Total Synthesis of (+)-Mutilin

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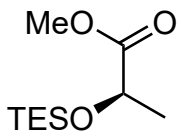
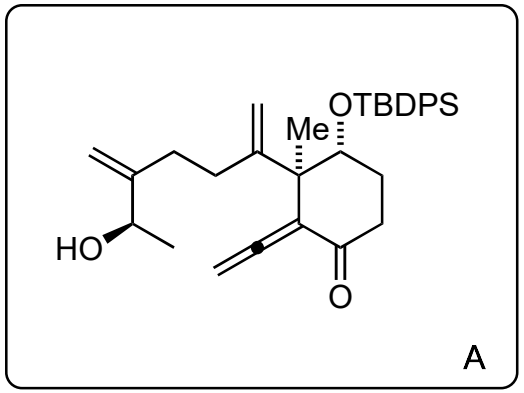
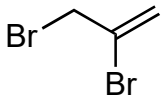


1-7

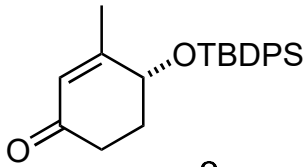


8-11

1) $CeCl_3$, $TMSCH_2MgCl$ (excess)
2) H_2SO_4
3) *n*-BuLi *then* **1**
4) TBSCl, imH
5) *t*-BuLi, (2-Th)Cu(CN)Li *then* **2**, TMSCl
6) TBAF, **3** *then* silica gel
7) $Et_3N{\cdot}HF$



1



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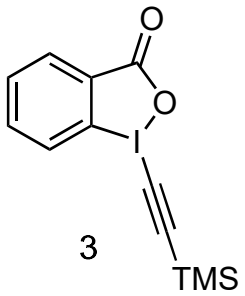


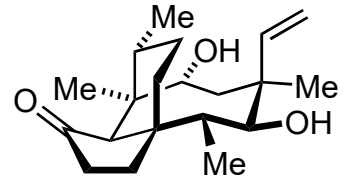
3

8) *t*-BuOK, *t*-BuOH
9) LiHMDS *then* MeOC(O)CN
10) toluene, reflux *then* NaOH, **MeOD/D_2O**
11) TBSOTf, 2,6-lutidine

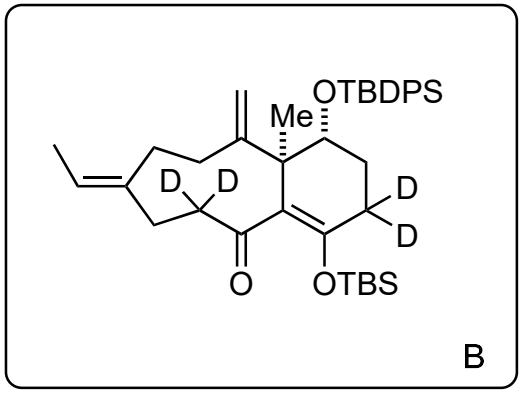
3) Name the rearrangement.
Brook rearrangement

6) Draw a mechanism for this transformation.
Cleavage of TMS, terminal addition of enolate, elimination of iodoarene and carbene formation, 1,2-H shift
7) TBDPS remains.

9) Hint: a tricycle is formed.
10) Name the reaction.
Claisen rearrangement

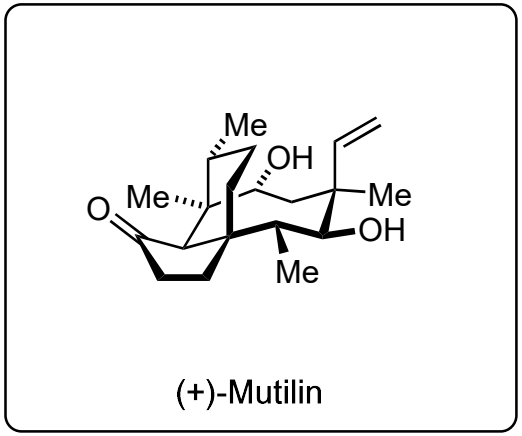


(+)-Mutilin



B

12-18



(+)-Mutilin

12) 365 nm *then* HF·py
13) PtO_2, H_2
14) LiHMDS *then* TIPSOTf *then* MeI
15) LDA *then* MeCHO
16) Martin's sulfurane
17) TBAF, reflux
18) Na, EtOH

12) Name the reaction. *DeMayo reaction*
Hint: the 5−6−8 skeleton is formed.
Rationalise why deuterium was incorporated in the previous step.
KIE to prevent 1,5-HAT from diradical intermediate.
14) Hint: 2 equiv. base, 1 equiv. electrophile each
16) Draw the structure of the reagent.
How does it work?
17) Hint: No deuterium present in the molecule after this step.