

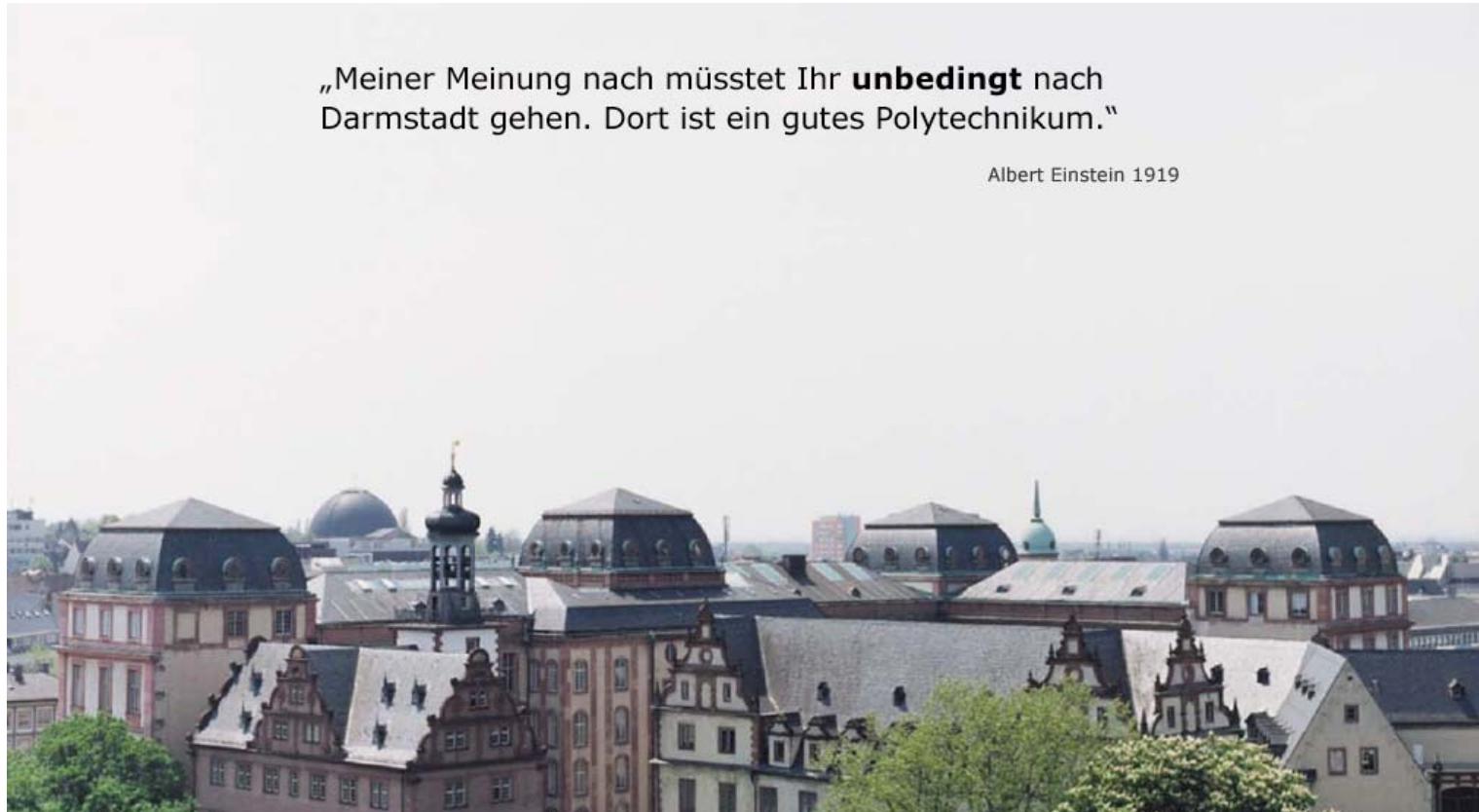
Matrix-unterstützte Wirkstoffsynthese, skalierbar von Hit bis Pilot



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„Meiner Meinung nach müsstet Ihr **unbedingt** nach
Darmstadt gehen. Dort ist ein gutes Polytechnikum.“

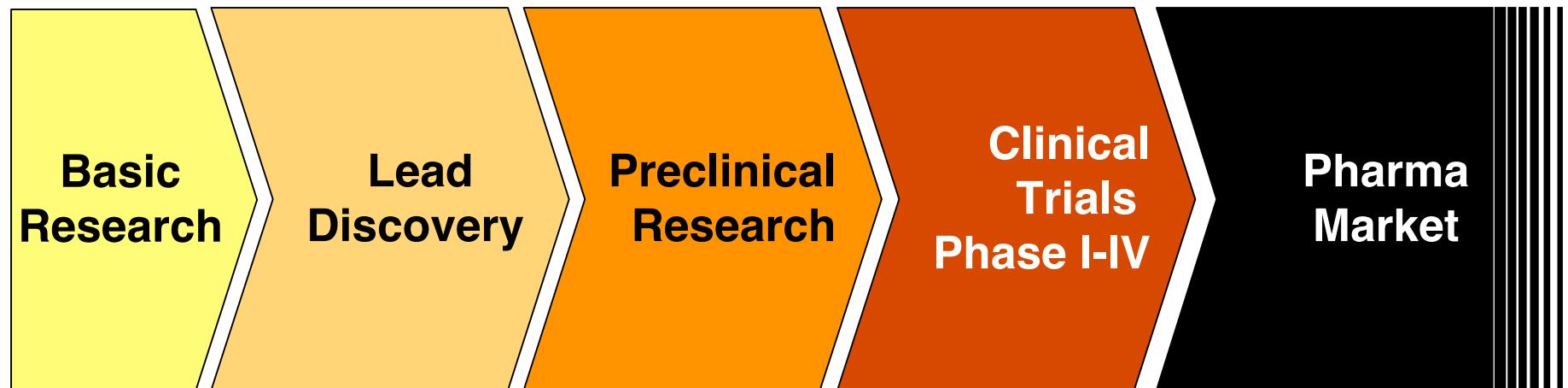
Albert Einstein 1919



Drug Development Process



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Hit Discovery
Combinatorial Chemistry
Solid-Phase Synthesis

Lead Optimization
Asymmetric Synthesis
Solution-Phase Synthesis

Drug Production
Technical Process
Solution-Phase Synthesis

3 Development Stages: Technology Gaps



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Discovery

Library Synthesis
Combinatorial Chemistry
Solid-Phase Synthesis

Lead

Parallel Synthesis
Asymmetric Synthesis
Solution-Phase Synthesis

Drug

Target Production
Technical Process
Solution-Phase Synthesis

10^{-6} - 10^{-1} g

10^0 - 10^3 g

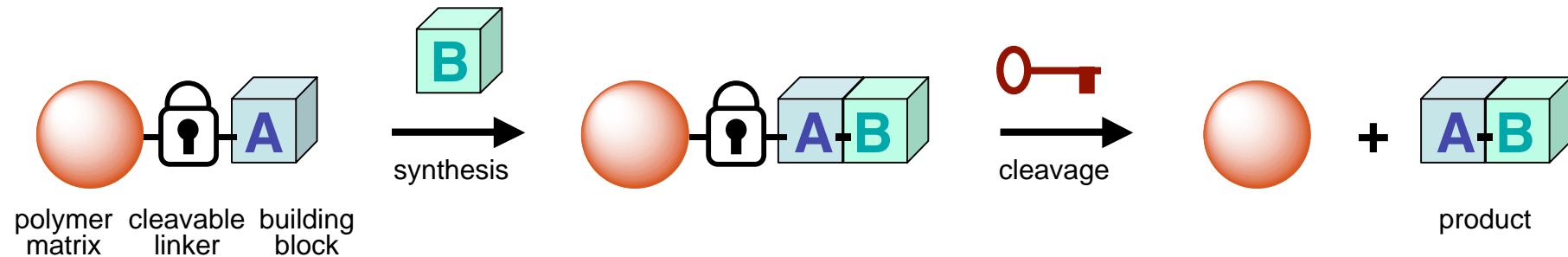
10^5 - 10^8 g



Solid-Phase Organic Synthesis (SPOS)

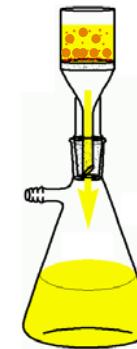


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- simple purification (filtration/washing)
- high substrate dilution
- high product purity
- adaptable to automation

- limited loading capacity (high material costs)
- limited mechanical stability
- low rates from diffusion limitations
- no purification of intermediates





ecological problems of conventional SPOS:

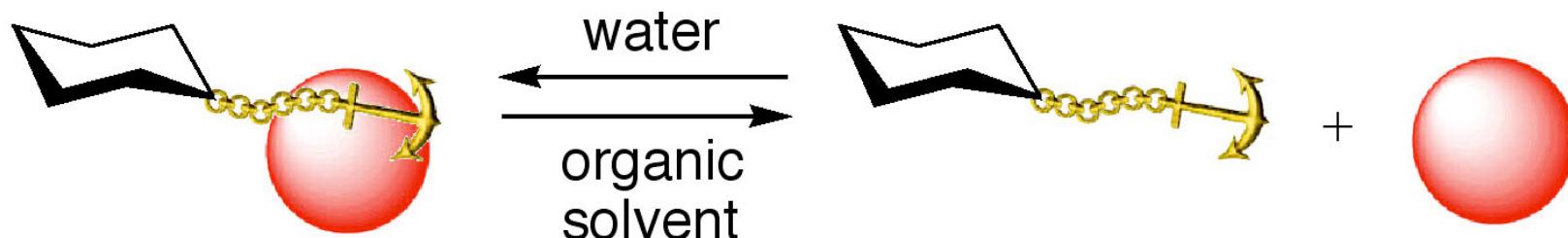
- large volumes of organic solvents
- large dosage of reagents
- inconvenient recycling of matrix
- uneconomical reuse

... only small scale applications — who cares?

Novel Concept: NC-SPOS



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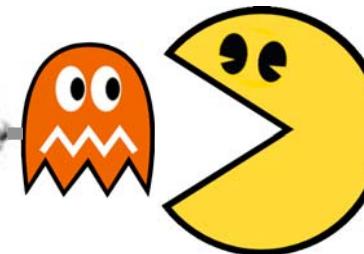
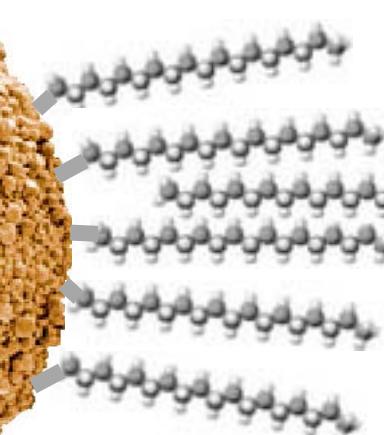
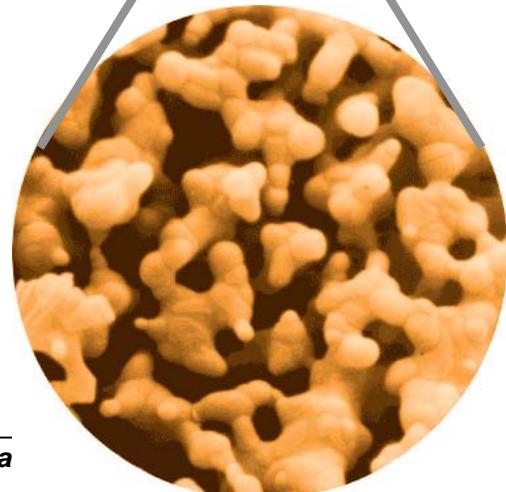
- **Non-Covalent attachment to solid phase**
- **fully reversible immobilization at any step**
- **binding by hydrophobic forces**
- **release controllable by solvent polarity**

A. Porzelle, W.-D. Fessner, *Angew. Chem. Int. Ed.* 2005, 44, 4724-4728

Solid Phase: RP-Silica



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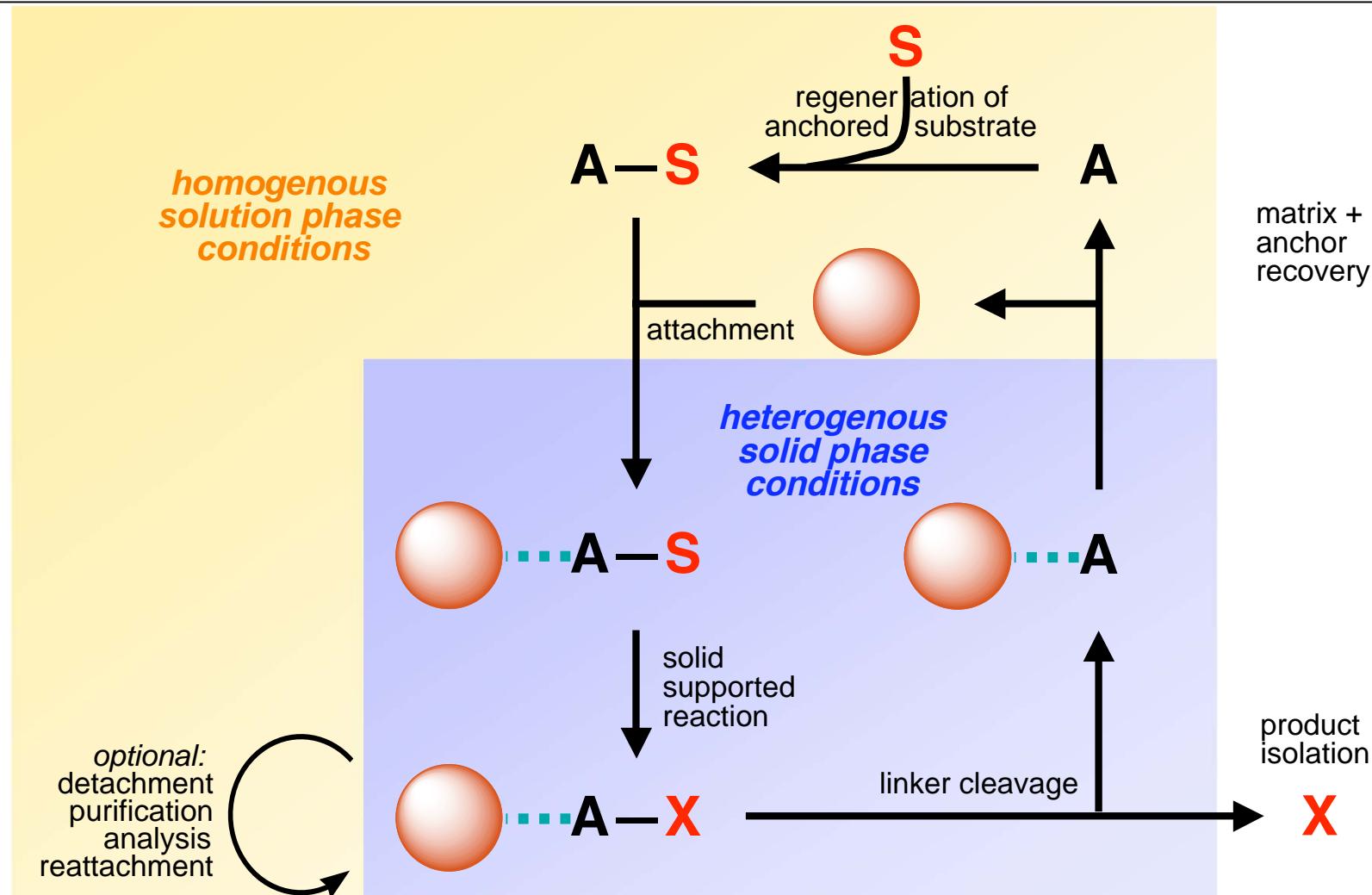
**reagent
chemocatalyst
biocatalyst**

- stable, solid particles
- many commercial matrices
- high loading capacity
- surface anchoring only
- large pore sizes
- good reagent accessibility

Application Principle



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Anchor Example: Reaction Screening

A. Porzelle
M. Adler

ultrasensitive monitoring
broad reaction space:

Reduction

Ozonolysis

Condensation

Michael

Suzuki

Sonogashira

Mukayama

Diels-Alder

Metathesis

Oxidation

Epoxidation

Mannich

Amination

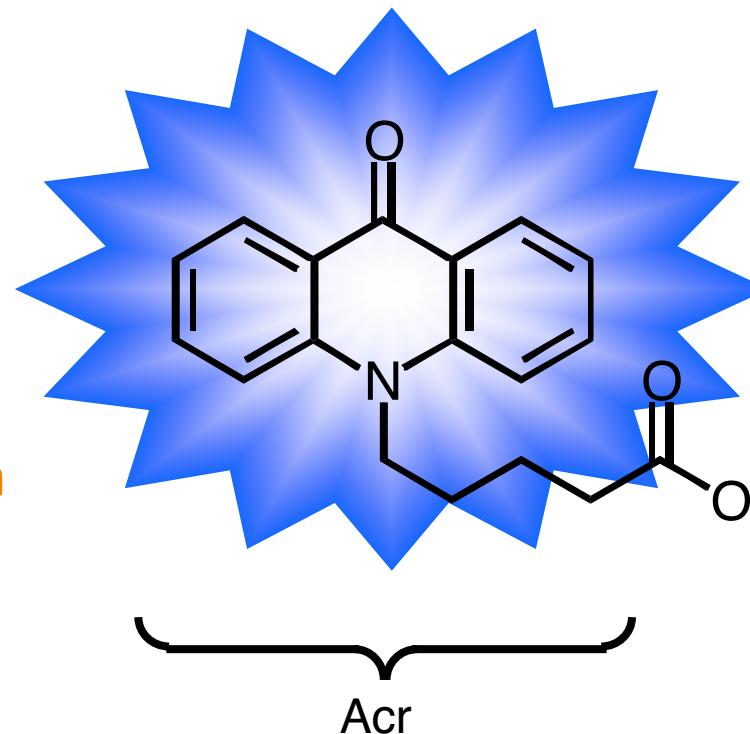
Heck

Barbier

Dihydroxylation

(3+2)

etc...



UV 366 nm

ester linker
(H^+/OH^- labile)

Acr

acridone as fluorescent tag

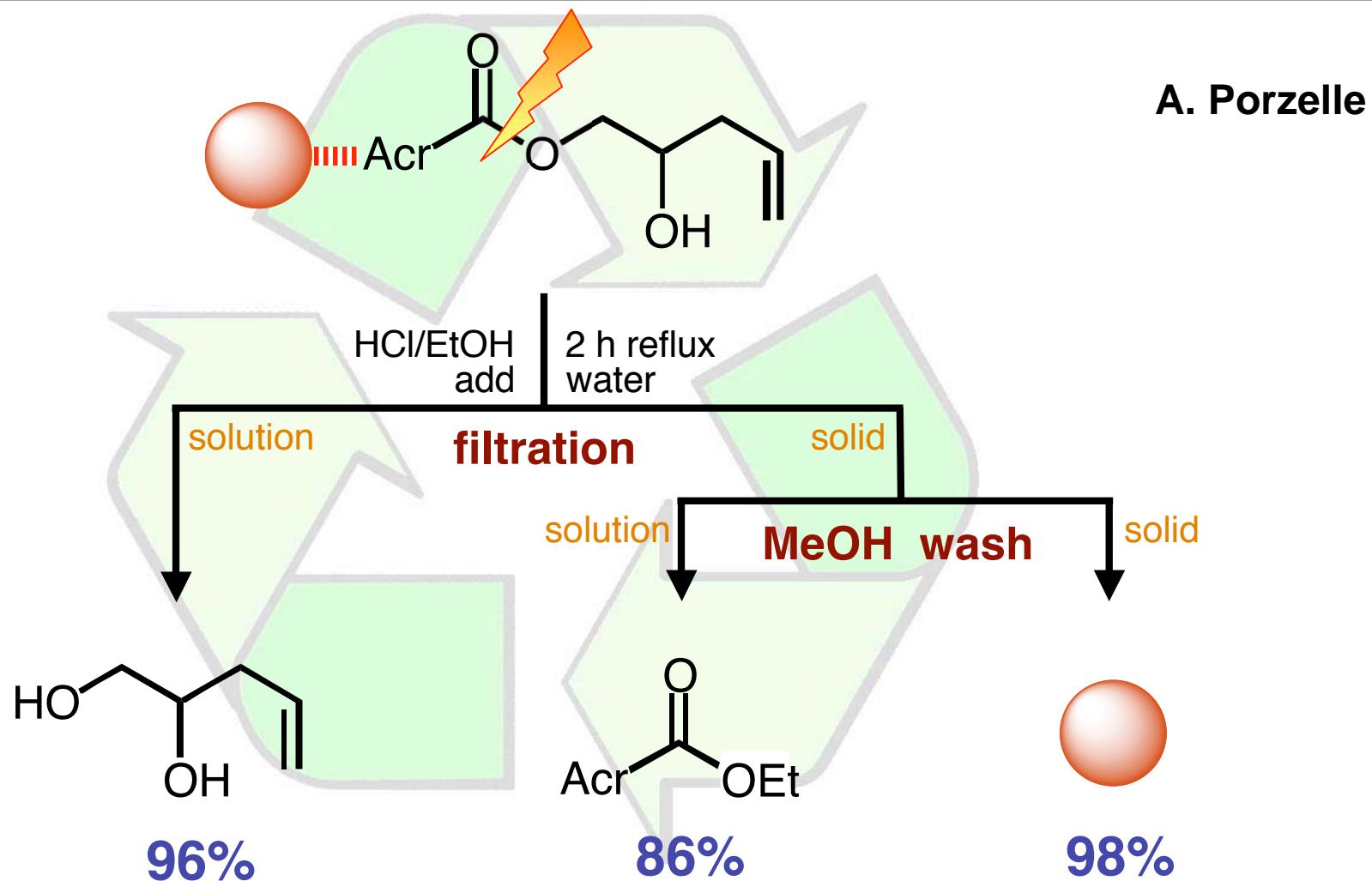
1 pmol detection limit (visual inspection)

good hydrophobicity (lgP 2.5)

Recycling



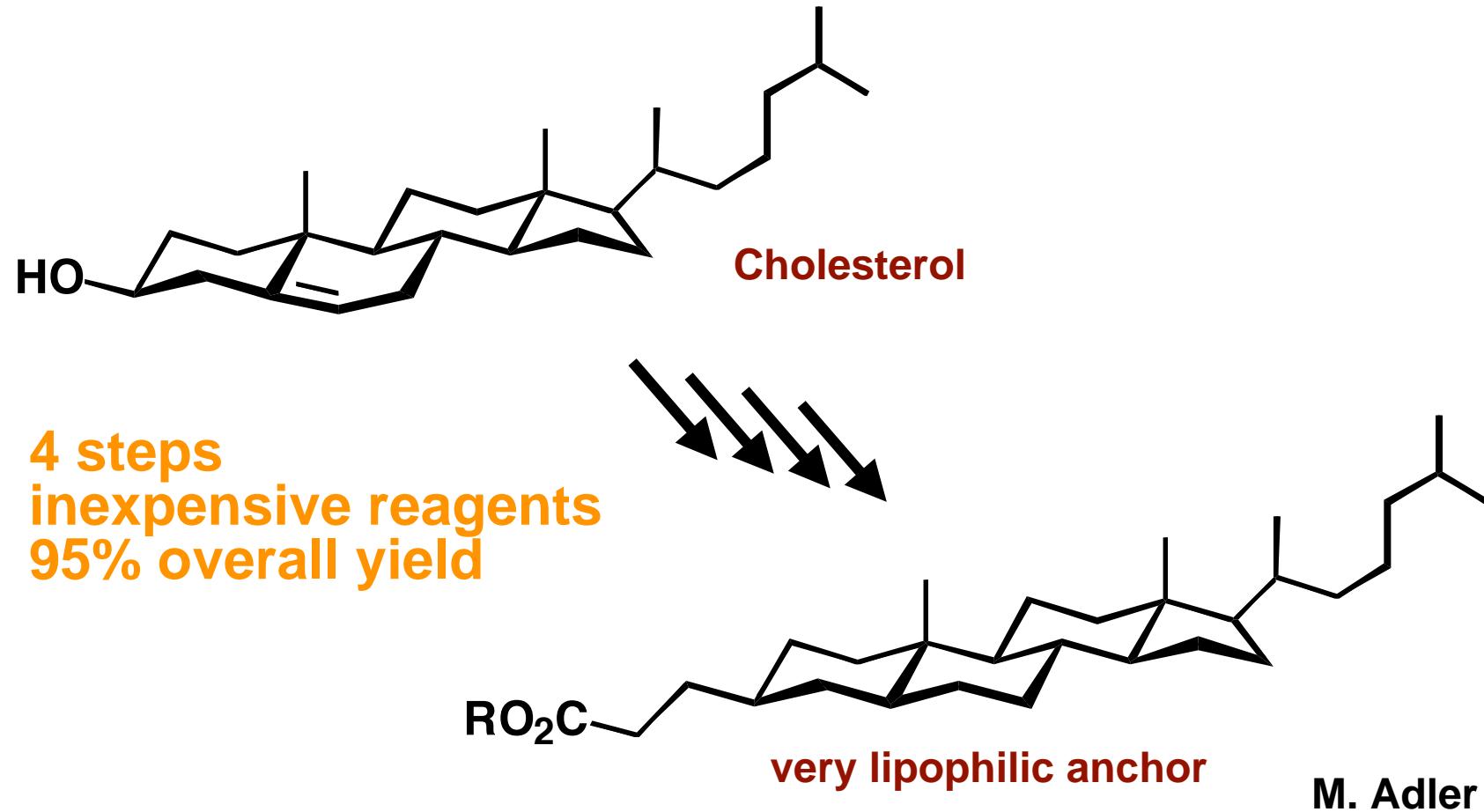
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Anchor Example: Large-scale Synthesis



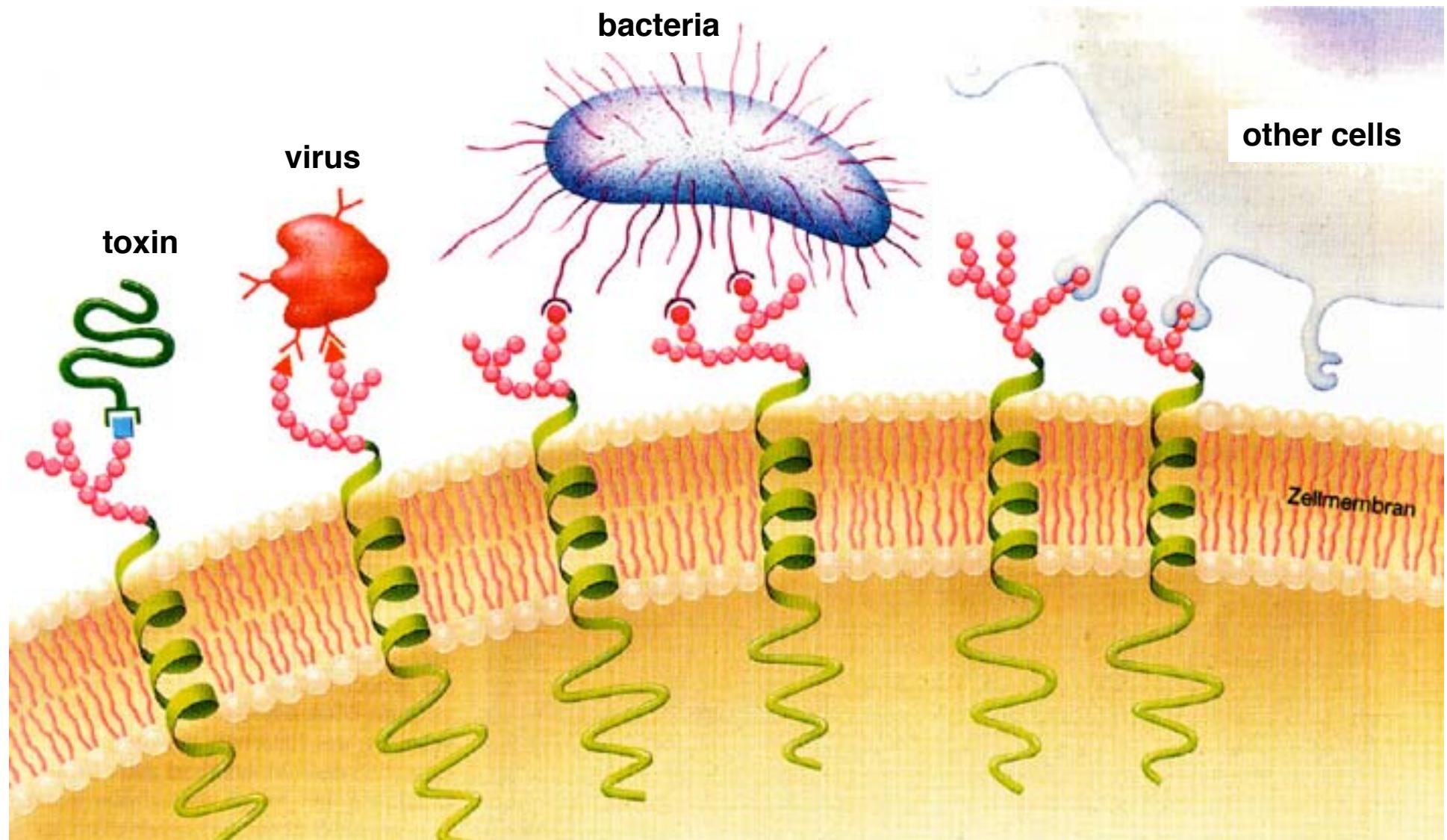
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Glycoconjugate Interactions



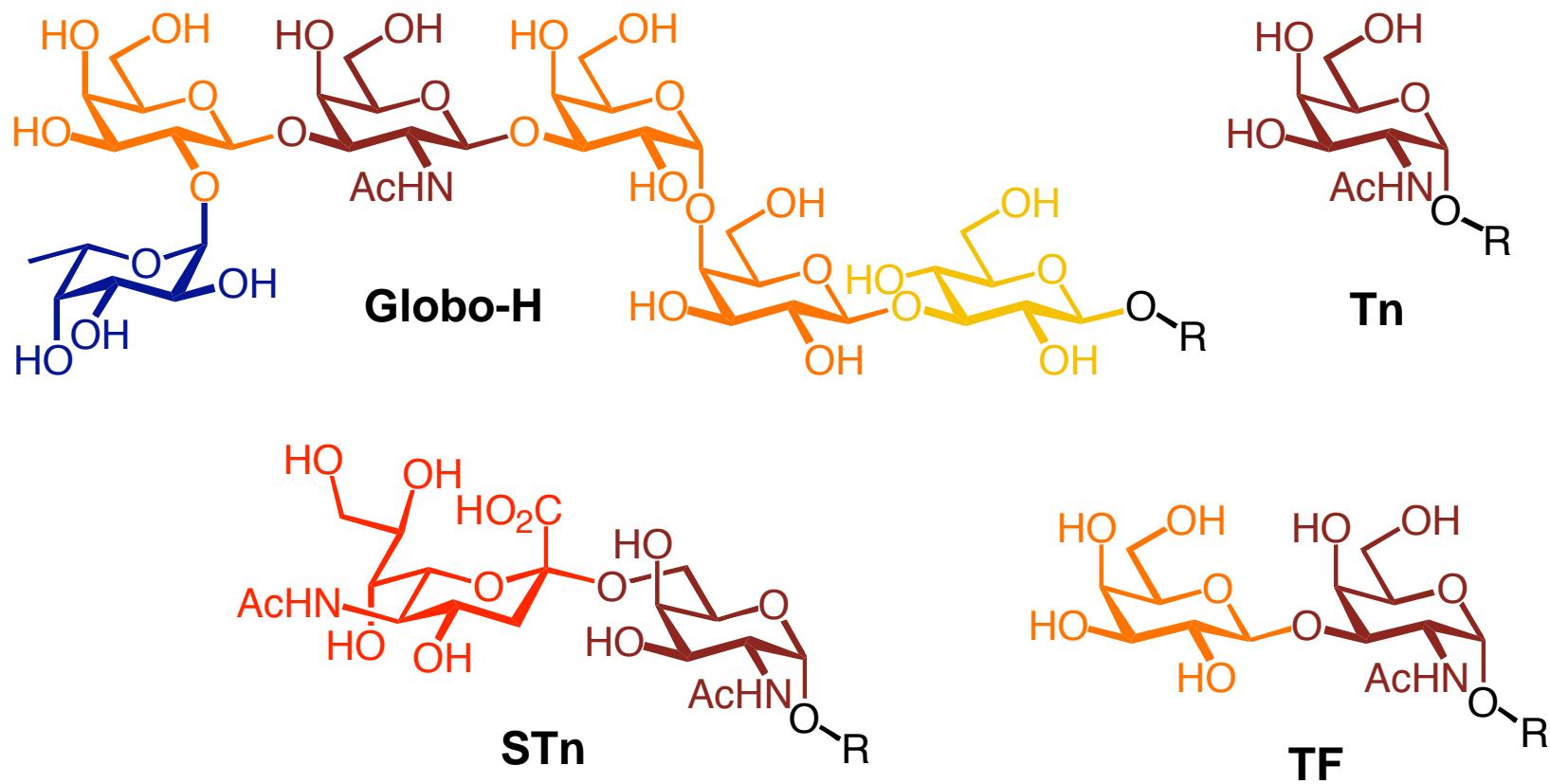
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Cancer-associated Oligosaccharide Antigens



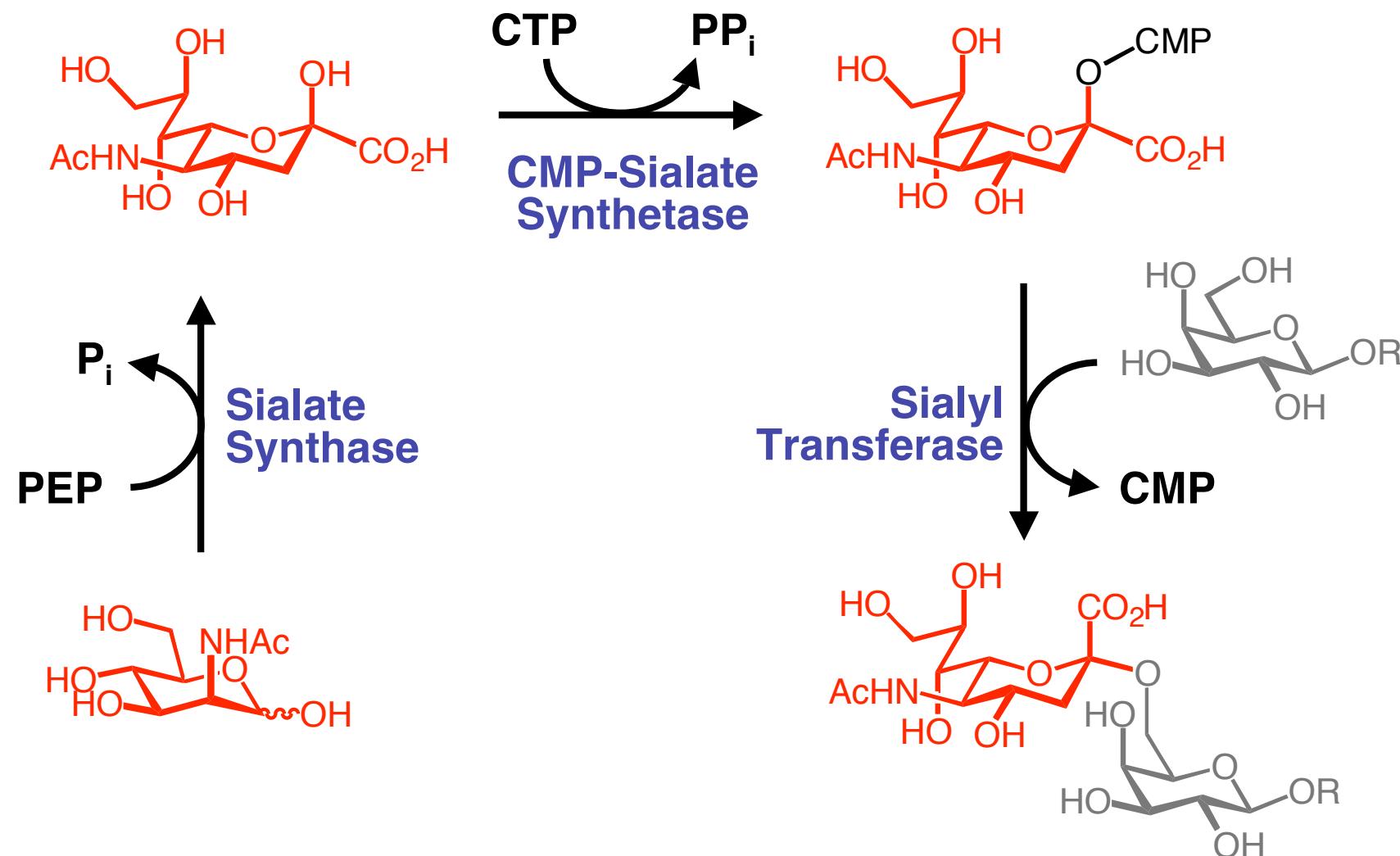
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Leloir-Path Sialylation



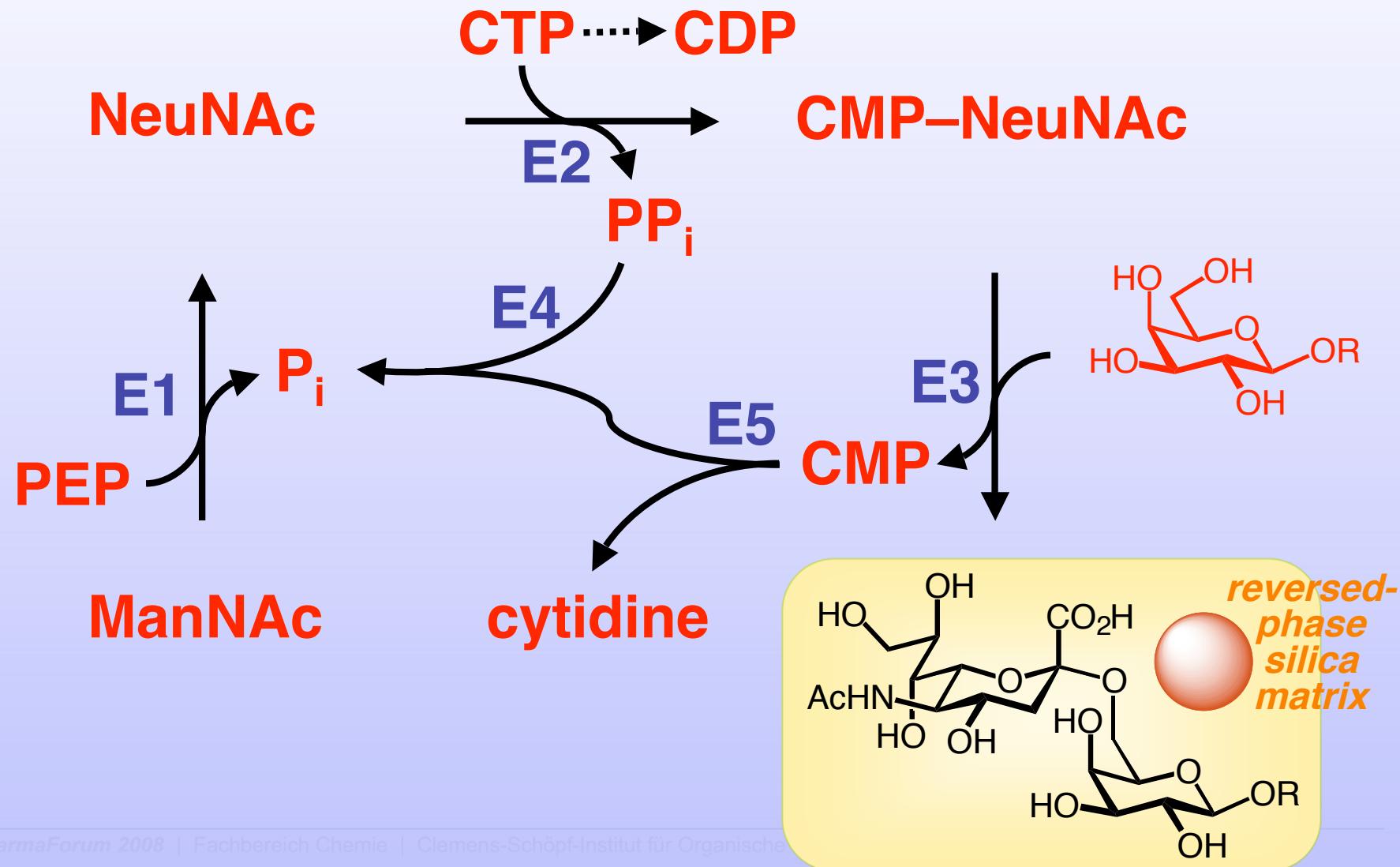
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Product Contamination



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2,3-Sialylated Oligosaccharide Library



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