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Total Synthesis of Isomalabaricane Triterpenoids

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Rhabdastrellic acid A and stelletin E

Presented by:

Sean Walsh

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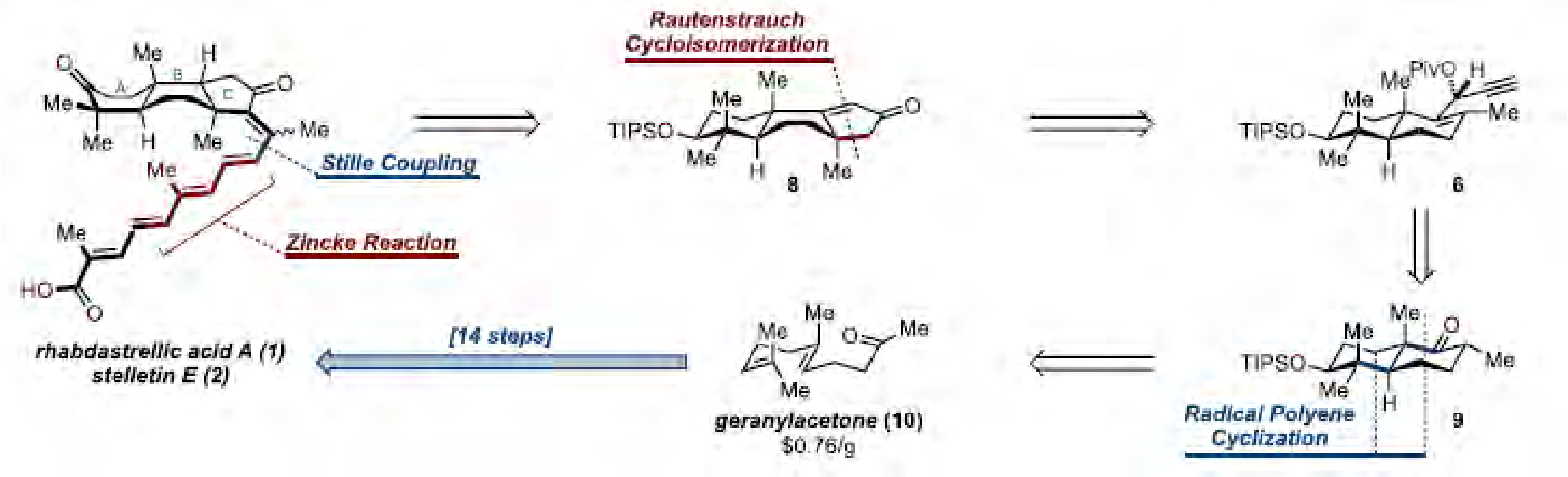
Background:

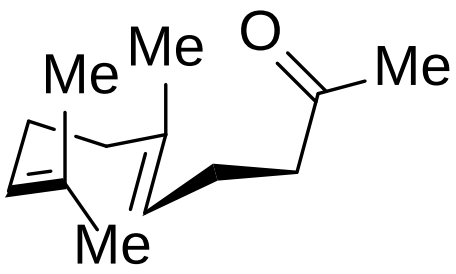
- Rrhabdastrellic acid A and stelletin E are “among flagship members of the isomalabaricane triterpenoids”
  - A rare family of marine natural products that are attractive for their remarkably specific antitumor properties.
  - They selectively induce cell death (apoptosis) in nanomolar concentrations against NCI-60 Human Tumor Cell Lines, leukemia, glioblastoma, and on-small cell lung cancer cell lines
  - They exhibit minimal toxicity within healthy tissues
  - Nanomolar mean GI50 concentrations against the NCI-60 Human Tumor Cell Lines panel
- Stelletin E exhibits a 117-fold increase in potency against HCT-116 human colon cancer cell lines compared to the wildtype human colon cancer cells.
- No mechanism of action has been proposed, no specific molecular targets have been confirmed, no pharmacophore has been elucidated for this molecular framework, and detailed studies have been precluded by the scarcity of these compounds.
- First isolation in 1981
  - J. Org. Chem. **1981**, *46* (10), 1998-2001
- This paper is the first total synthesis of the two compounds.

Retrosynthesis Plan



Step 1

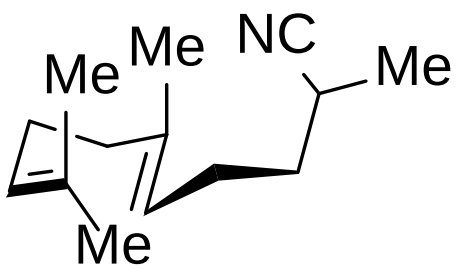
Modified van Leusen reductive cyanation



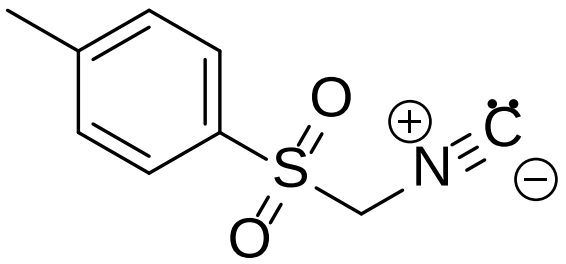
geranylacetone
(*E*)-6,10-dimethylundeca-5,9-dien-2-one
$0.20 / gram
269.7 mmol scale

TosMIC (1.3 equiv)
t-BuOK (2.4 equiv)

EtOH (2.0 equiv)
Et_2O / THF, 0o C



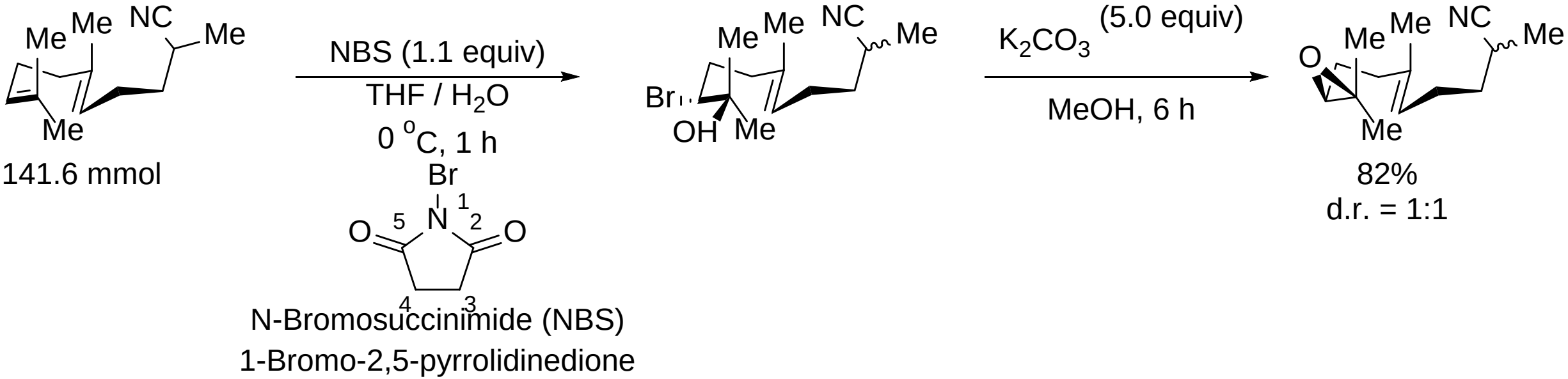
94%



Tosylmethyl isocyanide
(TosMIC)

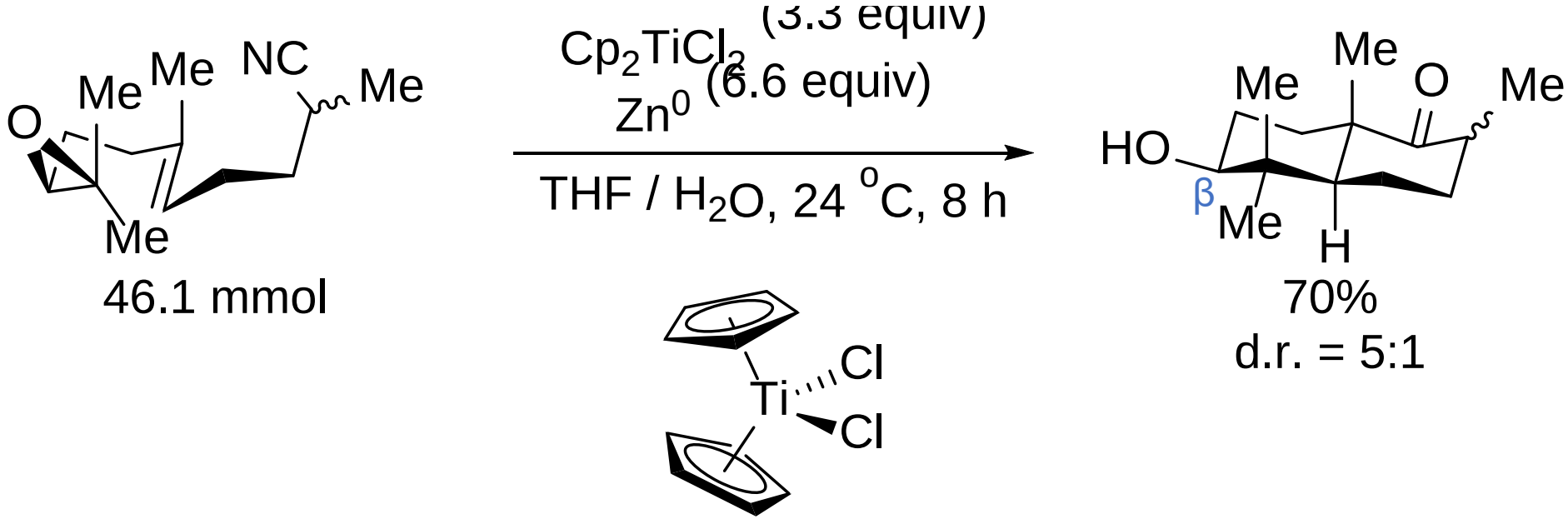
Step 2

Regioselective epoxidation



Step 3

Ti(III)-mediated reductive radical polyene cyclization

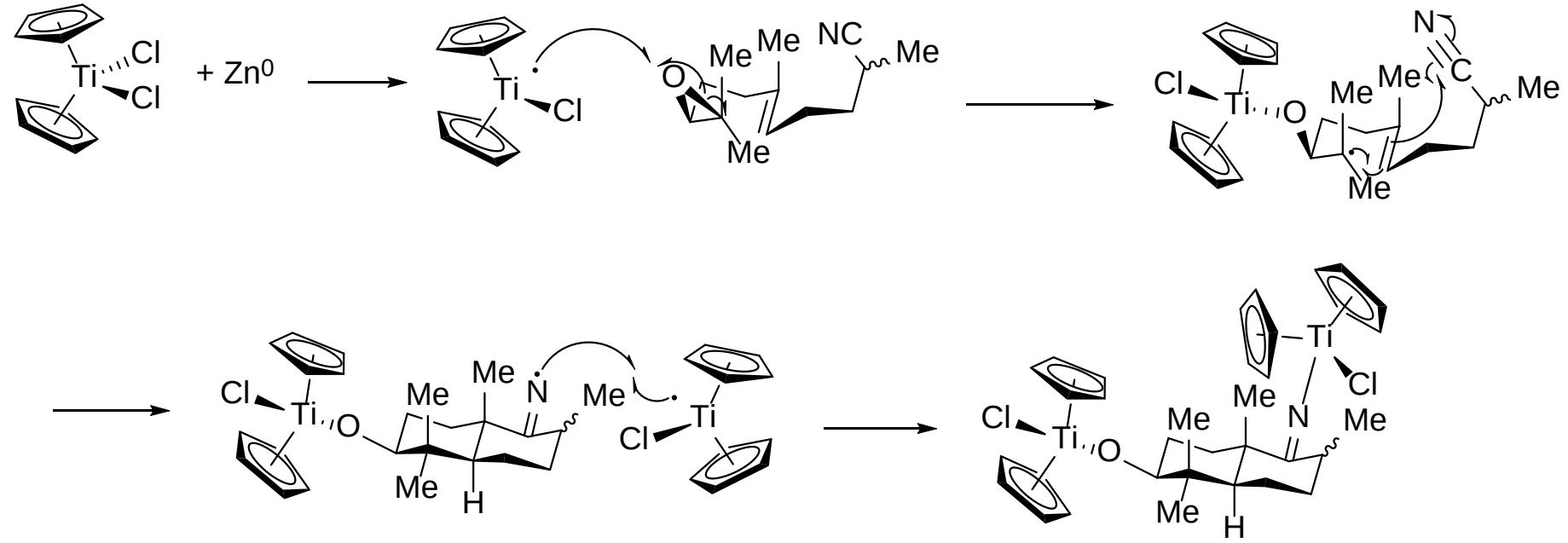


Titanocene dichloride

(Cp_2TiCl_2)

Major isomer (C3-β) was further purified by recrystallization from cold MeOH

How does this happen?

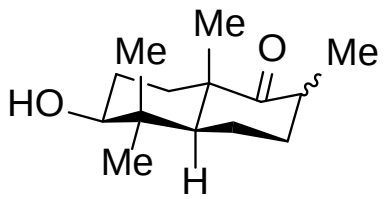


46.1 mmol

Cp_2TiCl_2 (3.3 equiv)

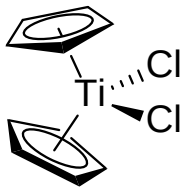
Zn^0 (6.6 equiv)

THF / H_2O, 24 °C, 8 h



70%

d.r. = 5:1

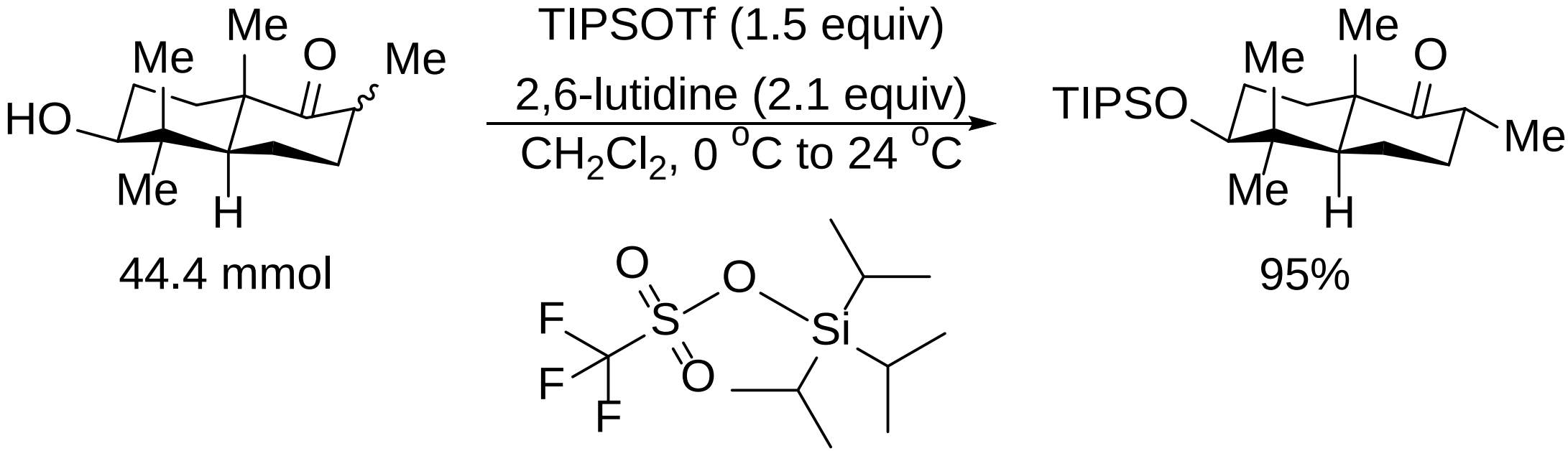


Titanocene dichloride

(Cp_2TiCl_2)

Step 4

Alcohol protection with TIPS and epimerization



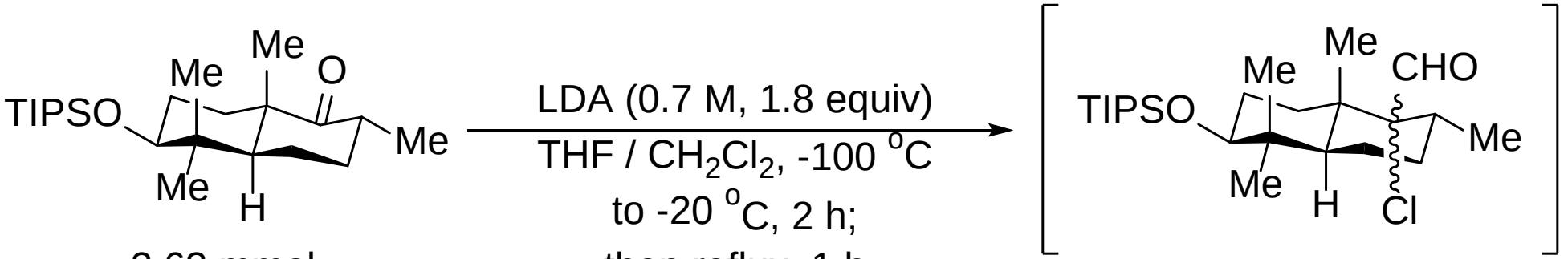
44.4 mmol

95%

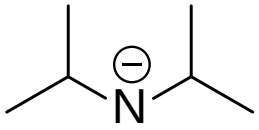
triisopropylsilyl trifluoromethanesulfonate
(TIPSOTf)

Step 5

Carbonyl Reduction with CH_2Cl_2 as a carbon source



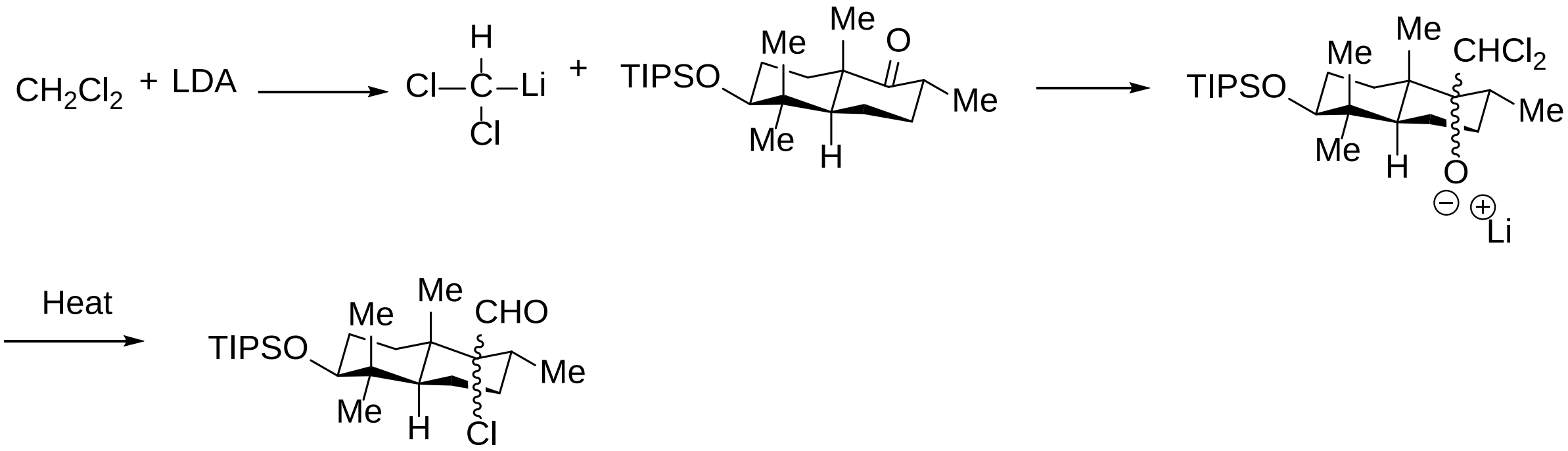
2.63 mmol



Lithium DiisopropylAmide
(LDA)

Taguchi, H.; Tanaka, S.; Yamamoto, H.; Nozaki, H. A new synthesis of α,β-unsaturated aldehydes including (e)2-methyl-2-alkenal. Tetrahedron Lett. **1973**, *14*, 2465−2468

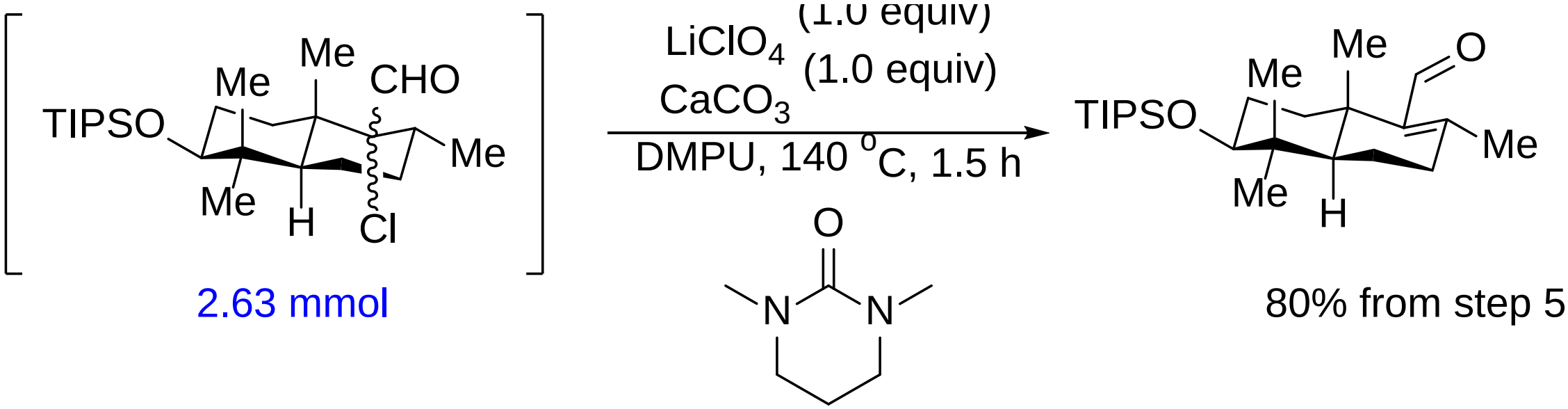
How does this happen?



Taguchi, H.; Tanaka, S.; Yamamoto, H.; Nozaki, H. A new synthesis of α,β-unsaturated aldehydes including (e)2-methyl-2-alkenal. Tetrahedron Lett. **1973**, *14*, 2465−2468

Step 6

Formation of an α,β-unsaturated aldehyde



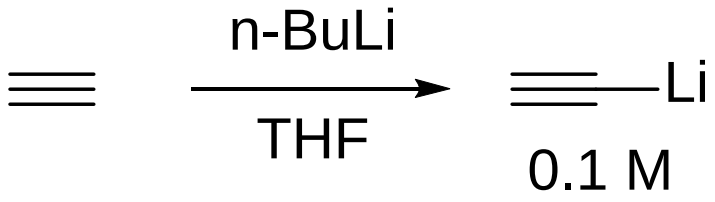
2.63 mmol

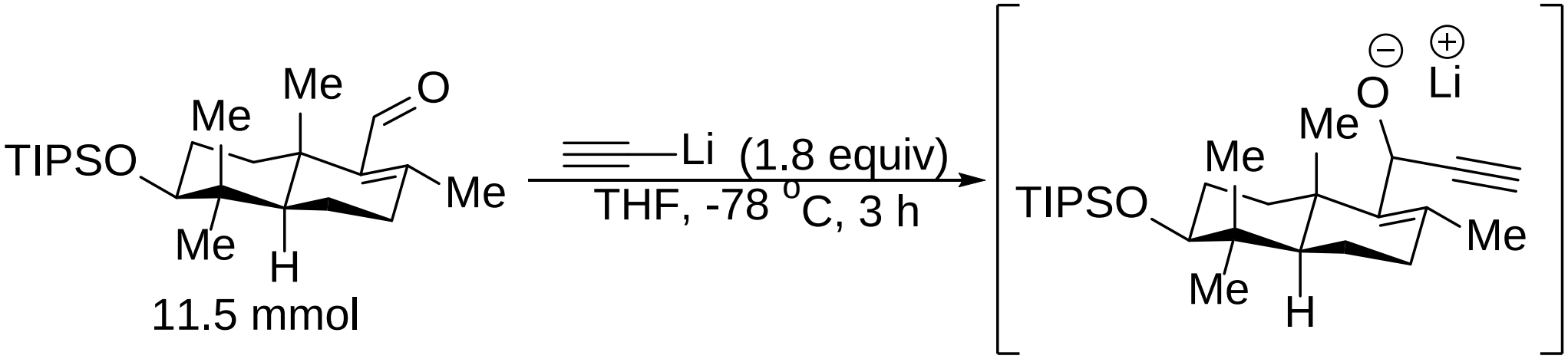
80% from step 5

N,N'-Dimethylpropylene urea
(DMPU)

Step 7

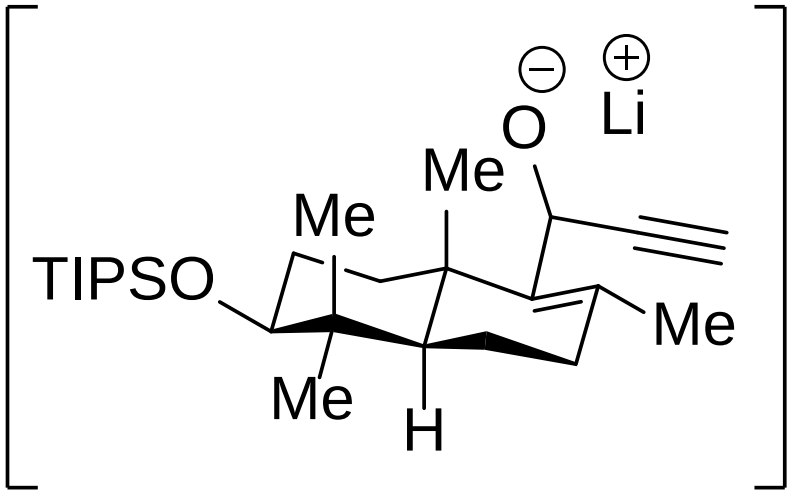
Alkyne addition





Step 8

Alcohol protection with Pivalate

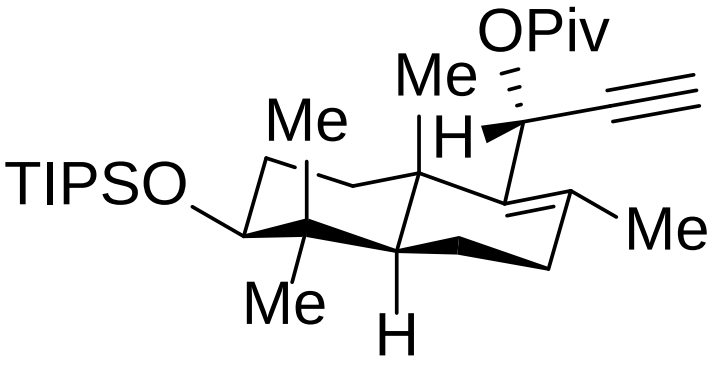


11.5 mmol

PivCl (2.0 equiv)

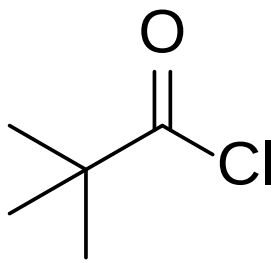
-78 °C to 24 °C

4 h



82% from step 7

d.r. > 20:1

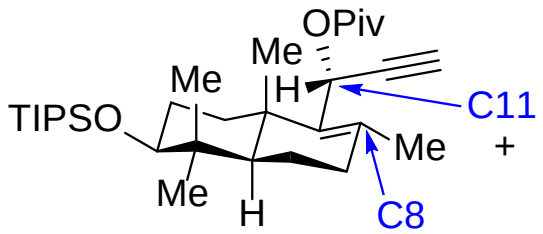


Pivaloyl chloride

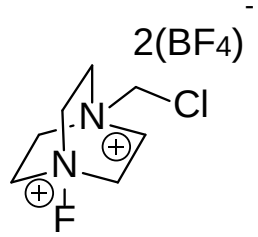
(PivCl)

Steps 9-10

$Au(PPH_3)Cl + AgOTf$ (2.5 mol %) —(No light), CH_2Cl_2, rt, 10 mins→ $Au(PPH_3)OTf + AgCl$



1.83 mmol

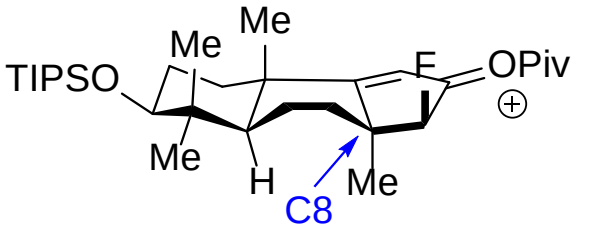


Selectfluor®

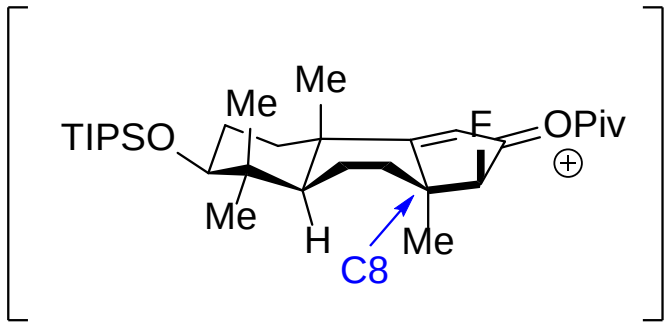
$Au(PPH_3)OTf$ Solution (CH_2Cl_2)

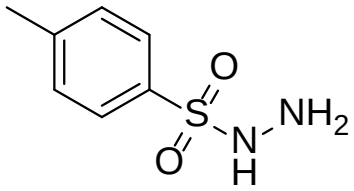
$MeCN / CH_2Cl_2$ (2.5 : 1), 24 °C, 1 - 2 h

Intermediate

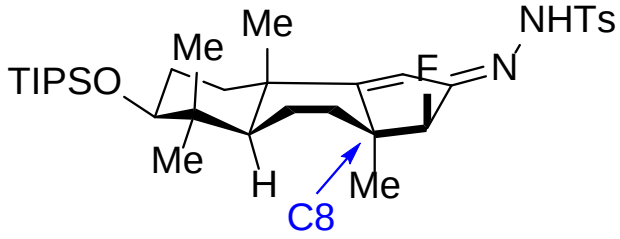


Intermediate





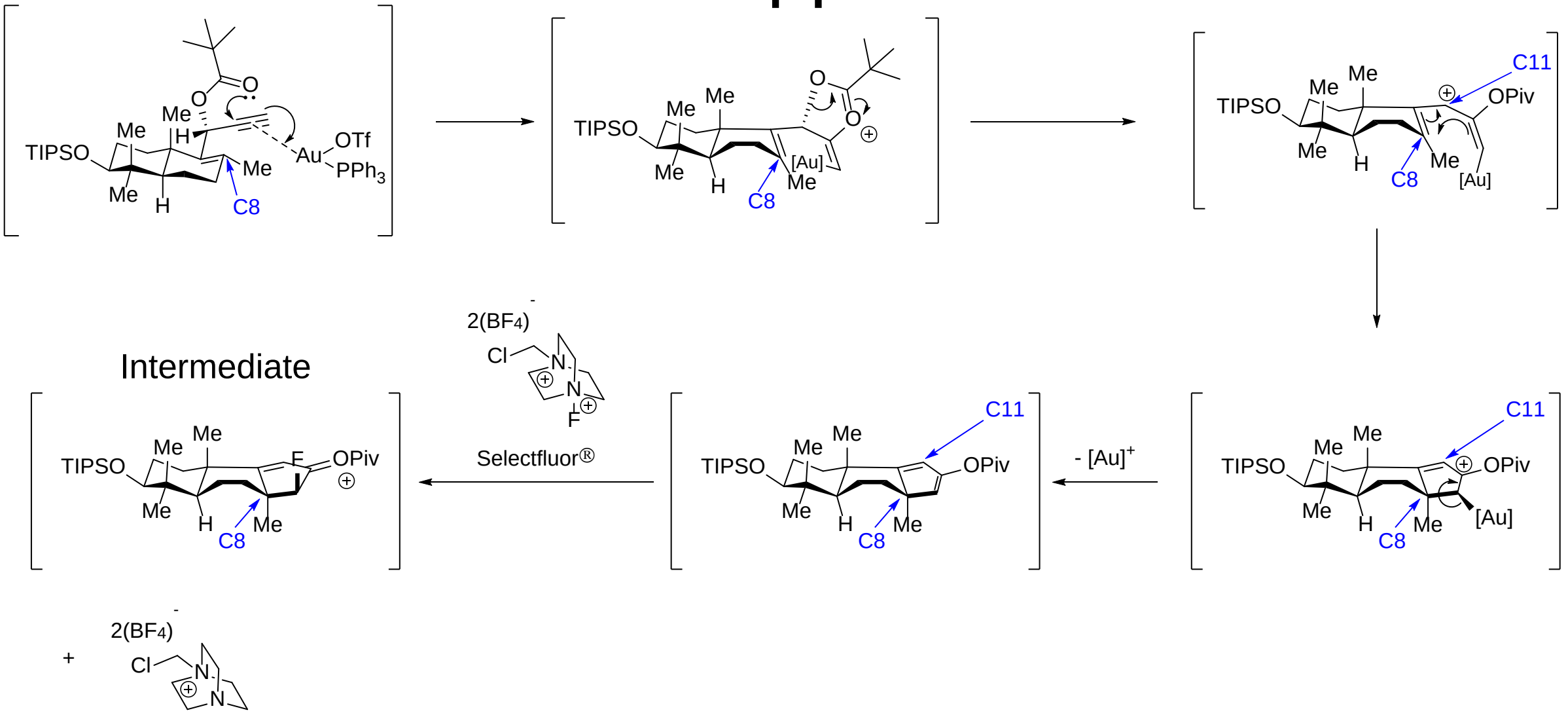
40 °C, 10 h



81%
d.r. > 20:1

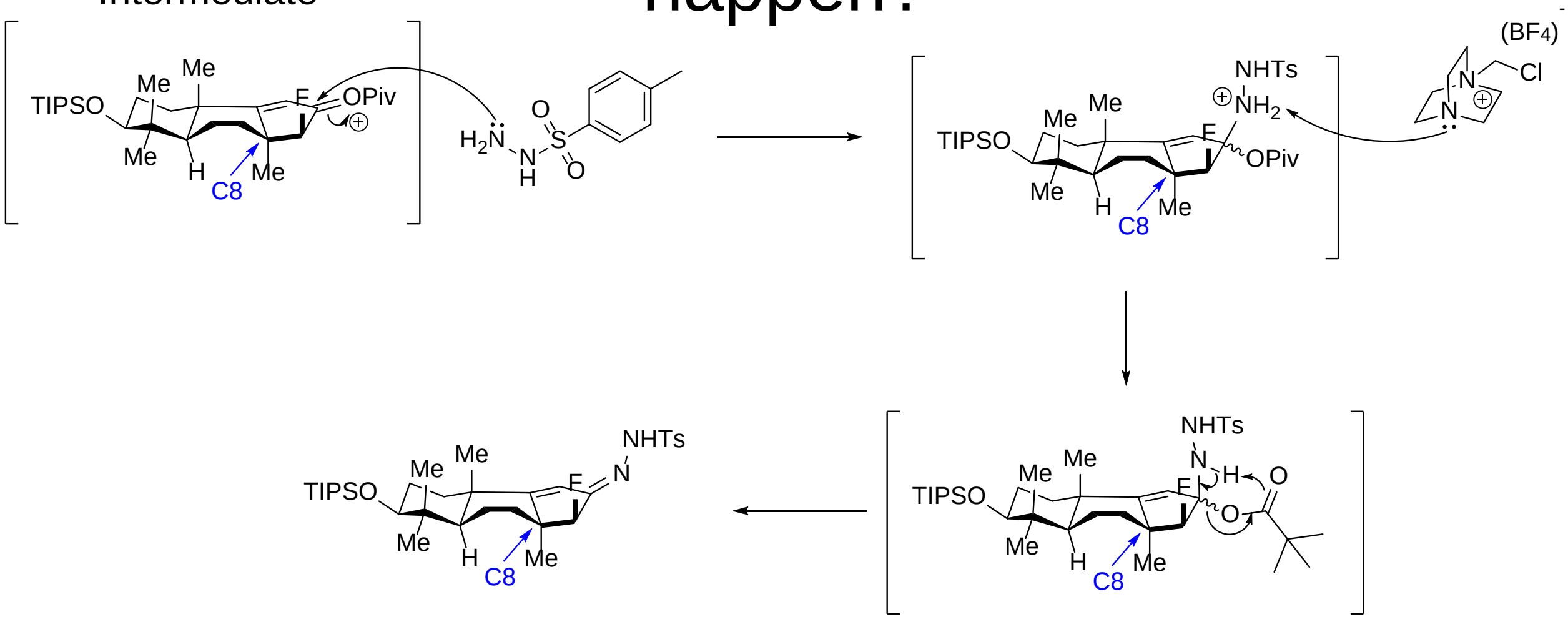
How does step 9 happen?

4 π electron electrocyclic ring closure

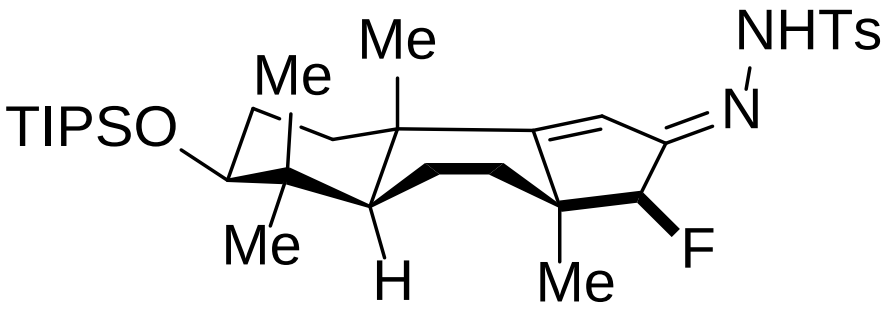


How does step 10 happen?

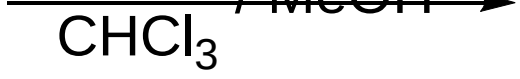
Intermediate

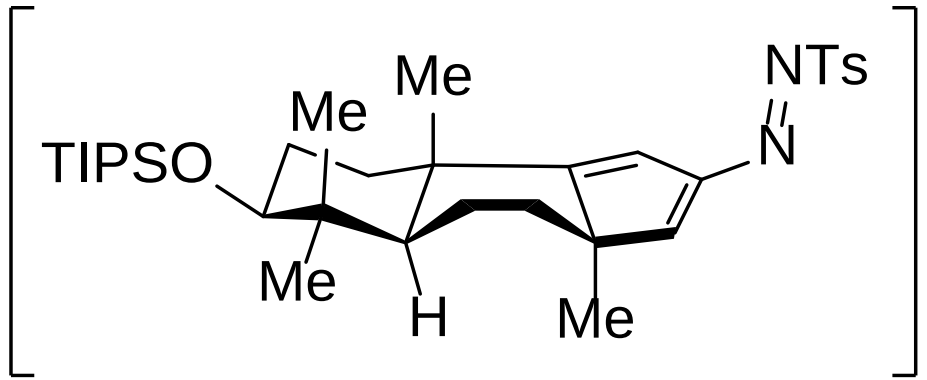


Step 11

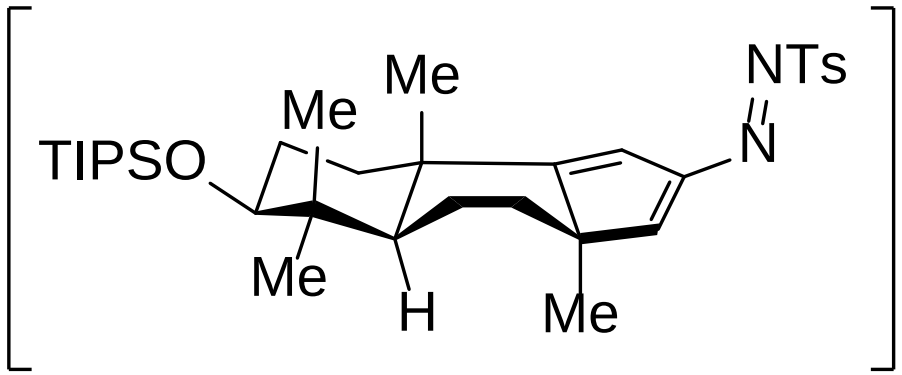


1.56 mmol

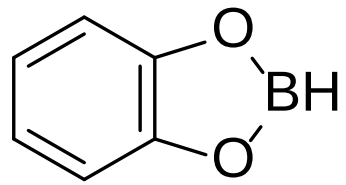




Kabalka modification of the Caglioti reaction: Steps 12 and 13



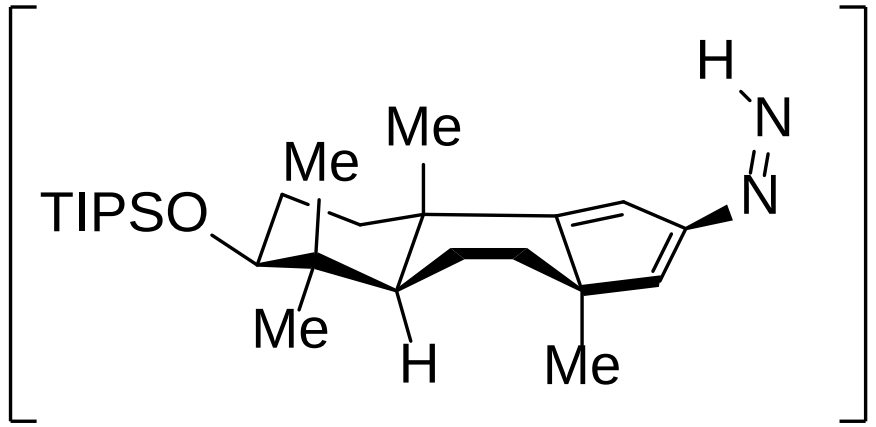
1.56 mmol



(1.5 equiv)

$CHCl_3$ / MeOH 0 °C,

5 mins; then rt, 3 h

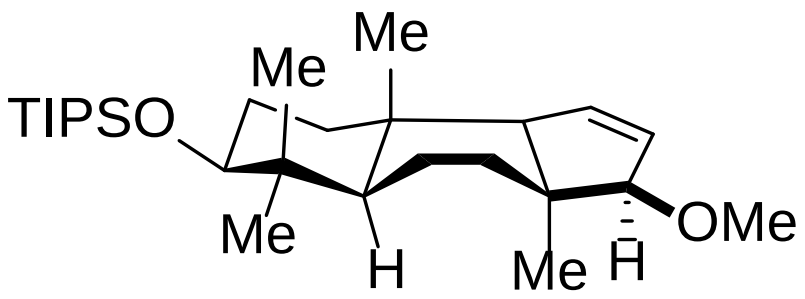


CsOAc

(2.5 equiv)

$CHCl_3$

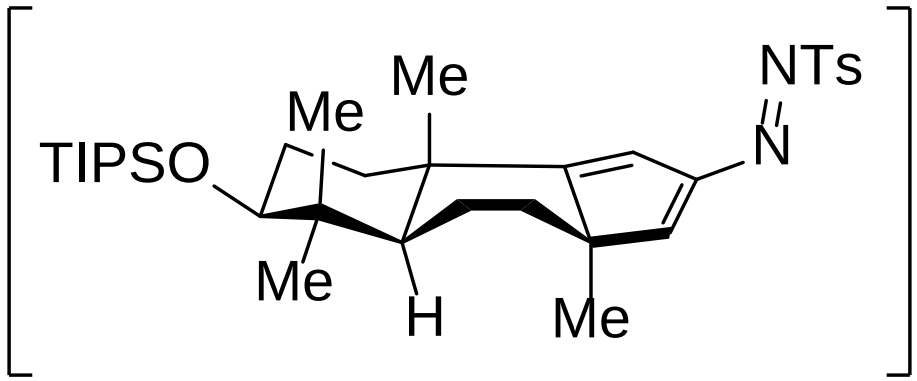
65 °C, 4 h



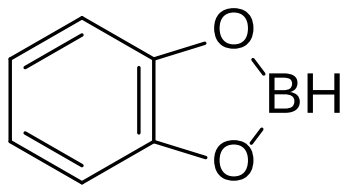
58% from step 11

d.r. > 20:1

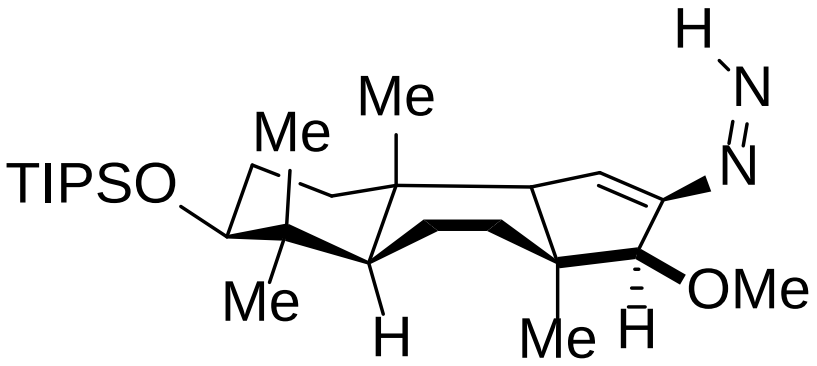
Kabalka modification of the Caglioti reaction: Steps 12 and 13



1.56 mmol



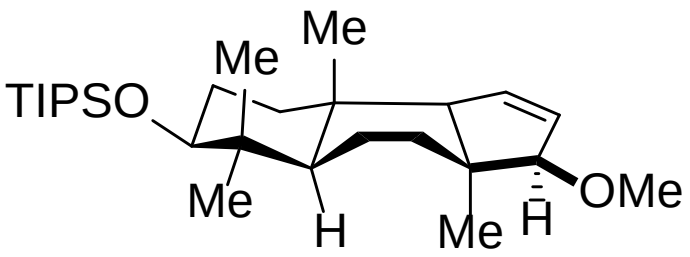
(1.5 equiv)
CsOAc
(2.5 equiv)
/ MeOH rt 3 h;
$CHCl_3$
then 65 ^{o}C, 4h



58% from step 11
d.r. > 20:1

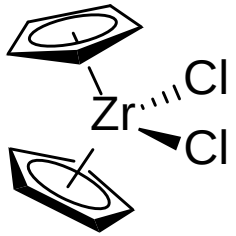
Step 14

Reductive zirconation



0.18 mmol

+



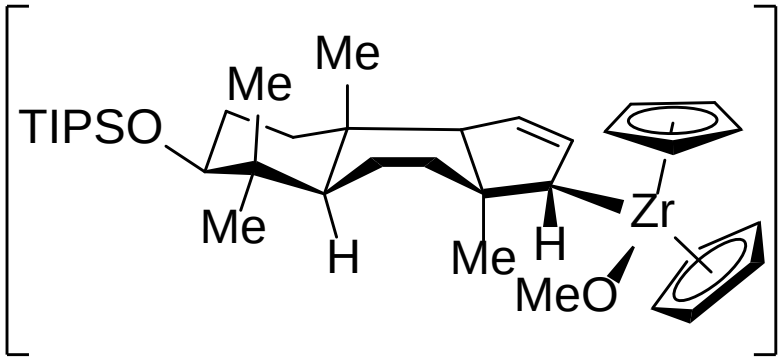
Zirconocene dichloride

(1.3 equiv)

n-BuLi (2.4 equiv)

THF, 0 °C, 10 min;

then rt, 36 h



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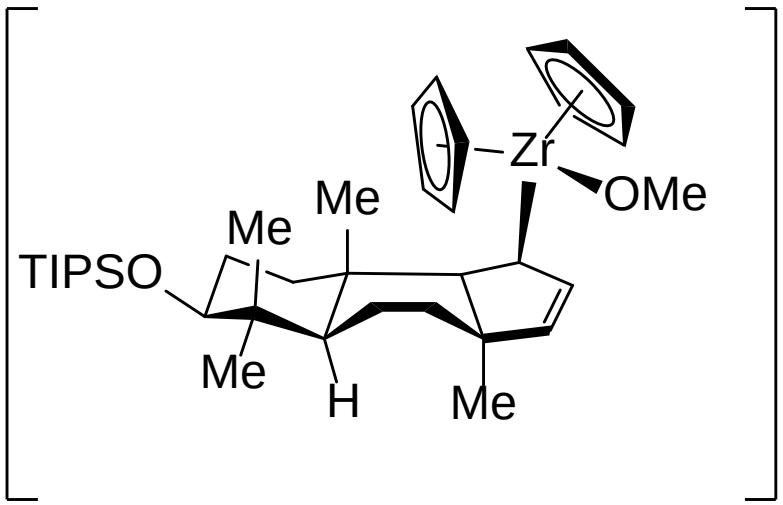
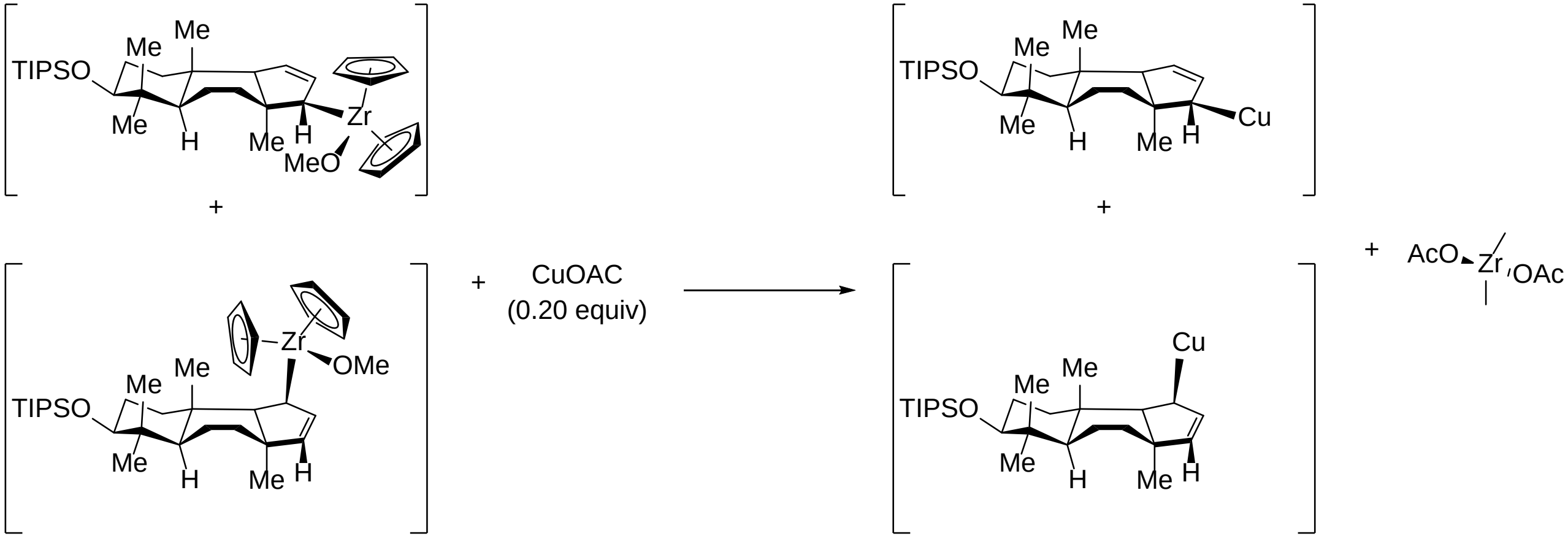
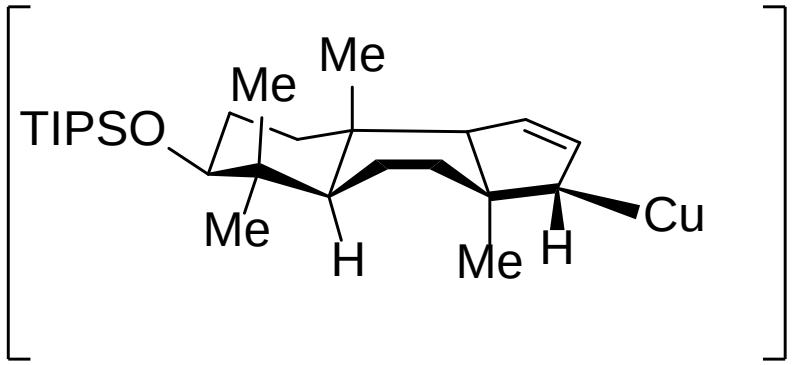


Step 15

Copper-catalyzed cross-coupling



Step 16



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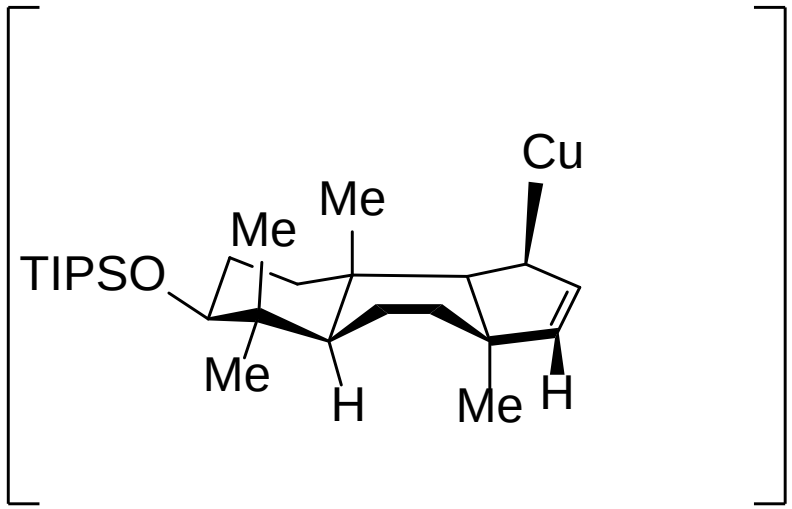
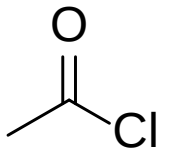
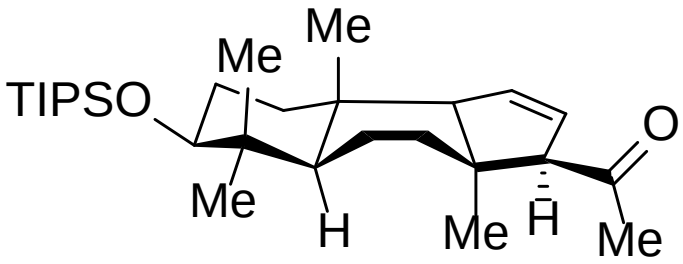




(4.0 equiv)

THF, 55 °C,

3 h



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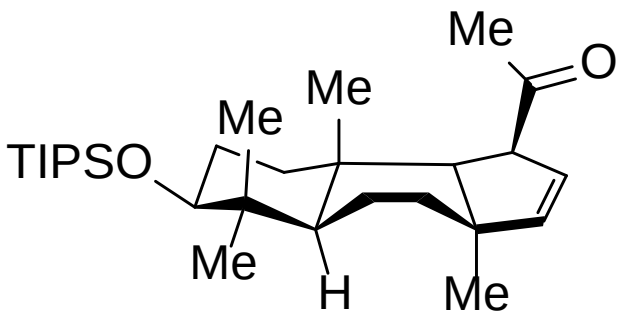
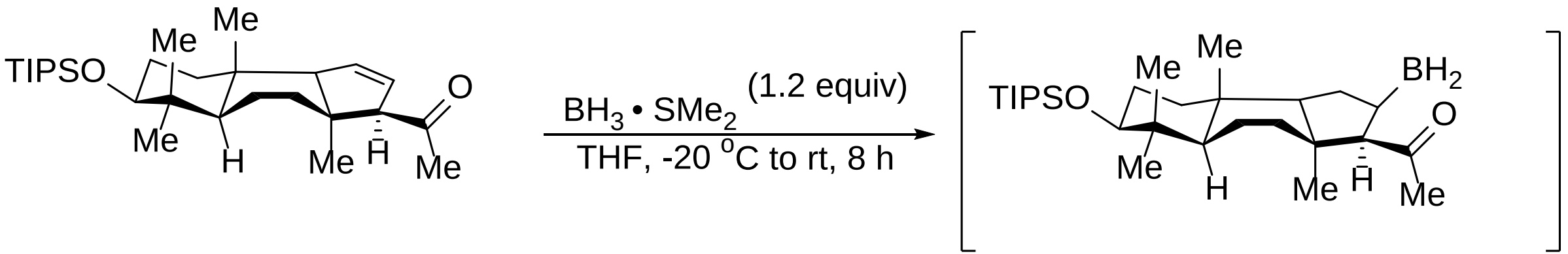


80% from step 14

4:1

Step 17

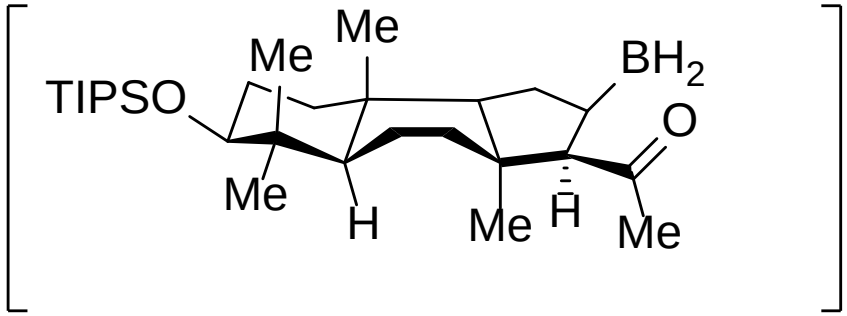
Relay hydroboration from the ketone



0.081 mmol

Step 18

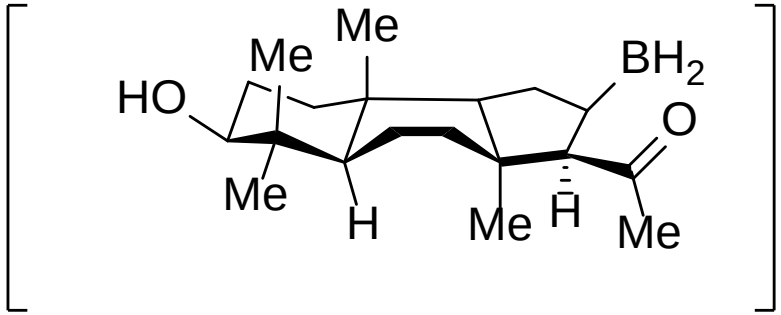
Deprotection



0.081 mmol

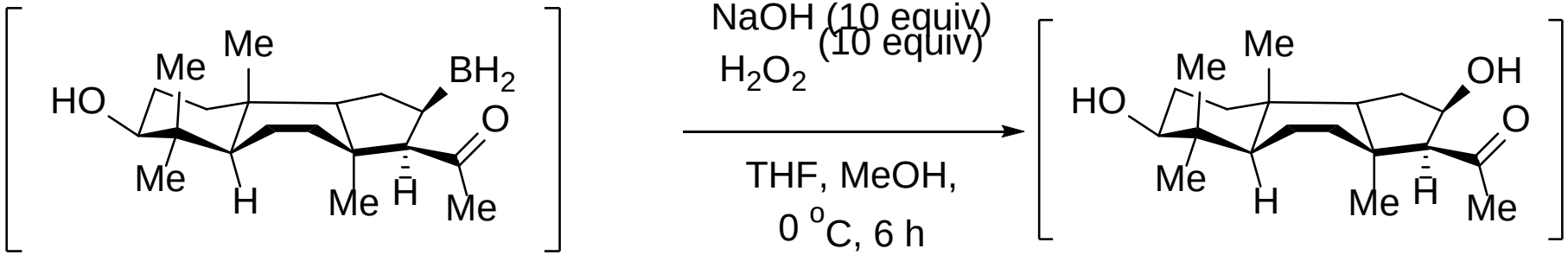
TfOH (2.0 equiv)

THF, 0 °C to rt, 2 h

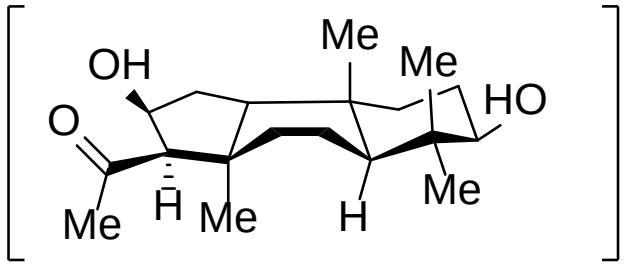


Step 19

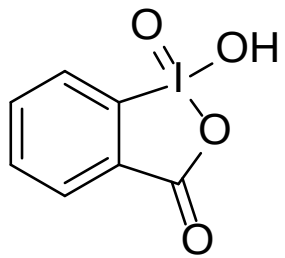
Oxidation



0.081 mmol



0.081 mmol

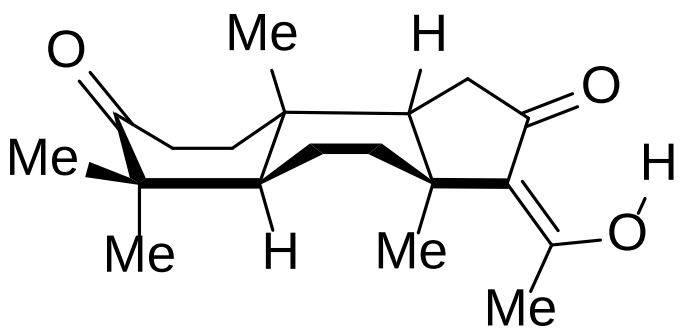


IBX

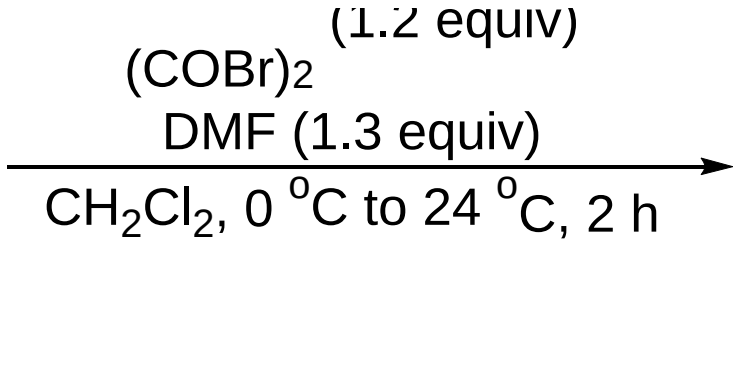
80% from step 17

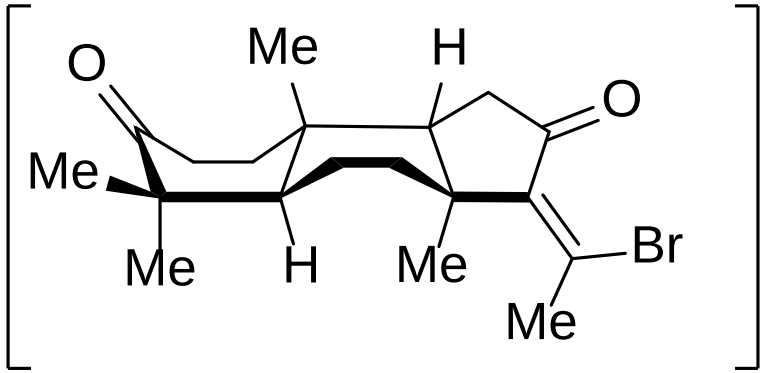
Step 20

Bromination with Vilsmeier reagent

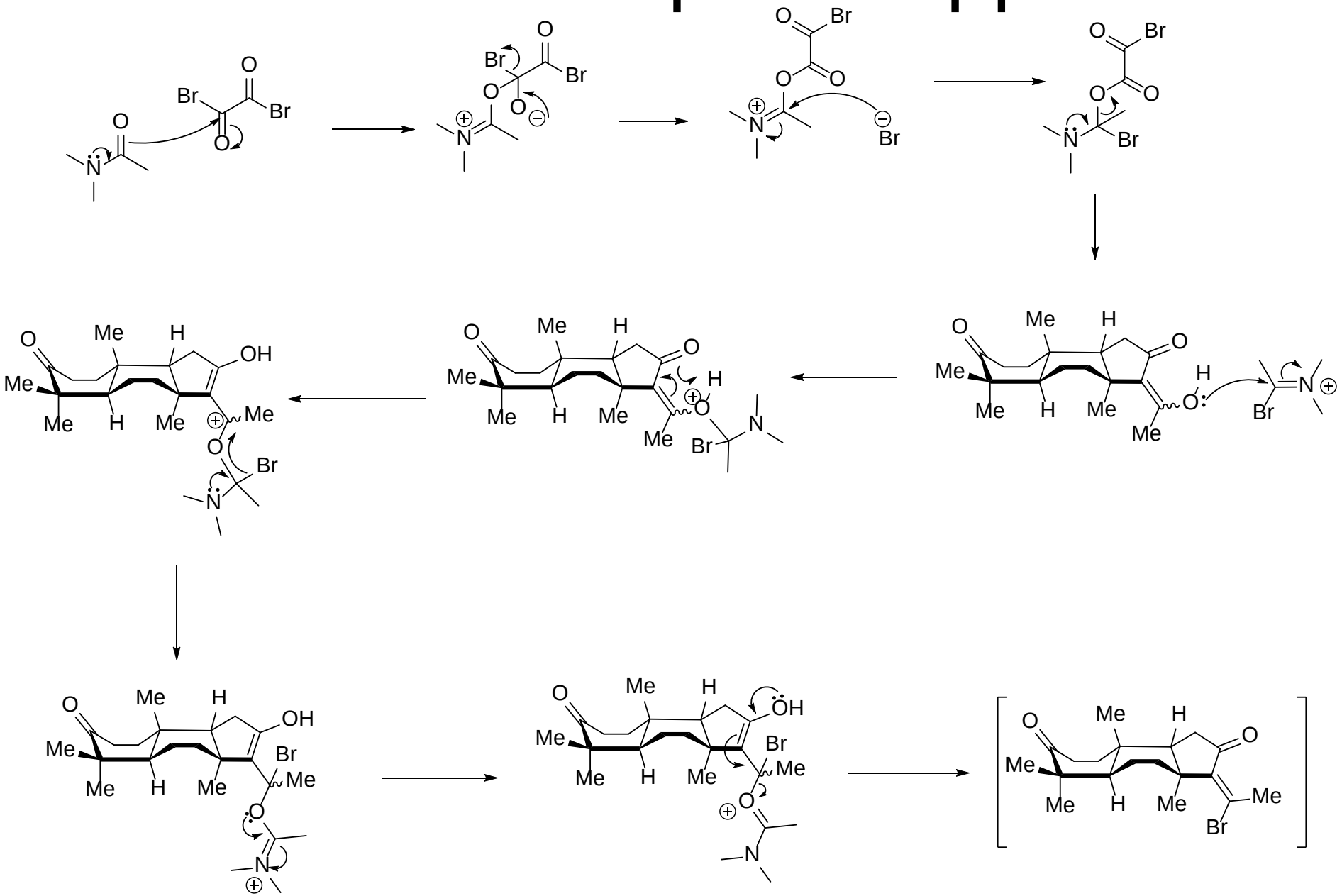


0.0191 mmol





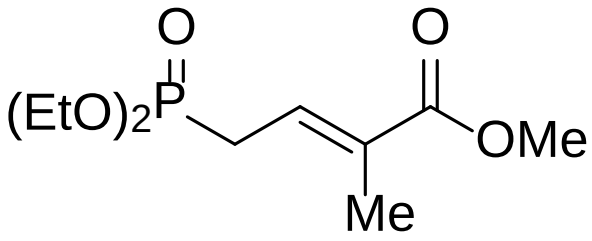
How does step 20 happen?

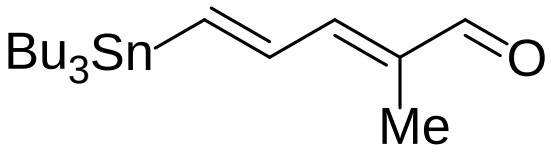


Mewshaw, R. E. Vilsmeier reagents: Preparation of β-halo-α,β-unsaturated ketones. Tetrahedron Lett. 1989, 30, 3753−3756.

Step 21

Horner-Wadsworth-Emmons olefination





(1.5 equiv)

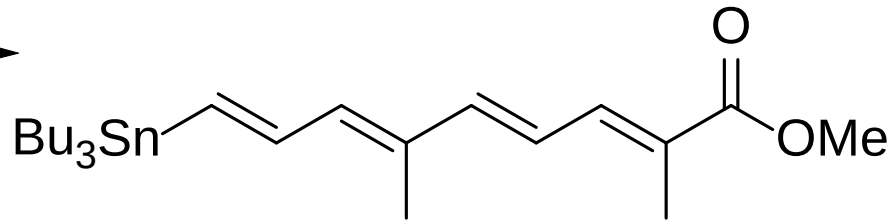
LHMDS (1.65 equiv)

HMPA (3.0 equiv)

THF, -78 °C to

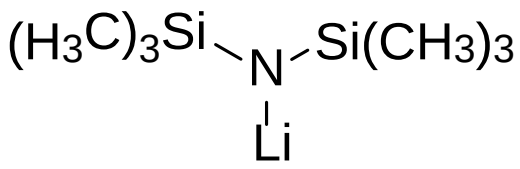
24 °C, 1.5 h

X

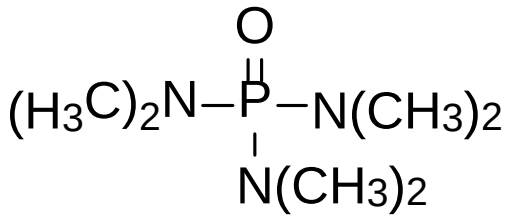


69%

LHMDS

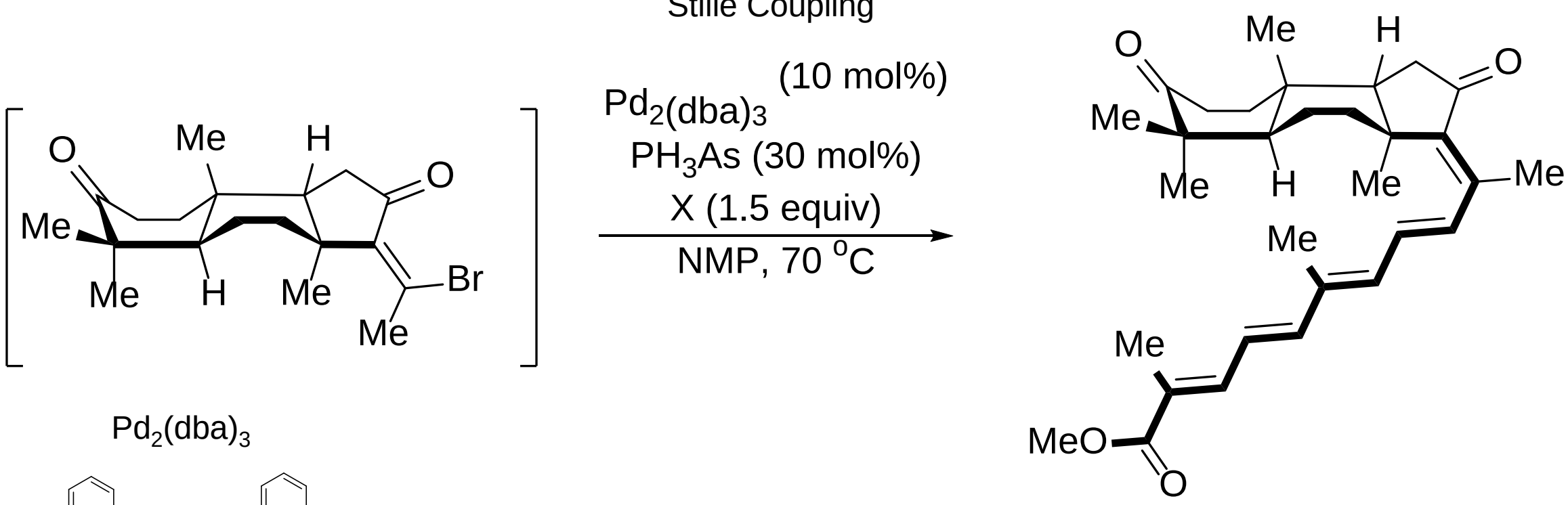


HMPA

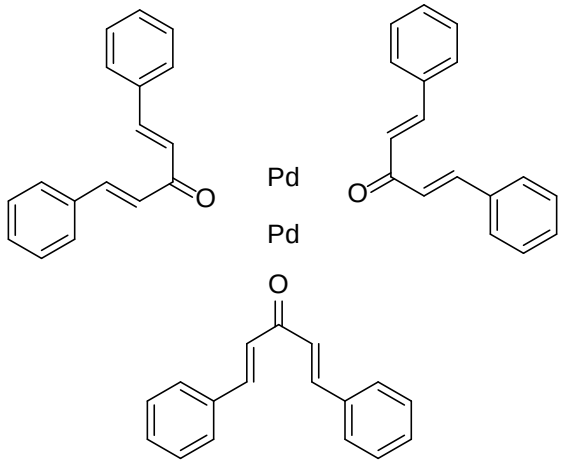


Step 22

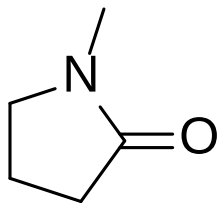
Stille Coupling



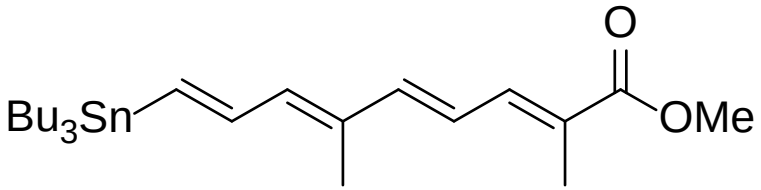
$Pd_2(dba)_3$



NMP

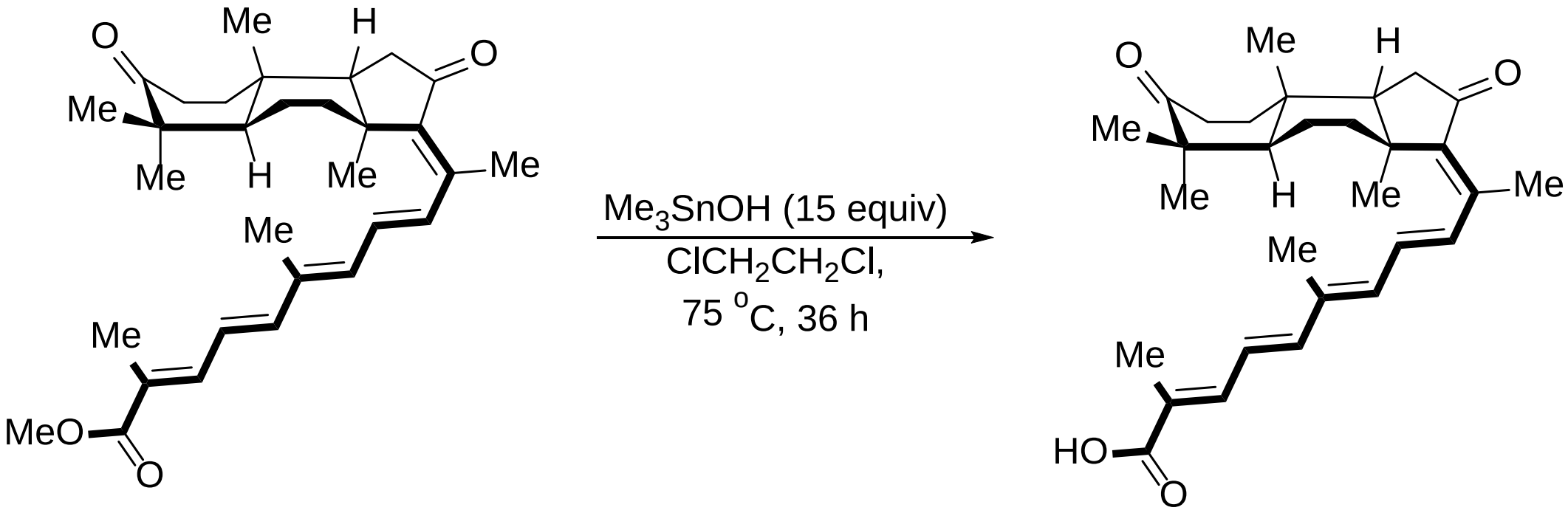


X



Step 23

Methyl ester reduction

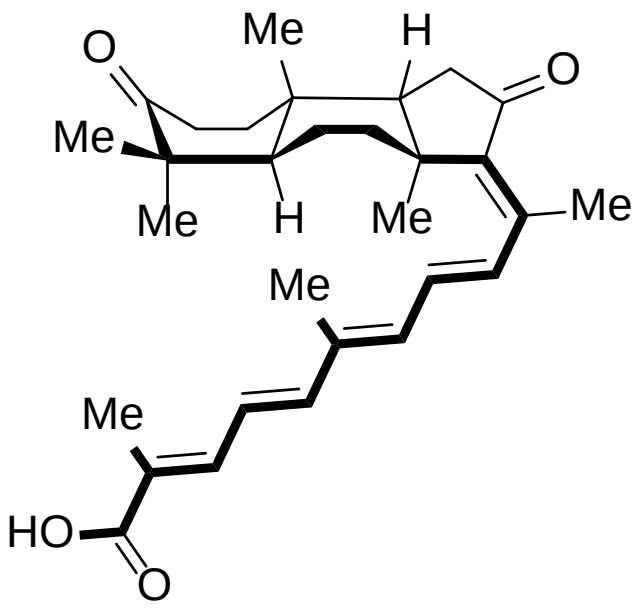


rhabdastrellic acid A

98%

Step 24

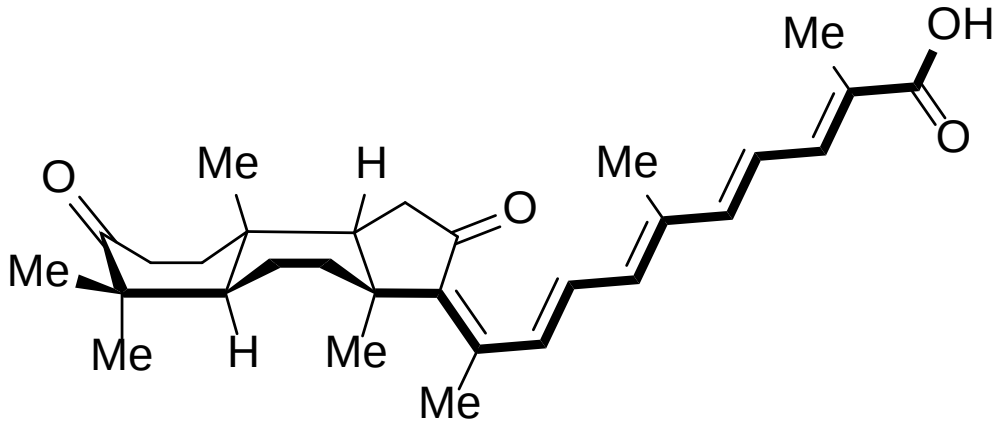
Isomerization



rhabdastrellic acid A

hv, 400 nm

MeCN, 24 ^{o}C, 3 min



stelletin E

34%

Thank you all for listening
Thank you Dr. Wulff for this project

Please ask questions ☺

All reaction information was taken from: J. Am. Chem. Soc. **2019**, *141*, 14131−14135