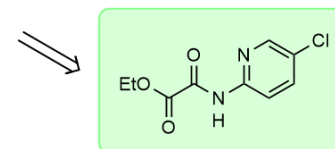
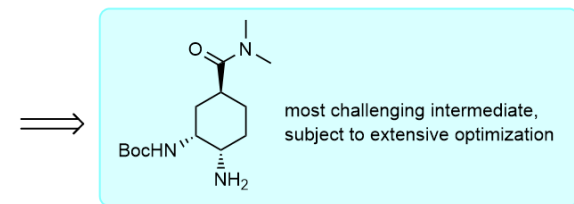
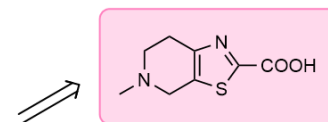
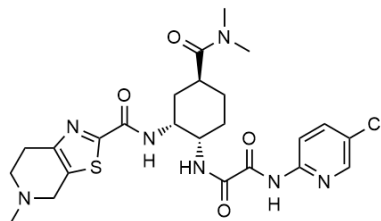
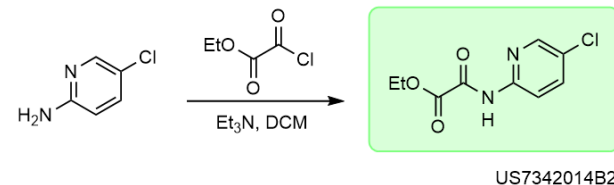
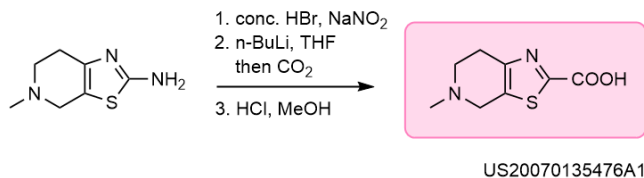
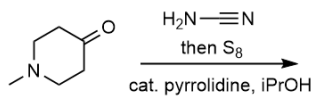


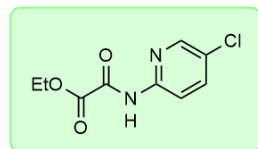
Background:

- Edoxaban is a direct oral anticoagulant that inhibits Factor Xa in the coagulation cascade
- Used to prevent stroke in patients with atrial fibrillation and to prevent Venous Thromboembolism (a clot lodged in the lung)
- Fewer drug interactions and risks than traditional anticoagulants like warfarin, which has a narrow therapeutic index
- Sold as Savaysa (US, FDA approved 2015) and Lixiana (EU, approved 2015)

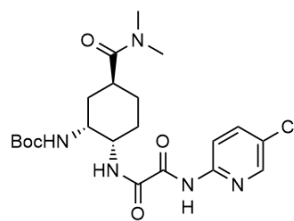
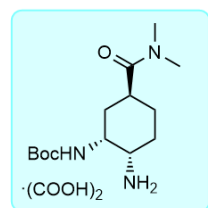
Org. Process Res. Dev. 2019, 23, 524

**Synthesis of other fragments:****Endgame:**

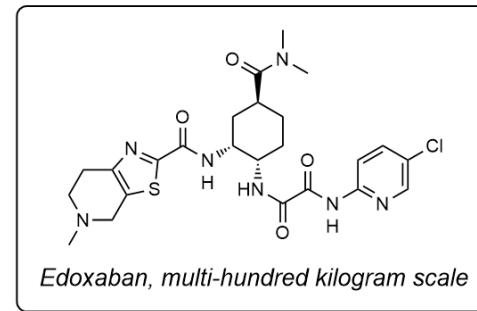
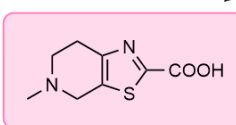
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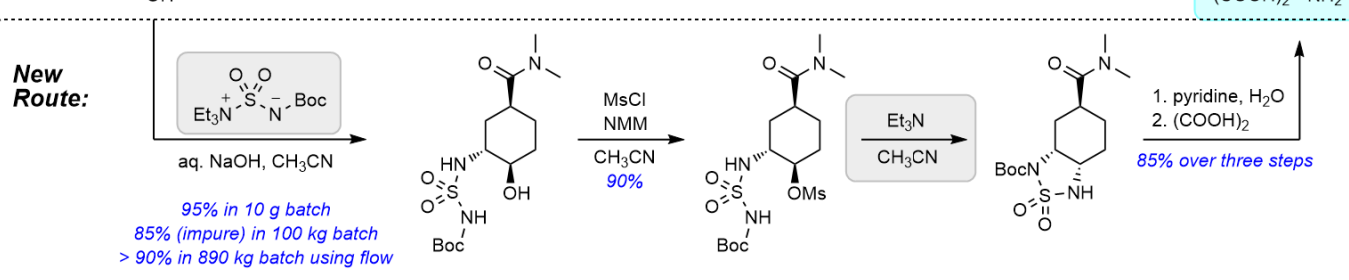
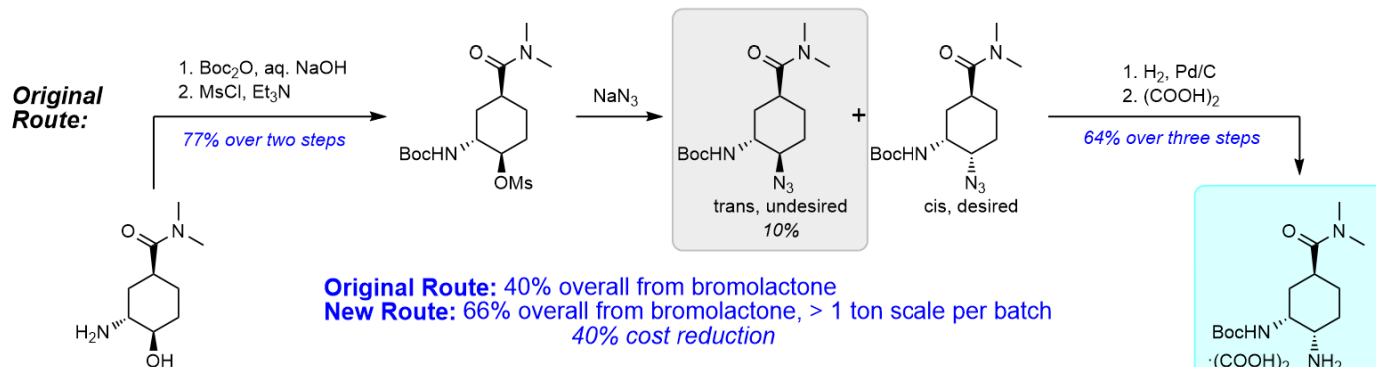
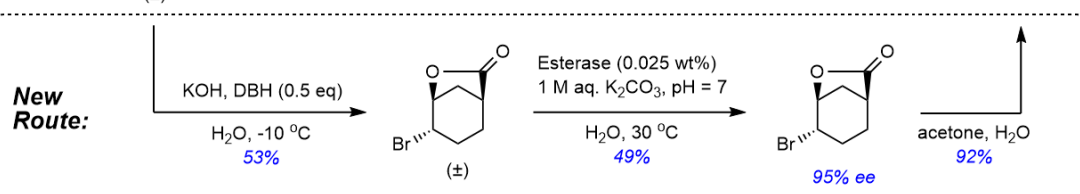
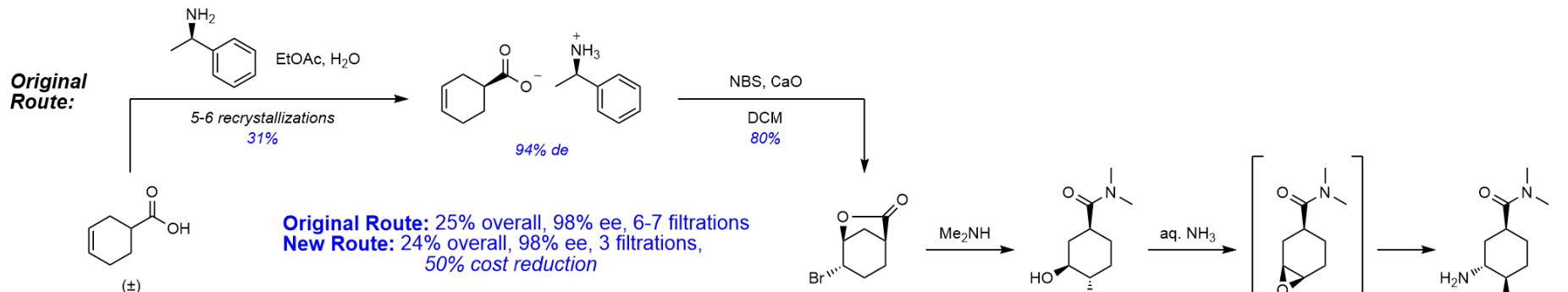


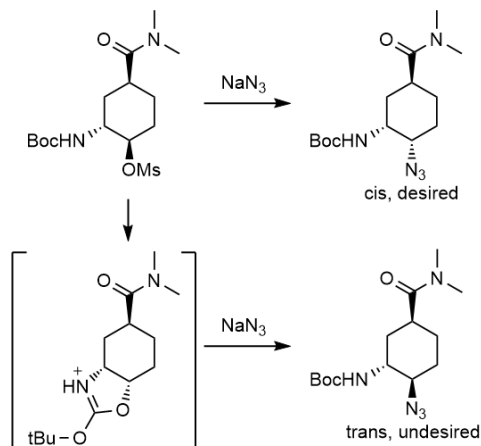
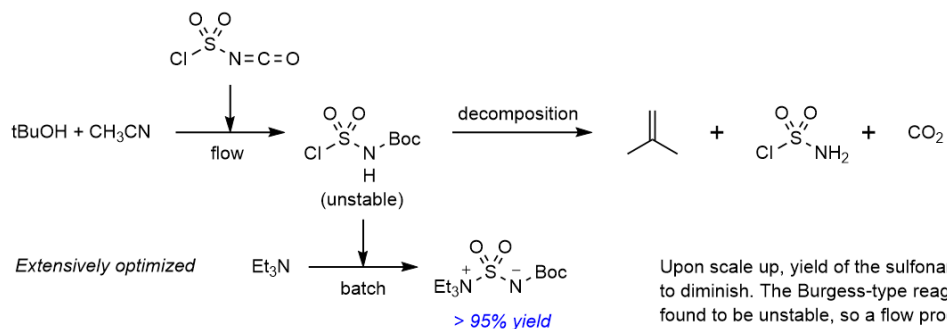
1. LiOH, H₂O
2. HOBt, EDC·HCl, DMF



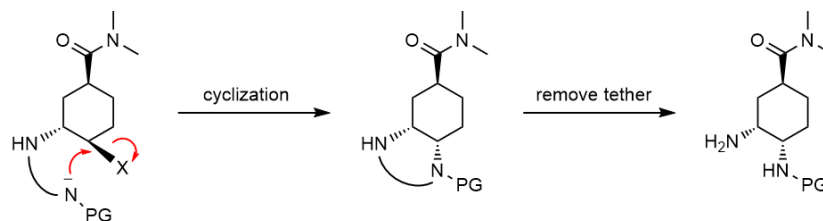
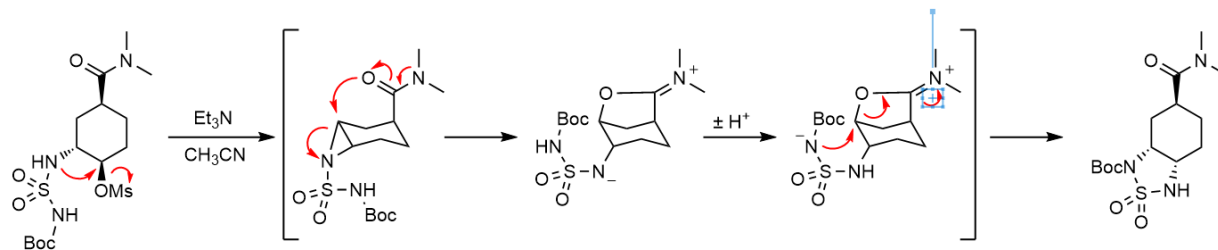
1. HCl, H₂O
2. HOBt, EDC·HCl, DMF





Trans side product inspired new approach:**Flow development to facilitate scale-up:**

Upon scale up, yield of the sulfonamide began to diminish. The Burgess-type reagent was found to be unstable, so a flow process was developed to generate it for immediate use.

New Strategy:**Proposed mechanism to explain actual product observed:**

Note: When an ethyl ester analogue was subjected to these conditions, only the aziridine was isolated

