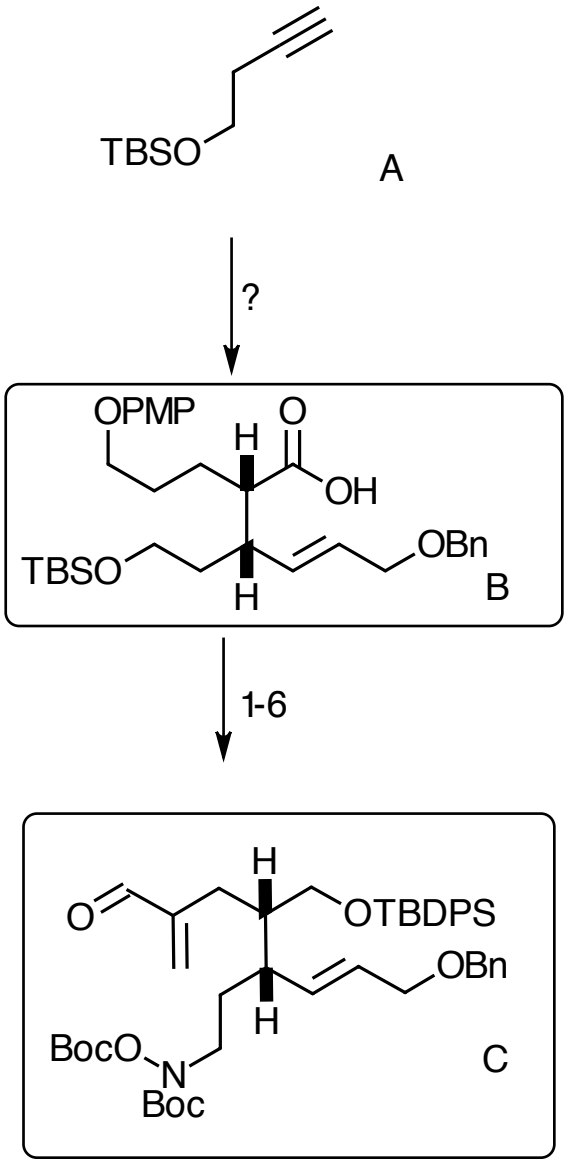
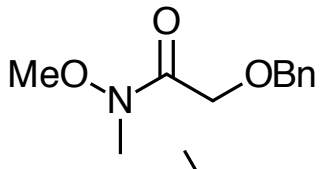
Synthesis Challenge # 34

Formal Synthesis of Sarain A: Intramolecular Cycloaddition of an Eight-Membered Cyclic Nitrone to Construct the 2-Azabicyclo-[3.3.1]nonane Framework, T. Higo, T. Ukegawa, S. Yokoshima,T. Fukuyama, *Angew. Chem.Int. Ed.* **2015**, DOI: 10.1002/anie.201501633



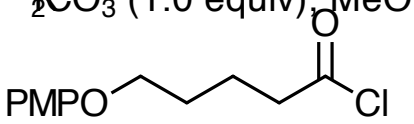


IV

1) 9-BBN, 1.05 equiv), then aq. $NaHCO_3$, aq. H_2O_2 (30 wt %)
2) DMP (1.2 equiv), CH_2Cl_2,
3) vinylmagnesium bromide
4) TBSCl, imidazole, DMF;

V

K_2CO_3 (1.0 equiv), MeOH,



VI

1) $ClCO_2Et$, Et_3N, THF, 0 °C ; $NaBH_4$, H_2O, 0 °C to RT
2) TBDPSCl, imidazole, DMF, RT; TFA, H_2O
3) BocNHOBoc, DEAD, Ph_3P, toluene, RT;
4) CAN, $NaHCO_3$, MeCN-H_2O, 0°C
5) $(COCl)_2$, DMSO, CH_2Cl_2, –78°C; Et_3N, 0°C
6) $H_2C{=}NMe_2{}^+I^-$, iPr_2NEt, CH_2Cl_2, reflux; MeI, RT

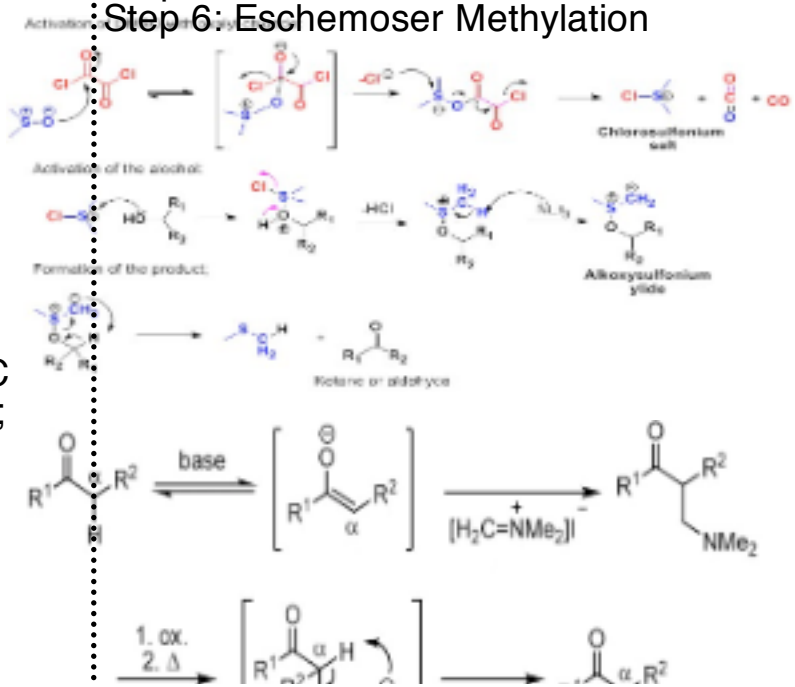
Please design an asymmetric synthesis of B starting from A.

a) *n*BuLi, THF, –78°C; **IV**, 0°C
b) **V** (2 mol%), HCO_2H-Et_3N (1:1), CH_2Cl_2, –78 to 0 °C
c) Red-Al, toluene, RT
d) **VI**, pyridine, CH_2Cl_2, 0 °C
e) LHMDS, TMSCl, Et_2O/THF

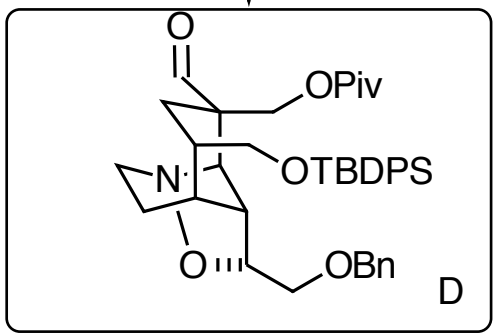
Please, provide a detailed mechanism for step 5 & 6.

Step 5: Swern Oxidation

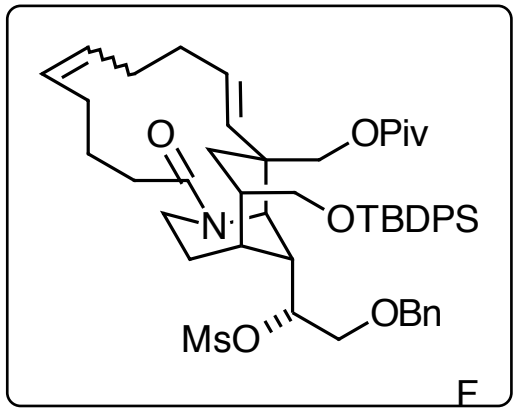
Step 6: Eschemoser Methylation



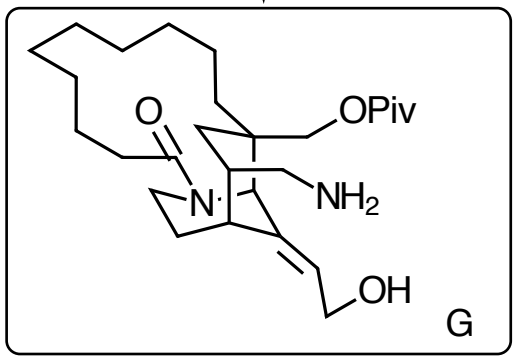
7-11



12-16



17-21

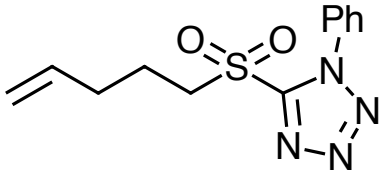


7) TFA, CH_2Cl_2, 40ºC; pyridine, 40ºC
8) 9-BBN, THF, RT;
aq. NaOH, aq. H_2O_2, RT
9) $(COCl)_2$, DMSO, CH_2Cl_2, –78 ºC;
Et_3N, 0 ºC
10) aq. HCHO, K_2CO_3, 1,4-dioxane, RT
11) toluene, 100ºC;
PivCl, pyridine, DMAP, 100ºC

12) **I**, LHMDS, THF, –78 to 0ºC
13) Zn, AcOH-Et_2O (1:2), RT
14) **II**, aq. $NaHCO_3$, CH_2Cl_2, 0ºC
15) MsCl, $Me_2N(CH_2)_3NMe_2$, CH_2Cl_2
16) Grubbs II, CH_2Cl_2, RT

17) TBAF, THF, RT; *t*BuOK
18) MsCl, *i*Pr_2NEt, CH_2Cl_2, 0ºC;
TESOTf
19) NaN_3, DMSO, 90ºC; TBAF, 60ºC
20) PivCl, pyridine, DMAP, toluene,
100 ºC
21) H_2 (1 atm), $Pd(OH)_2/C$,
AcOH/MeOH (1:19), RT

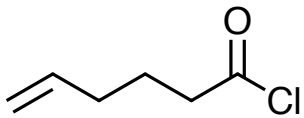
Please, provide a detailed mechanism for step 7.



I

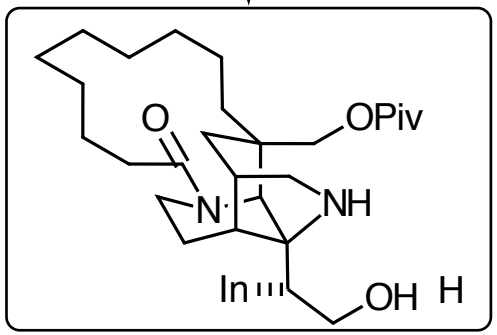
Please, provide a detailed mechanism for step 12.

Julia Kocienski Olefination



II

22-24



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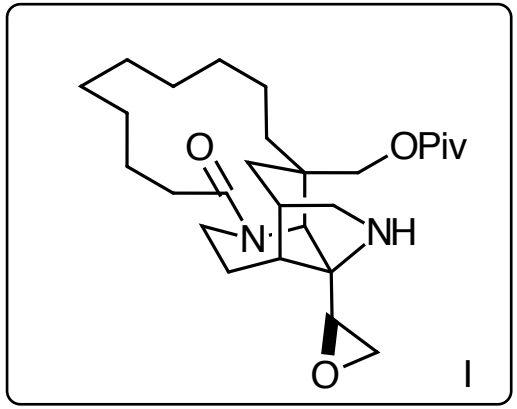

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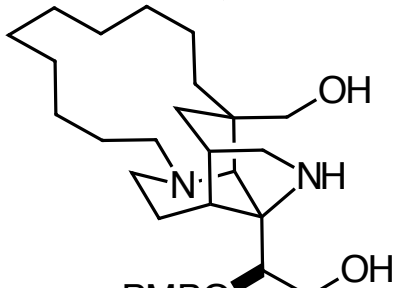
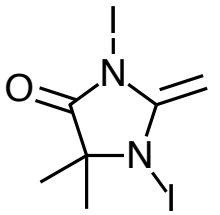


22) TsCl, aq. $NaHCO_3$, CH_2Cl_2, RT
23) TIPSOTf, *i*Pr_2NEt, CH_2Cl_2, 0ºC
24) **III**, I_2, Cs_2CO_3, CH_2Cl_2, RT

25) TBAF, THF, RT
26) lithium naphthalenide, THF, –78 ºC

27) AcOH, 50 ºC
28) TFAA, pyridine, THF, 0 ºC ;
aq. $NaHCO_3$, RT
29) $PMBOC(=NH)CCl_3$, TfOH, CH_2Cl_2
30) $LiBH_4$, MeOH, THF, 50ºC
31) $LiAlH_4$, $AlCl_3$, Et_2O/THF (14:1)



III