


Synthesis of nimbolide and its analogues and their application as poly(ADP-ribose) polymerase-1 trapping inducers

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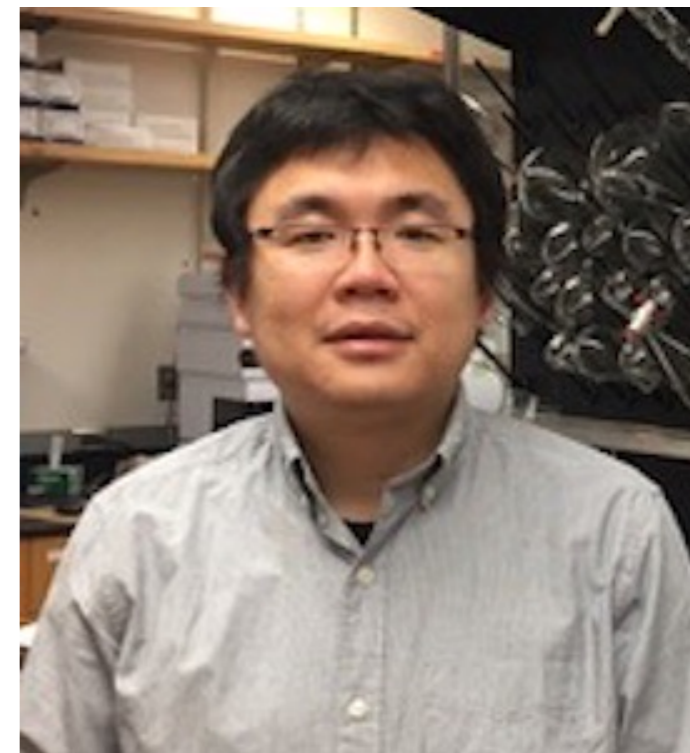
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Heping Deng^{1,3}, Hejun Deng^{1,3}, Chiho Kim^{1,2}, Peng Li¹, Xudong Wang^{1,2}, Yonghao Yu^{1,2}✉ & Tian Qin¹✉

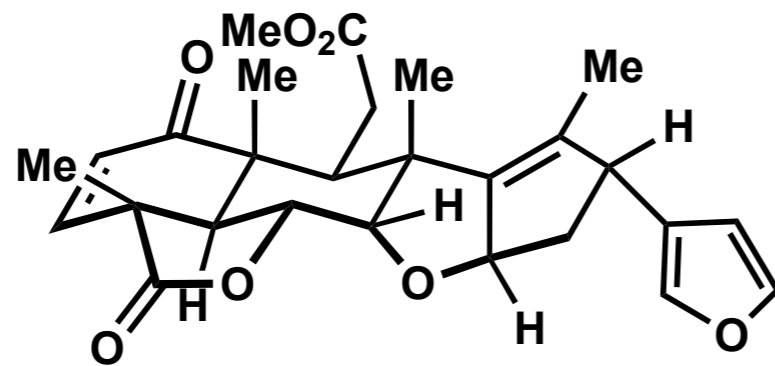
Nimbolide, a ring seco-C limonoid natural product, was recently found to inhibit the poly(ADP)-ribosylation (PARylation)-dependent ubiquitin E3 ligase RNF114. In doing so, it induces the ‘supertrapping’ of both PARylated PARP1 and PAR-dependent DNA-repair factors. PARP1 inhibitors have reshaped the treatment of cancer patients with germline *BRCA1/2* mutations partly through the PARP1 trapping mechanism. To this end, modular access to nimbolide analogues represents an opportunity to develop cancer therapeutics with enhanced PARP1 trapping capability. Here we report a convergent synthesis of nimbolide through a late-stage coupling strategy. Through a sulfonyl hydrazone-mediated etherification and a radical cyclization, this strategy uses a pharmacophore-containing building block and diversifiable hydrazone units to enable the modular synthesis of nimbolide and its analogues. The broad generality of our synthetic strategy allowed access to a variety of analogues with their preliminary cellular cytotoxicity and PARP1 trapping activity reported.



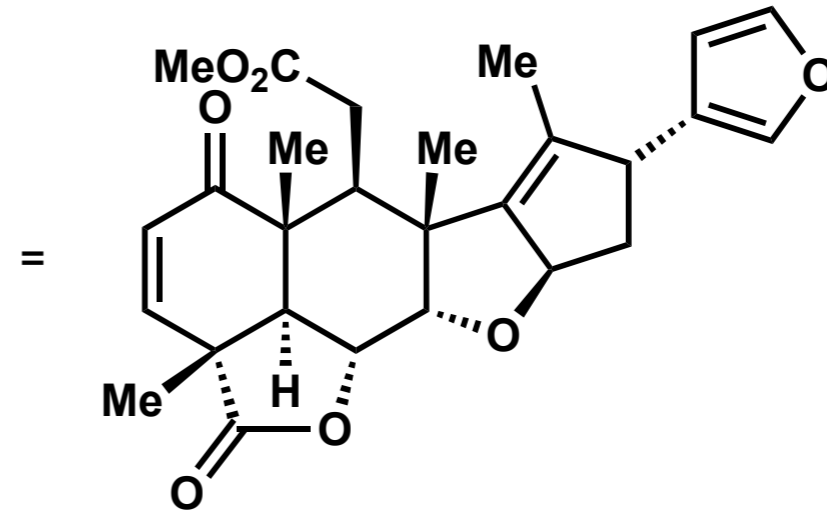
Education and Career

- BSc degree in chemistry at the University of Science and Technology of China
- PhD at Boston University (*Advisor: Prof. J. Porco*)
- Postdoctorate studies at Scripps Research (*Advisor: Prof. P. Baran*)
- Assistant professor at UT Southwestern since 2018

Nimbolide, a terpene natural product



nimbolide (1)

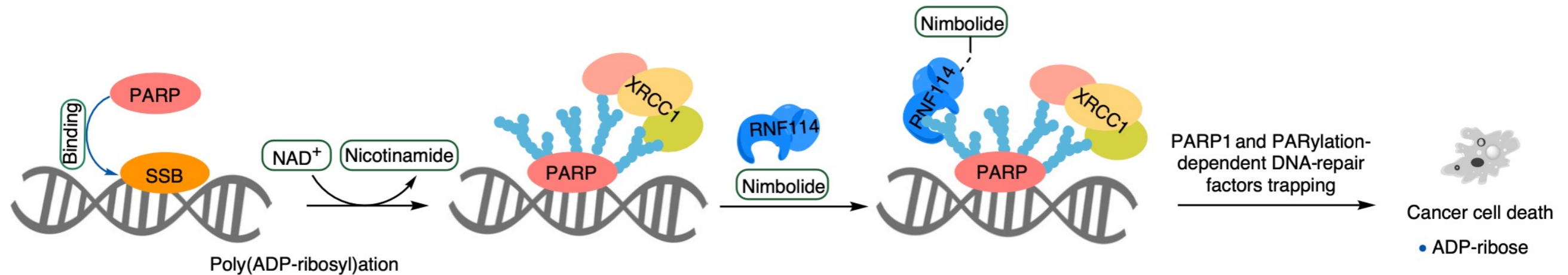


- Nimbolide is a natural product obtained from the leaves and flowers of Nee.
- It has been shown to possess multiple therapeutic effects, like anti-malaria and anti-bacterial.
- It also inhibits tumorigenesis and metastasis without causing any toxicity around a wide range of cancers.



Neem tree leaves (*Azadirachta indica*)

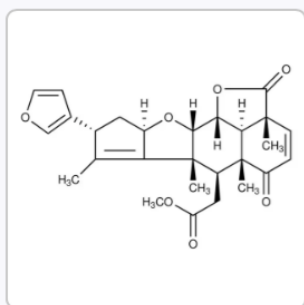
DNA damage: an overview



- **SSB**: single-stranded DNA break.
- **PARP**: it is a protein that stands for poly-ADP ribose polymerase. It helps damaged cells to repair themselves. As a cancer treatment, PARP inhibitors stop the PARP from doing its repair work in cancer cells and the cell dies.
- **XRCC1**: it is a protein involved in DNA damage repair.
- **RNF114**: this protein is a E3 ubiquitin ligase, involved in protein homeostasis and removal of unwanted or damaged proteins.

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Nimbolide

★★★★★ (0) [Write a review](#)

from *Azadirachta indica*, ≥98%

Synonym(s):

NSC-309909

Empirical Formula (Hill Notation):

C₂₇H₃₀O₇

CAS Number:

25990-37-8

Molecular Weight:

466.52



PubChem Substance ID:

329825074

NACRES:

NA.25

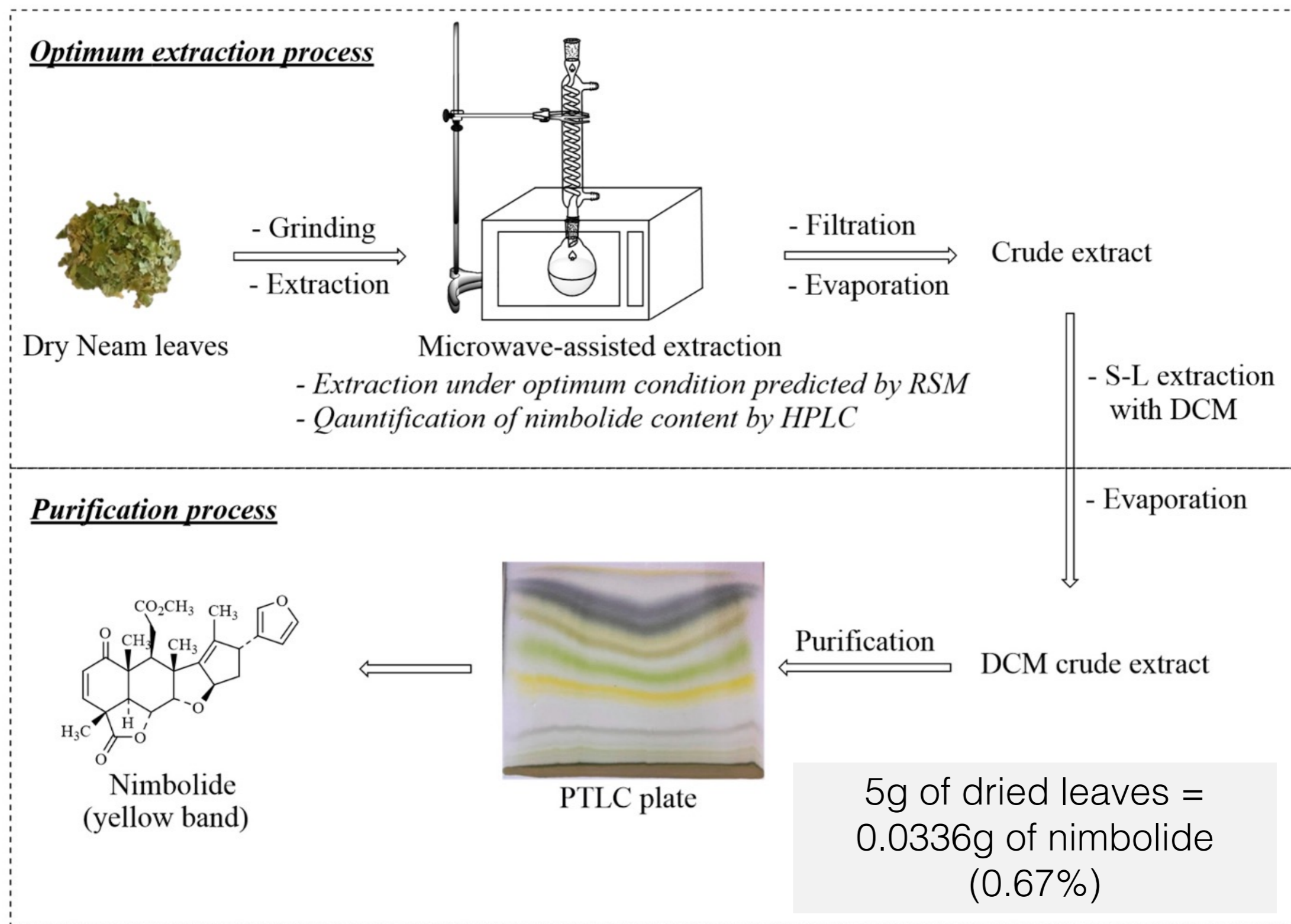
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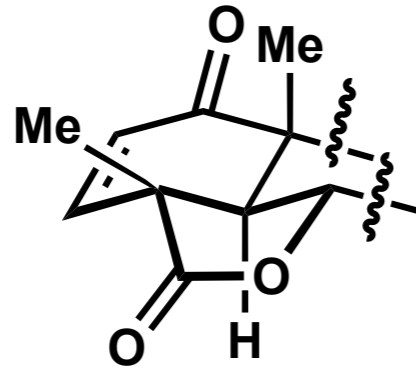
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Extraction and Purification of Nimbolide



Pharmacophore meets strategy

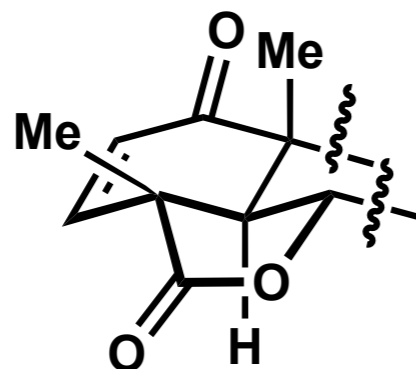


nimbolide
pharmacophore

The enone moiety and lactone ring of nimbolide were identified as the essential pharmacophore for the observed activity

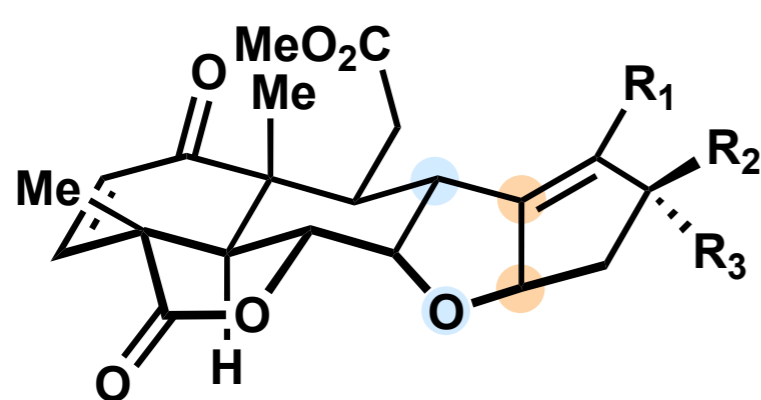


Pharmacophore meets strategy

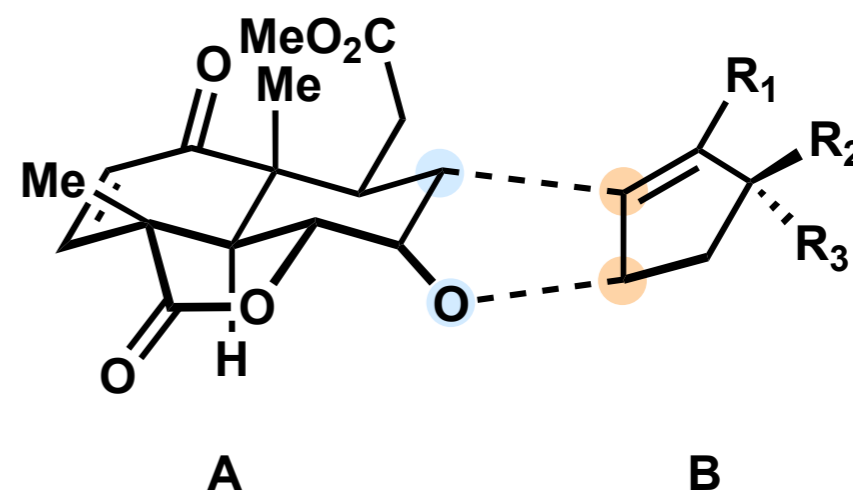


nimbolide
pharmacophore

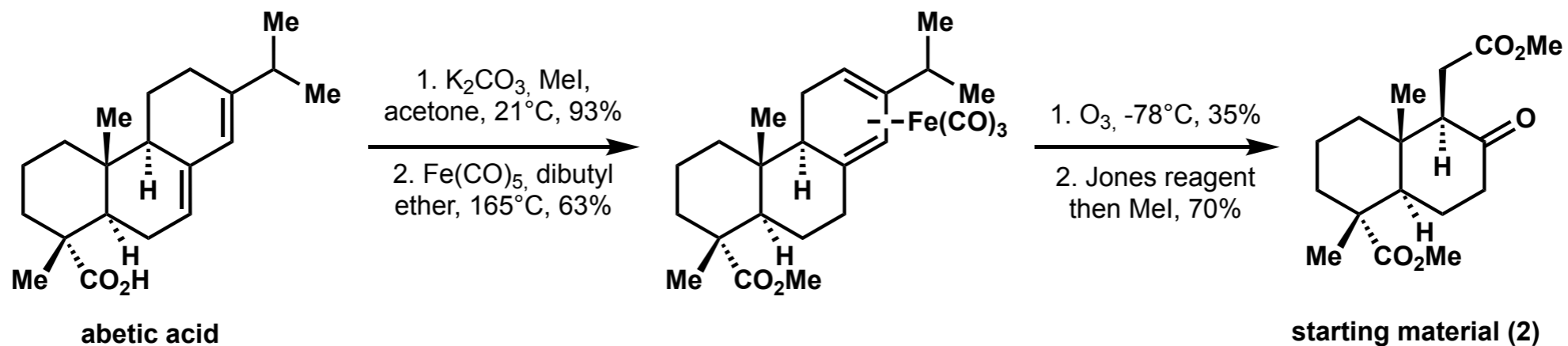
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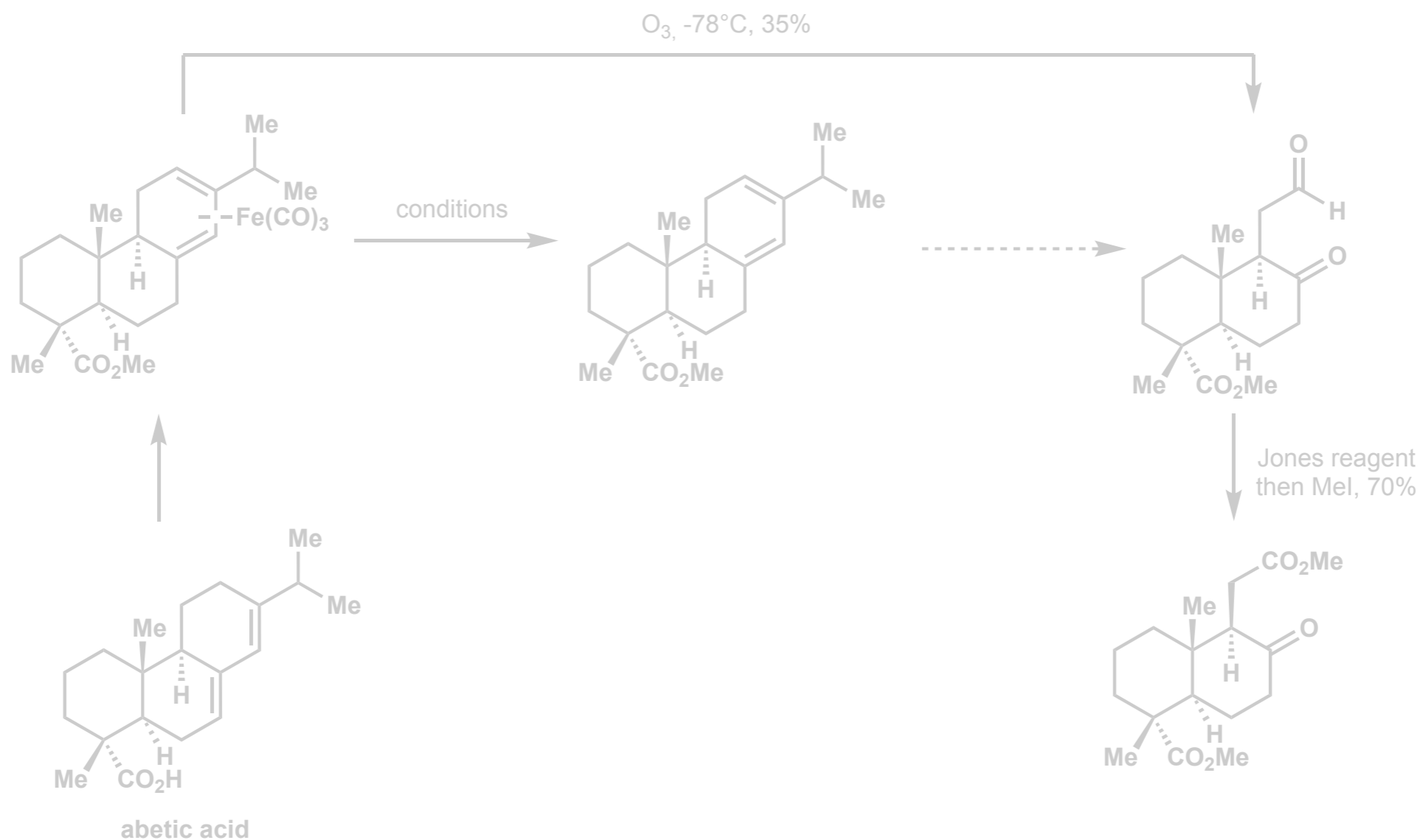
late-stage
pharmacophore
oriented coupling



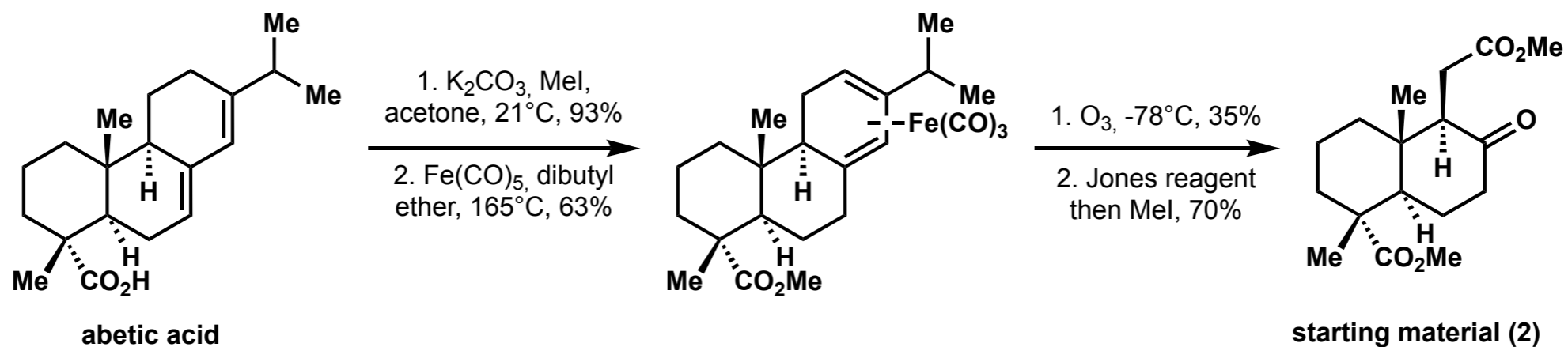
Let's talk about their starting material



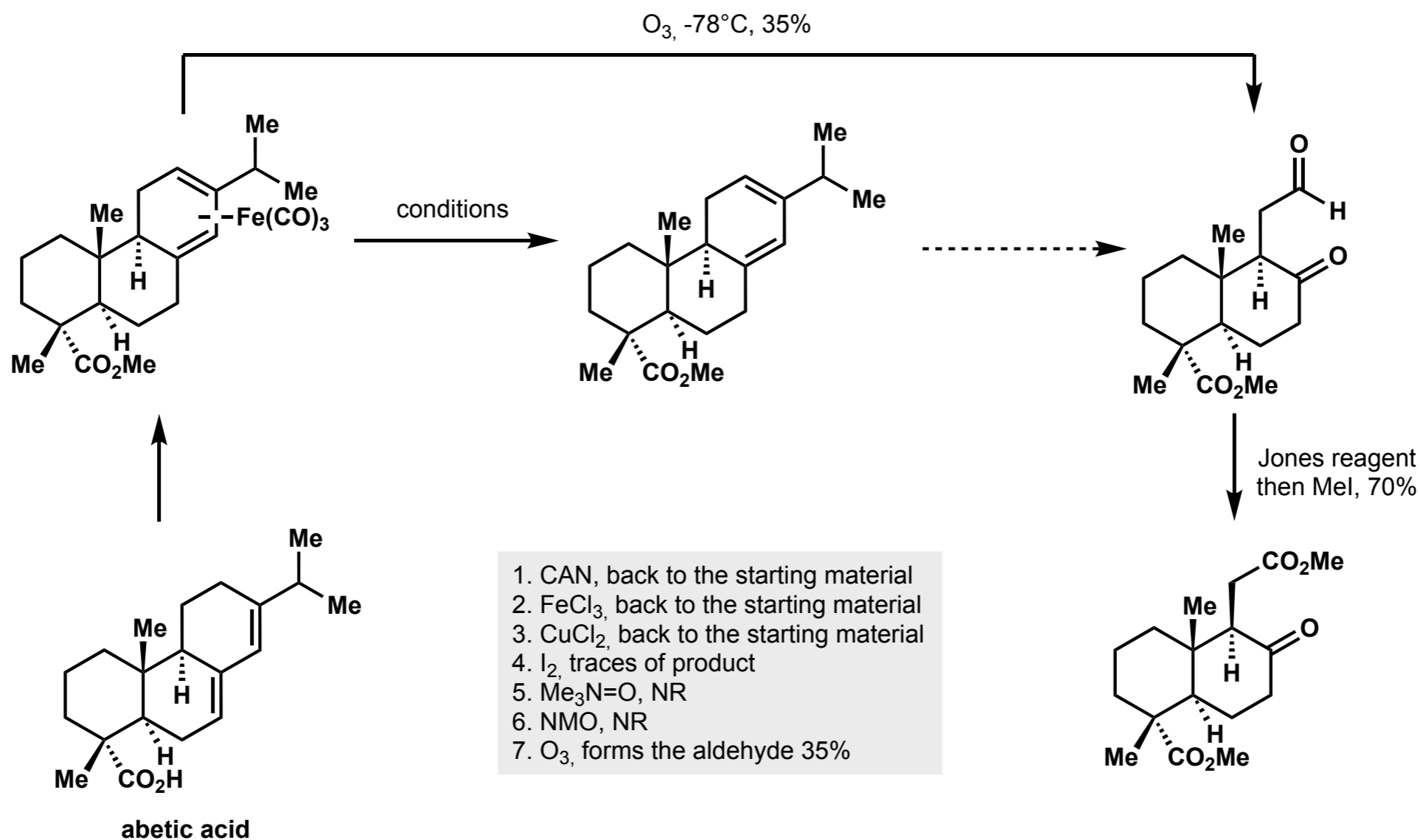
First-generation optimization:



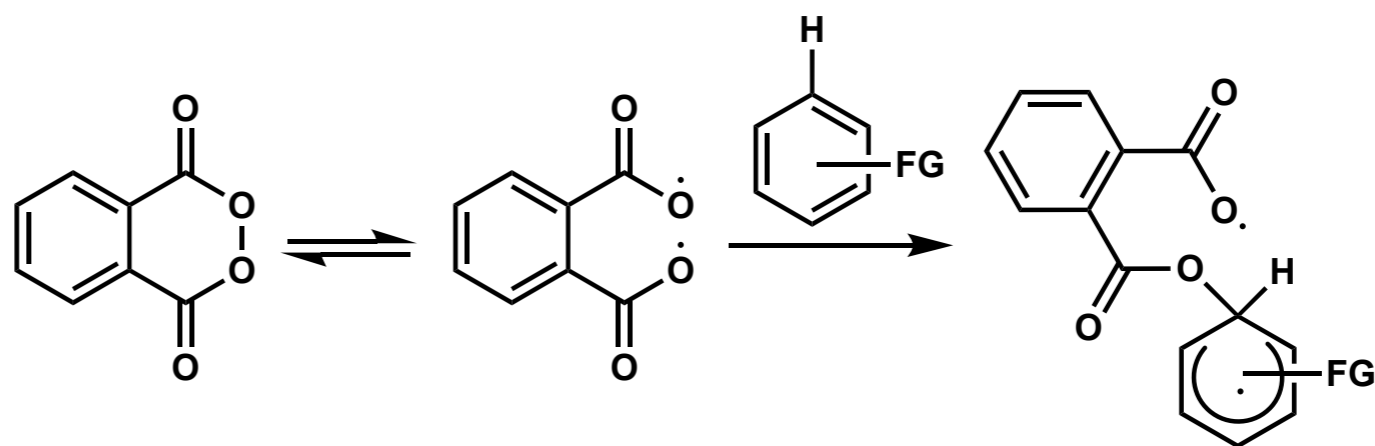
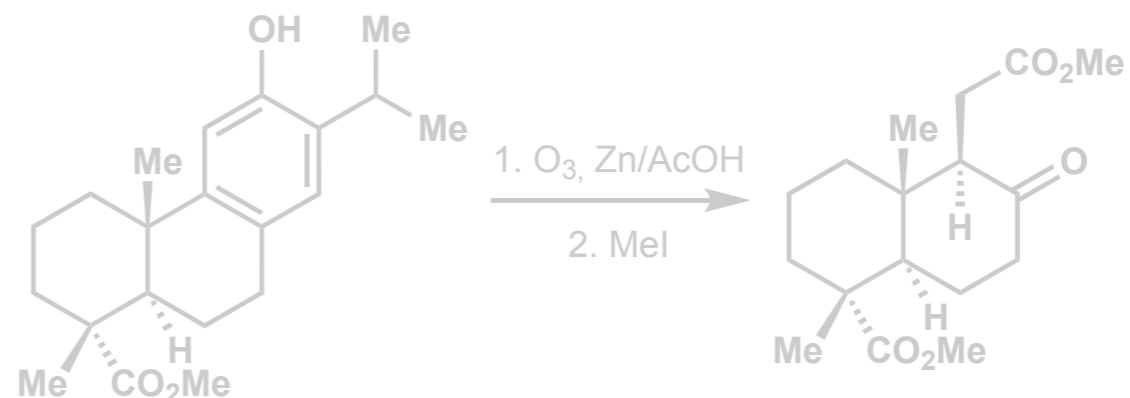
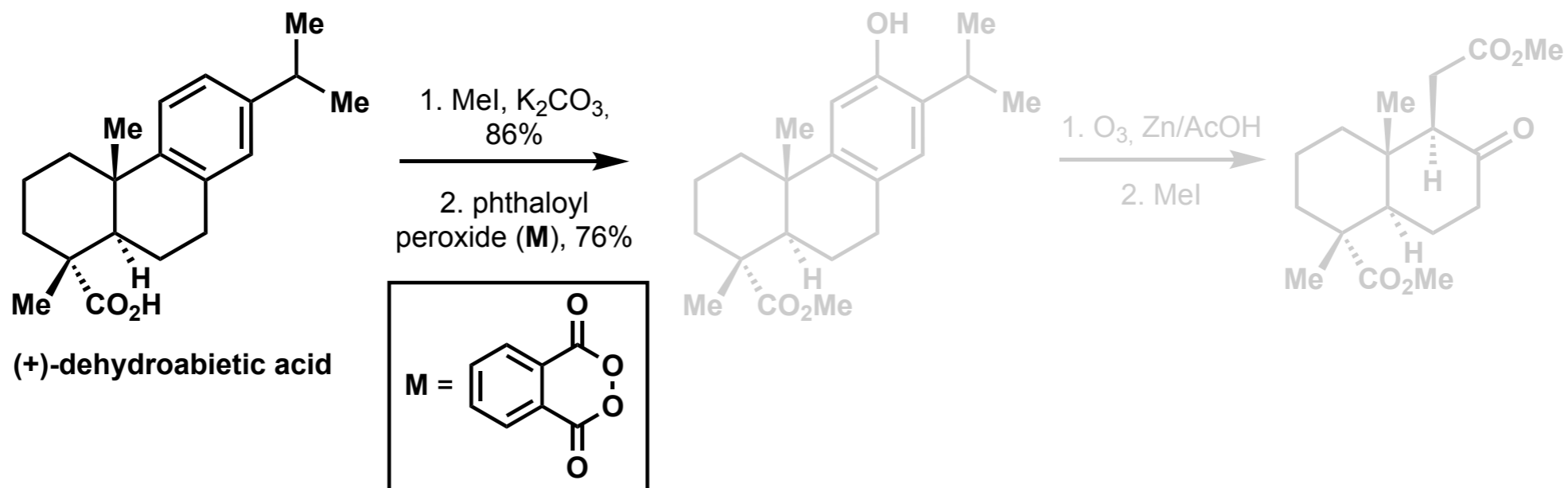
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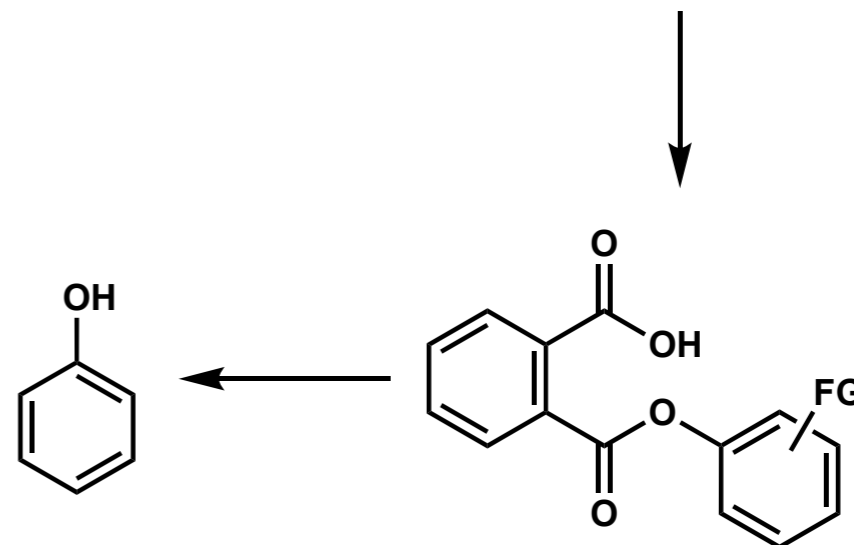
First-generation optimization:



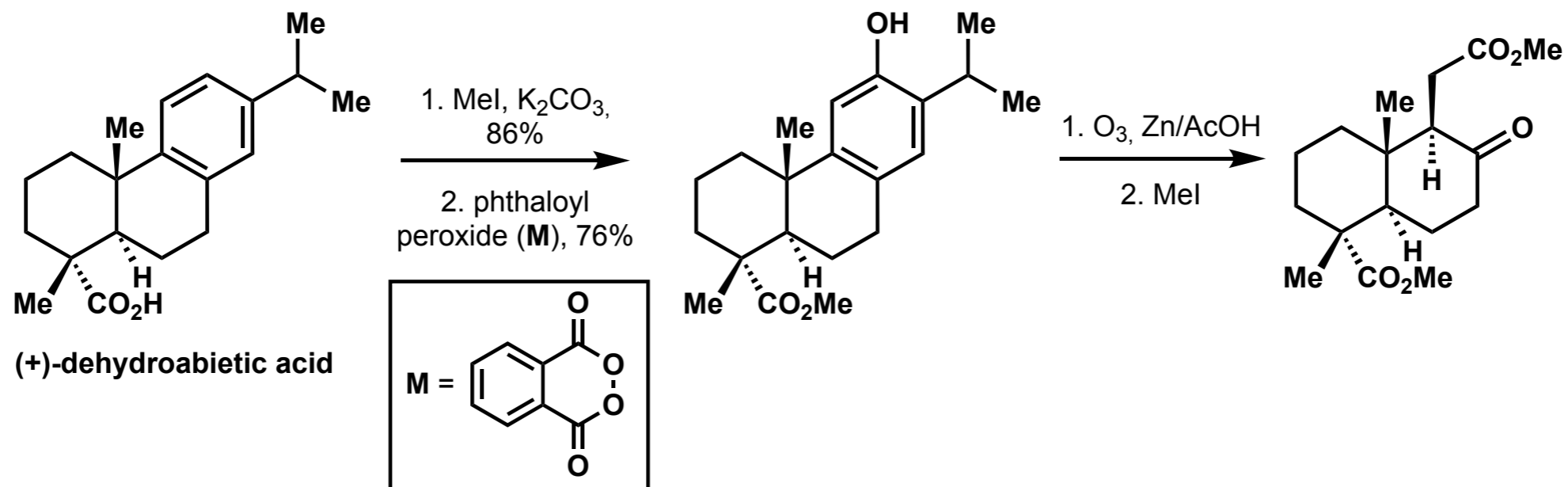
Let's talk about their starting material



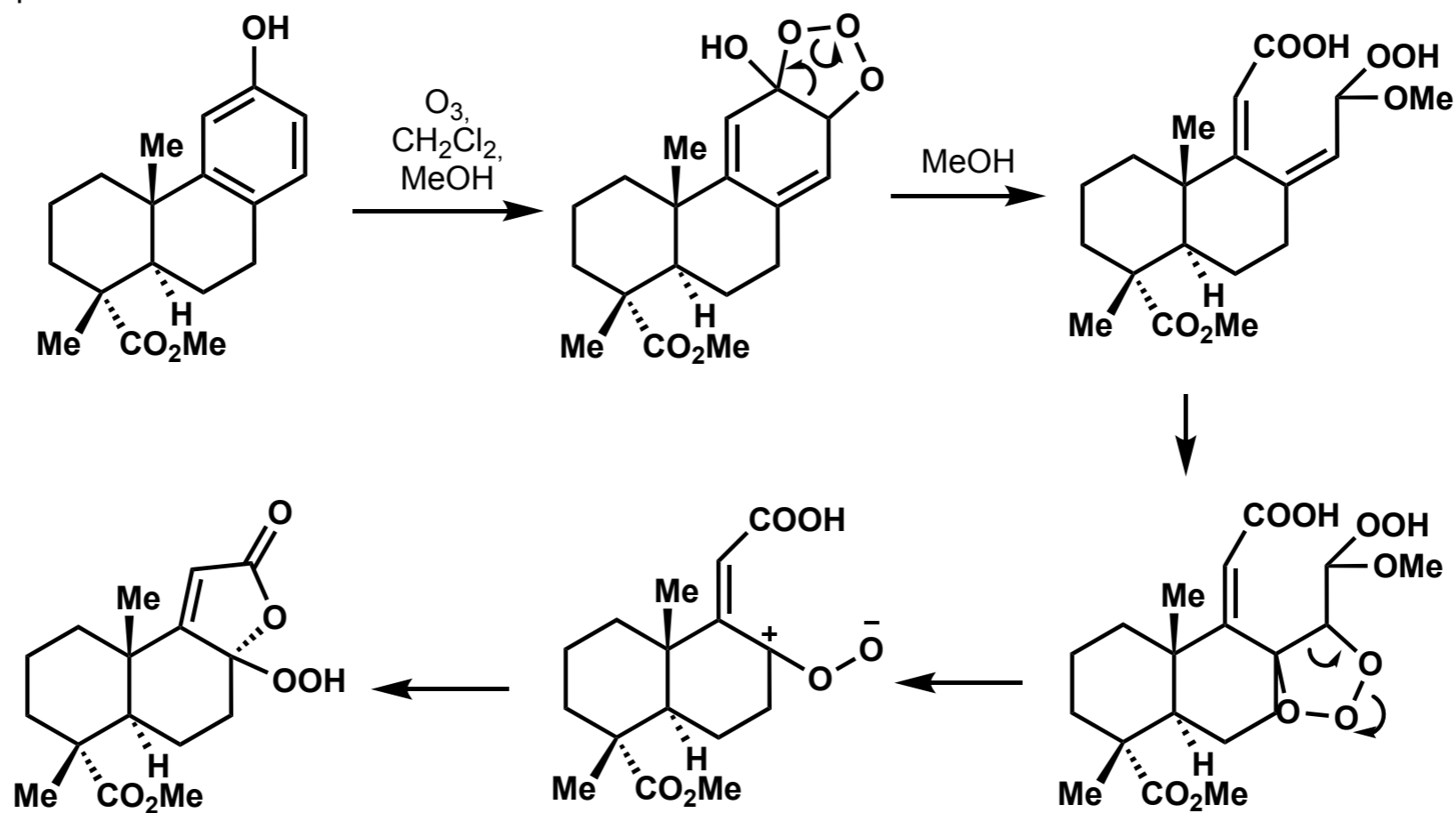
Preparation of phenols
using phthaloyl peroxide:



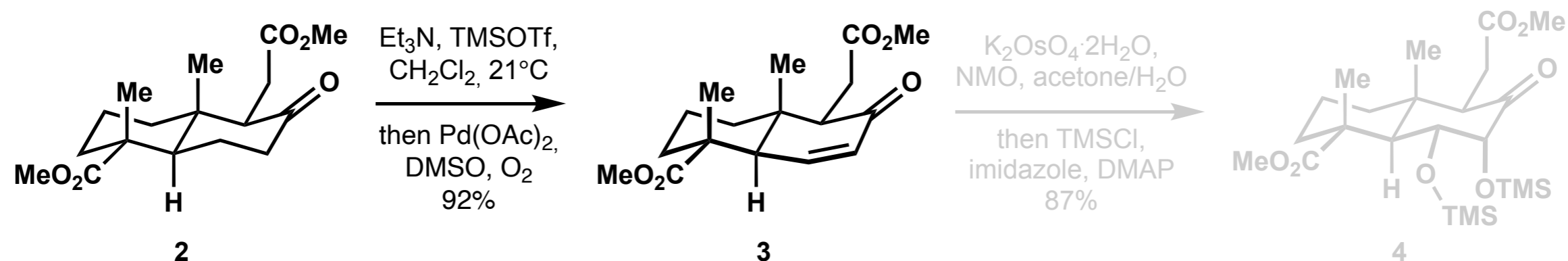
Let's talk about their starting material



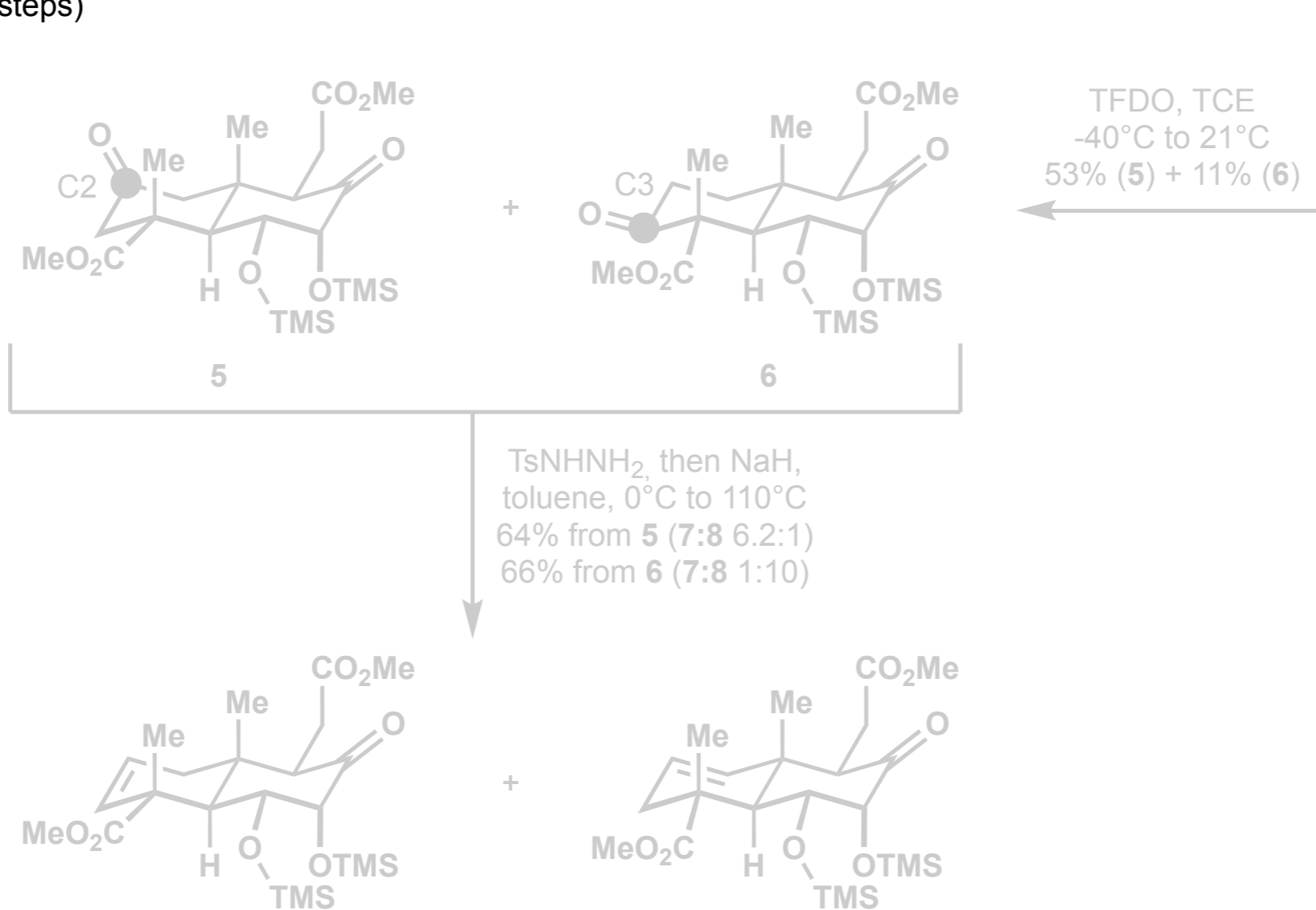
Ozonolysis of phenols



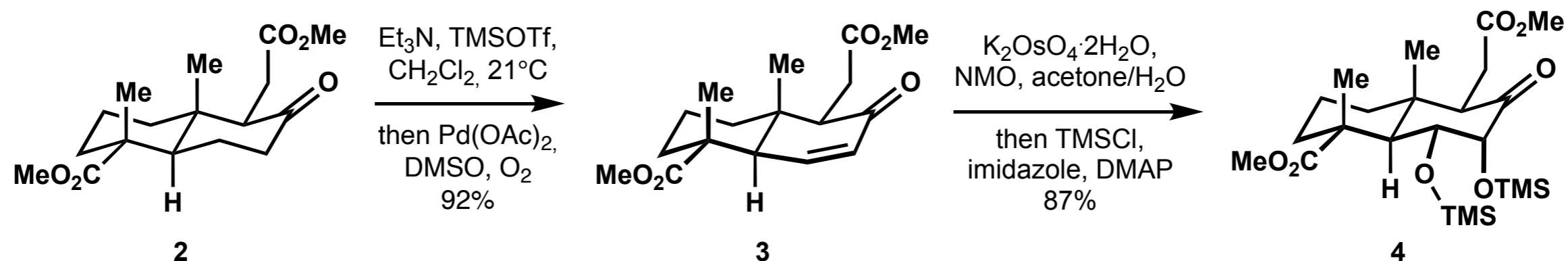
Synthesis of the pharmacophore-contained building



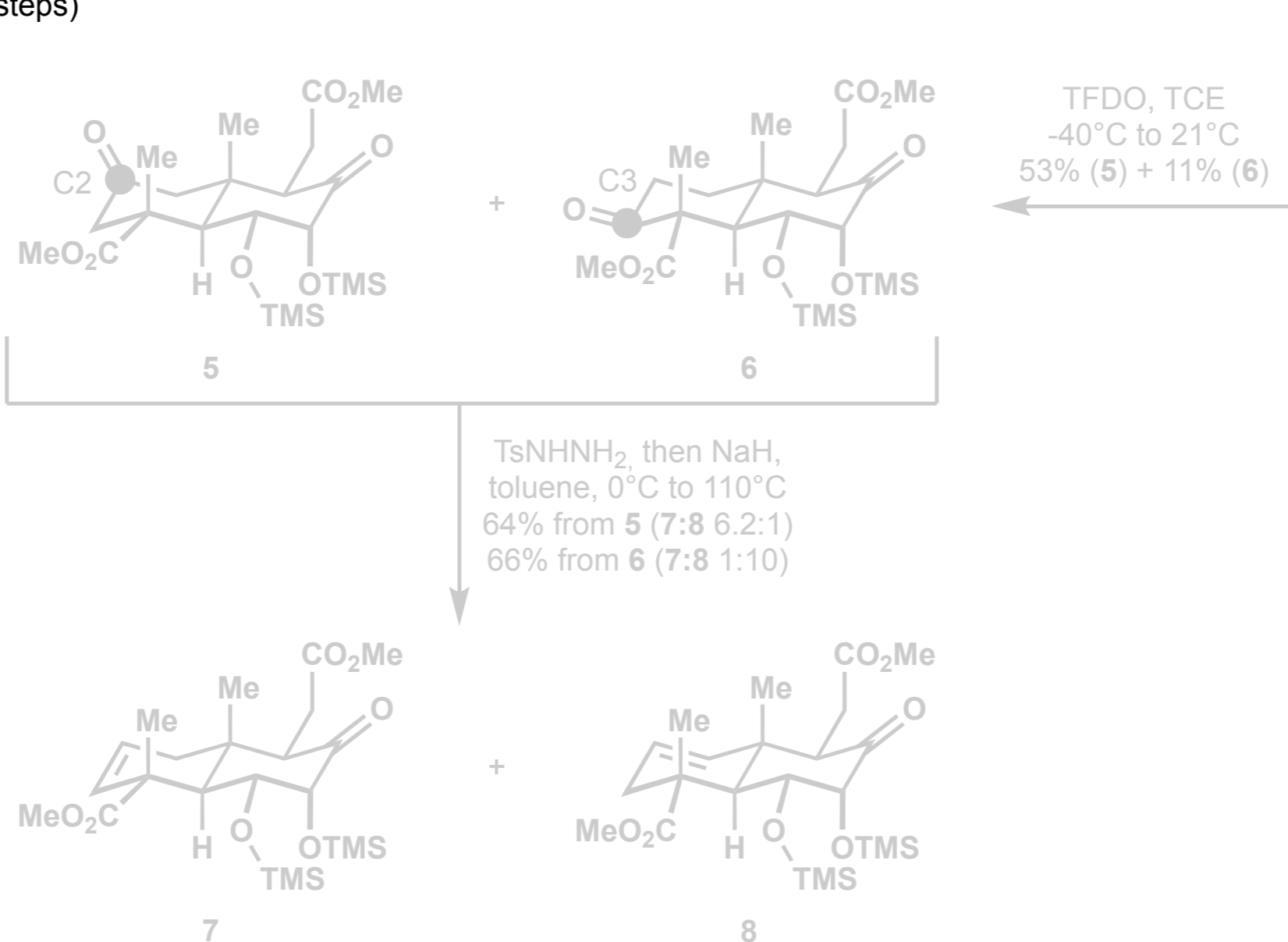
from abietic acid (3 steps) or
dehydroabietic acid (5 steps)



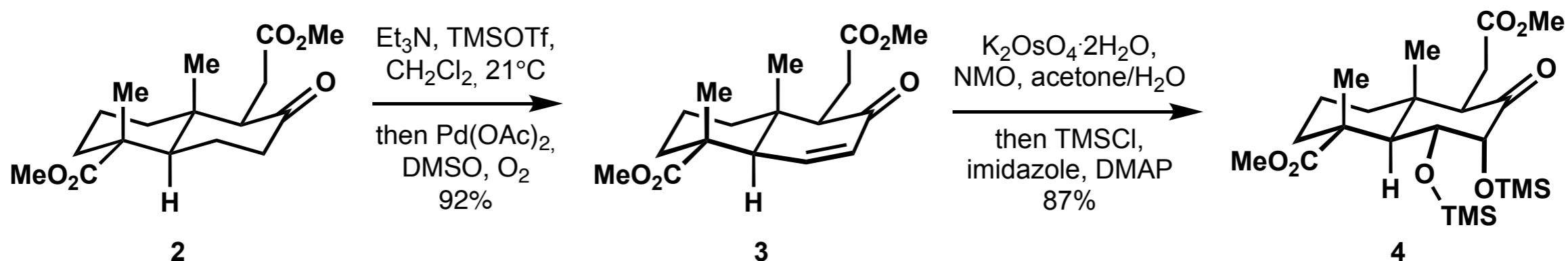
Synthesis of the pharmacophore-contained building



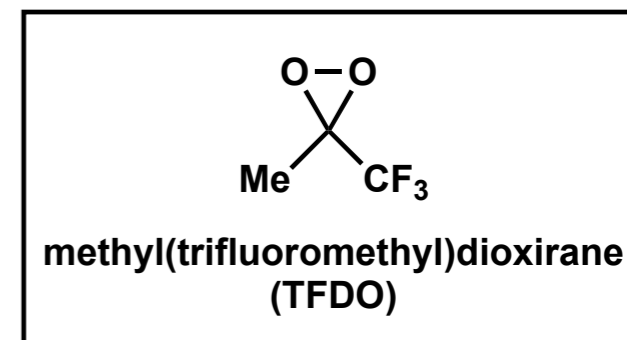
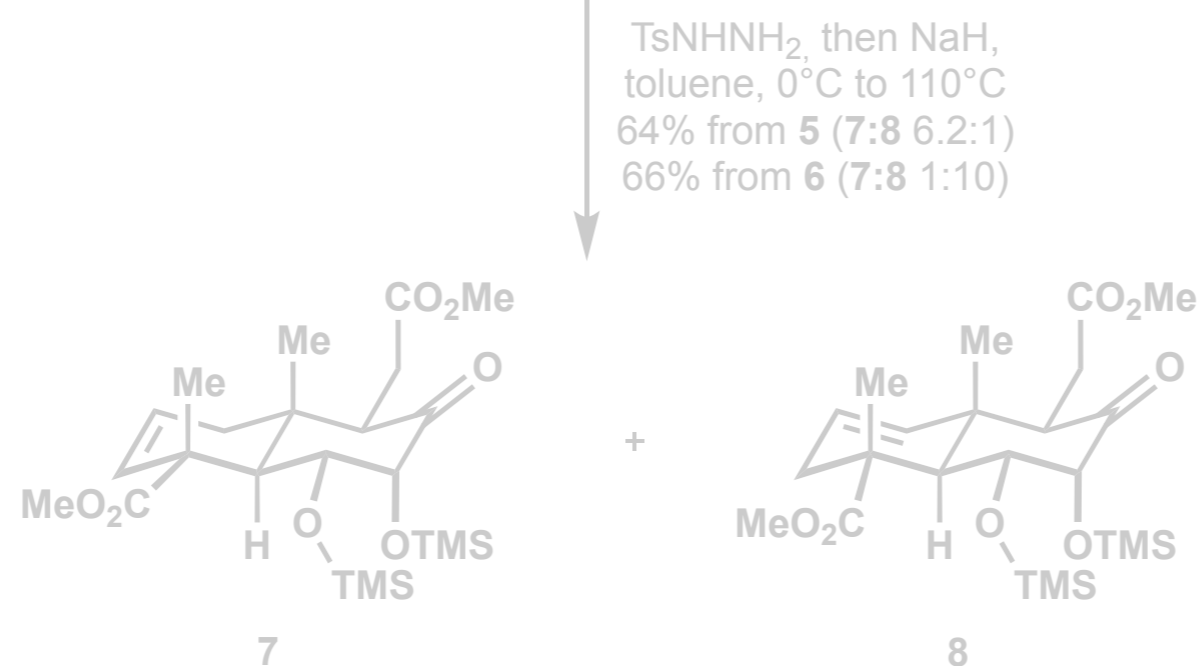
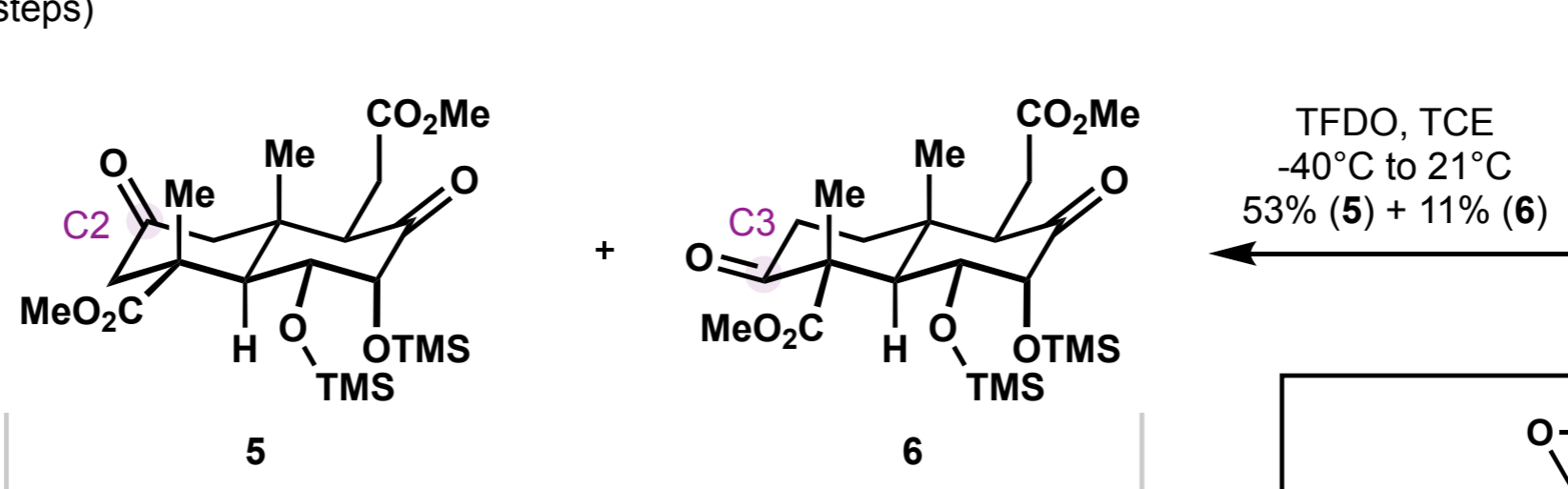
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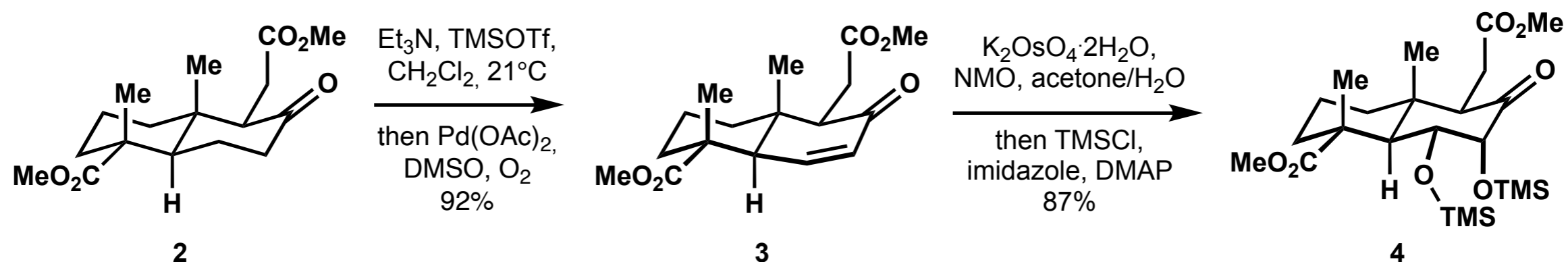
Synthesis of the pharmacophore-contained building



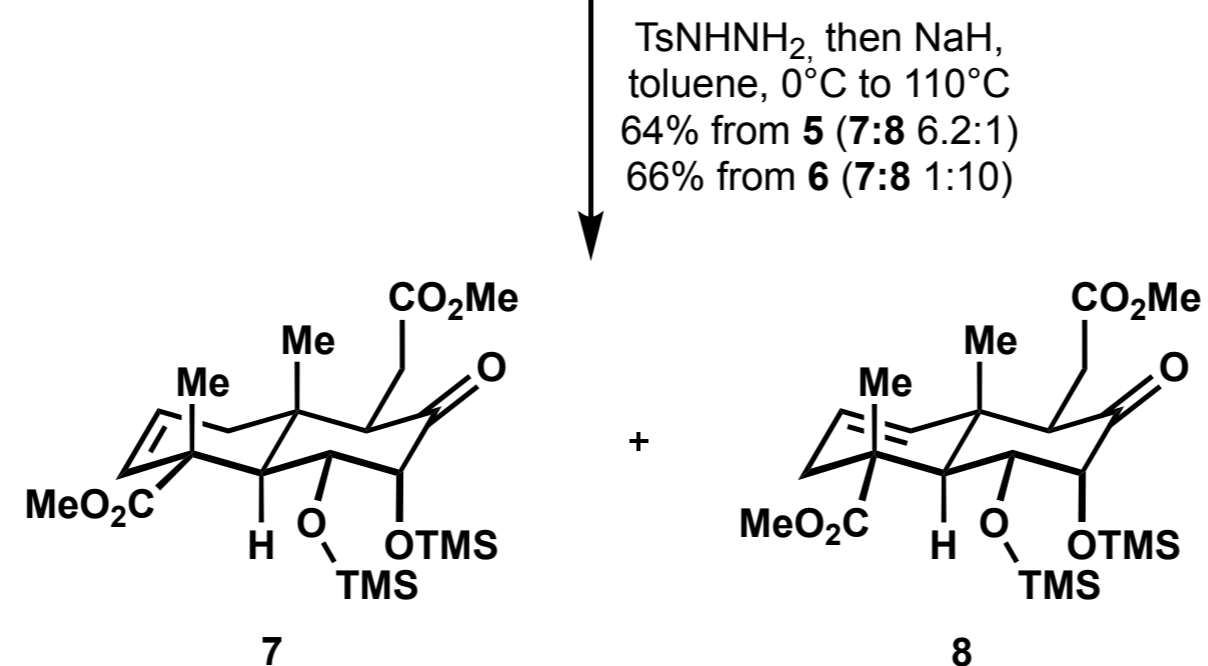
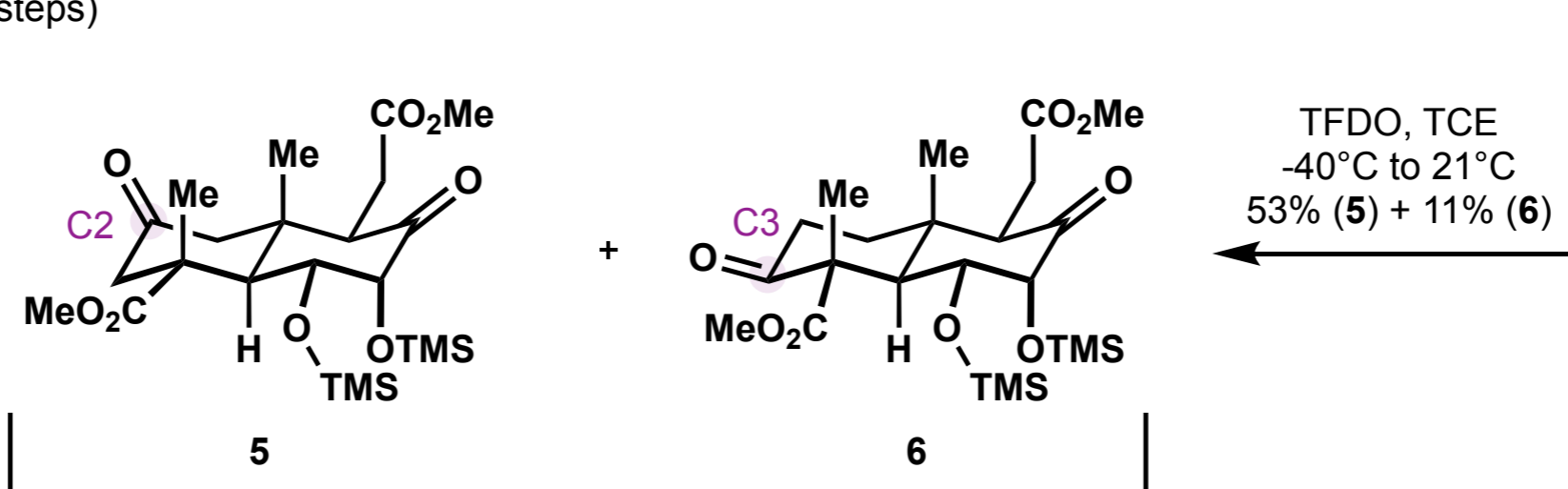
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Synthesis of the pharmacophore-contained building

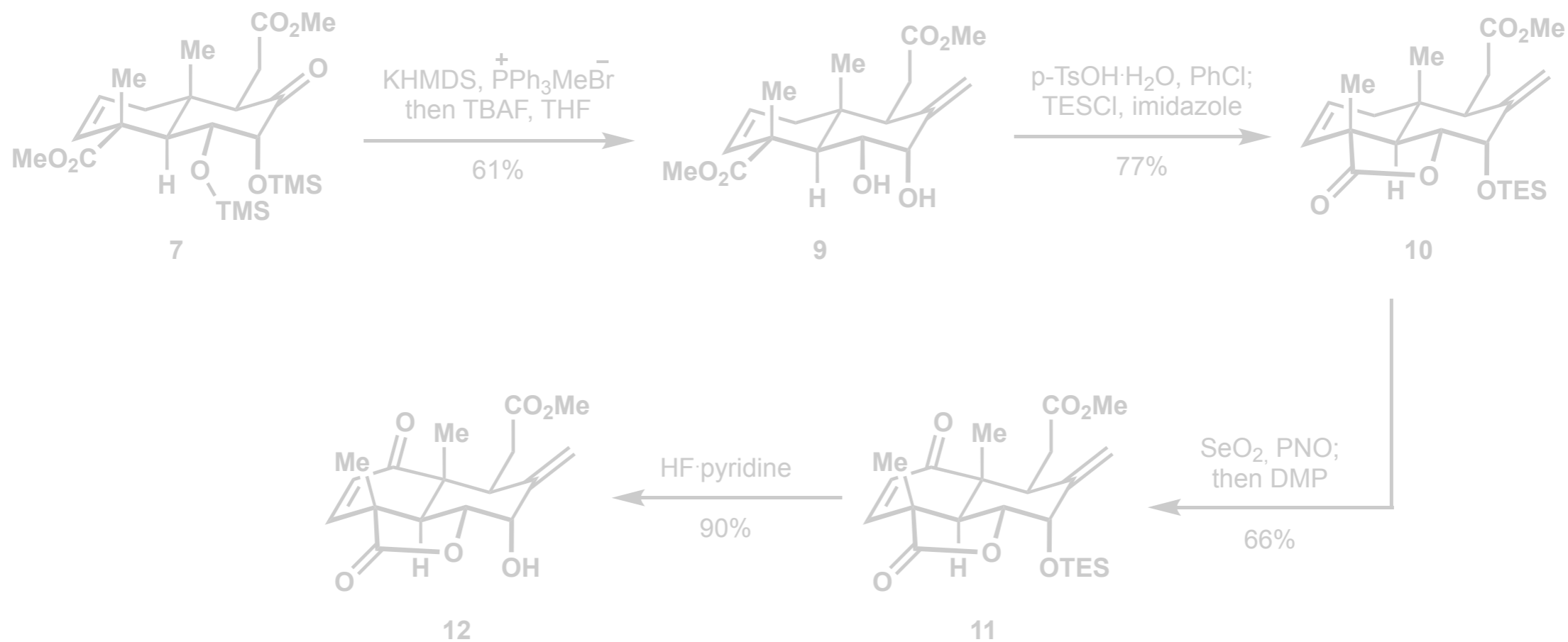
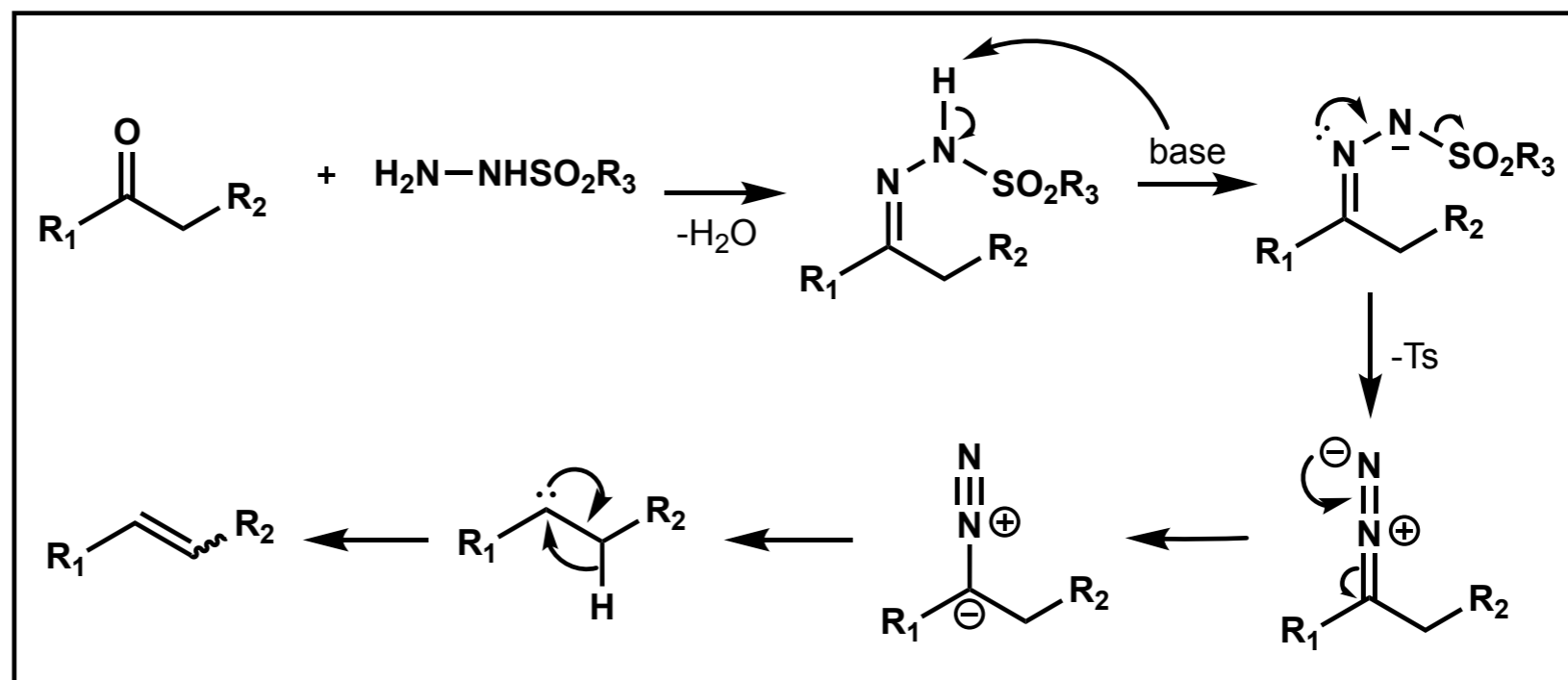


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dehydroabietic acid (5 steps)



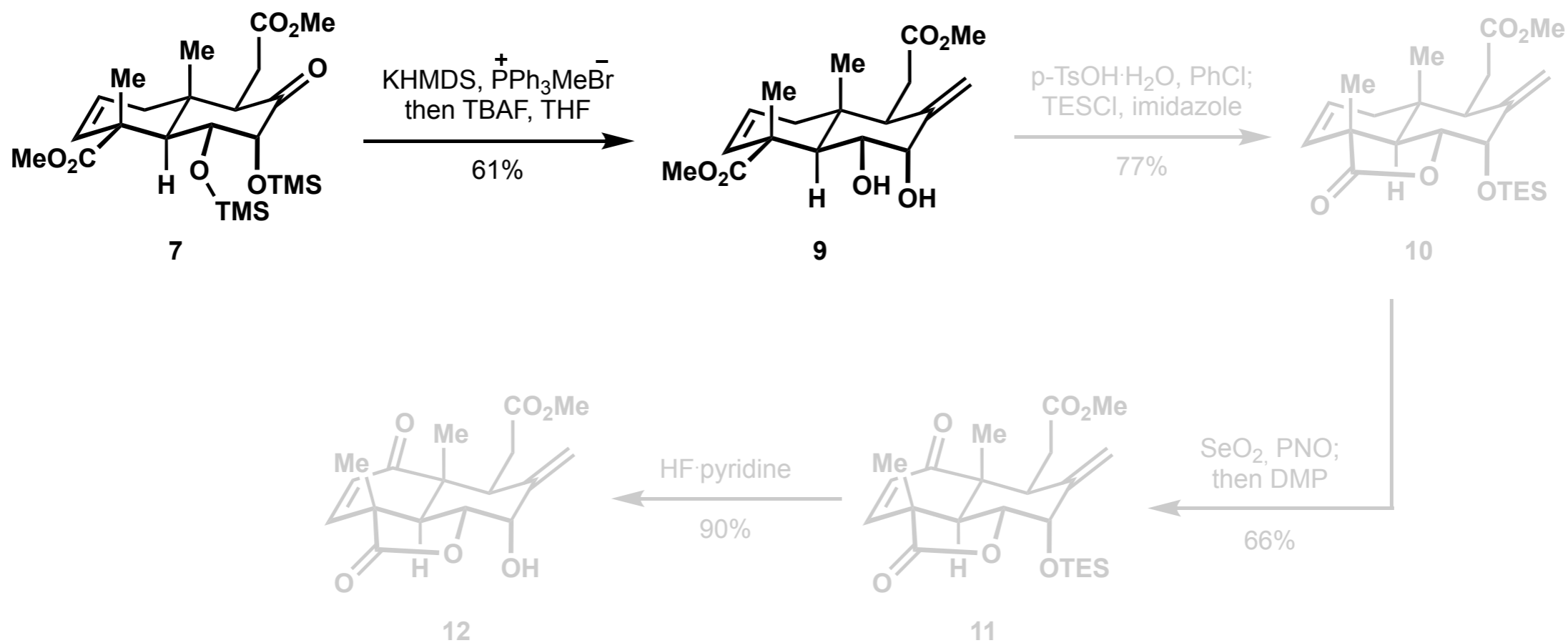
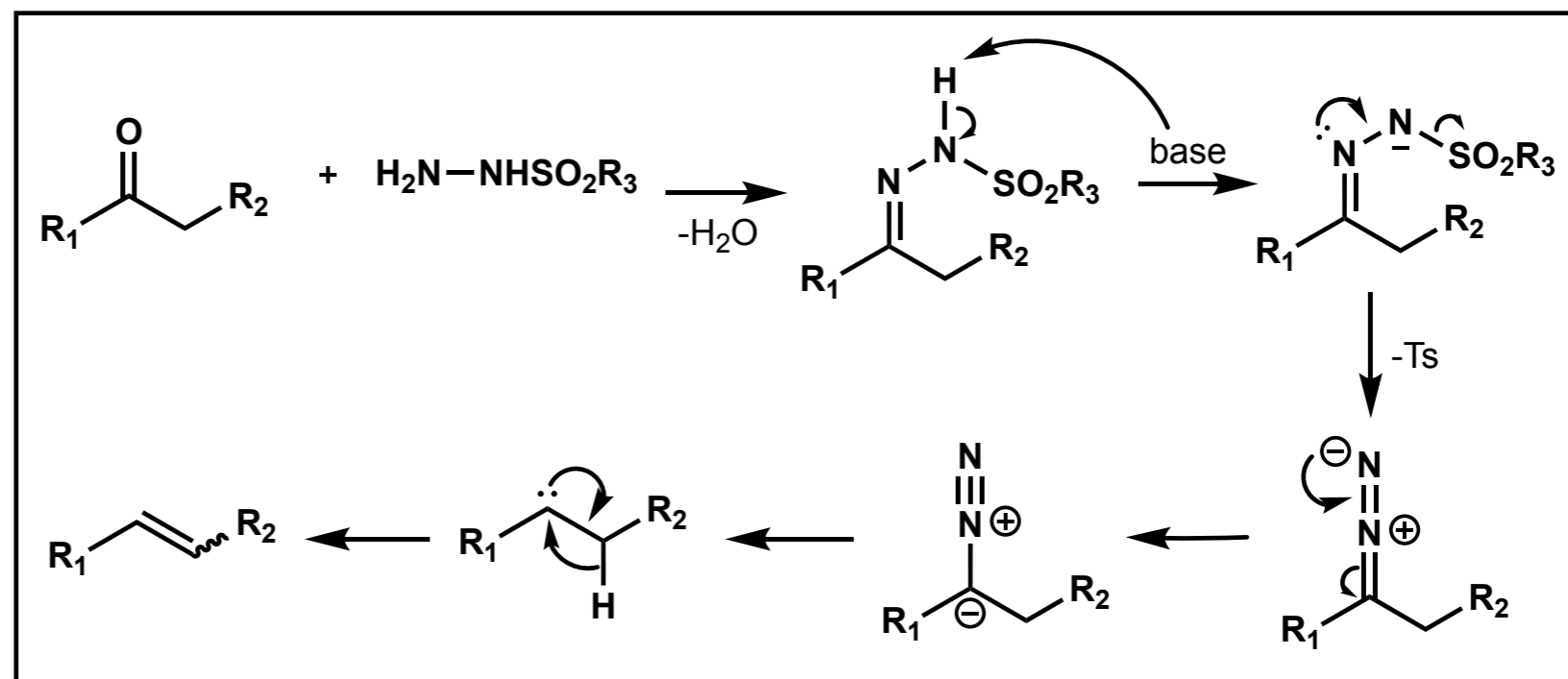
Synthesis of the pharmacophore-contained building

Bamford-Stevens mechanism



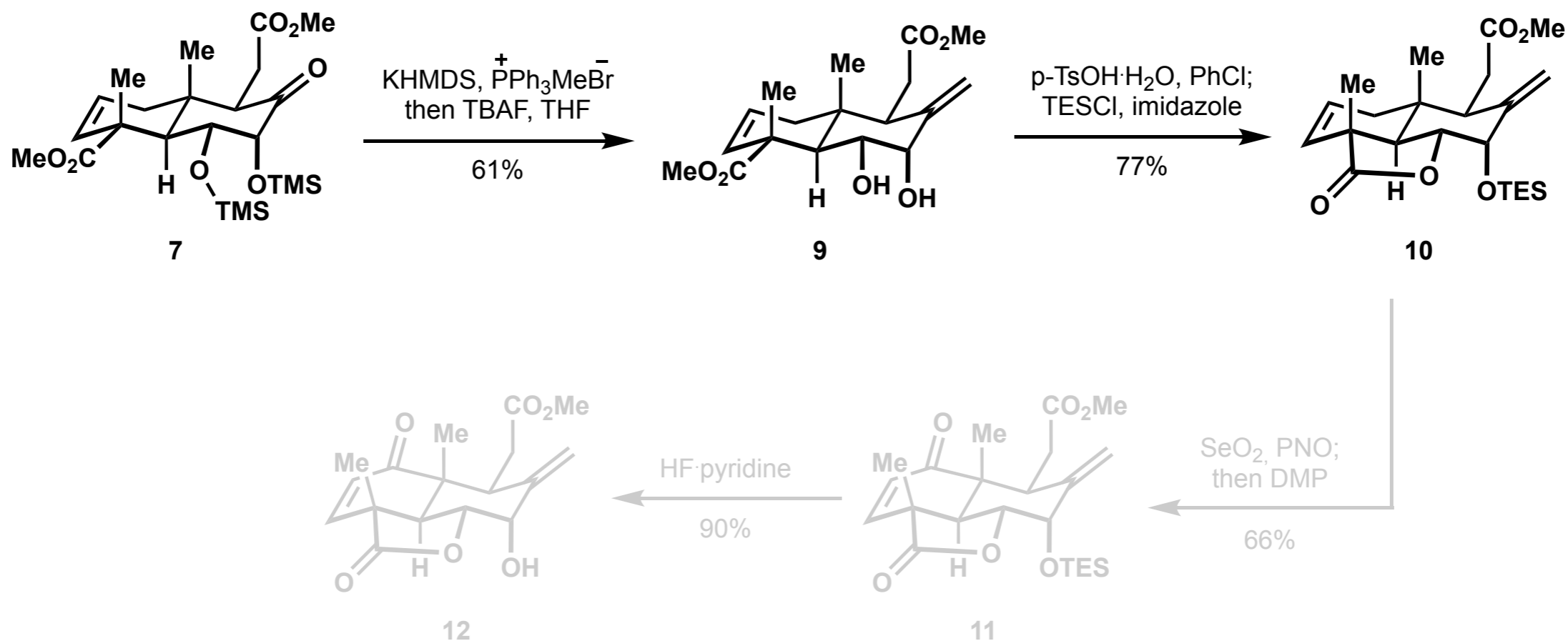
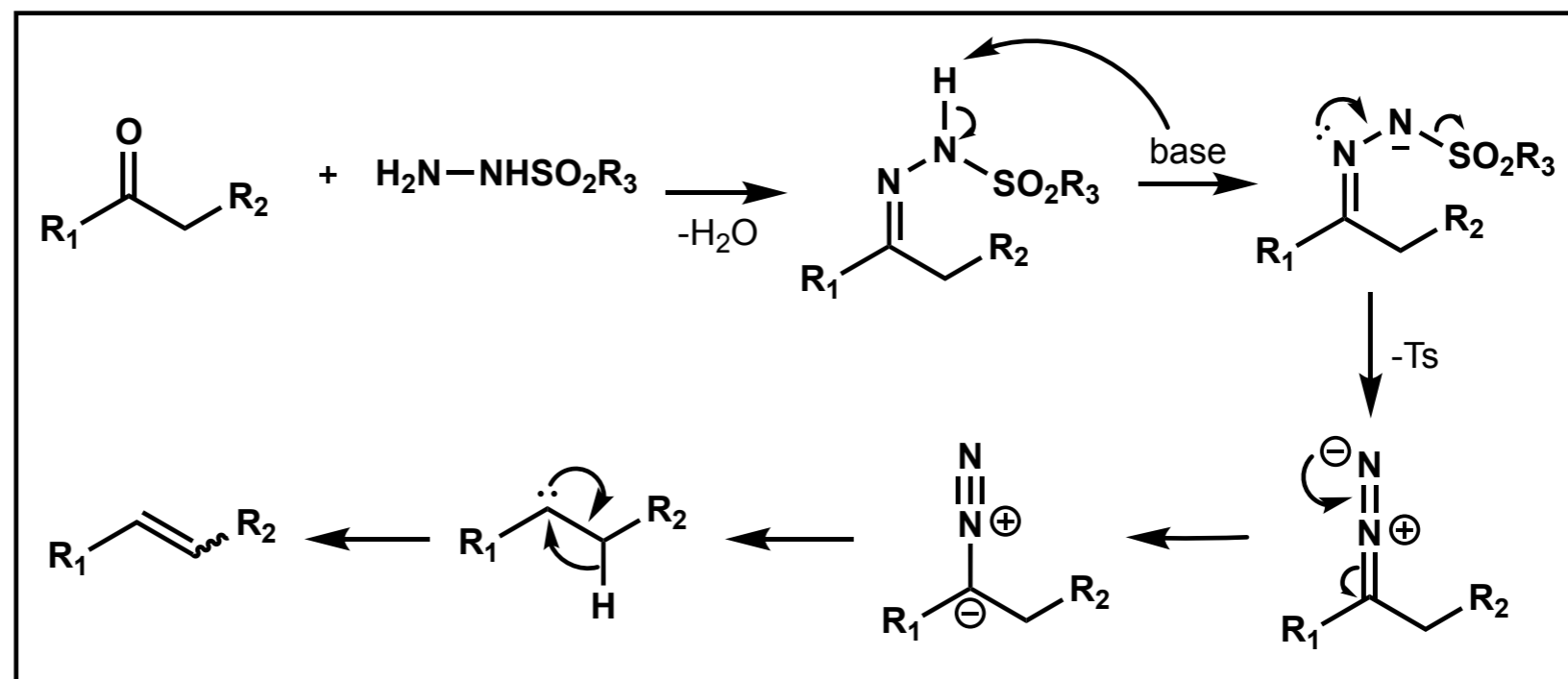
Synthesis of the pharmacophore-contained building

Bamford-Stevens
mechanism



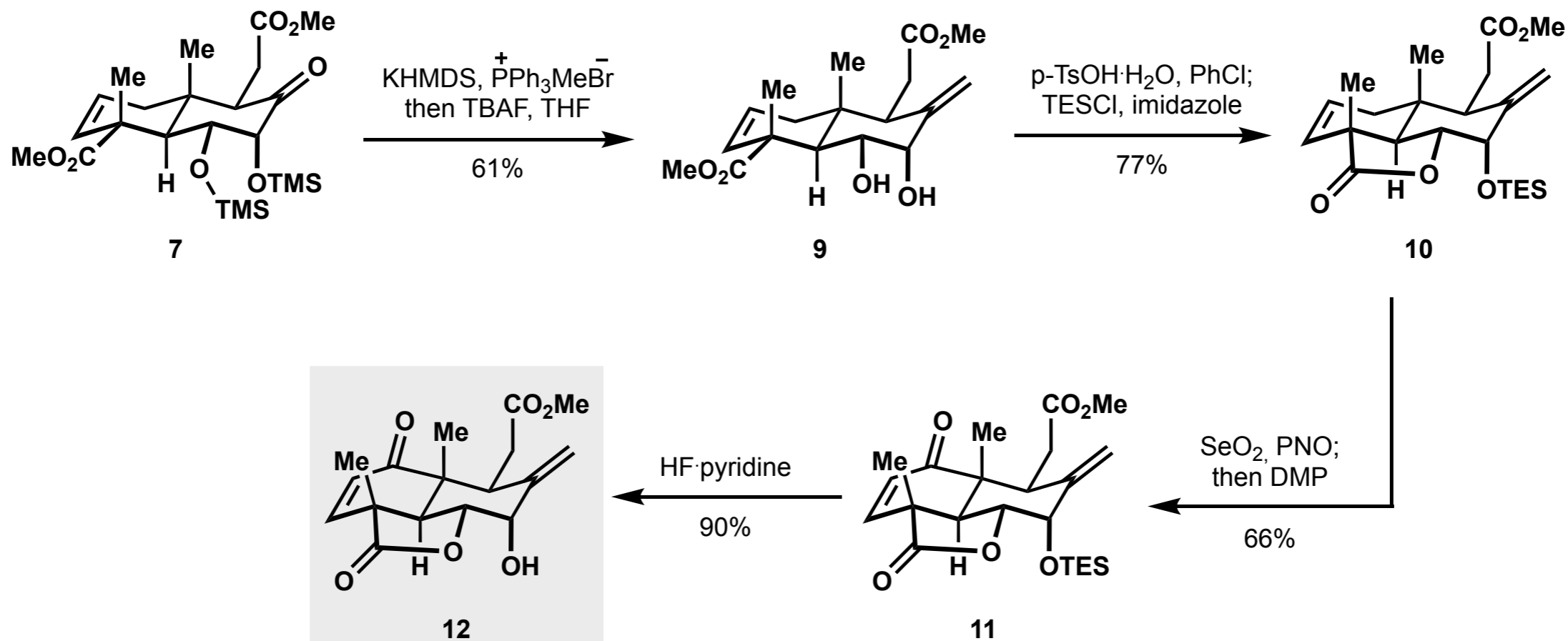
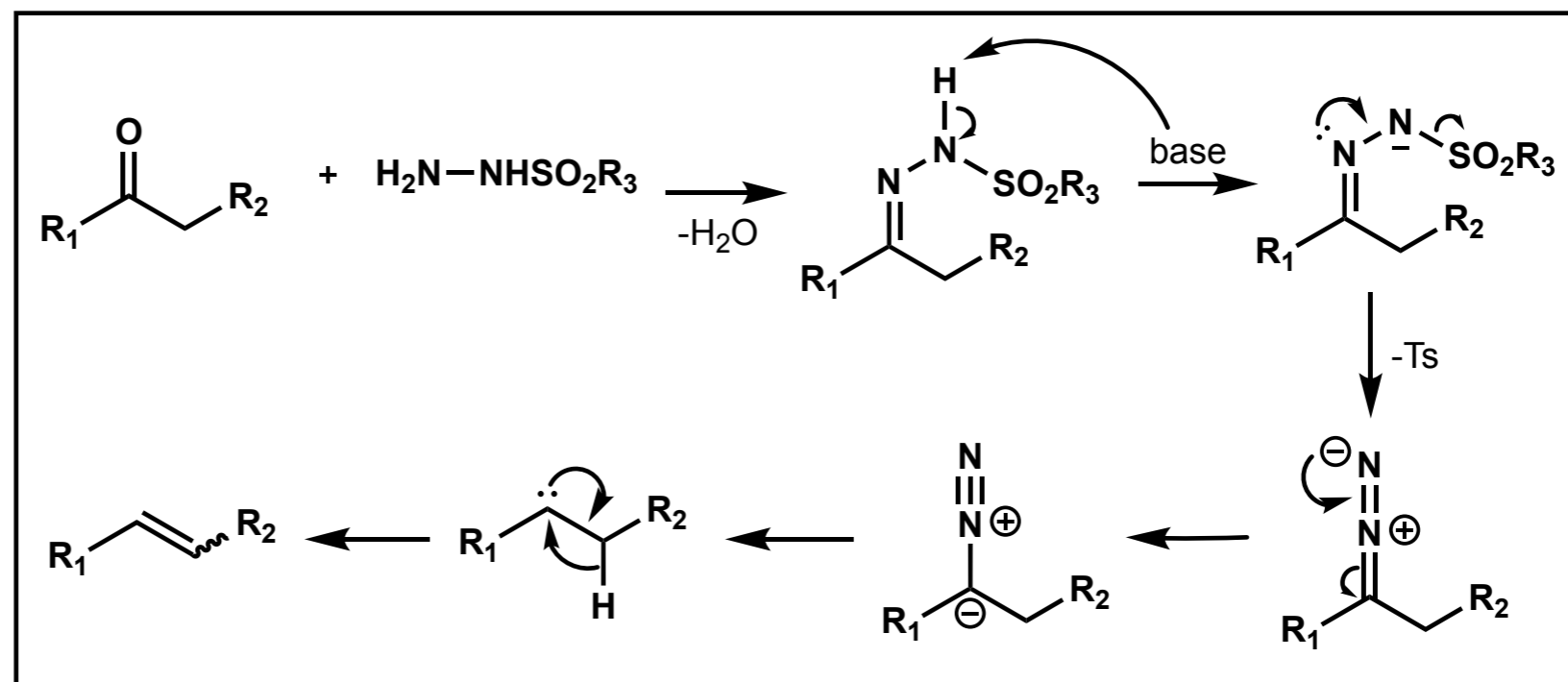
Synthesis of the pharmacophore-contained building

Bamford-Stevens
mechanism

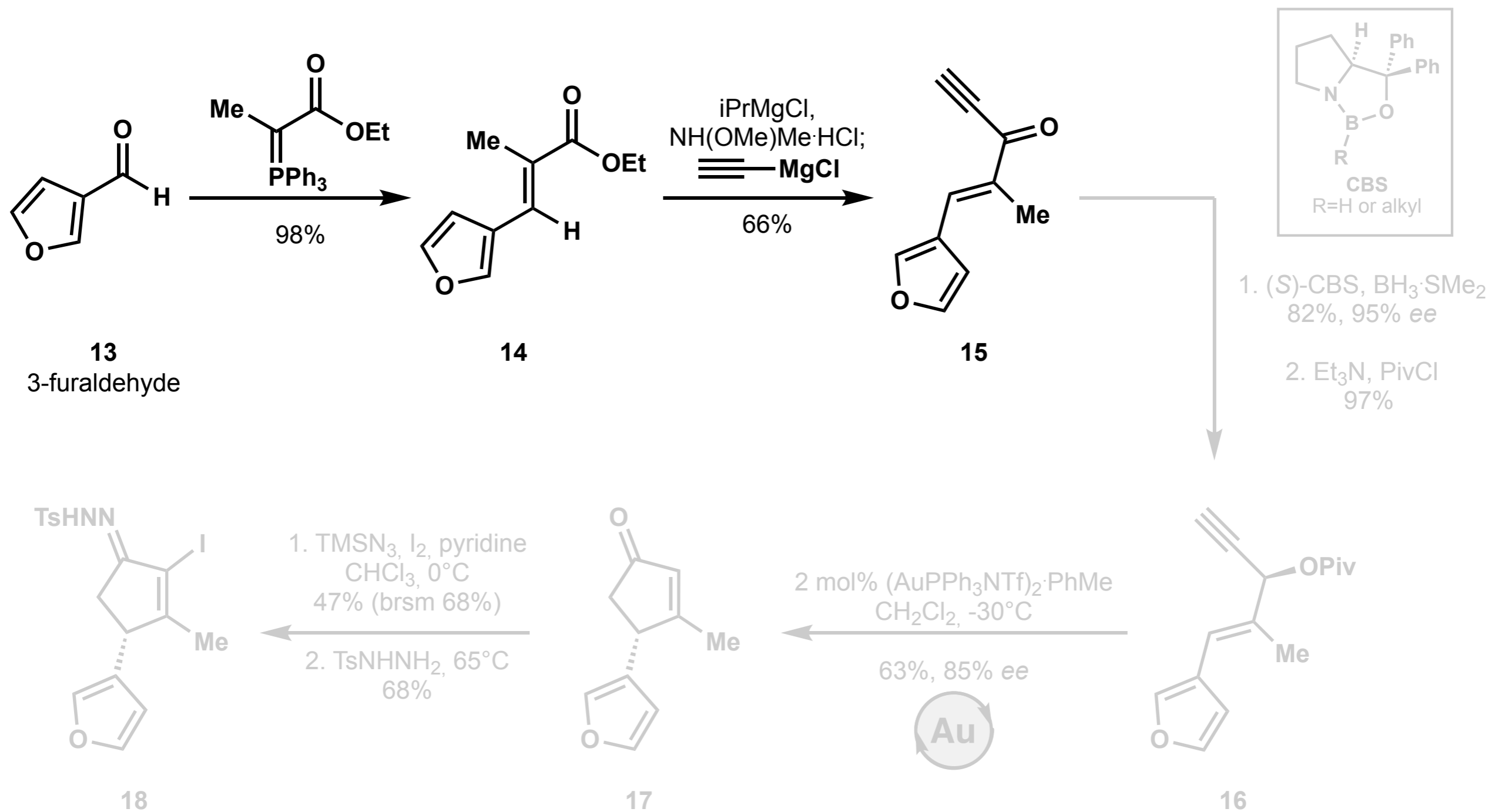


Synthesis of the pharmacophore-contained building

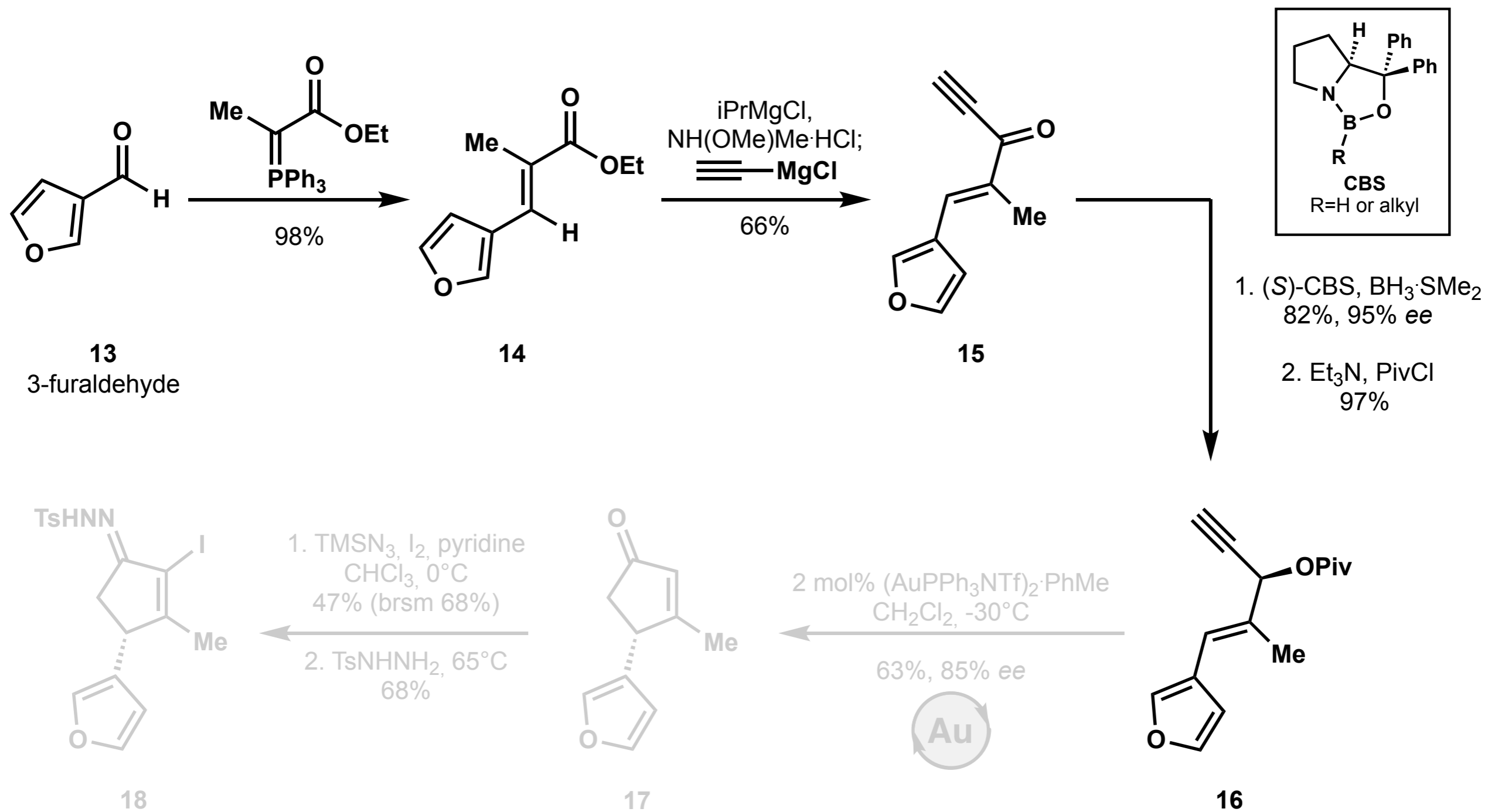
Bamford-Stevens
mechanism



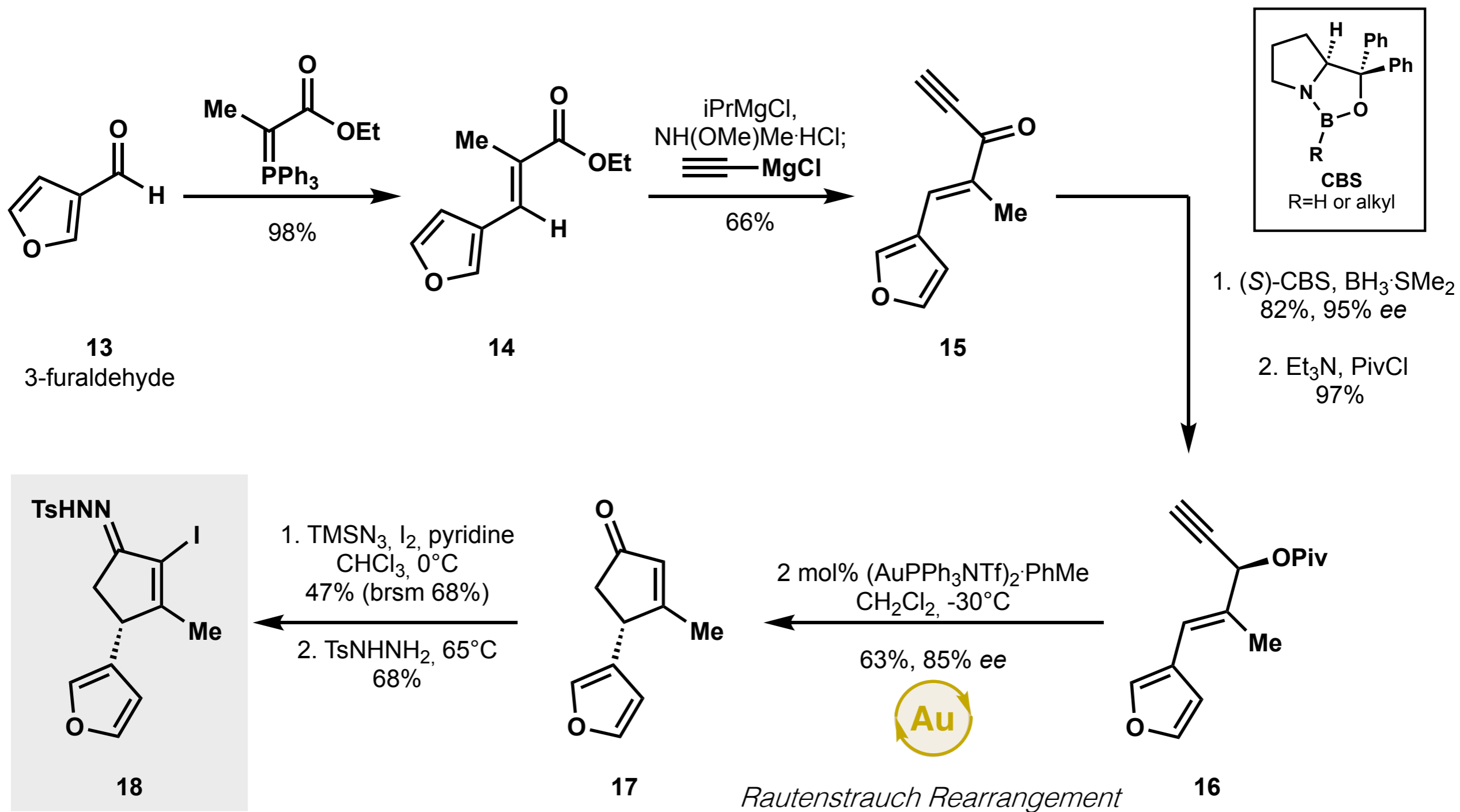
Synthesis of the diversifiable unit



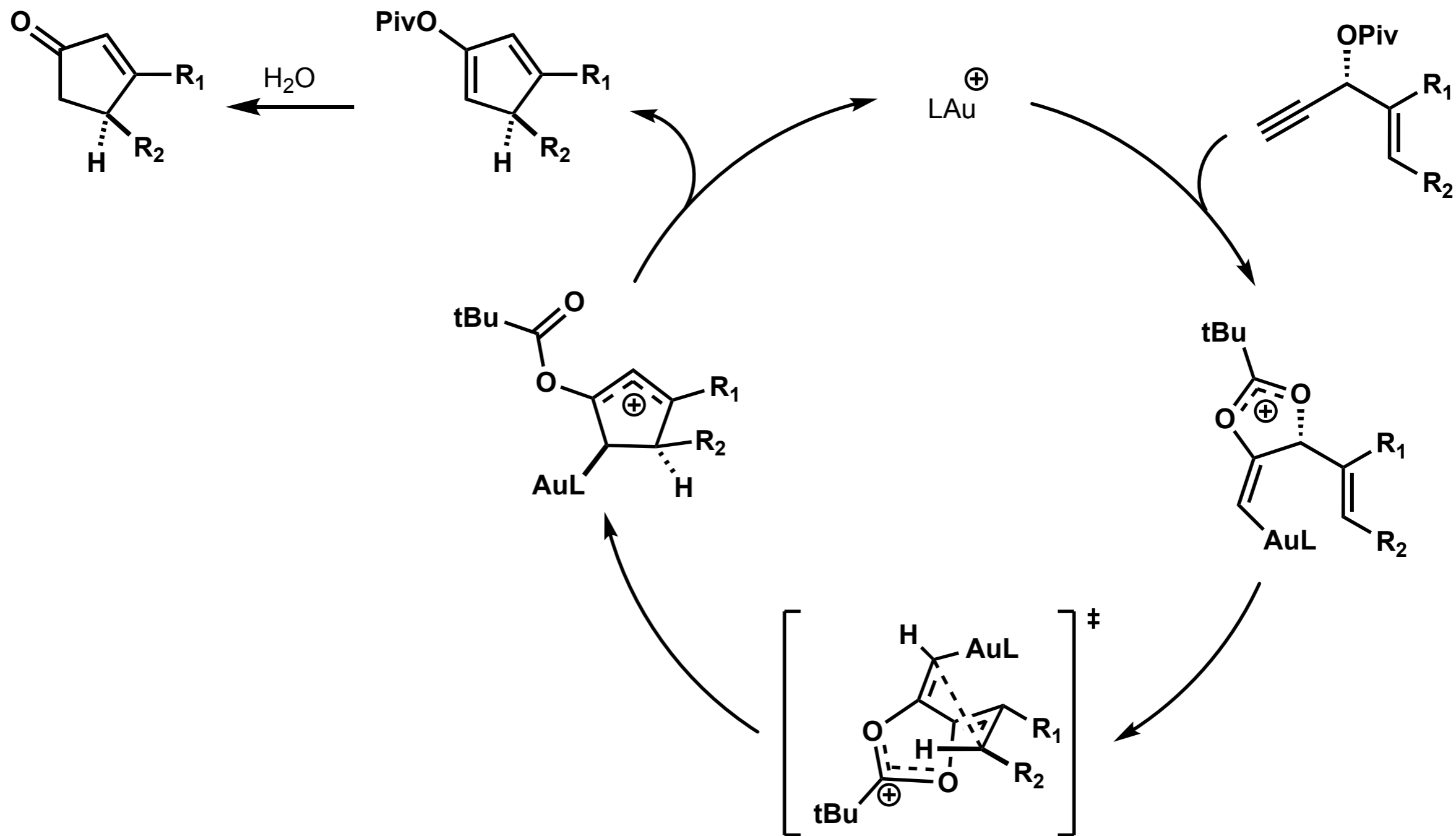
Synthesis of the diversifiable unit



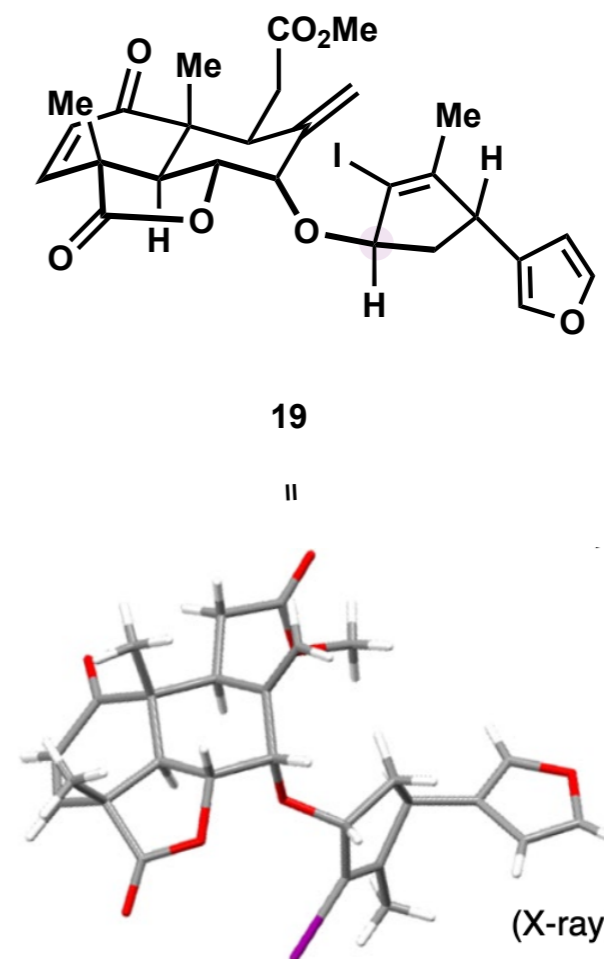
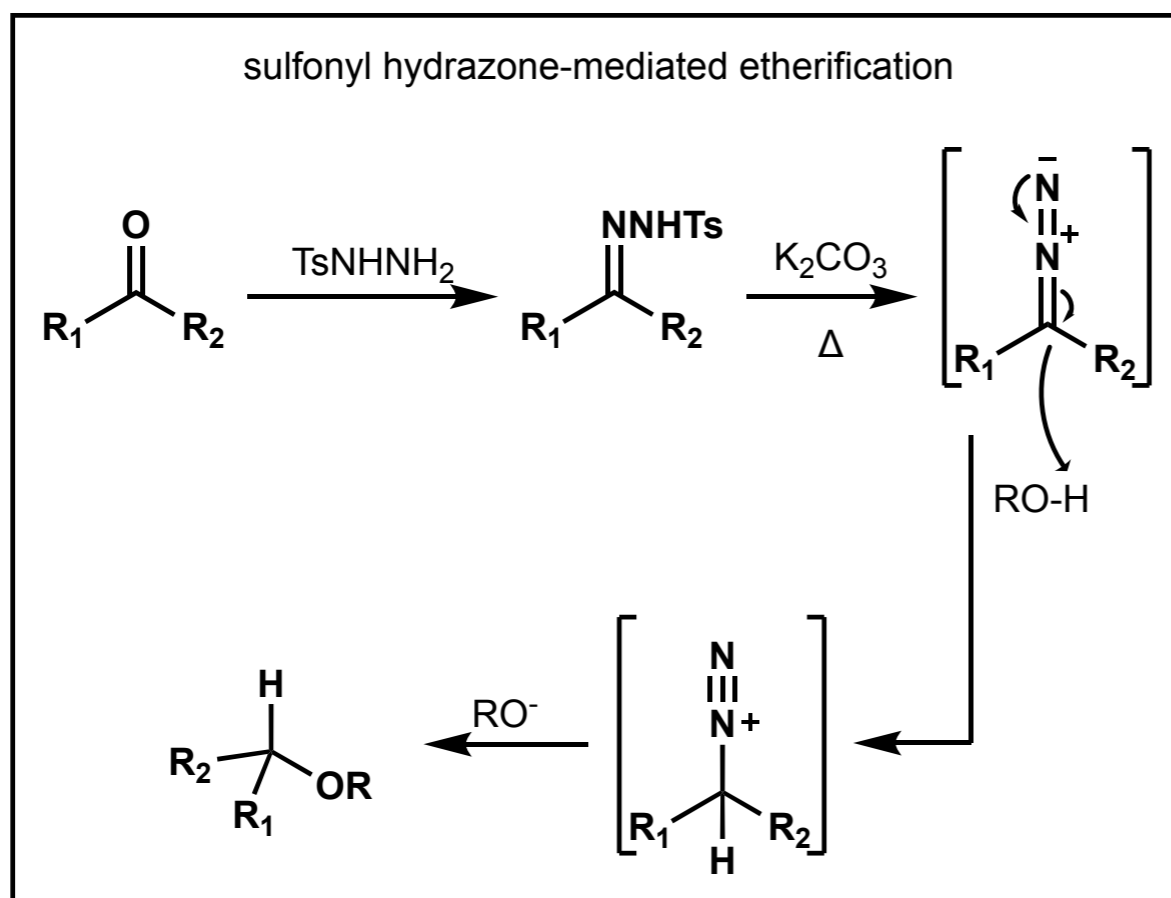
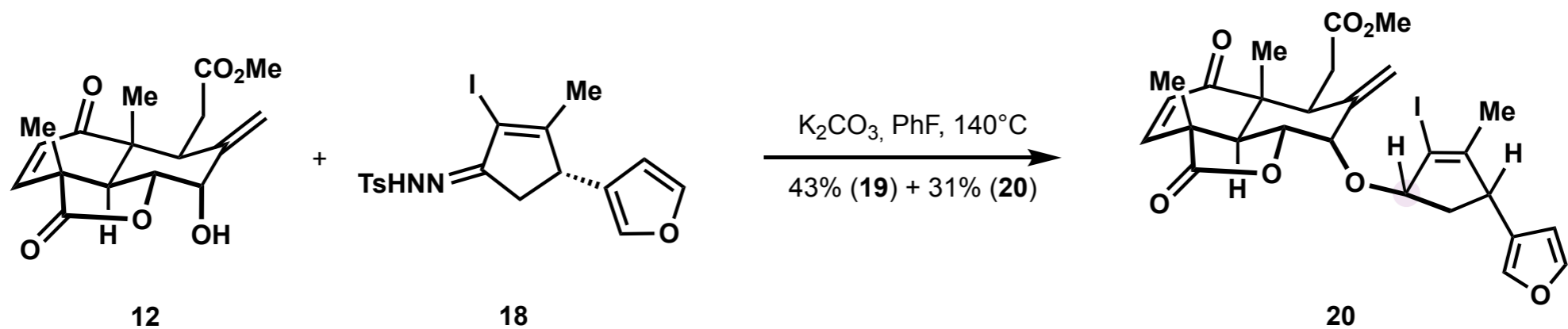
Synthesis of the diversifiable unit



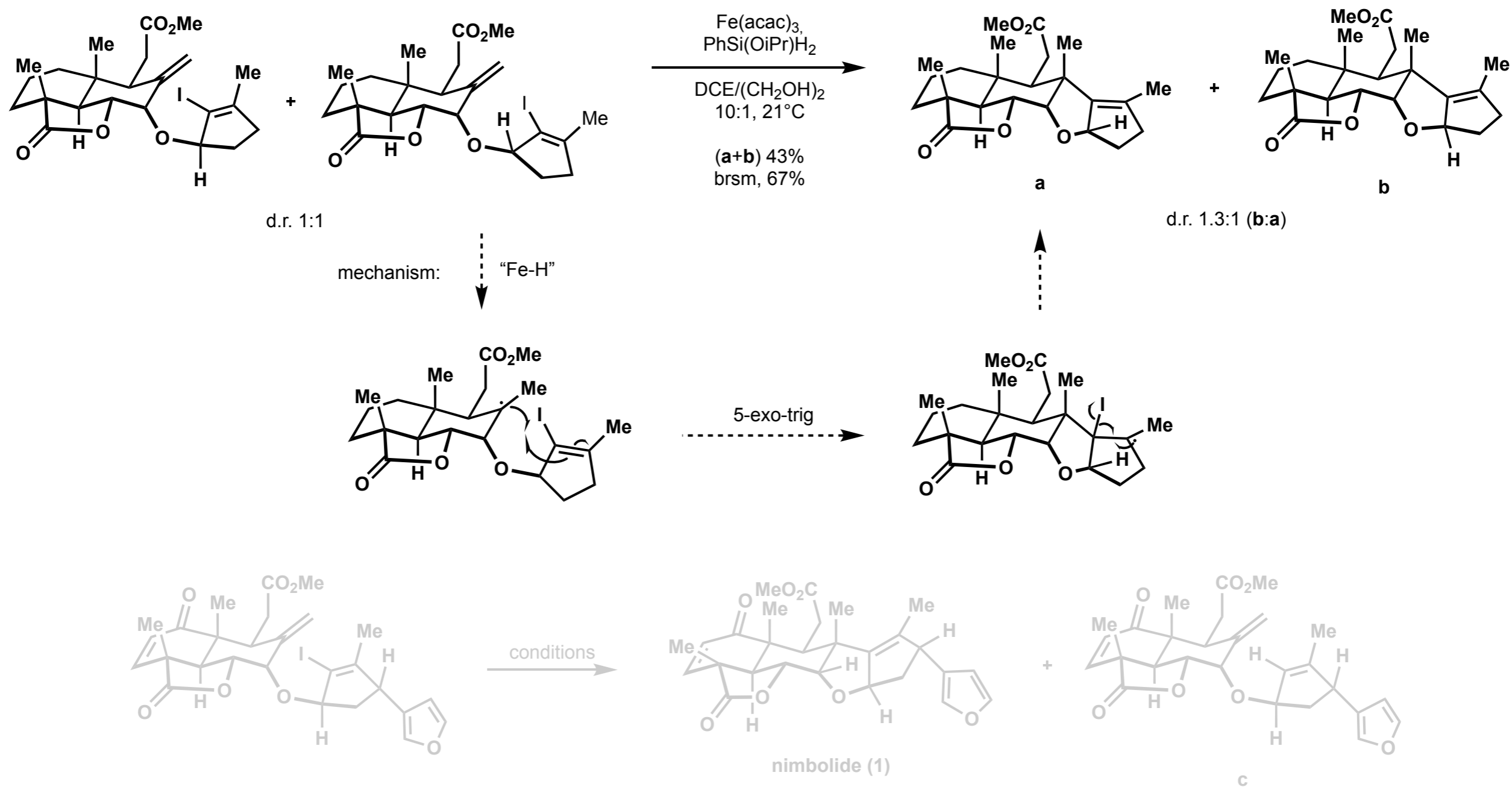
Rautenstrauch Rearrangement



Towards Nimbolide Endgame

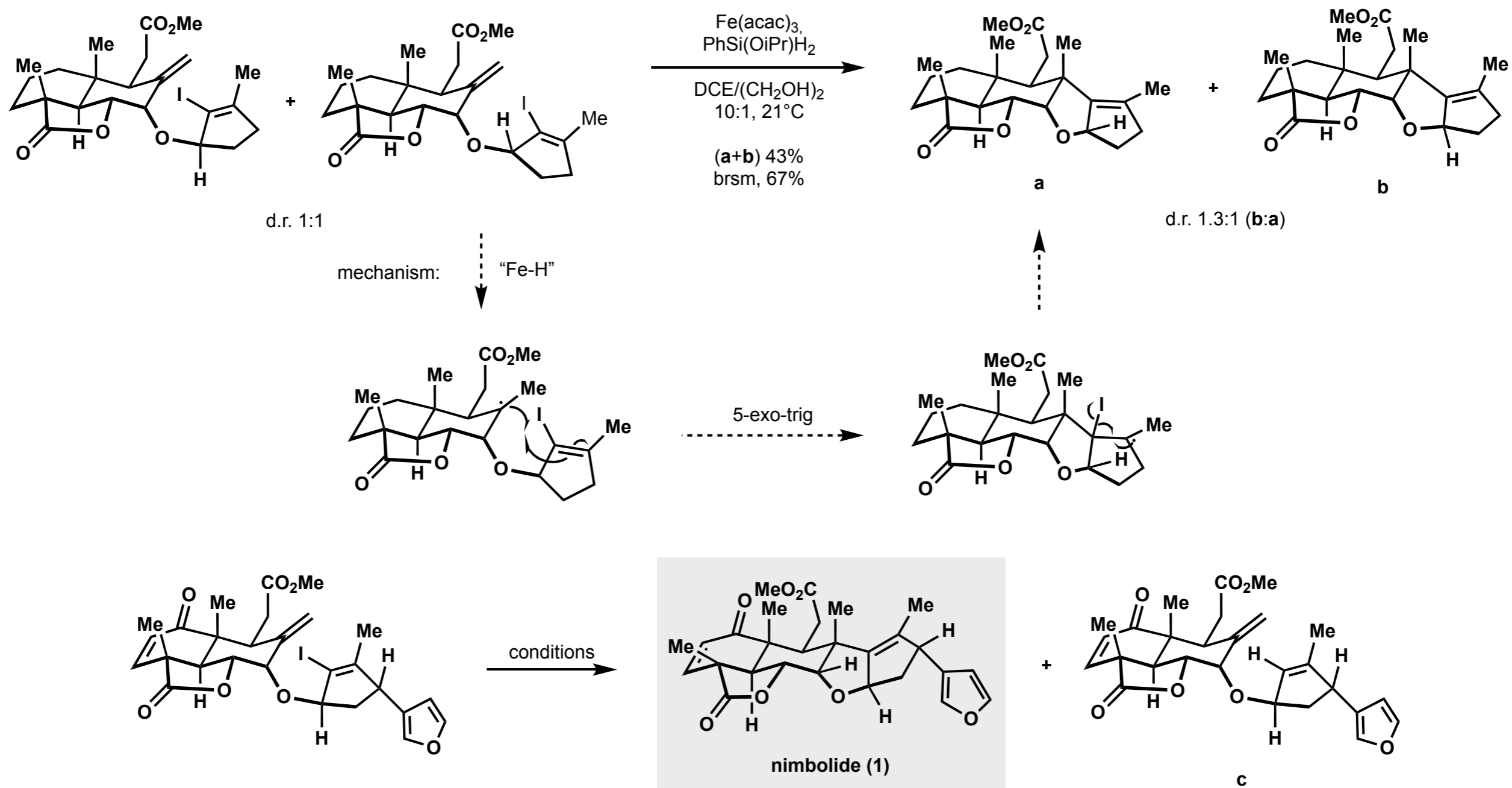


Model study for cyclization to nimbolide



MHAT: decomposition
 AIBN, Bu_3SnH in toluene or benzene: the major product was c, trace of 1
 AIBN, Bu_3SnH , PhF: 1 24%
 AIBN, Bu_3SnH , C_6F_6 : 1 47%

Model study for cyclization to nimbolide



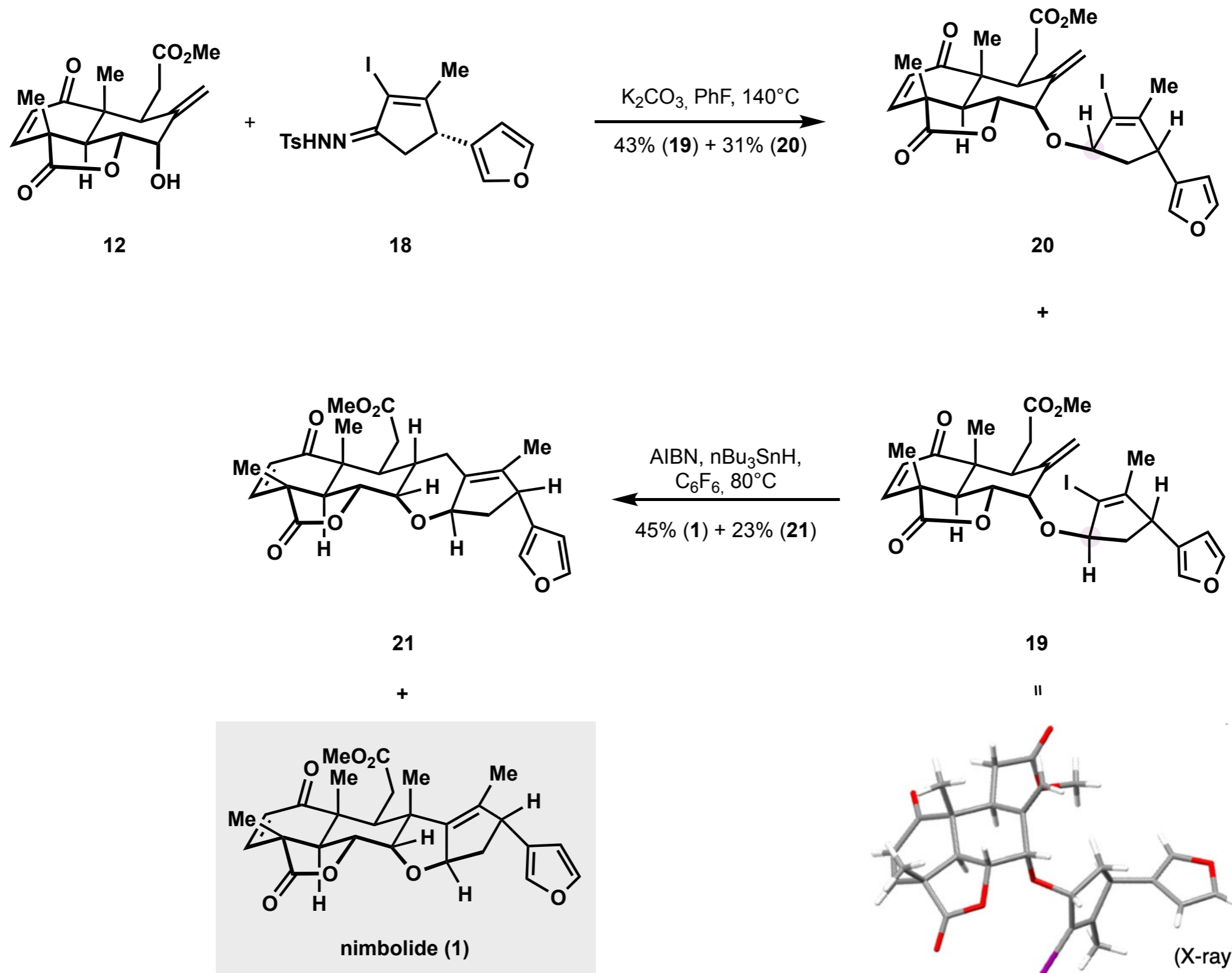
MHAT: decomposition

AIBN, Bu_3SnH in toluene or benzene: the major product was **c**, trace of **1**

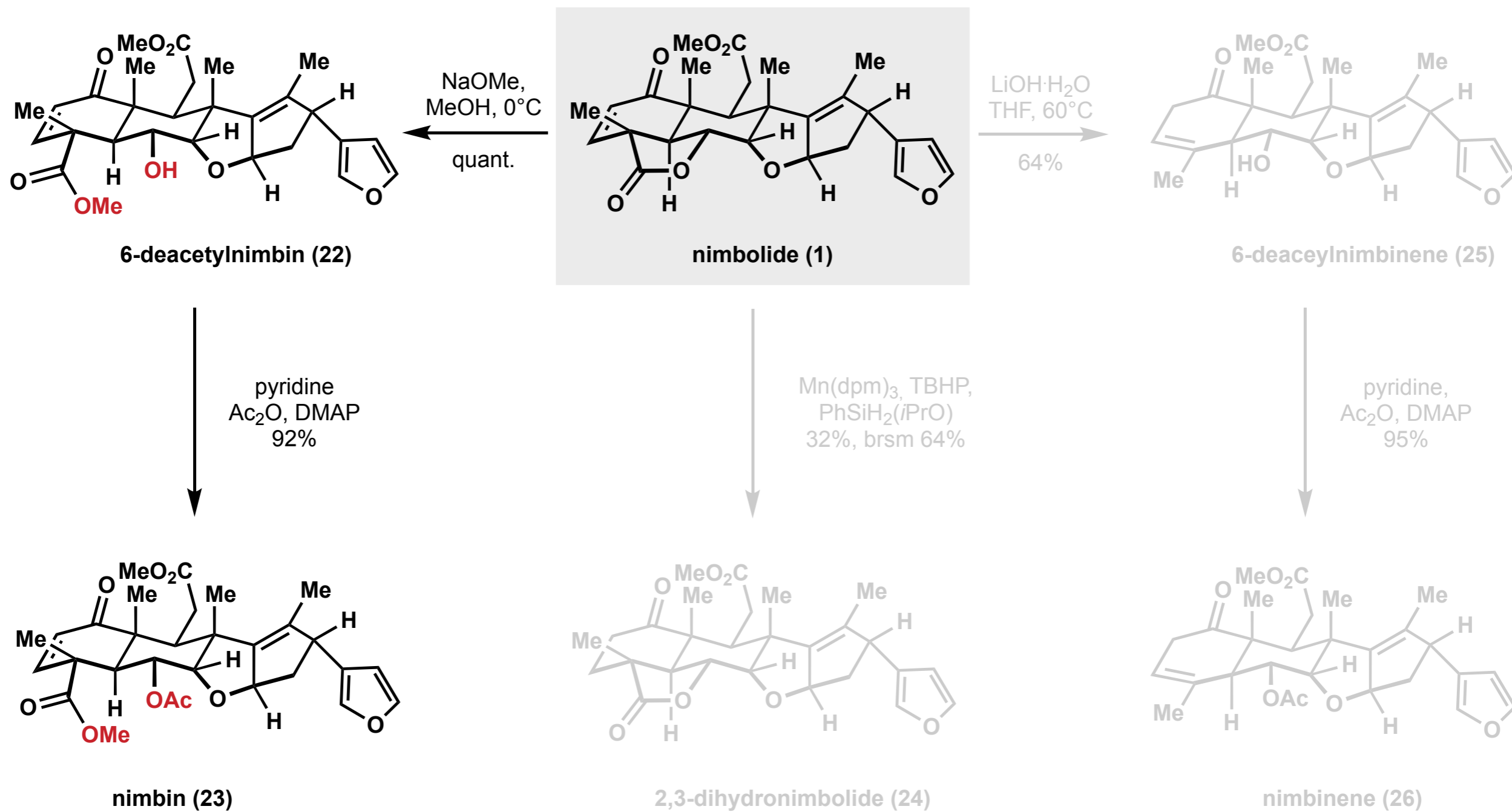
AIBN, Bu_3SnH , PhF: **1** 24%

AIBN, Bu_3SnH , C_6F_6 : **1** 47%

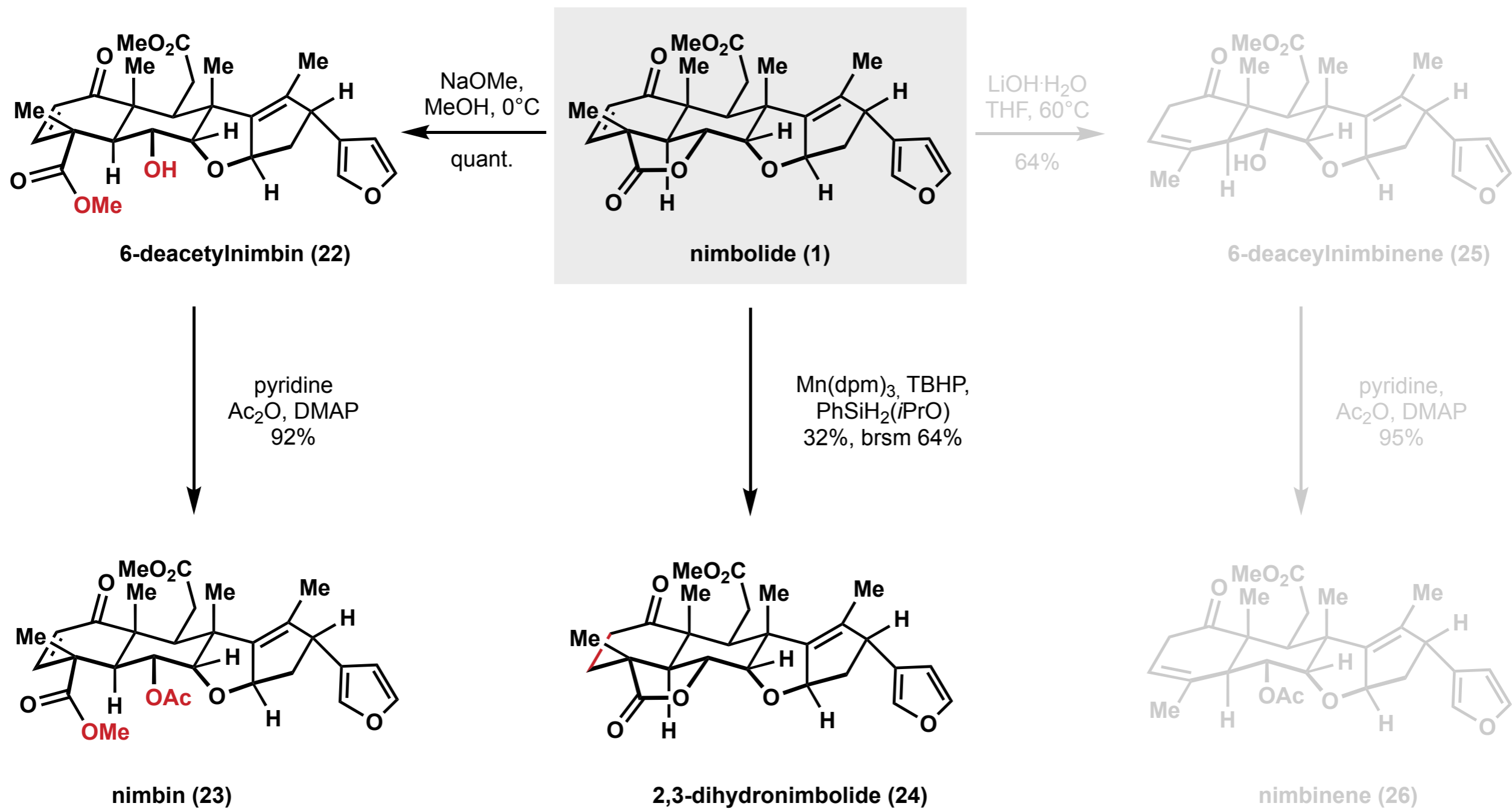
Nimbolide Endgame



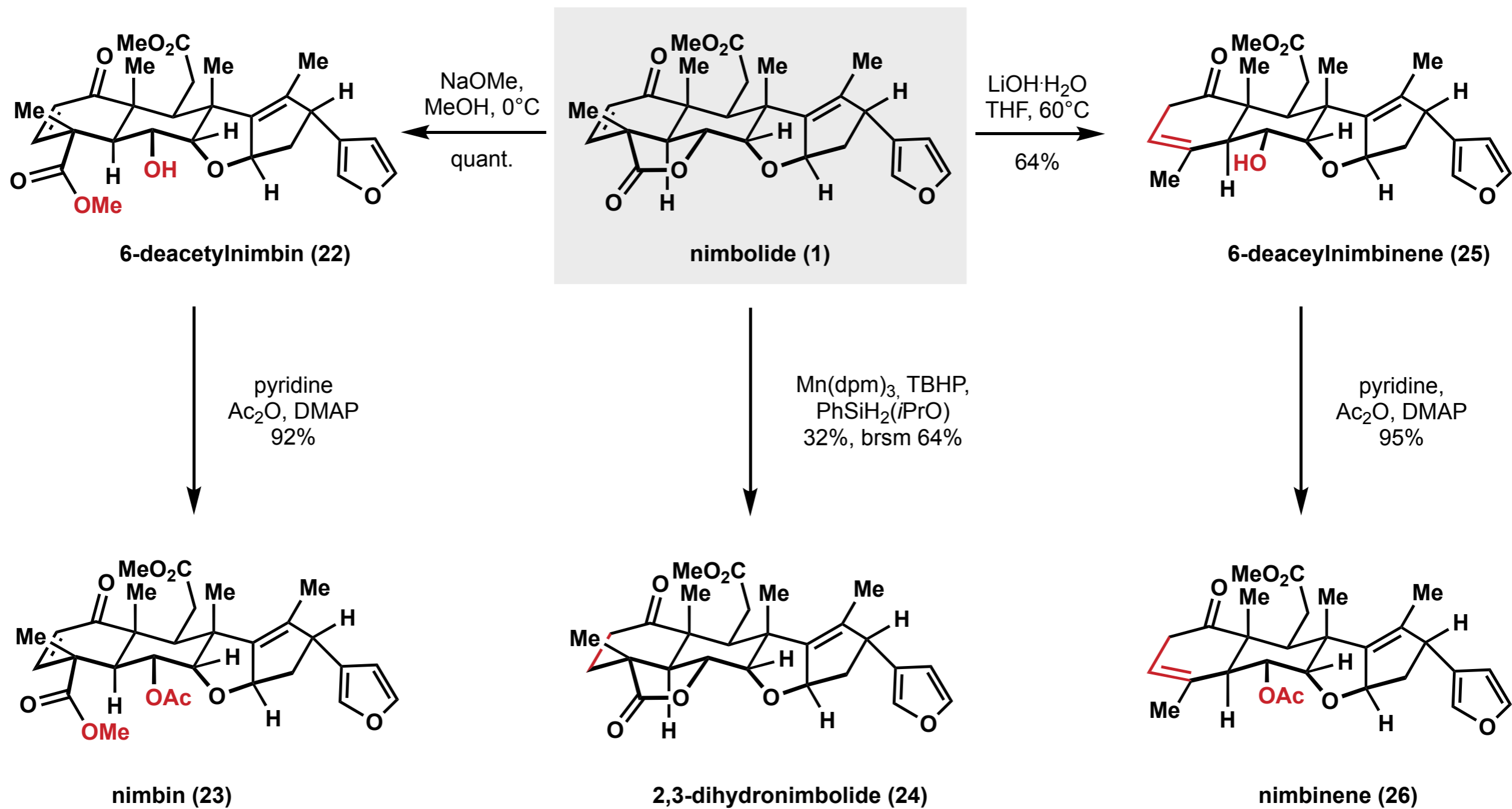
Late stage diversifications

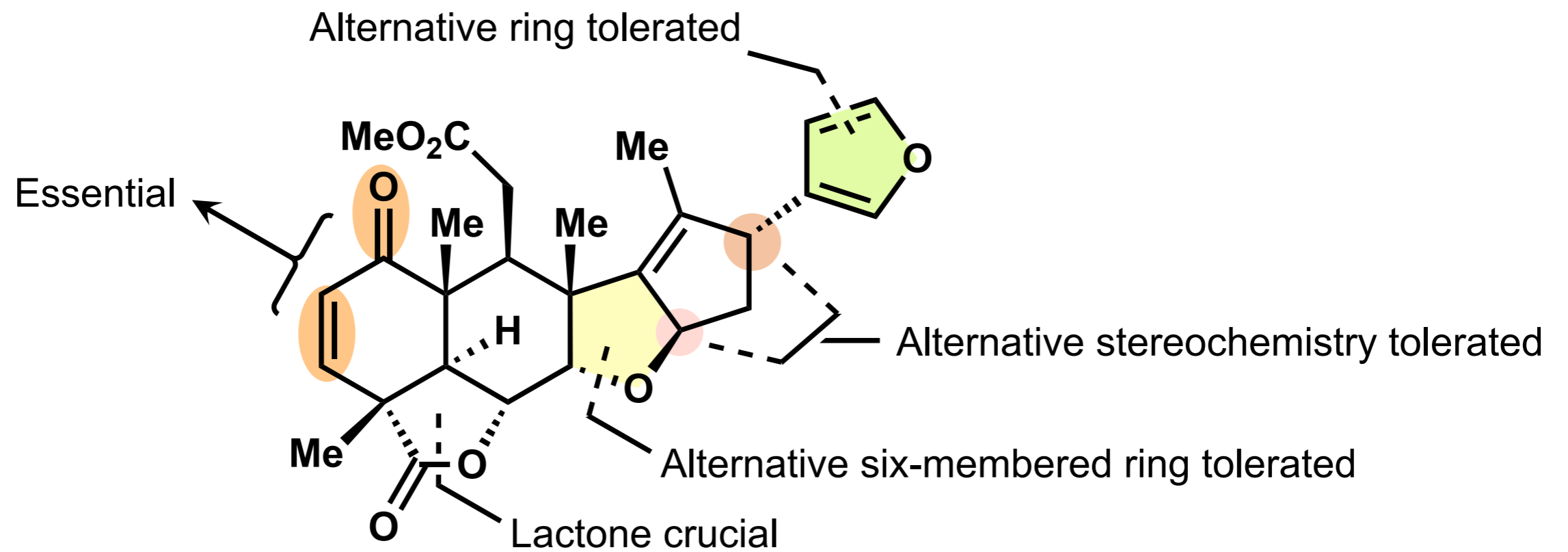


Late stage diversifications



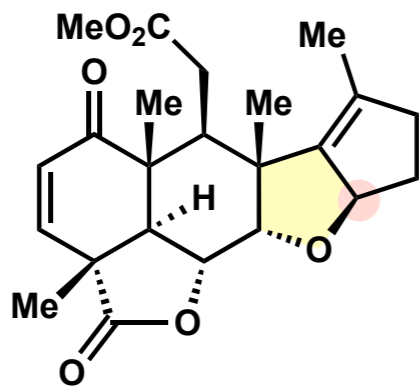
Late stage diversifications



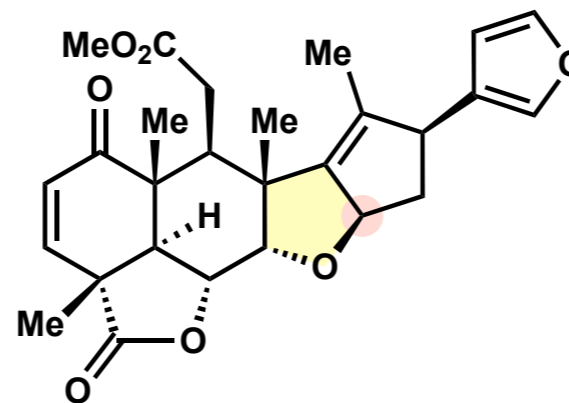


Cytotoxicity and studies on the analogues

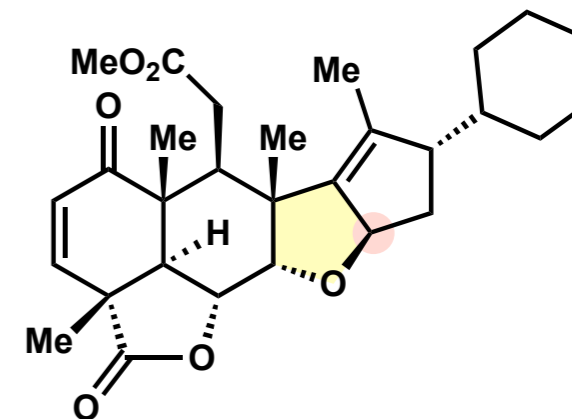
Nimbolide analogues with a five-membered C ring and downstream natural products



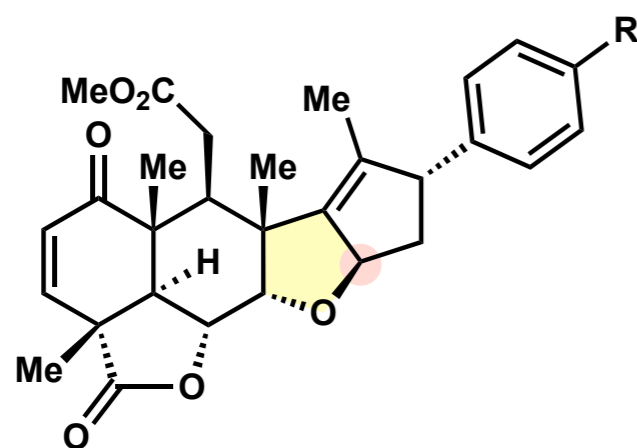
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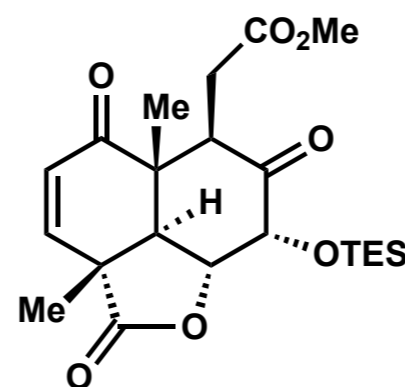
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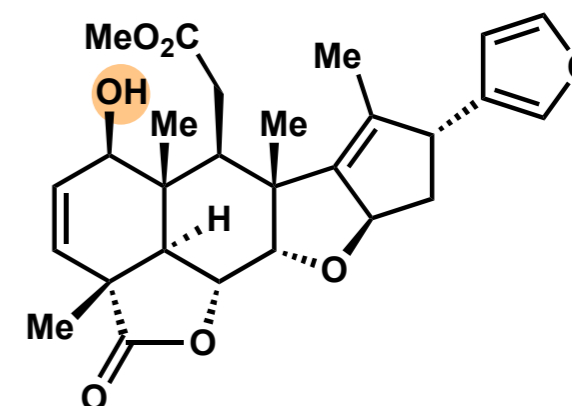
29



30 R = H
31 R = OMe
32 R = OTBS



44



45

Downstream natural products

Compound	IC ₅₀ (μM)
22	> 10
23	> 10
24	> 10
25	> 10
26	> 10

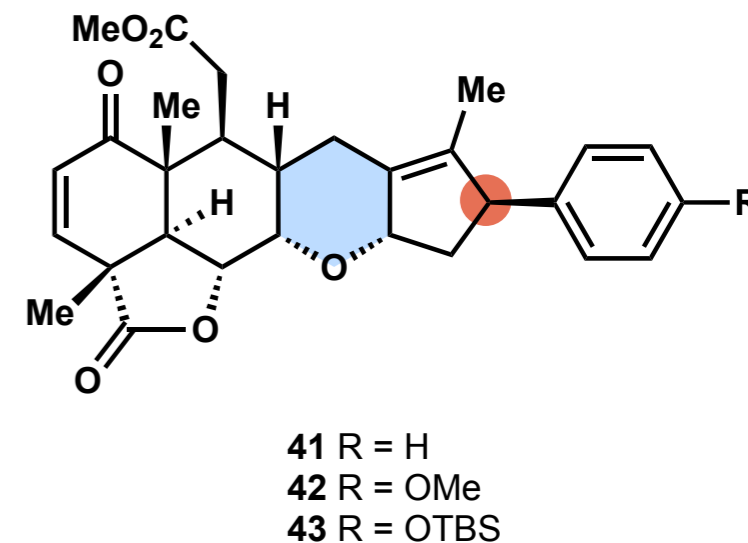
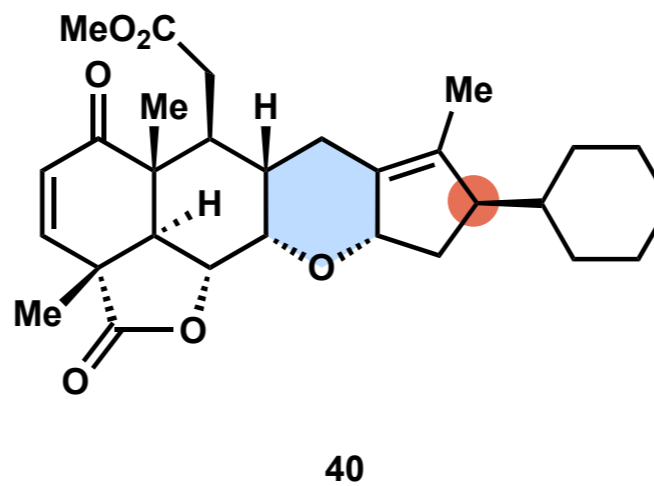
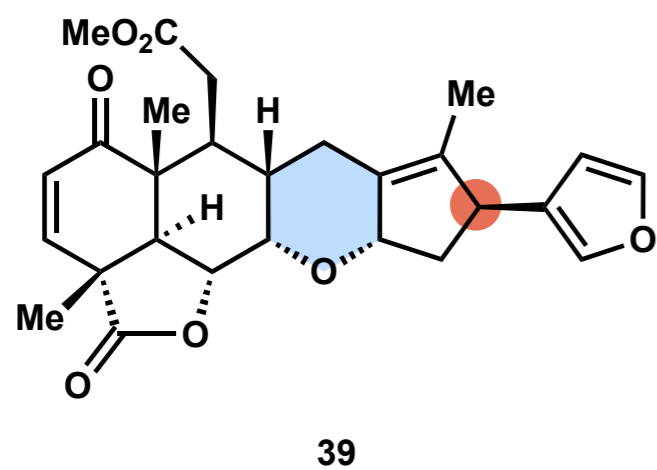
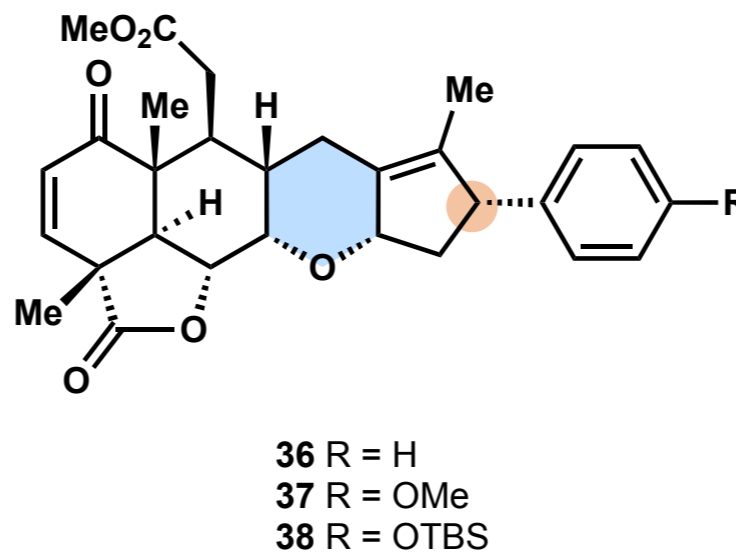
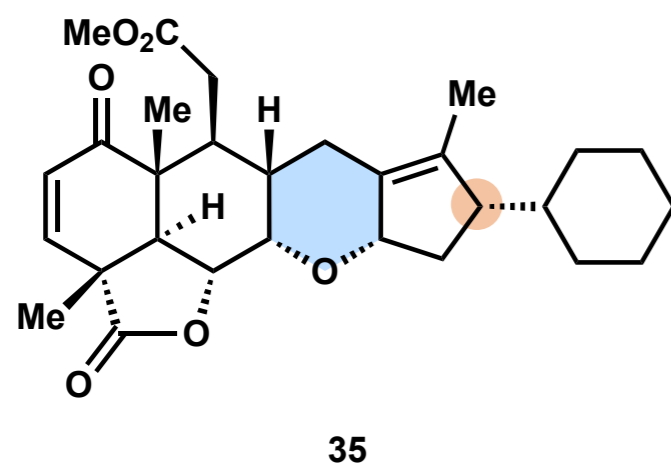
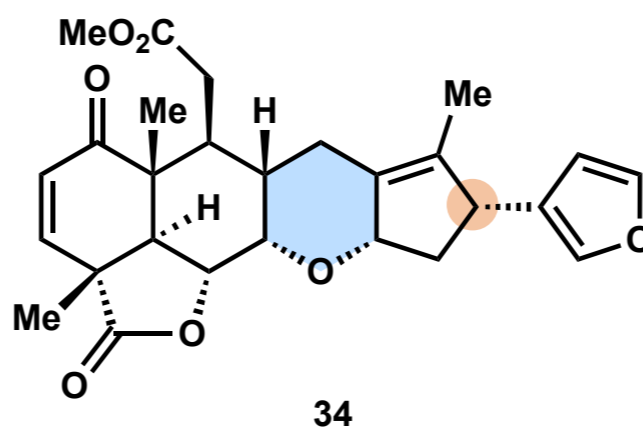
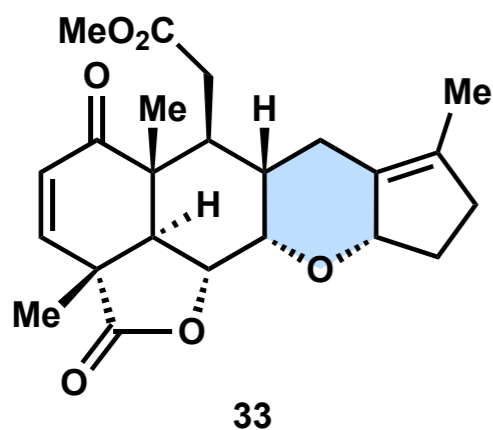
Intermediate/related structure

Compound	IC ₅₀ (μM)
1	0.34 ± 0.05
12	> 10
19	0.23 ± 0.04
44	0.88 ± 0.11
45	> 10

Five-membered C ring

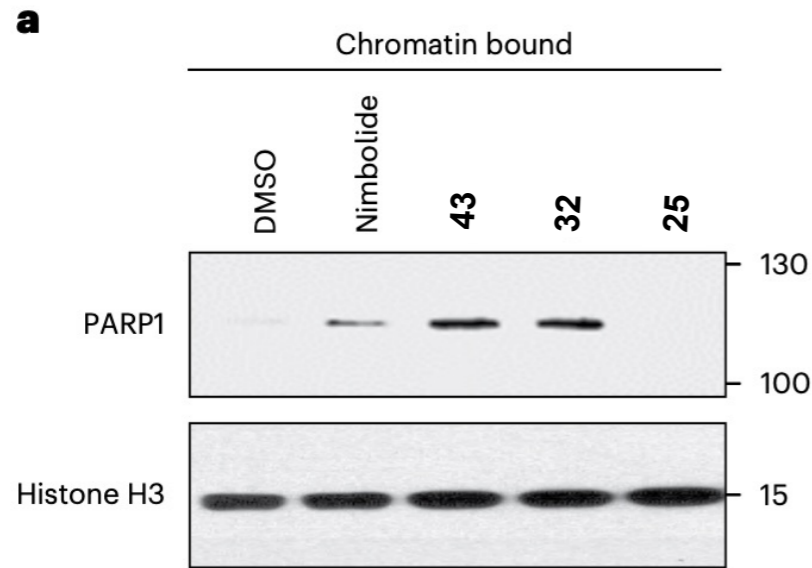
Compound	IC ₅₀ (μM)
27	1.45 ± 0.19
28	0.98 ± 0.13
29	0.21 ± 0.05
30	0.30 ± 0.05
31	0.27 ± 0.05
32	0.079 ± 0.01

Nimbolide analogues with a six-membered C ring



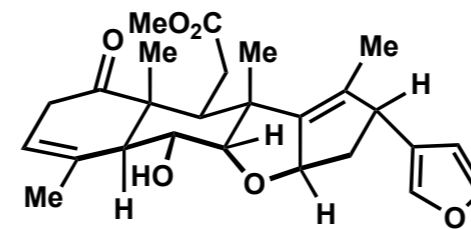
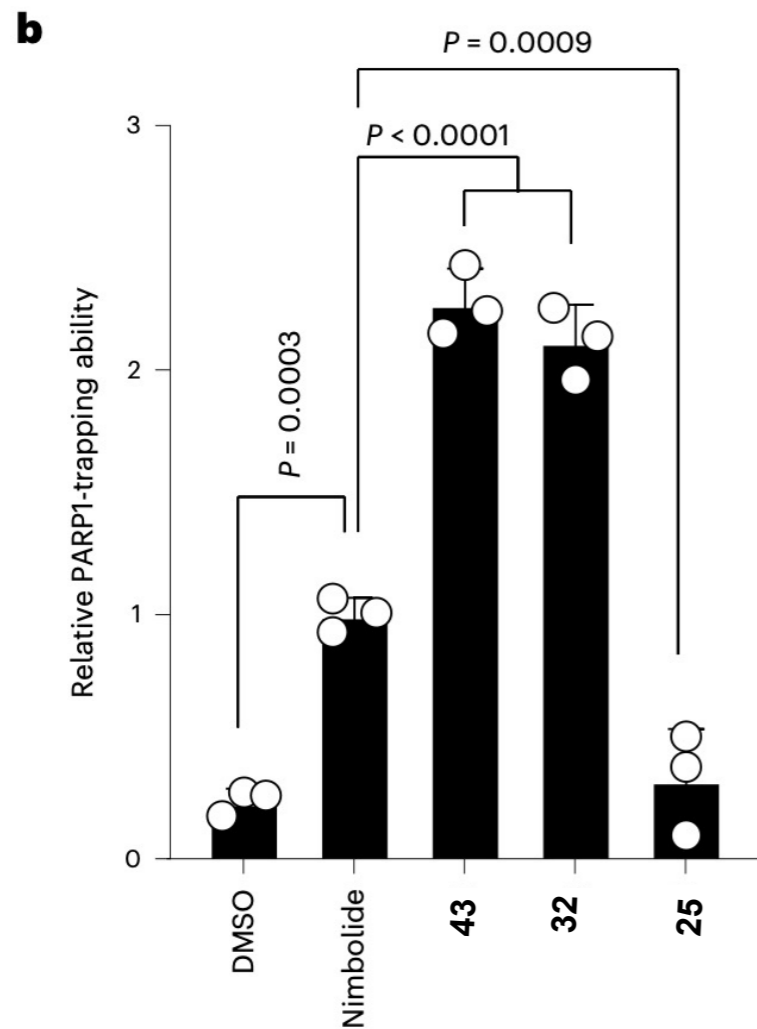
Six-membered C ring	
Compound	IC ₅₀ (μM)
21	0.49 ± 0.04
34	0.49 ± 0.07
36	0.17 ± 0.03
35	0.16 ± 0.04
37	0.11 ± 0.03
38	0.18 ± 0.04
33	0.80 ± 0.09
39	0.88 ± 0.11
41	0.16 ± 0.03
40	0.20 ± 0.05
42	0.17 ± 0.04
43	0.05 ± 0.04

PARP1 trapping studies and selected analogues

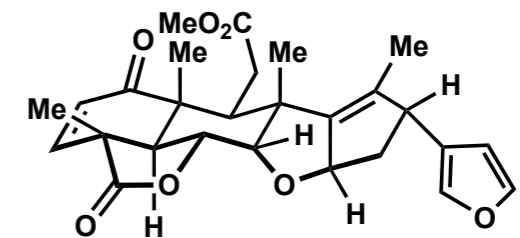


Is the PARP1 still efficiently trapped at the DNA-damage site by the nimbolide analogues?

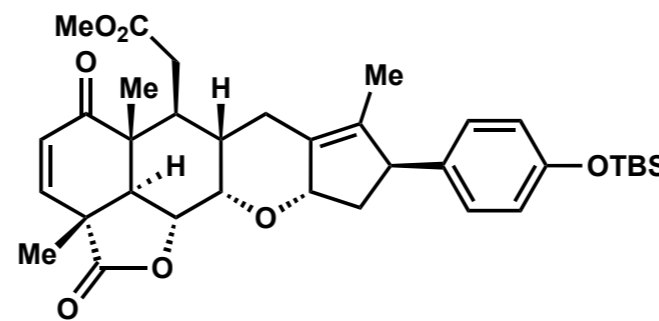
Yes!



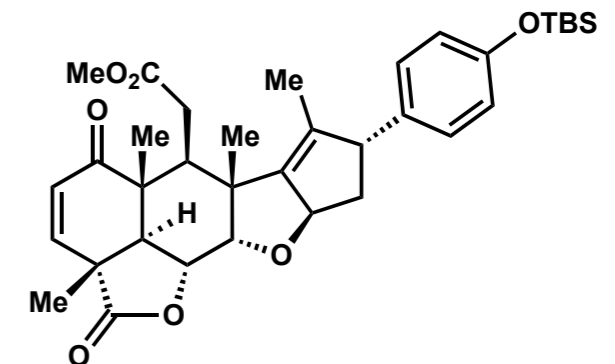
25
 $IC_{50} (> 10 \mu M)$



nimbolide (1)
 $IC_{50} (0.34 \pm 0.05 \mu M)$

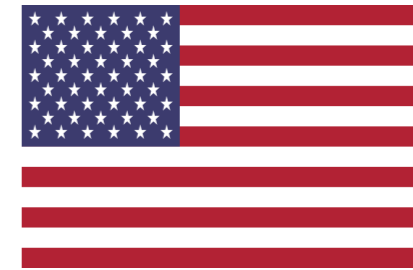


43
 $IC_{50} (0.05 \pm 0.04 \mu M)$



32
 $IC_{50} (0.079 \pm 0.01 \mu M)$

Thank you for the attention



Grazie dell'attenzione



Mulțumesc pentru atenția



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