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Synthesis of (−)-Mitrephorone A via a Bioinspired Late Stage C−H Oxidation of (−)-Mitrephorone B

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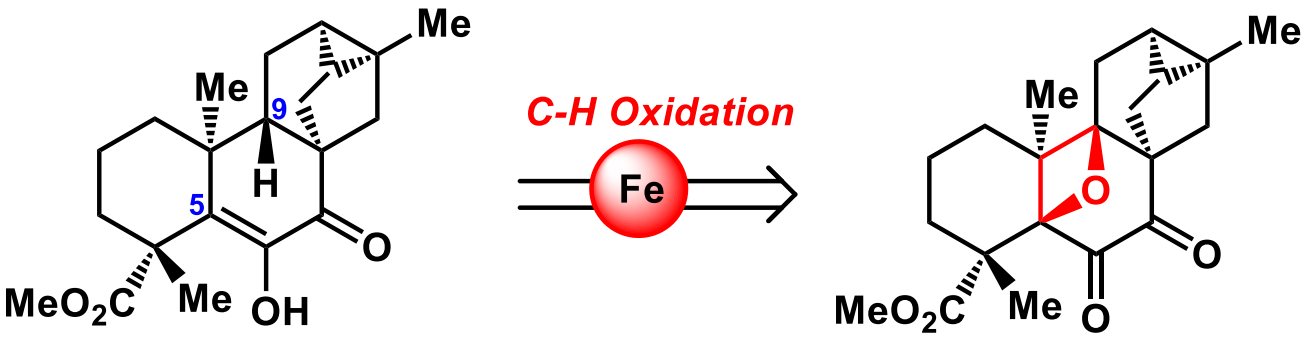
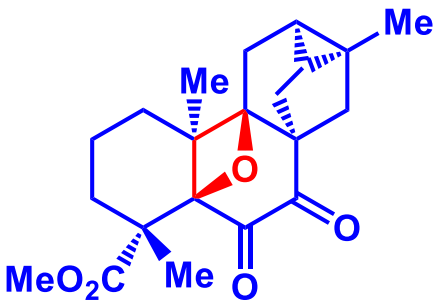
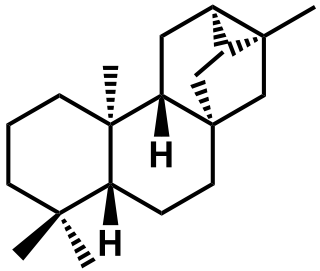


mitrephorone B (2)

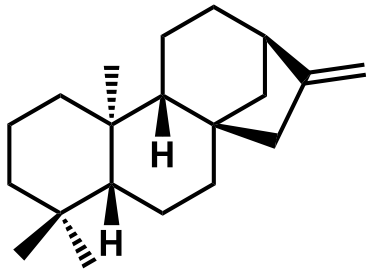
mitrephorone A (1)



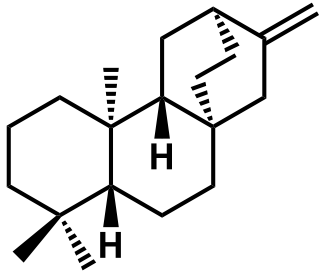
mitrephorone A (1)



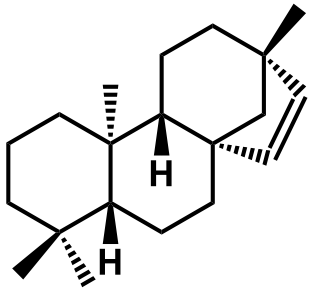
ent-trachylobane



ent-kaurene

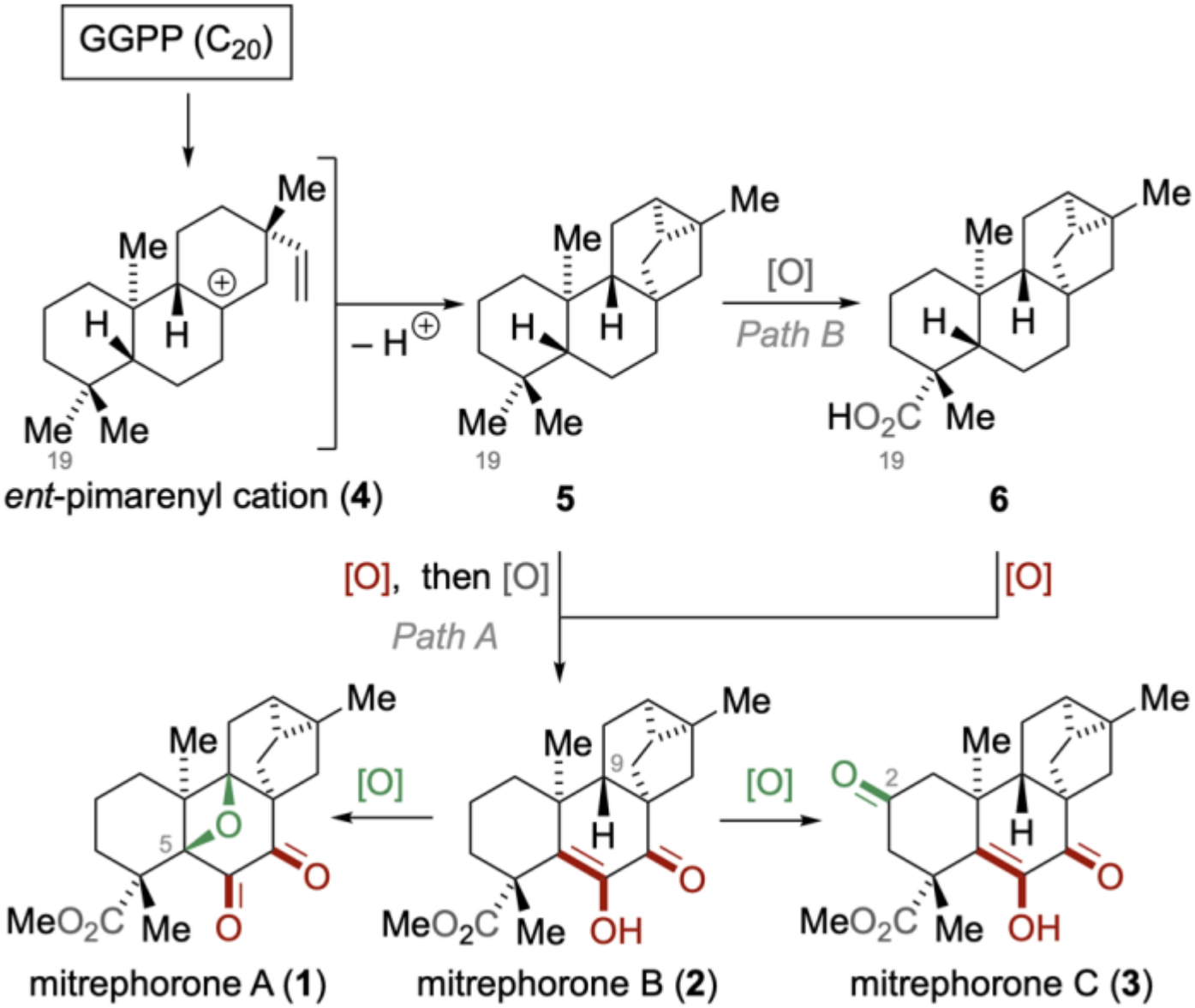


ent-atiserene

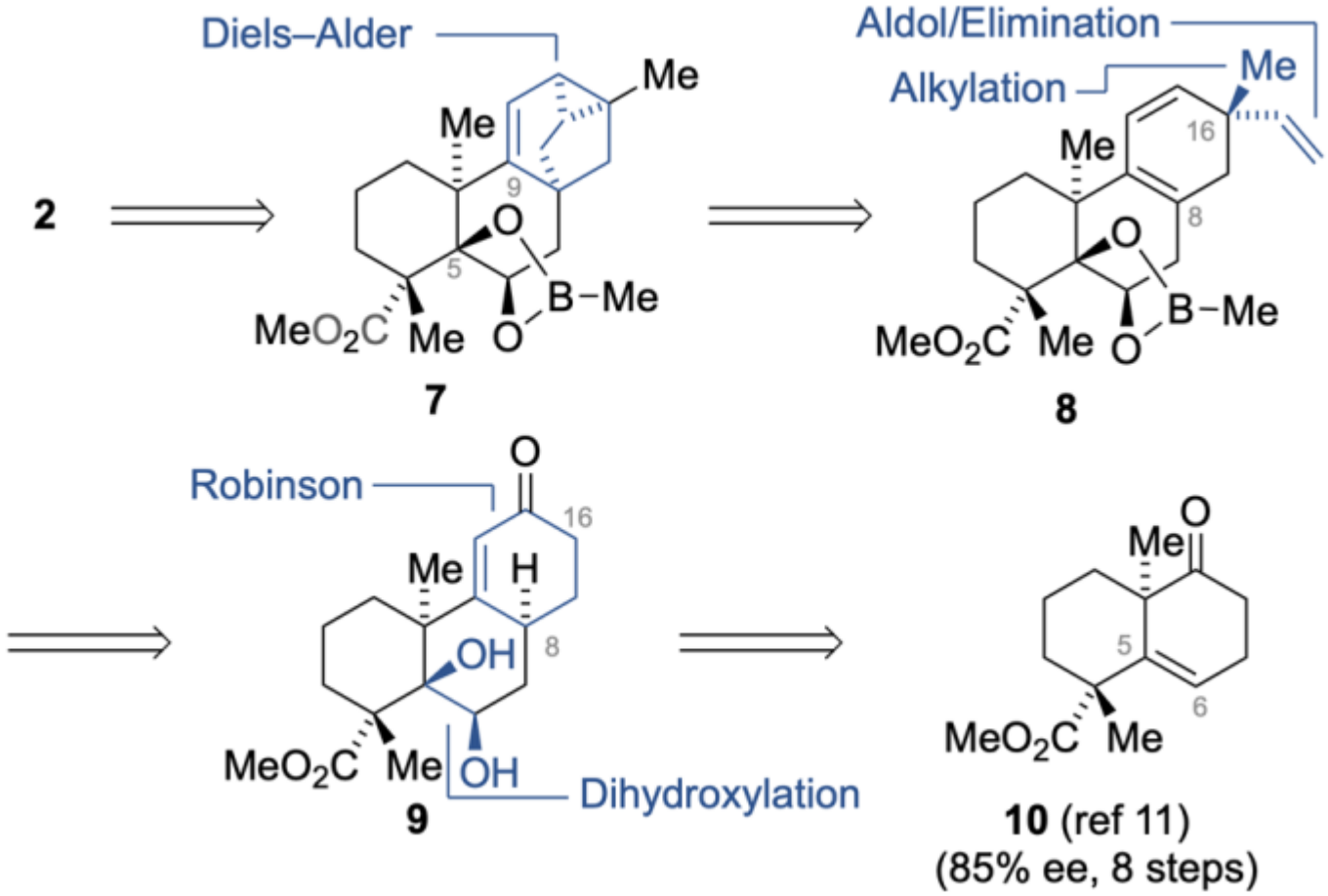


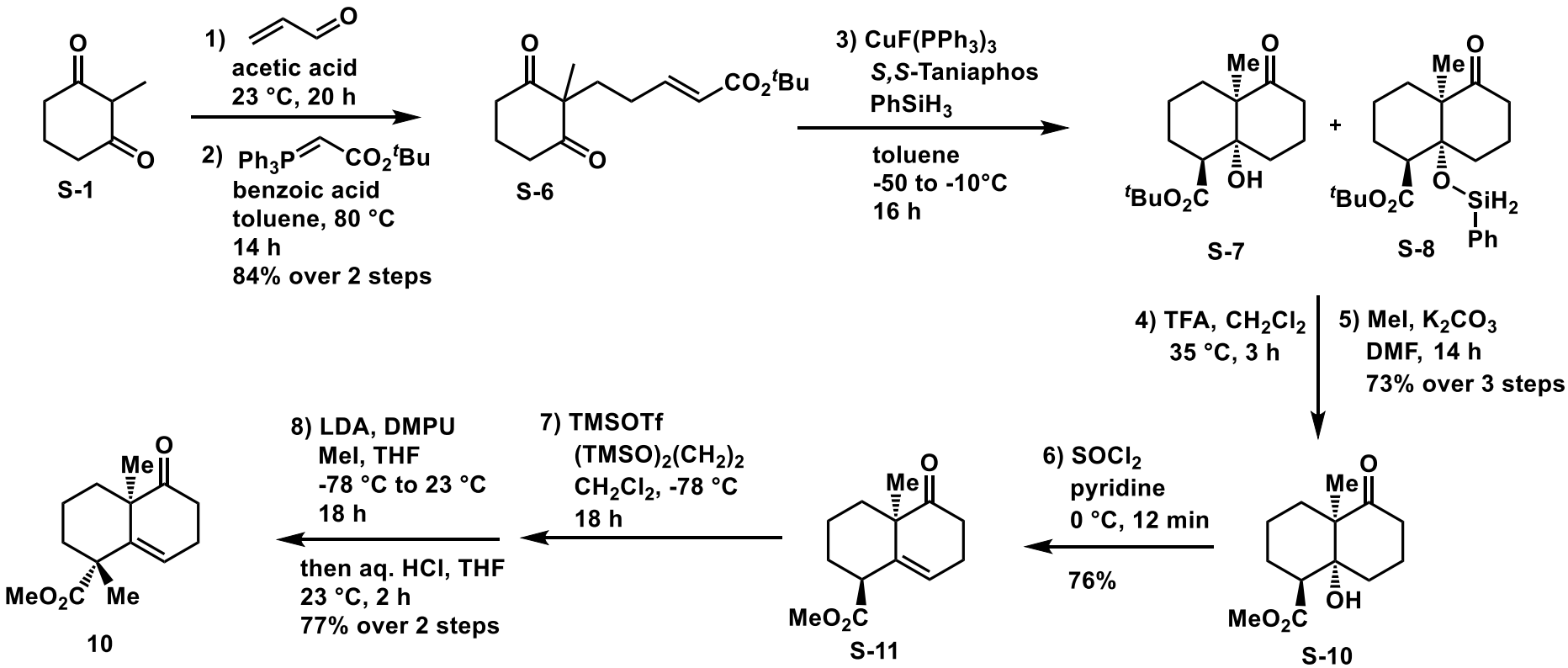
ent-beyerene

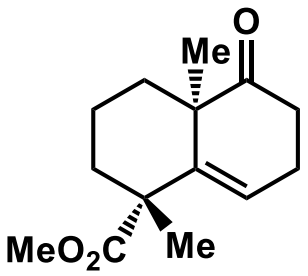
Schematic Biosynthesis of Mitrephorone A (1), B (2), and C (3)



Retrosynthetic Analysis



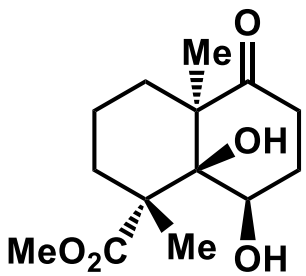

S-1
1)
acetic acid
23 °C, 20 h
2)
benzoic acid
toluene, 80 °C
14 h
84% over 2 steps
S-6
3) CuF(PPh3)3
S,S-Taniaphos
PhSiH3
toluene
-50 to -10°C
16 h
S-7
S-8
4) TFA, CH2Cl2
35 °C, 3 h
5) MeI, K2CO3
DMF, 14 h
73% over 3 steps
S-10
6) SOCl2
pyridine
0 °C, 12 min
76%
S-11
7) TMSOTf
(TMSO)2(CH2)2
CH2Cl2, -78 °C
18 h
8) LDA, DMPU
MeI, THF
-78 °C to 23 °C
18 h
then aq. HCl, THF
23 °C, 2 h
77% over 2 steps
10



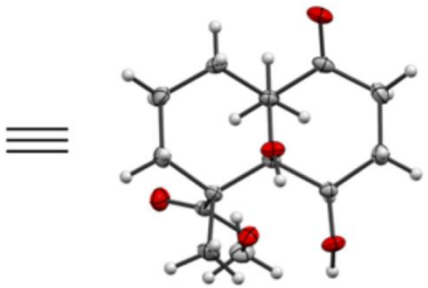
10

a) OsO_4, NMO
DABCO

acetone-H_2O
90 °C, 72 h
83%



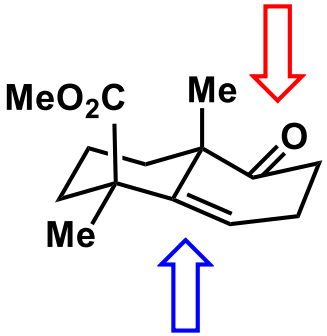
11

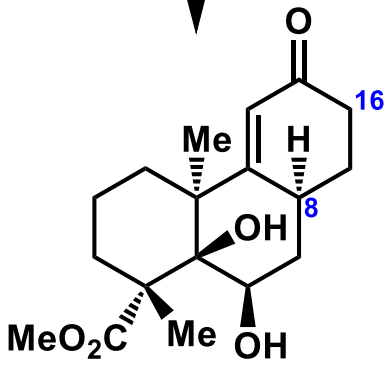


[X-ray]

b) NaH, then
MeOCHO
THF-PhMe
0 °C to 23 °C
4 h

c) MVK, NEt_3
CH_2Cl_2, 23 °C
96 h, then
NaOMe, MeOHO
44 °C, 4 h
57% over 2 steps

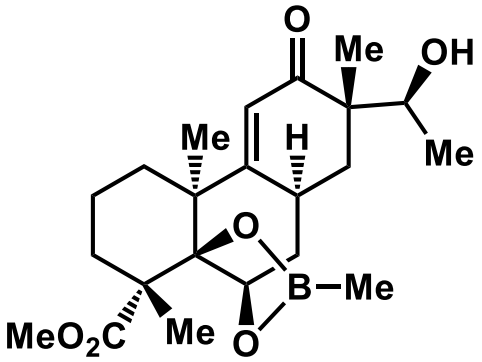




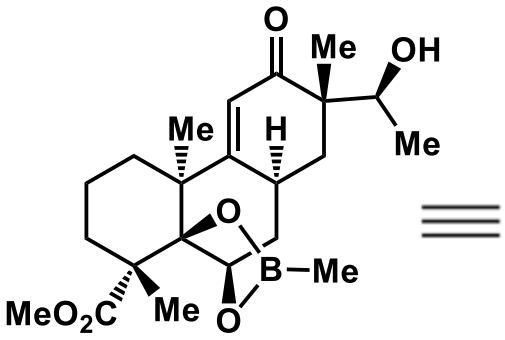
9 (dr = 20:1)

d) $MeB(OH)_2$, C_6H_6
30 °C, 2 h, 90%
e) LiHMDS, MeI, THF
-50 to 23 °C, 13 h,
82%

f) LDA, TMEDA, MeCHO
THF, -20 to -78 °C, 3 h
59%



12



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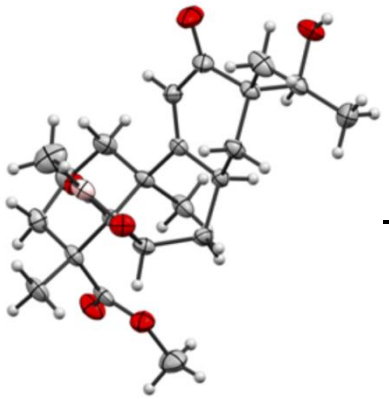
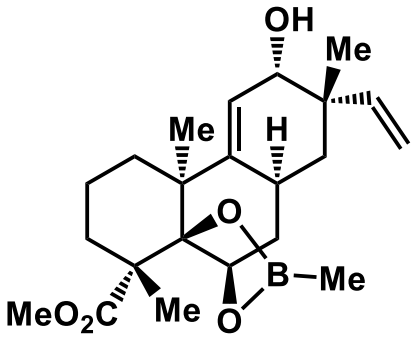


[X-ray]

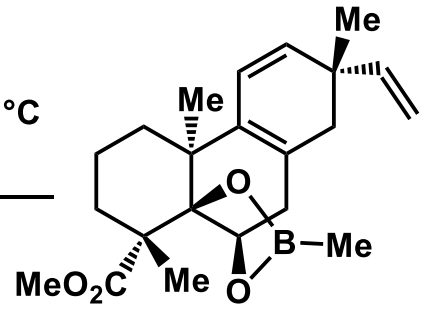
g) Martin sulfurane
23 °C, 2 h
89%

h) $NaBH_4$,
$CeCl_3 \cdot H_2O$
MeOH, 0 °C
3 h, 93%



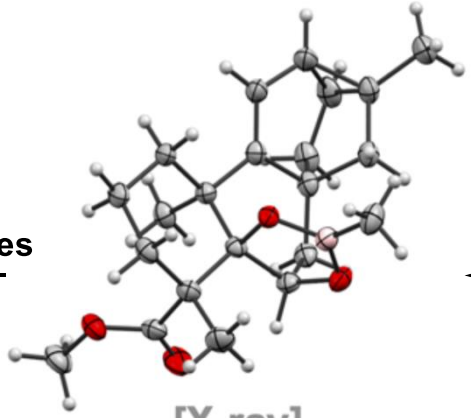
13

i) *p*-TsOH
4 Å MS, PhMe
23 °C, 40 h
96%



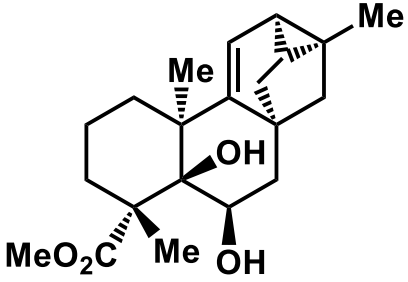
8

j) PhMe, 170 °C
3 h, 98%



[X-ray]

l) KHF_2
$MeOH\text{-}H_2O$
40 °C, 24 h
72%
over 3 cycles



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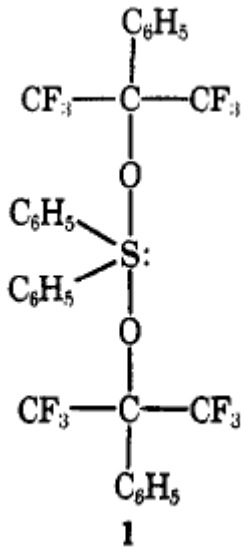
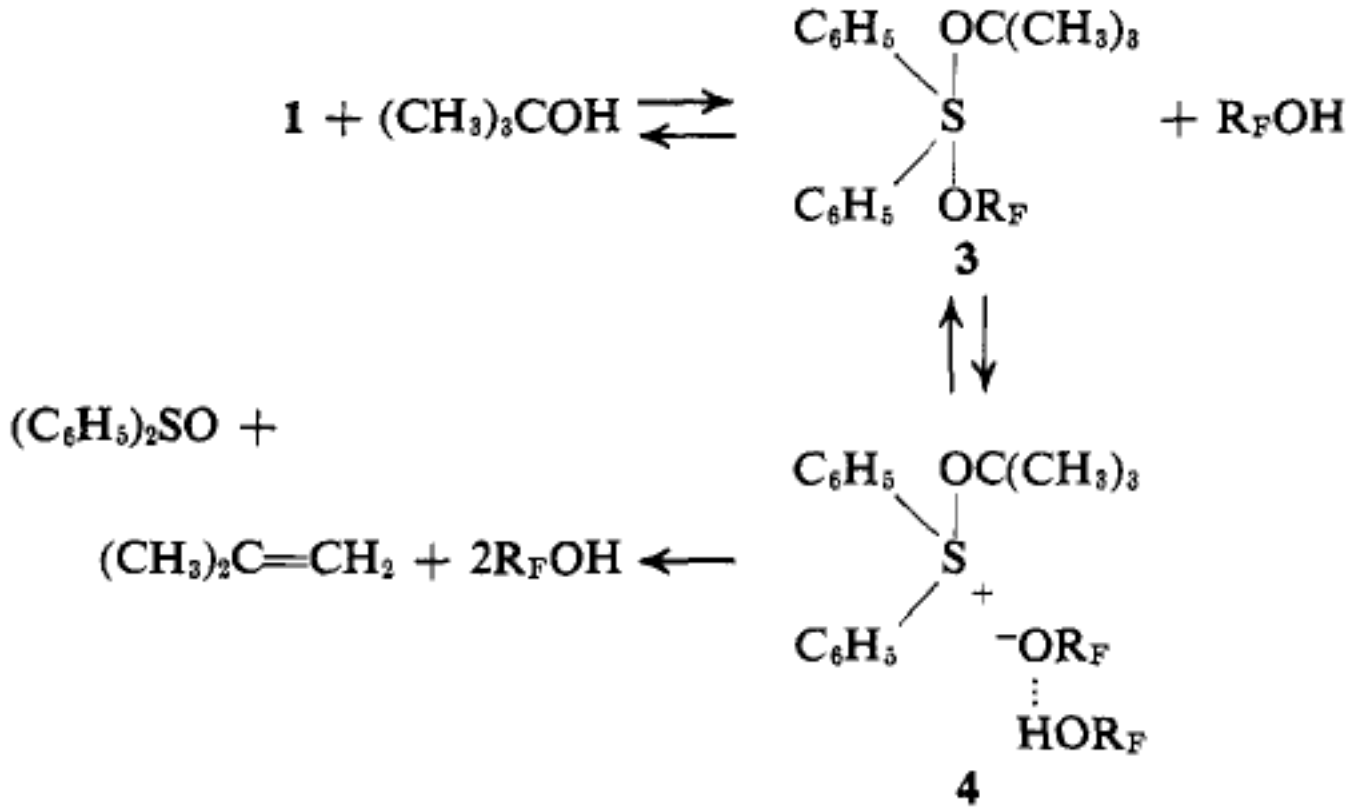
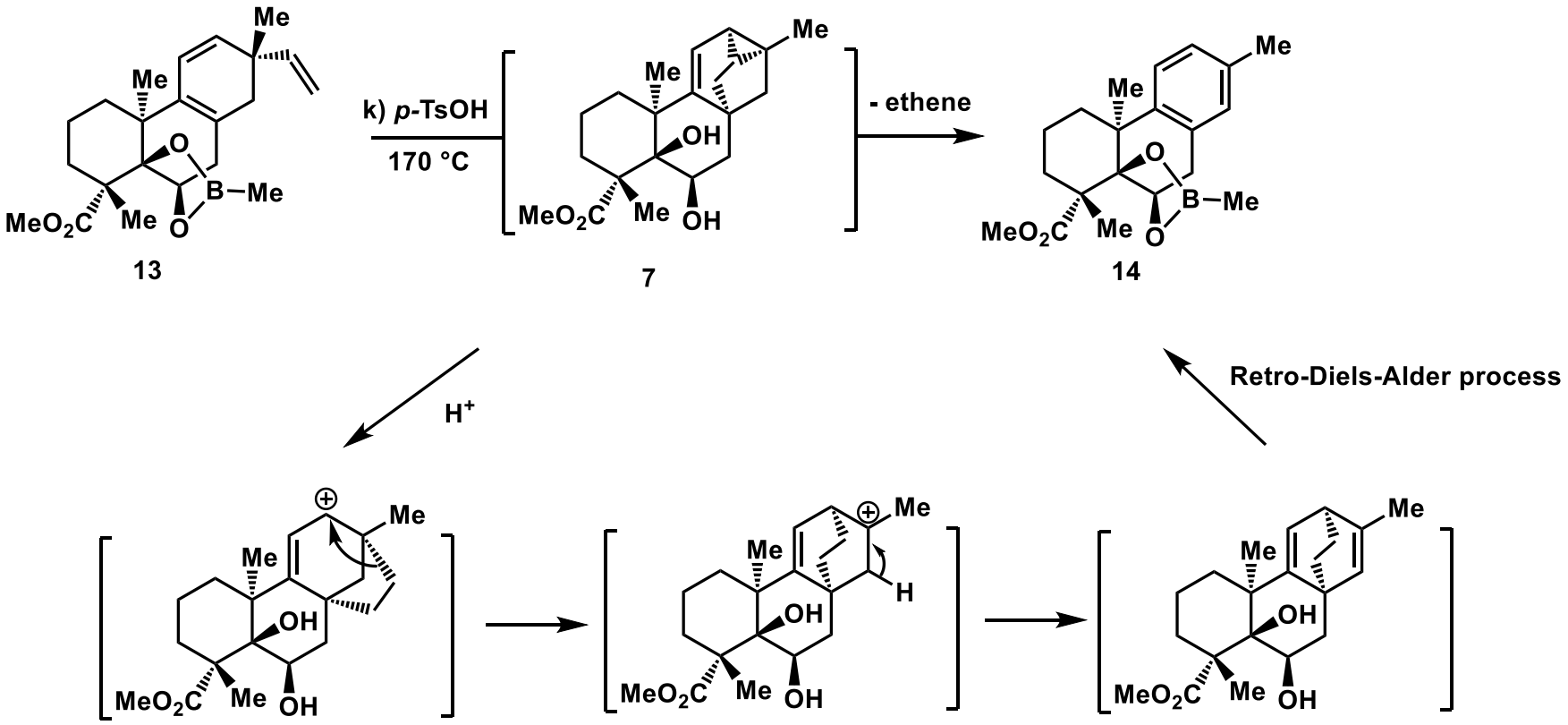


1



Martin sulfurane



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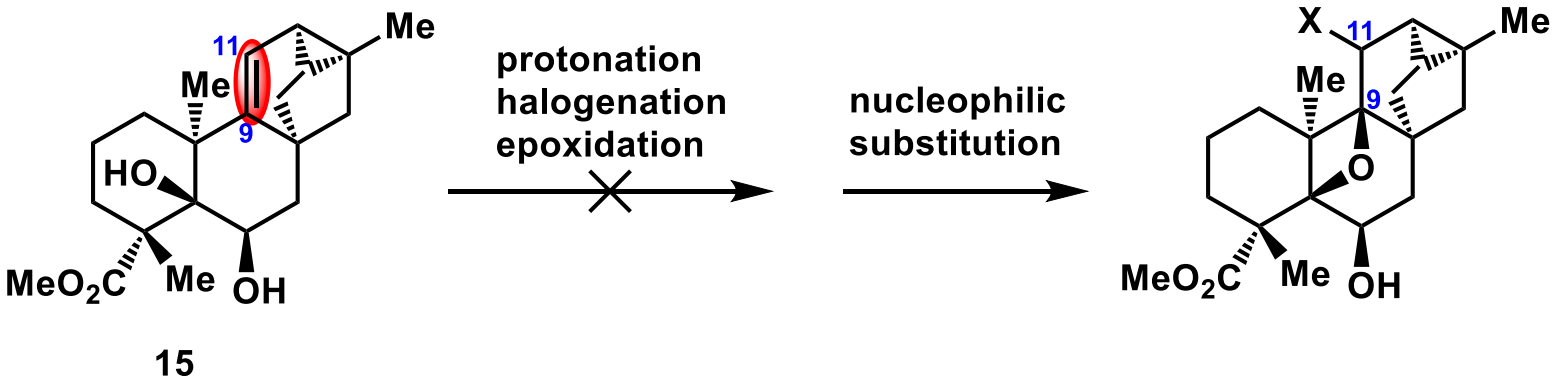
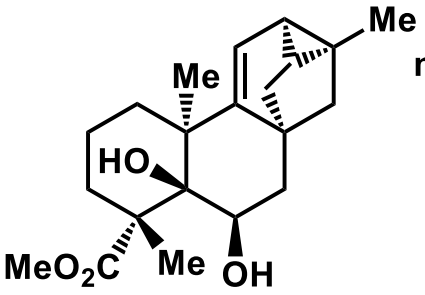

11
Me
Me
9
HO
MeO2C
Me
OH
protonation
halogenation
epoxidation
nucleophilic
substitution
X
11
Me
Me
9
O
MeO2C
Me
OH

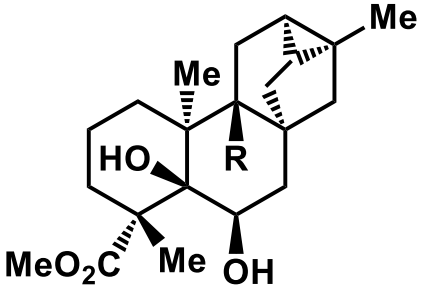
15



15

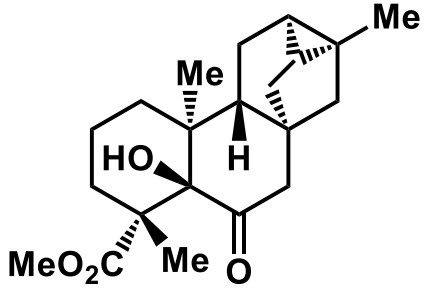
m) $Mn(dpm)_3$
$PhSiH_3$
t-BuOOH

i-PrOH
23 °C, 17 h



16: R = H (75%)
17: R = OH (22%)

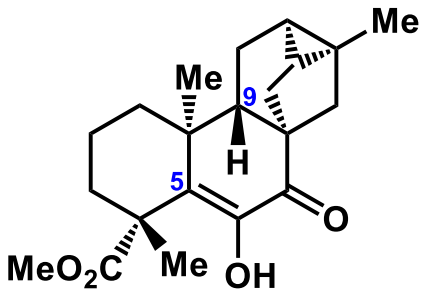
n) TPAP, NMO
4 Å MS, CH_2Cl_2
23 °C, 3 h
77%



18

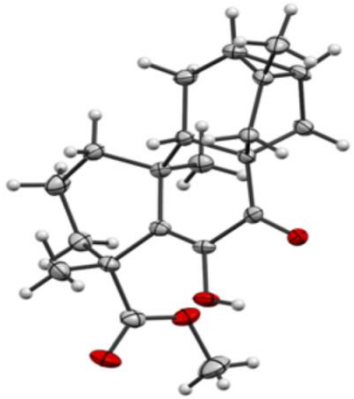
o) SmI_2
THF-MeOH
23 °C, 20 min
74%

p) SeO_2,
1,4-dioxane
100 °C, 7 h
70%

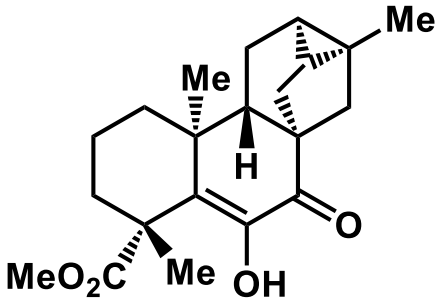


mitrephorone B (2)

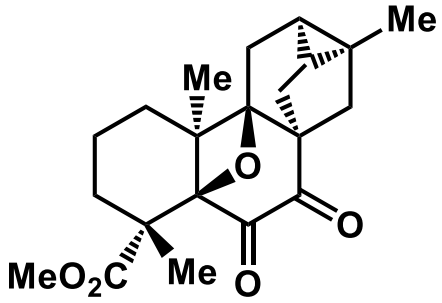
≡



[X-ray] C5–H9: 2.64 Å



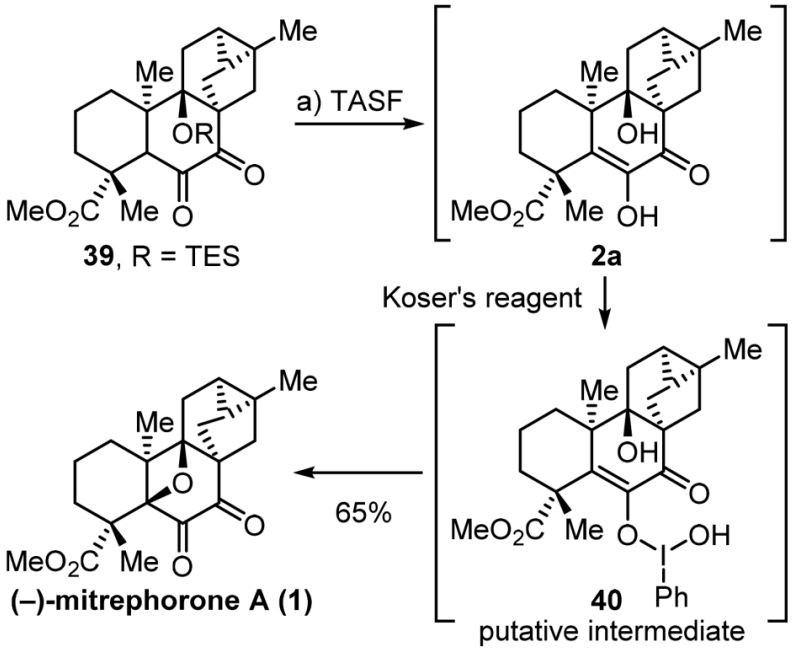
mitrephorone B (2)



mitrephorone A (1)

Conditions for C–H Oxidation

Entry	Conditions	Yield
q)	**Fe(*R*,*R*)-PDP, H_2O_2**	**60%**
r)	Fe(*S*,*S*)-PDP, H_2O_2	30%
s)	quinuclidine, 0.2 mA, 1.4–1.7 V, (+)C/(–)Ni	49%
t)	TBADT, air, MeCN, 365 nm	14%



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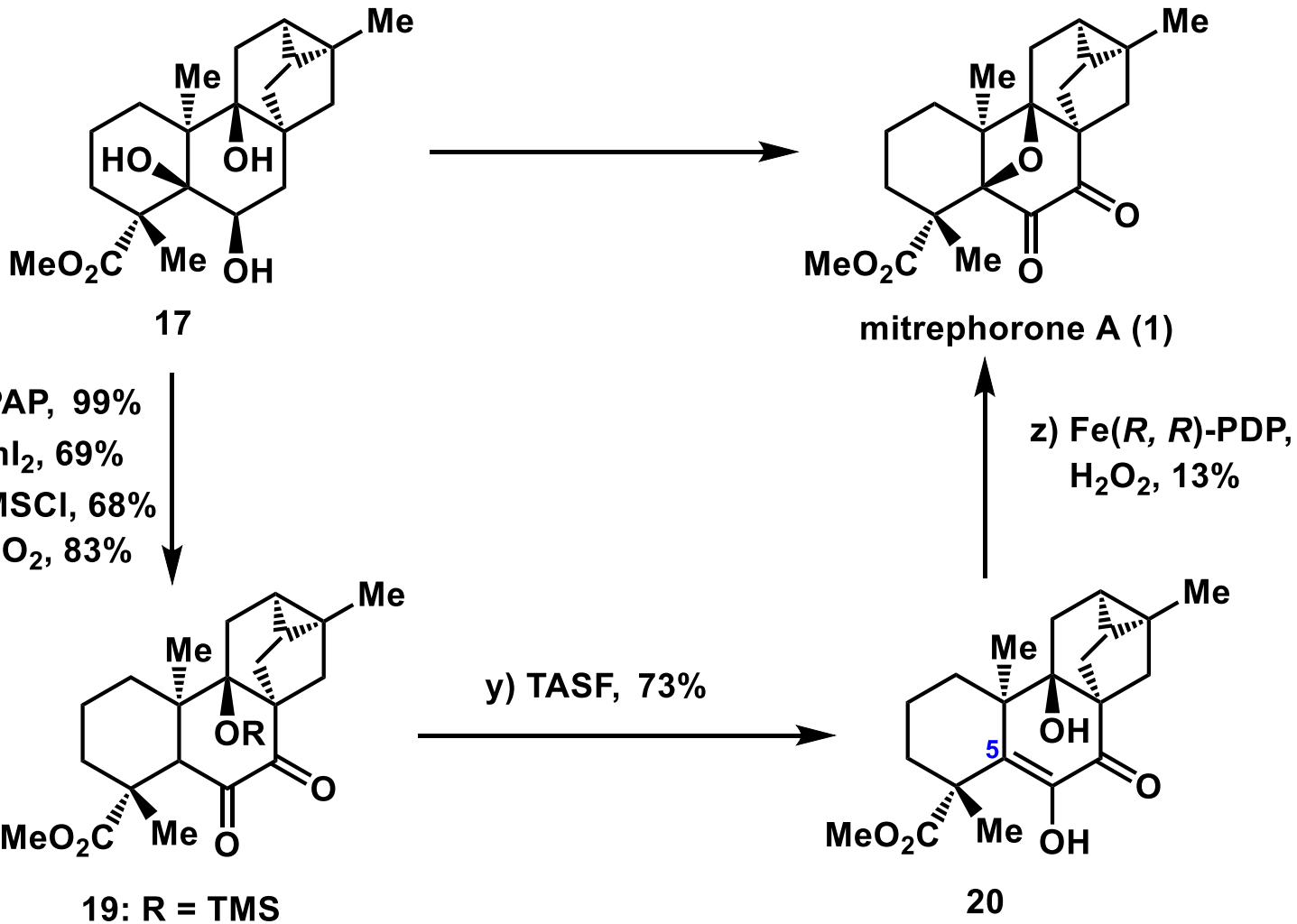
Me
Me
HO
OH
MeO2C
Me
OH
17
mitrephorone A (1)
u) TPAP, 99%
v) SmI2, 69%
w) TMSCl, 68%
x) SeO2, 83%
z) Fe(R, R)-PDP,
H2O2, 13%
y) TASF, 73%
OR
19: R = TMS
5
20

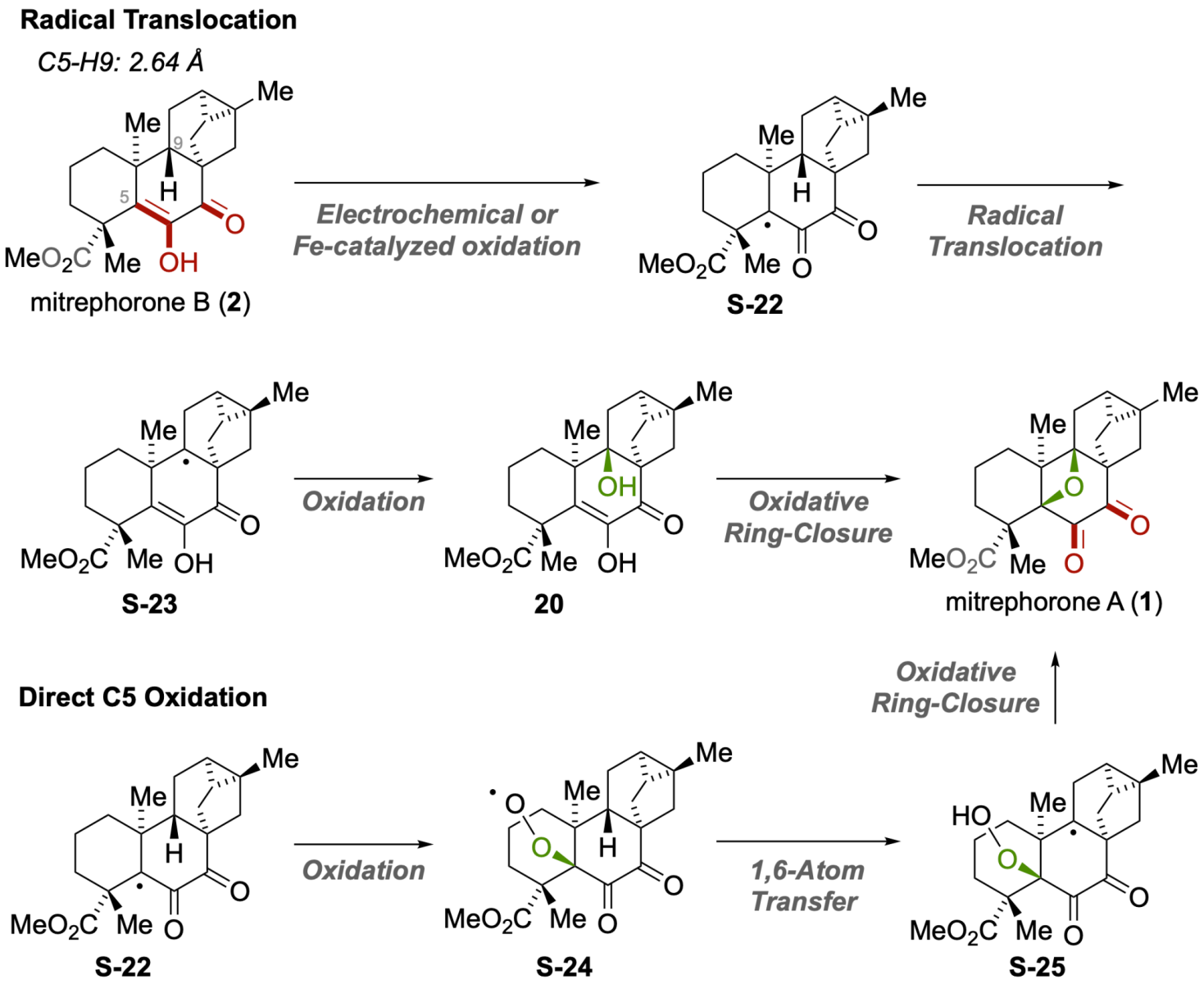

Figure 3. Putative mechanistic scenarios for selective C–H oxidation of mitrephorone B (**2**) to mitrephorone A (**1**).