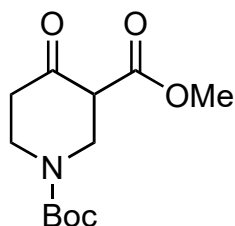


Scalable, Stereoselective Second-Generation Route for CXCR7 Antagonist ACT-1004-1239

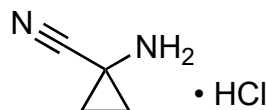
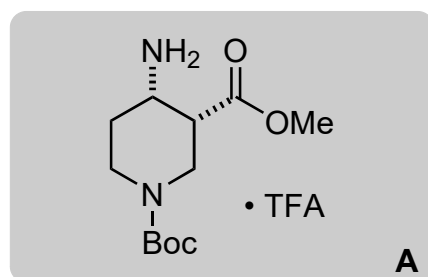
G. Schäfer, T. Fleischer, A. Merot, M. Erhardt, B. Mathys, *Org. Process Res. Dev.* **2024**, 28, 2103.

G. Schäfer, T. Fleischer, M. Ahmetovic, P. Guerry, S. Abele, *Org. Process Res. Dev.* **2024**, 28, 2090.

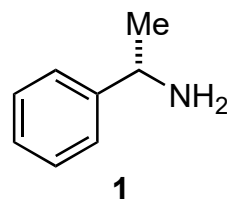
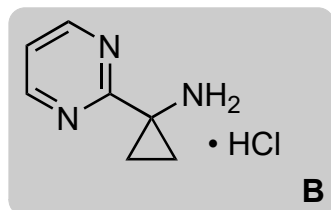
G. Schäfer, M. Ahmetovic, T. Fleischer, S. Abele, *Org. Process Res. Dev.* **2020**, 24, 1735.



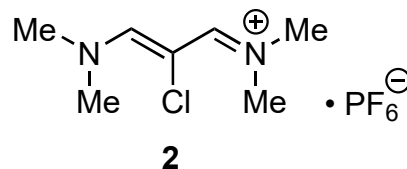
1-3



4-8

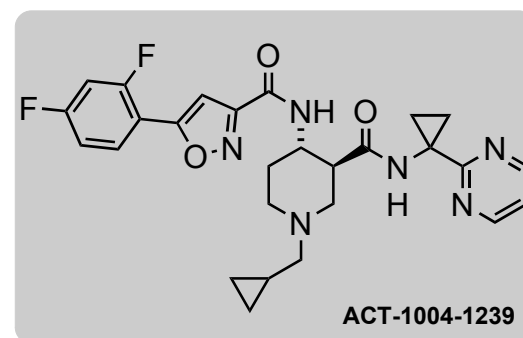


- 1) Na_2SO_4 , 2-MeTHF, **1**, r.t., 14 h
- 2) NaBH_4 , 2-Me-THF, addition of TFA at -15°C then addition of solution from Step 1
- 3) H_2 (1 bar), $\text{Pd}(\text{OH})_2/\text{C}$ (10% w/w), MeOH, r.t., 2 h

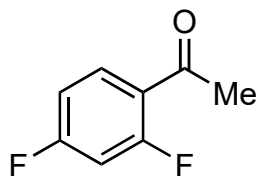


- 4) CbzCl, NaHCO_3 , 2-Me-THF/ H_2O 1:1, r.t., 1 h
- 5) AcCl, MeOH, TBME, 0°C to r.t., 16 h
- 6) 7 N NH_3 in MeOH, MeOH, r.t., 2 h
- 7) **2**, NMM, DMAc, 75°C , 3 h
- 8) $\text{Pd}(\text{OH})_2/\text{C}$, NaOMe, MeOH, H_2 (1 bar), 1-2 h, r.t. then iPrOH / 5 M HCl in iPrOH

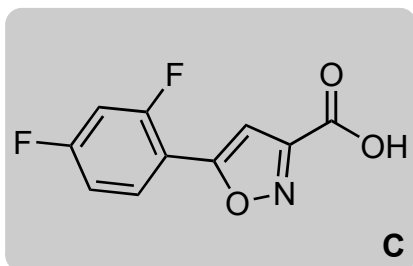
- 1) PDT of step 1 kept as a solution
- 2) Hint: PDT of step 2 is a result of selective crystallization of the cis-3R,4S enantiomer as a TFA salt



- 5) What functional group is generated?
An imide
- 6) What functional group is generated?
An amidine

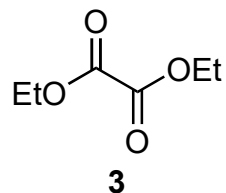
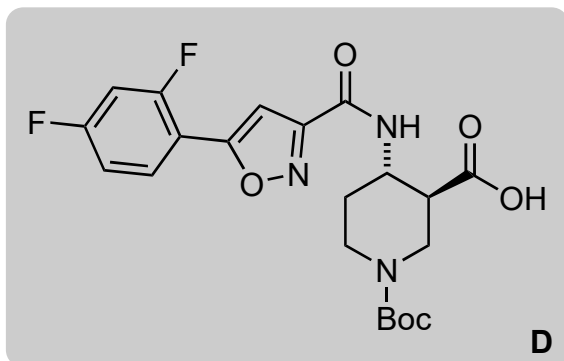


9-11



A + C

12-14

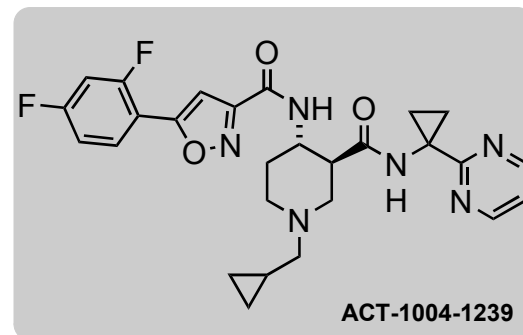


- 9) **3**, NaOEt in EtOH, THF, r.t., 15 min
 10) $\text{NH}_2\text{OH} \cdot \text{HCl}$, EtOH, 60 °C, 1.5 h
 11) 1 M aq. NaOH, THF, 40 °C, 15 min

- 12) CDI, DMSO, r.t., 30 min
 13) KOiPr, iPrOH, r.t., 2 h
 14) 2 M aq. KOH, iPrOH, -5 °C, 24 h

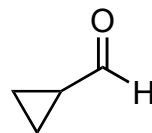
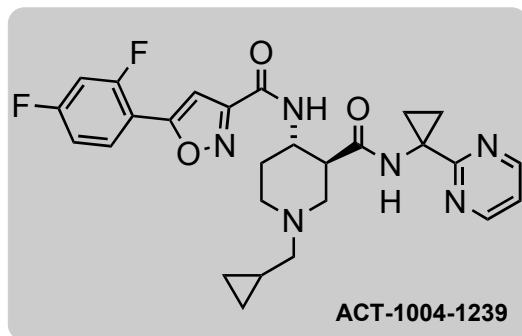
- 9) Name of reagent **3**?
 Diethyl oxalate
 10) Name of rxn?
 Claisen isoxazole synthesis

- 12) Name three more reagents that are suitable for this rxn.
 T3P, DCC, EDC, HATU, etc.
 13) Hint: Transesterification occurs followed by epimerization
 - Provide a reason why iPrOH, KOiPr conditions were chosen. Steric bulk



D

15-17

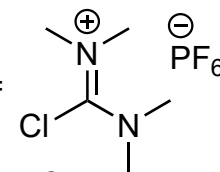


4

- 15) **B**, TCFH, NMI, MeCN, r.t., 30 min
16) 5-6 M HCl in iPrOH, iPrOH, 50 °C, 5 h
17) **4**, NaBH(OAc)₃, NEt₃, DMSO, r.t., 30 min

15) Hint:

TCFH =



17) Name of rxn?

Reductive amination