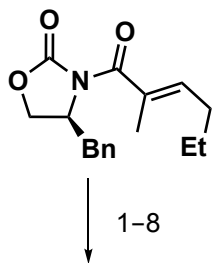
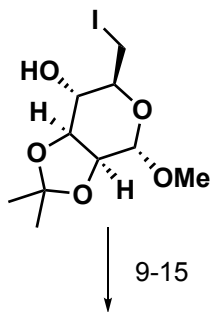
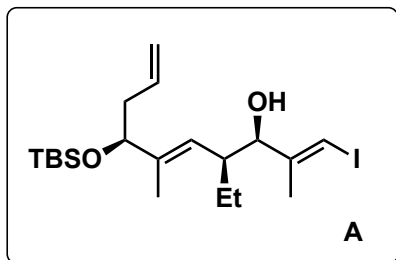


Total Synthesis of the Glycosylated Macrolide Antibiotic Fidaxomicin

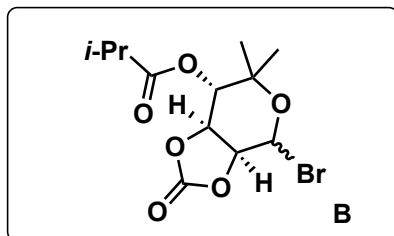
Kaufmann, E.; Hattori, H.; Miyatake-Ondozabal, H.; Gademann, K.; *Org. Lett.*, **2015**, *17*, 3514–3517;
 Miyatake-Ondozabal, H.; Kaufmann, E.; Gademann, K.; *Angew. Chem. Int. Ed.* **2015**, *54*, 1933–1936.



1-8



9-15

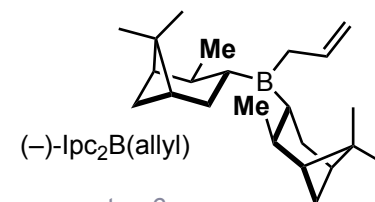
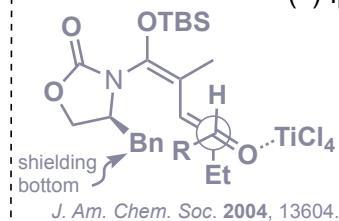


- 1) NaHMDS, THF, then TBSCl
- 2) (*E*)-3-iodo-2-methylacrylaldehyde, TiCl₄, d.r. > 20:1
- 3) *p*-nitrobenzoic acid, DEAD, PPh₃, THF
- 4) NaBH₄
- 5) MnO₂
- 6) (-)-Ipc₂B(allyl), then aq. NaBO₃, d.r. = 20:1
- 7) TBSOTf, 2,6-lutidine
- 8) DIBAL-H

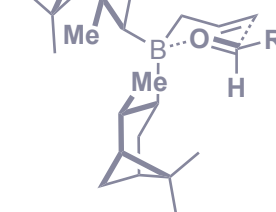
- 9) Zn, NH₄Cl, MeOH, 60 °C
- 10) CSA, 2,2'-dimethoxypropane, MeOH
- 11) O₃, CH₂Cl₂, MeOH, NaOH
- 12) MeMgBr (3.0 equiv.)
- 13) TFA, MeOH, 100 °C, microwave, α:β = 2:1
- 14) CDI, DCE then Et₃N, *i*-PrCOCl
- 15) HBr, AcOH

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

step 2:



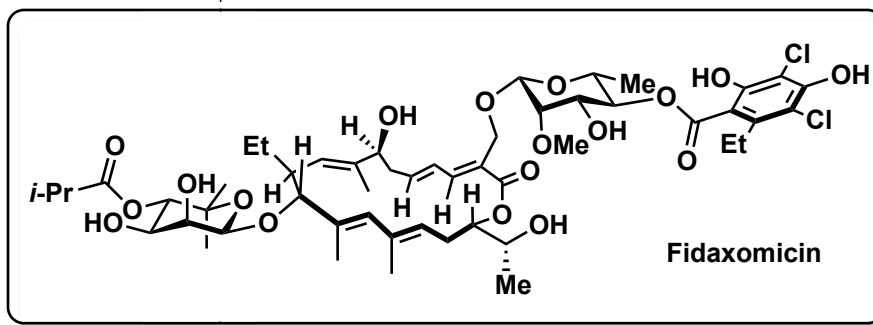
step 6:

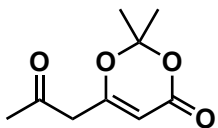


J. Am. Chem. Soc. **1986**, 5919.

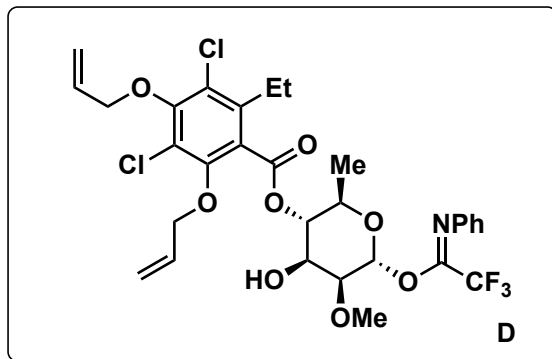
What sugar is the starting material of step 9 derived from? *D*-mannose

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



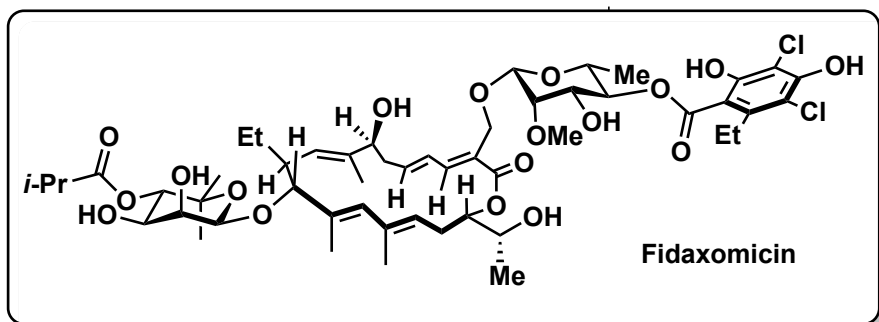


16-22



B

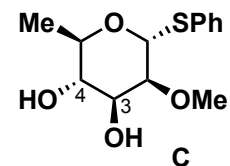
23-30



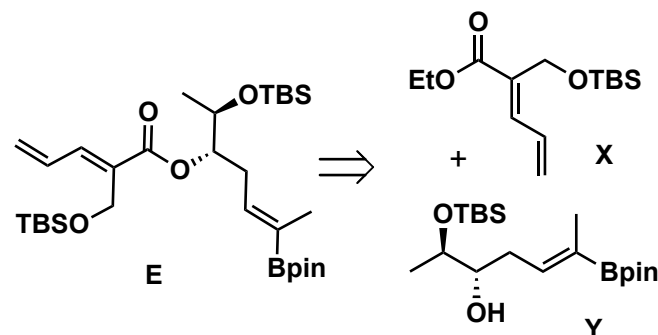
- 16) LDA, propionylimidazole, then Et₃N
- 17) SO₂Cl₂, CH₂Cl₂, reflux
- 18) K₂CO₃, allyl-Br
- 19) **C**, NaH
- 20) K₂CO₃, allyl-Br
- 21) NBS, acetone/H₂O, α:β = 5:1
- 22) ClC(NPh)CF₃

- 23) **A**, HgO, HgBr₂, 4 Å MS, α:β = 1:3
- 24) **E**, Pd(PPh₃)₄ (20 mol%), TIOEt
- 25) Grubbs II (20 mol%), 100 °C, *E:Z* = 2:1
- 26) 3 HF·Et₃N, THF, MeCN, 0 °C - RT
- 27) **D**, TBSOTf (20 mol%), 3 Å MS, α:β = 1:4
- 28) 3 HF·Et₃N, THF, 50 °C
- 29) Barton's base, wet CH₂Cl₂
- 30) Pd(PPh₃)₄ (10 mol%), morpholine

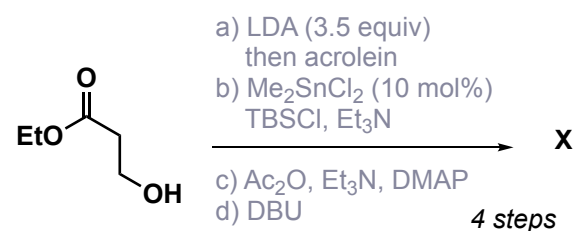
Hint: the product of step 16 is aromatic



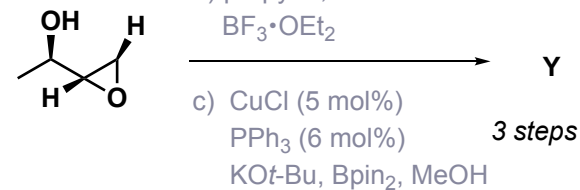
Step 19:
Initially the O-3 ester is formed
and transesterification to O-4 is
observed over time



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



- a) LDA (3.5 equiv)
then acrolein
- b) Me₂SnCl₂ (10 mol%)
TBSCl, Et₃N
- c) Ac₂O, Et₃N, DMAP
- d) DBU



- a) TBSCl, imidazole
- b) propyne, *n*-BuLi
BF₃·OEt₂
- c) CuCl (5 mol%)
PPh₃ (6 mol%)
KO^t-Bu, Bpin₂, MeOH