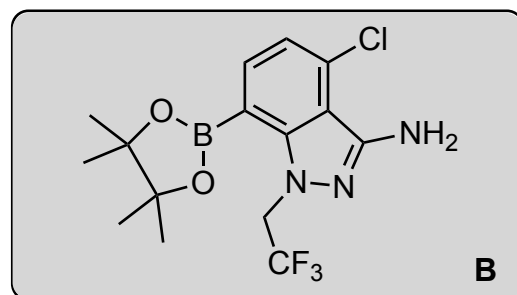
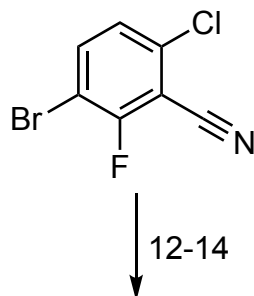
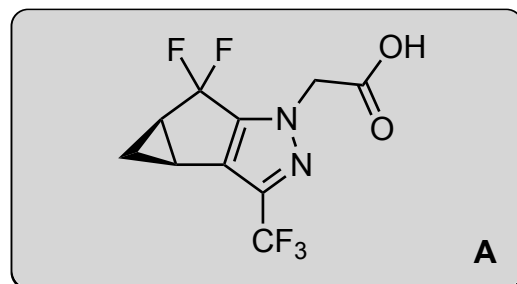
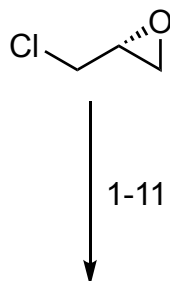


Synthetic Development and Scale-Up of a Complex Pyrazole Fragment of Lenacapavir: Gilead Team, *Org. Process Res. Dev.*, **2024**, 28, 3368-3381

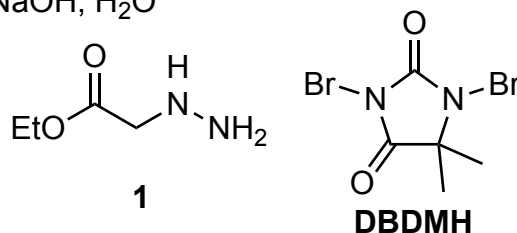
Synthesis of Lenacapavir Sodium: Active Pharmaceutical Ingredient Process Development and Scale-up: Gilead Team, *Org. Process Res. Dev.*, **2024**, 28, 3382-3395

Discovery of Lenacapavir: First-in-Class Twice-Yearly Capsid Inhibitor for HIV-1 Treatment and Pre-exposure Prophylaxis: Gilead Team, *J. Med. Chem.*, **2025**, 68, 21072-21094

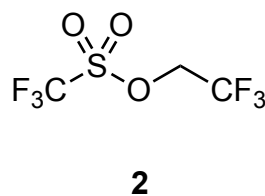
Clinical targeting of HIV capsid protein with a long-acting small molecule: Gilead Team, *Nature*, **2020**, 584, 614-618



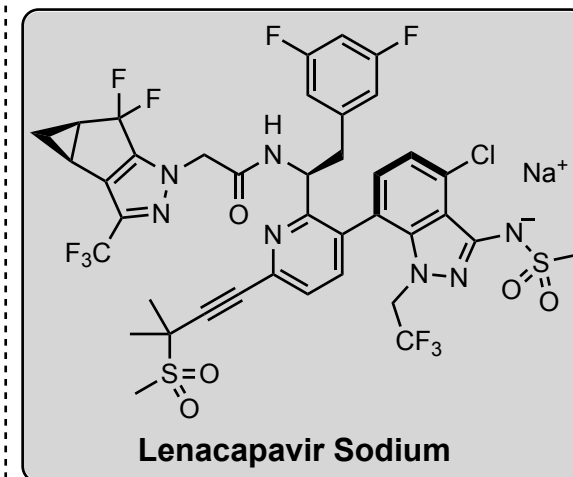
- 1) allyl MgCl, -5°C
- 2) KOH
- 3) *n*-BuLi, 2,2,6,6-TMP, -5°C
- 4) NaOCl, TEMPO
- 5) KO^tBu, CF₃CO₂Et
then NaNO₂, H₃PO₄, H₂O
- 6) (CH₂SH)₂, *p*-TsOH, AcOH
- 7) *p*-TsOH, MEK/H₂O
- 8) LiHMDS, CF₃CO₂Et
- 9) **1**, LiCl, HCl, EtOH
- 10) Olah's reagent, DBDMH
- 11) NaOH, H₂O

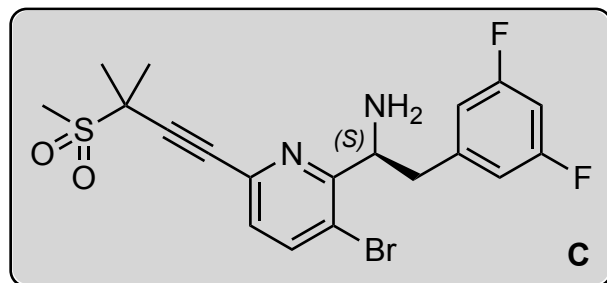
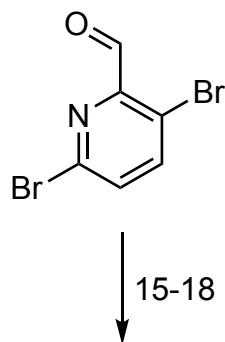


- 12) Hydrazine monohydrate, EtOH, 80°C
- 13) Cs₂CO₃, **2**
- 14) B₂pin₂, Pd(PPh)₂Cl₂, KOAc, 130°C

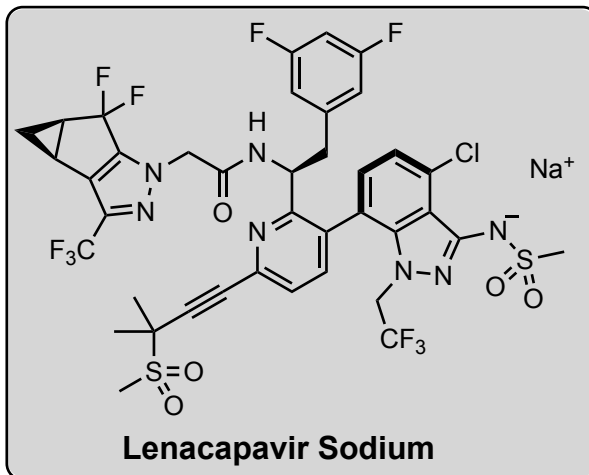


- 1) Name of starting material?
(*R*)-epichlorohydrin
- 3) Hint: 1 ring is broken and 2 rings are formed. Product is 1*R*, 2*R*, 5*S*
Name of reaction?
Hodgson cyclopropanation
- 5) pK_a of H₃PO₄?
pK_{a1}: 2.15, pK_{a2}: 7.20, pK_{a3}: 12.37
No fluorine in product
- 9) Hint: a ring is formed
Name of ring formed?
Pyrazole
- 10) Hint: 2 transformations, start with DBDMH
- 12) Hint: Heterocycle formation
Heterocycle name and pK_a?
Indazole, pK_a = 13.86
- 14) Name of reaction?
Miyaura Borylation

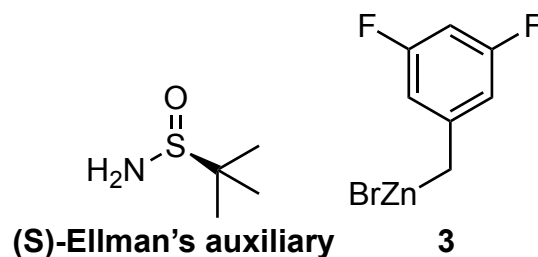




19-22



- 15) (S)-Ellman's auxiliary, Cs_2CO_3
- 16) **3**, DMF
- 17) HCl, ACN, CPME
- 18) 3-methyl-3-(methylsulfonyl)but-1-yne (1 eq.), $\text{Pd}(\text{PPh}_3)_3\text{Cl}_2$, TEA, 75°C

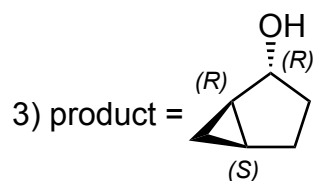
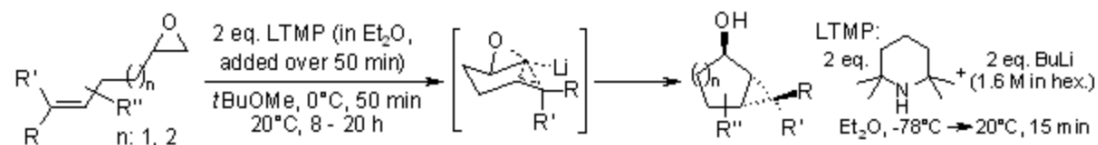


- 19) **A**, T3P, DIPEA
- 20) **B**, PdCl_2 , CyPPh_2 , 70°C , then
MsOH, *n*-PrOH, *n*-Bu₂O
- 21) MsCl (2 equiv.), TEA
- 22) NaOH

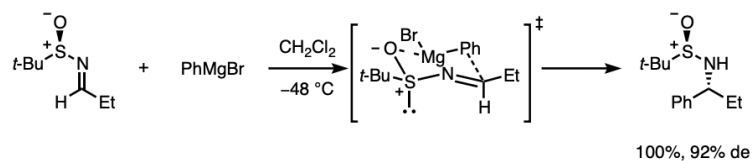
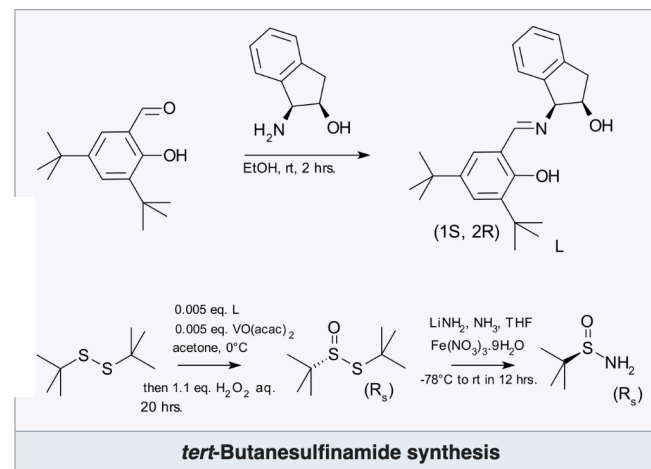
- 15) How is Ellman's auxiliary made?
- 16) Hint: Stereocenter formed is S
Provide a stereochemical rationale
- 18) Hint: The medicinal chemistry route originally included CuI in this step; process development found that removing CuI and increasing to 75°C had better outcomes
What undesired byproduct is formed when CuI is included/name of undesired reaction?
alkyne homocoupling, Glaser coupling

- 20) MsOH, *n*-PrOH, *n*-Bu₂O are added to recrystallize one atropisomer
Name of reaction?
Suzuki coupling

Gilead located in foster city, CA
 Lenacapavir 397 million in sales first half of 2026
 Yeztugo once daily, sunlenca treatment
 inhibits HIV replication by binding capsid protein
 capsid protein - a structural protein in the virus



(1R,2R,5S)-bicyclo[3.1.0]hexan-2-ol



https://myers.faculty.chemistry.harvard.edu/sites/g/files/omnuum7271/files/myers/files/15-ellman_auxiliary.pdf