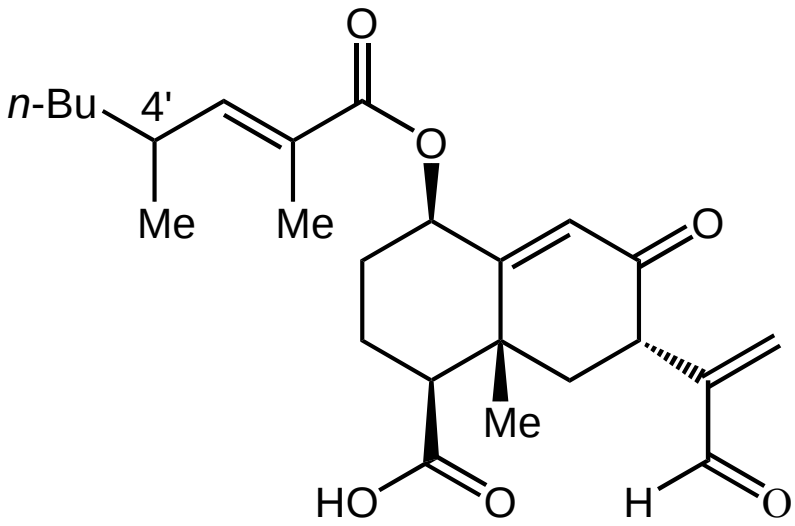
**Literature Report**

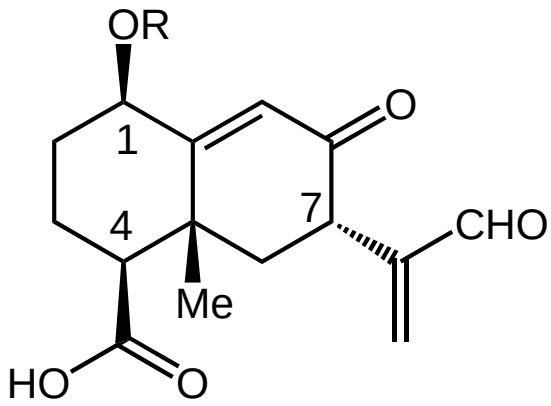
Changbin Yu 2009-11-10 检查: 高凯

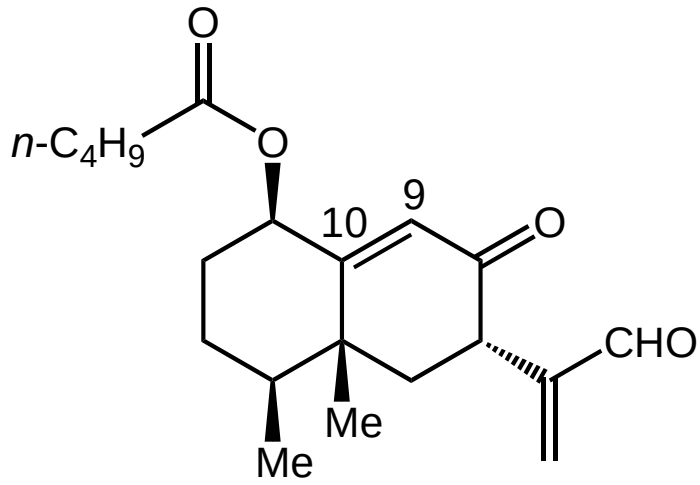
# Total Synthesis and Absolute Stereochemistry of Integric Acid

Floris P. J. T. Rutjes. *et al*. *J. Org. Chem.* **2009**, *74*, 5516

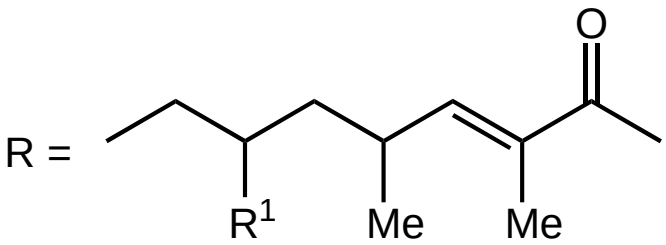



integric acid

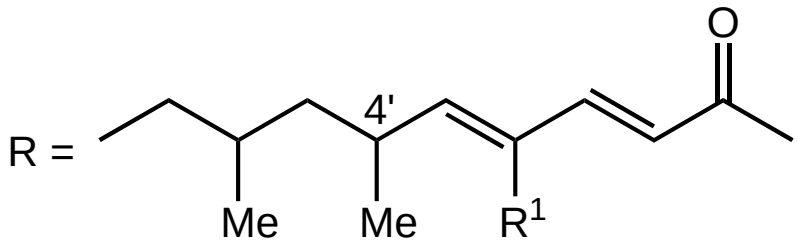


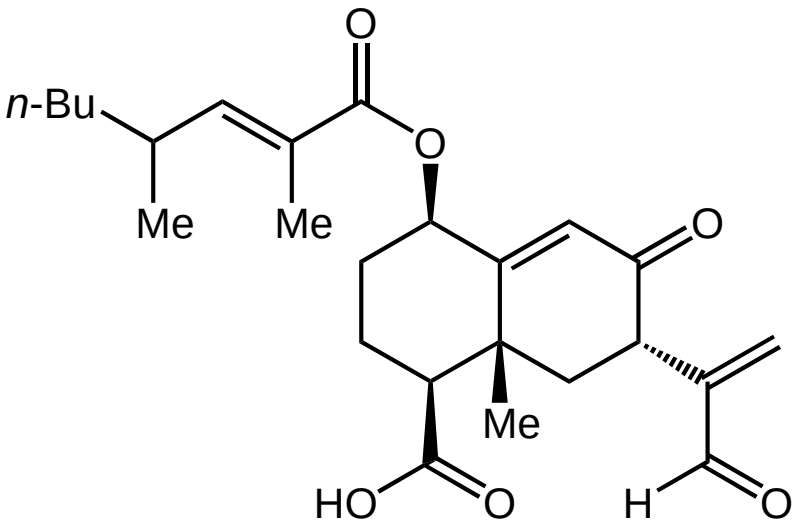

**4a**: xylarenal A
**4b**: xylarenal B: 9,10-epoxy




**1**: $R^1$ = H; integric acid
**2b**: $R^1$ = Me; eremoxylarin B




**3**: $R^1$ = H; 07H239-A
**2b**: $R^1$ = Me; eremoxylarin A

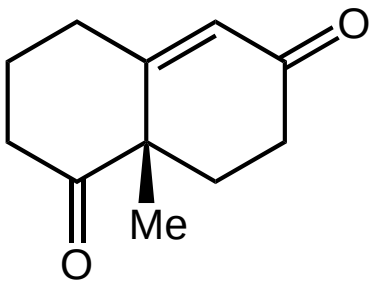



integric acid

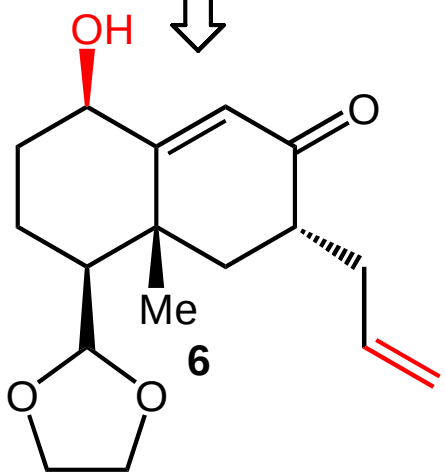
esterification

5

oxidative cleavage

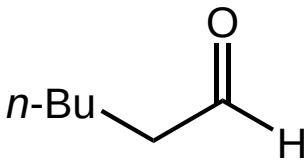



**7**: Wieland-Miescher ketone

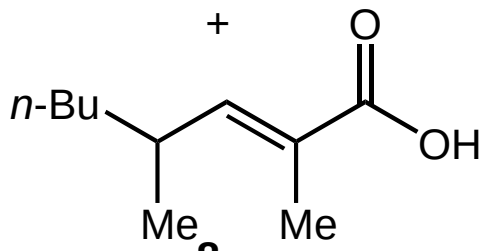



**6**

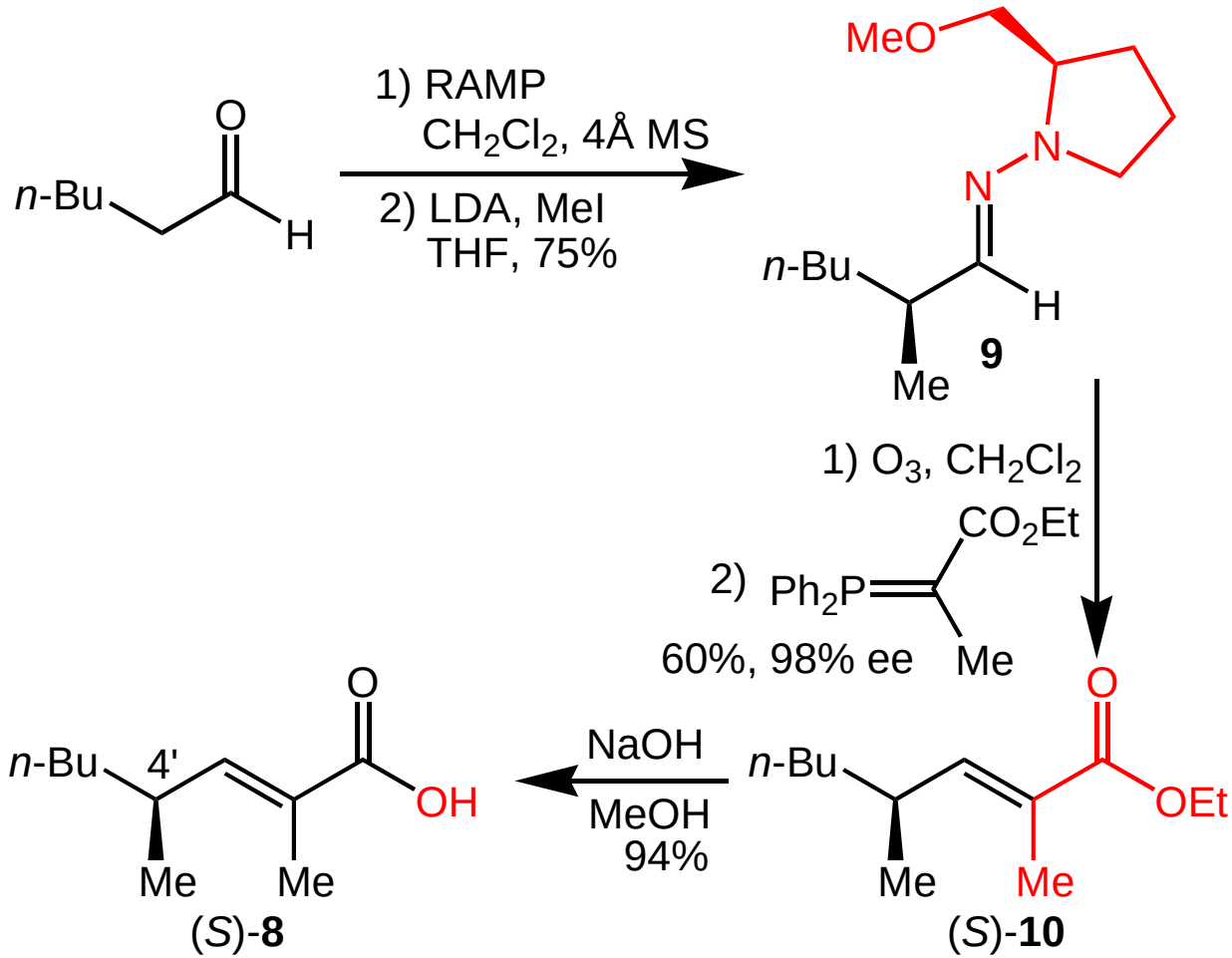
+

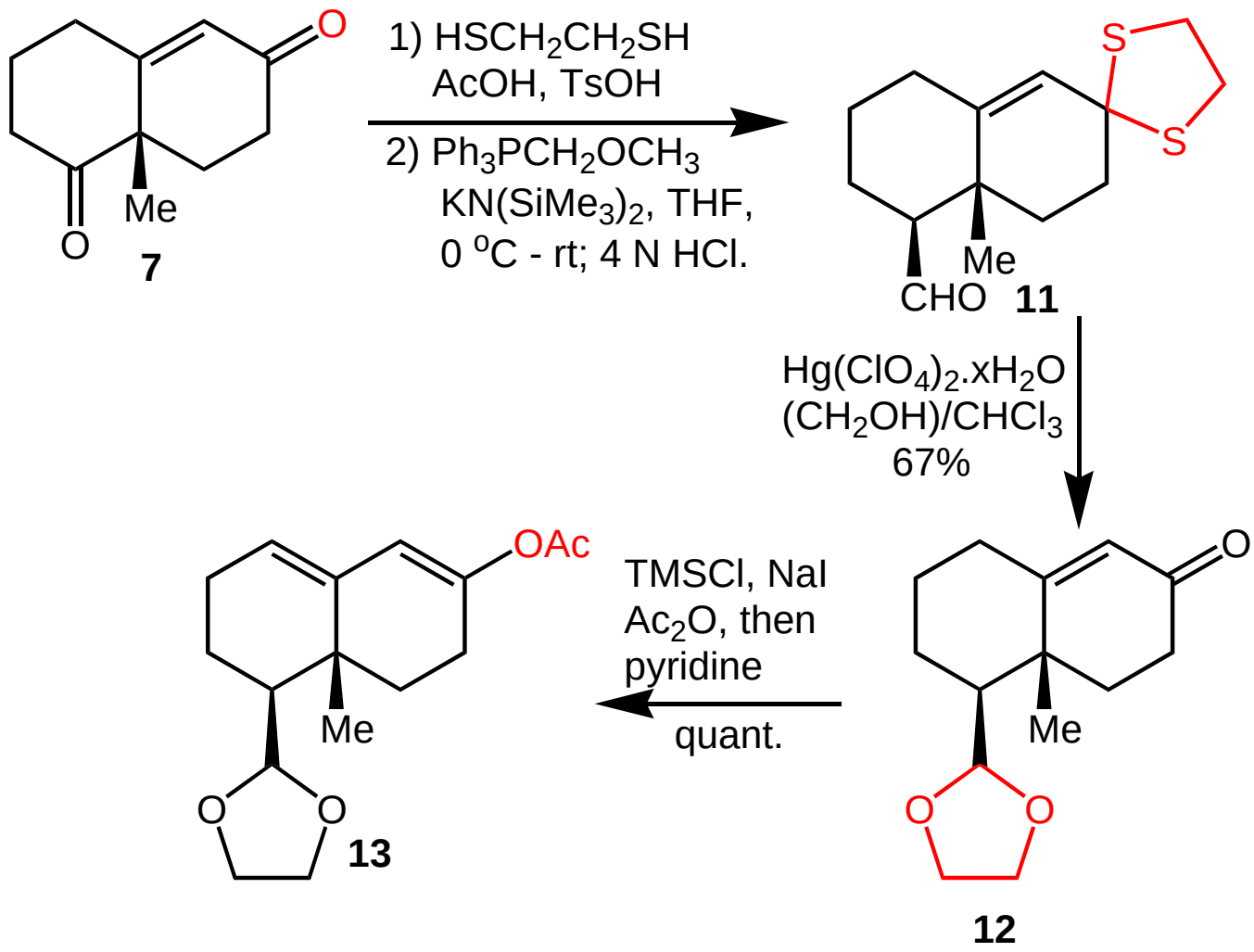


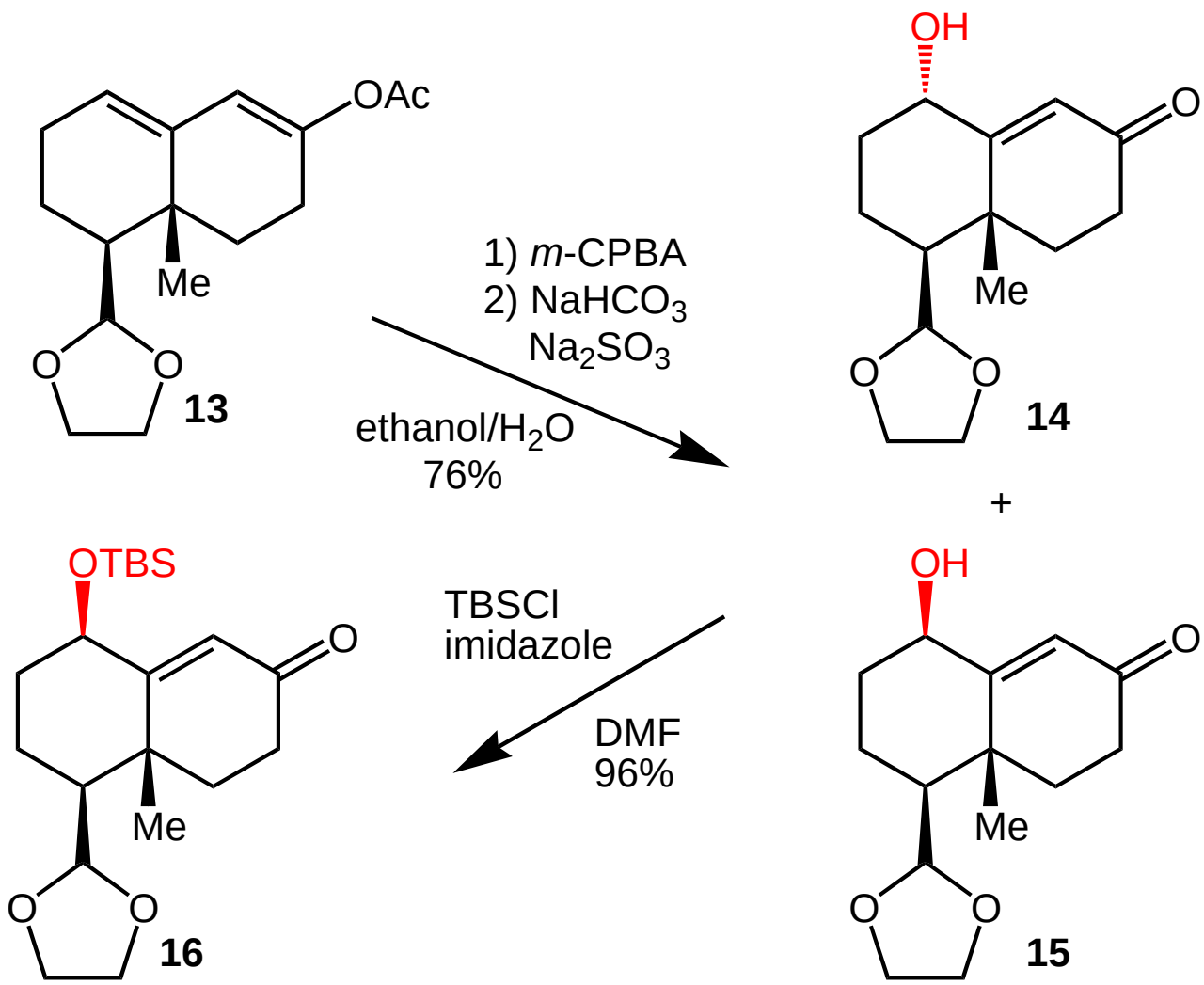

hexanal

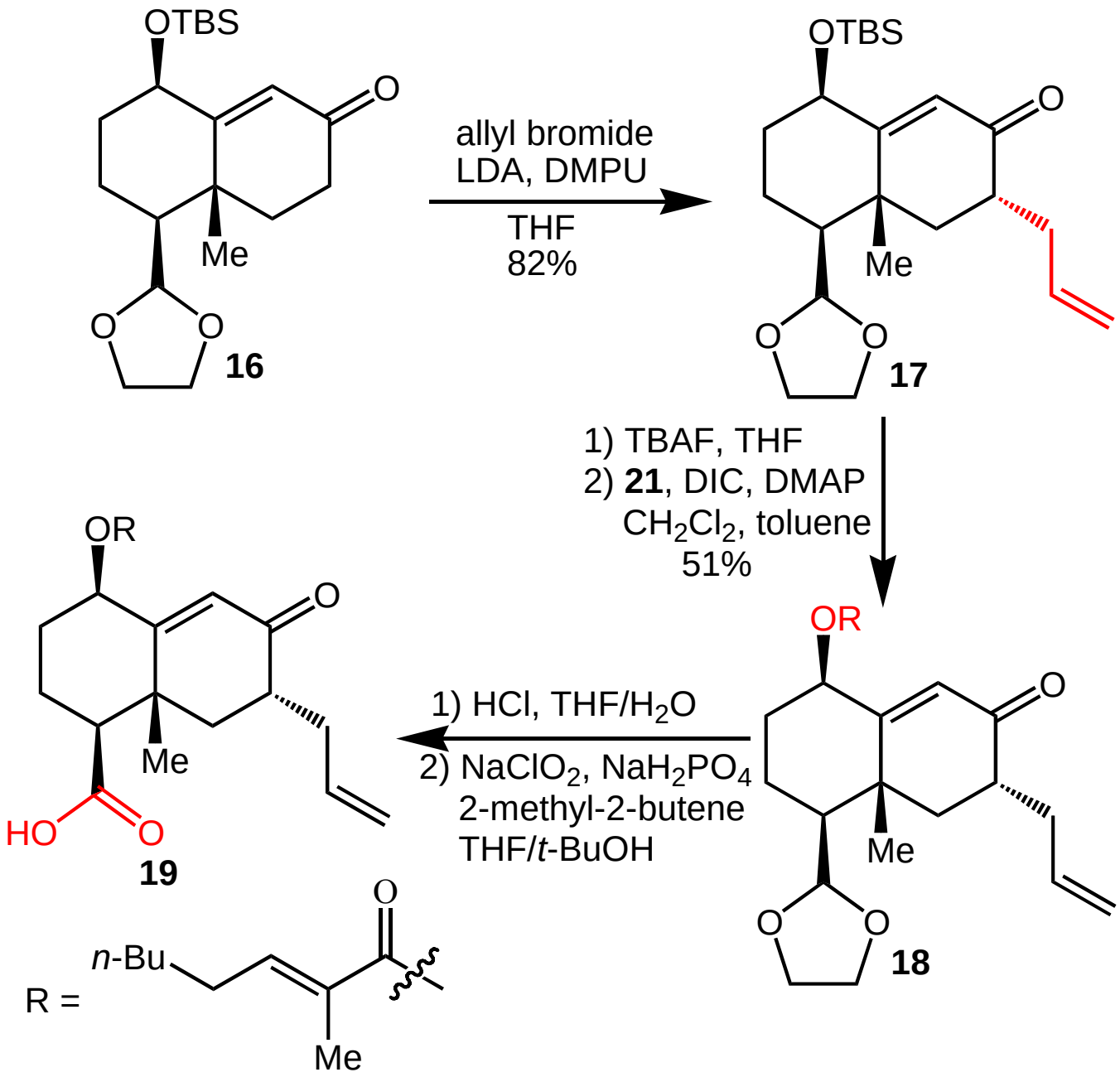


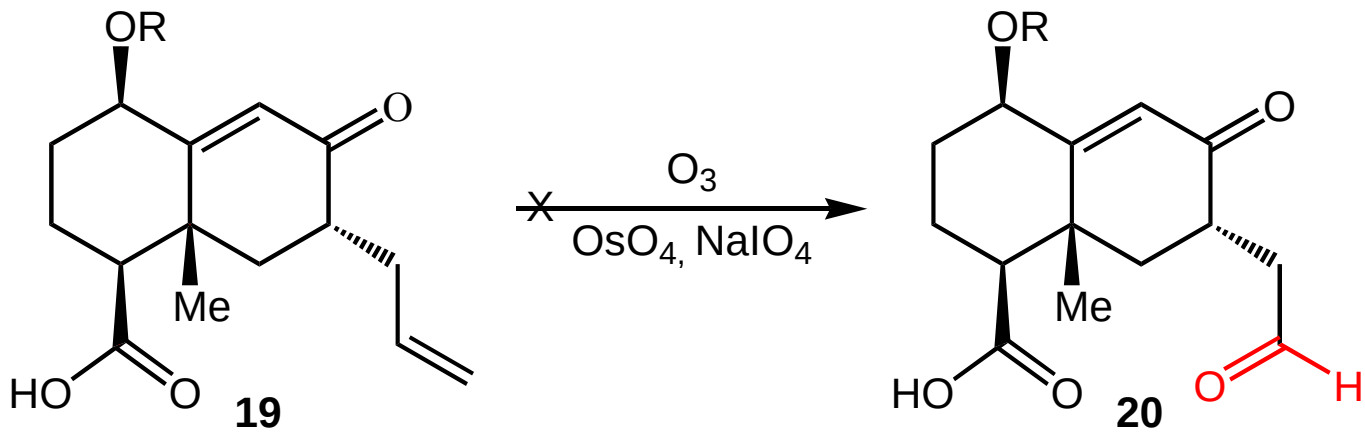

**8**

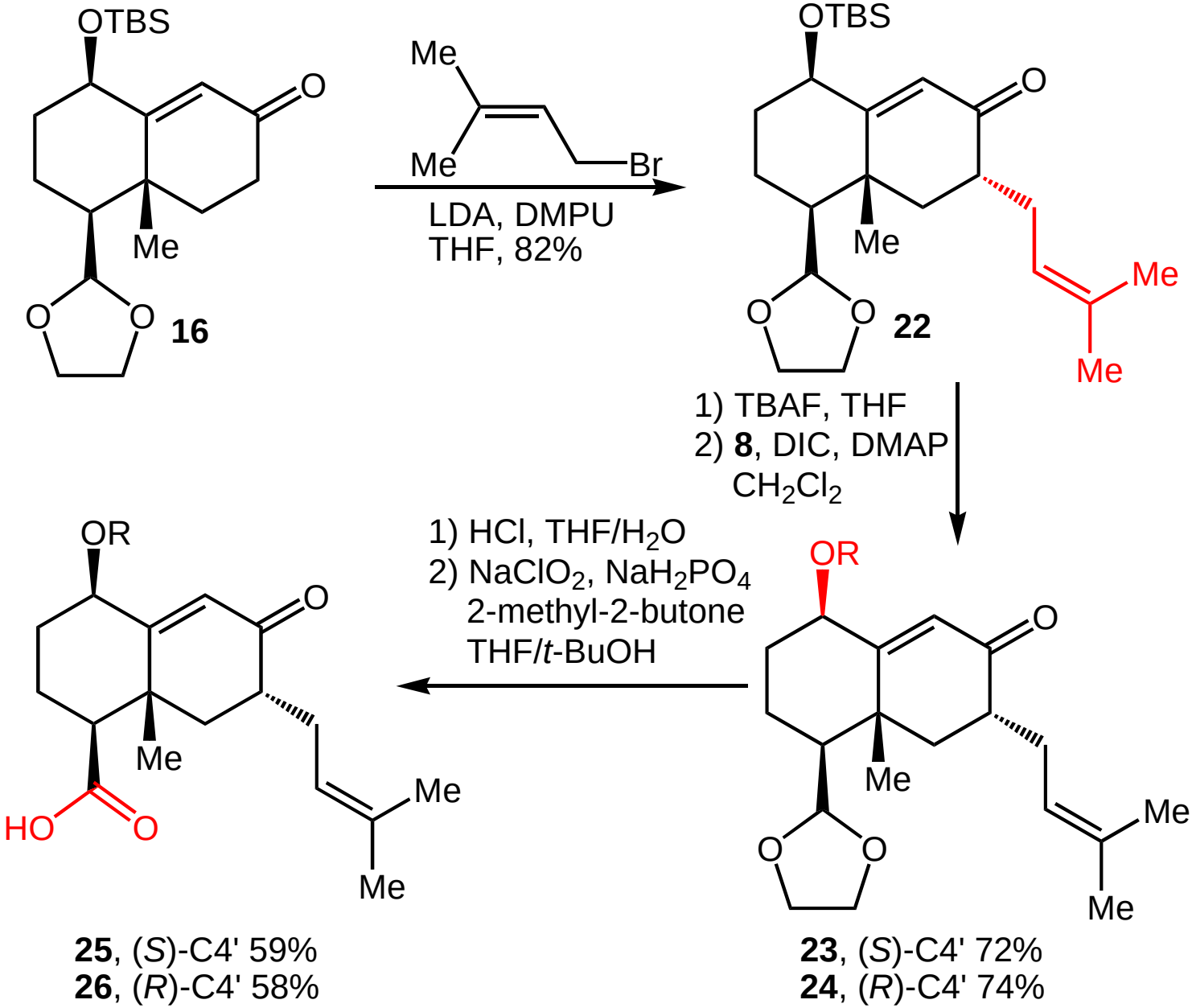

1) RAMP
CH2Cl2, 4Å MS
2) LDA, MeI
THF, 75%
n-Bu
H
O
MeO
N
N
n-Bu
H
Me
9
1) O3, CH2Cl2
2)
CO2Et
Ph2P
Me
60%, 98% ee
O
n-Bu
OEt
Me
Me
(S)-10
NaOH
MeOH
94%
n-Bu
4'
OH
O
Me
Me
(S)-8

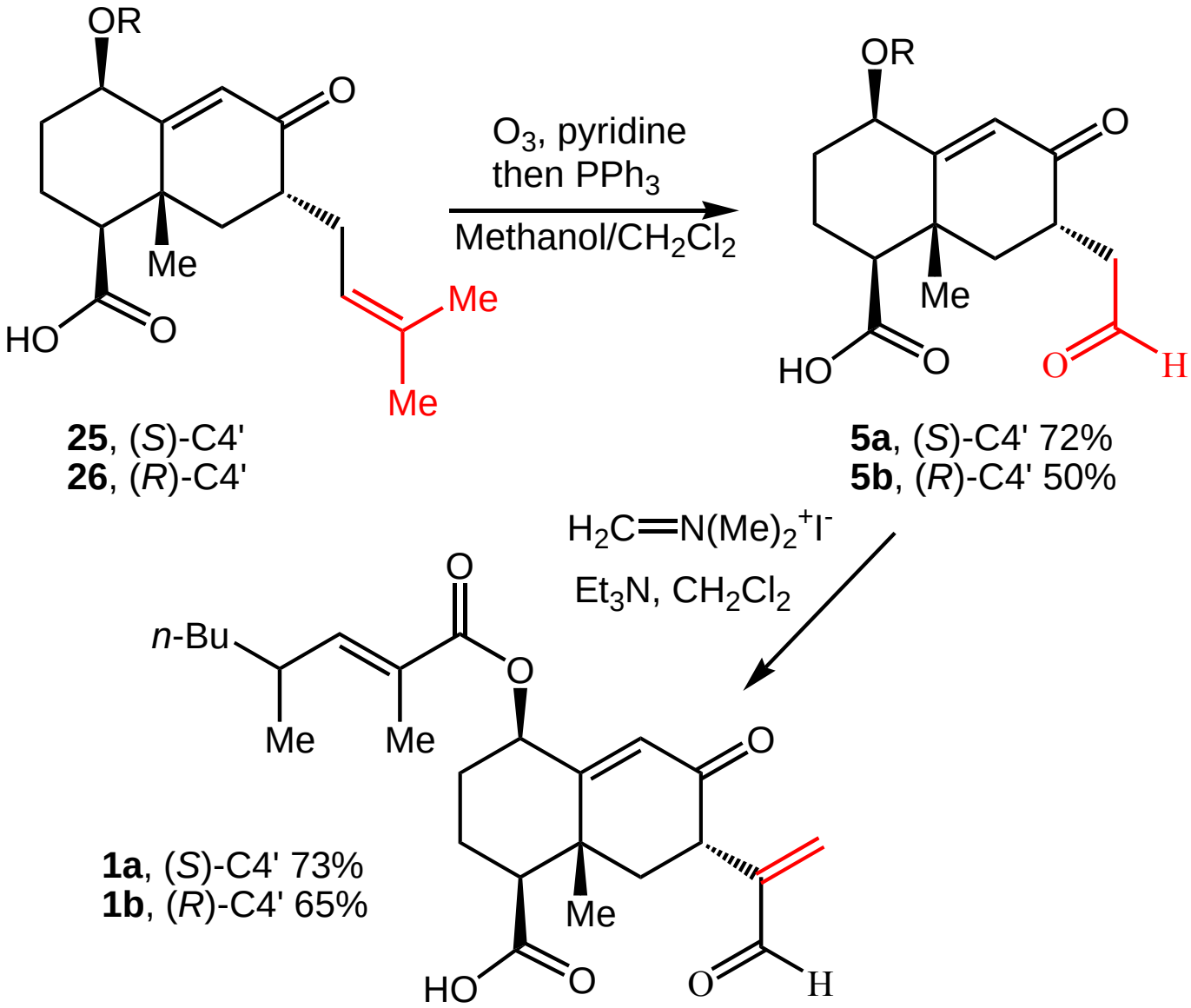

O
Me
O
7
1) HSCH2CH2SH
AcOH, TsOH
2) Ph3PCH2OCH3
KN(SiMe3)2, THF,
0 °C - rt; 4 N HCl.
S
S
Me
CHO
11
Hg(ClO4)2.xH2O
(CH2OH)/CHCl3
67%
O
Me
O
O
12
TMSCl, NaI
Ac2O, then
pyridine
quant.
OAc
Me
O
O
13


OAc
Me
O
O
13
1) m-CPBA
2) NaHCO3
Na2SO3
ethanol/H2O
76%
OH
O
Me
O
O
14
+
OTBS
O
Me
O
O
16
TBSCl
imidazole
DMF
96%
OH
O
Me
O
O
15


OTBS
O
Me
O
O
16
allyl bromide
LDA, DMPU
THF
82%
OTBS
O
Me
O
O
17
1) TBAF, THF
2) 21, DIC, DMAP
CH2Cl2, toluene
51%
OR
O
Me
O
O
18
1) HCl, THF/H2O
2) NaClO2, NaH2PO4
2-methyl-2-butene
THF/t-BuOH
OR
O
Me
HO
O
19
R =
n-Bu
O
Me


OR
O
Me
HO
O
19
O3
OsO4, NaIO4
OR
O
Me
HO
O
O
H
20

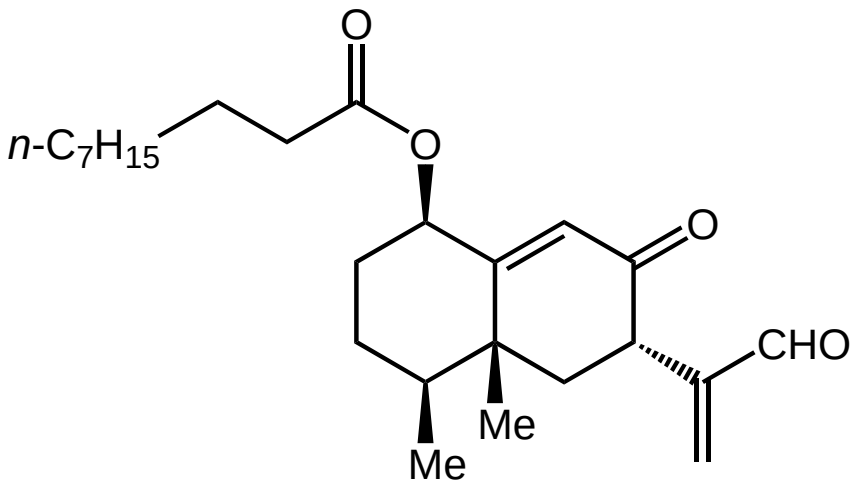

OTBS
O
Me
O
O
16
Me
Me
Br
LDA, DMPU
THF, 82%
OTBS
O
Me
O
O
22
Me
Me
1) TBAF, THF
2) 8, DIC, DMAP
CH2Cl2
OR
O
Me
O
O
Me
Me
23, (S)-C4' 72%
24, (R)-C4' 74%
1) HCl, THF/H2O
2) NaClO2, NaH2PO4
2-methyl-2-butone
THF/t-BuOH
OR
O
Me
HO
O
Me
Me
25, (S)-C4' 59%
26, (R)-C4' 58%




**25**, (*S*)-C4'
**26**, (*R*)-C4'

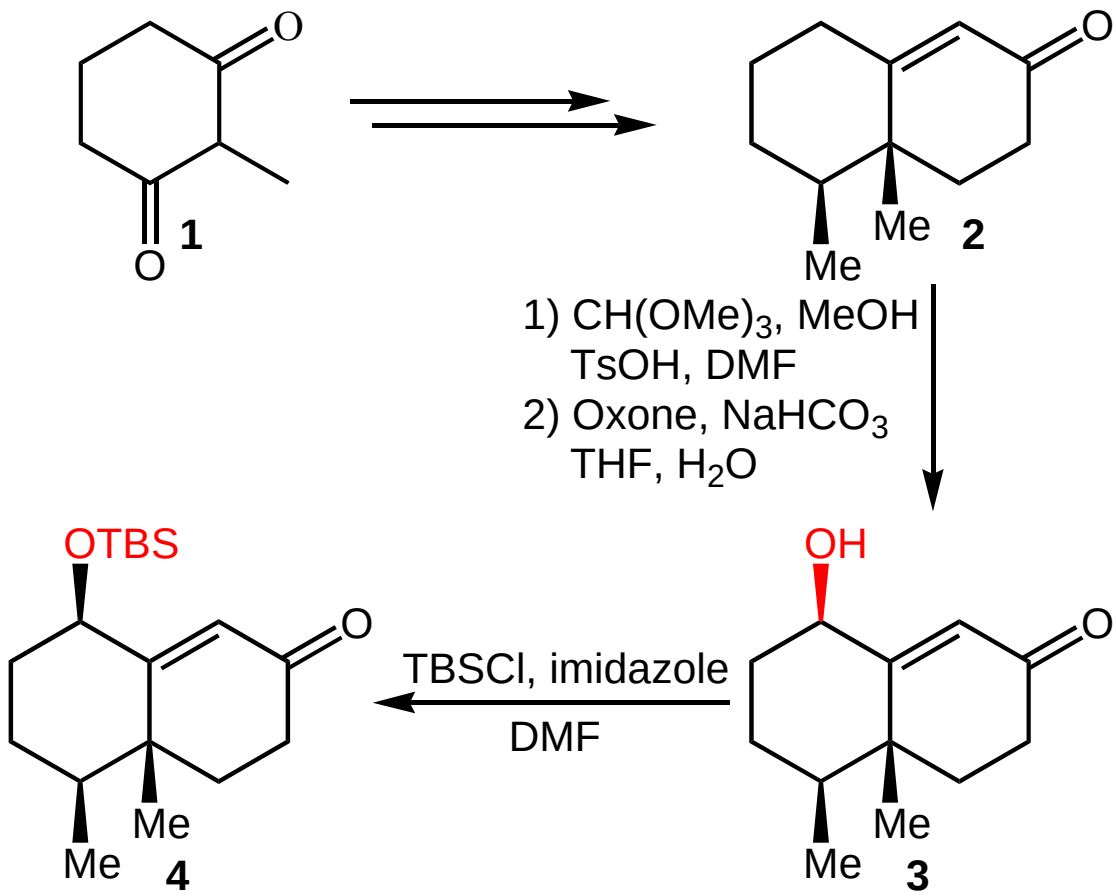
**5a**, (*S*)-C4' 72%
**5b**, (*R*)-C4' 50%

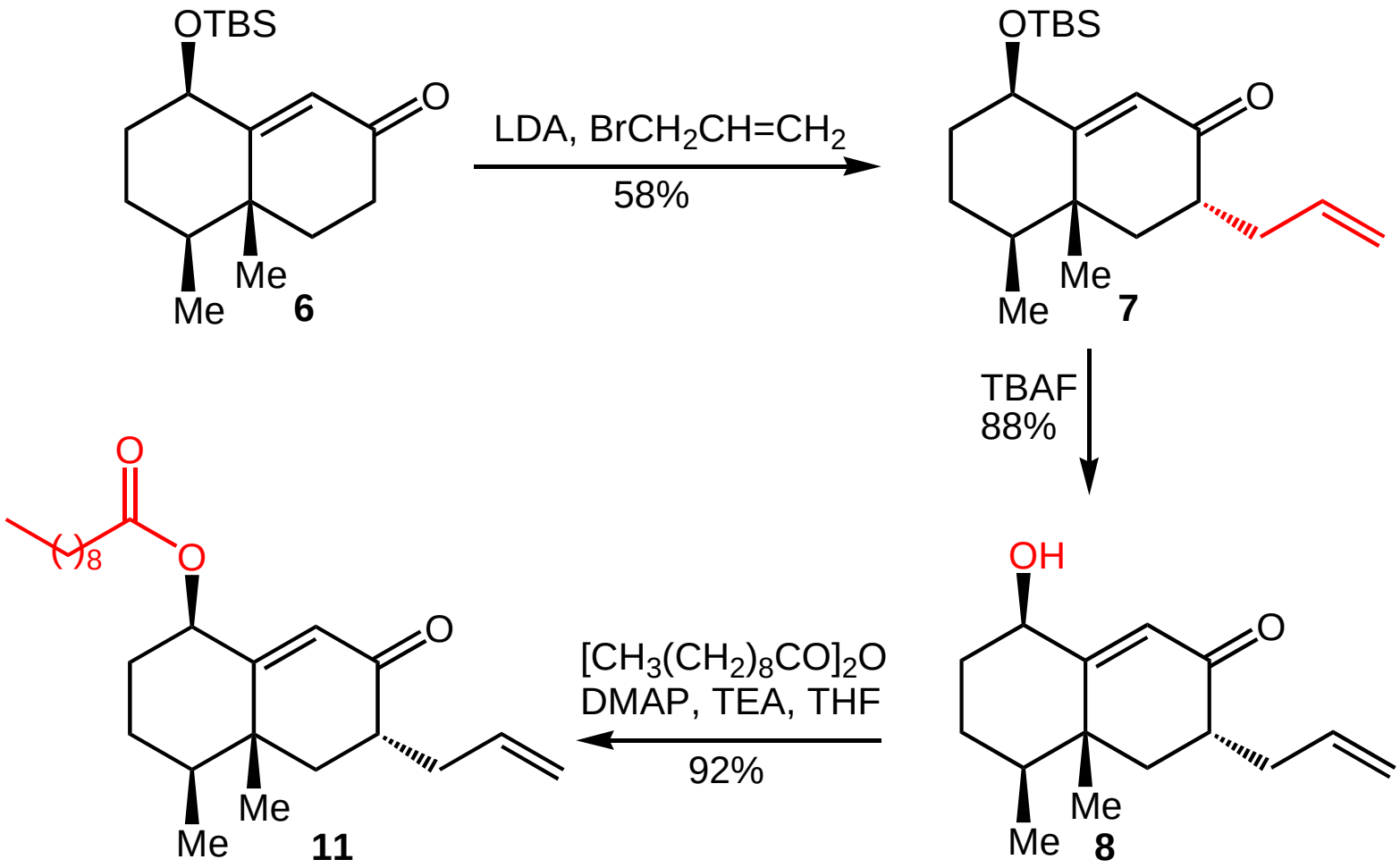
**1a**, (*S*)-C4' 73%
**1b**, (*R*)-C4' 65%

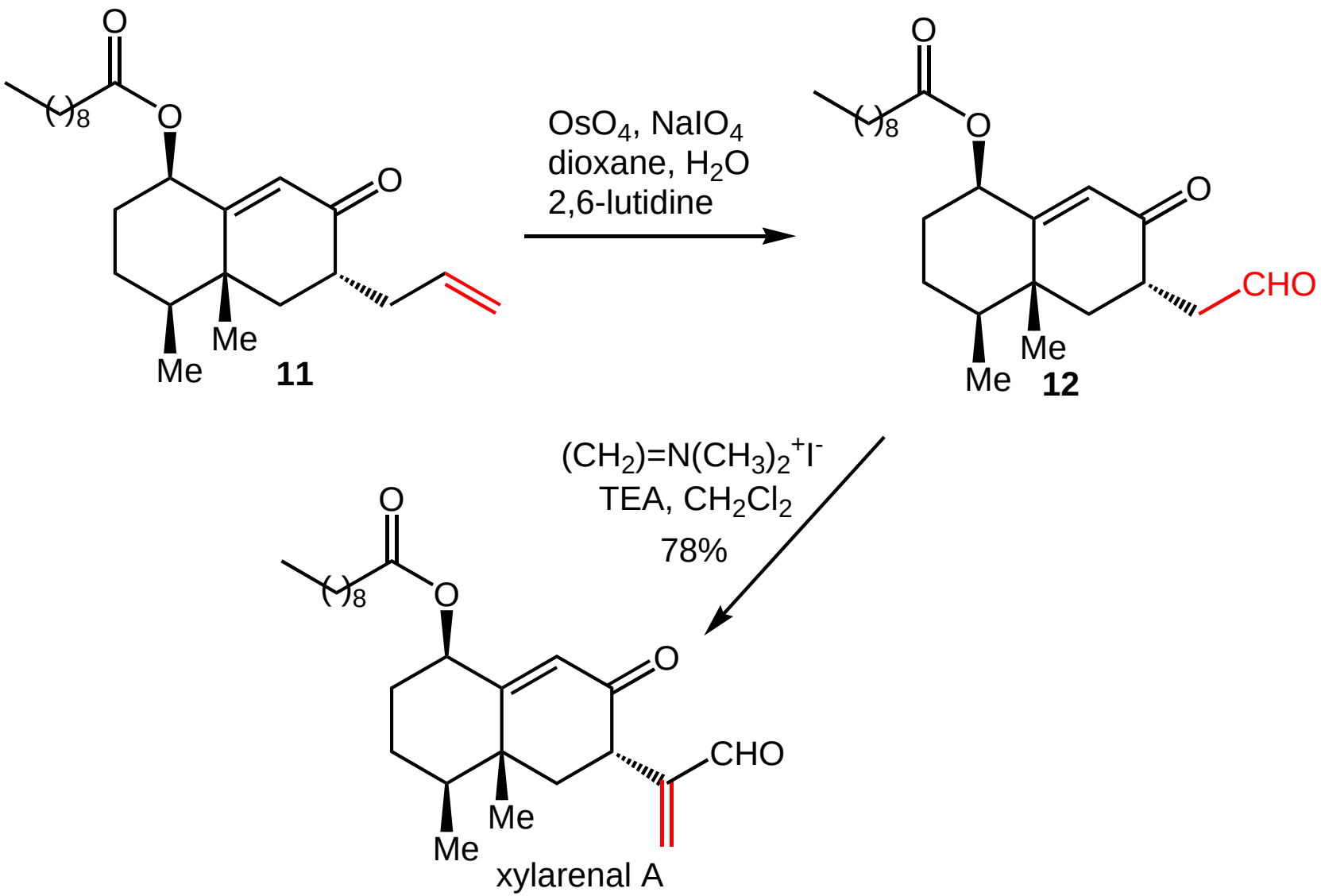



xylarenal A

Josep Bonjoch *et al*. *J. Org. Chem.* **2005**, *70*, 3749


O
O
1
Me
Me
2
1) CH(OMe)3, MeOH
TsOH, DMF
2) Oxone, NaHCO3
THF, H2O
OH
O
Me
Me
3
TBSCl, imidazole
DMF
OTBS
O
Me
Me
4


OTBS
O
Me
Me
6
LDA, BrCH2CH=CH2
58%
OTBS
O
Me
Me
7
TBAF
88%
OH
O
Me
Me
8
[CH3(CH2)8CO]2O
DMAP, TEA, THF
92%
O
()8
O
O
Me
Me
11


O
O
8
O
Me
Me
11
OsO4, NaIO4
dioxane, H2O
2,6-lutidine
O
O
8
O
CHO
Me
Me
12
(CH2)=N(CH3)2+I-
TEA, CH2Cl2
78%
O
O
8
O
CHO
Me
Me
xylarenal A

In 1999 integric acid (1) was isolated from the fermentation broth of *Xylaria sp*. The interest for HIV-1 integrase inhibitors has steadily increased over the past few years and efforts in this field have recently been rewarded with FDA approval of the first HIV-1 integrase inhibitor Raltegravir (2007). The eremophilane sesquiterpenoid structure of **1** is also encountered in natural products such as the NPY receptor inhibitors xylarenals A(**4a**) and B(**4b**), the cytotoxic 07H239-A(**3**) , and eremoxylarins A(**2a**) and B(**2b**) showing antimicrobial activity (Figure 1). Except for xylarenal **A**, no total syntheses have been developed to access this valuable compound class. In addition, the absolute configuration of integric acid was determined by the synthesis of the corresponding PGME amides. However, the stereochemistry of the chiral center at C4' in the side chain could not be assigned. Basic hydrolysis of the ester afforded (E)-2,4-dimethyloct-2-enoic acid with an optical rotation of $[\alpha]^{22}_{D}$ + 9.5 (c 0.42, MeOH),which is only indicative of(*S*)-stereochemistry at C4'.

In conclusion, we have developed an efficient total synthesis of integric acid and its C4' diastereoisomer, which has led to the unambiguous assignment of (*S*)-stereochemistry at the C4' position. The newly developed pathway in principle also allows for the synthesis of related compounds by variation of the ester substituent, such as the eremoxylarins, 07H239-A, and other derivatives.