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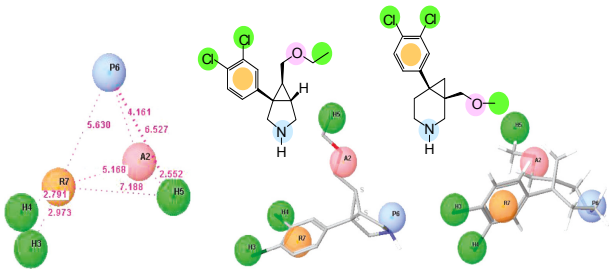
Medicinal Chemistry Case Study: Triple Reuptake Inhibitors (TRUI) Project

Objective:

• Discovery of novel highly potent and selective chemical entities able to influence the reuptake of three aminergic neurotransmitters (serotonin/noradrenaline/dopamine) by their transporters (SERT≥NET>DAT)

Challenge:

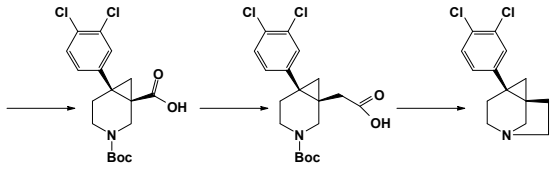
• To find synthetic pathways towards a novel class of potential triple monoamine reuptake inhibitors, with a"cage" substructure not published previously



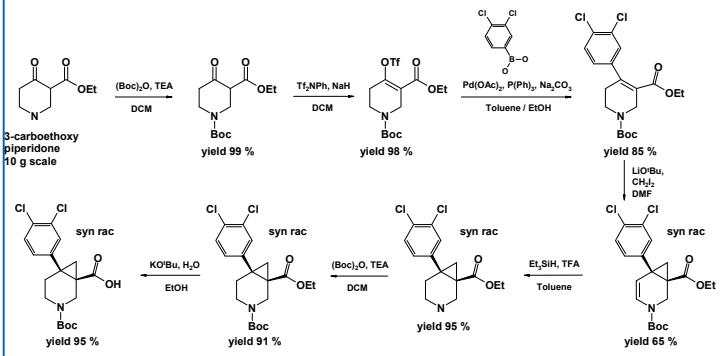
Secondary/tertiary amine fundamental for achieving the primary activity at the three transporters
Decoration of the aromatic region provides an appropriate "titration" of the SERT/NET/DAT components

Key steps in synthetic approach:

- Synthesis of azabicyclo[4.1.0]heptane scaffold
- Carboxylic acid C-1 homologation
- Final cyclization of "cage" structure



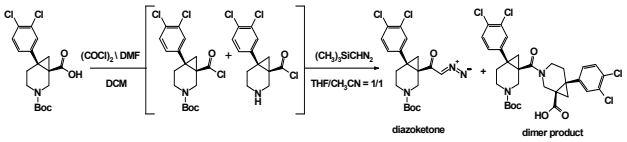
Synthesis of azabicyclo[4.1.0]heptane scaffold:



Carboxylic acid C-1 homologation

7 steps synthesis on 10 g scale of crucial carboxylic acid intermediate A was performed using known conditions, method robust enough for kg scale (44% yield)

Development of one-carbon carboxylic acid homologation by Arndt-Eistert reaction



Challenge:

- Avoiding the formation of dimer product due to the Boc-deprotection by HCl formed in the reaction mixture

Solution:

- Addition of base (TEA) in the first reaction step

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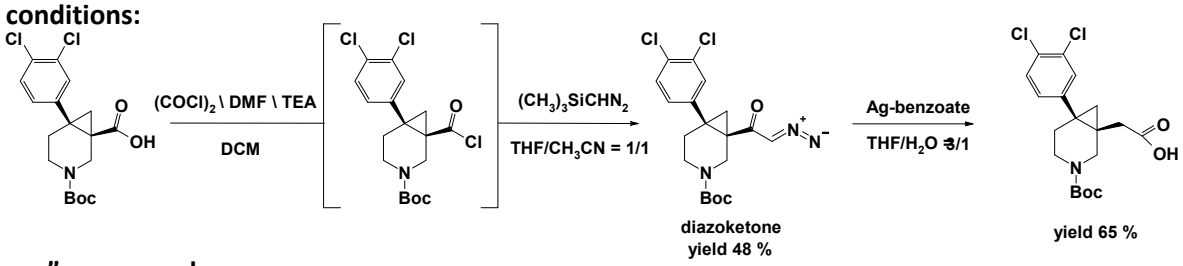
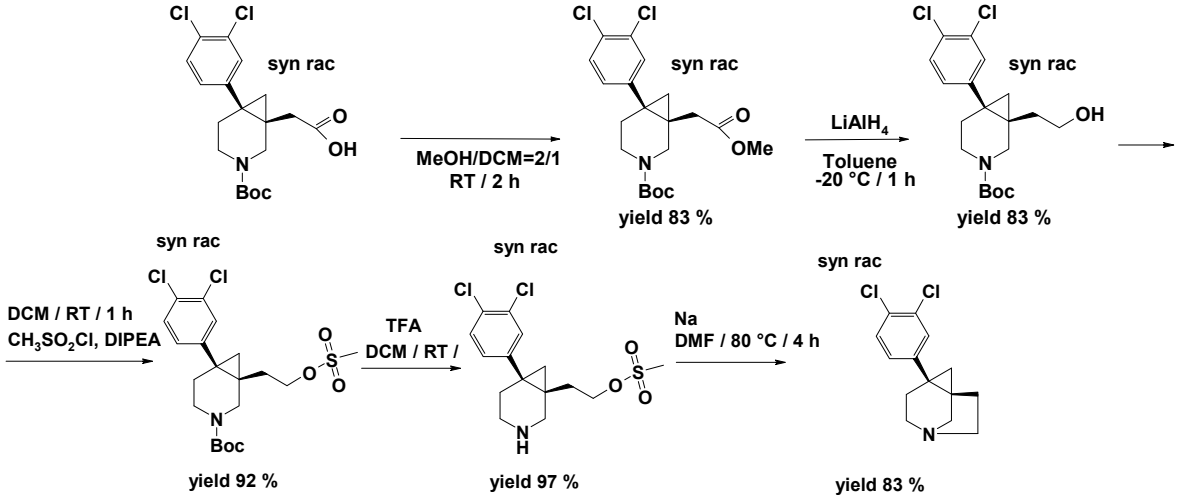
Optimized reaction conditions:



Synthesis of final "cage" compound



- Two enantiomers separated by chiral HPLC
- First ever synthesis of this molecule

Summary

- Target compound was synthesized in 14 reaction steps (overall yield: 7 %)
- Various synthetic methods utilized to generate the novel scaffold
- Synthetic problems were successfully solved to generate a clinical candidate
- Good levels of potency for all three transporters were achieved with the core scaffold
- GlaxoSmithKline 2009 Exceptional Science Award

References

1. WO 2010/146025 and WO 2008/031772
2. F. Micheli, M. Roscic et al., *J. Med. Chem.* **53** (13) (2010) 4989-5001

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