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

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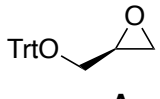
Org. Process Res. Dev. **2020**, *24*, 2853–2863.
U.S. Patent 20,190,106,434 A1, 2019.



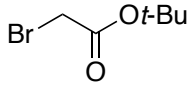
A

1

1) Me_3SI (3 eq.), *n*-BuLi (3 eq.), *then* **A**

Please provide a mechanism for this transformation.

B



W

2 – 4

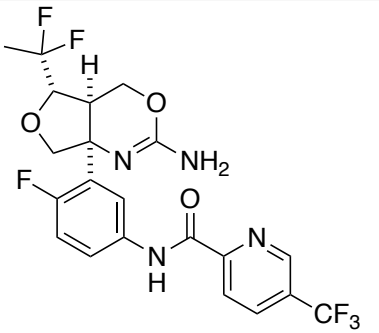
2) **W**, $(Bu_4N)_2SO_4$, NaOH (aq.)
3) DIBAL-H
4) $NH_2OH \cdot HCl$, NaOAc

C

5

5) NaOCl

Please provide a mechanism for this transformation.



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D

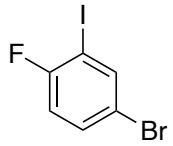
6 – 8

E

9 – 12

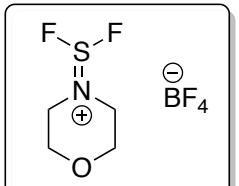
F

13, 14



X

6) **X**, iPrMgCl • LiCl
then BF_3 • OEt_2
7) AcCl, DMAP, pyridine
8) HCO_2H



Xtalfluor-M

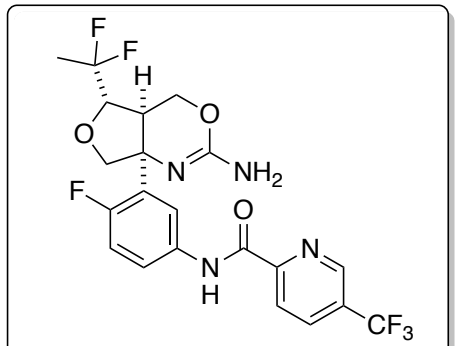
9) TEMPO, PIDA
10) CDI, *then* MeHNOMe • HCl
11) MeMgBr, *then* HCl
12) Xtalfluor-M (3.1 eq.),
3 HF • Et_3N (2.2 eq.)

13) HCl (aq.)
14) Zn (4.5 eq.), AcOH/H_2O (1:1)

Name the heterocycles before and after conducting step 6.

Do you know an alternative name for CDI?

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



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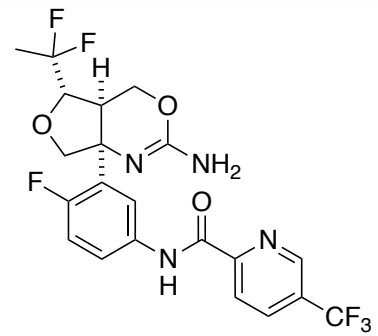
G

15

H

16, 17



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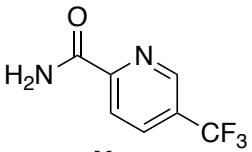
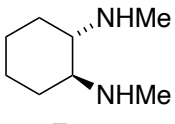
15) PhCONCS,
then DMSO, TMS-Cl



Y



Z

16) **Y** (2 eq.), **Z** (30 mol%), CuI (10 mol%), NaI (2 equiv.), K_2CO_3, 4 Å MS

17) $MeONH_2$ • HCl, pyridine

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 Aβ in the brain of Alzheimer's patients, thus could help slow or stop the disease.

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

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