Enantioselective Synthesis of (–)-C10-Hydroxyacutuminine

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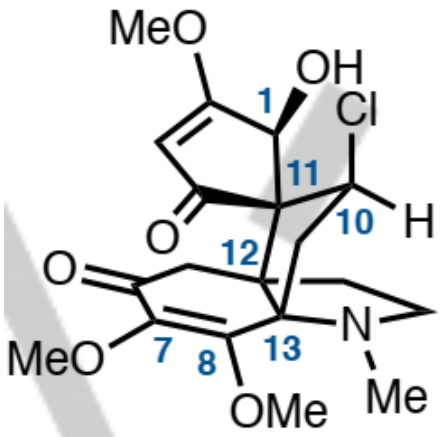
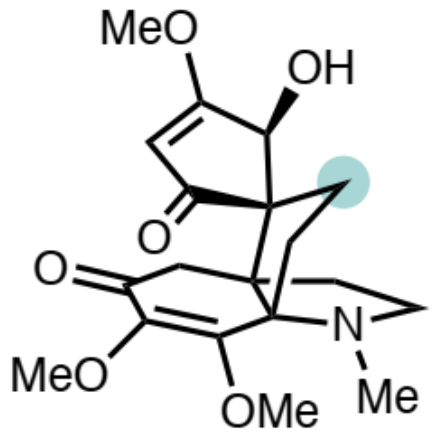
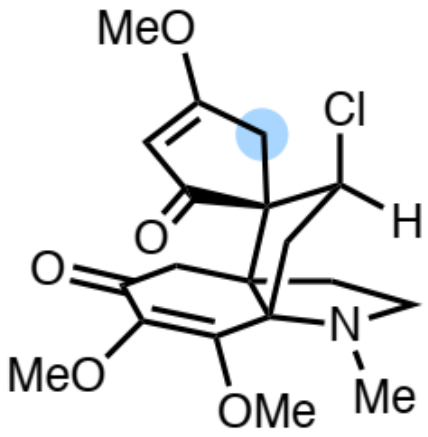


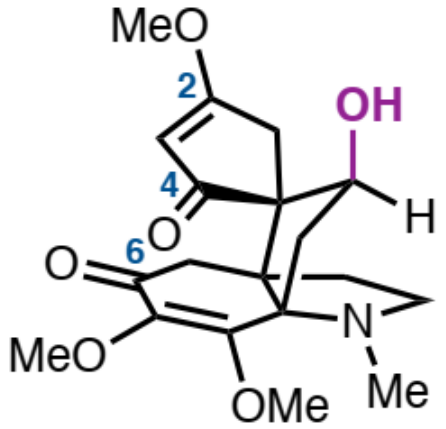
(–)-acutumine (**1**)



(–)-dechloroacutumine (**2**)



(–)-acutuminine (**3**)



(–)-C10-hydroxyacutuminine (**4**)

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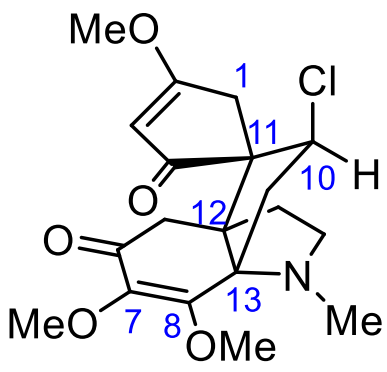
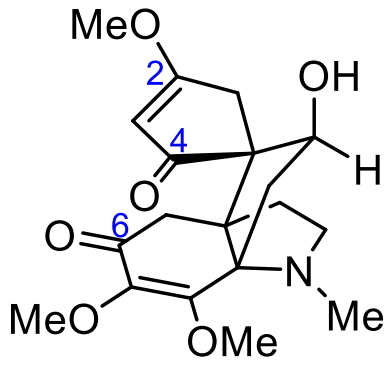
Retrosynthetic analysis of (-)-acutuminine (3)



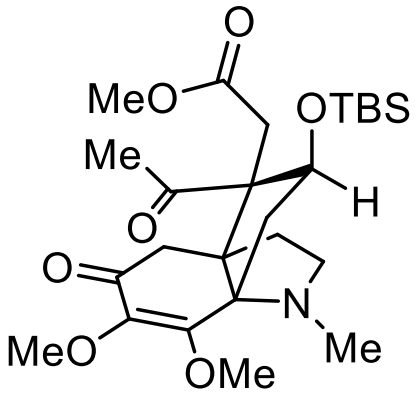
(-)-acutuminine (**3**)

deoxychlorination



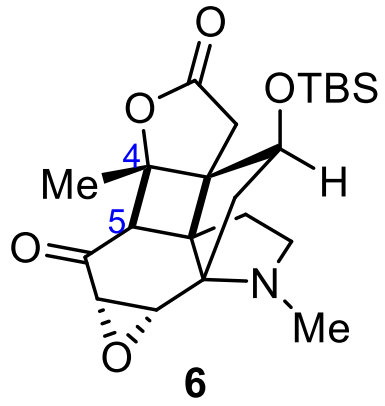
(-)-C10-hydroxyacutuminine (**4**)

Dieckmann condensation



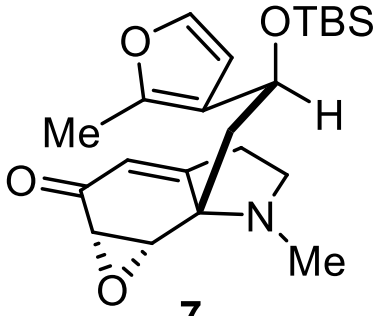
5

retro-aldol



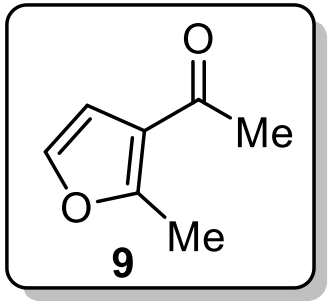
6

[2+2]

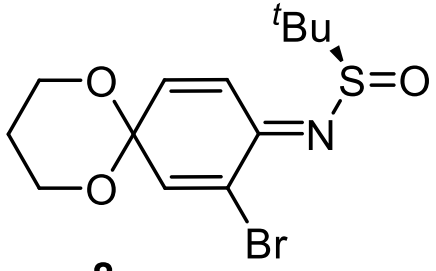


7

1,2-addition/ pyrrolidine formation

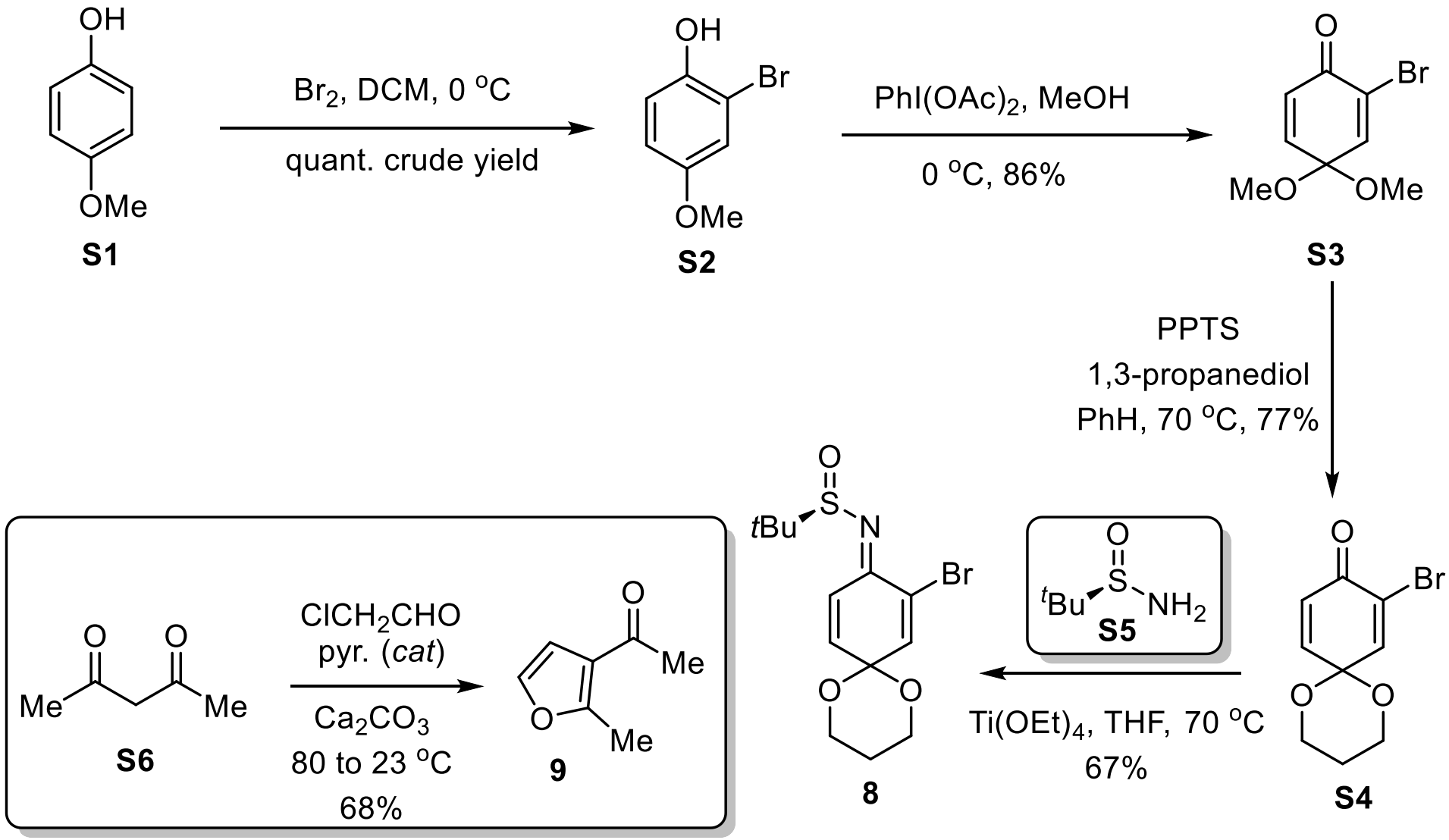


9

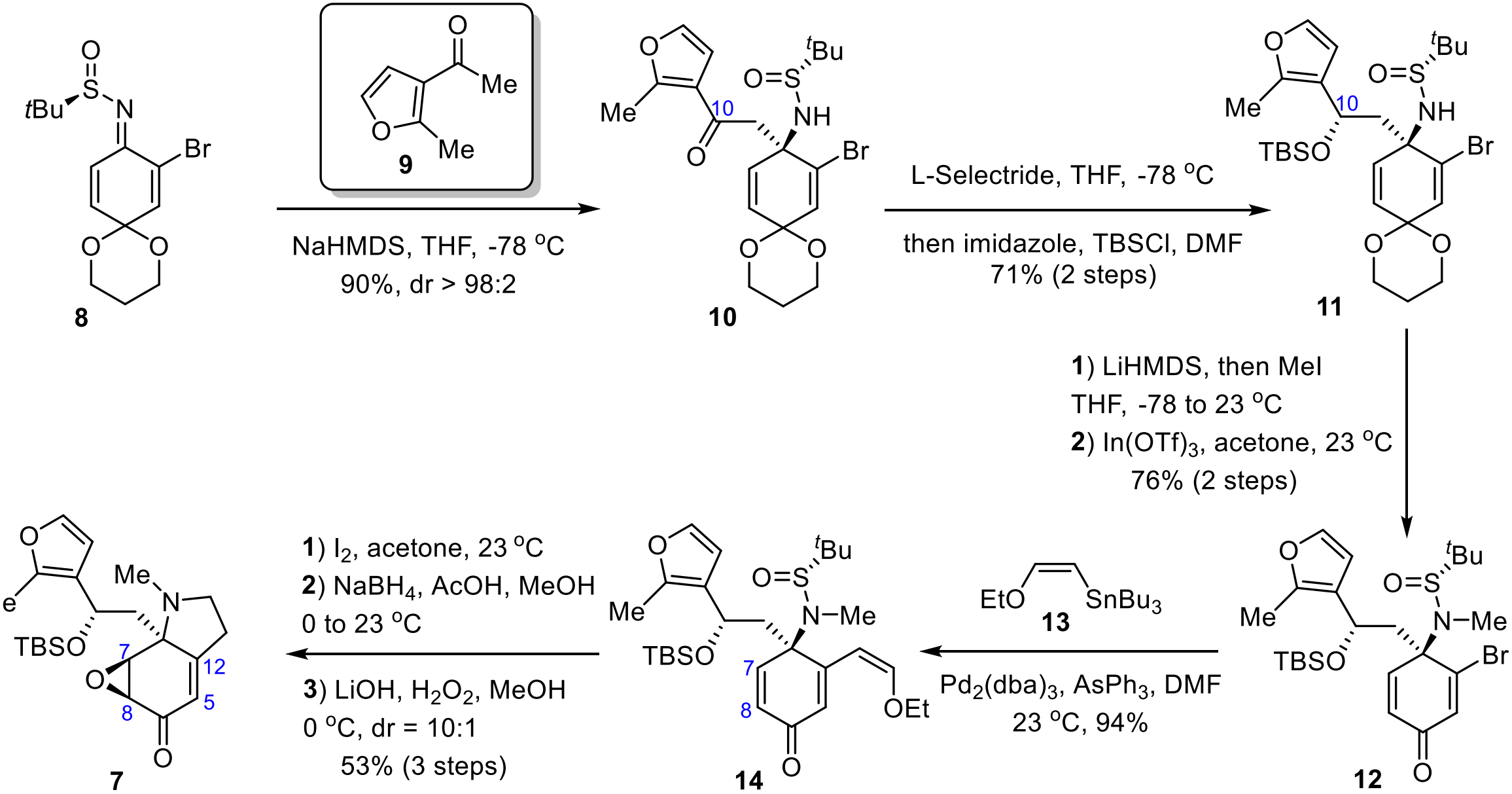


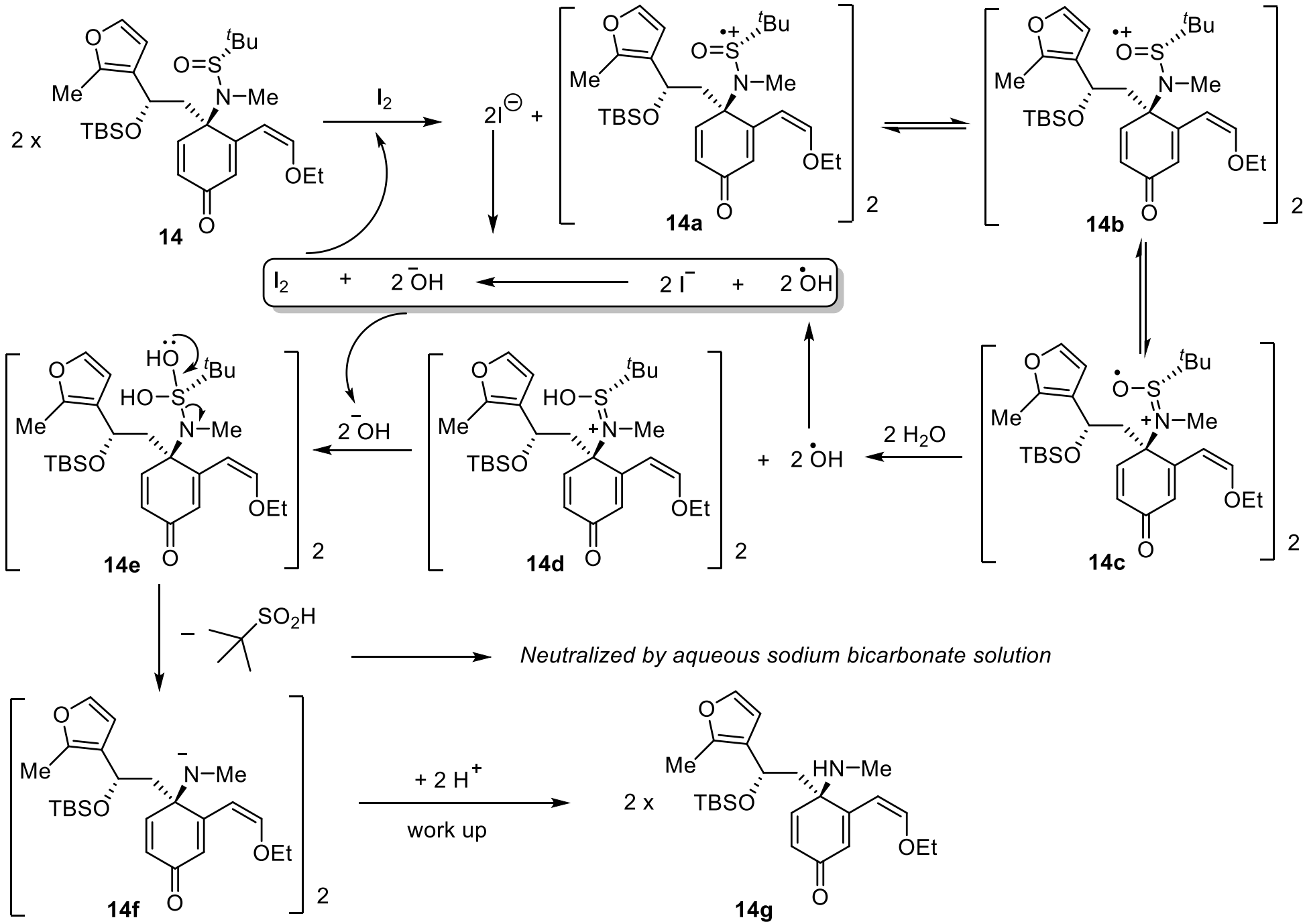
8

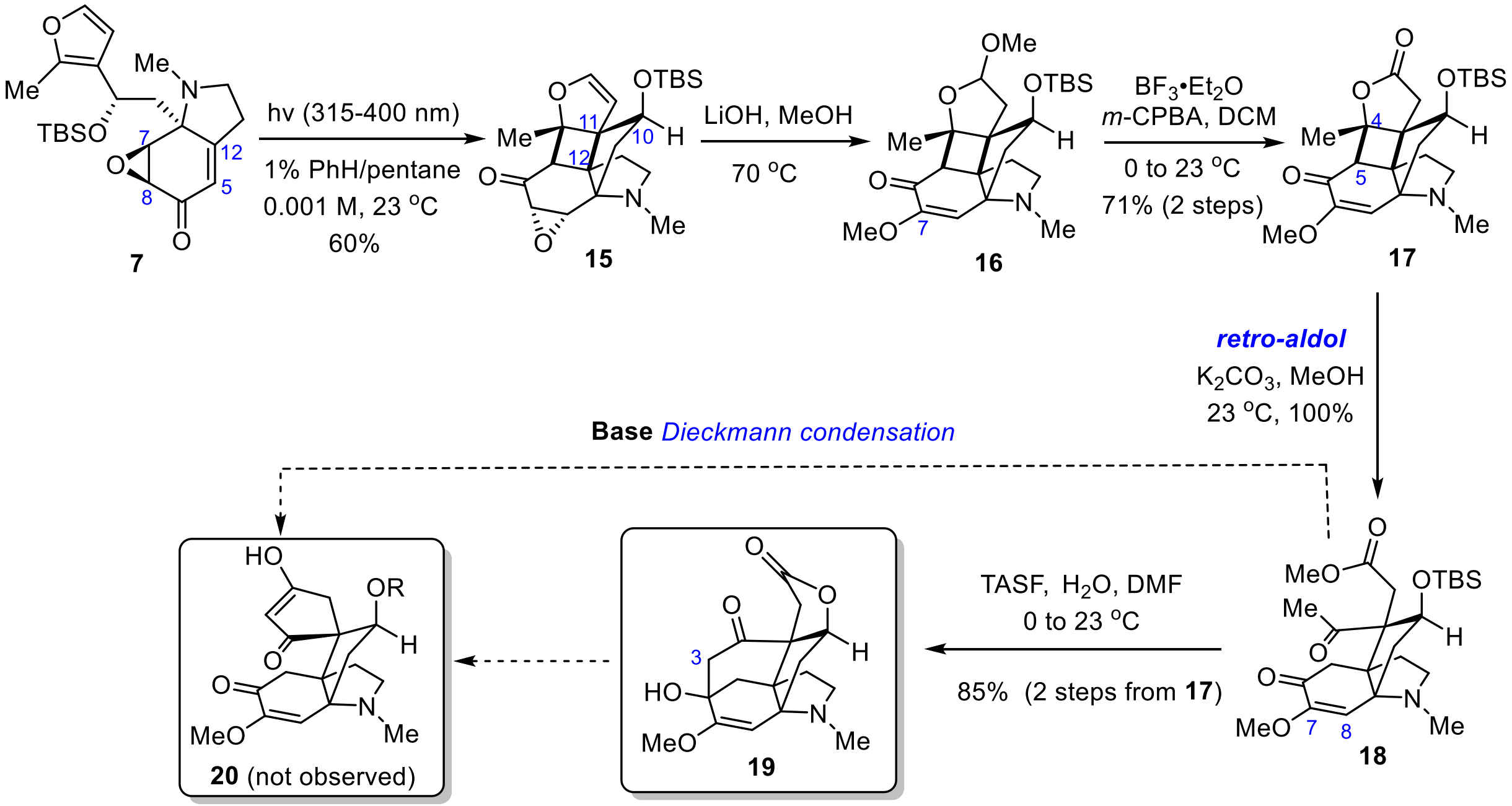
Preparation of starting materials 8 and 9

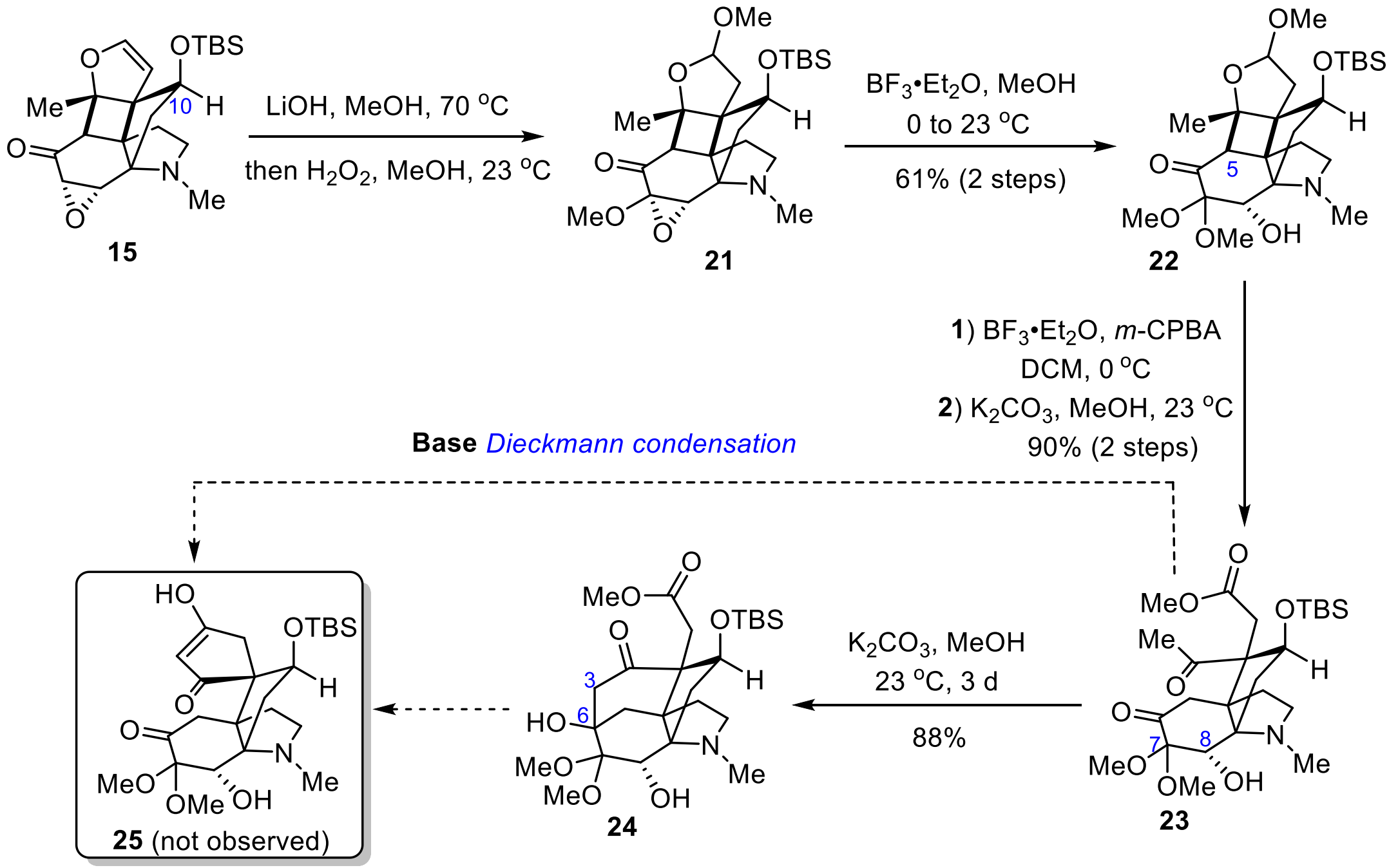


Total Synthesis of (-)-C10-hydroxyacutuminine (4)

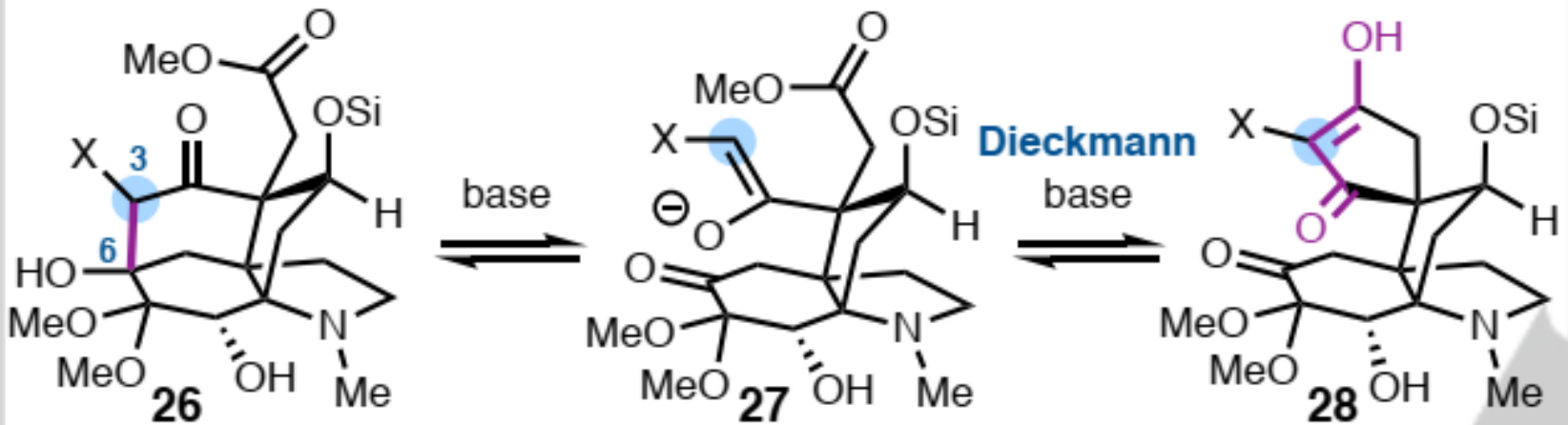



2 x
14
I2
2I⊖ +
14a
2
14b
2
I2 + 2 ⁻OH
2 I⁻ + 2 ⁻OH
14c
2
2 H2O
+ 2 ⁻OH
14d
2
2 ⁻OH
14e
2
– SO2H
Neutralized by aqueous sodium bicarbonate solution
14f
2
+ 2 H+
work up
2 x
14g

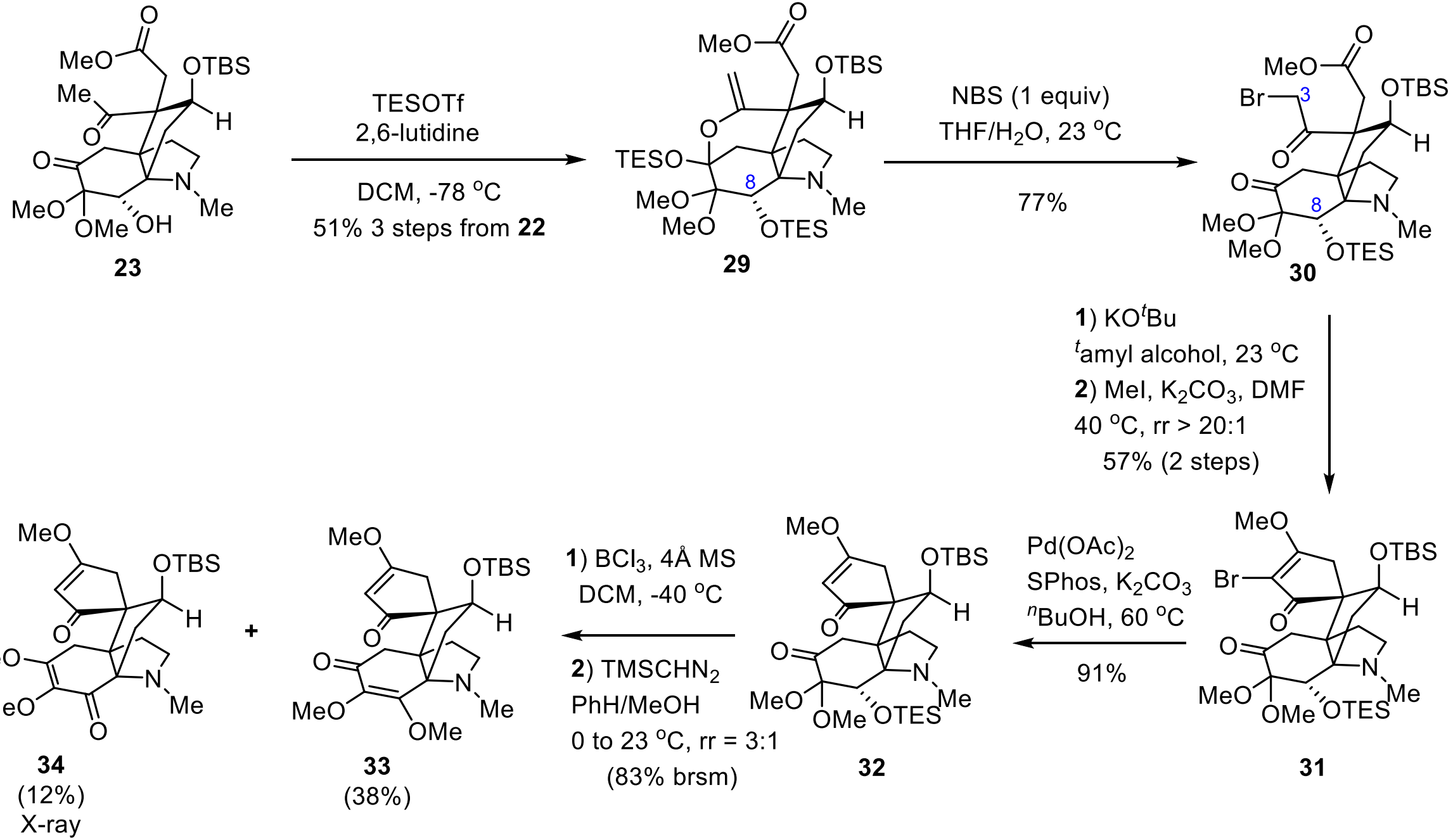

hv (315-400 nm)
1% PhH/pentane
0.001 M, 23 °C
60%
LiOH, MeOH
70 °C
BF3•Et2O
m-CPBA, DCM
0 to 23 °C
71% (2 steps)
retro-aldol
K2CO3, MeOH
23 °C, 100%
Base Dieckmann condensation
TASF, H2O, DMF
0 to 23 °C
85% (2 steps from 17)
7
15
16
17
18
19
20 (not observed)

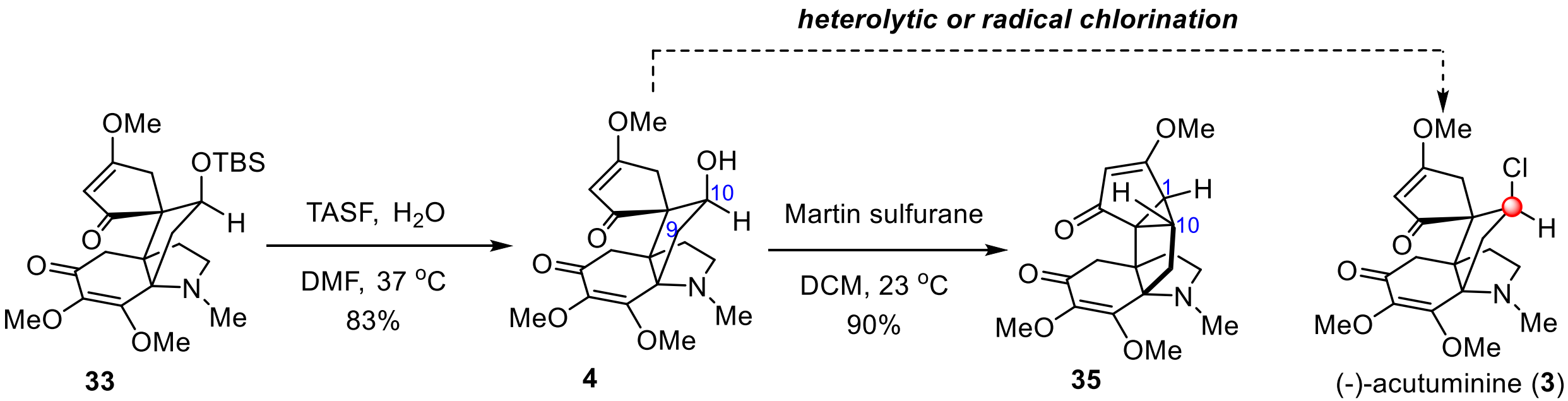

OTBS
O
Me
10
H
O
N
Me
O
15
LiOH, MeOH, 70 °C
then H2O2, MeOH, 23 °C
OMe
OTBS
21
BF3•Et2O, MeOH
0 to 23 °C
61% (2 steps)
5
22
1) BF3•Et2O, m-CPBA
DCM, 0 °C
2) K2CO3, MeOH, 23 °C
90% (2 steps)
Base Dieckmann condensation
MeO
OMe
OH
23
K2CO3, MeOH
23 °C, 3 d
88%
3
6
24
HO
25 (not observed)

Dieckmann cyclization hypothesis:



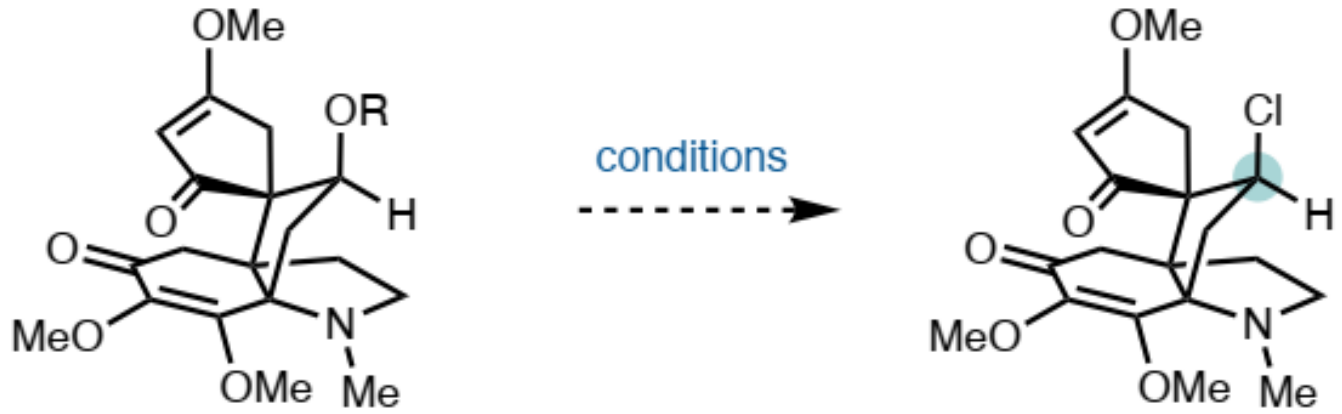
■ lower pKa at C3 to render **26** formation reversible


23
TESOTf
2,6-lutidine
DCM, -78 °C
51% 3 steps from 22
29
NBS (1 equiv)
THF/H2O, 23 °C
77%
30
1) KOtBu
tamyl alcohol, 23 °C
2) MeI, K2CO3, DMF
40 °C, rr > 20:1
57% (2 steps)
31
Pd(OAc)2
SPhos, K2CO3
nBuOH, 60 °C
91%
32
1) BCl3, 4Å MS
DCM, -40 °C
2) TMSCHN2
PhH/MeOH
0 to 23 °C, rr = 3:1
(83% brsm)
33
(38%)
34
(12%)
X-ray



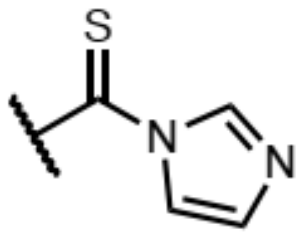
33 **4** **35** (-)-acutuminine (**3**)

Reaction conditions investigated for the chlorination of (–)-C10-hydroxyacutuminine (**4**).

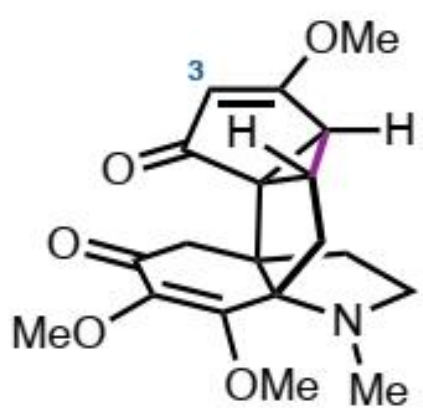


R = H, (–)-C10-hydroxyacutuminine (**4**) **(–)-acutuminine** (**3**)

R =	conditions	result
H	$SOCl_2$, PhMe or CH_2Cl_2, 0 to 40 °C	no chlorination
	$SOCl_2$, $ZnCl_2$, CH_2Cl_2, 0 °C	decomposition
	$SOCl_2$, then $TiCl_4$, CH_2Cl_2, 0 °C	no chlorination
	oxalyl chloride, PhH, 23 °C, then sodium pyrithione, CCl_4, reflux[8a]	no chlorination

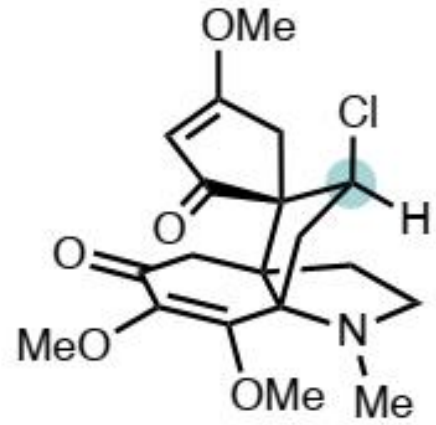
	$^{n}Bu_4NCl$, then Martin sulfurane, CH_2Cl_2, 23 °C	complex mixture
	Cl_2SPh_2, CH_2Cl_2, 23 to 40 °C	unreacted **4** and trace **35**
Ms	$^{n}Bu_4NCl$, PhMe, 100 °C	no reaction
	di-tert-butyl hyponitrite, ethyl trichloroacetate or NCS, PhH, 60 °C	decomposition
	Et_3B, hexachloroacetone, PhH, air, 23 °C	decomposition
	$Ir[dFCF_3ppy]_2(bpy)PF_6$, $^{sec}BuBF_3K$, ethyl trichloroacetate, EtOAc, 23 °C, blue LED[8b]	complex mixture

Reaction conditions investigated for the chlorination of cyclopropane **35**.



35

conditions



(–)-acutuminine (3)

conditions	**result**
HCl, Et_2O, 0 to 23 °C	no reaction, then demethylation upon prolonged stirring
HCl, HFIP, 0 °C	demethylation
LiCl, w/ and w/o CSA, DMF, *d*-DMSO, or PhMe, μ-wave, 100–160 °C	no reaction, then demethylation, followed by decomposition
TMSCl, NaCl, CH_3CN, 23 °C	no reaction

$^{n}Bu_4NCl$, CH_2Cl_2 or HFIP, 23 to 40 °C	no reaction
$^{n}Bu_4NCl$, then Martin sulfurane, CH_2Cl_2, 23 °C	C3–H chlorination
SO_2Cl_2, 2,6-lutidine, CH_2Cl_2, 0 °C	no reaction
$PhICl_2$, CH_2Cl_2, 23 to 45 °C	C3–H chlorination
BCl_3, 4 Å MS, CH_2Cl_2, –40 °C	no reaction
$FeCl_3$ or $CeCl_3$, CH_3CN, 23 to 80 °C	no reaction
Li_2CuCl_4, THF, 23 to 80 °C	no reaction

$SnCl_4$, CH_2Cl_2, 23 to 80 °C	no reaction, then demethylation at 80 °C
UV (310 nm), ethyl trichloroacetate	no reaction
UV (310 nm), hexachloroacetone	decomposition
UV (310 nm), dimethyl 2,2-dichloromalonate, PhH	complex mixture