Literature Report 2010-06-29

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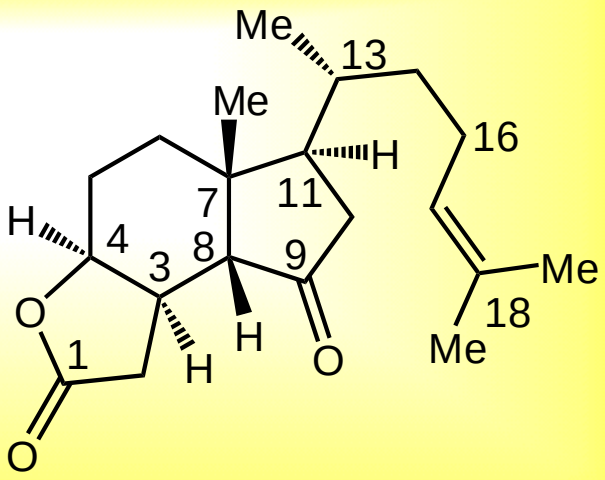
Total Synthesis of (±)-Aplykurodinone-1

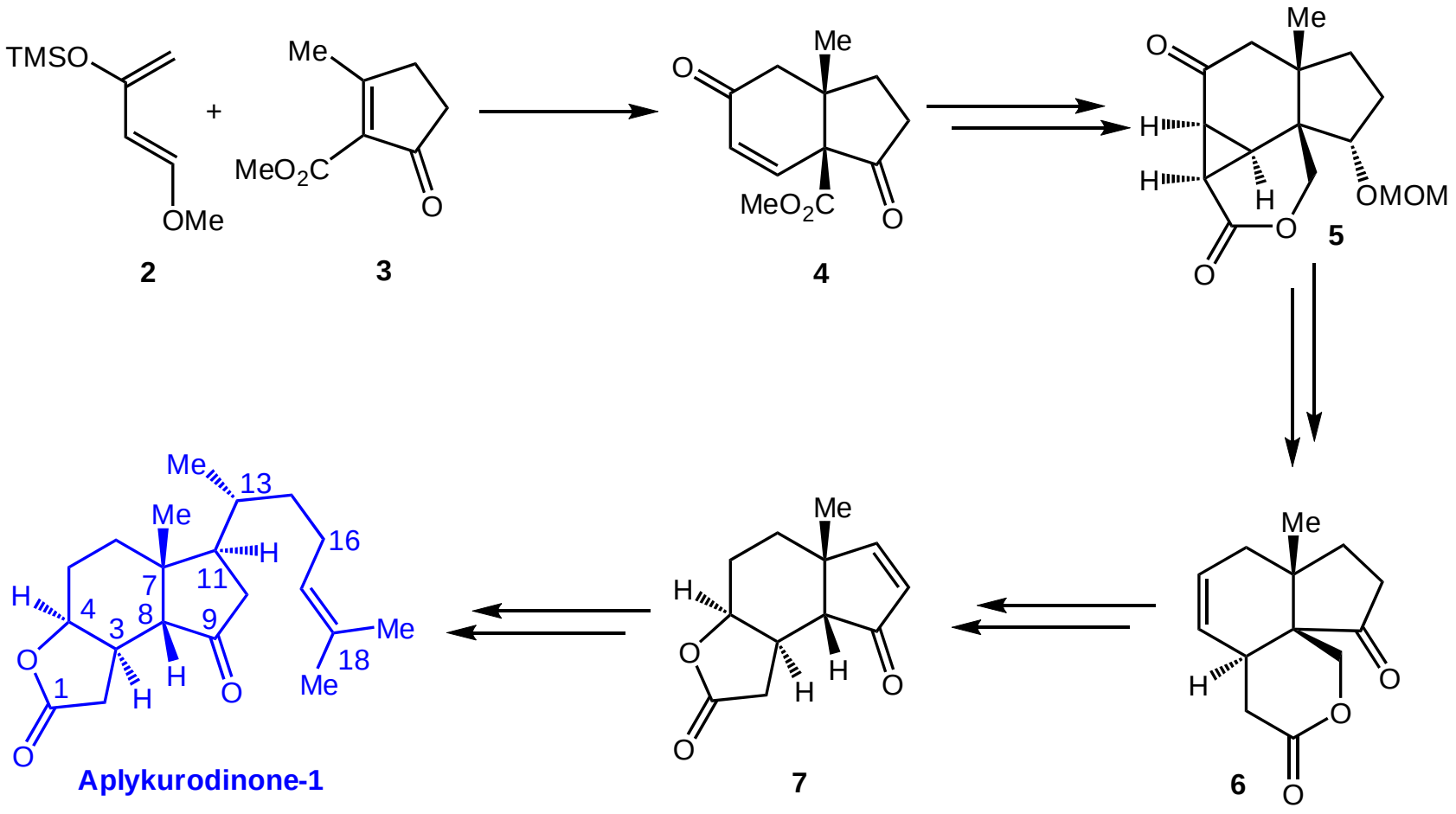
Danishefsky, S. J.* *et al*
J. Am. Chem. Soc. **2010**, *ASAP*.

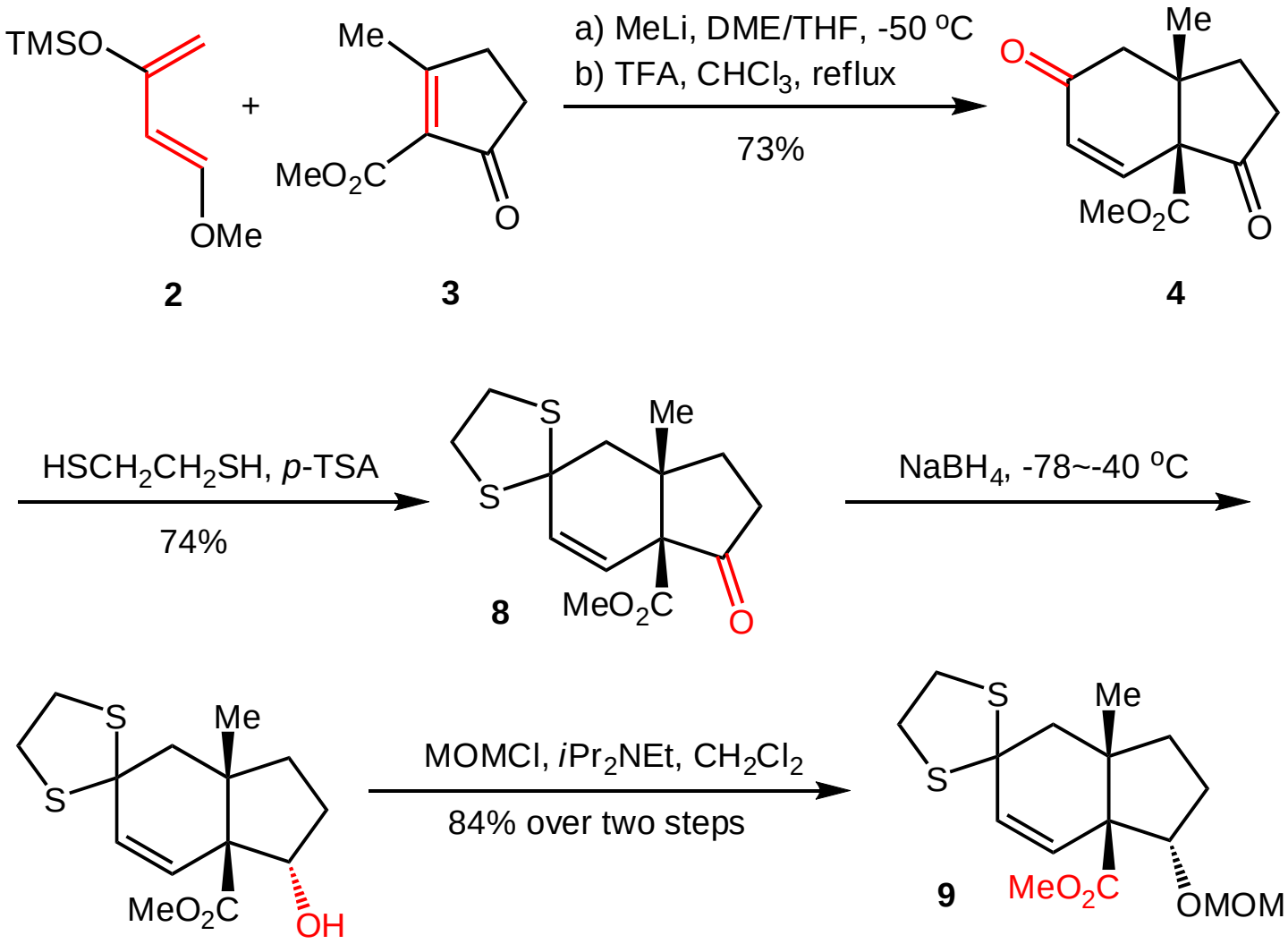
Aplykurodinone-1

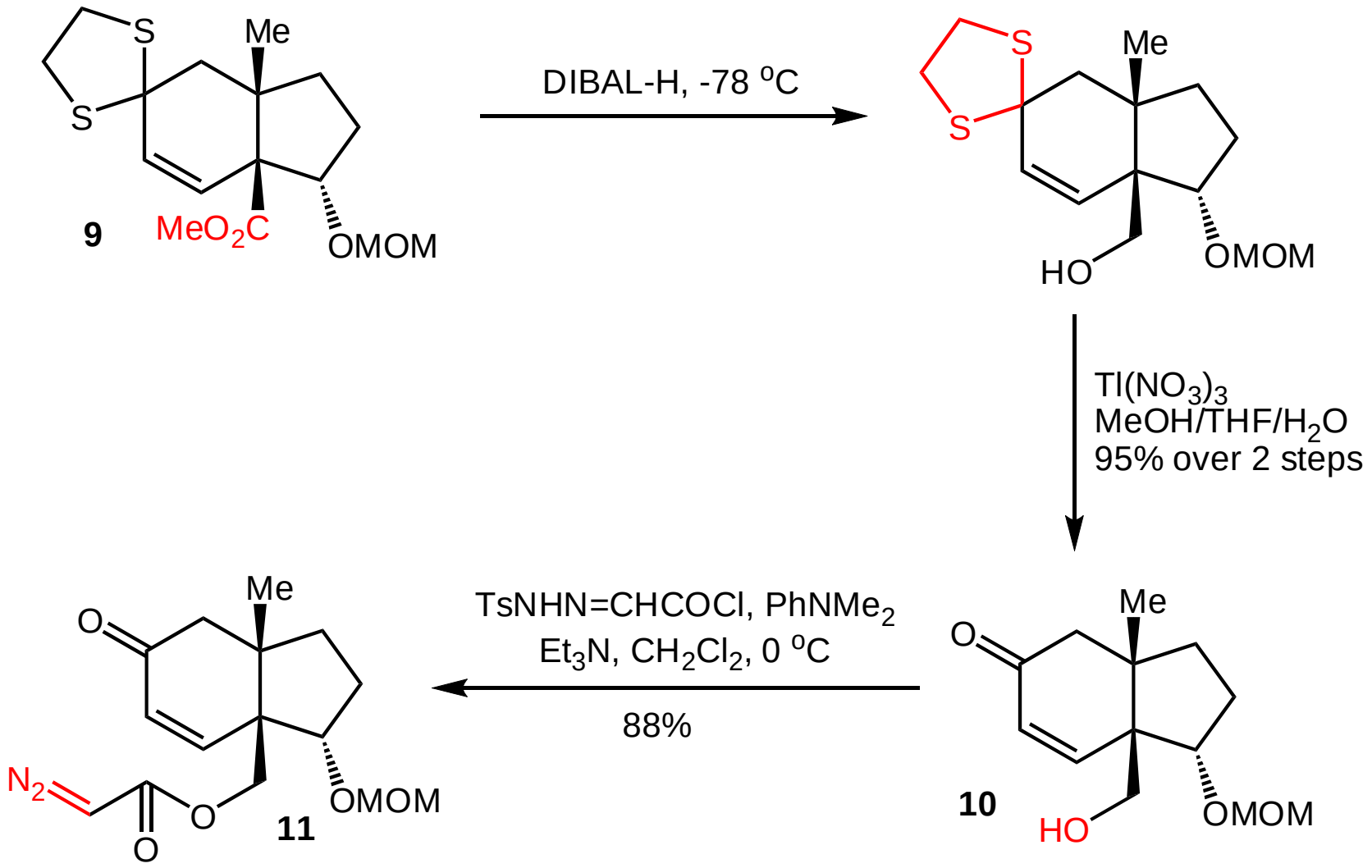


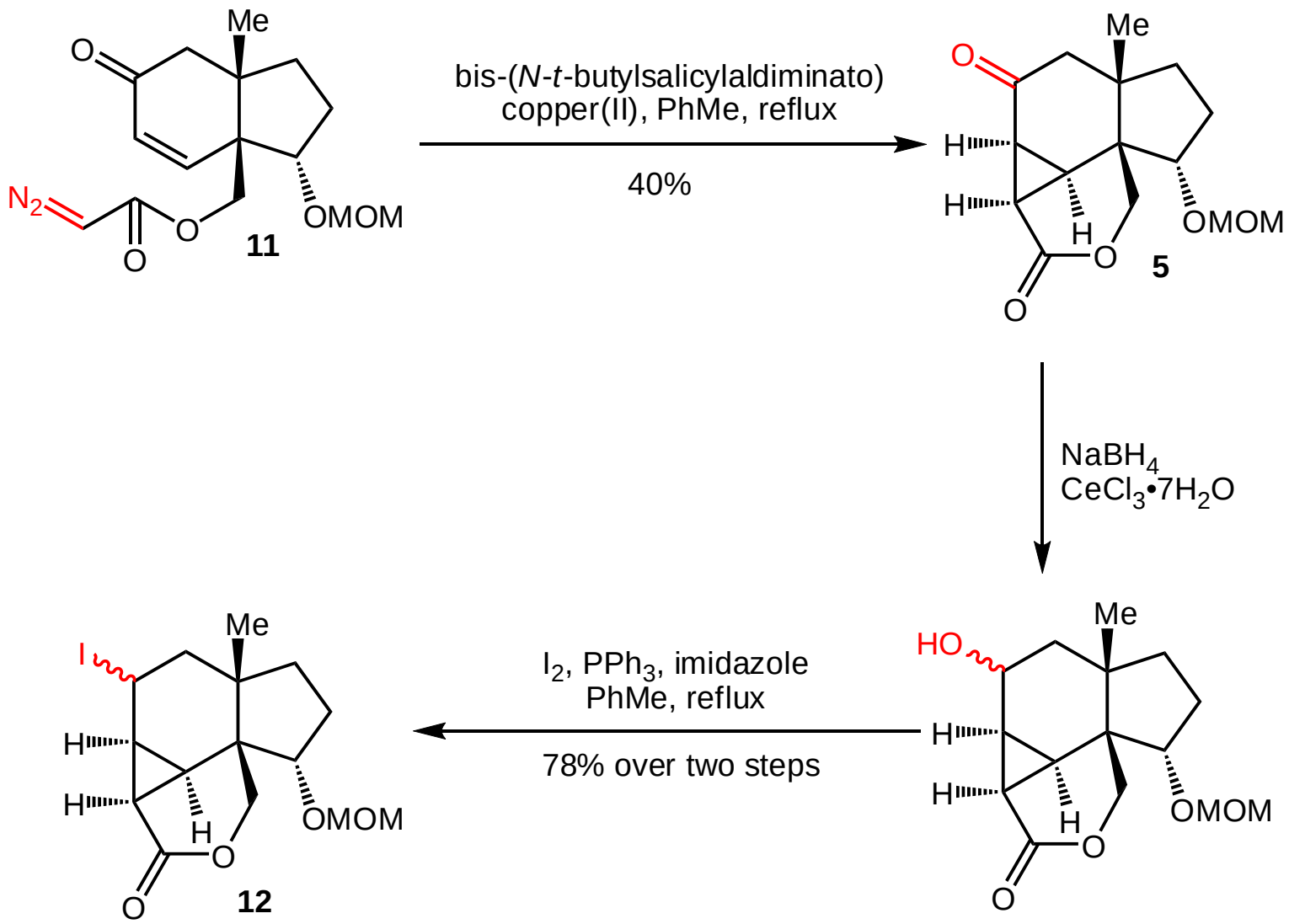
Aplykurodinone-1

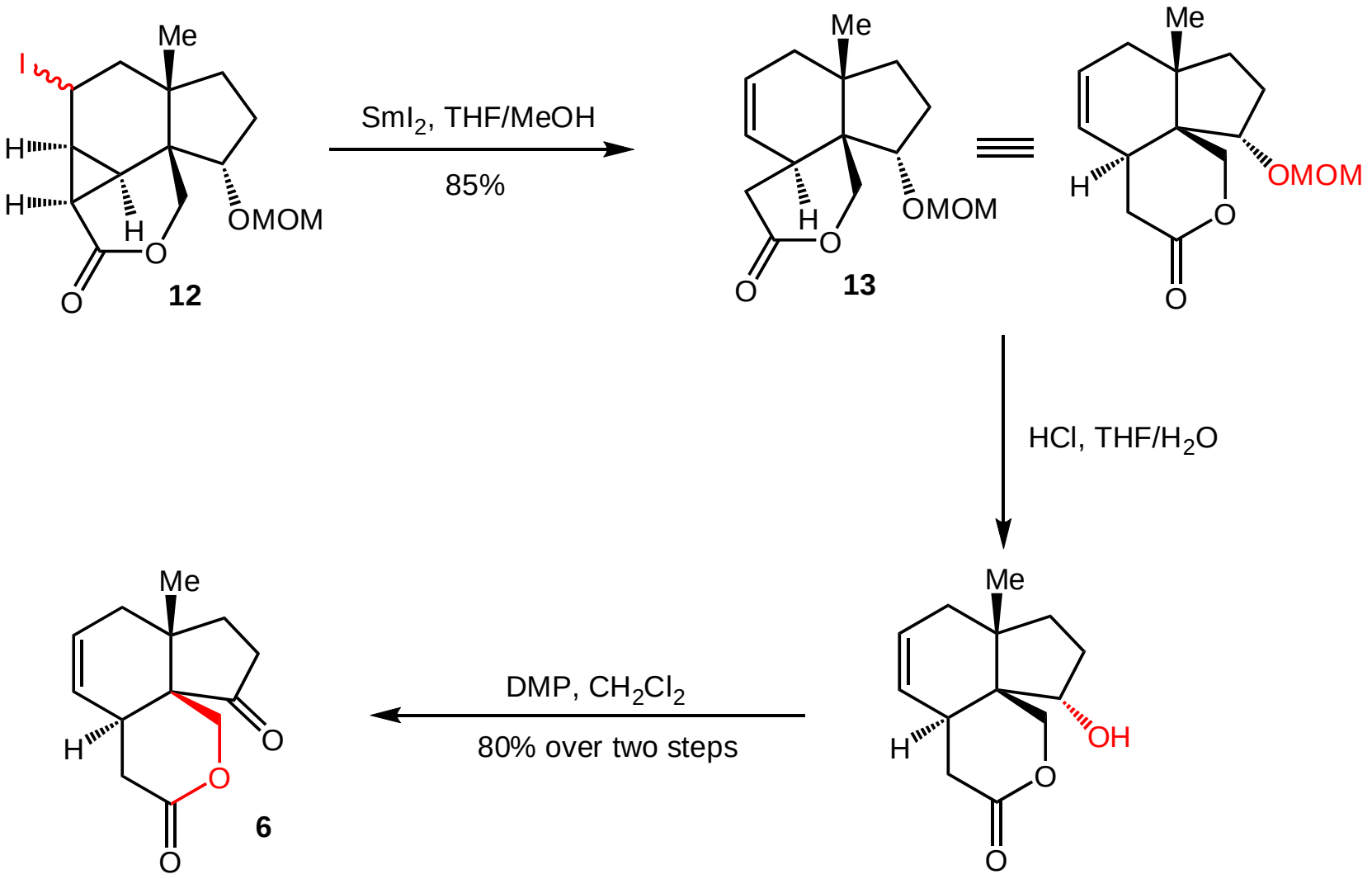
Synthetic Strategy toward Aplykurodinone-1 (1)

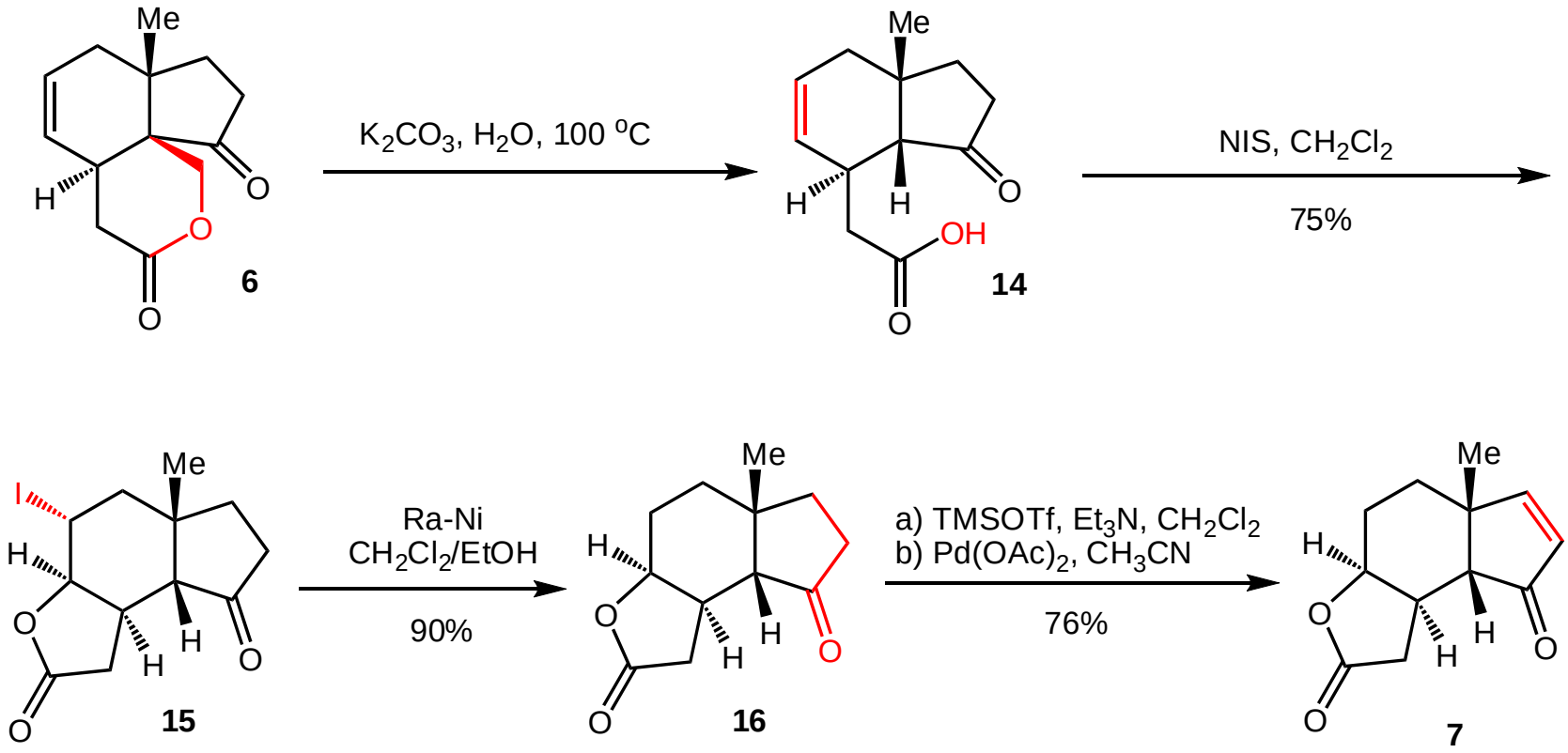


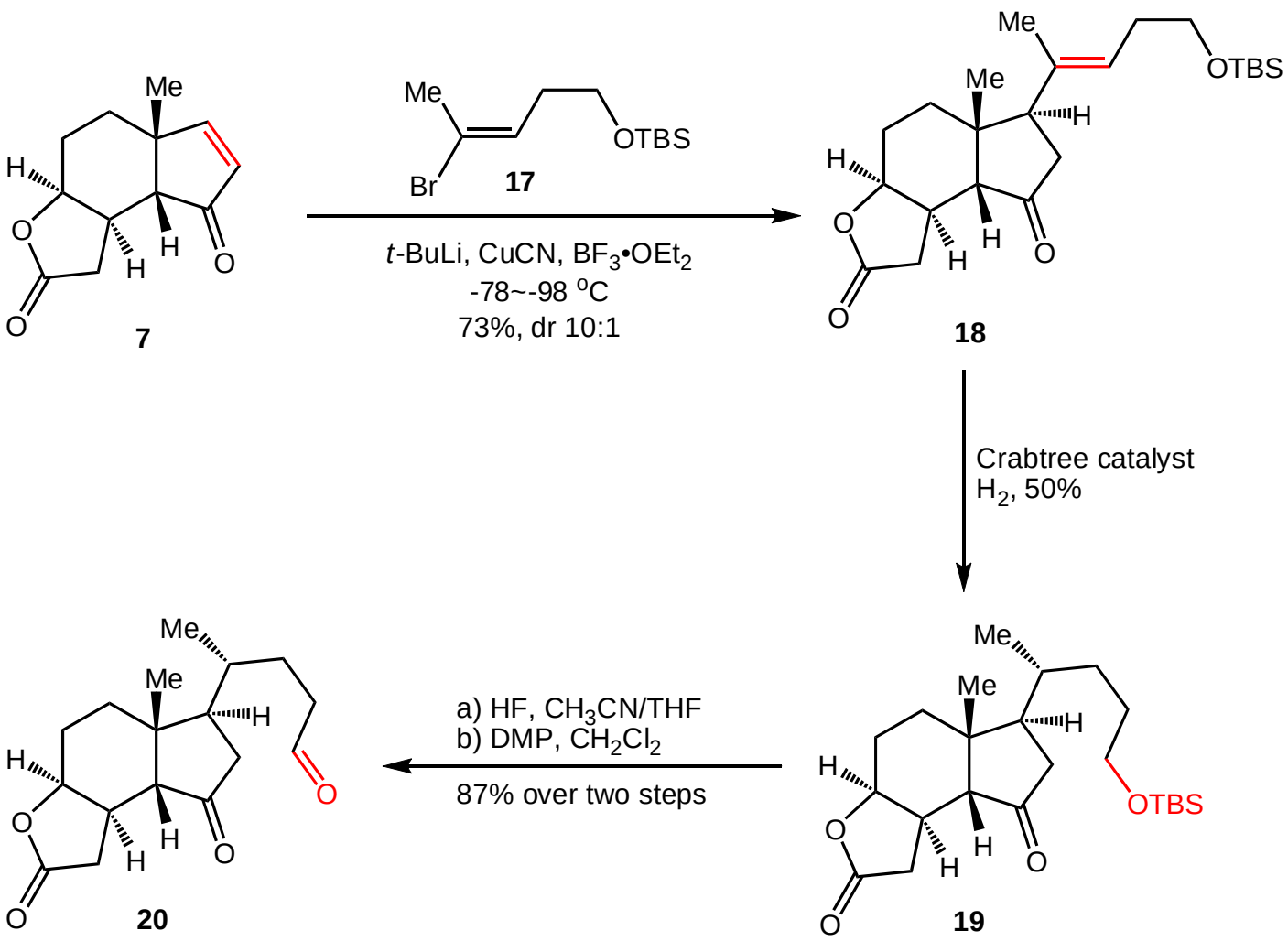

TMSO
OMe
Me
MeO2C
O
a) MeLi, DME/THF, -50 °C
b) TFA, CHCl3, reflux
73%
Me
O
MeO2C
O
2
3
4
HSCH2CH2SH, p-TSA
74%
S
S
Me
MeO2C
O
8
NaBH4, -78~-40 °C
S
S
Me
MeO2C
OH
MOMCl, iPr2NEt, CH2Cl2
84% over two steps
S
S
Me
MeO2C
OMOM
9

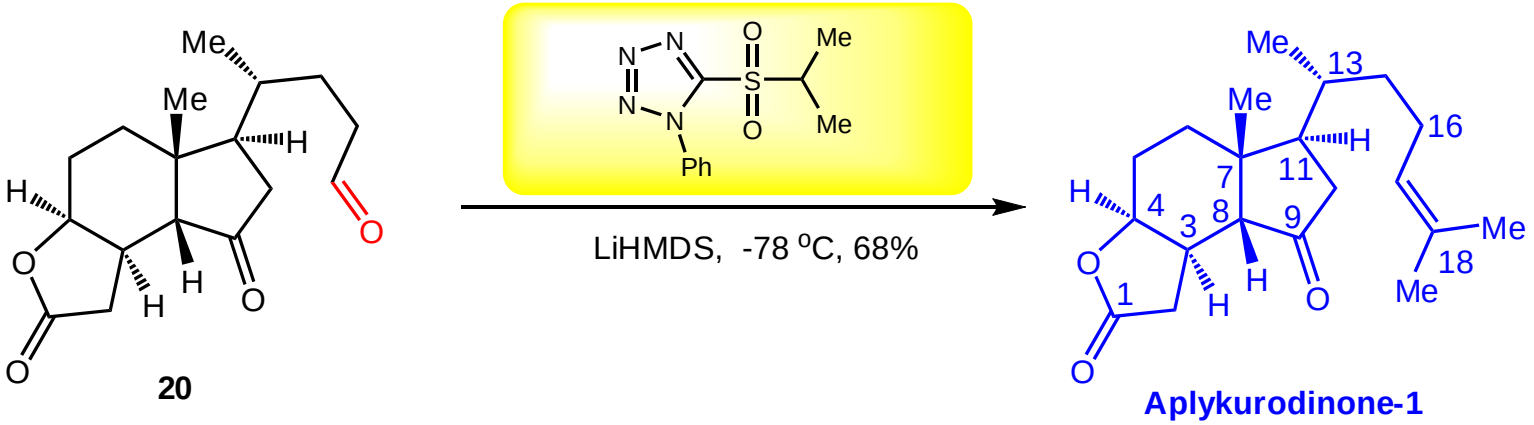

S
Me
S
MeO2C
OMOM
9
DIBAL-H, -78 °C
S
Me
S
HO
OMOM
Tl(NO3)3
MeOH/THF/H2O
95% over 2 steps
Me
O
HO
OMOM
10
TsNHN=CHCOCl, PhNMe2
Et3N, CH2Cl2, 0 °C
88%
Me
O
N2
O
O
OMOM
11


Me
O
N2
O
O
OMOM
11
bis-(N-t-butylsalicylaldiminato)
copper(II), PhMe, reflux
40%
Me
O
H
H
H
O
OMOM
O
5
NaBH4
CeCl3•7H2O
Me
HO
H
H
H
O
OMOM
O
I2, PPh3, imidazole
PhMe, reflux
78% over two steps
Me
I
H
H
H
O
OMOM
O
12

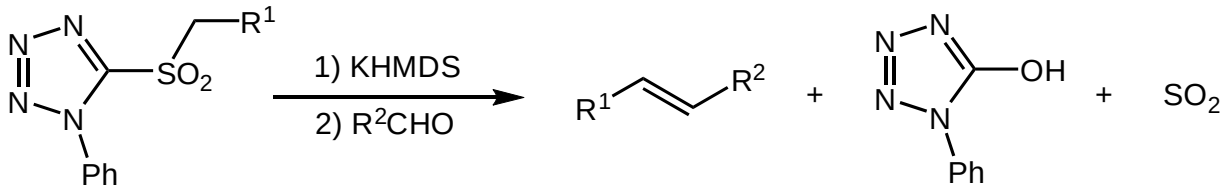

Me
I
H
H
H
O
O
OMOM
12
SmI2, THF/MeOH
85%
Me
H
O
O
OMOM
13
Me
H
O
O
OMOM
HCl, THF/H2O
Me
H
O
O
OH
DMP, CH2Cl2
80% over two steps
Me
H
O
O
O
6

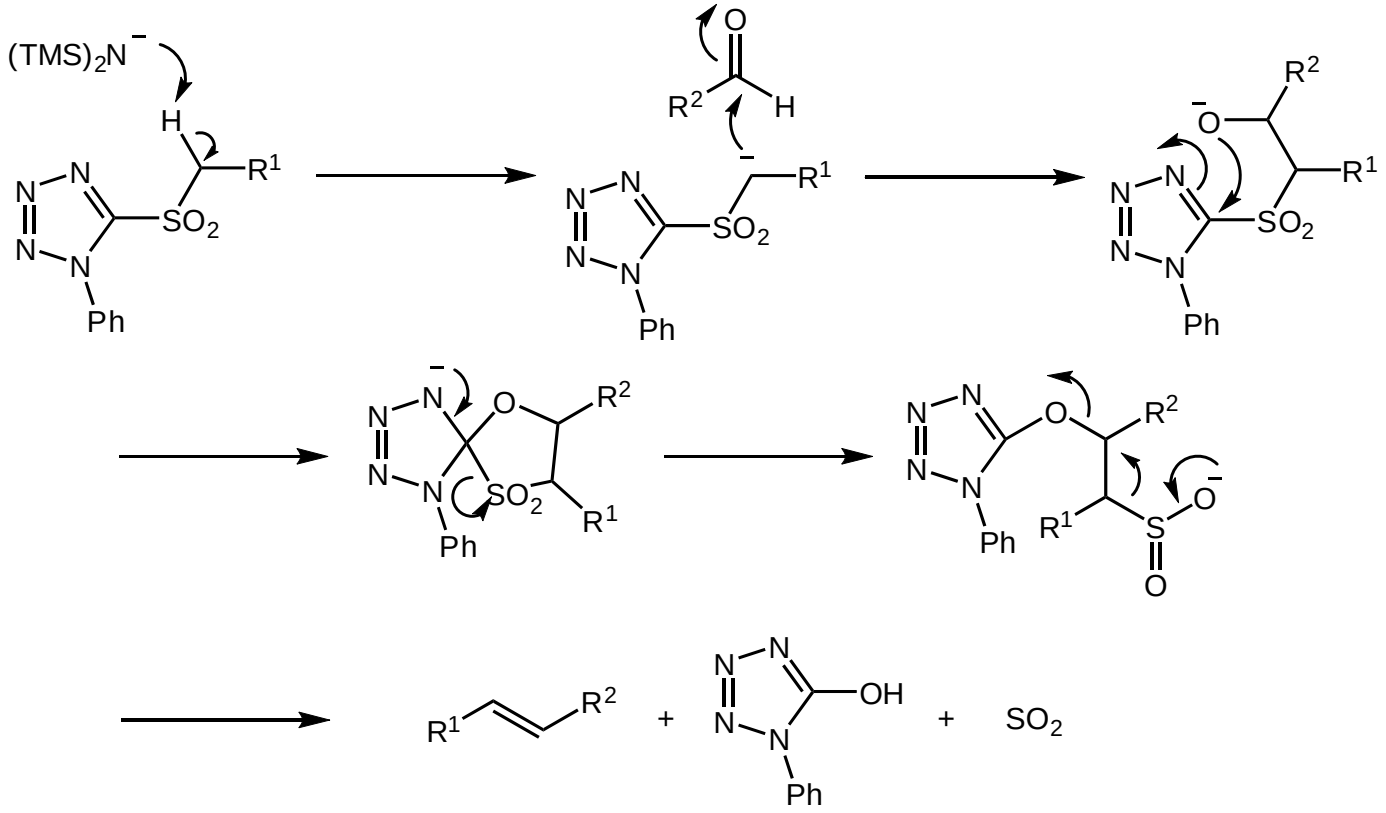

Me
H
O
O
O
6
K2CO3, H2O, 100 °C
Me
H
H
O
OH
O
14
NIS, CH2Cl2
75%
I
Me
H
O
H
H
O
O
15
Ra-Ni
CH2Cl2/EtOH
90%
Me
H
O
H
H
O
O
16
a) TMSOTf, Et3N, CH2Cl2
b) Pd(OAc)2, CH3CN
76%
Me
H
O
H
H
O
O
7


Me
H
O
H
O
O
7
Me
Br
17
OTBS
t-BuLi, CuCN, BF3•OEt2
-78~-98 °C
73%, dr 10:1
Me
Me
OTBS
H
H
O
H
O
O
18
Crabtree catalyst
H2, 50%
Me
Me
H
H
O
H
O
OTBS
19
a) HF, CH3CN/THF
b) DMP, CH2Cl2
87% over two steps
Me
Me
H
H
O
H
O
O
20

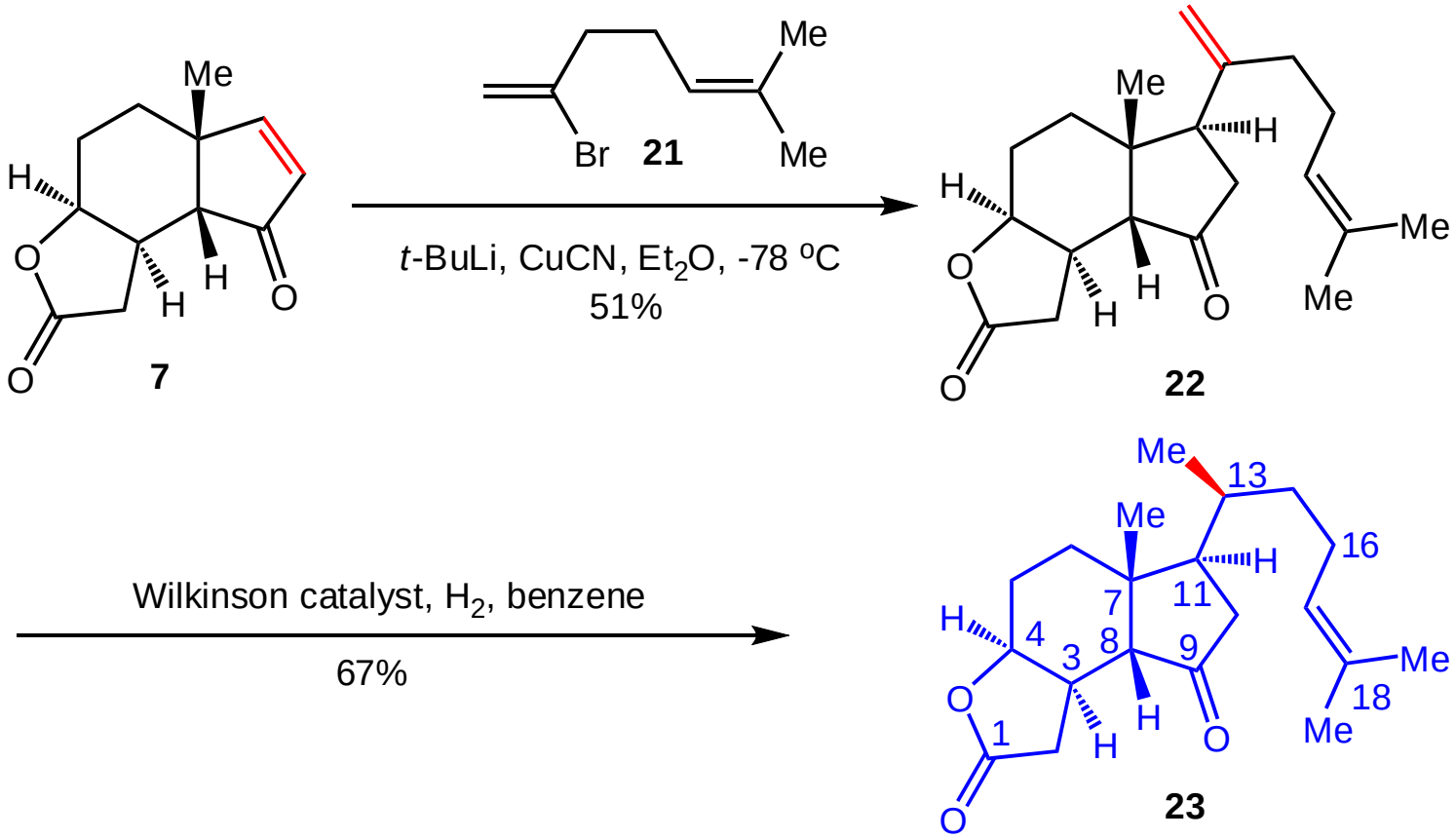

Me
Me
H
H
O
H
H
O
O
20
N
N
N
N
Ph
S
O
O
Me
Me
LiHMDS, -78 °C, 68%
Me
13
Me
16
H
7
11
H
4
3
8
9
Me
18
Me
O
1
H
H
O
O
Aplykurodinone-1

Julia–Kocienski Olefination

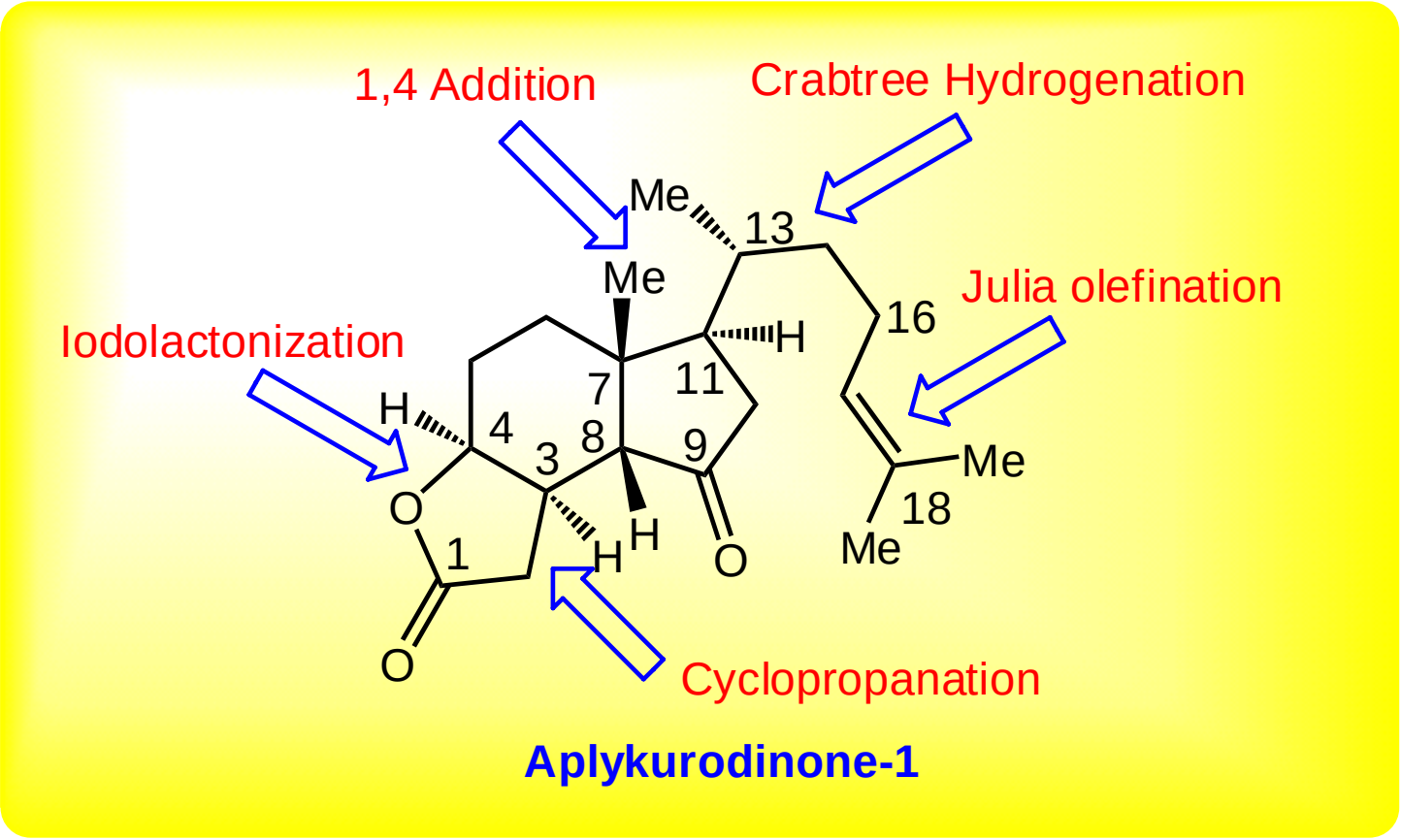




Synthesis of 13-Epi-aplykurodinone-1 (23)



Summary



Aplykurodinone-1

We note that various aplykurodines exhibit cytotoxic activity against a range of human cancer cell lines. Notwithstanding the potential elements of chemistry and medicinal chemistry-based points of interest, surprisingly little attention at the level of synthesis has been directed to the aplykurodines. Our laboratory took particular note of a recently isolated member of the family, aplykurodinone-1 (**1**). Following its isolation from the sea hare *Synphonota geographica* in 2005, the structure of aplykurodinone-1 (**1**) was elucidated through a combination of spectroscopic methods, X-ray crystallography, and chemical correlation. As shown in Scheme 1, **1** was found to possess a *cis*-fused C-D ring with epimeric C8 (steroidal numbering) and an unsaturated side chain (as compared to cholesterol).

In summary, the total synthesis of aplykurodinone-1 (**1**) has been accomplished. A key feature of the effort involved an anionically mediated cycloaddition of a metallo-enolate derived from **2** with **3** (see formation of **4**). The seemingly extraneous oxymethyl C1 function at C8 was used to govern the configurational relationship between C3 and C7. The C8 function is ultimately excised. The stereochemistry at C13 is managed with good stereoselectivity based on the suitable order of introduction of H to this carbon.