Asymmetric synthesis of batrachotoxin: Enantiomeric toxins show functional divergence against Na_V

Logan, M. M., Toma, T., Thomas-Tran, R., Du Bois, J.

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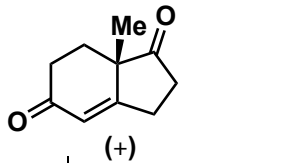
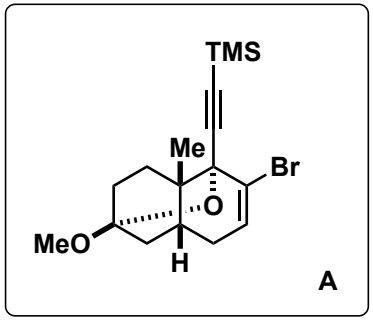
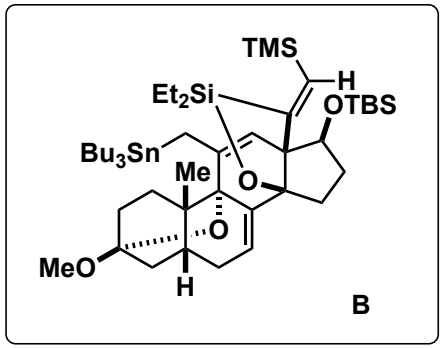


1–5

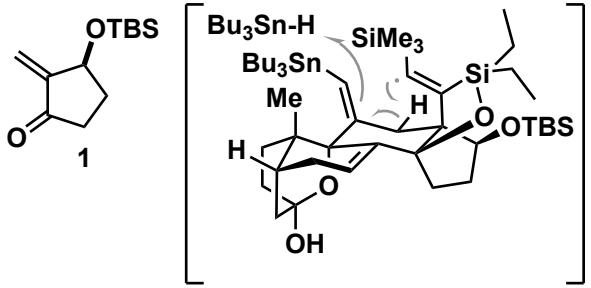


6–9



1) H_2, Pd/C, HCl, ethylene glycol
2) TESOTf, Et_3N
3) $CHBr_3$, KO*t*-Bu
4) TMSC≡CLi, THF
5) camphor sulfonic acid, MeOH

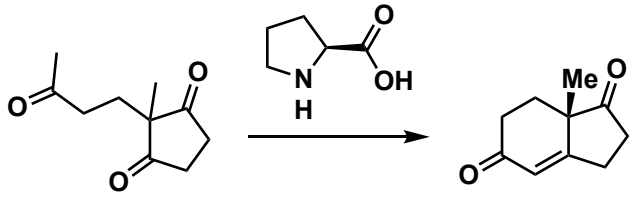
6) *t*-BuLi, THF, –90 °C, then **1**
7) K_2CO_3, MeOH
8) TMSC≡C$SiEt_2Cl$, imidazole
9) *n*-Bu_3SnH, O_2, Et_3B, Ph_2O, 150 °C



6-endo-trig followed by 1,4-H atom transfer

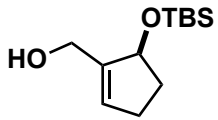
Please name the starting material.
How would you make it?

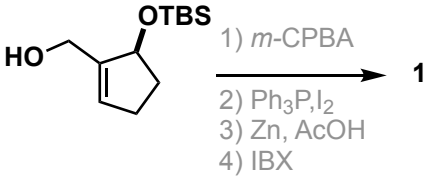
(*S*)-(+)-Hajos-Parrish diketone, (*S*)-Hajos dione, (*S*)-Hajos ketone, (*S*)-Hajos-Wiechert ketone



Hajos–Parrish–Eder–Sauer–Wiechert reaction

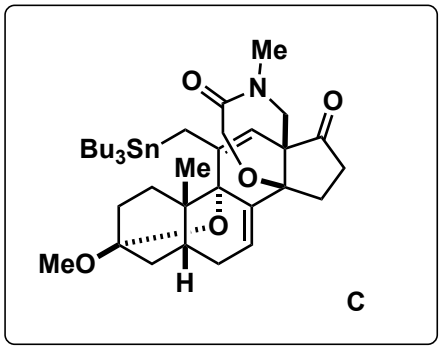
How would you make intermediate **1** from:





Step 9: Please provide the mechanism.

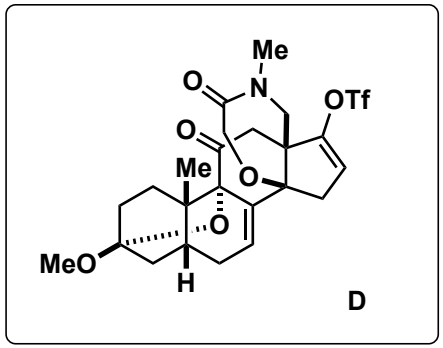
10–14



C

10) TBAF, THF, 60 °C
11) IBX, OsO_4, $NaIO_4$
12) $MeNH_2$, $NaB(O_2CCF_3)_3H$
13) $ClCH_2COCl$, 2,6-lutidine
14) NaOEt/EtOH

15–20



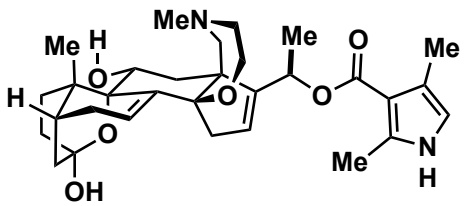
D

15) KHMDS, $PhNTf_2$
16) $CuCl_2$, O_2
17) $NaClO_2$, NaH_2PO_4, DMSO/H_2O
18) $SOCl_2$, pyridine
19) NaN_3, acetone/H_2O
20) AcOH/H_2O, 90 °C

Step 20: Please name the reaction.

D

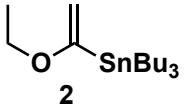
21–25



(–)-Batrachotoxin (BTX)

LD_{50} = 2 μg/kg

21) *p*-TsOH, 4Å MS, $PMBCH_2OH$
22) **2**, $Pd(PPh_3)_4$, LiCl, CuCl, then 1 M oxalic acid
23) AlH_3
24) *p*-TsOH, acetone/H_2O
25) Et_3N, **3**



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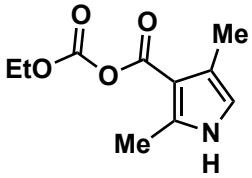

3

Step 23: How would you make AlH_3?

$AlCl_3 + 3LiAlH_4 \longrightarrow 3\ AlH_3 + LiCl$