

Syllabus

1. Occurrence and Functions of Peptides in Nature and Every Day Life

...hormones, neurotransmitters, therapeutics, artificial sweetener, ...

2. Peptide Synthesis

- a) **Aspartam**: Properties of amino acids; nomenclature; solution phase synthesis
- b) **Glucagon**: Solid phase peptide synthesis
- c) **Fuzeon, an anti HIV drug**: Solution and solid phase peptide synthesis

3. Peptide Structures – Nanostructured Materials – Self-assembly

- a) **Fuzeon**: α -helices and coiled-coil structures
- b) **Amyloids**: β -sheets
- c) **Collagen**: PPII helices

4. Applications of Peptides in Chemistry, Biology and Material Sciences

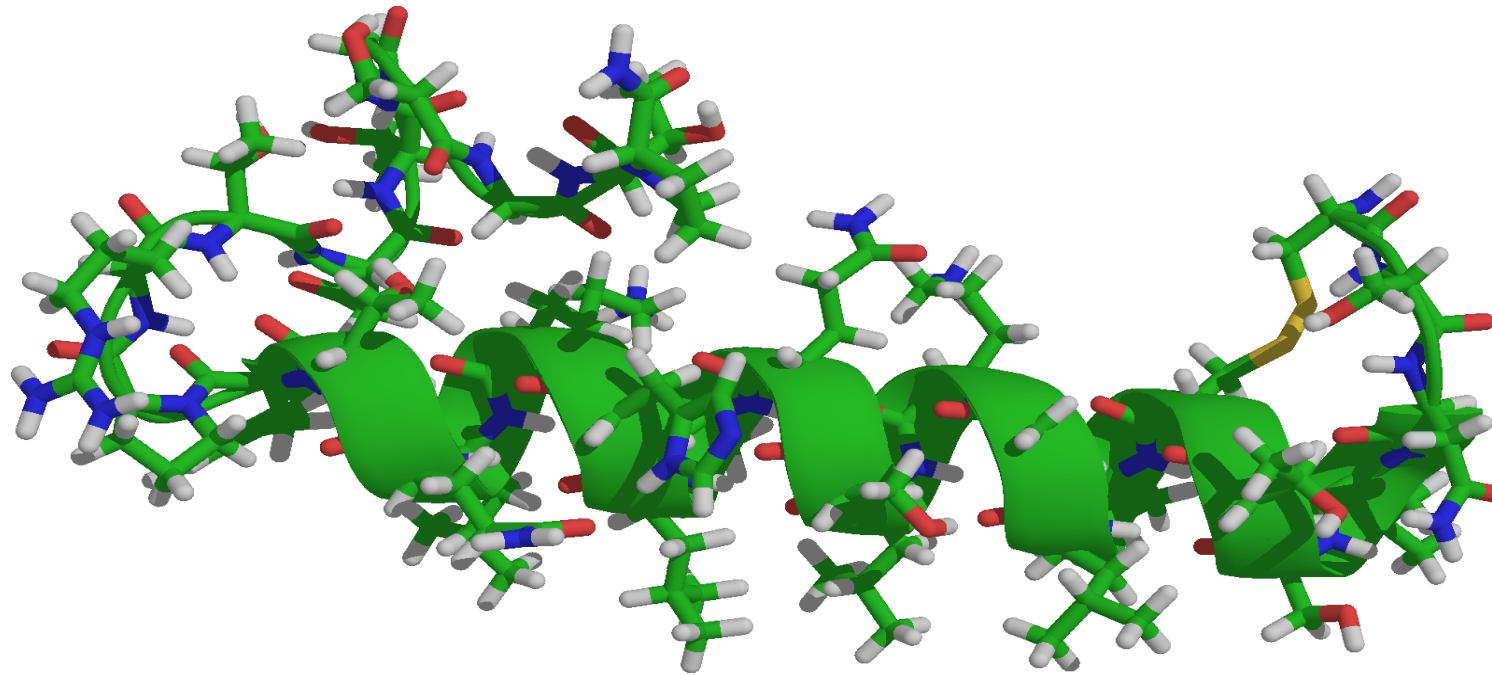
- a) Peptide-based materials
- b) Therapeutically active peptides
- b) Cyclic peptides and cancer imaging
- c) Asymmetric Catalysis with Peptides – Combinatorial chemistry

Solution Phase: Calcitonin (salmon)

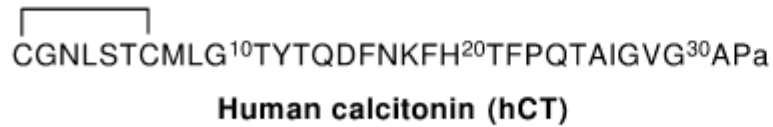


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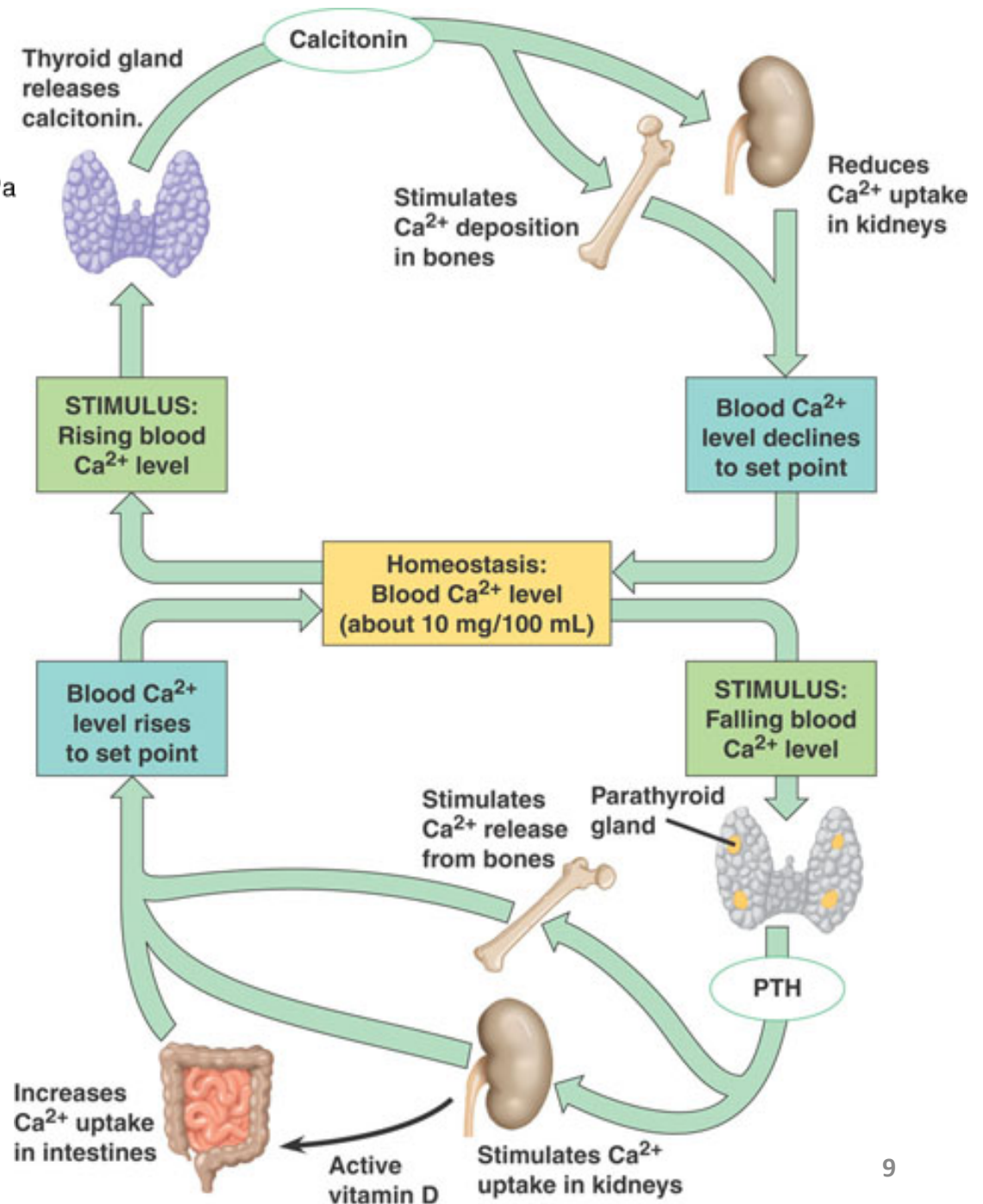
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Calcitonin

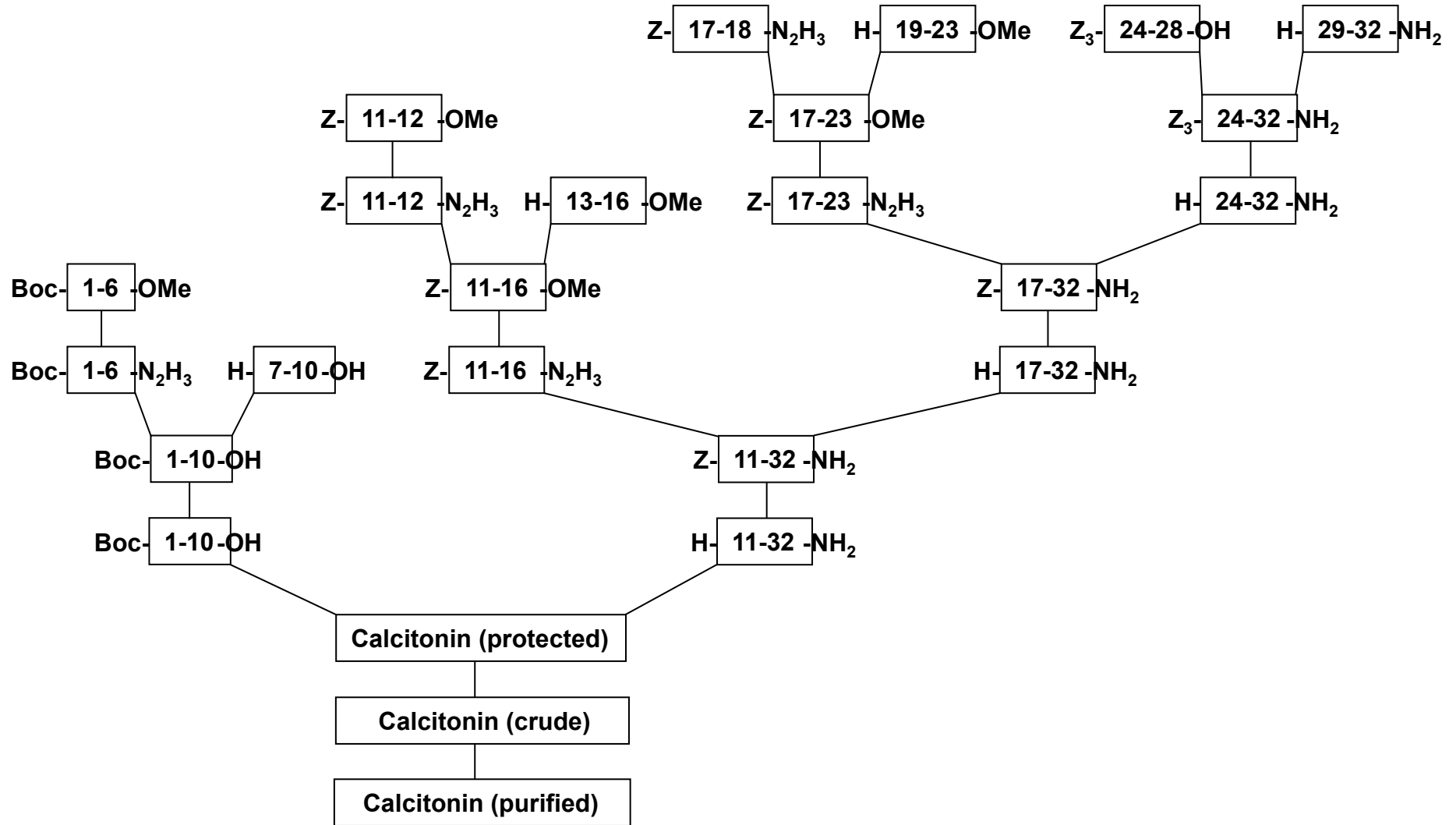


„Adversary“ of calcitonin:
 Parathyroid Hormon (PTH)



From: N. Sewald, H.-D. Jakubke, "Peptides: Chemistry and Biology", 2nd Ed., Wiley-VCH, Weinheim, 2009

Solution Phase: Calcitonin (salmon)



Solution Phase Peptide Synthesis – Scale

Calcitonin

- **Produced since** **1986**
- **Synthetic steps** **104**
- **Purification** **CCD**
 two-dim. HPLC
- **Derivatives needed** **158 kg**
 for the production
 of 1kg
- **Time for completion** **2.5 years**

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Solid Phase Peptide Synthesis (SPPS) (Nobelprize for Chemistry 1984: Bruce Merrifield)

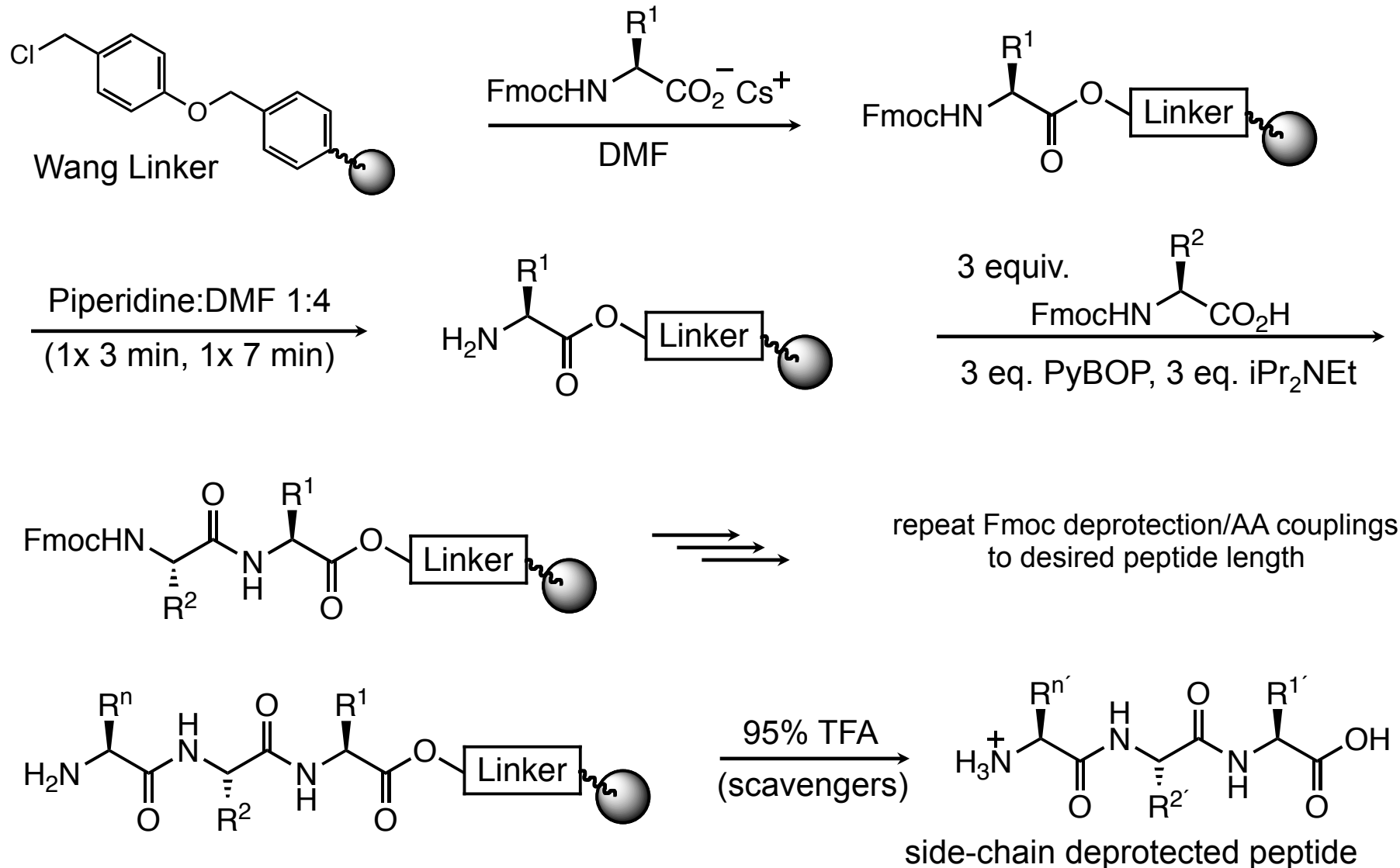
Peptidsynthesizer

1966



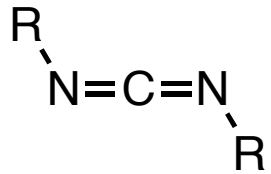
Solid Phase Peptide Synthesis (SPPS) – Fmoc/tBu Strategie

in the example: Wang Linker



Kupplungsreagenzien

Carbodiimide

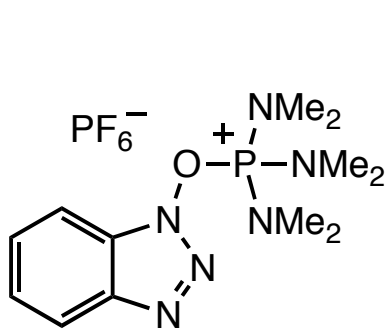


R = R' = cyclohexyl: *N,N'*-Di-Cyclohexyl Carbodiimid (DCC)

R = R' = *iso*-propyl: *N,N'*-Di-Isopropyl Carbodiimid (DIC)

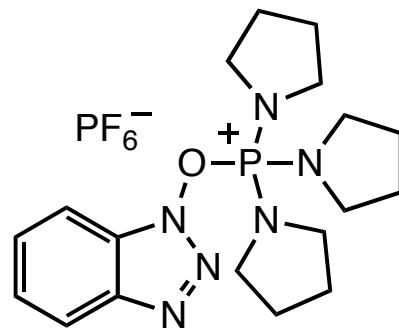
R = Et, R' = CH₂CH₂CH₂NMe₂ : *N*-Ethyl-*N'*-(3-Dimethylaminopropyl) Carbodiimid (EDC)

Phosponium Reagenzien

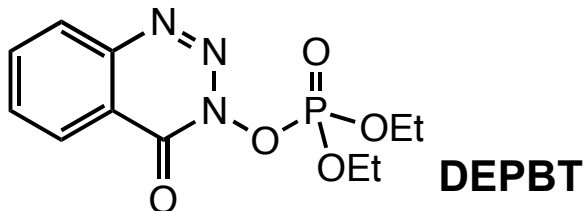


BOP

(Castro's Reagent)

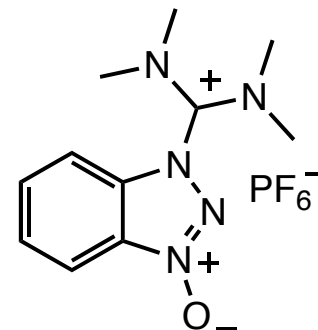


PyBOP

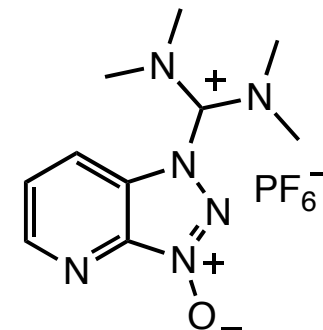


DEPBT

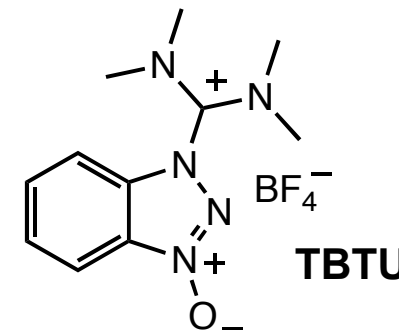
Guanidinium/Uronium Reagenzien



HBTU



HATU



TBTU

Commonly used acid sensitive protecting groups for the functional groups of the amino acid side chains

Fmoc: α -NH group

Boc: Lysine, Tryptophan, Histidine

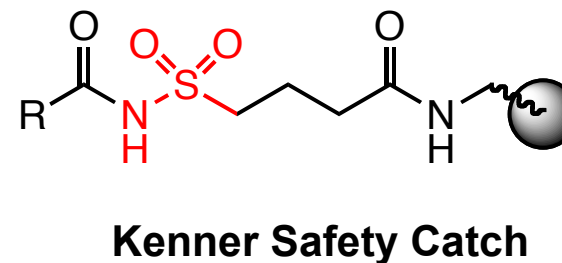
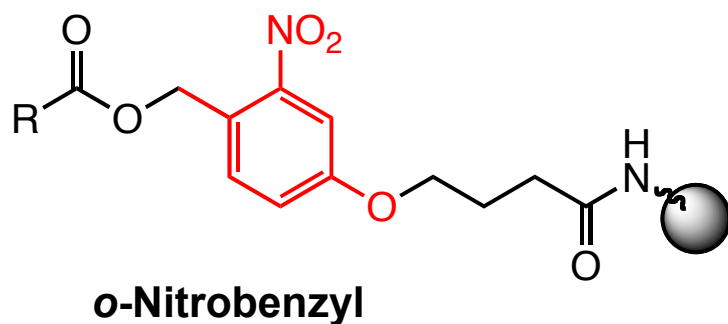
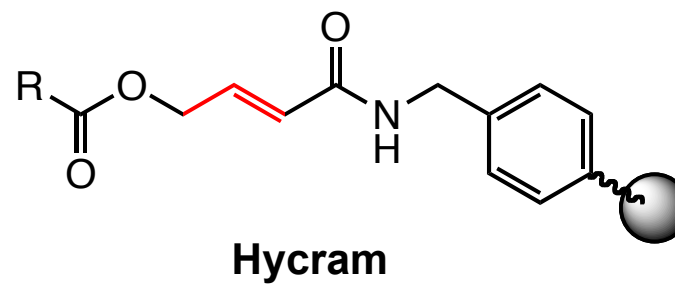
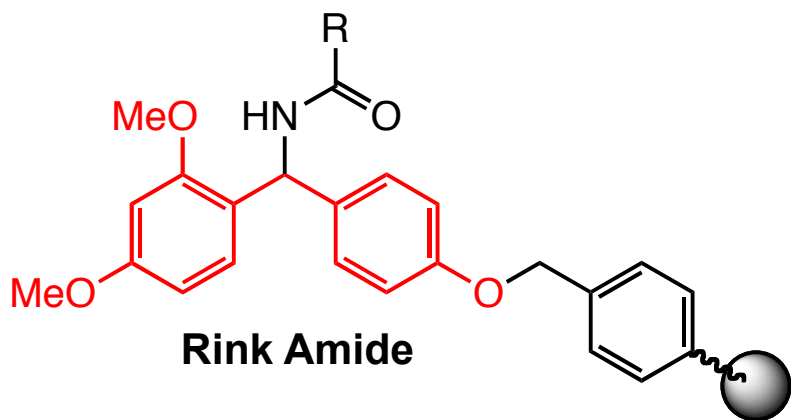
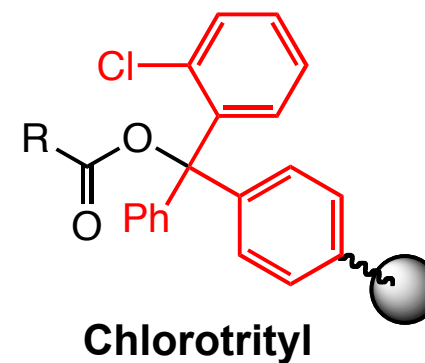
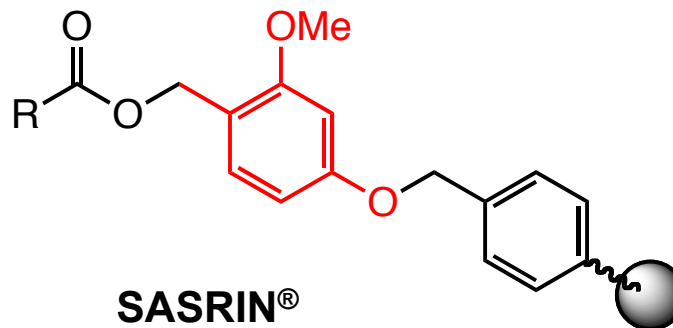
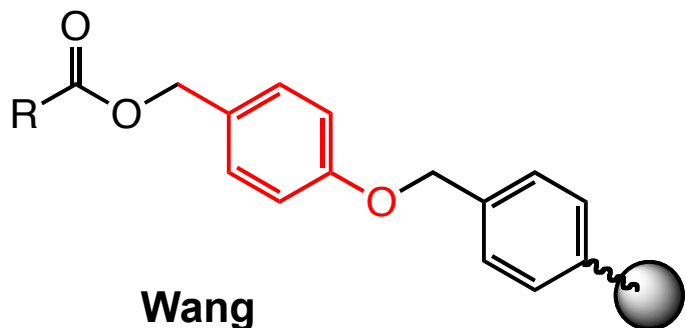
Pbf: Arginine

Trt: Cysteine, Aspartic acid, Glutamic acid

Acm: Cysteine

tBu: Serine, Threonine, Hydroxyproline, Tyrosine

Linker für die Festphasensynthese



Peptidsynthese an fester Phase

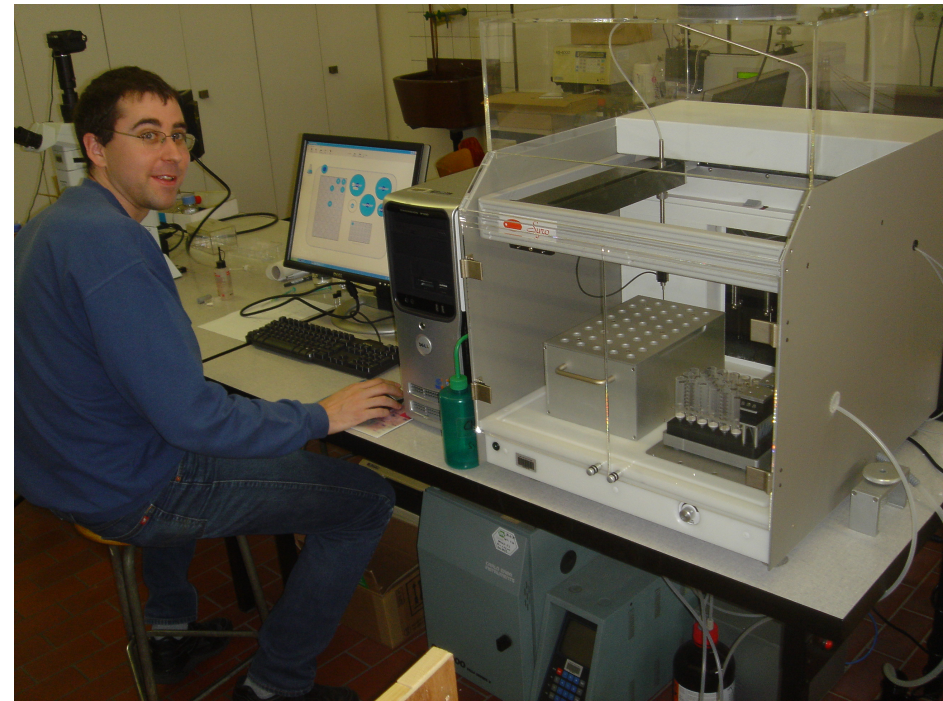
(Nobelpreis für Chemie 1984 für Bruce Merrifield)

Peptidsynthesizer

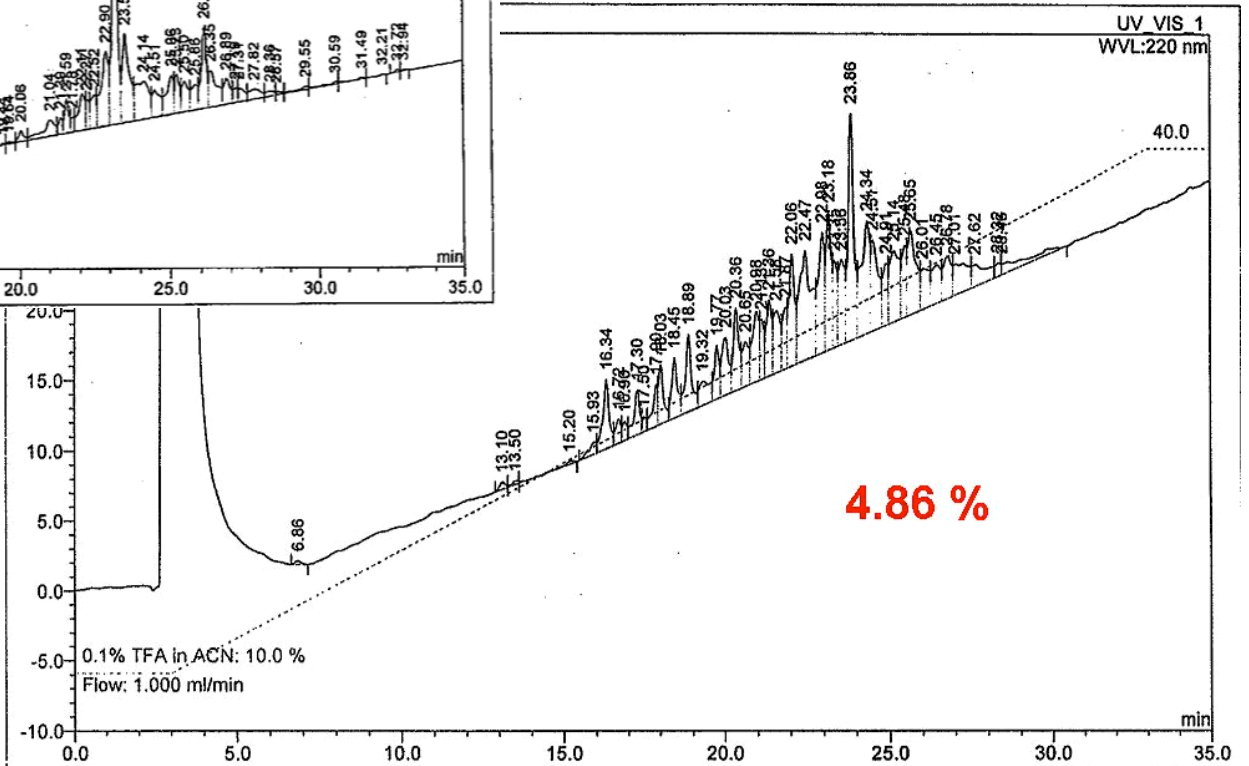
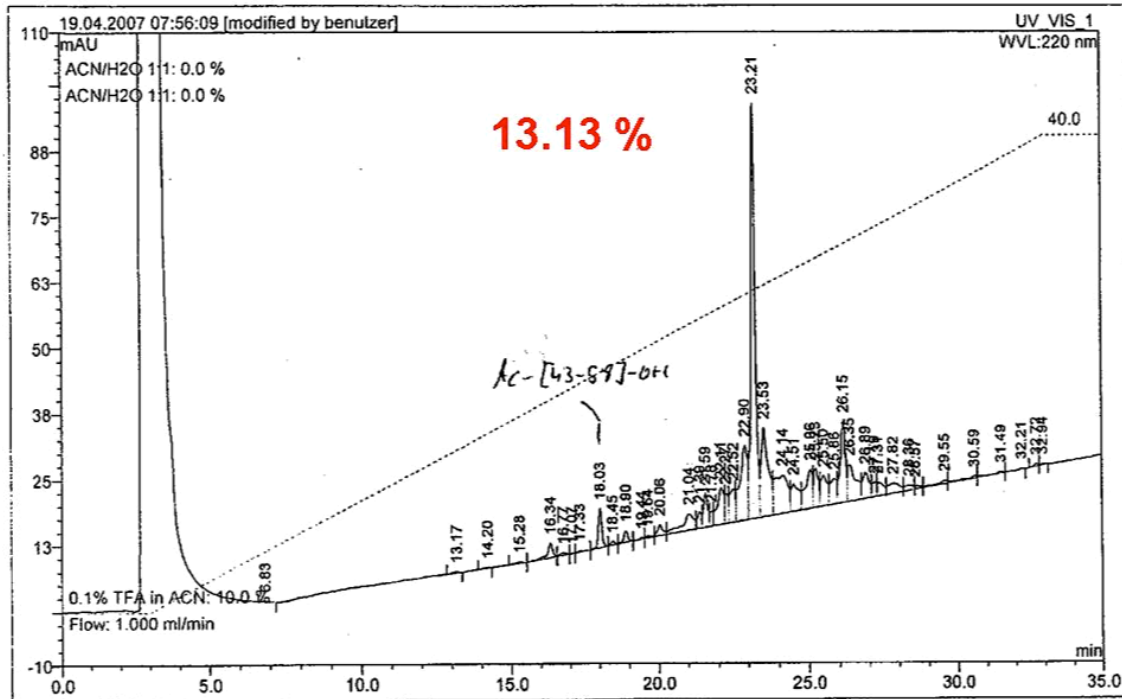
1966



heute

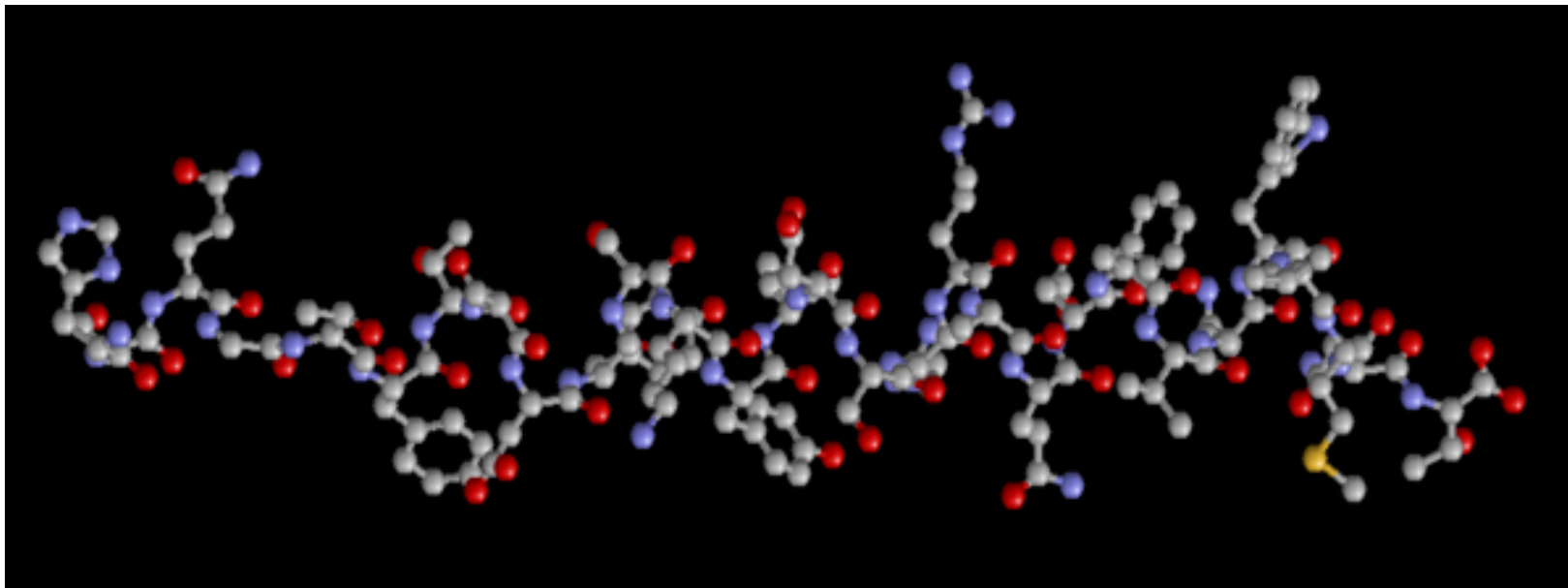


Examples of Crude Purity



Solid Phase: Glucagon (1-29, human)

HSQGTFTSDYSKYLDSRRAQDFVQWLMNT

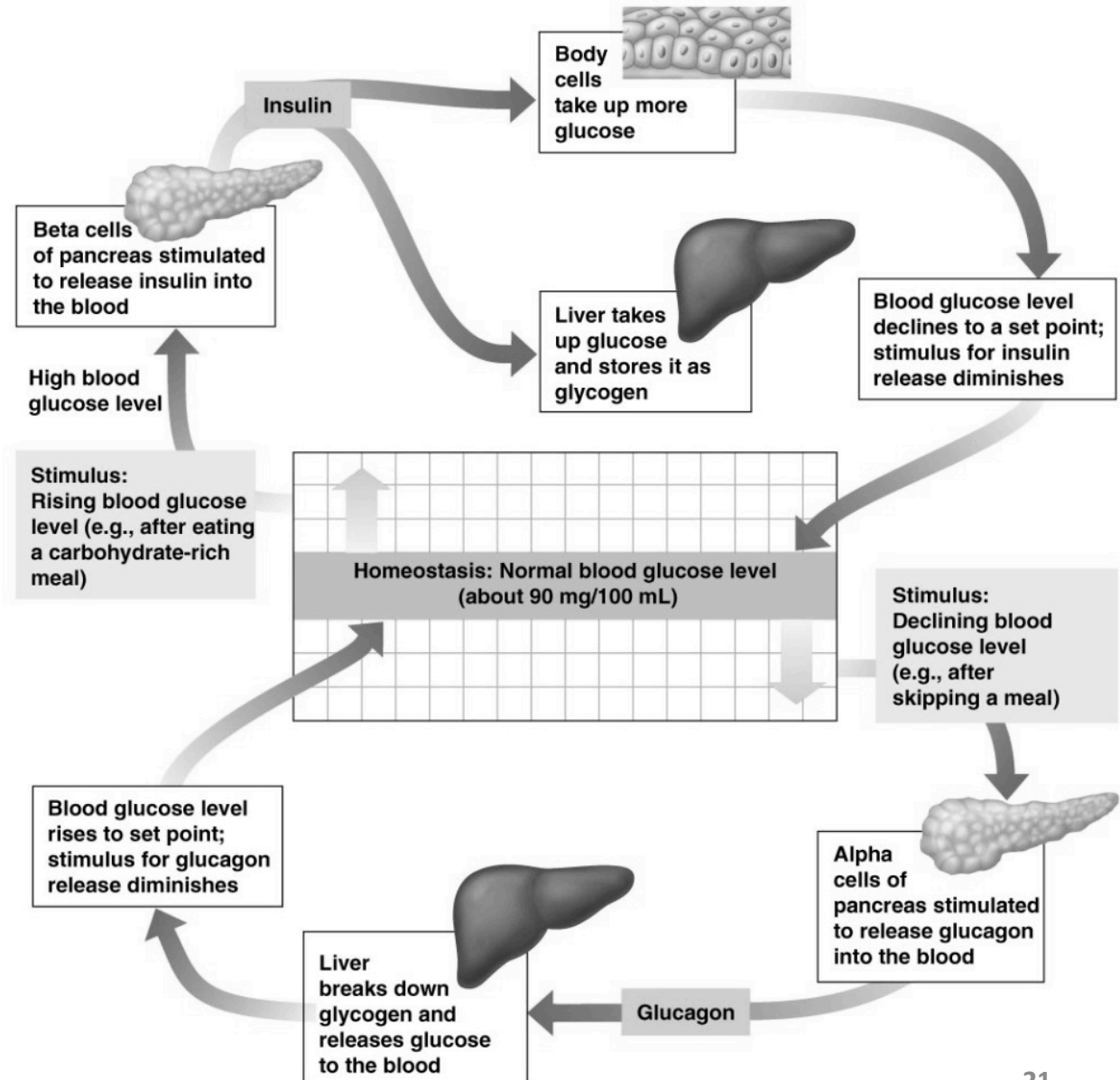
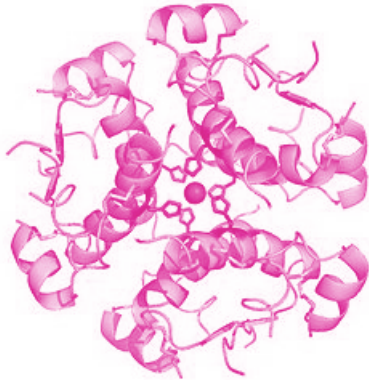


Insulin and Glucagon

Glucagon (Secretin Family)



Insulin (Insulin Superfamily) inactive hexameric form – bound to Zn^{2+} :



Comparison: Solution vs. Solid Phase

	Calcitonin	Glucagon
- Produced since	1986	1996
- Synthetic steps	104	56
- Purification	CCD two-dim. HPLC	three-dim. HPLC
- Derivatives needed for the production of 1kg	158 kg	29 kg
- Time for completion	2.5 years	0.6 years