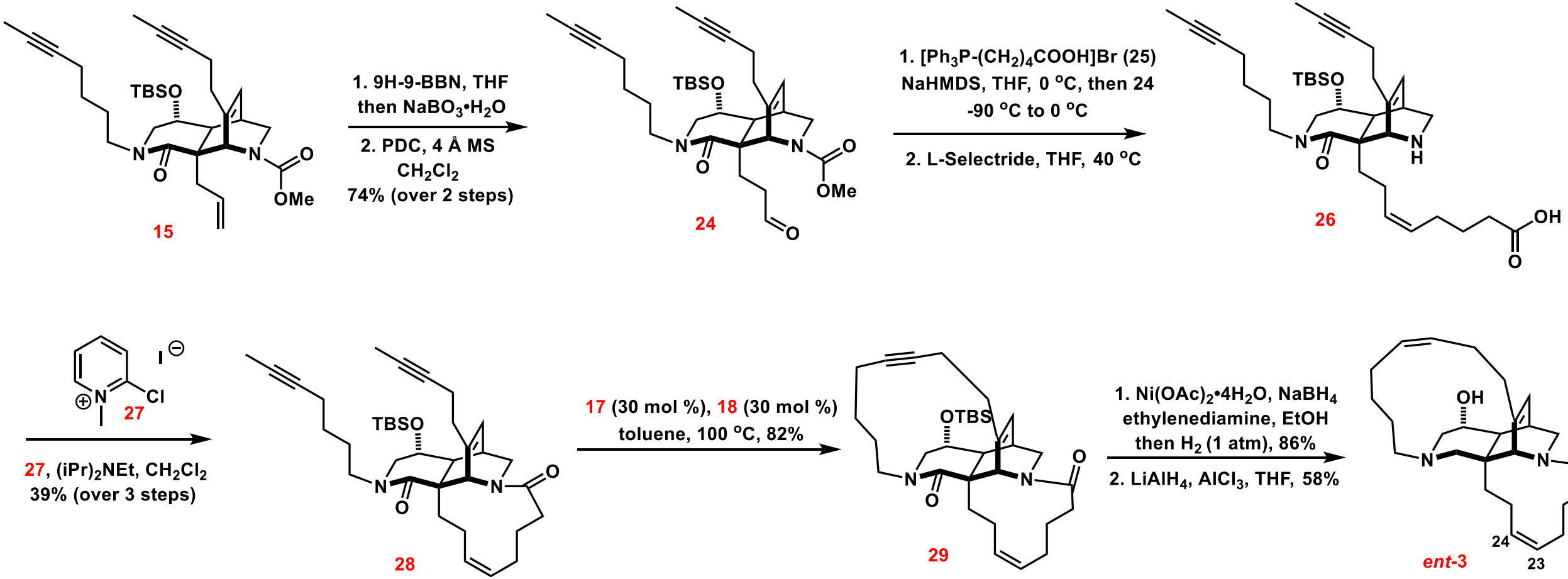
Scheme 5

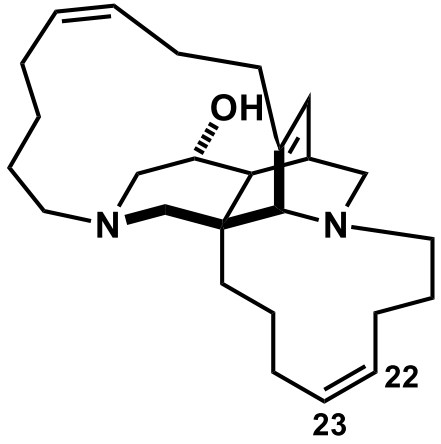

6
9
LiHMDS, THF
-78 °C
10
K2CO3, MeCN, reflux
43% (over 2 steps)
11
Pd(PPh3)4 (10 mol %),
toluene, 50 °C, quant.
12
1. NaBH4, MeOH, 0 °C
2. MsCl, Et3N, DMAP
CH2Cl2
81% (over 2 steps)
13
2,6-lutidine, 170 °C, then
TBSOTf, CH2Cl2, RT, 72%
14
NaH, 7-iodo-2-heptyne
DMF, 0 °C, 91%
15
17 (25 mol %), 18 (25 mol %)
toluene, 110 °C, 85%
16
17
X =
18

Scheme 6

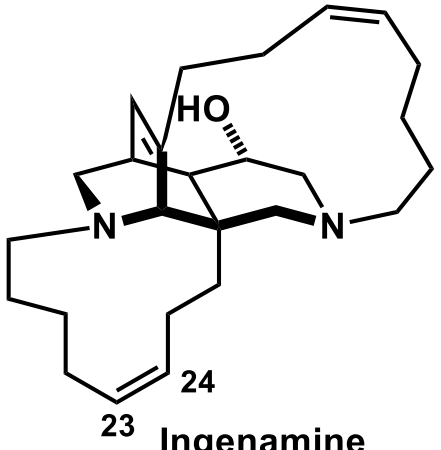

OTBS
N
O
N
O
OMe
16
1. L-Selectride, THF
2. 19, CH_2Cl_2,
$NaBH(OAc)_3$
89% (over 2 steps)
20
I
(i) 9H-9-BBN, THF
(ii) H_2O, HOAc, THF
(iii) THF, $NaHCO_3$
(iv) $[(dppf)PdCl_2]$ cat.
$AsPh_3$ cat., and Tl_2CO_3
THF/DMF/H_2O (6:3:1)
48%
(+ regioisomer)
B
21
19
L-Selectride:
Li^+
H
22
23
Dibal-H, THF
then MeOH, 57%
OH
(-)-1
22
23

Scheme 7

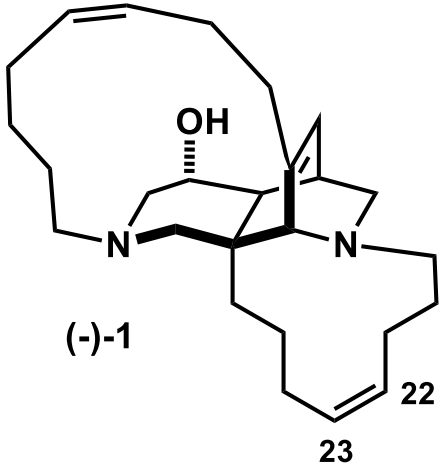

TBSO
N
O
N
O
OMe
15
1. 9H-9-BBN, THF
then NaBO3•H2O
2. PDC, 4 Å MS
CH2Cl2
74% (over 2 steps)
24
1. [Ph3P-(CH2)4COOH]Br (25)
NaHMDS, THF, 0 °C, then 24
-90 °C to 0 °C
2. L-Selectride, THF, 40 °C
H
OH
26
I
Cl
27
27, (iPr)2NEt, CH2Cl2
39% (over 3 steps)
28
17 (30 mol %), 18 (30 mol %)
toluene, 100 °C, 82%
OTBS
29
1. Ni(OAc)2•4H2O, NaBH4
ethylenediamine, EtOH
then H2 (1 atm), 86%
2. LiAlH4, AlCl3, THF, 58%
ent-3
24
23



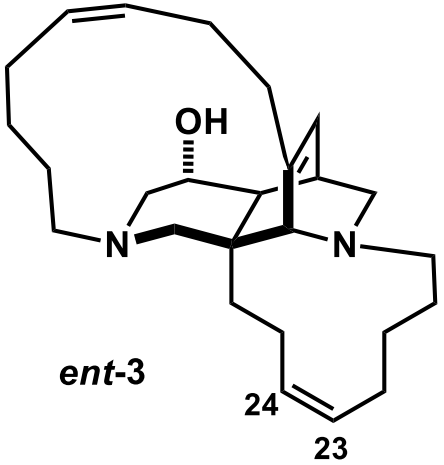
Xestocyclamine A
(-)-1
as originally assigned



Ingenamine
(+)-3



(-)-1



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