Total Synthesis of (-)-histrionicotoxin and (-)-histrionicotoxin 235A

Gilbert Stork and Kang Zhao

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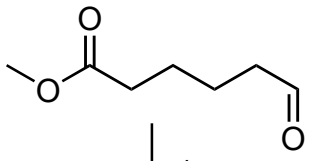
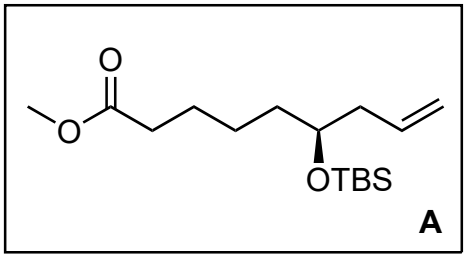
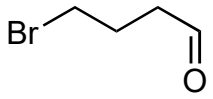


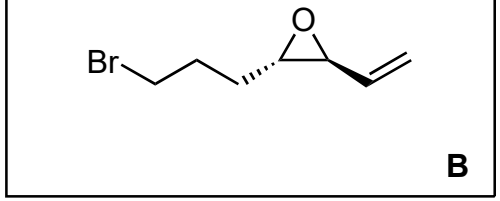
1



A

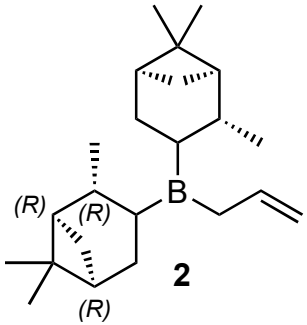


2-6



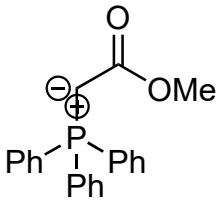
B

1) **2**, -78 °C, 2 h *then*
TBSCl, imidazole, DCM, DMAP



2

2) **1**, THF
3) DIBAL
4) (R, R)-Diethyltartrat, (+)-DET, $Ti(O^iPr)_4$, ^tBuOOH
5) $(COCl)_2$, DMSO, NEt_3
6) $Me^+PPh_3I^-$, NaHMDS, THF



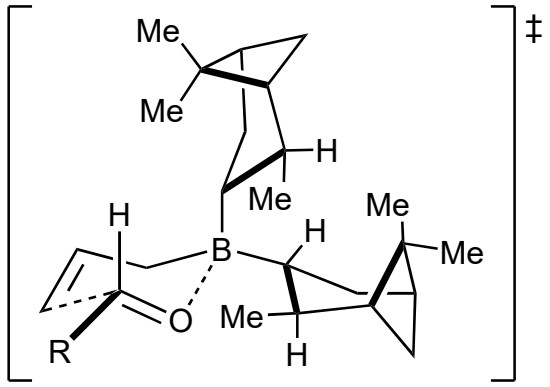
1

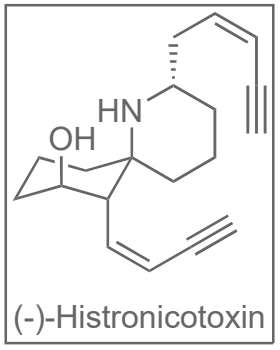
Using a boran reagent, how would you accomplish this transfromation?

What model would be used to predict the sterochemistry? →

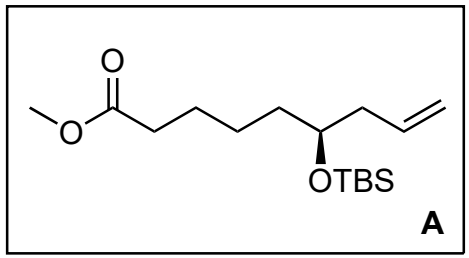
Name of step 1?

Brown Allylation
- How do you make the catalyst?
- BH_3 reduction of (+)-alpha-pinene





(-)-Histronicotoxin

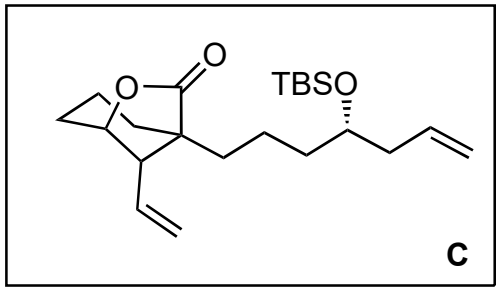


A

7

7) LDA, -78 °C, HMPA/THF (6:11 v/v), **B**
then LDA, -78 °C, 2 h

What is the mechanism of step 7?
Explain the selectivity.



C

8-9

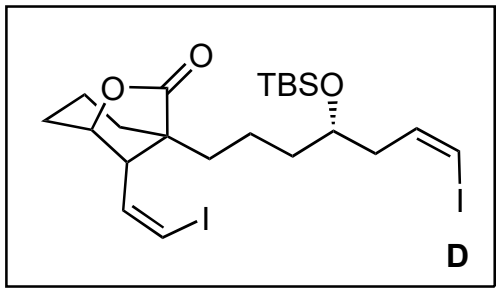
8) O_3, *then* PPh_3
9) $(Ph_3P^+CH_2I)I^-$, $NaN(TMS)_2$

What is the name of step 9 and its mechanism
Stork - Zhao

hint: our collegue runs this reaction in complete darkness.

bigger hint: Look at the authors of this paper

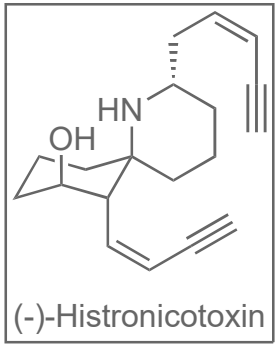
What is the name of $NaN(TMS)_2$
NaHMDS (old lit may use this name)

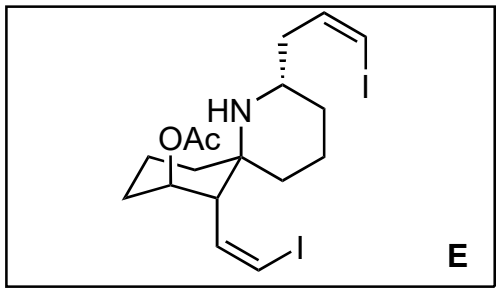


D

10-15

10) 5% HCl, THF
11) Ph_3P, CBr_4, ether
12) NH_4Cl, $AlMe_3$,PhH, 40 °C
13) AcO_2, Py, DMAP
14) $(CF_3CO_2)_2IPh$, MeCN, H_2O
15) Et_3N, DCE, 70 °C

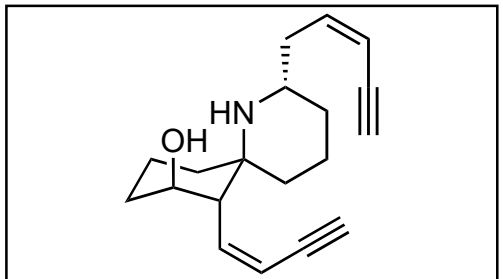




E

16) $Pd(PPh_3)_4$, CuI, PhH, TMS-acetylene
17) $Bu_4N^+F^-$
18) K_2CO_3, MeOH

16-18

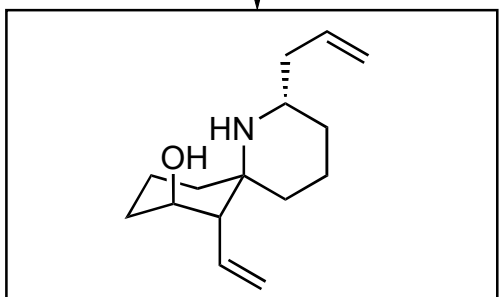


(-)-Histronicotoxin

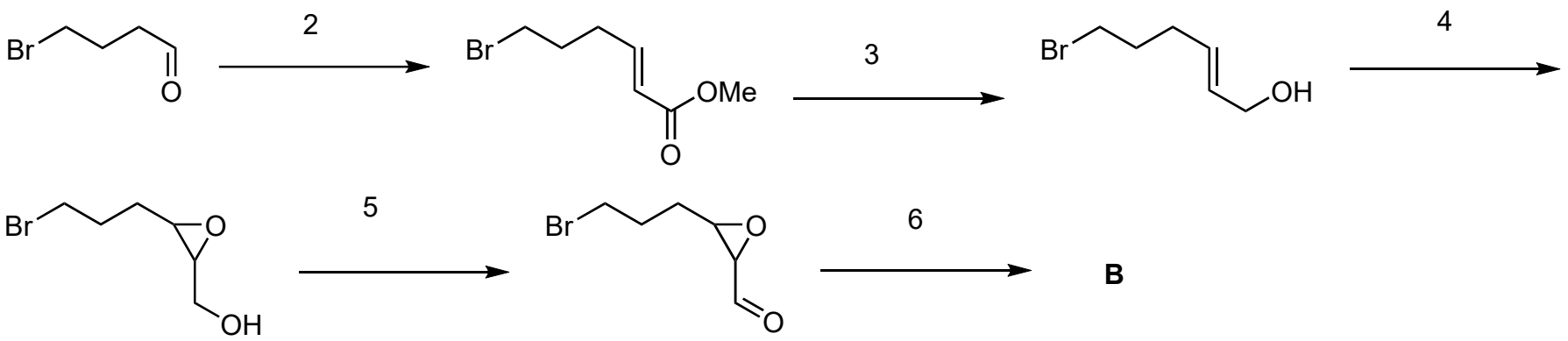
C

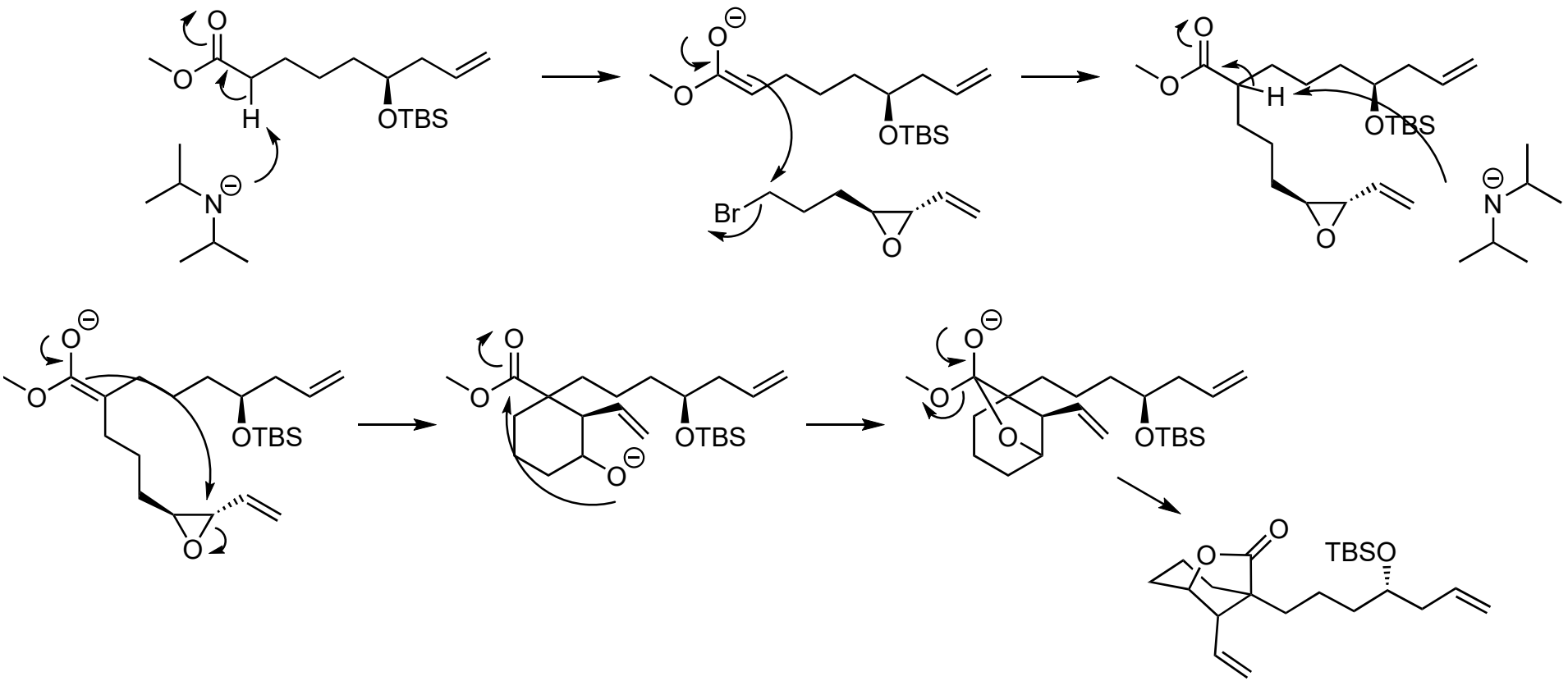
19-25

19) 5% HCl, THF
20) Ph_3P, CBr_4, ether
21) NH_4Cl, $AlMe_3$,PhH, 40 °C
22) AcO_2, Py, DMAP
23) $(CF_3CO_2)_2IPh$, MeCN, H_2O
24) Et_3N, DCE, 70 °C
25) MeOH, Na_2CO_3 (aq)



(-)-Histronicotoxin 235A


Br
O
2
Br
OMe
O
3
Br
OH
4
Br
O
OH
5
Br
O
O
6
B


O
O
H
OTBS
N
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OTBS
Br
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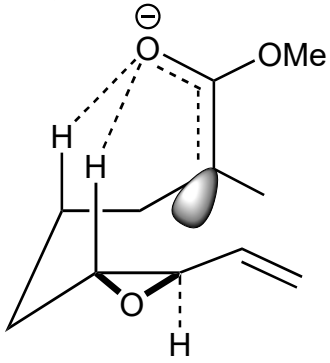
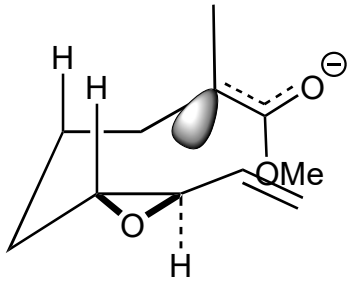
TBSO

Selectivity



I

disfavored



II

favored

Sterically strained
- Carbanion must remain perpendicular to carbonyl to open epoxide
- Avoid 1,3-diaxial interactions with TS **II**
- Authors argue this resembles that of a ^{t}Bu group.