Enantioselective Total Synthesis of Mandelalide A and Isomandelalide A: Discovery of a Cytotoxic Ring-Expanded Isomer

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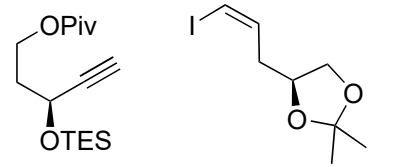
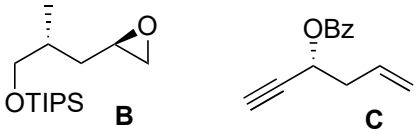


1–12

A



B **C**

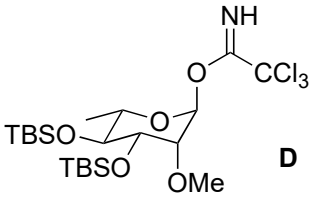
13–23

E

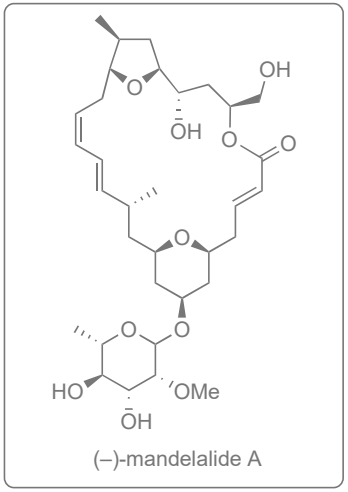
1) $Pd(PPh_3)_4$, CuI, *i*Pr_2NH
2) $(DHQD)_2PHAL$, $K_2OsO_4 \cdot 2H_2O$
3) BzCl, Et_3N
4) HF•Py
5) $AgBF_4$, PhMe, reflux; then MeLi•LiBr, Et_2O
6) TBSOTf, 2,6-Lutidine
7) Cp_2TiMe_2, PhMe, 90 ºC
8) Rh/Al_2O_3, H_2
9) DIBAL-H
10) Ms_2O, Et_3N
11) NaI, acetone
12) PPh_3, PhMe, heat

13) **C**, *n*BuLi, then B, $BF_3 \cdot OEt_2$
14) $AgBF_4$, PhMe, reflux
15) NaOMe, MeOH
16) TBAF
17) DMP, $NaHCO_3$
18) $Ph_3P{=}CHCO_2Et$
19) $NaBH_4$
20) **D**, TIPSOTf, MS 4Å
21) DIBAL-H
22) DMP, $NaHCO_3$
23) Grubbs-II, $H_2C{=}CHCO_2Me$

Mechanism of Step 5?



D



(–)-mandelalide A

A

24–29

F

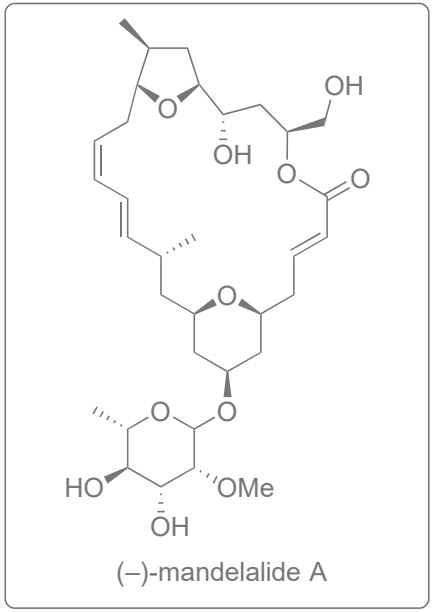
30–31

(–)-mandelalide A

24) NaHMDS; then **E**
25) TFA/DCM/H_2O
26) TBSOTf, 2,6-lutidine
27) DIBAL-H
28) MnO_2
29) $NaClO_2$

30) 2,4,6-trichlorobenzoyl chloride
DMAP, Et_3N
31) TAS-F

Structure of TAS-F?



(–)-mandelalide A