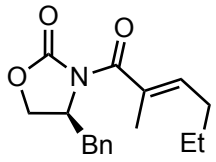
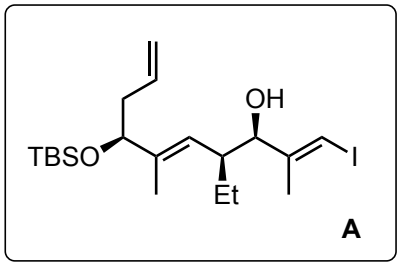
Total Synthesis of the Glycosylated Macrolide Antibiotic Fidaxomicin

Kaufmann, E.; Hattori, H.; Miyatake-Ondozabal, H.; Gademann, K.; *Org. Lett.* **2015**, *17*, 3514–3517;
Miyatake-Ondozabal, H.; Kaufmann, E.; Gademann, K.; *Angew. Chem. Int. Ed.* **2015**, *54*, 1933–1936.

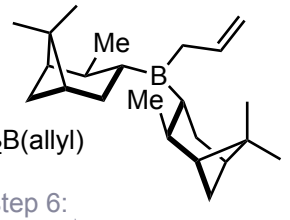


1–8



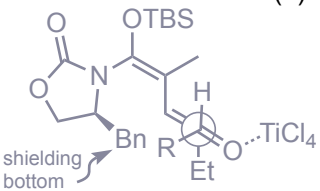
1) NaHMDS, THF, then TBSCl
2) *(E)*-3-iodo-2-methylacrylaldehyde, $TiCl_4$, d.r. > 20:1
3) *p*-nitrobenzoic acid, DEAD, PPh_3, THF
4) $NaBH_4$
5) MnO_2
6) (–)-Ipc_2B(allyl), then aq. $NaBO_3$, d.r. = 20:1
7) TBSOTf, 2,6-lutidine
8) DIBAL-H

Please name all named reactions/conditions and explain the stereochemical outcome of all reactions.



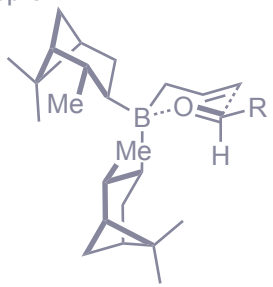
(–)-Ipc_2B(allyl)

step 2:

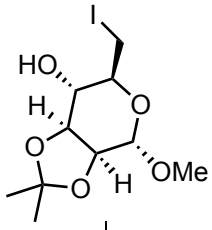


J. Am. Chem. Soc. **2004**, 13604.

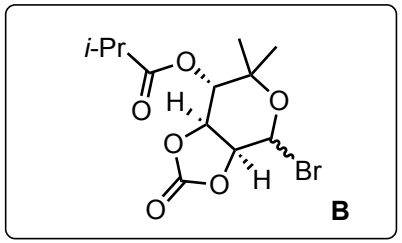
step 6:



J. Am. Chem. Soc. **1986**, 5919.



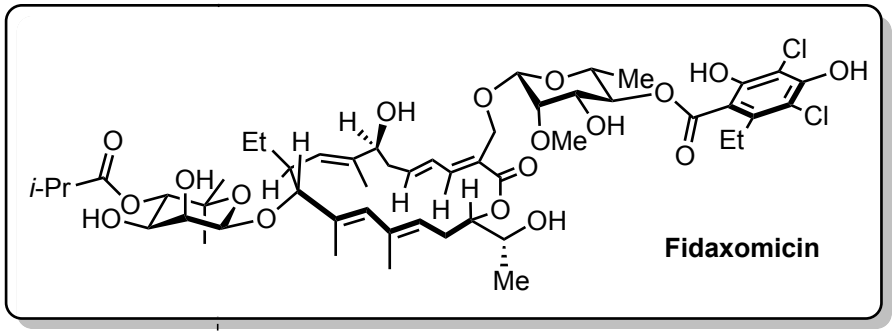
9-15

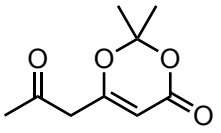


9) Zn, NH_4Cl, MeOH, 60 °C
10) CSA, 2,2'-dimethoxypropane, MeOH
11) O_3, CH_2Cl_2, MeOH, NaOH
12) MeMgBr (3.0 equiv.)
13) TFA, MeOH, 100 °C, microwave, α:β = 2:1
14) CDI, DCE then Et_3N, *i*-PrCOCl
15) HBr, AcOH

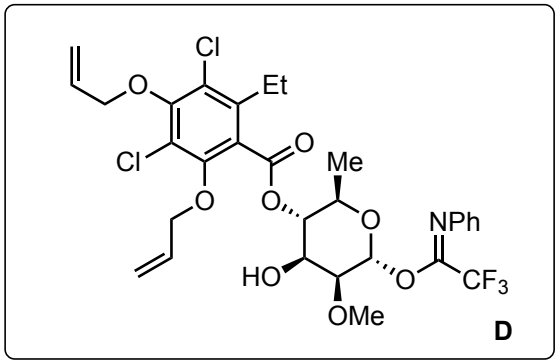
What sugar is the starting material of step 9 derived from? D-*mannose*

Provide a name for sugars with the substitution pattern of ***B****?* D-*noviose*





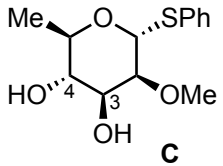
16-22



D

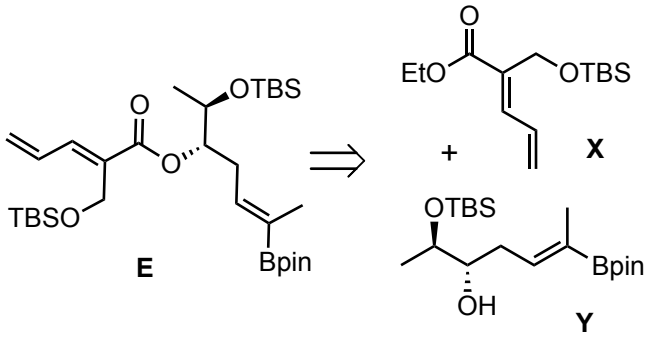
16) LDA, propionylimidazole, then Et_3N
17) SO_2Cl_2, CH_2Cl_2, reflux
18) K_2CO_3, allyl-Br
19) **C**, NaH
20) K_2CO_3, allyl-Br
21) NBS, acetone/H_2O, α:β = 5:1
22) $ClC(NPh)CF_3$

Hint: the product of step 16 is aromatic



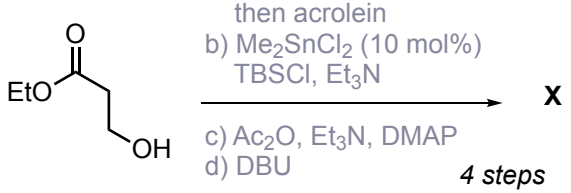
C

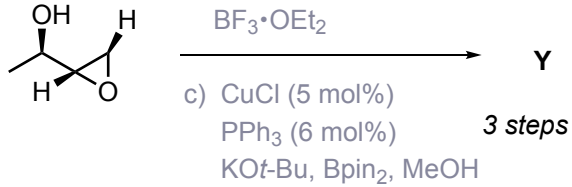
Step 19:
Initially the O-3 ester is formed and transesterification to O-4 is observed over time



E **X** **Y**

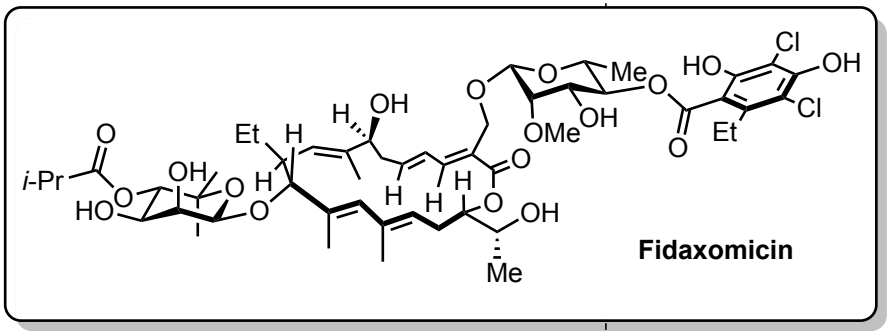
*How would you synthesize the intermediates of **E** from the given starting materials?*





B

23-30



Fidaxomicin

24) **E**, $Pd(PPh_3)_4$ (20 mol%), TlOEt
25) Grubbs II (20 mol%), 100 °C, *E*:*Z* = 2:1
26) 3 HF•Et_3N, THF, MeCN, 0 °C - RT
27) **D**, TBSOTf (20 mol%), 3 Å MS, α:β = 1:4
28) 3 HF•Et_3N, THF, 50 °C
29) Barton's base, wet CH_2Cl_2
30) $Pd(PPh_3)_4$ (10 mol%), morpholine