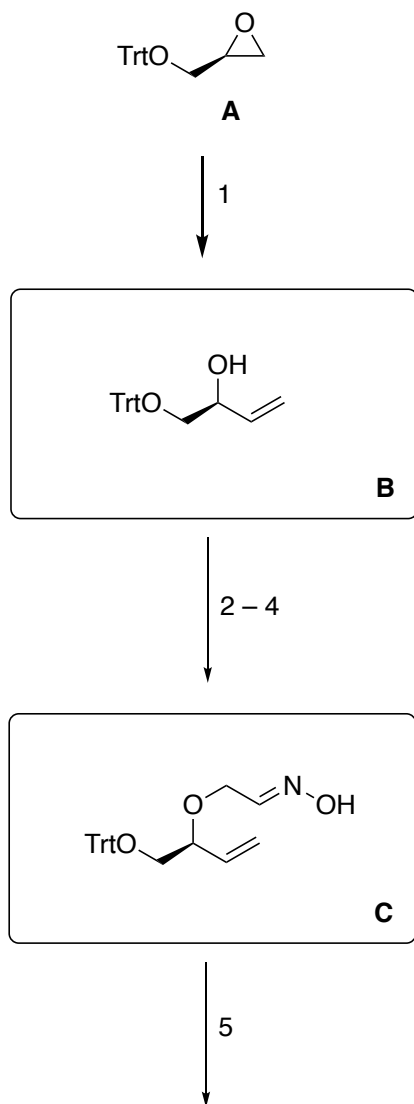
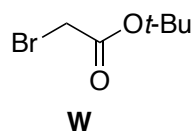


A selective BACE-1 inhibitor for the treatment of Alzheimer's disease

Jeffery Richardson,* Peter J. Lindsay-Scott, Vladimir Larichev, and Emily Pocock
Org. Process Res. Dev. **2020**, *24*, 2853–2863.
U.S. Patent 20,190,106,434 A1, 2019.



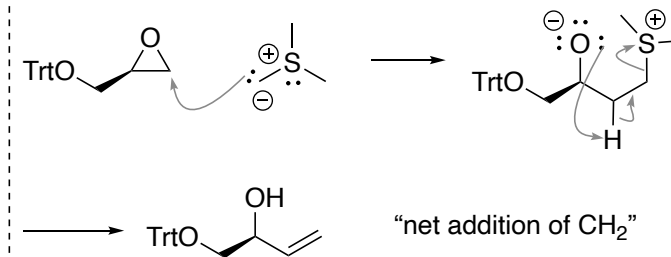
1) Me_3Si (3 eq.), $n\text{-BuLi}$ (3 eq.), then **A**



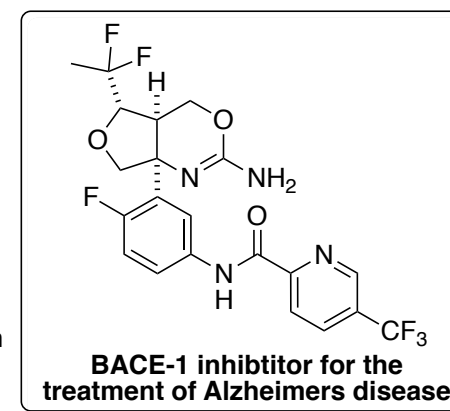
2) **W**, $(\text{Bu}_4\text{N})_2\text{SO}_4$, NaOH (aq.)
3) DIBAL-H
4) $\text{NH}_2\text{OH} \cdot \text{HCl}$, NaOAc

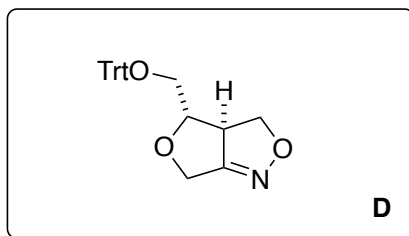
5) NaOCl

Please provide a mechanism for this transformation.

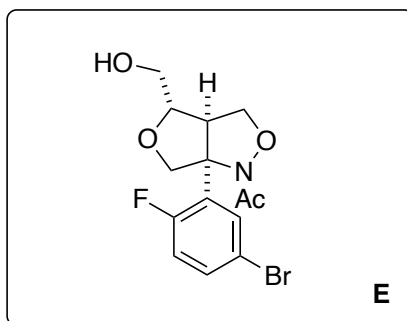


Please provide a mechanism for this transformation.

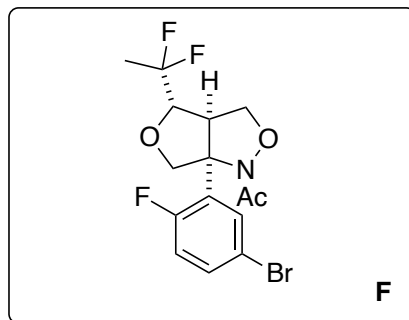




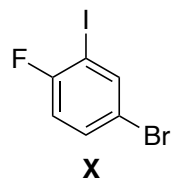
6 – 8



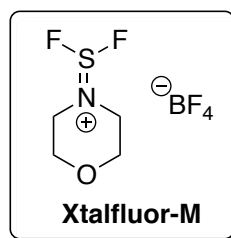
9 – 12



13, 14

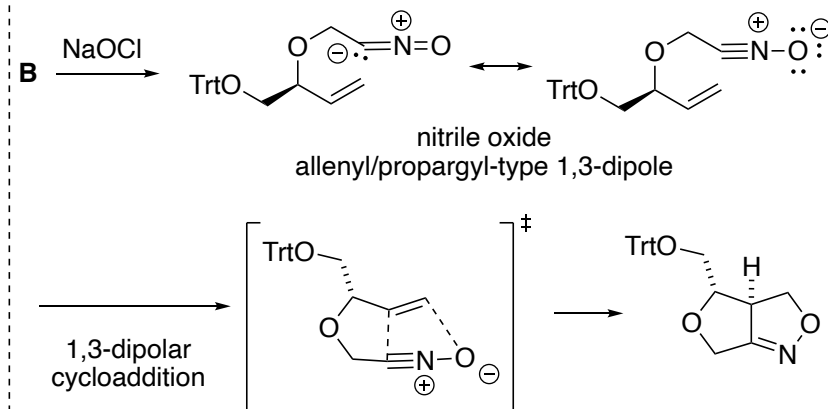


- 6) **X**, *i*-PrMgCl • LiCl
then BF₃ • OEt₂
- 7) AcCl, DMAP, pyridine
- 8) HCO₂H

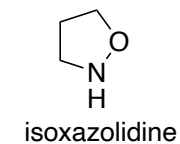
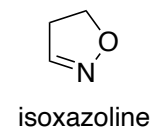


- 9) TEMPO, PIDA
- 10) CDI, then MeHNOMe • HCl
- 11) MeMgBr, then HCl
- 12) Xtalfluor-M (3.1 eq.),
3 HF • Et₃N (2.2 eq.)

- 13) HCl (aq.)
- 14) Zn (4.5 eq.), AcOH/H₂O (1:1)



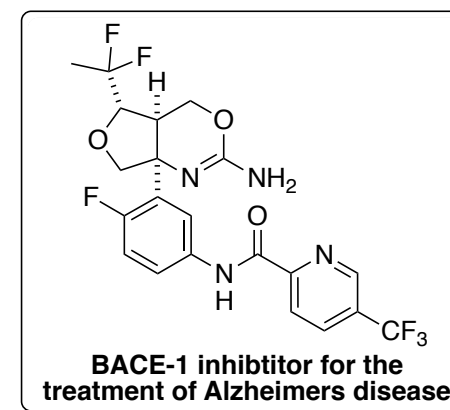
Name the heterocycles before and after conducting step 6.

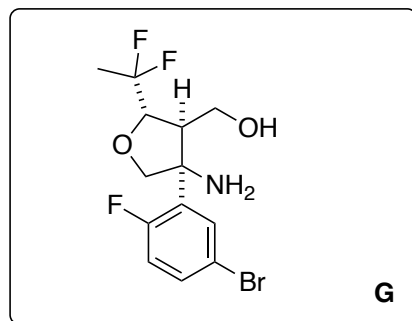


Do you know an alternative name for CDI?

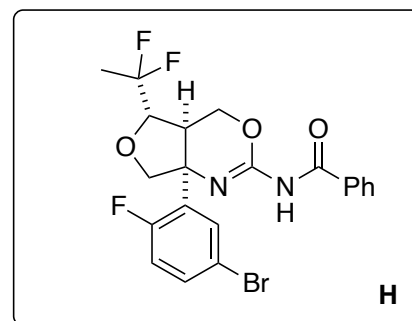
Staab's reagent

Can you propose a mechanism for the transformation in step 12?

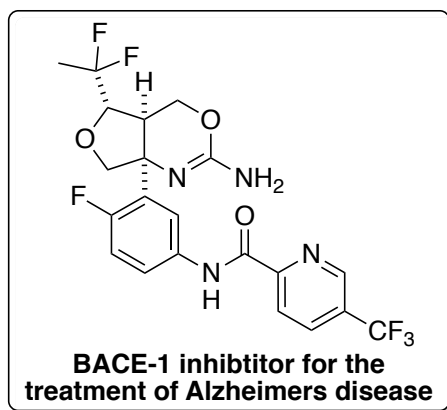




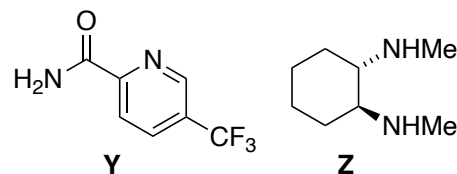
15



16, 17



15) PhCONCS,
then DMSO, TMS-Cl

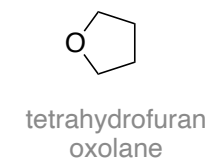
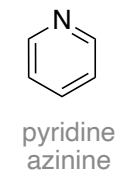
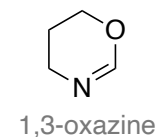


16) **Y** (2 eq.), **Z** (30 mol%), CuI (10 mol%),
NaI (2 equiv.), K₂CO₃, 4 Å MS
17) MeONH₂ · HCl, pyridine

KEY step: This transformation has been performed on >500 g scale and provided **H** in 96% yield. Please provide a mechanism.

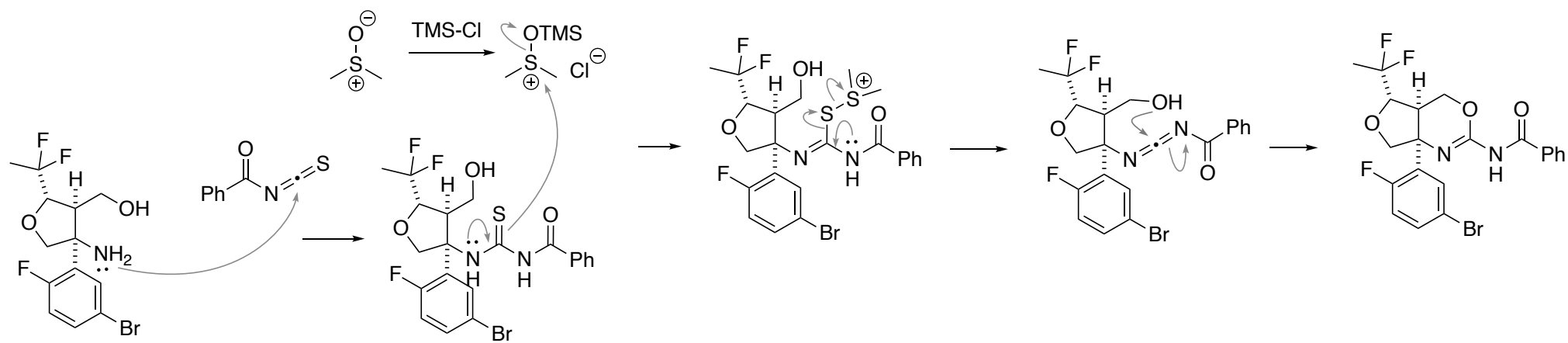
Step 16:
aromatic Finkelstein-type reaction
S. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 14844–14845.

Name the heterocycles present in the final compound. Provide the IUPAC names according to Hantzsch-Widman nomenclature and the trivial names if applicable.



BACE-1 is an aspartic acid protease that is responsible for the generation of amyloid- β peptides in neurons. Inhibition would prevent the accumulation and aggregation of A β in the brain of Alzheimer's patients, thus could help slow or stop the disease.

Mechanism of step 15



Proposed mechanism for step 12

