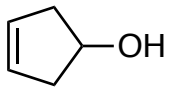
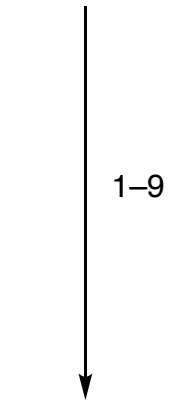
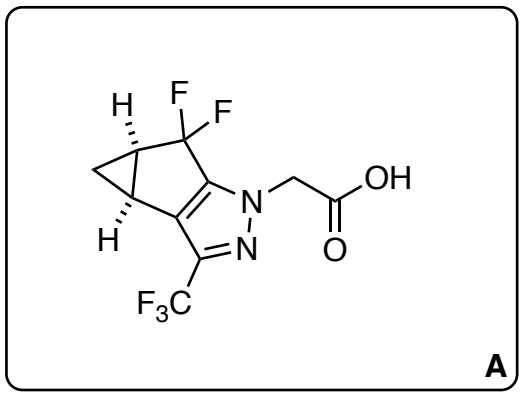
Clinical targeting of HIV capsid protein with a long-acting small molecule

Link, J. O.; Rhee, M. S.; Tse, W. C. *et al.*

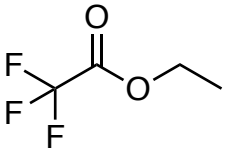
Nature **2020**, *584*, 614–618.



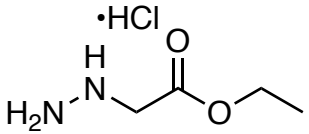




A

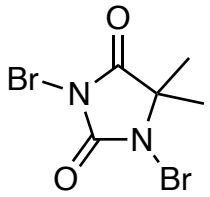


1



2

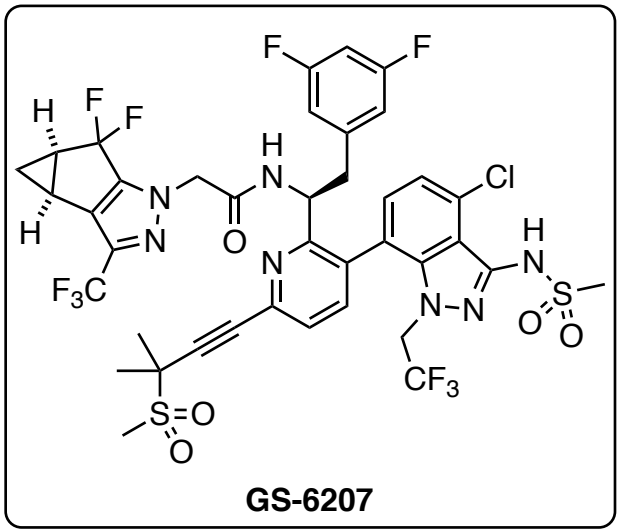
1) $ZnEt_2$, CH_2I_2
2) DMP
3) **1**, LiHMDS
4) **2**, HCl, EtOH
5) $NaClO_2$, NHPI
6) NaOH, MeTHF *then* HCl
7) Ethanedithiol, BF_3•2 AcOH
8) HF•pyridine, **3**
9) Separation of enantiomers by chiral SFC



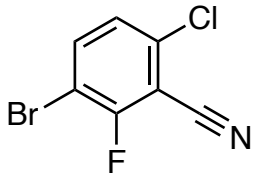
3

1) Please provide the name of this reaction.
Simmons–Smith cyclopropanation

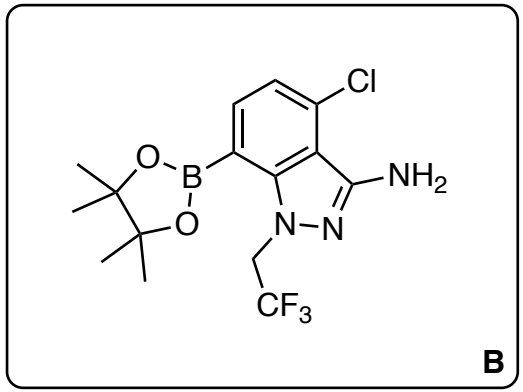
6) Despite its higher cost, MeTHF is normally preferred in process chemistry over THF. Can you state why?
MeTHF is not miscible with water; avoids formation of emulsions during workup; still retains properties of THF



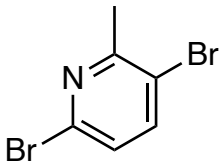
GS-6207



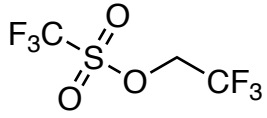
10–13



B

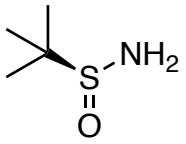


13–18

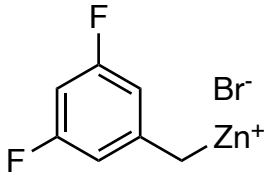


4

10) hydrazine hydrate, Δ
11) **4**, Cs_2CO_3
12) B_2pin_2, $Pd(PPh_3)_2Cl_2$, K(*n*-PrO), Δ



5



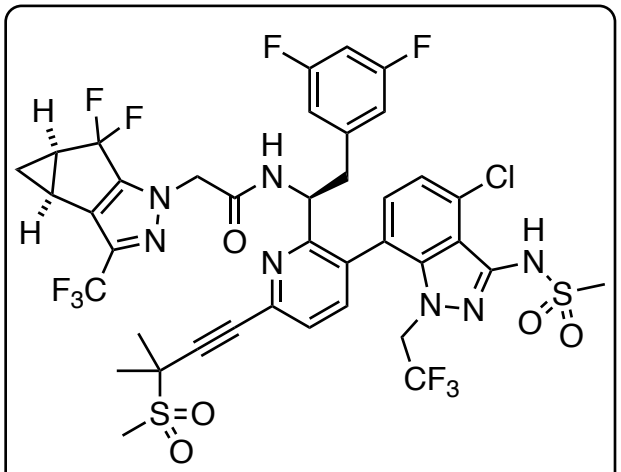
6

13) NBS, AIBN, Δ
14) $AgNO_3$, H_2O, Δ
15) **5**, Cs_2CO_3
16) **6**
17) HCl
18) Boc_2O, $NaHCO_3$, MeTHF, H_2O

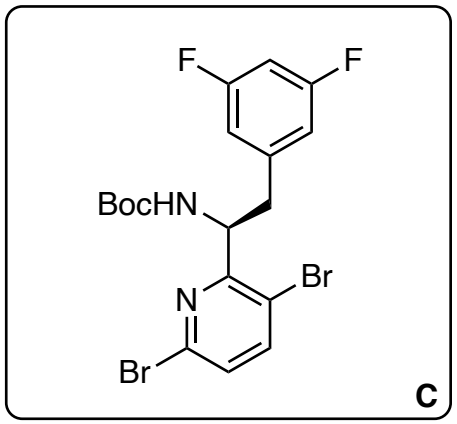
12) Please provide the name of this reaction.
Miyaura borylation

13) Hint: The reaction occurs twice in the same position.

15) Who introduced compound **5**?
Jonathan Ellman

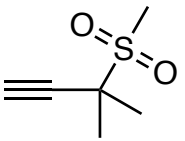


GS-6207



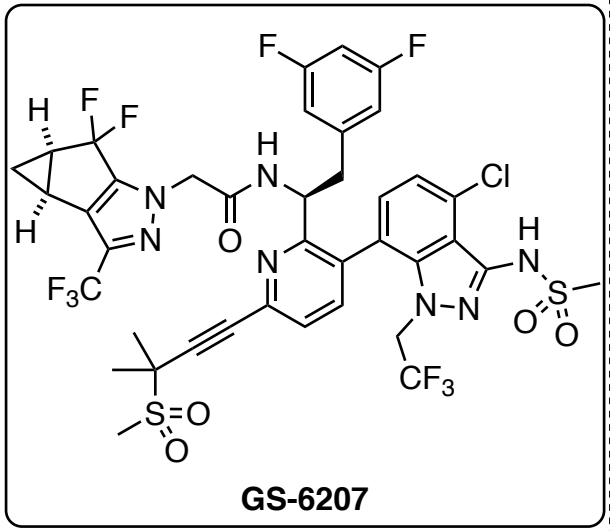
C

19–23



7

19) **7**, CuI, $Pd(PPh_3)_2Cl_2$, Et_3N
20) **B**, $Pd(dppf)Cl_2$, Cs_2CO_3, Δ
21) MsCl, Et_3N
22) TFA
23) **A**, HATU *then* LiOH



GS-6207

GS-6207 (also known as lenacapavir) is a HIV capsid inhibitor and is currently in phase 2/3 clinical trials. It inhibits replication of HIV in cells at 105 pM and significantly reduces the viral load in patiens with multi-drug resistant HIV, while staying at antiviral levels in the plasma over 6 months. In contrast to previous agents that target enzymes in the HIV life cycle (do you know which ones?) GS-6207 actually accelerates capsid assembly, leading to malformed capsids, that can not replicate anymore.