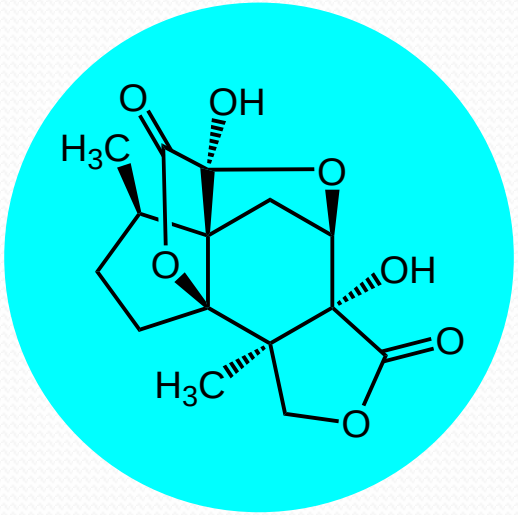
Literature Report 2014-07-08

Huang, W.-X. checker: Shi, L.

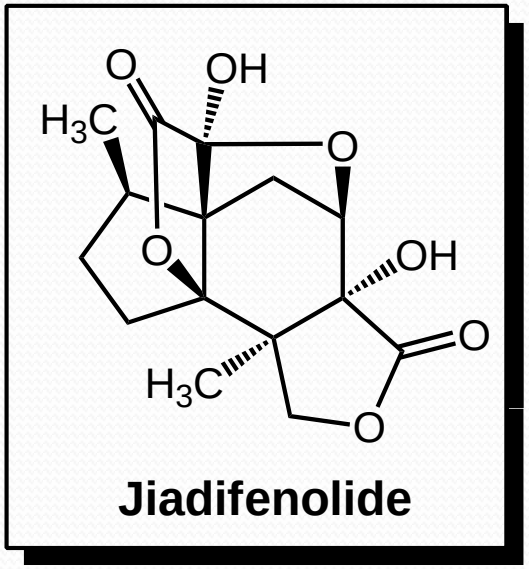
Total Synthesis of Jiadifenolide



Paterson, I. *et al.*
Angew. Chem. Int. Ed. **2014**, *53*, 7286.

Contents

1. Introduction of Jiadifenolide

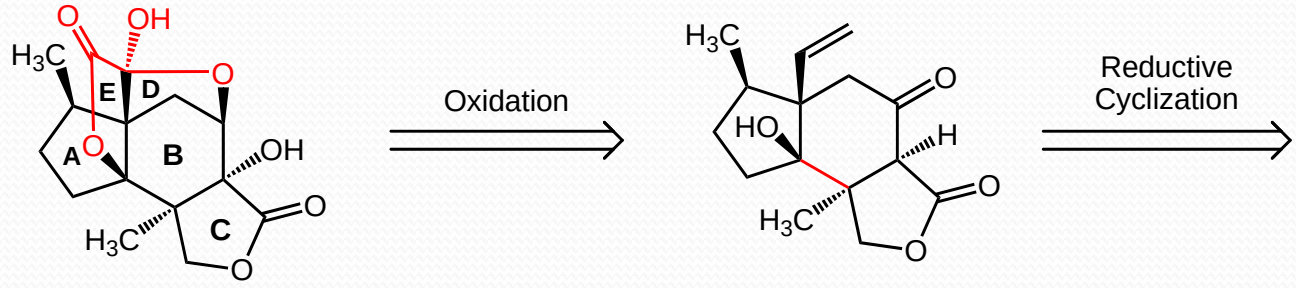


Jiadifenolide

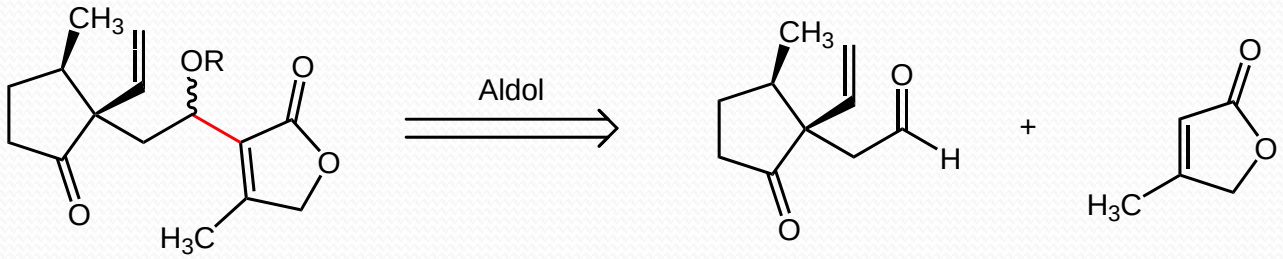
1. **Isolated from the pericarps of Chinese plant *Ilicium jiadifengpi*;**
2. **Significantly potentiate neurite outgrowth;**
3. **Intricate ring system with seven contiguous stereocenters.**

2. Total Synthesis by Paterson Group

2.1 Retrosynthetic Analysis

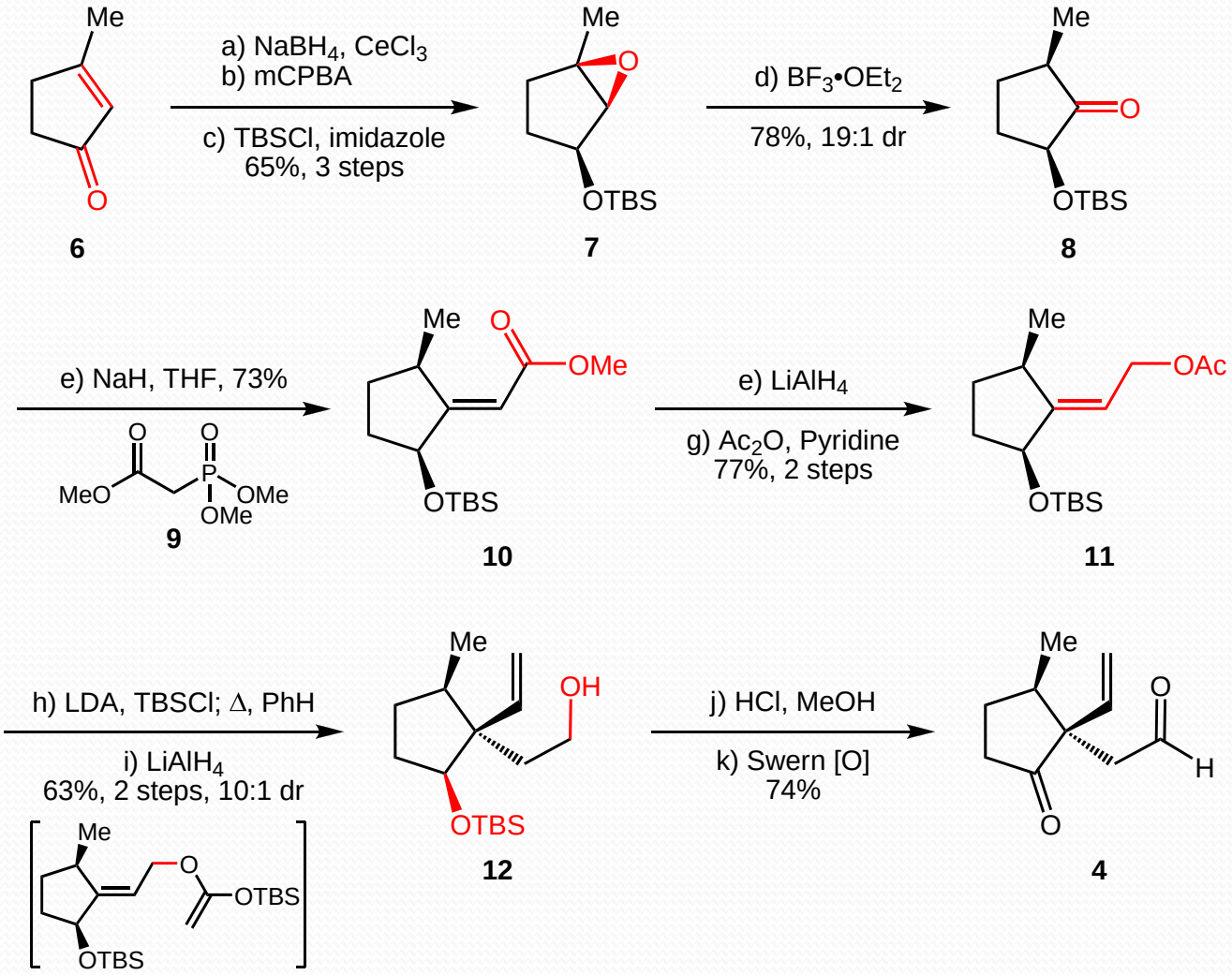


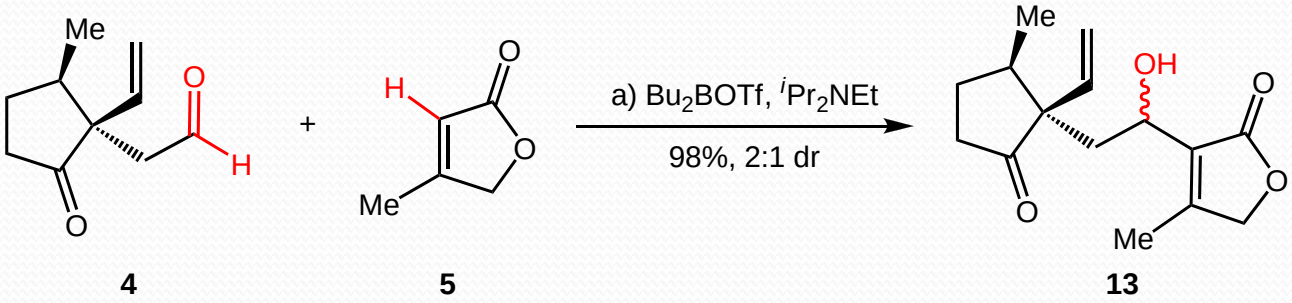
1: Jiadifenolide **2**

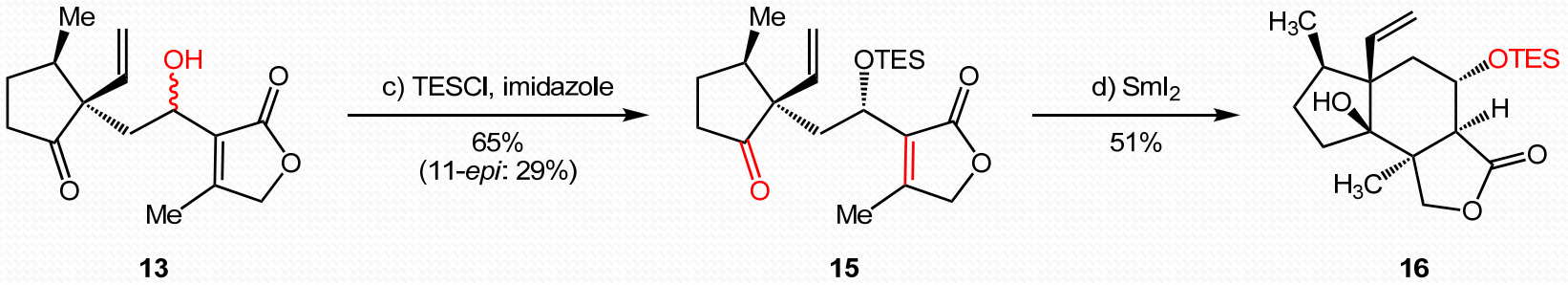


3 **4** **5**

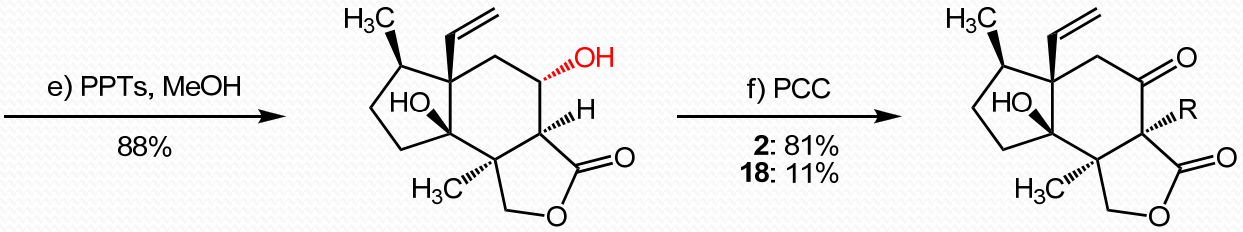
Paterson, I. *et al. Angew. Chem. Int. Ed.* **2014**, *53*, 7286.


Me
O
6
a) NaBH4, CeCl3
b) mCPBA
c) TBSCl, imidazole
65%, 3 steps
Me
O
OTBS
7
d) BF3•OEt2
78%, 19:1 dr
Me
O
OTBS
8
e) NaH, THF, 73%
O
O
MeO
P
OMe
OMe
9
Me
O
OMe
OTBS
10
e) LiAlH4
g) Ac2O, Pyridine
77%, 2 steps
Me
OAc
OTBS
11
h) LDA, TBSCl; Δ, PhH
i) LiAlH4
63%, 2 steps, 10:1 dr
Me
O
OTBS
OTBS
Me
OH
OTBS
12
j) HCl, MeOH
k) Swern [O]
74%
Me
O
H
O
4


Me
O
H
O
4
+
H
O
O
Me
5
a) Bu_2BOTf, $^iPr_2NEt$
98%, 2:1 dr
Me
OH
O
O
O
Me
13
b) DMP, 83%
Me
O
O
O
O
Me
14
H_3C
HO
O
H
O
H_3C
O
2

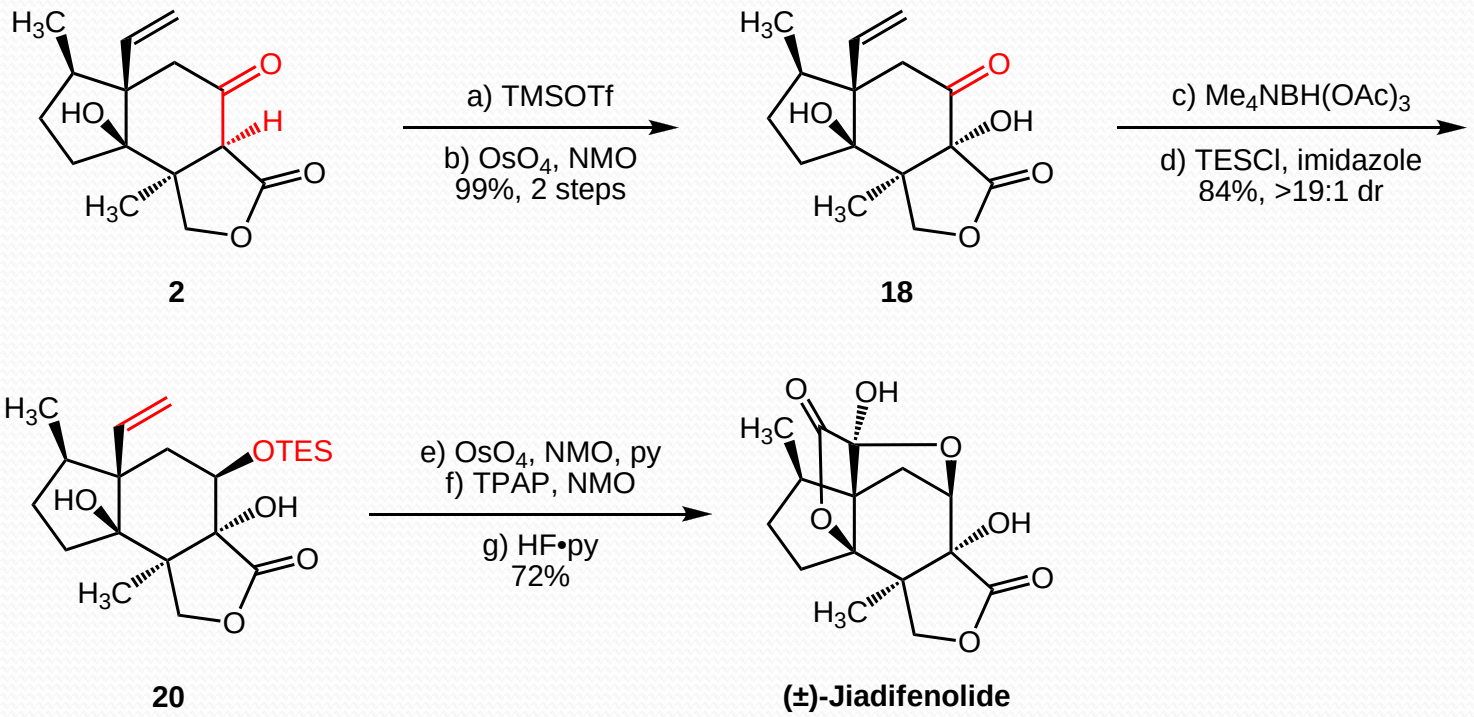


13 **15** **16**



17

2: R = H
18: R = OH

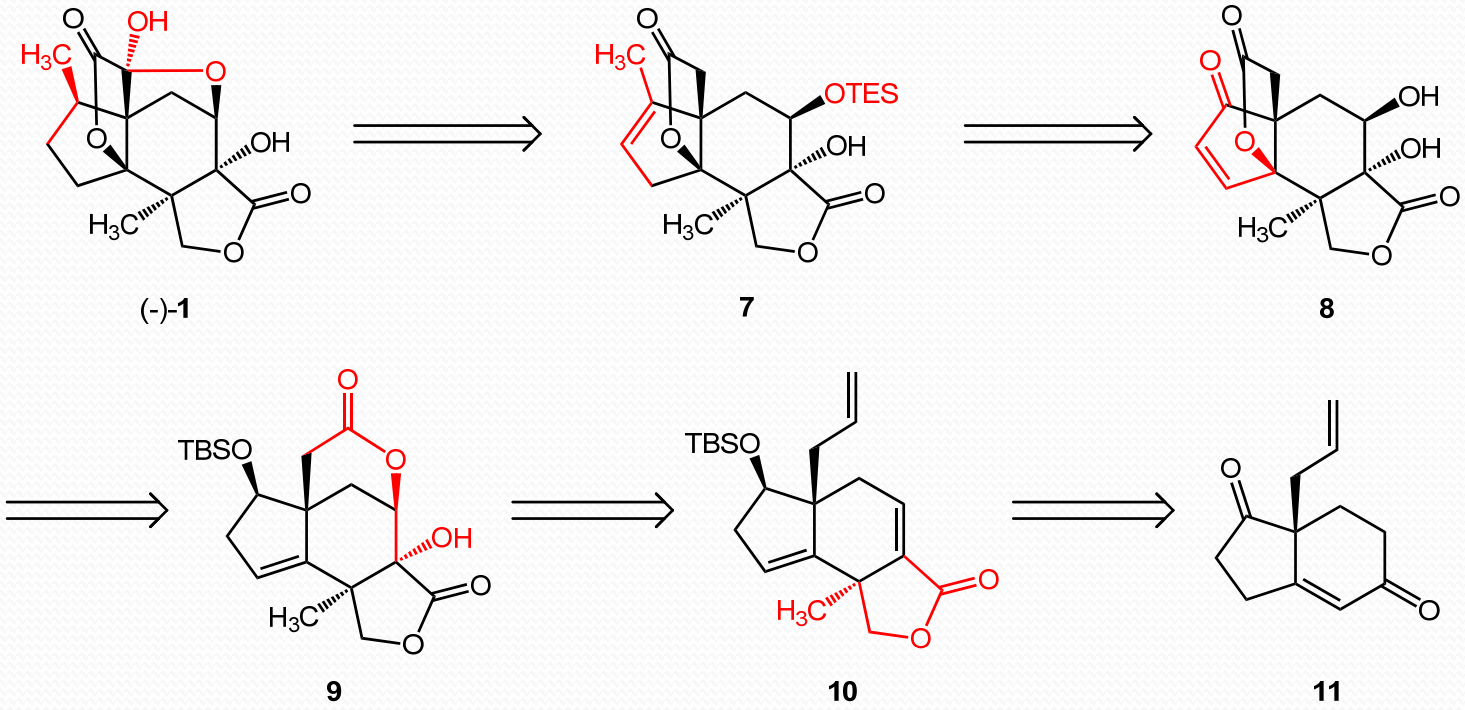


2 **18**

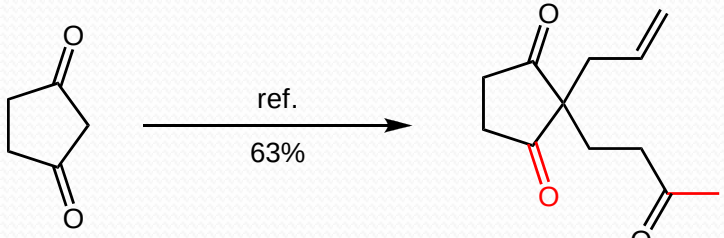
20 **(±)-Jiadifenolide**

3. Total Synthesis by Theodorakis Group

3.1 Retrosynthetic Analysis



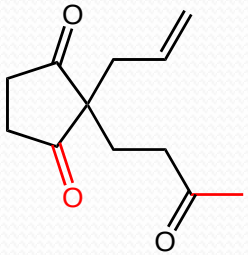
Theodorakis, E. A. *et al. Angew. Chem. Int. Ed.* **2011**, *50*, 3672.



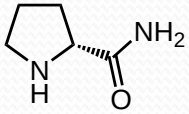
12

ref.

63%

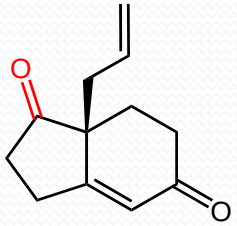


13



a) D-prolinamide, PPTS
40 °C, 14 days

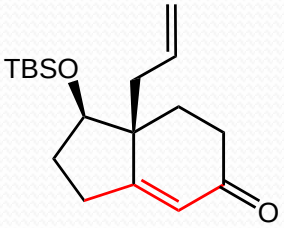
74%, >90% ee



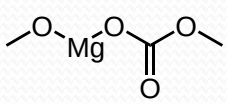
11

b) $NaBH_4$, EtOH

c) TBSCl, NH_4NO_3
92%, 2 steps

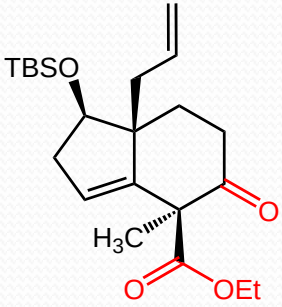


14



d) MMC, then $Et_3O^+BF_4^-$, $^iPr_2NEt$

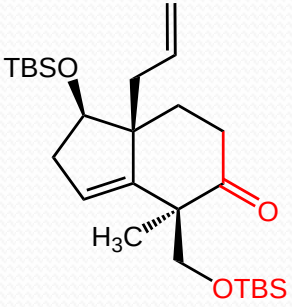
e) TMSOTf, 2,6-lutidine, then TBAF, MeI
43%, 2 steps



15

f) $LiAlH_4$
g) TBSCl, imidazole

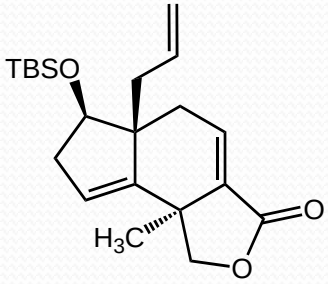
h) IBX
85%, 3 steps



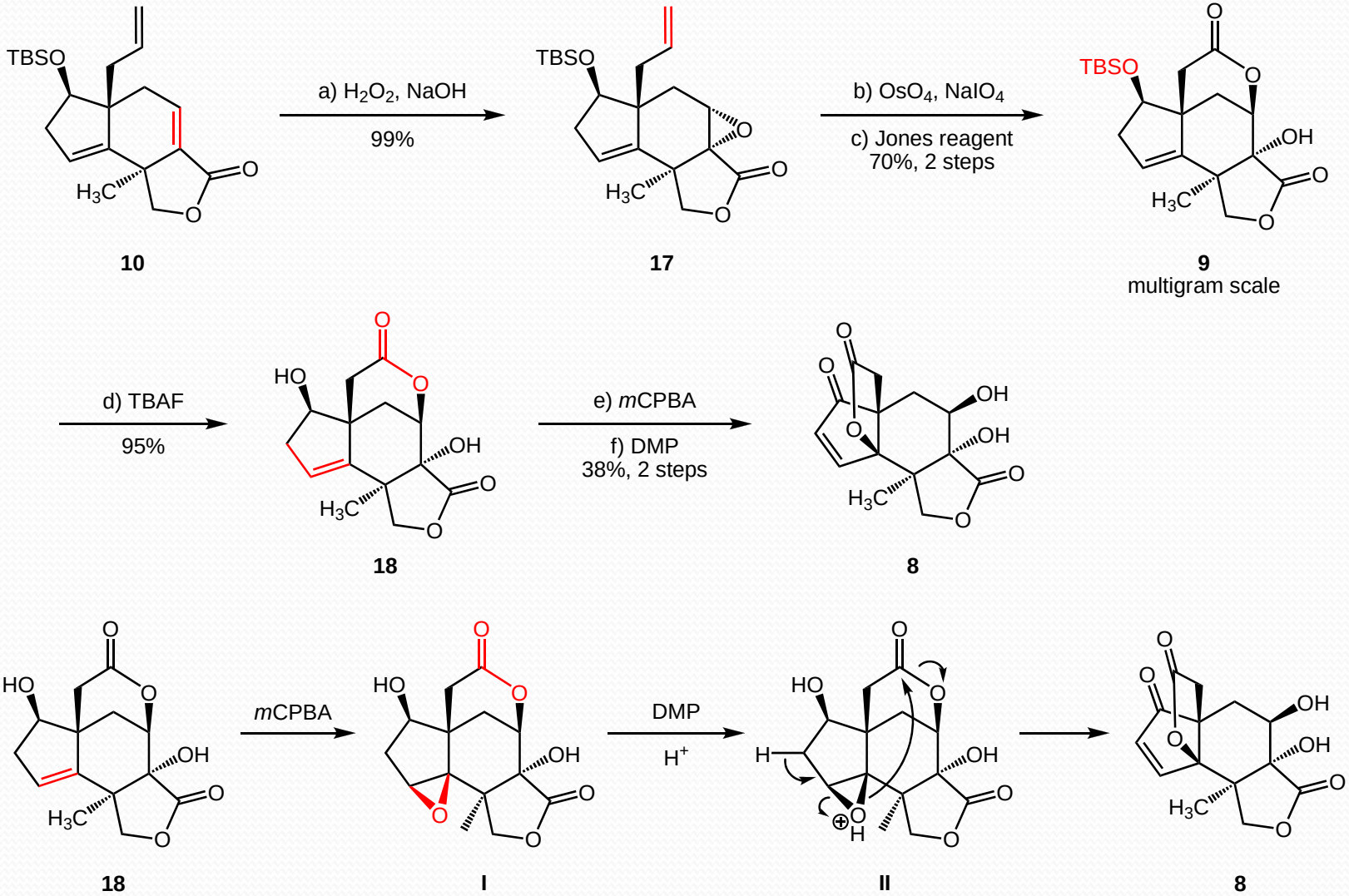
16

i) KHMDS, $PhNTf_2$

j) CO, $Pd(PPh_3)_4$, MeOH, Et_3N
then TFA
69%, 2 steps



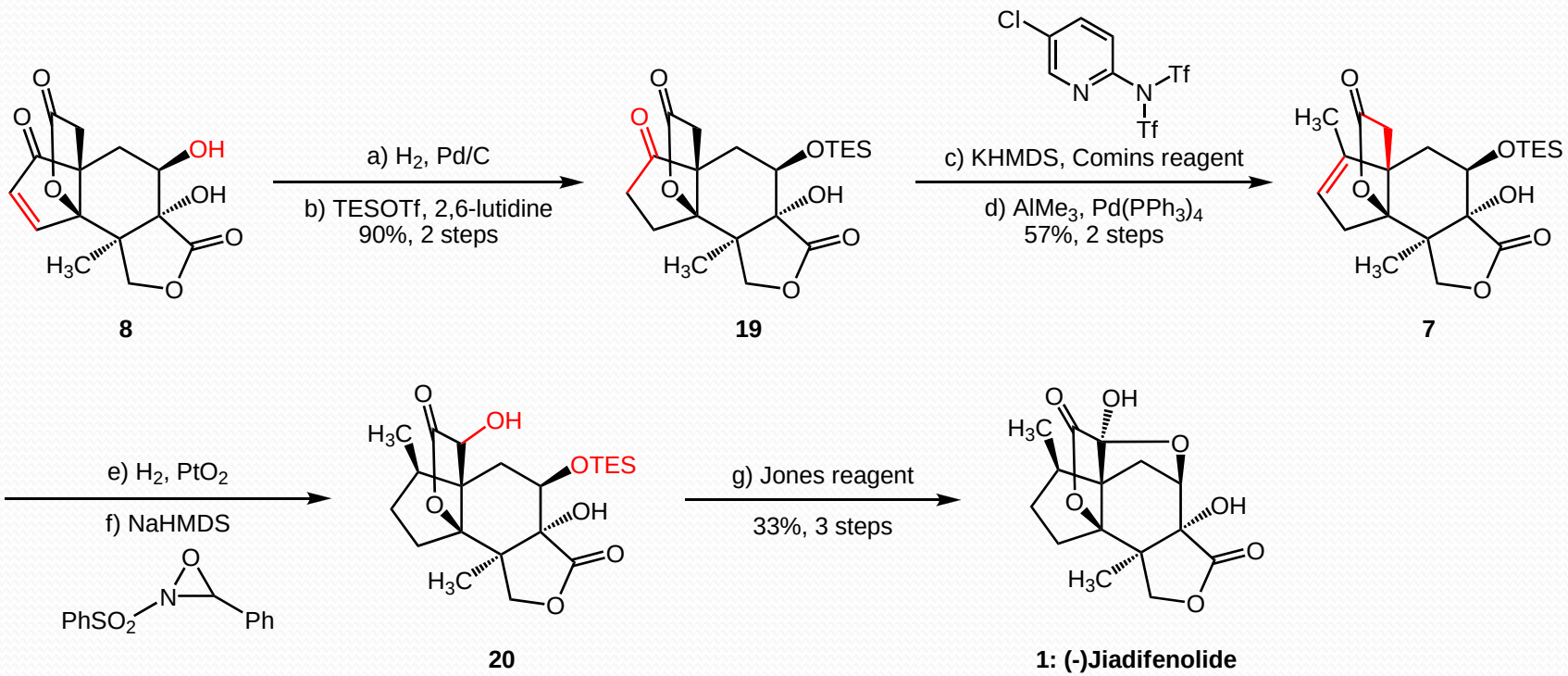
10



10 **17** **9** multigram scale

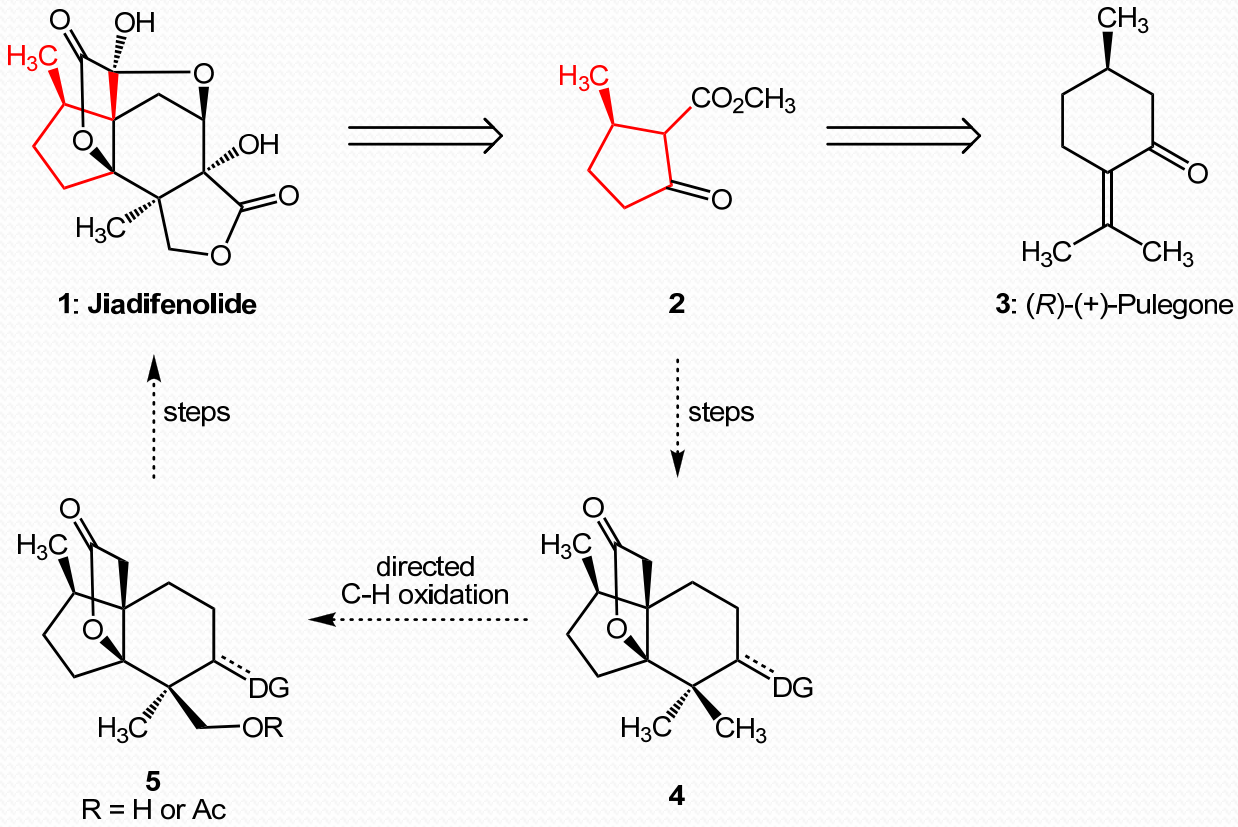
18 **8**

18 **I** **II** **8**

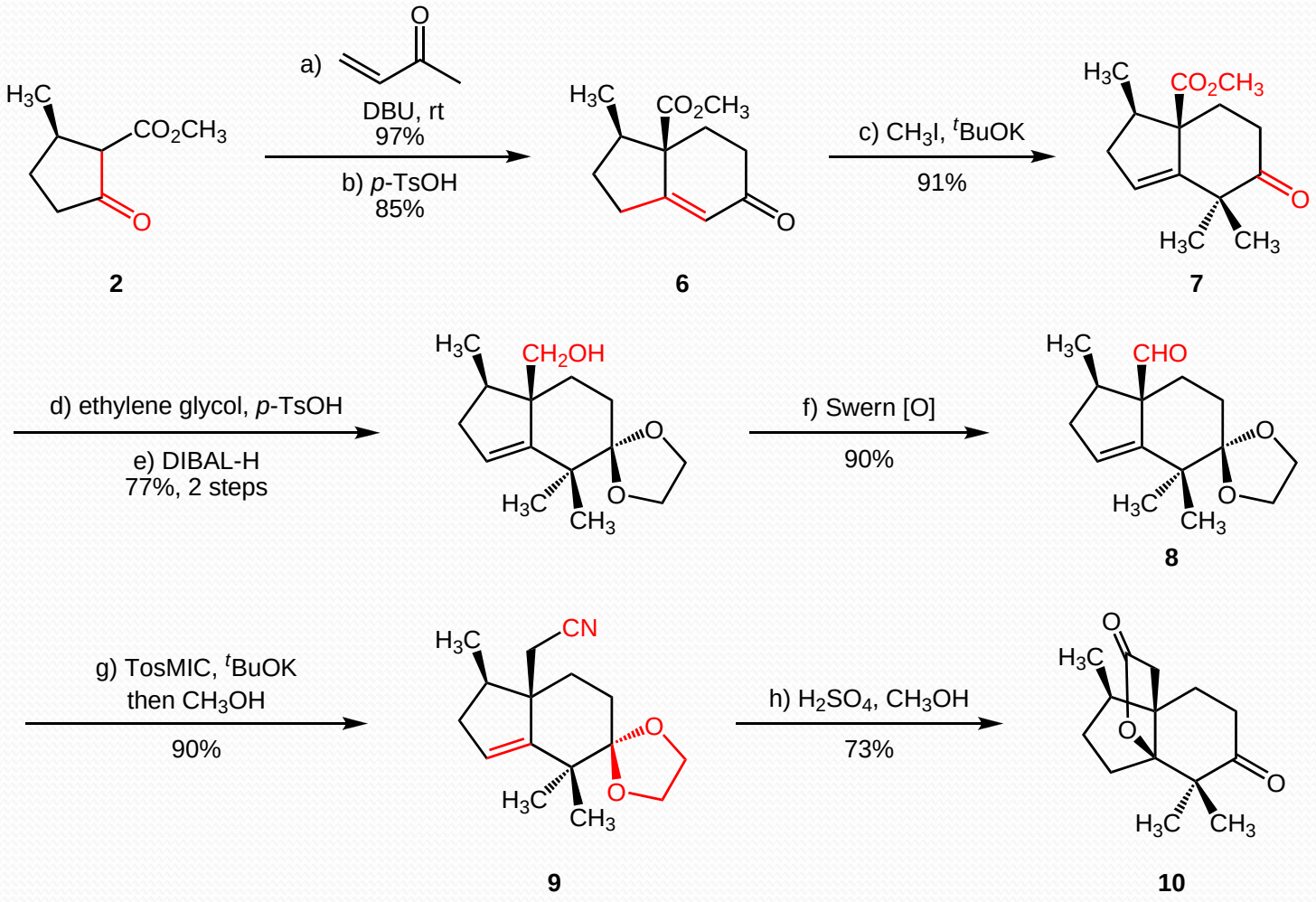

a) H2, Pd/C
b) TESOTf, 2,6-lutidine
90%, 2 steps
c) KHMDS, Comins reagent
d) AlMe3, Pd(PPh3)4
57%, 2 steps
e) H2, PtO2
f) NaHMDS
g) Jones reagent
33%, 3 steps
8
19
7
20
1: (-)Jiadifenolide

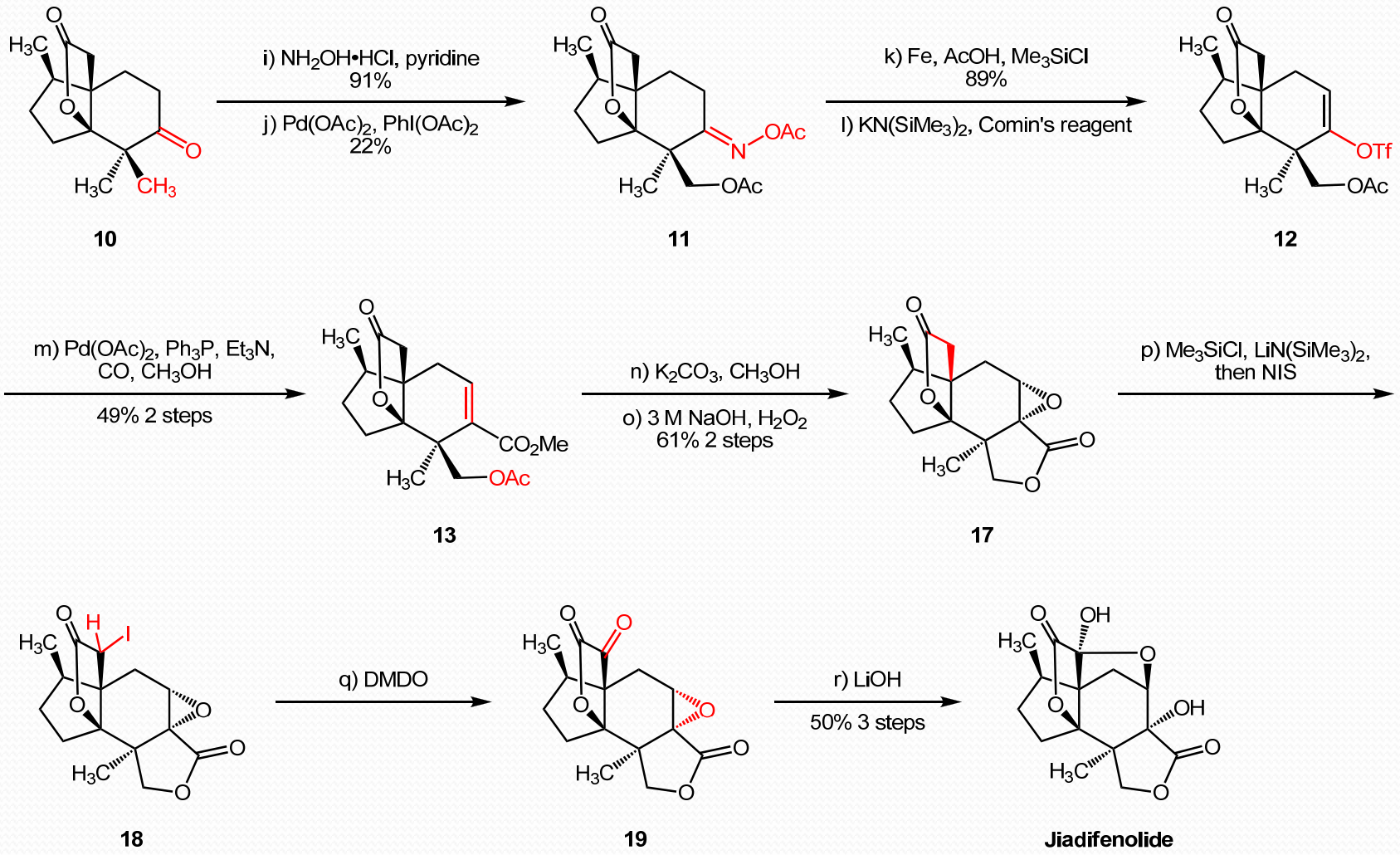
4. Total Synthesis by Sorensen Group

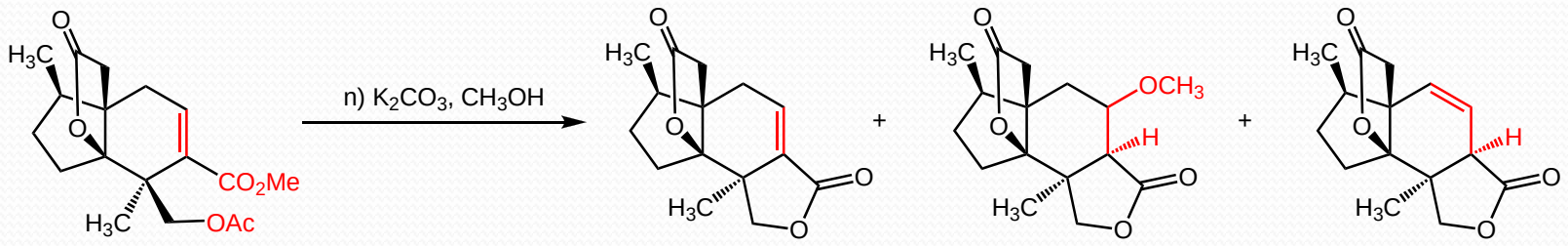
4.1 Retrosynthetic Analysis



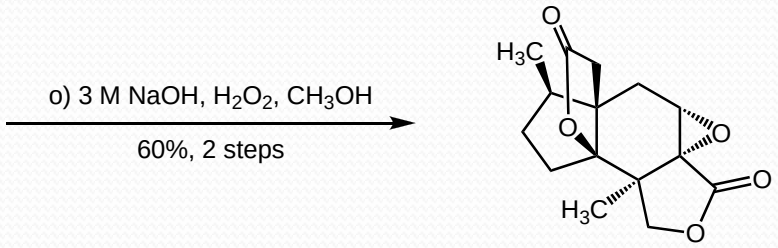
Sorensen, E. J. *et al. Angew. Chem. Int. Ed.* **2014**, *53*, 5332.


a)
DBU, rt
97%
b) p-TsOH
85%
c) CH3I, tBuOK
91%
d) ethylene glycol, p-TsOH
e) DIBAL-H
77%, 2 steps
f) Swern [O]
90%
g) TosMIC, tBuOK
then CH3OH
90%
h) H2SO4, CH3OH
73%
2
6
7
8
9
10


i) NH2OH•HCl, pyridine
91%
j) Pd(OAc)2, PhI(OAc)2
22%
k) Fe, AcOH, Me3SiCl
89%
l) KN(SiMe3)2, Comin's reagent
m) Pd(OAc)2, Ph3P, Et3N,
CO, CH3OH
49% 2 steps
n) K2CO3, CH3OH
o) 3 M NaOH, H2O2
61% 2 steps
p) Me3SiCl, LiN(SiMe3)2,
then NIS
q) DMDO
r) LiOH
50% 3 steps
10
11
12
13
17
18
19
Jiadifenolide

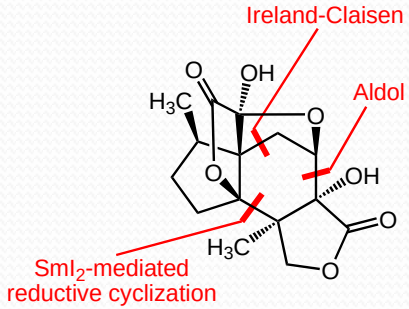


13 **14** (43%) + **15** (26%) + **16** (20%)



17

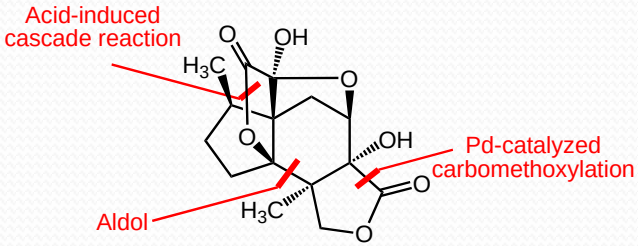
5. Summary



(±)-Jiadifenolide

Paterson group in 2014:

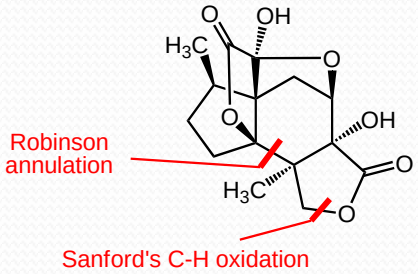
1. racemic total synthesis;
2. 23 steps, 2.3% overall yield.



(-)-Jiadifenolide

Theodorakis group in 2011:

1. enantiospecific total synthesis;
2. 25 steps, 1.5% overall yield.



(-)-Jiadifenolide

Sorensen group in 2014:

1. enantiospecific total synthesis;
2. 18 steps, 0.9% overall yield.

5.1 Introduction of the Corresponding Author

Ian Paterson
Cambridge University

E. A. Theodorakis
University of California at San Diego

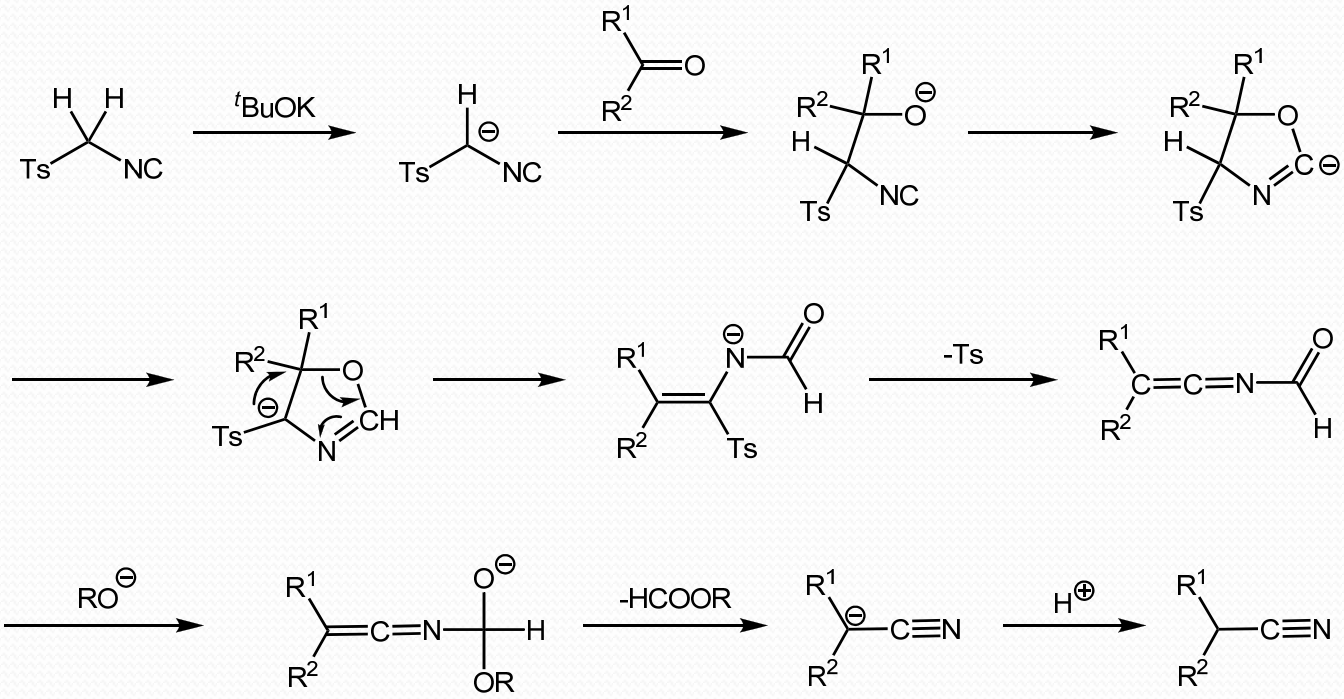
Erik J. Sorensen
Princeton University

Jiadifenolide is an architecturally complex sesquiterpenoid first isolated from the pericarps of the Chinese plant *illicium jiadifengpi* by Fukuyama and coworkers in 2009. Preliminary biological investigation revealed potent neurotrophic activity, promoting neurite outgrowth in primary cultured rat cortical neurons at concentrations as low as 10 nm. Given the important regulatory role of neurotrophins in the central nervous system, jiadifenolide represents a valuable small-molecule lead for the potential therapeutic treatment of neurodegenerative conditions such as Alzheimers disease. Its low natural abundance (1.5 $mgkg^{-1}$ plant material) makes total synthesis of particular importance for the preparation of sufficient quantities for further biological evaluation and to enable access to a range of analogues for structure–activity relationship (SAR) profiling.

In summary, we have completed the total synthesis of the neurotrophic agent jiadifenolide in 2.3% yield over 23 steps, showcasing a pivotal SmI_2-mediated reductive cyclization reaction to establish the tricyclic core. Notably, the synthesis demonstrates a high degree of solely substrate-based stereocontrol to establish this densely functionalized structure, wherein the full relative configuration is templated for by a single C5 alcohol stereocenter. Starting from known (*S*)-3-methyl-cyclopentenol should thus render this approach asymmetric. Work to prepare quantities of this valuable scaffold for further biological evaluation and analogue synthesis will be reported in due course.

谢谢大家，请多批评指正！

Mechanism of Aldehyde to Nitrile



Van Leusen, A. M. *et al. J. Org. Chem.* **1977**, *42*, 3114.