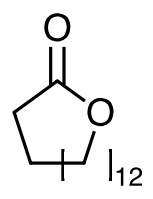
Synthesis Challenge #84

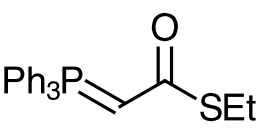
Total Synthesis of a Mycolic Acid from Mycobacterium tuberculosis
N.Tahiri, P. Fodran, D. Jayaraman, J. Buter, M. D. Witte,
T. A. Ocampo, D. B. Moody, I. Van Rhijn, A. J. Minnaard,
Angew. Chem. Int. Ed. **2020**, *59*, 2 – 8
19.3.2020

7)

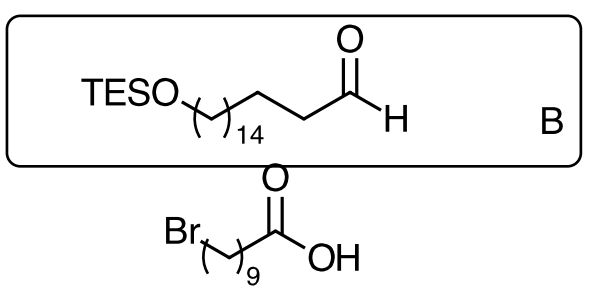


1-3 A

1) DIBAL, CH_2Cl_2, –78°C, 1 h
2) **I**, THF/toluene (2:1), 75°C, 16 h
3) Et_3SiH, Pd/C, acetone, 0°C to rt



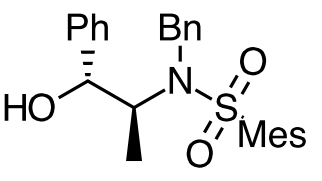
I



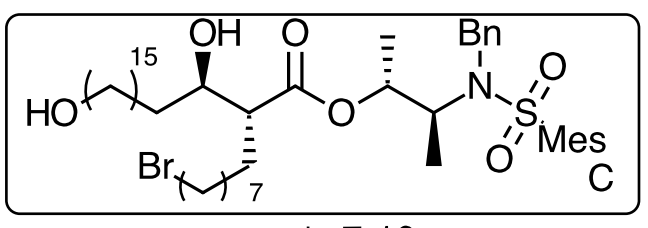
B

4-6

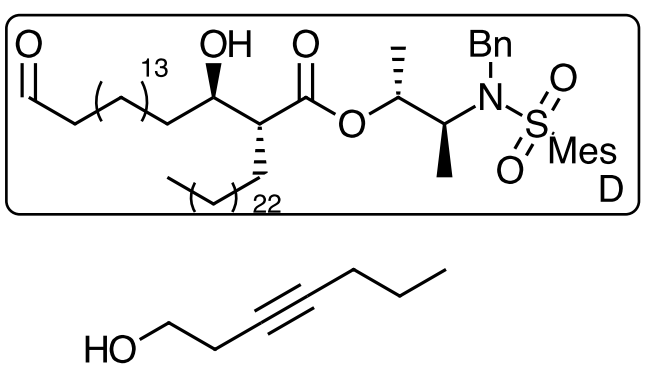
4) $(COBr)_2$, **II**, pyridine, CH_2Cl_2, 0°C to rt, 3 h
5) Cy_2BOTf, NEt_3, THF, –78°C, then B
6) 2M HCl_{aq}, THF, rt, 2 h



II



7-10



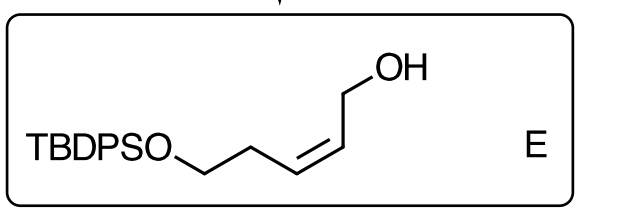
7) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C to rt, 3 h
8) 1-hexadecene, 9-BBN, $Pd(PCy_3)_2$ (10 mol%), $K_3PO_4{\cdot}H_2O$, THF, rt, 16 h
9) pyridine·HF, THF, 0°C to rt, 4 h
10) DMP, CH_2Cl_2, rt 1 h

ABIKO–MASAMUNE Asymmetric Aldol Reaction

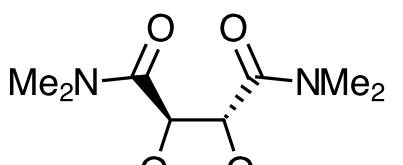
11-14

11) NaH, 1,3-diaminopropane, 70°C
12) TBDPSCl, CH_2Cl_2, 0°C to rt
13) *n*-BuLi, paraformaldehyde, THF, 0°C to rt
14) $NaBH_4$, $Ni(OAc)_2{\cdot}4H_2O$, H_2, ethylenediamine, EtOH, rt

Alkyne zipper reaction

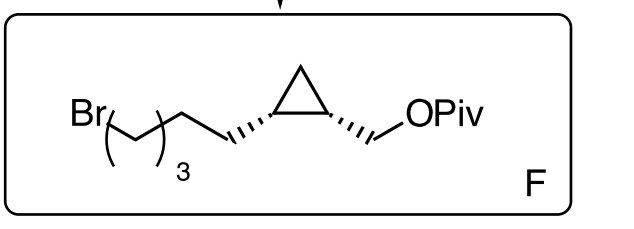


E



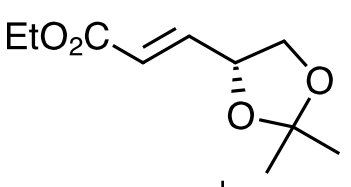
15-18

15) 1,2-dimethoxyethane, diethylzinc, diiodomethane, **III**, CH_2Cl_2, –15°C to rt
16) PivCl, DMAP, pyridine, CH_2Cl_2, 0°C to rt
17) TBAF, THF, 08C to rt, 16 h
18) CBr_4, PPh_3, CH_2Cl_2, 0°C to rt



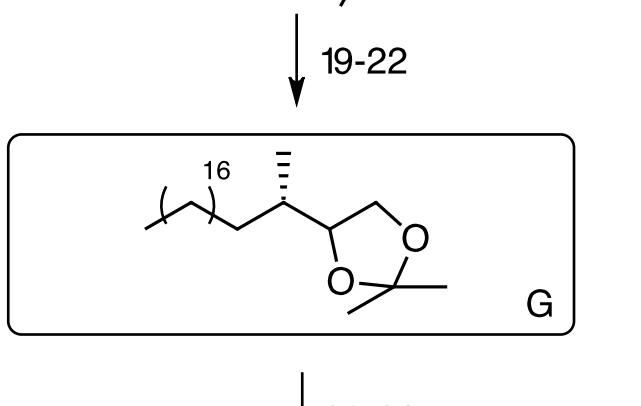
F

IV

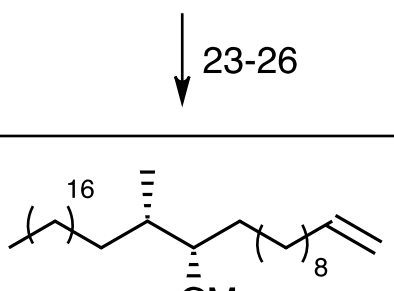


19-22

19) MeLi·LiBr, Et_2O, –78°C
20) $LiAlH_4$, THF, 0°C
21) CBr_4, PPh_3, CH_2Cl_2, 0°C to rt
22) 9-BBN, 1-hexadecene, K_3PO_4, cat. $Pd(PCy_3)_2$, THF

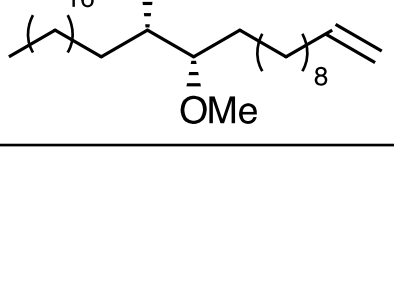


G

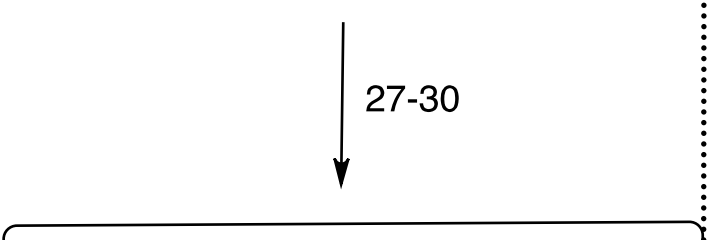


23-26

23) 2M HCl_{aq}, THF, 95°C
24) NaH, tosylimidazole, THF, rt
25) **IV**, CuCl (5 mol%), THF, –10°C
26) MeI, NaH, THF, rt

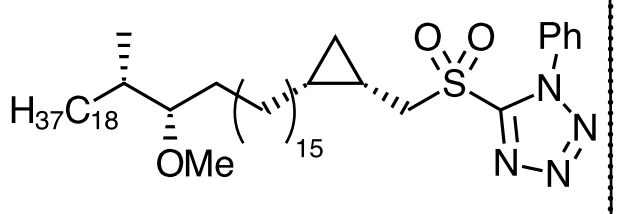


H



27-30

27) 9- BBN, 1-hexadecene, F, K_3PO_4, $Pd(PCy_3)_2$ (7 mol%), THF
28) $LiAlH_4$, THF, 0°C, 15 min
29) phenyl-1H- tetrazole-5-thiol, PPh_3, DIAD, THF, 0°C to rt
30) H_2O_2 (30%), $(NH_4)_6Mo_7O_{28}{\cdot}4H_2O$, THF, EtOH, *n*-BuOH, rt



Julia–Kocienski olefination

31-34

31) LiHMDS, D, –35°C
32) flavine cat., hydrazine hydrate, THF, EtOH, *n*-BuOH, rt, 5–7 d
33) HF·pyridine, $CHCl_3$, 0°C,
34) *n*-Bu_4NOH,(1.5 M in water), THF ,rt

For step 32), see:
J. Org. Chem. **2008**, *73*, 9482 – 9485