Synthesis of Streptolydigin, a Potent Bacterial RNA Polymerase Inhibitor

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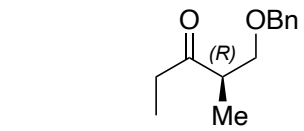
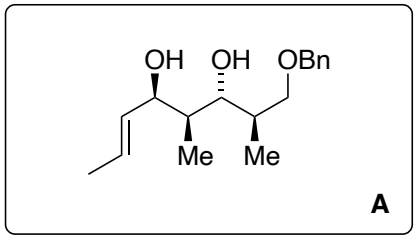
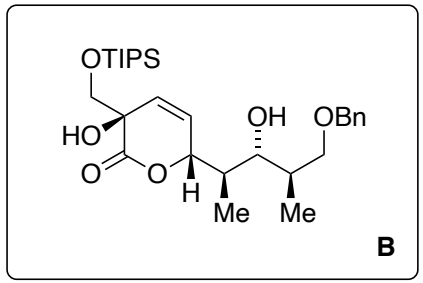


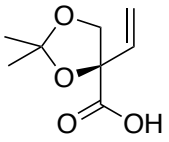
1 – 3



4 – 7



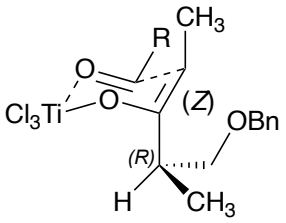
1) $TiCl_4$, $Ti(O\textit{i}\text{-}Pr)_4$, DIPEA,
(*E*)-crotonaldehyde
2) SmI_2, MeCHO, THF
3) K_2CO_3, MeOH, H_2O



1

4) DCC, DMAP, **1**
5) 4 N HCl, THF
6) TIPSCl (1 equiv.), imidazole, DMAP
7) HG-II

1) Please explain the selectivity.



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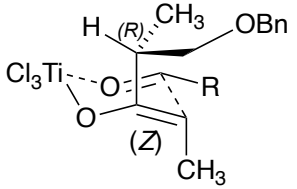

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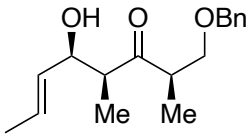
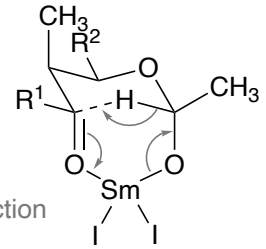
2) What is the name of this reaction? Explain the selectivity with a model. Do you know alternative reaction conditions resulting in the same selectivity? How could you obtain the opposite selectivity?

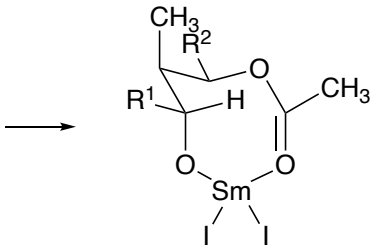


SmI_2, MeCHO

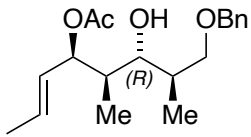


Evans Tishchenko reduction

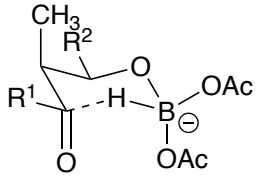
anti



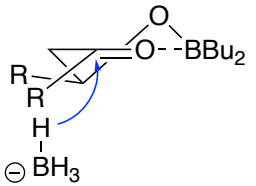
H_3O^+



Alternative anti reduction:
Evans–Saksena reduction
conditions: $Me_4NBH(OAc)_3$

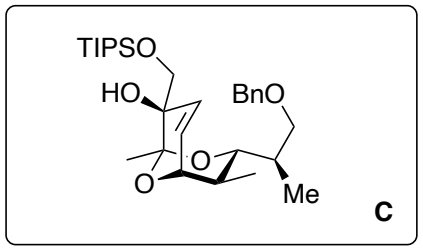


Syn-1,3-diol selectivity:
Narasaka–Prasad reduction
conditions: Bu_2BOMe, $NaBH_4$

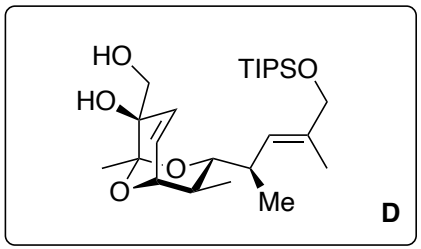


Attack according to Fuerst–Plattner rule

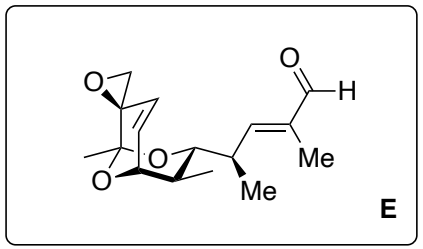
8 – 10



11 – 16



17 – 19

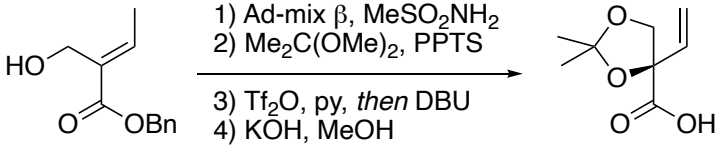


8) MeNHOMe • HCl, *i*-PrMgCl
9) MeLi
10) TsOH

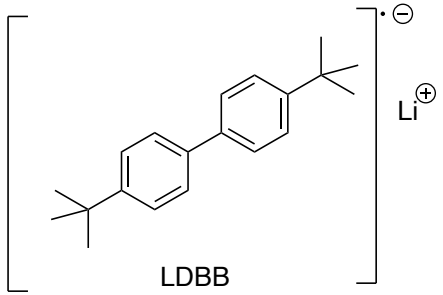
11) LDBB
12) DMP
13) $Ph_3PC(Me)CO_2Et$, PhMe, Δ
14) DIBAL-H
15) TIPS-Cl, imidazole, DMAP
16) LAH

17) Tf_2O, pyridine, DBU
18) TBAF
19) DMP

How could you access **1** fom **X**?

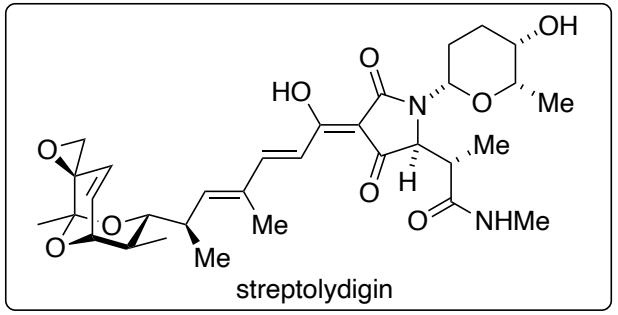


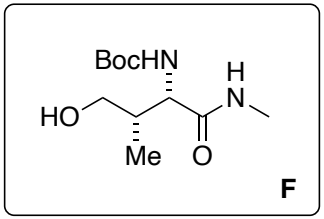
What is the structure of LDBB?



Freeman's reagent

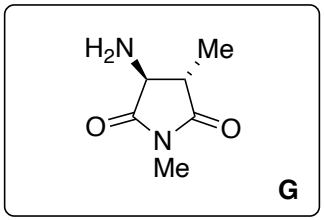
Hint: Step 16 is a selective monodepotection





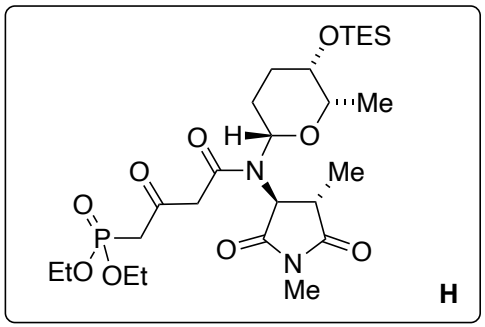
F

20, 21



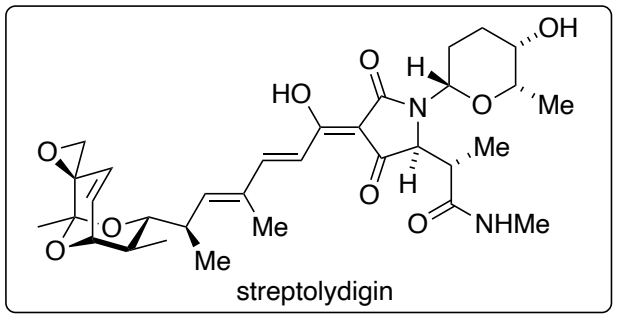
G

22, 23



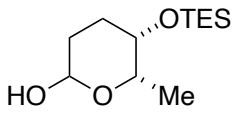
H

24



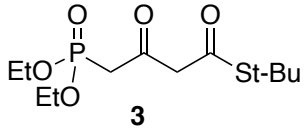
streptolydigin

Hint: A cyclization takes place
20) TEMPO, PIDA
21) TFA, basic alumina



2

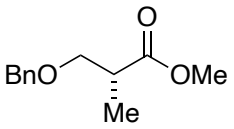
22) **2**, MeOH
23) **3**, CF_3CO_2Ag, 5Å MS



3

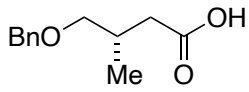
24) *t*-BuOK, THF, *then* **E**, *then* aq. HCl

How would you prepare **F**?

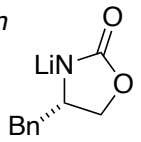


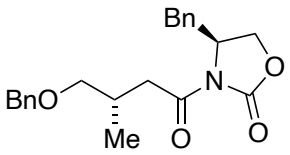
(*R*)-Roche ester

1) LAH
2) NBS, PPh_3
3) Mg, $(CH_2Br)_2$, *then* CO_2

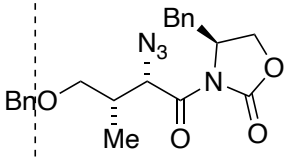


PivCl, NEt_3
then

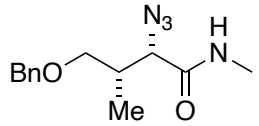




KHMDS
then $TrisylN_3$



$MeNH_2$



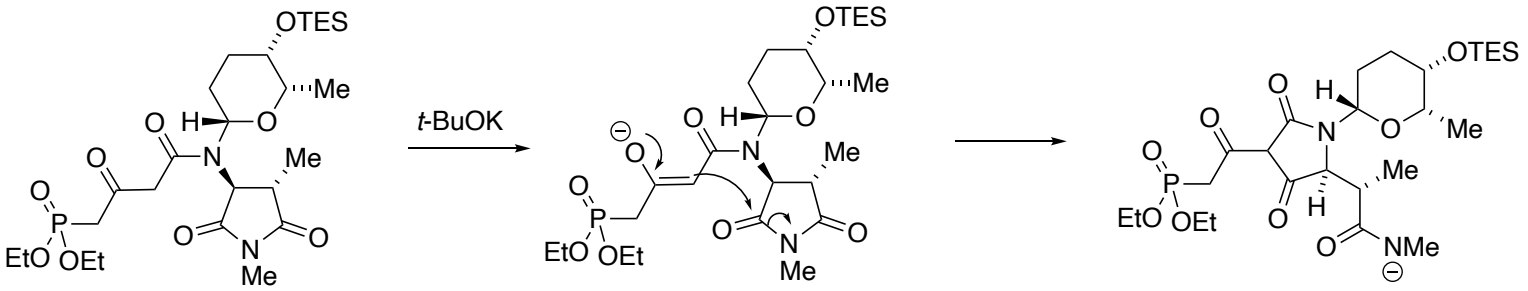
H_2, Pd/C
Boc_2O

F

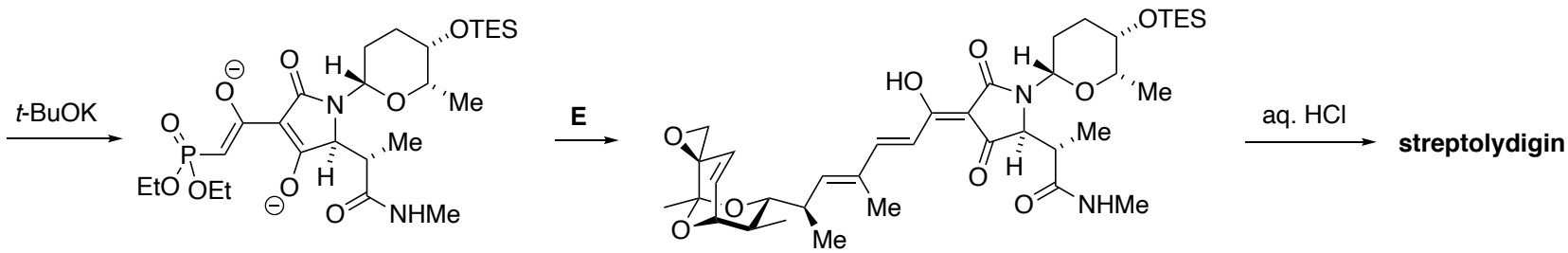
Name at least one alternative method to synthesize α-amino acids.
Strecker reaction, asymmetric vaiants available
Schöllkopf method
Sharpless aminohydroxylation
…

Key step: please provide a mechanism

Mechanism of step 24



Dieckmann cyclization
+ imide opening



Horner–Wadsworth–
Emmons olefination