Scale-up synthesis of 1-methyladamantane – key precursor to chiral methyl-phenyl-adamantane carboxamide with promising in vitro activity against Ebola virus

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Background and aim of the project

Chemistry incentives for the work to carry out:

• 1-methyladamantane and its derivatives are rare chemotypes for industrial and wide research use;

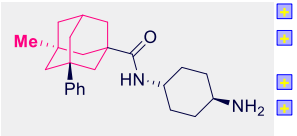
• existing methods for the synthesis of 1-methyladamantane are unsafe, lead to inseparable mixtures, or use expensive starting materials;

• 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 beneficial from the biological assessment viewpoint;

• recent example of efficient 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

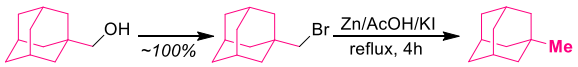
Aim: *to develop scalable synthetic approach to methyladamantane backbone and efficient methods of its broad scope derivatization*

Synthetic investigations

Optimization and scale-up synthesis of 1-methyladamantane

• LiAlH4 reduction of the bromide has several drawbacks, making it expensive and inefficient on a large scale;

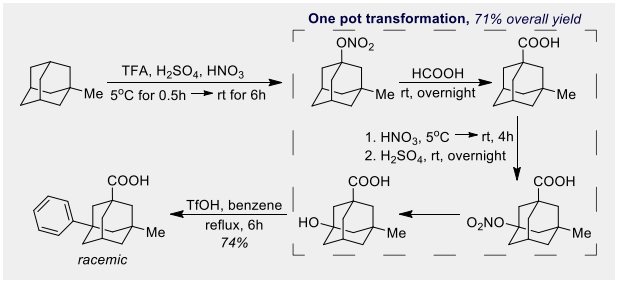
• adding a catalytic amount (1-2.5% mole) of tributyltin hydride decreased the reaction time to 24h; however, scaling the procedure higher than 100 g of the bromide led to significant increase in a content of side-products.



commercially available

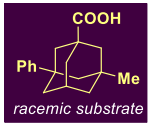
- *100% conversion*
- *94% yield*
- *96% purity (GC/MS)*
- *250 g scale*

Hundred grams scale approach to racemic 3-methyl-5-phenyladamantane-1-carboxylic acid



Combined "crystallization/chiral chromatography" approach

Chiral chromatography for enantioseparation of 3-methyl-5-phenyladamantane-1-carboxylic acid



• a mixture of hexane (0.1% TFA) and isopropyl alcohol (IPA) was used as a mobile phase;

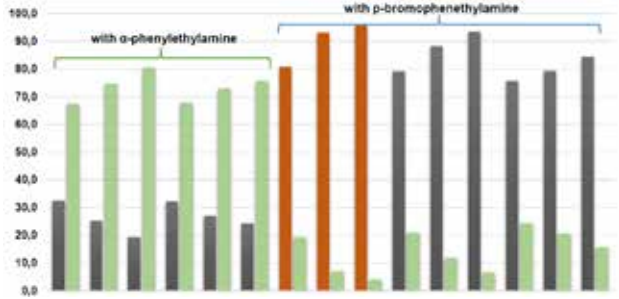
• polysaccharide-based chiral stationary phase was applied;

• Chiralcel OJ-H with hexane:IPA 80:20 mobile phase is the most promising stationary phase/solvent system combination for further scale-up.

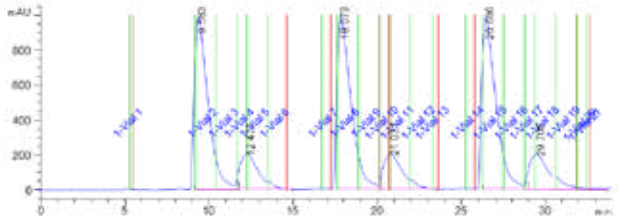
Column	%, IPA	k', min	Rs
Chiralpak IA	30	1.8	0.24
	5	5.0	1.15
Chiralpak IB	10	No separation	
	5	3.6	0.45
	1	17.04	1.91
Chiralpak IC	30	2.1	1.57
	5	5.8	2.57
Chiralpak AD-H	30	No separation	
Chiralpak AS-H	30	1.75	0.91
	5	3.8	1.59
	3	8.35	2.29
Chiralcel OJ-H*	30	4.35	3.42
	20	5.1	3.89

Crystallization approach for enantioseparation of 3-methyl-5-phenyladamantane-1-carboxylic acid

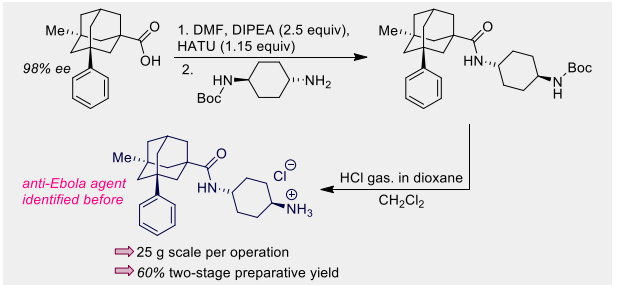
• solvent/resolving agent pairs performance in three-step crystallization of the acid, % ee of major/minor enantiomers (y-axis) vs sample (x-axis)



Combined crystallization/stacked injection chiral chromatography method



Multigram synthesis of the anti-Ebola agent



- 25 g scale per operation
- *60% two-stage preparative yield*

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Results have been published as

Selective α-Methylation of Ketones. *Frolov A.. I. et al., J. Org. Chem.* **2021**, *86*, 7333–7346. https://doi.org/10.1021/acs.joc.1c00148

One more paper is underway