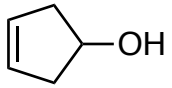
Clinical targeting of HIV capsid protein with a long-acting small molecule

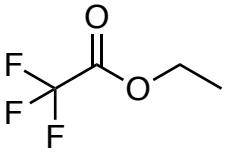
Link, J. O.; Rhee, M. S.; Tse, W. C. *et al.*

Nature **2020**, *584*, 614–618.

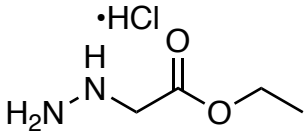


1–9

A

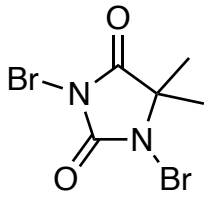


1



2

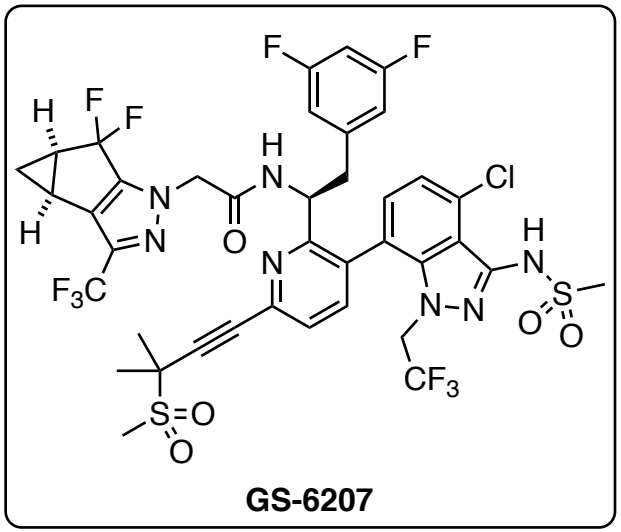
1) $ZnEt_2$, CH_2I_2
2) DMP
3) **1**, LiHMDS
4) **2**, HCl, EtOH
5) $NaClO_2$, NHPI
6) NaOH, MeTHF *then* HCl
7) Ethanedithiol, BF_3•2 AcOH
8) HF•pyridine, **3**
9) Separation of enantiomers by chiral SFC



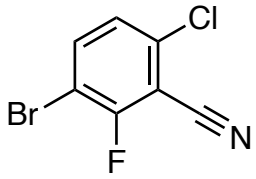
3

1) Please provide the name of this reaction.

6) Despite its higher cost, MeTHF is normally preferred in process chemistry over THF. Can you state why?

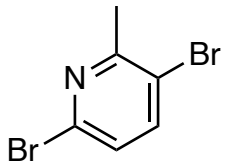


GS-6207

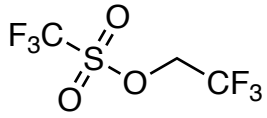


10–13

B

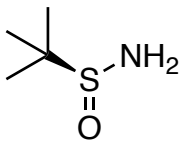


13–18

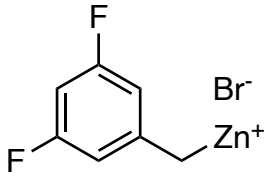


4

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



5



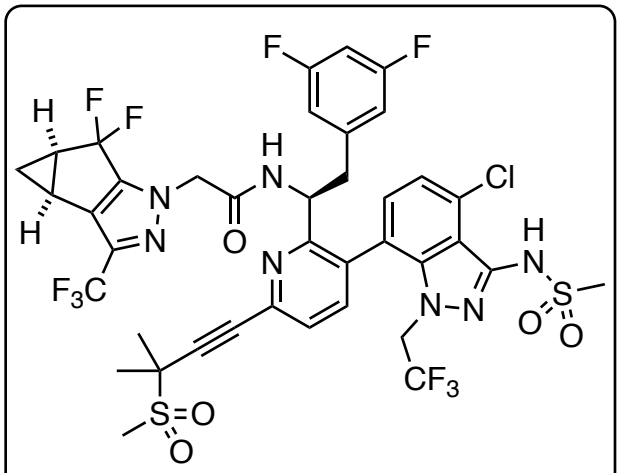
6

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

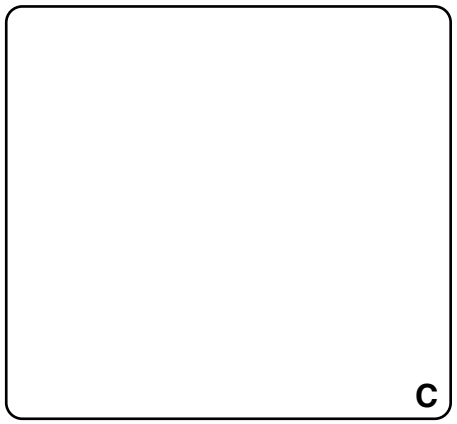
12) Please provide the name of this reaction.

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

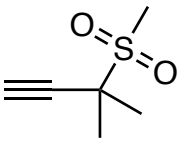
15) Who introduced compound **5**?



GS-6207

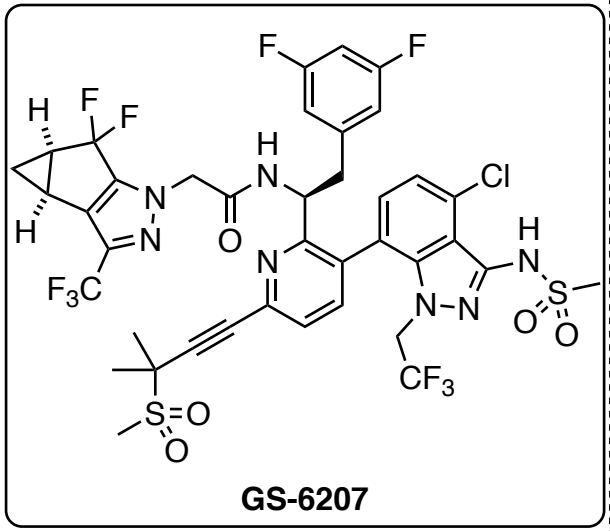


19–23



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.