Total Synthesis of Rapamycin

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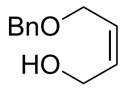
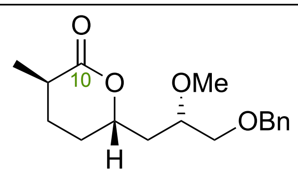
ACIE **2007**, *46*, 591–597 (*et al. CEJ* **2009**, *15*, 2874–2914)



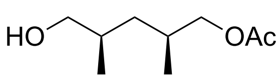
1-11



A

12-13

B



22-34

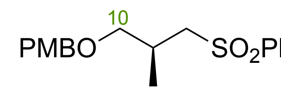
1) Ti(O*i*-Pr)$_4$, (+)-DET, *t*-BuOOH, CH_2Cl_2, −25 ℃
2) py.SO_3, Et_3N, DMSO, CH_2Cl_2, 0 ℃ to rt
3) LiCl, $(EtO)_2P(O)CH_2CO_2Me$, DBU, MeCN, rt
4) DIBAL-H, CH_2Cl_2, −78 ℃
5) Ti(O*i*-Pr)$_4$, (−)-DET, *t*-BuOOH, 4-Å M.S. CH_2Cl_2, −23 ℃
6) *cat.* TPAP, NMO, CH_2Cl_2/ MeCN, 4-Å M.S.
7) $MePPh_3Br$, 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

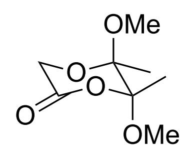
1), 2), 3), 6), 21) Name reactions?

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



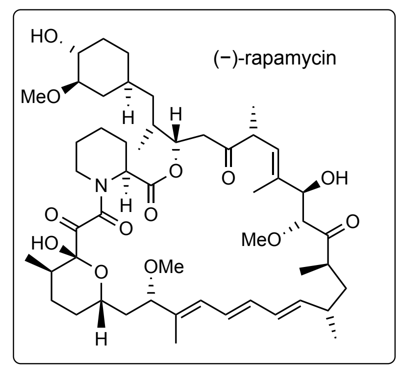
1

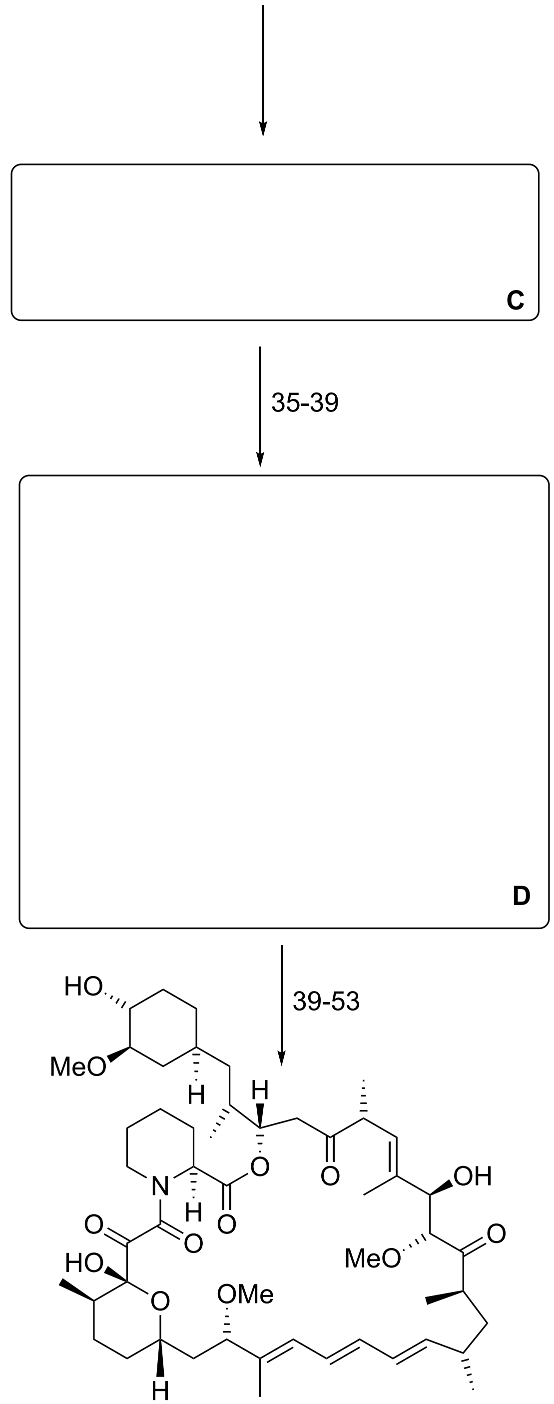
12/13, 19/20) Why reduce/ protect C-10 of lactone to reoxidize later?



2

From which commodity chemical is **2** derived? Explain the observed stereoselectivity for the Aldol addition (name model).





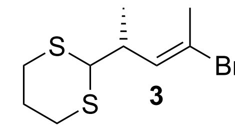
(−)-rapamycin

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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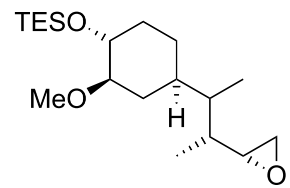
33) Stereochemical model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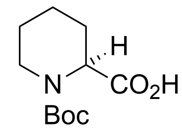
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47-49) !? What are they trying to achieve? How otherwise might this be done?

50) What is the role of dimedone?