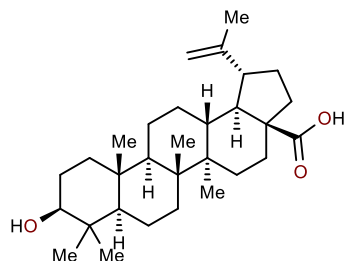


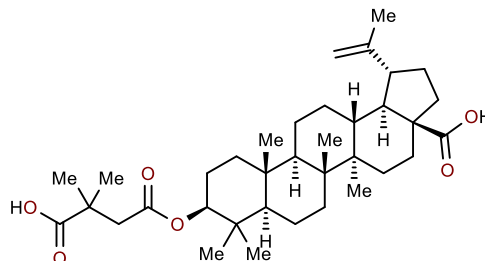
HIV-1 (Human immunodeficiency virus type-1)

- 2020: 38 million patients worldwide
- With modern drugs this disease can be managed
- Different classes of drugs (NRTIs, NNRTIs, PIs, INSTIs, FIs, CCR5 antagonists, CIs)
- Maturation inhibitors (MIs)
- Binding to Gag protein, blocking proteolytic cleavage, release of immature non-infectious virus particles



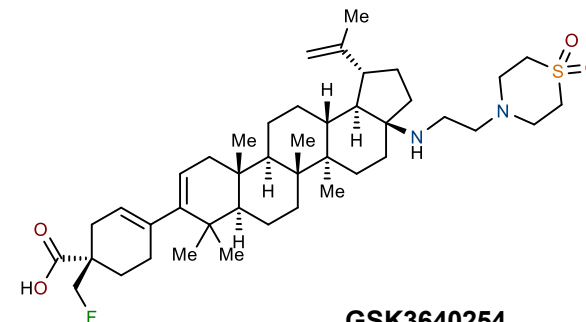
betulinic acid

- naturally occurring (bark of white birch)
 - 418 \$ per 500 mg (Sigma)
- weak inhibitor of HIV-1 replication



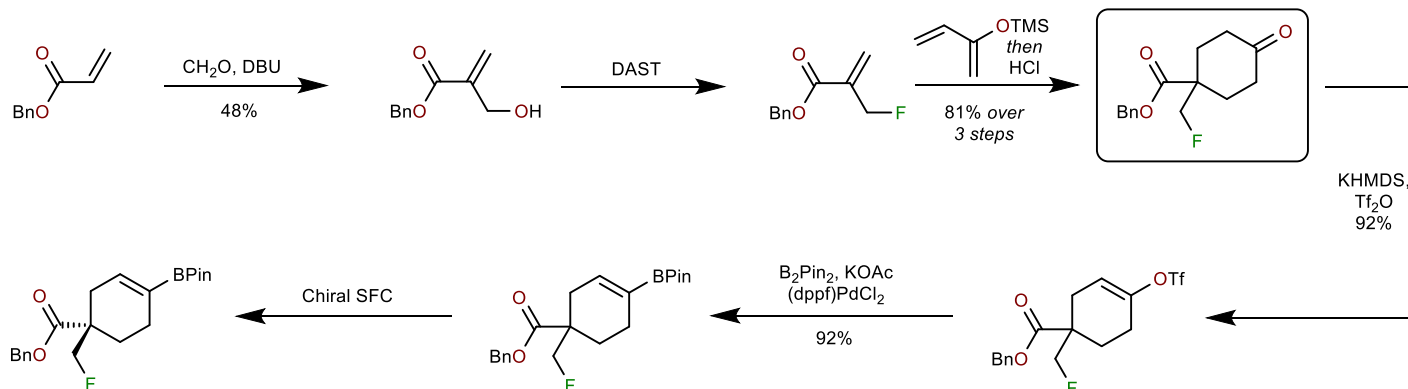
bevirimat (PA-457)

- failed phase II clinical trials
- high protein binding (>99.9%)
- poor aqueous solubility



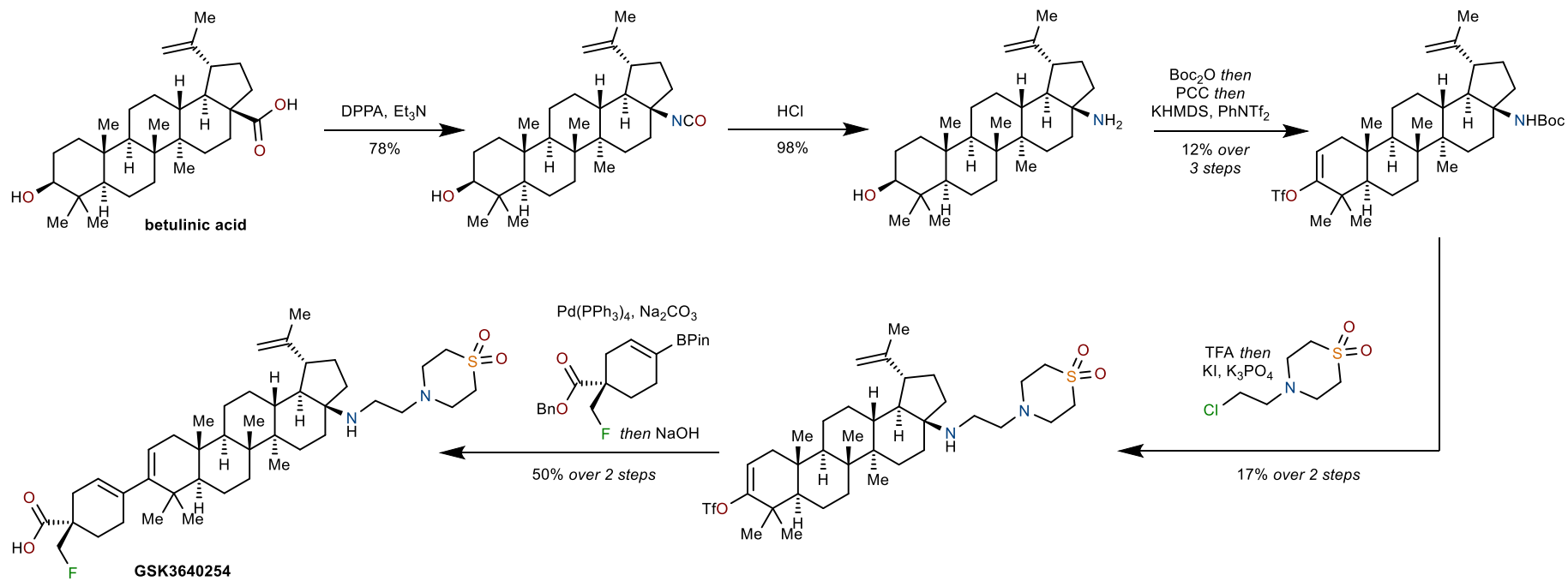
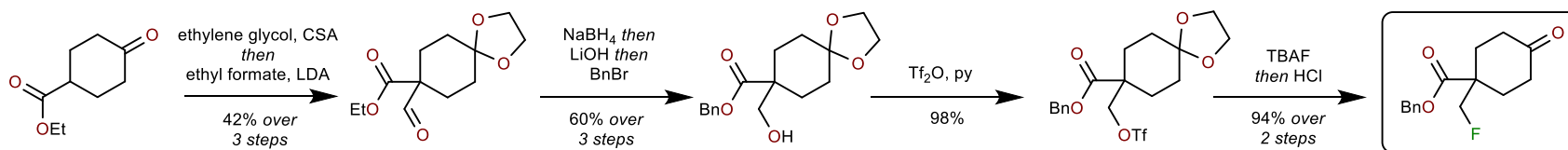
GSK3640254

- phase IIb clinical trials
- lower protein binding (86%)
- undesirable basicity of amine side chain

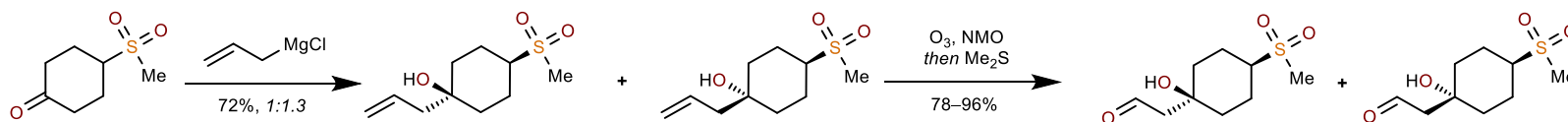
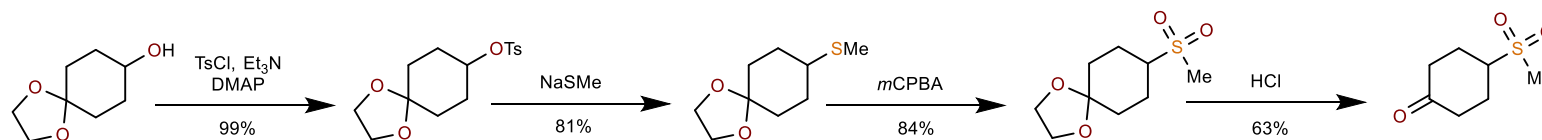
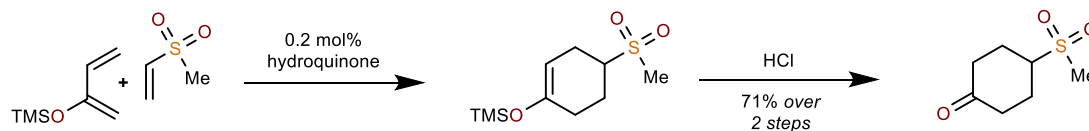
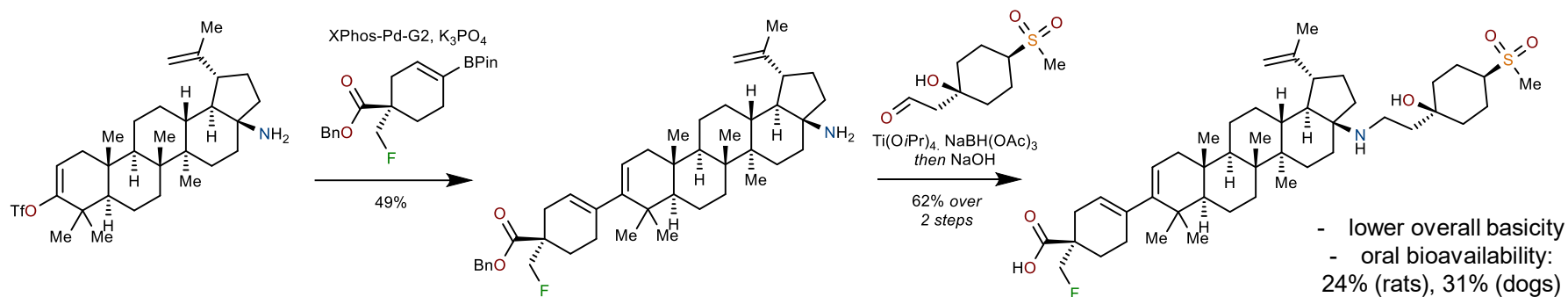


Regueiro-Ren A., Meanwell N. A., K. *J. Med. Chem.* **2022**, 65, 11927. <https://doi.org/10.1021/acs.jmedchem.2c00879>

Scalable route to ketone intermediate



Synthesis of an improved derivative



Hartz R. A., *J. Med. Chem.* **2022**, 65, 15935. <https://doi.org/10.1021/acs.jmedchem.2c01618>