Easy-to-perform large scale approach to 1-methyladamantane and its derivatives – scarce though prominent medchem building-blocks

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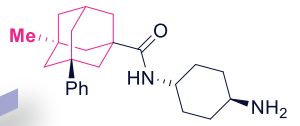
Background and aim of the investigation

CHEMISTRY-RELATED INCENTIVES FOR THE WORK TO CARRY OUT:
- 1-methyladamantane and its derivatives are rare chemotypes for industrial and wide research use;
- existing methods for the synthesis of 1-methyladamantane are unsafe, lead to inseparable mixtures, or use expensive starting materials;
- low synthetic availability of 1-methyladamantane derivatives leads to their poor representation in medicinal chemistry research compared to 1,3-analogues.

PHARMACOLOGY BOOSTER FOR THE WORK TO PERFORM:
- 1-methyladamantane is a perfect platform for synthesizing chiral molecules with cage-derived chirality, which might be very MedChem beneficial;
- recent fabulous example of *anti*-Ebola virus agent:

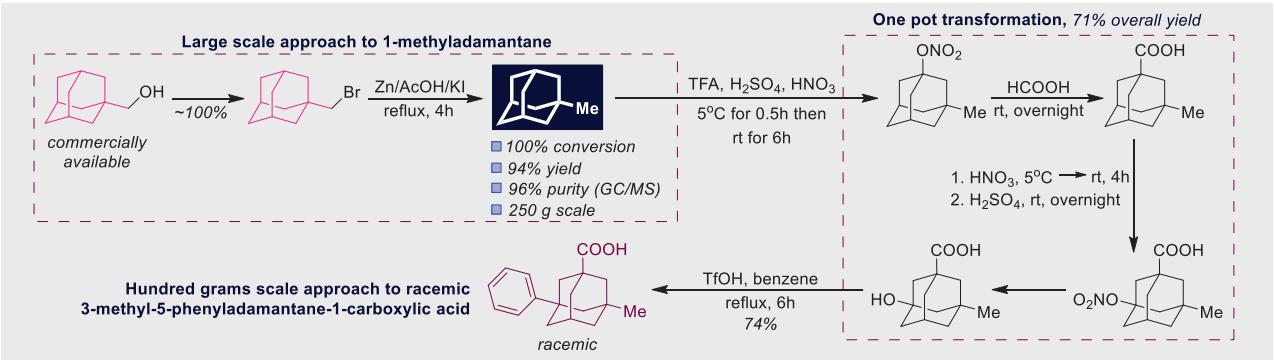


- EC_{50} = 14 nM (pEBOV infectivity assays)
- low hundred nanomolar EC_{50} against wild type EBOV
- aqueous solubility >20 mg/mL
- attractive metabolic stability in liver microsomes

AIM: to develop a scalable synthetic approach to Me-adamantane backbone and efficient methods of its broad scope derivatization

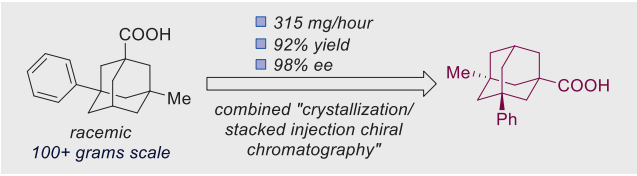
Synthetic part of the research

Optimization and scale-up synthesis of 1-methyladamantane:
- $LiAlH_4$ reduction of the bromide has several drawbacks, making it expensive and inefficient on a large scale;
- adding a catalytic amount (1-2.5% mole) of tributyltin hydride decreased the reaction time to 24h; however, scaling the procedure higher than

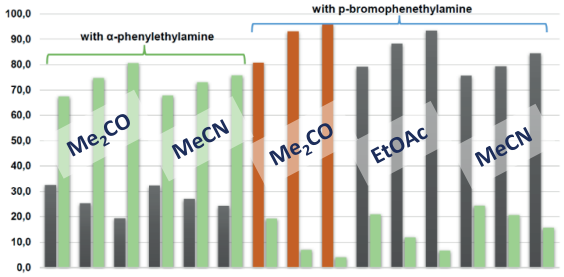


Chromatographic part of the research

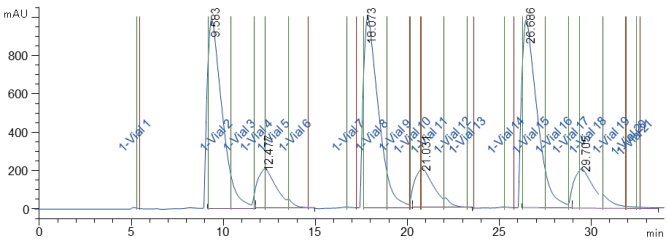
Chiral chromatography for enantioseparation of 3-methyl-5-phenyladamantane-1-carboxylic acid:
- polysaccharide-based chiral stationary phase was applied;
- Chiralcel OJ-H with hexane/IPA 80:20 mobile phase is the most promising stationary phase/solvent system combination for the further scale-up.



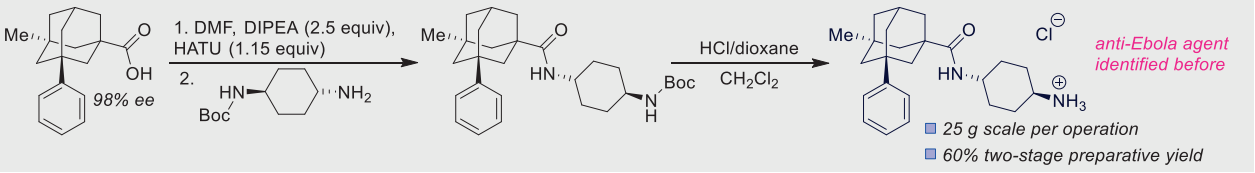
Solvent/resolving agent pairs performance in three-step crystallization of the acid, % *ee* of major/minor enantiomers (y-axis) *vs* sample (x-axis):



Combined crystallization/stacked injection chiral chromatography method:
- the stacked injections approach allowed us to isolate pure (98% *ee*) optical antipodes of the acid with up to 180 mg of product scale per 1 run (315 mg per hour) and 92% preparative yield.



Multigram synthesis of the *anti*-Ebola agent



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