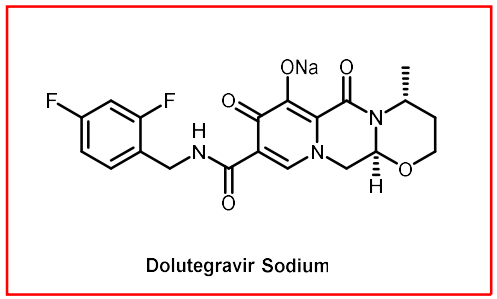
POTW: Dolutegravir Sodium (Tivicay)

SHIONOGI

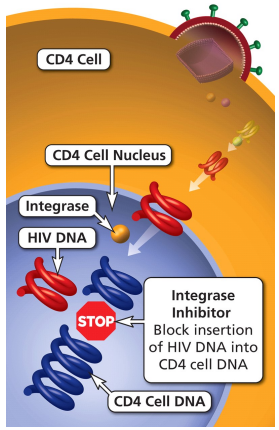
ViiV Healthcare

J. Med. Chem. **2012**, *55*, 8735−8744.
J. Med. Chem. **2013**, *56*, 1124−113.
Org. Process Res. Dev. **2019**, *23*, 558−564.
Org. Process Res. Dev. **2019**, *23*, 565−570.

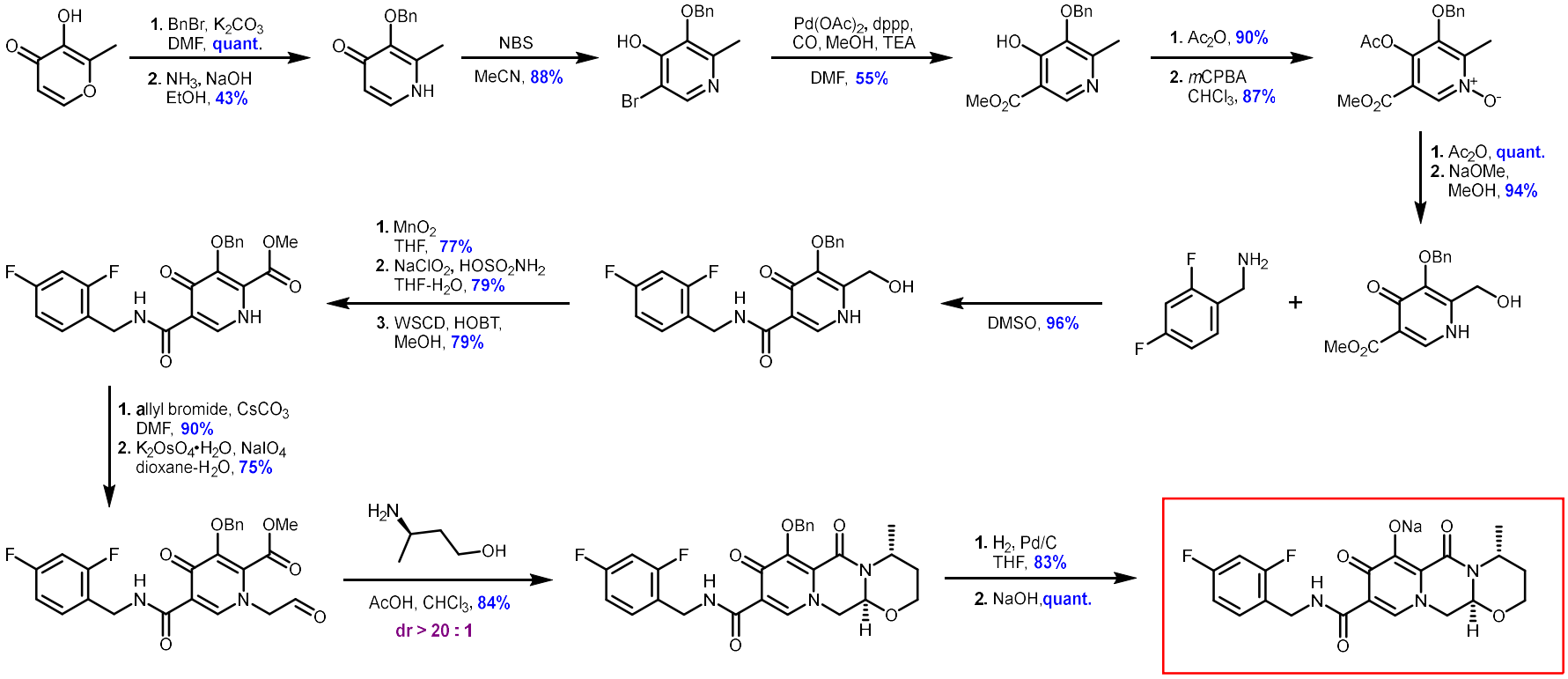


Dolutegravir Sodium

- Integrase inhibitor for HIV-1/AIDS that blocks the strand transfer step of integration in the viral genome into the host cell (INSTI)
- Two metal binding pharmacophore, chelating to both Mg^{2+} sites of the enzyme
- High antiviral activity and high genetic barrier to resistance
- IC_{50} ($^{MT4}PAIC_{50}$) of 38.4 ng/mL
- bioavailability of 53.4%
- 130 ng/mL of plasma concentration at 24 h postdosing (C_{24})
- no CYP inhibition nor metabolic concerns
- FDA approved on August 12, 2013



Discovery Route:



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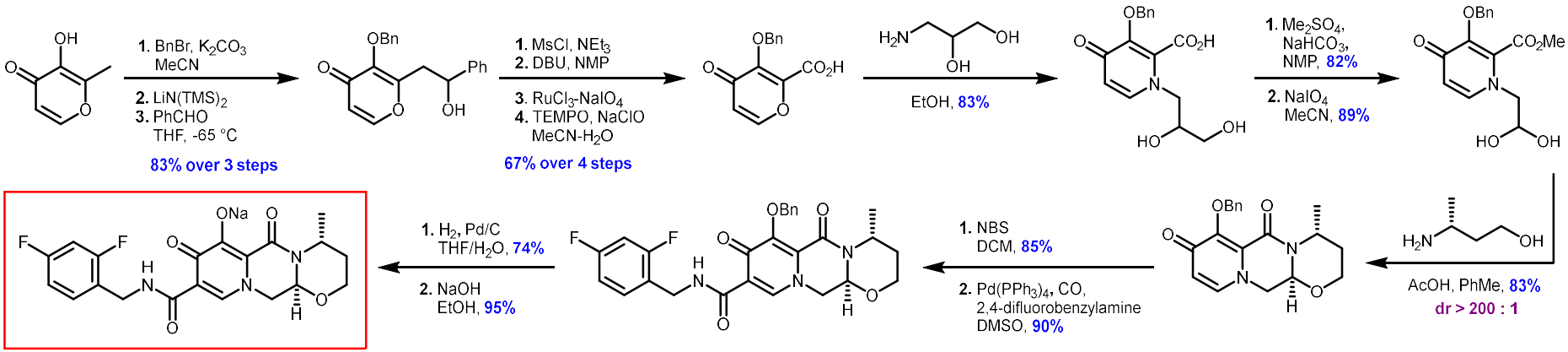
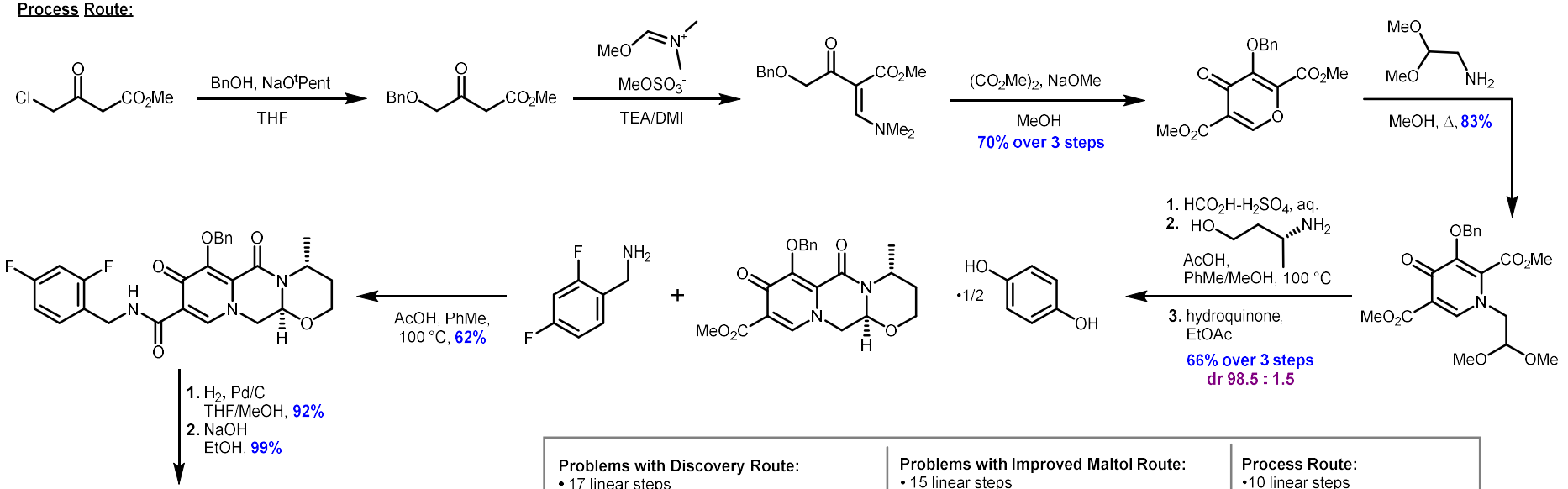
Improved Maltol Route:



Process Route:



Problems with Discovery Route:
- 17 linear steps
- 2% overall yield
- maltol functionalization strategy not practical for scale production
- numerous chromatographic purifications
- includes oxidative cleavage and bromination

Problems with Improved Maltol Route:
- 15 linear steps
- 15% overall yield
- includes cryogenic reaction
- includes oxidative cleavage and bromination
- use of heavy metals

Process Route:
- 10 linear steps
- 22% overall yield
- no cryogenic steps
- no oxidation
- practical for scale production
- each intermediate crystalline
- no chrmoatographic purification
- improved atom efficiency
- increase atom economy