

Amino Acids, Peptides, and Glycoconjugates –

Current Projects

Group Seminar

02.10.2020

Raffael C. Wende

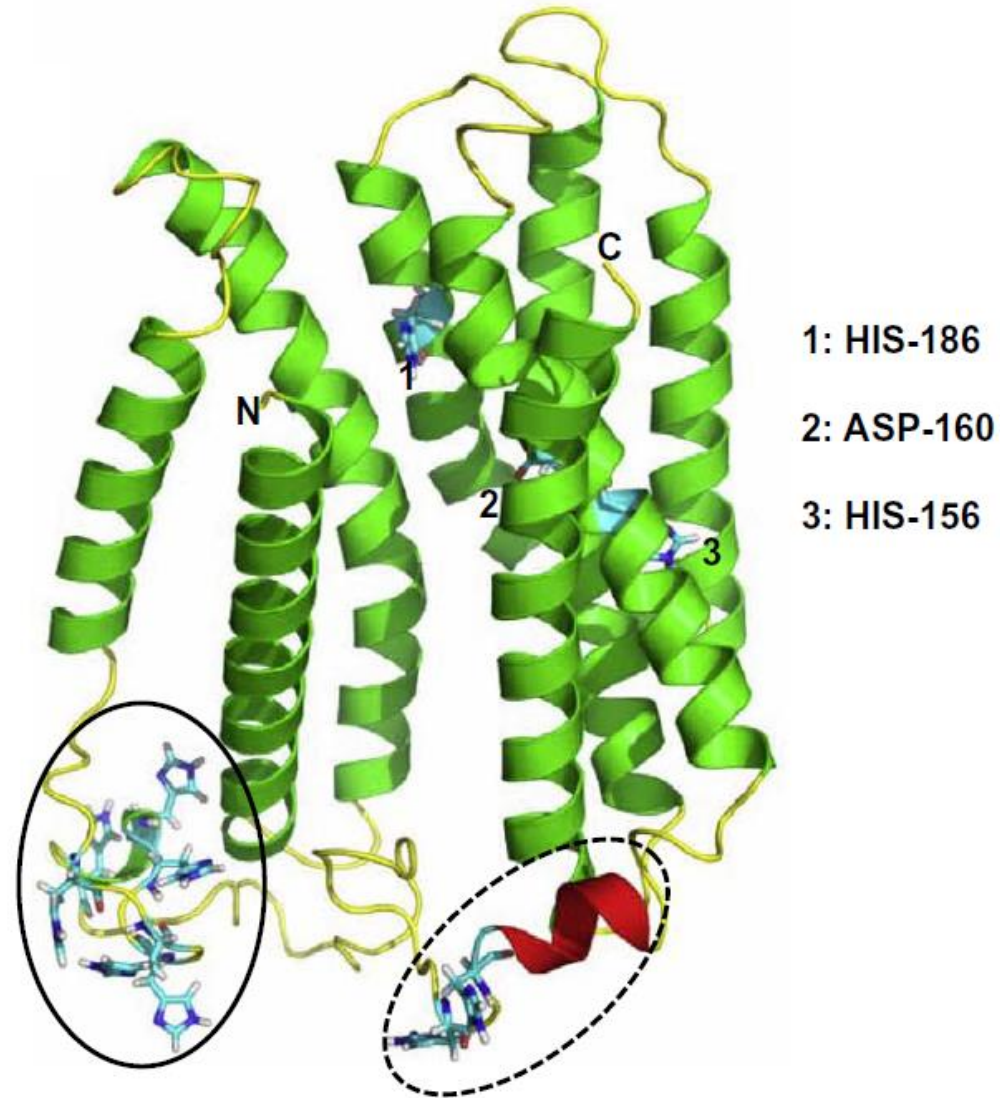
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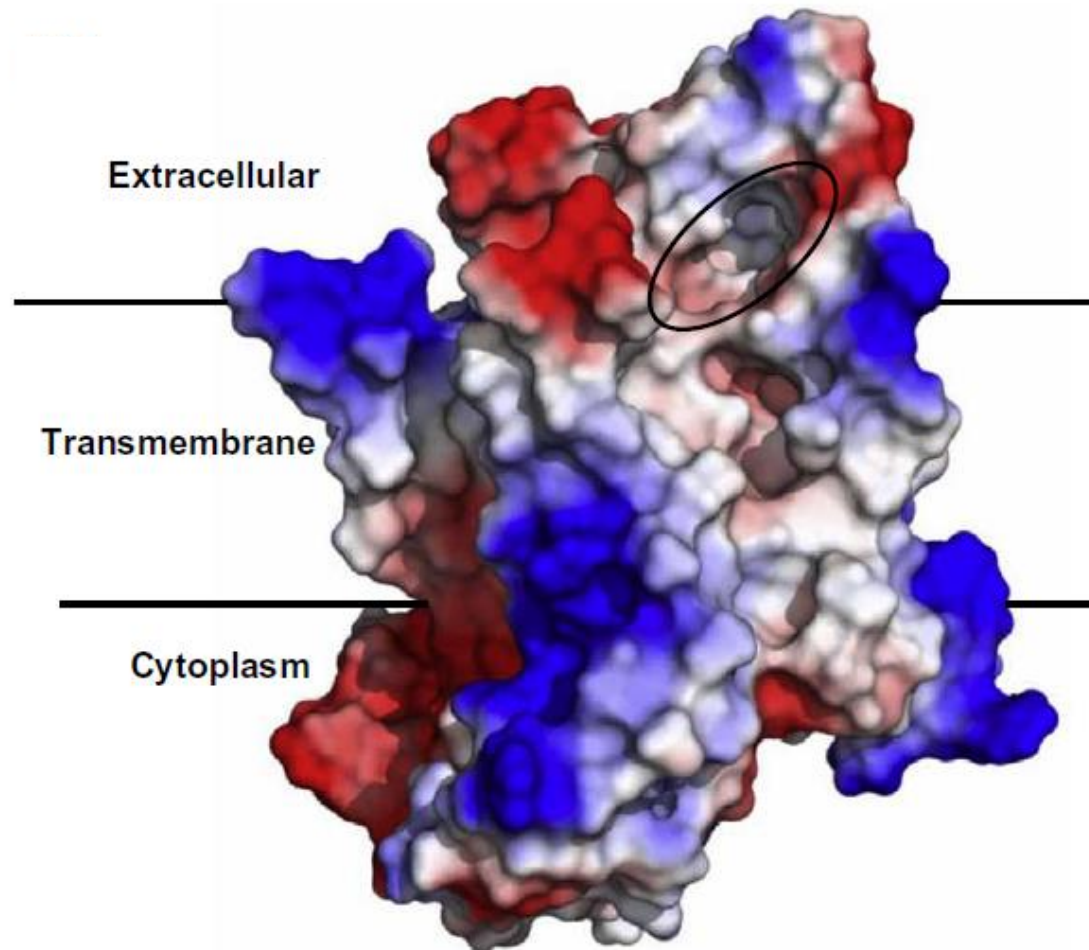


Targeting the Testosterone Binding Site of ZIP9 with Andromimetic Peptides

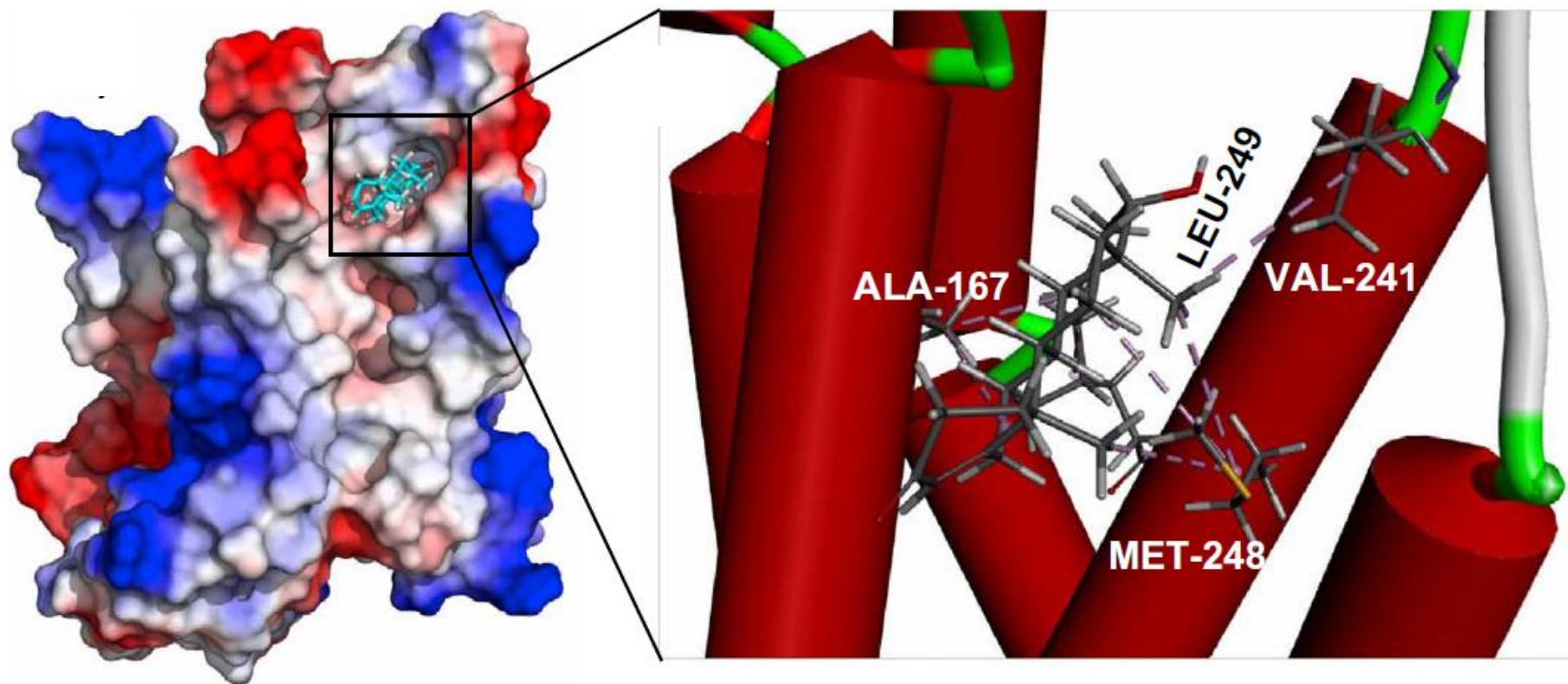
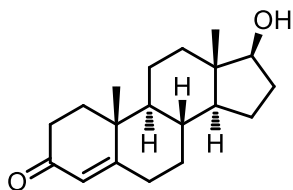


- Membrane-bound protein originally identified as a Zn^{2+} transporter
- Also binds testosterone
- Triggers the activation of the Src, Ras, Raf, Erk1/2, CREB, and ATF-1 signaling cascade
- Cascade is mediated through the interaction of ZIP9 with G-proteins
- Represents an interesting pharmacological target





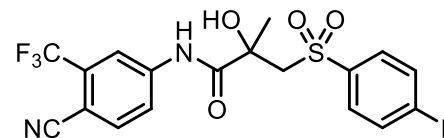
Binding of Testosterone



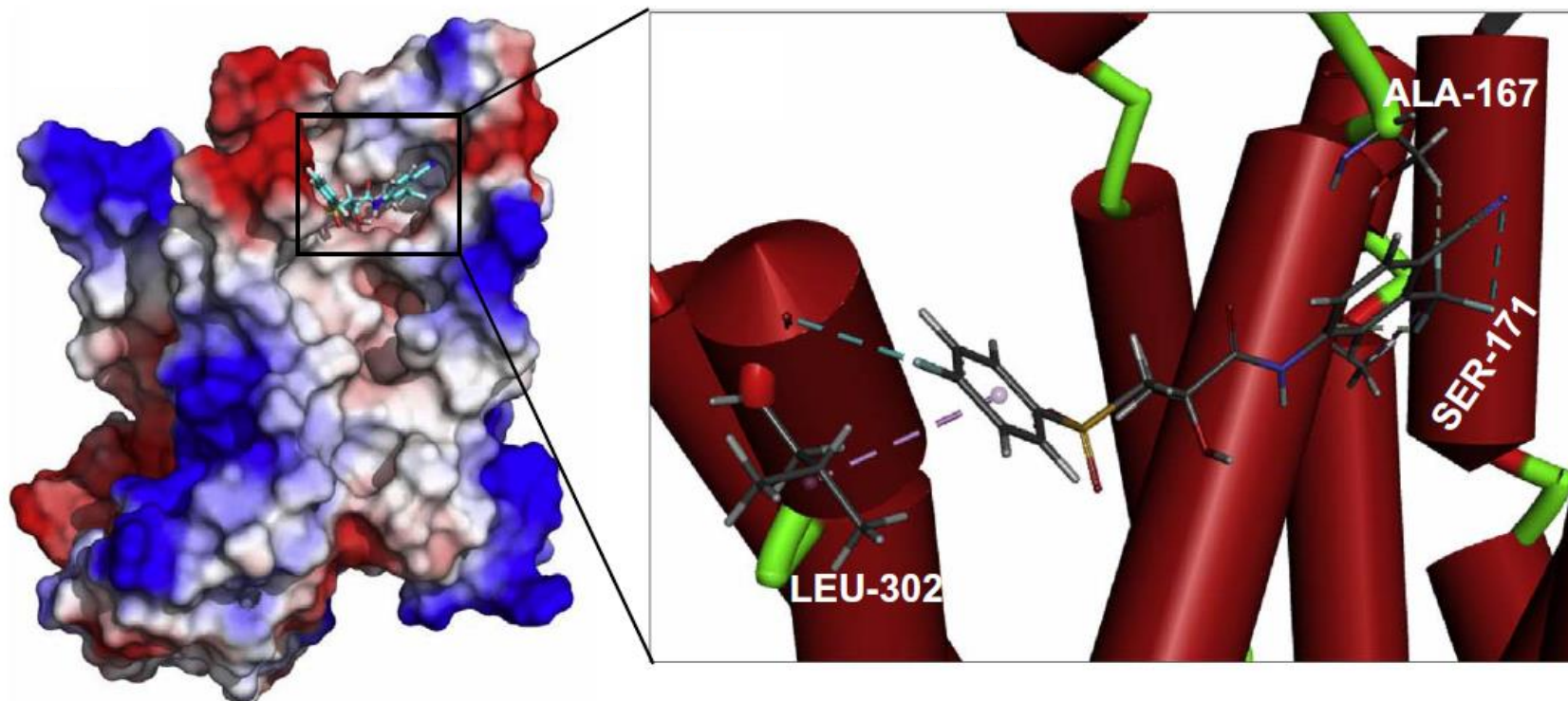
The Antiandrogen Bicalutamide



- Significant clinic impact
- Accommodates same binding pocket as testosterone
- Severe side-effects

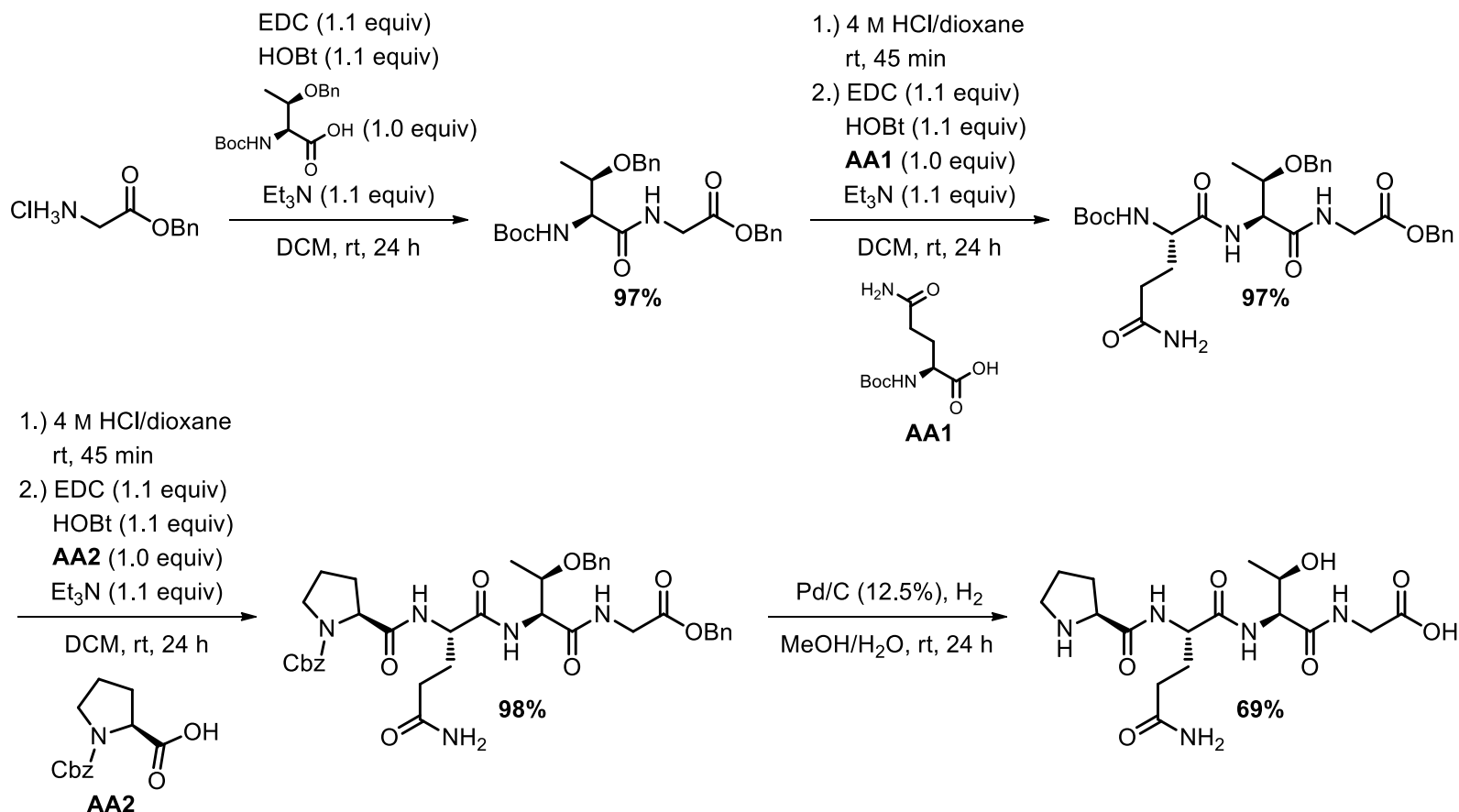


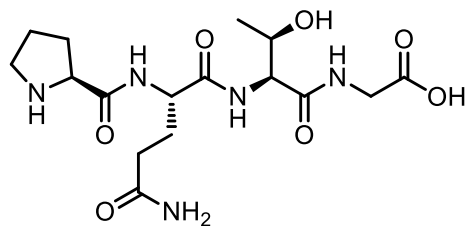
1.3 billion US\$ world wide sales in 2007
13.4 billion US\$ as of the end of 2018



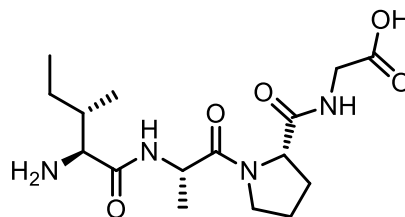


- In silico design of potential antiandrogenic peptides
- Six candidates identified that may bind to ZIP9

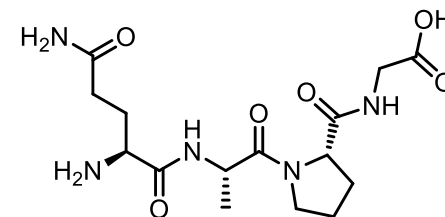




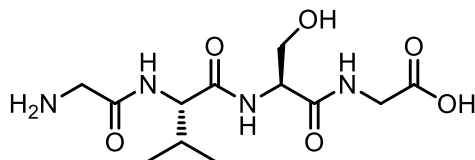
64%, 27.5 mg



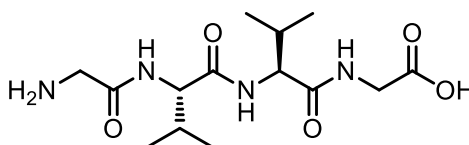
53%, 55.0 mg



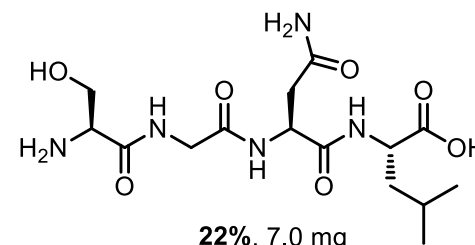
33%, 28.2 mg



60%, 27.4 mg

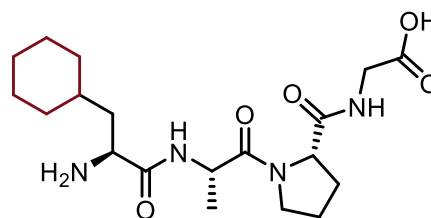
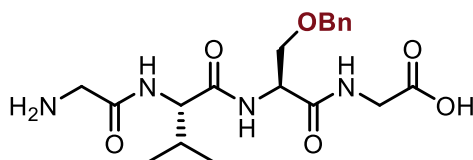


54%, 16.4 mg

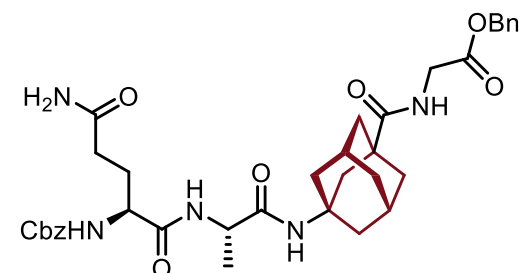


22%, 7.0 mg

- All peptides showed andromimetic activity



27%, 29.1 mg



90%, 273 mg



Commonly applied osteoporosis therapy:

- Basis: calcium and vitamin D
- Biphosphonates, SERMs, calcitonin, estrogens, progesterone
- Fluorides, parathyroid hormone, strontium, **testosterone**

Side effects of testosterone:

- Liver damage, lipid metabolism disorder, risk of thrombosis
- Virilization symptoms (female), “awake” clinically silent prostate cancer (male)

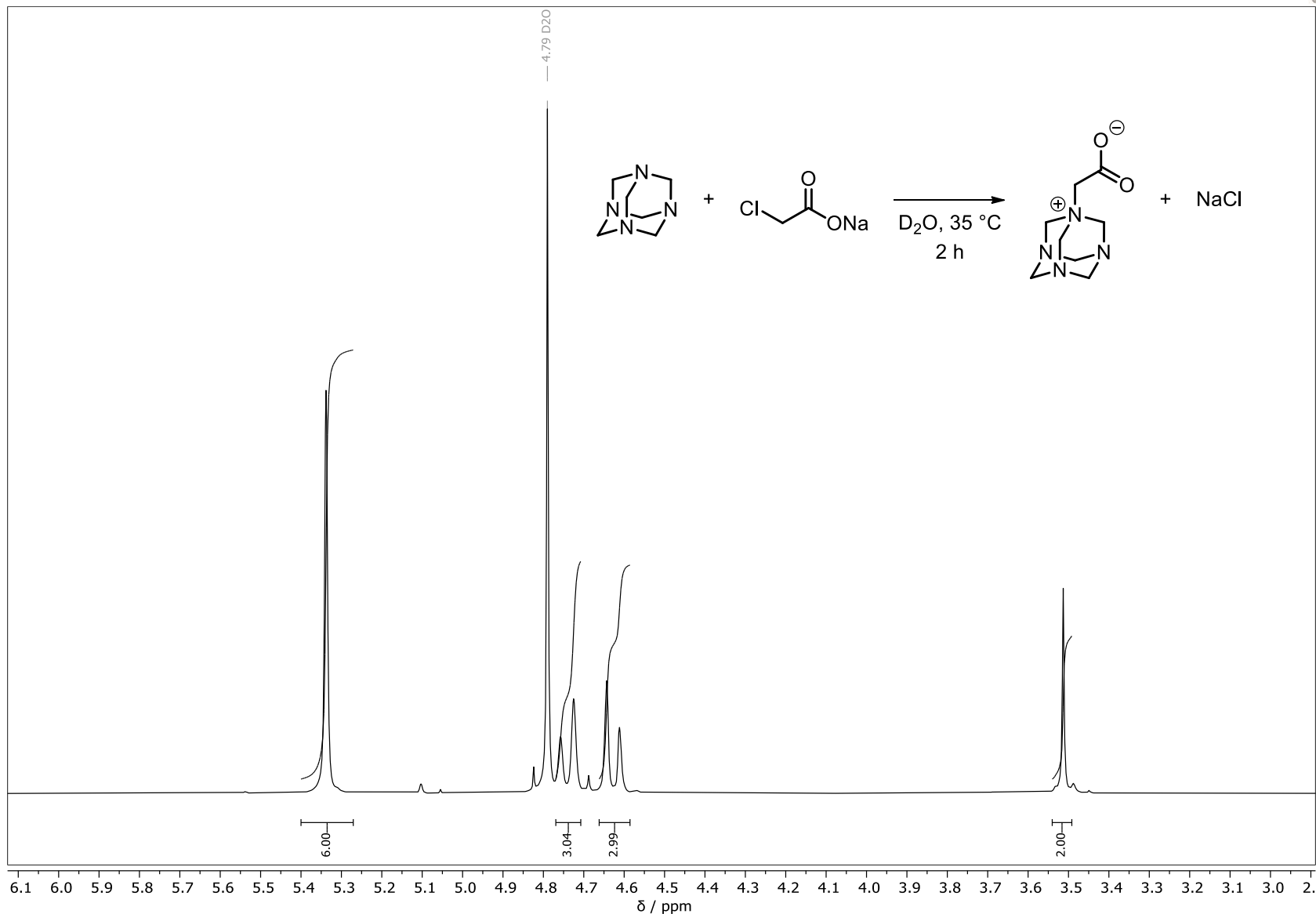
Andromimetic Peptides: **showed activation of osteoblasts**
(cooperation Prof. Dr. K. Lips)



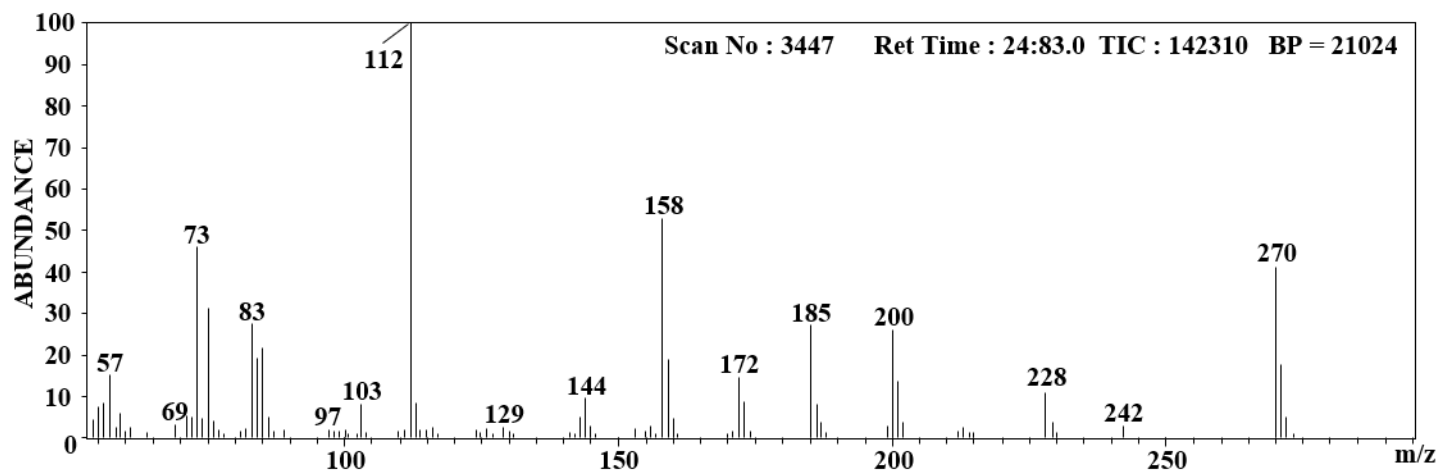
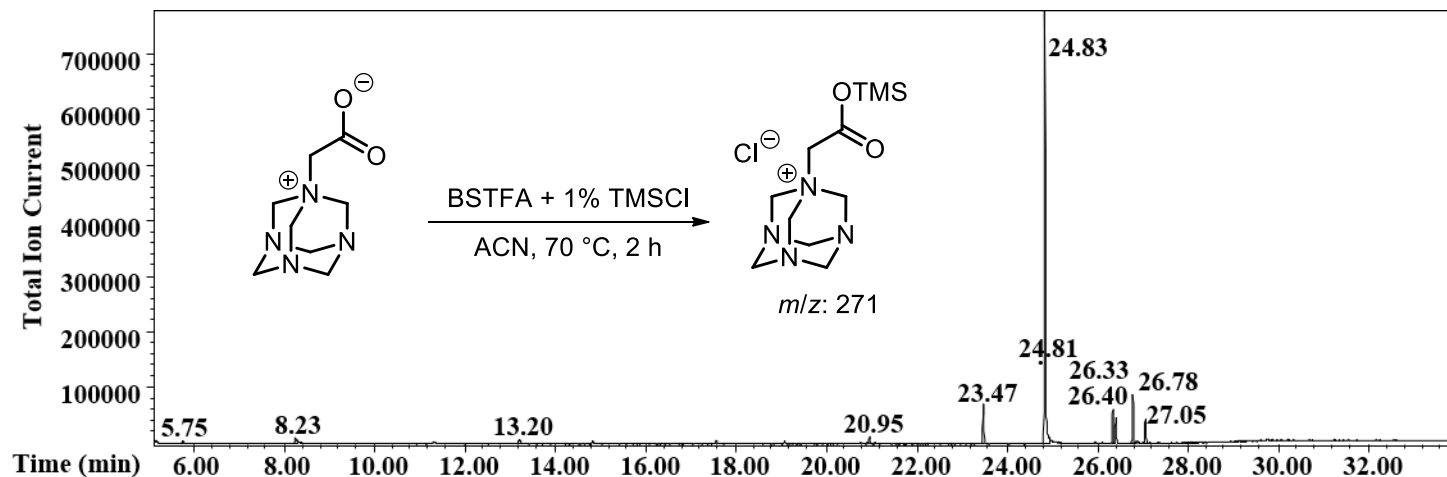
Synthesis of 2,3-Diaminopropanoic Acid Derivatives



An "Unknown" Compound from Flow Pyrolysis

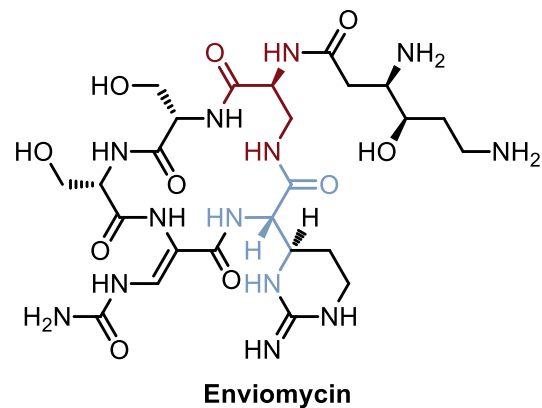
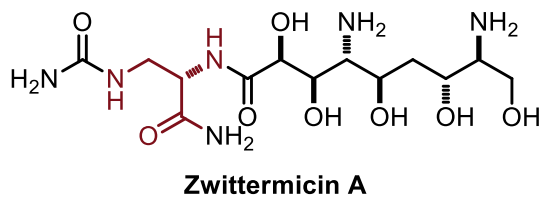
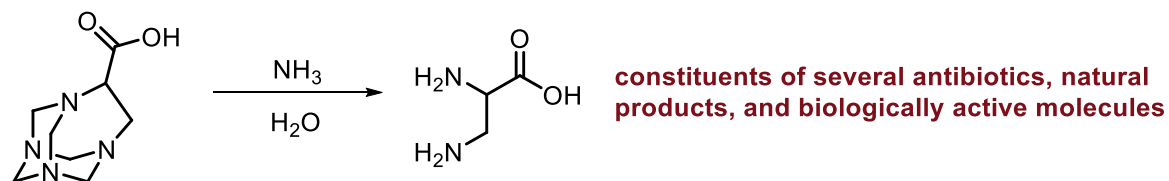
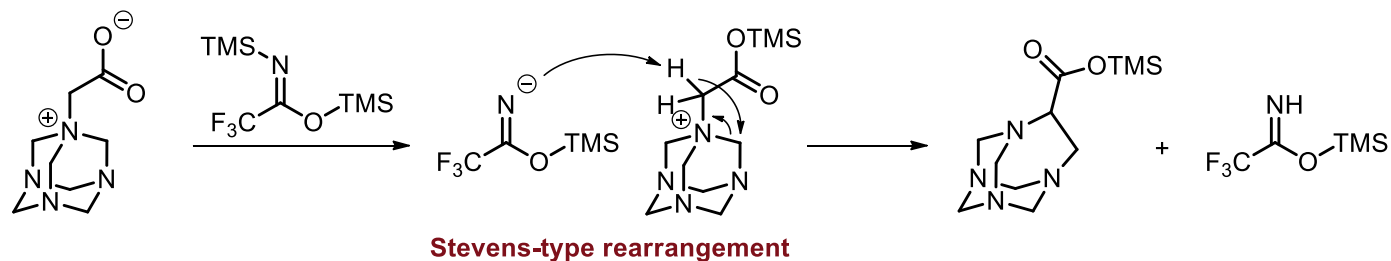


An "Unknown" Compound from Flow Pyrolysis

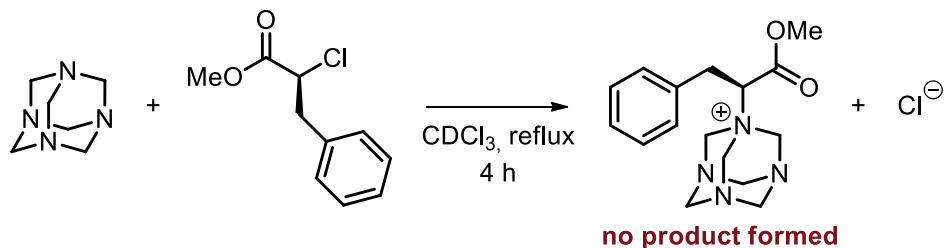
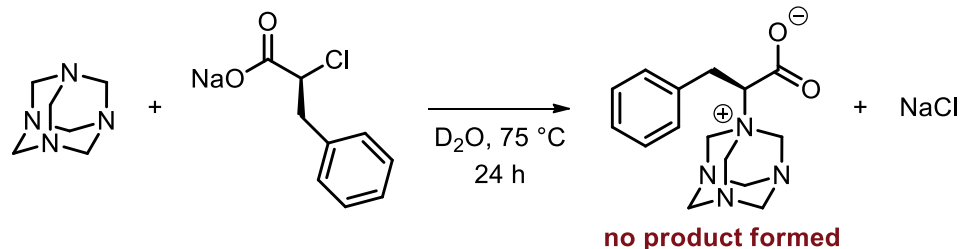
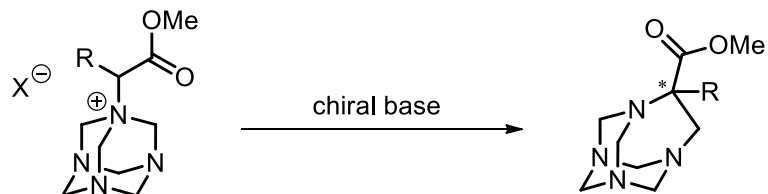
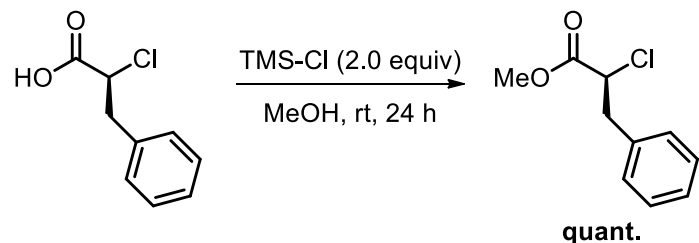
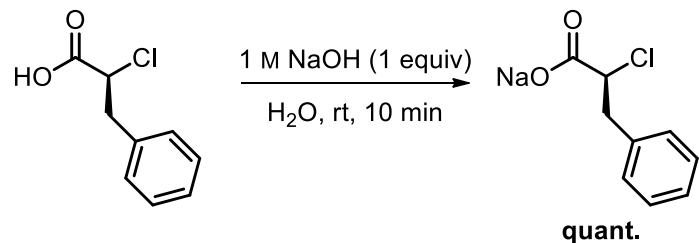
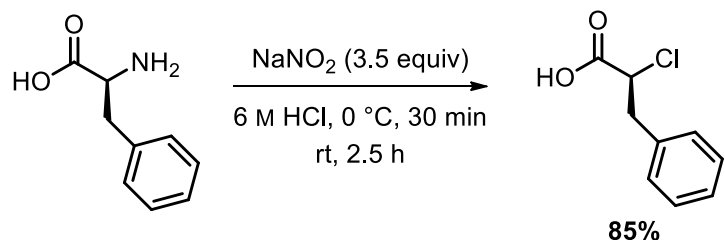




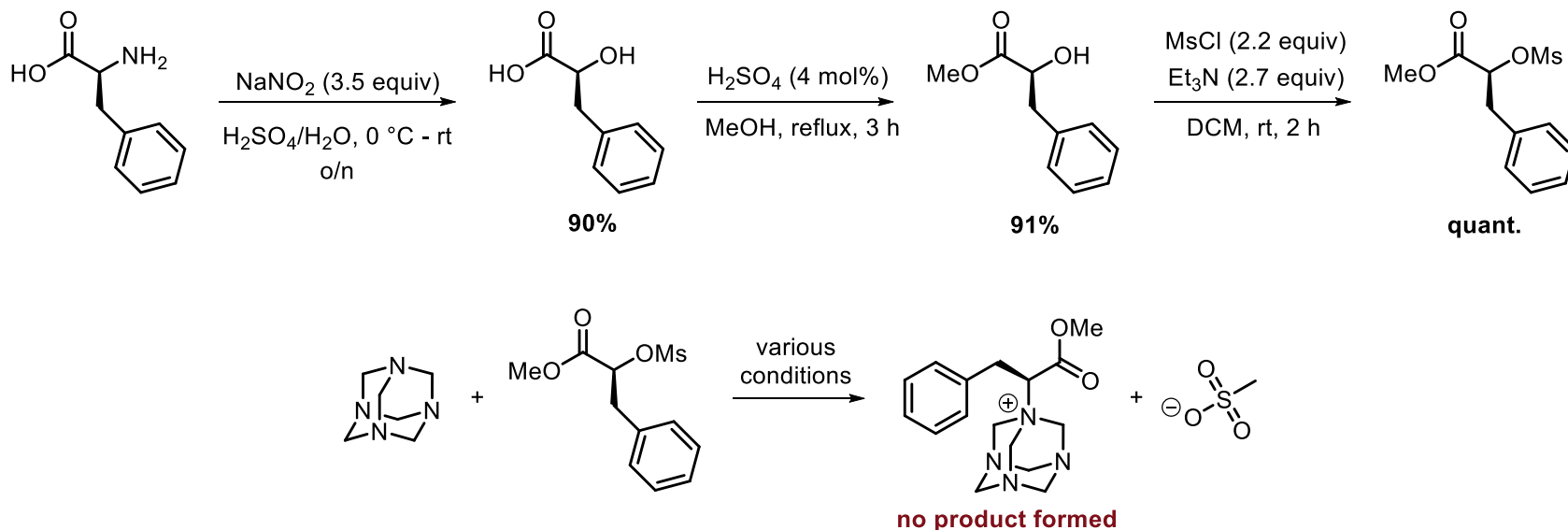
Proposed Mechanism



Synthesis of Quaternary Diamino Acids



Better leaving group is probably necessary



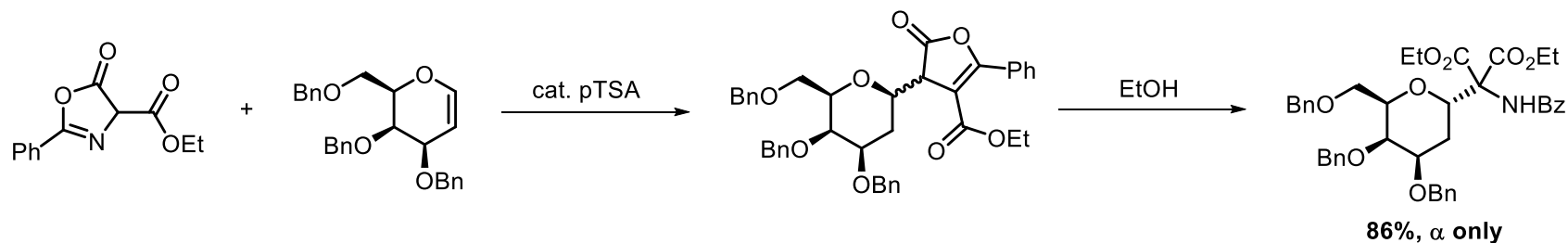
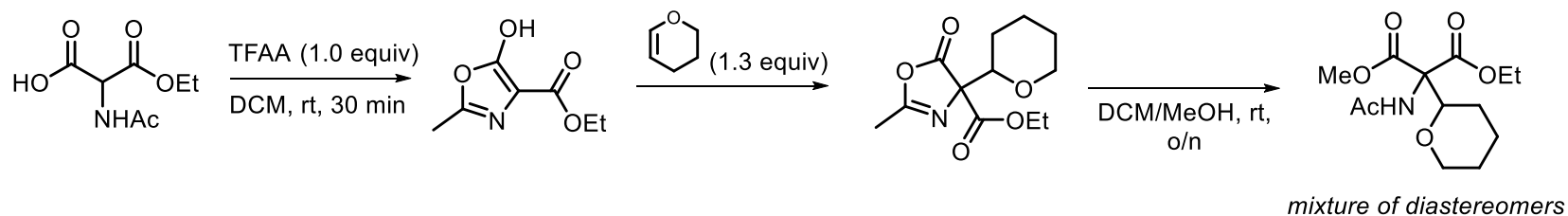
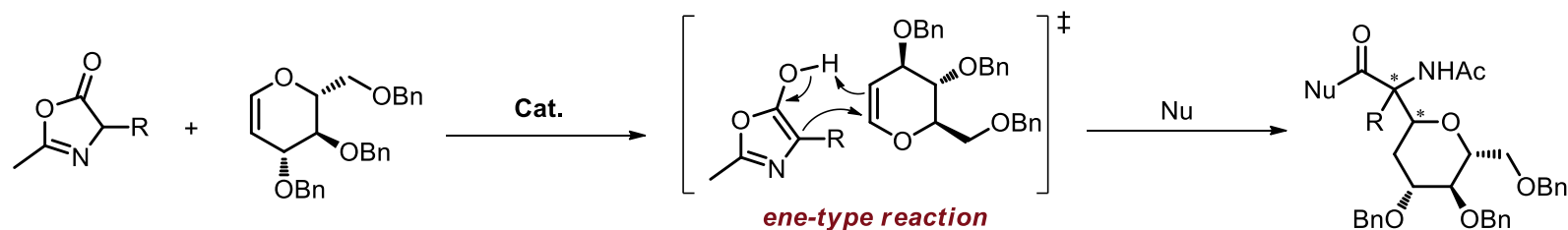
Next Steps:

- Installation of Tf-protecting group
- Optimization of the rearrangement using chiral bases
- Optimization of the hydrolysis and purification of the diamino acids



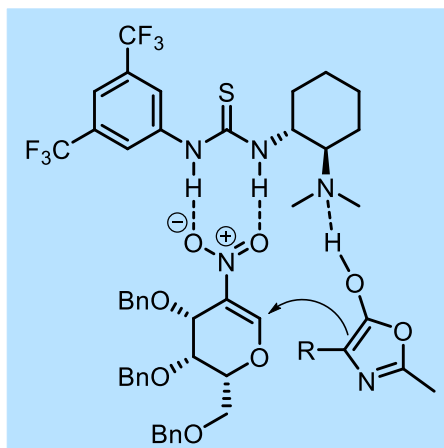
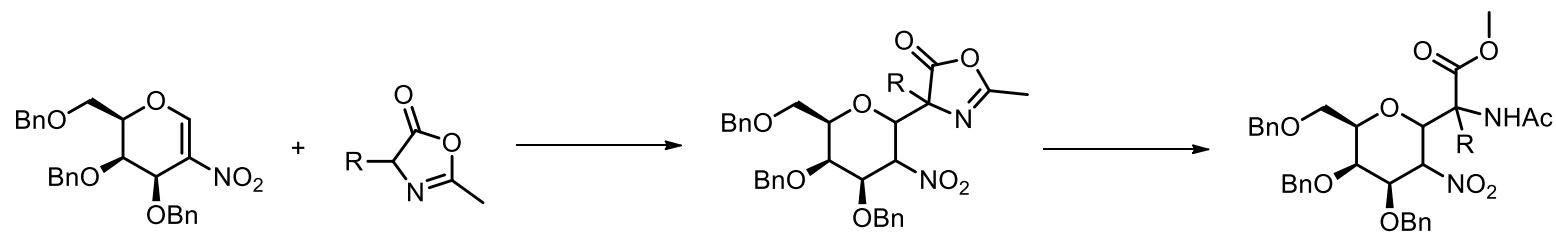
A novel approach towards glycoconjugates

Synthesis of 2-Deoxy-C-Glycosyl α -Amino Acids

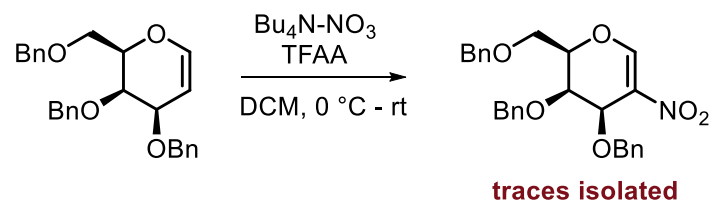
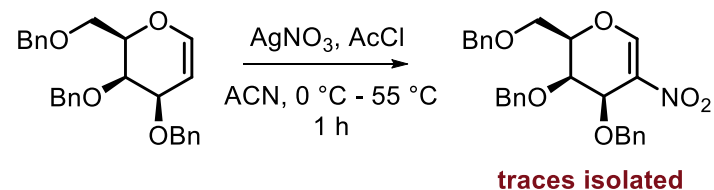
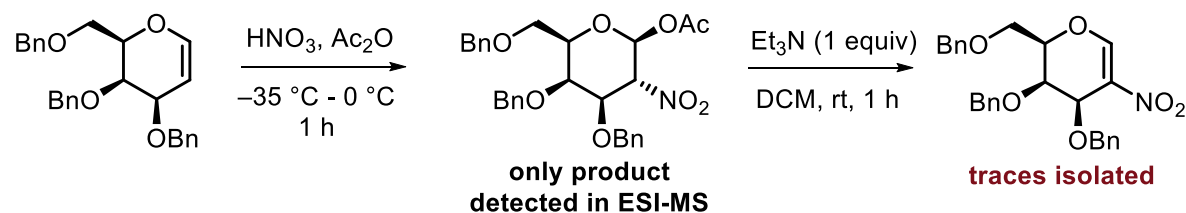
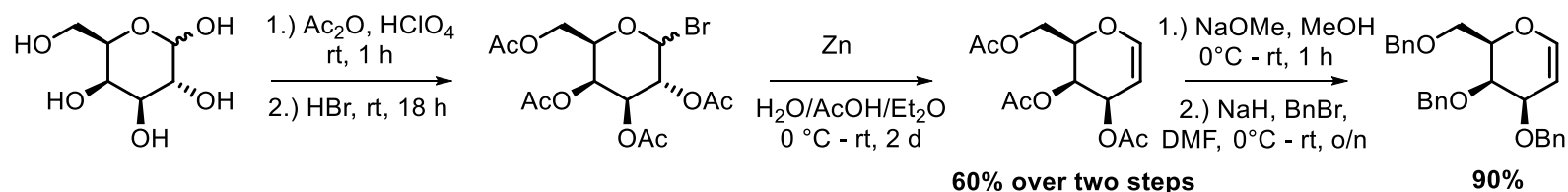


Reaction not (yet) broadly applicable!

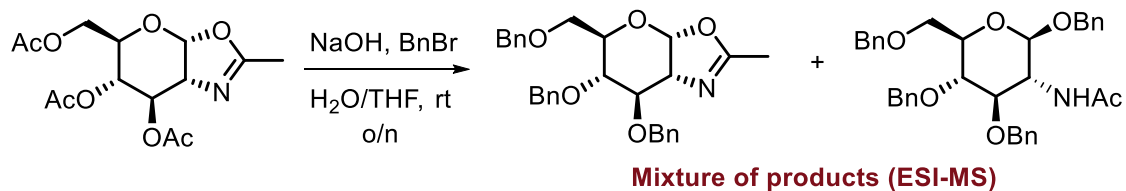
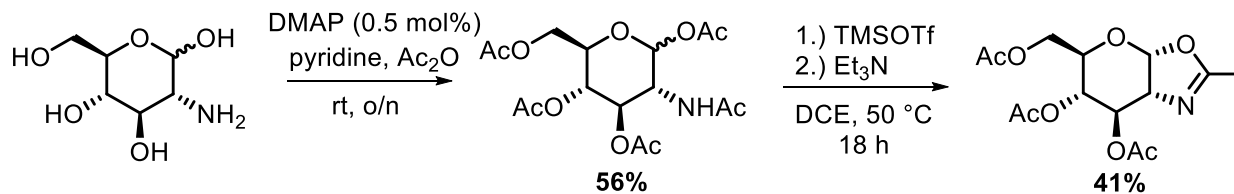
Synthesis of 2-Nitro-C-Glycosyl α -Amino Acids



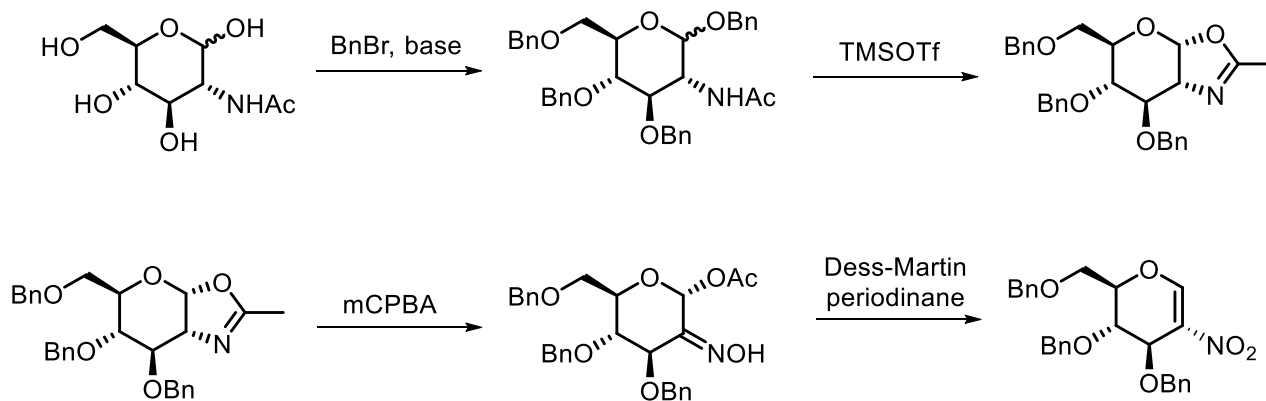
Activation of the nucleophile and electrophile



**None of the methods
really reliable!**

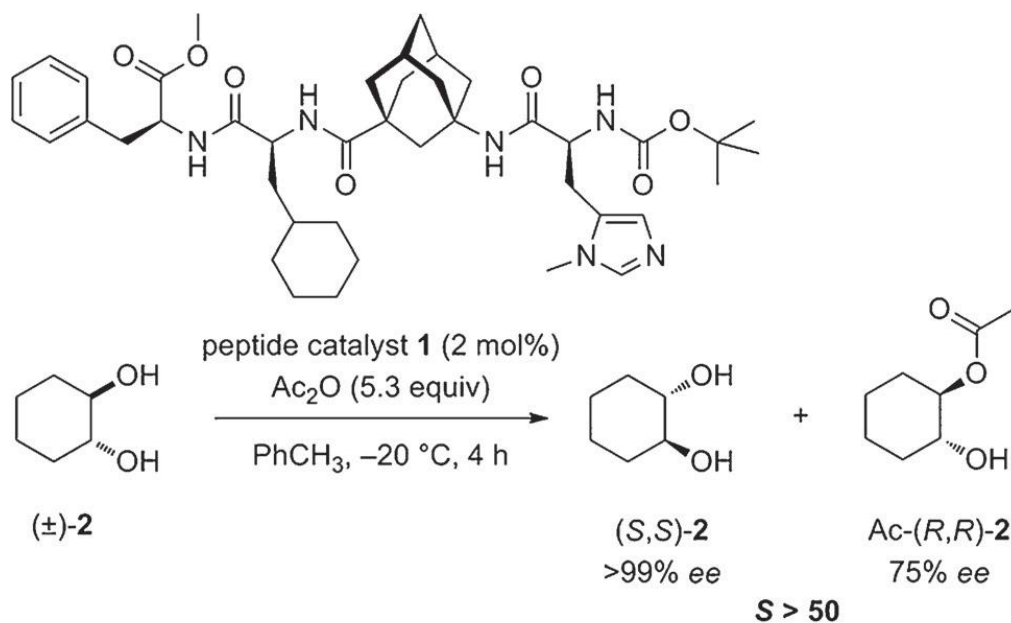


Envisaged alternative route:

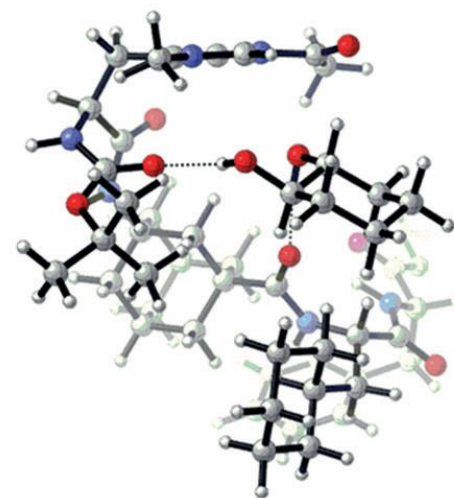


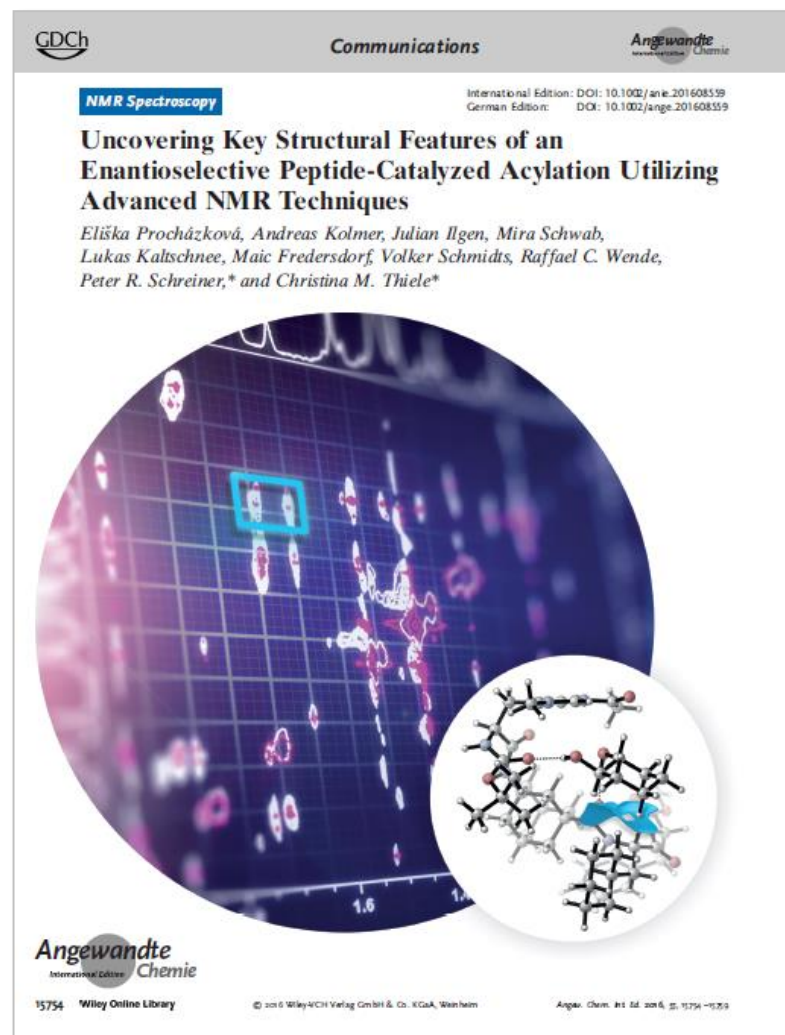
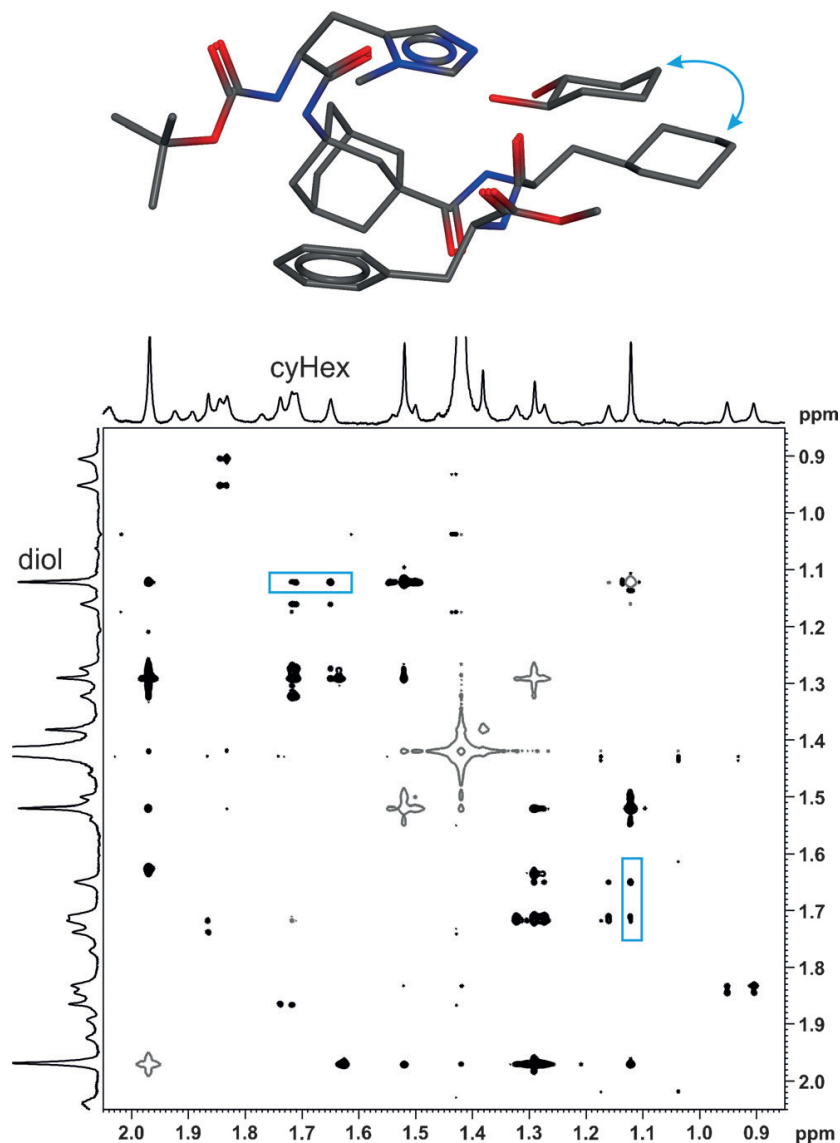


Identification of selective peptides for the kinetic resolution of *trans*-diols by NMR analyses



Proposed dynamic binding pocket
of acylium ion/catalyst adduct







Peptide may form dimers in solution:

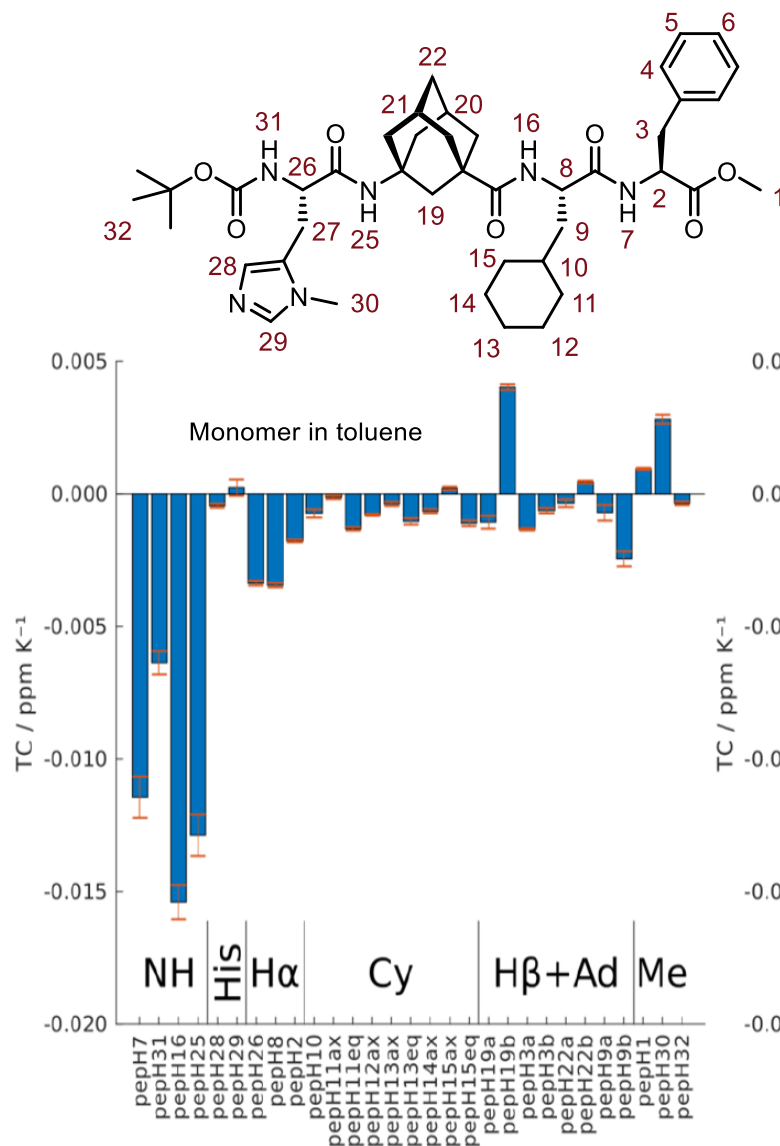
- Measurement of chemical shift in dependency of temperature and concentration
- Determination of equilibrium constant for each temperature
- Calculation of chemical shift for monomer and dimer
- Plotting chemical shift vs. temperature, slope = temperature coefficient (TC)
- Monomer and dimer undergo conformational changes and/or equilibrium is shifted



Whitlock *et al.*, *Med. Chem. Commun.* **2011**, 2, 669:

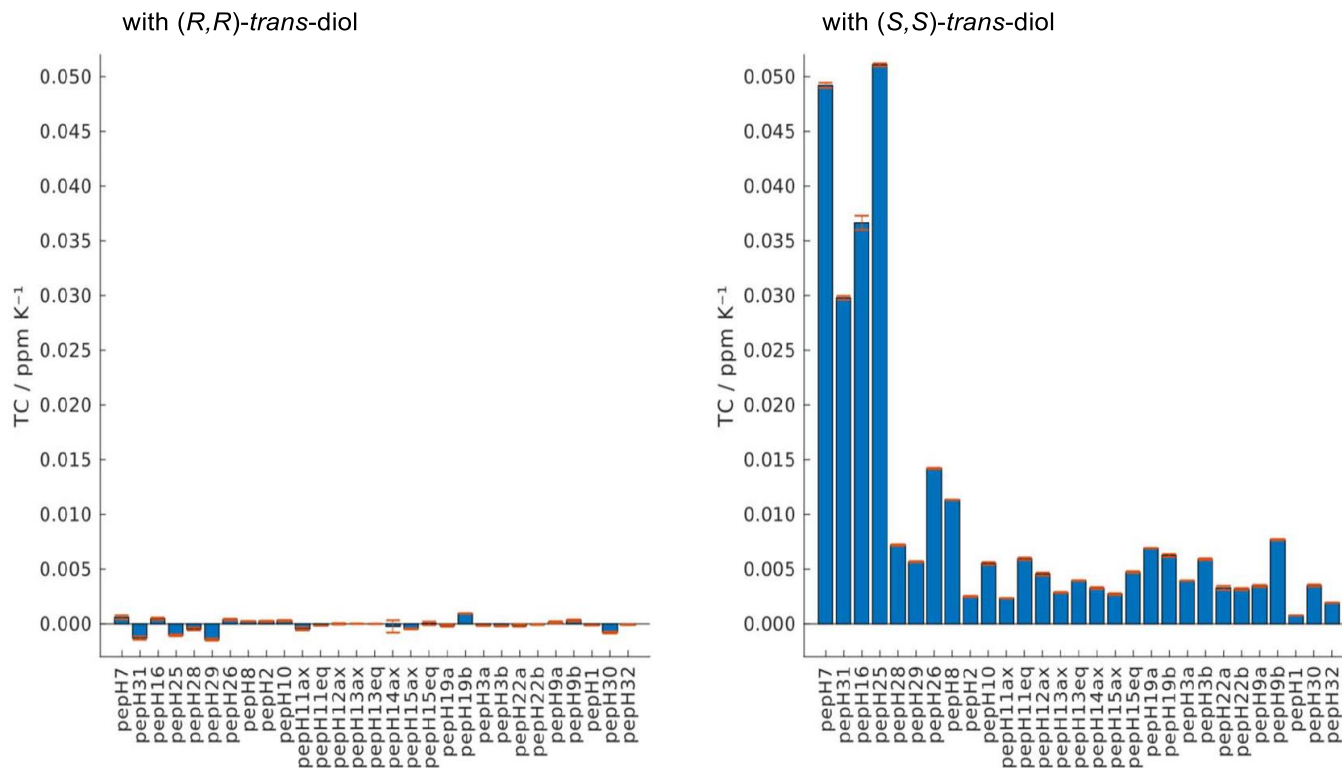
Temperature coefficient in lipophilic solvents

- TC > -3 ppb K⁻¹: strong intramolecular H-bond
- 5 < TC < -3 ppb K⁻¹: weak intramolecular H-bond
- 8 < TC < -5 ppb K⁻¹: no intramolecular H-bond
- 8 < TC ppb K⁻¹: large conformational changes





Plot of difference of measured and predicted chemical shift vs. temperature:
only influence of diol on peptide (background subtracted)

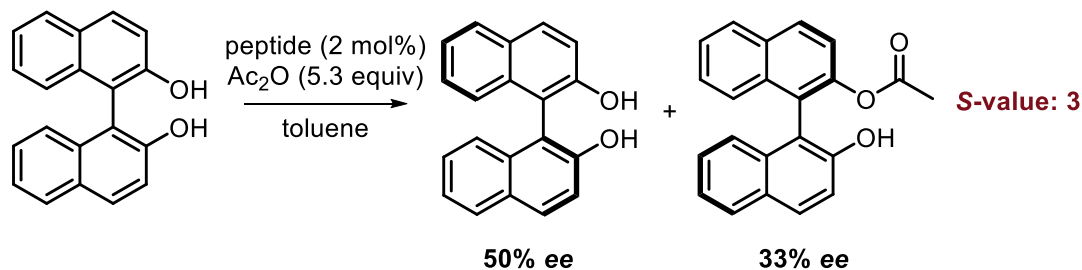
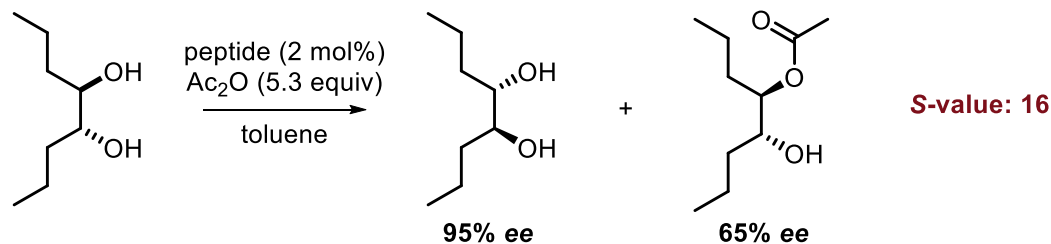


Conformational changes and/or change in equilibrium for all diols but (R,R)-diol

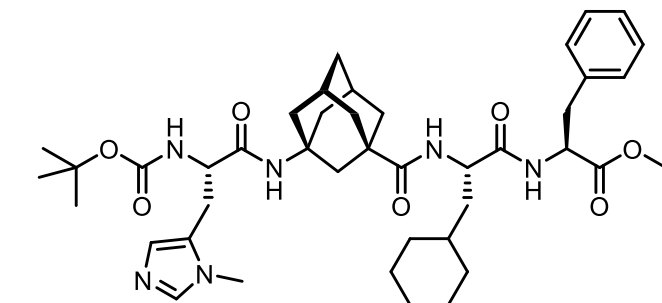
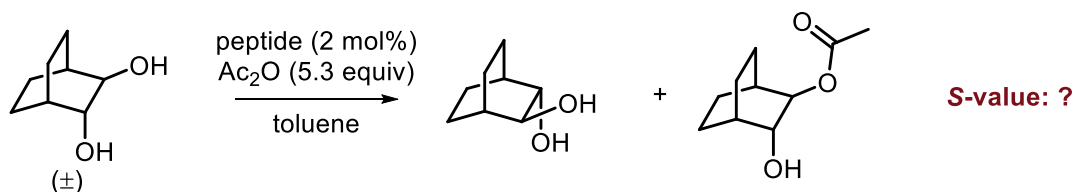
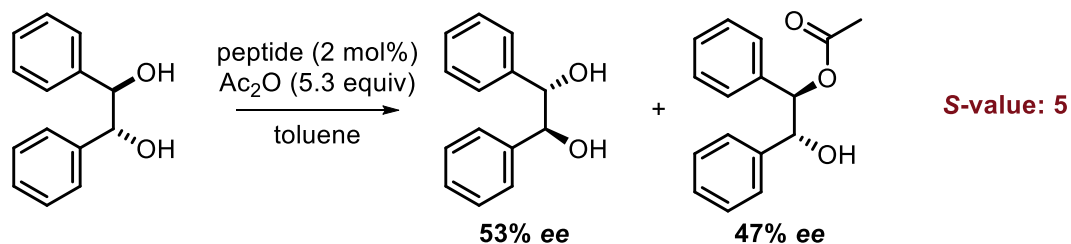
Can We Identify a Selective Peptide by NMR?



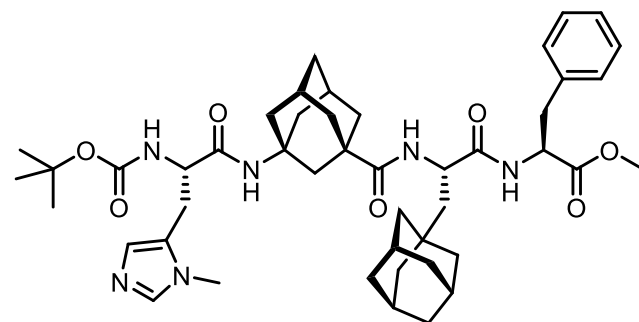
Müller *et al.*, 2013:



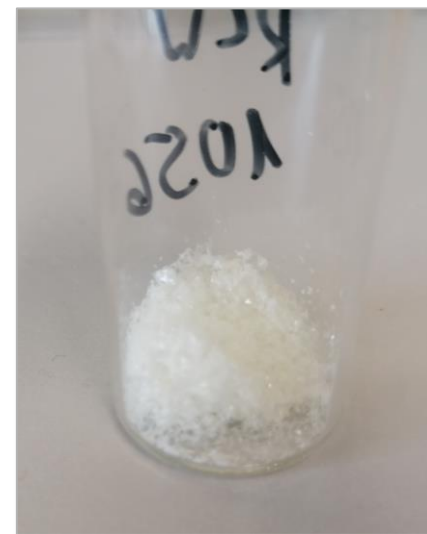
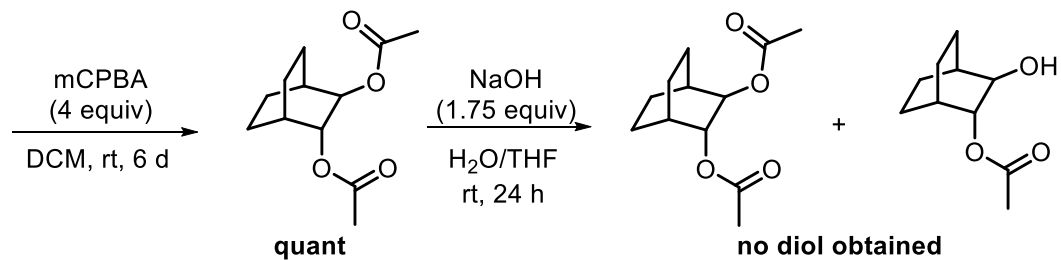
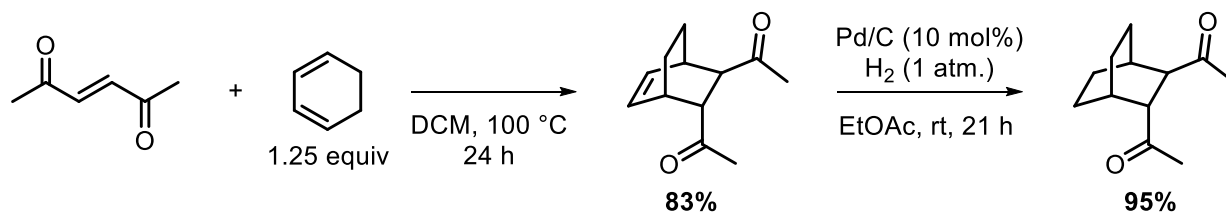
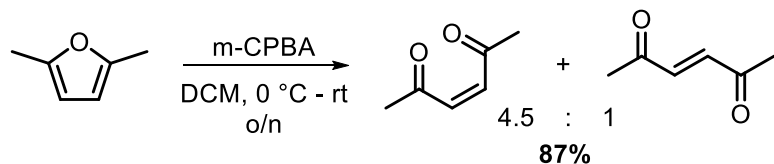
New Substrates:

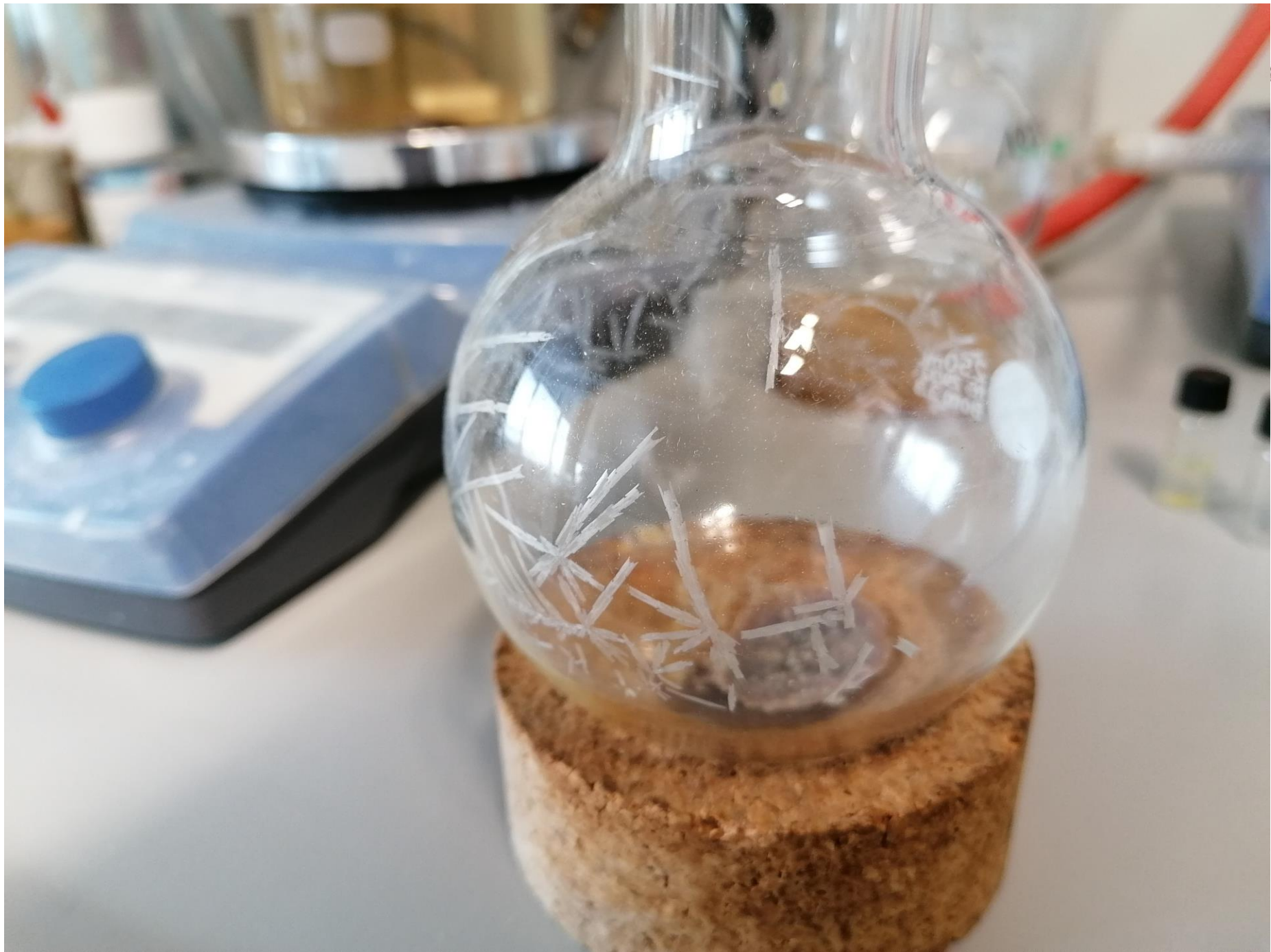


New Catalyst:



Synthesis of the Desired Diol





Acknowledgement



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