Total Synthesis of Rapamycin

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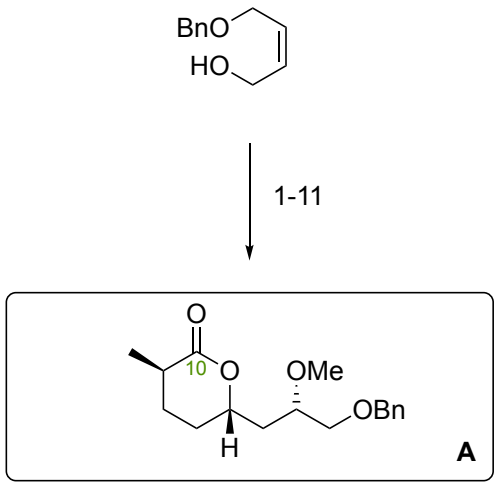
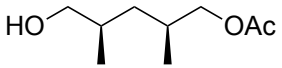
ACIE **2007**, *46*, 591–597 (*et al. CEJ* **2009**, *15*, 2874–2914)





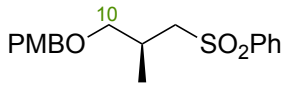
1) $Ti(O\textit{i}\text{-}Pr)_4$, (+)-DET, *t*-BuOOH, CH_2Cl_2, −25 ℃
2) $py.SO_3$, Et_3N, DMSO, CH_2Cl_2, 0 ℃ to rt
3) LiCl, $(EtO)_2P(O)CH_2CO_2Me$, DBU, MeCN, rt
4) DIBAL-H, CH_2Cl_2, −78 ℃
5) $Ti(O\textit{i}\text{-}Pr)_4$, (−)-DET, *t*-BuOOH, 4-Å M.S. CH_2Cl_2, −23 ℃
6) *cat.* TPAP, NMO, CH_2Cl_2/ MeCN, 4-Å M.S.
7) $MePPh_3Br$, KHMDS, THF, 0 ℃ to rt
8) $Fe_2(CO)_9$, degassed THF
9) CO, 280 atm., PhH, 2 days
10) Adam's catalyst, H_2, 1 atm, EtOAc, rt
11) LDA, THF, −78 ℃; MeI
d.r. = 60:40

12) DIBAL-H, PhMe, −78 ℃
13) TBSCl, ImH, *cat.* DMAP, DMF, rt
14) Pearlman's catalyst, H_2, EtOAc, rt
15) *cat.* TPAP, NMO, CH_2Cl_2/ MeCN, 4-Å M.S.
16) MeMgBr, Et_2O, THF, −78 ℃
17) *cat.* TPAP, NMO, CH_2Cl_2/ MeCN, 4-Å M.S.
18) $(EtO)_2P(O)CH_2CN$, NaHMDS, THF, 0 ℃; **substrate**, −78 ℃
19) DIBAL-H, PhMe, −78 ℃
20) TBAF, AcOH/H_2O/THF, rt
21) $CrCl_2$, CHI_3, THF/dioxane, 0 ℃

22) TBSCl, ImH, CH_2Cl_2, 0 ℃ to rt
23) K_2CO_3, MeOH, rt
24) NaH, PMBCl, *cat.* TBAI, THF, 0 ℃ to rt
25) TBAF, THF, 0 ℃
26) $py.SO_3$, DIPEA, DMSO, CH_2Cl_2, rt
27) **2**, LiHMDS, −78 ℃; **substrate**, −78 ℃; AcOH, −78 ℃ to rt

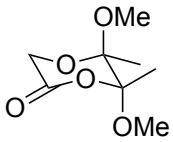
1), 2), 3), 6), 21) Name reactions?
Sharpless asymmetric epoxidation
Parikh--Doering oxidation
Horner--Wadsworth--Emmons olefination
Ley--Griffith oxidation
Takai olefination (Evans--Black modification)

Suggest a more reliable route to **A** with better stereocontrol, installing the problematic stereocentre with **1**.



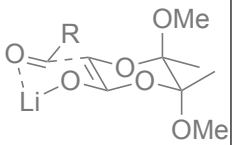
1

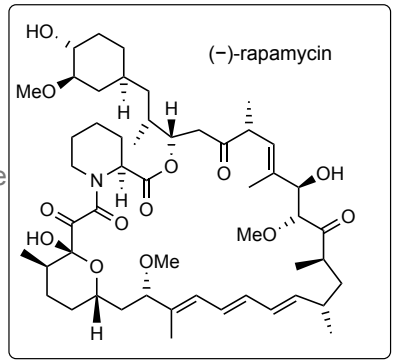
12/13, 19/20) Why reduce/ protect C-10 of lactone to reoxidize later?
C-11 epimerizes under these reaction conditions

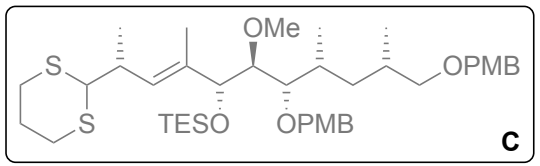


2

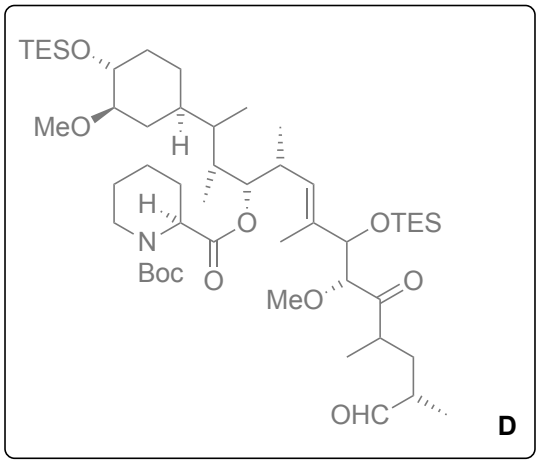
From which commodity chemical is **2** derived? Explain the observed stereoselectivity for the Aldol addition (name model).
Glycolic acid and Felkin--Anh



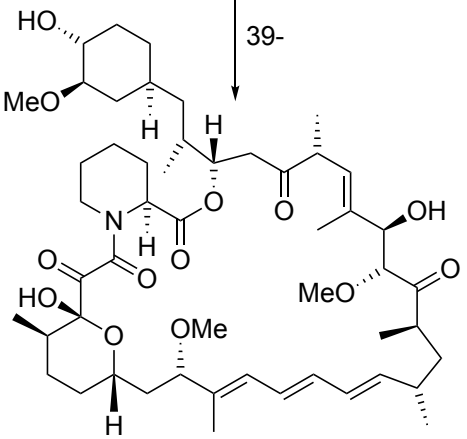




35-39



39-



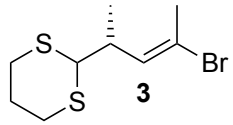
(−)-rapamycin

28) PMBTCA, *cat.* $TrBF_4$, THF, rt
29) (±)-CSA, MeOH, rt
30) Ag_2O, CH_3I, CH_2Cl_2, 50 ℃
31) LiHMDS, MeO(Me)NH.HCl, −20 ℃;
substrate, −20 ℃ to −10 ℃
32) **3**, *t*-BuLi, −100 ℃; **substrate**, −100 ℃ to −78 ℃
33) $Zn(BH_4)_2$, Et_2O, −20 ℃, 2 days
34) TESCl, ImH, DMF, 50 ℃

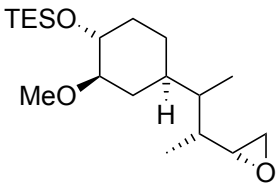
35) **4**, *t*-BuLi, THF/HMPA (9:1), −78 ℃ to −40 ℃
36) PIFA, THF/MeOH/H_2O (10:9:1), rt
37) **5**, DCC, *cat.* DMAP, CH_2Cl_2, −5 ℃, 24 h
38) DDQ, pH 7 buffer, CH_2Cl_2, rt
39) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2

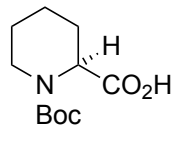
40) $CrCl_2$, CHI_3, THF, 0 ℃ to rt
41) *cat.* $[Pd(PFur_3)_2Cl_2]$, $(Me_3Sn)_2$, NMP, dark, rt
42) **B**, *cat.* $[Pd(PFur_3)_2Cl_2]$, $(Me_3Sn)_2$, NMP, dark, rt
43) $LiAlH(Ot\text{-}Bu)_3$, THF, −5 ℃
44) Alloc-Cl, 4-pyrrolidinopyridine, CH_2Cl_2
45) 0.1 M aq. LiOH, THF, 5 ℃ M
45) TESOTf, 2,6-lut, CH_2Cl_2, −20 ℃ to rt
46) $BrCH_2CO_2Br$, 2,6-lut, CH_2Cl_2, −20 ℃
47) catechol, DCC, DMAP, CH_2Cl_2, 0 ℃ to rt
48) K_2CO_3, DMF, rt
49) LiHMDS, THF, −78 ℃ to −20 ℃
50) $[Pd(PPh_3)_4]$, dimedone, THF, rt
51) PIDA, MeCN/H_2O (10:1), 0 ℃
52) DMP, py, CH_2Cl_2, rt,
53) HF.py, THF, 50 ℃

How would you make **3** from Roche ester (and which enantiomer)? see C*EJ* **2009**, *15*, 2874–2914



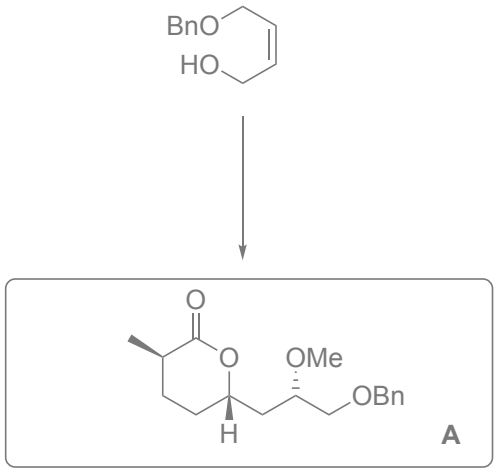
33) Stereochemical model





47-49) !? What are they trying to achieve? How otherwise might this be done?
Macrocyclization (Dieckmann architecture)
Amide formation

50) What is the role of dimedone?
Nucleophile and regenerates Pd catalyst
see *ACIE* 2012, *51*, 8648-8651



TL **1994**, *35*, 2095–2098

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2) py.SO_3, Et_3N, DMSO, CH_2Cl_2, 0 ℃ to rt
3) $MePPh_3Br$, KHMDS, THF, 0 ℃ to rt
4) DIBAL-H, PhMe, −78 ℃
5) *n*-BuLi, Et_2O; BOC-ON, THF, rt
6) IBr, PhMe, CH_2Cl_2, −85 ℃ to rt
7) K_2CO_3, MeOH, rt
8) MeI, Ag_2O, DMF, rt
9) **1**, *n*-BuLi, THF, −78 ℃; substrate, $BF_3.Et_2O$, THF, −78 ℃ to rt
10) 1 M Lithium naphthalenide, THF, −90 ℃
11) DDQ, CH_2Cl_2, H_2O, rt
12) *cat.* TPAP, NMO, CH_2Cl_2, 4-Å M.S.

Suggest a more reliable route to **A** with better stereocontrol

1