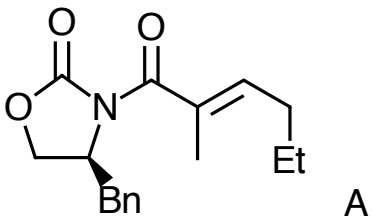
Synthesis Challenge # 37

Total Synthesis of the Protected Aglycon of Fidaxomicin (Tiacumicin B, Lipiarmycin A3)

H.Miyatake-Ondozabal, E. Kaufmann, K. Gademann, *Angew. Chem. Int. Ed.* **2015**, *54*, 1933–1936.

23.07.2015

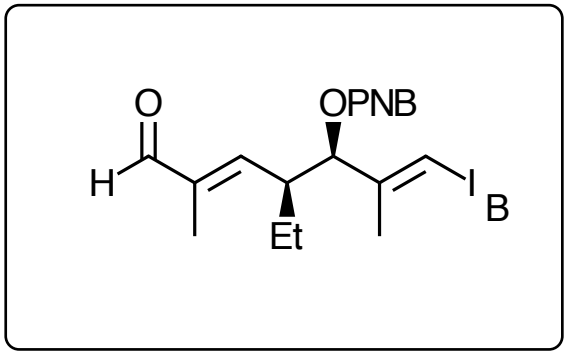


A

How would you prepare compund A

1-5

1) NaHMDS, THF, –78ºC; then TBSCl
2) (*E*)-3-iodo-2-methylacrylaldehyde, $TiCl_4$, CH_2Cl_2, –78ºC to –30ºC
3) *para*-nitrobenzoic acid, DEAD, PPh_3, THF, 0 ºC
4) $NaBH_4$, THF/H_2O
5) MnO_2, CH_2Cl_2



B

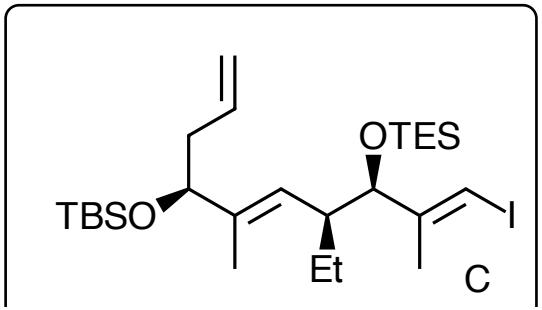
Please, provide detailed mechanism for step 2.

6-9

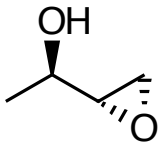
6) (–)-Ipc_2B(allyl), Et_2O, –78ºC then aq. $NaBO_3$
7) TBSOTf, 2,6-lutidine, CH_2Cl_2
8) K_2CO_3, $MeOH/H_2O$
9) TESOTf, 2,6-lutidine, CH_2Cl_2

Please provide a detailed mechanism for step 6).

Brown allylation

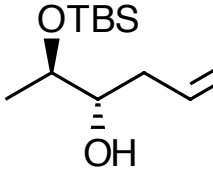


C

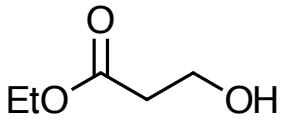


D

10-12

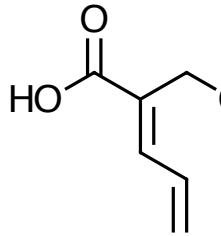


E



F

13-19



G

10) TBSCl, Imid, CH_2Cl_2
11) propyne, *n*BuLi, $BF_3{\cdot}Et_2O$, THF, –78°C to 0°C
12) $Pd(OAc)_2$, PCy_3, Bu_3SnH, hexane

How would you prepare compund D?

K inetic resolution of 3-buten-2-ol by using Sharpless epoxidation
Tetrahedron Lett. **1983**, *24,* 4539–4542

Please provide a detailed mechanism for step 12).

P d-catalyzed hydrostannylation

13) LDA (3.5 equiv), THF, –78°C; then acrolein, –78°C
14) Me_2SnCl_2 (10 mol%), TBSCl, Et_3N
15) Ac_2O, Et_3N, DMAP, CH_2Cl_2
16) DBU, CH_2Cl_2, *E*:*Z*=5.5:1
17) DIBAH, CH_2Cl_2, –10°C;
18) MnO_2, CH_2Cl_2
19) $NaClO_2$, KH_2PO_4, 2-methyl-2-butene, tBuOH/H_2O

Please provide a detailed mechanism for step 13).

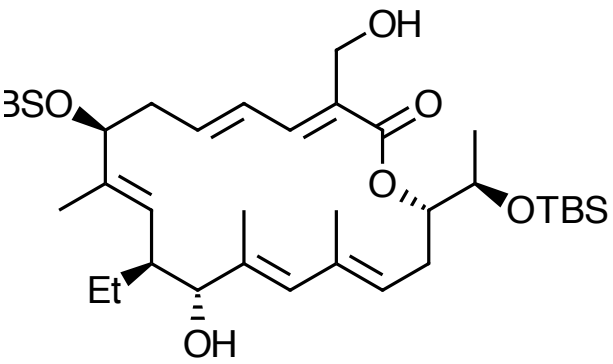
Aldolreaction

What is the name of the reaction in step 19)

Lindgren–Pinnick oxidation

C

23-25



20) **E**, CuTC, $[Pd(PPh_3)_4]$,
$[Bu_4N]^+[Ph_2PO_2]^-$, DMF
21) **G**, $Cl_3C_6H_2COCl$, Et_3N, DMAP, PhMe
22) Grubbs cat. II (15 mol %), PhMe, 40ºC (microwave irradiation), 10 min, E/Z = 2:3 ; then 100 ºC, 18 h, E/Z = 2 :1
23) $HF{\cdot}Et_3N$, THF/MeCN 1:1, 0ºC to 23ºC

Please provide a detailed mechanism for steps 20)-22).

Step 20): *Stille coupling*
Step 21): *Yamaguchi esterfication*
Step 22): *Ring closing metathesis*