

## ***Chapter 25 — synthesis in action***

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Exemplary syntheses of important compounds:

Saccharin (reactions of sulfonyl groups)

Salbutamol (Friedel-Crafts, benzyl protecting group)

Thyroxine (nucleophilic aromatic substitution, diazonium chemistry)

Peptides and proteins

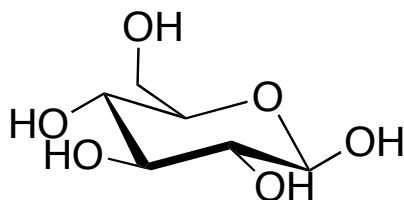
Completing our table of protecting groups (more for amines and carboxylic acids)

# Sweetness and chemical structure

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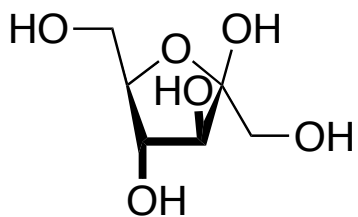
“Relative sweetness” (Sucrose = 100)

glucose



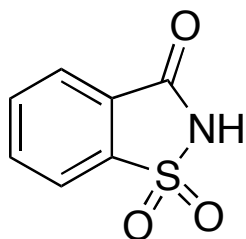
70

fructose



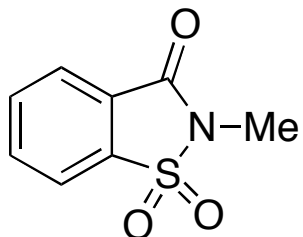
140

saccharin



~ 28000

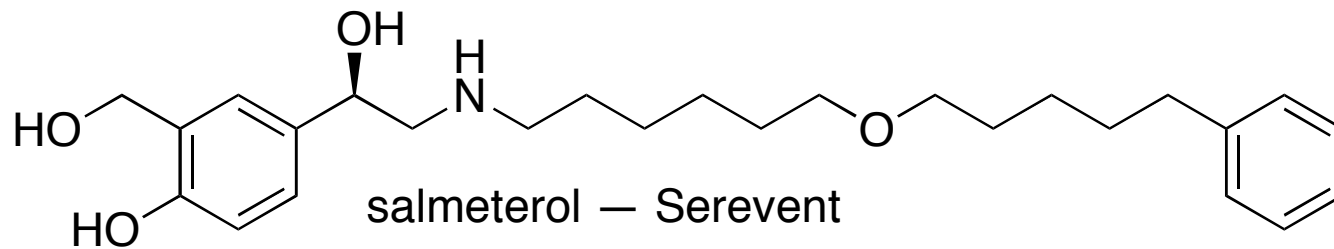
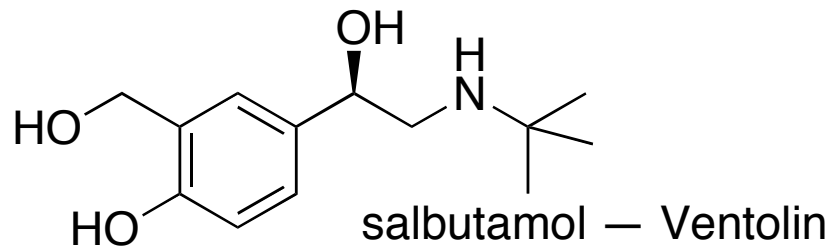
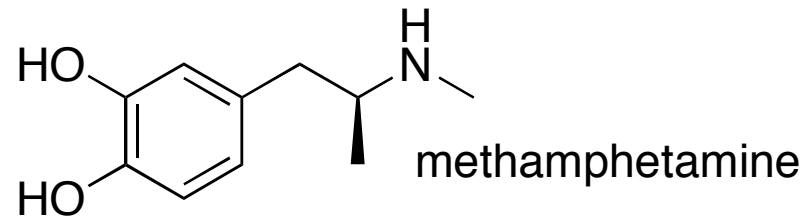
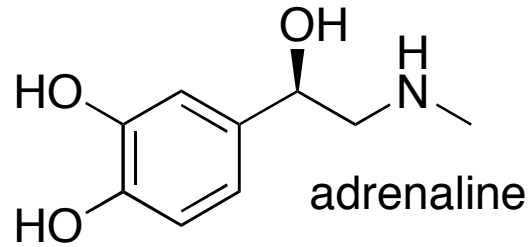
N-methyl saccharin



not sweet

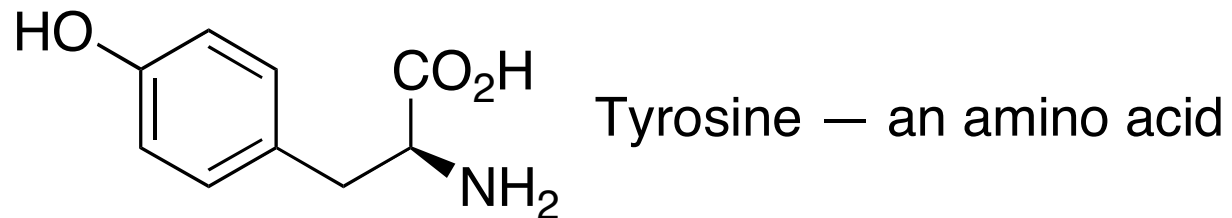
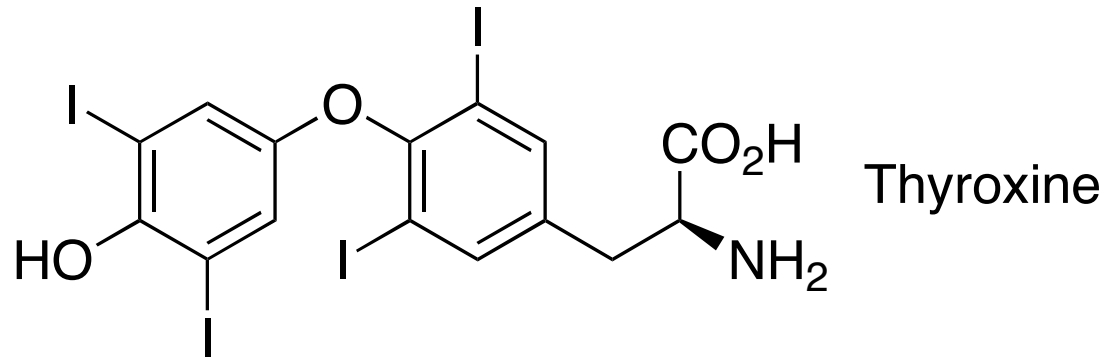
## ***Asthma drugs — bronchodilators***

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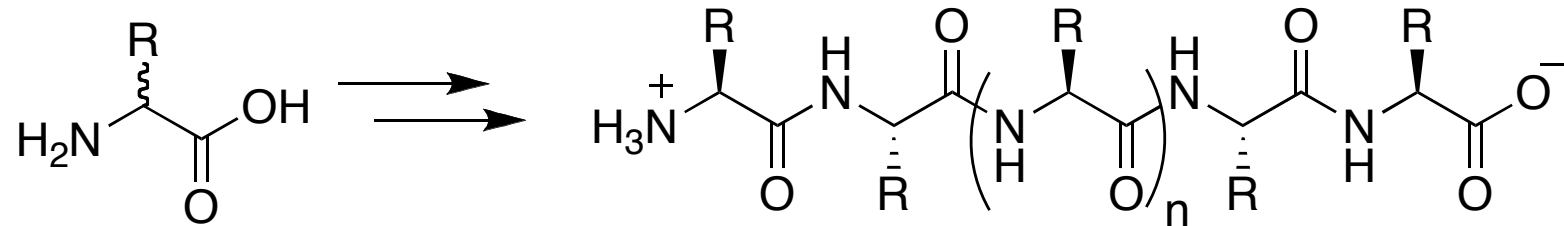
## Thyroid hormone — Thyroxine

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## ***Peptides and proteins — polymers of amino acids***

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Amino acid

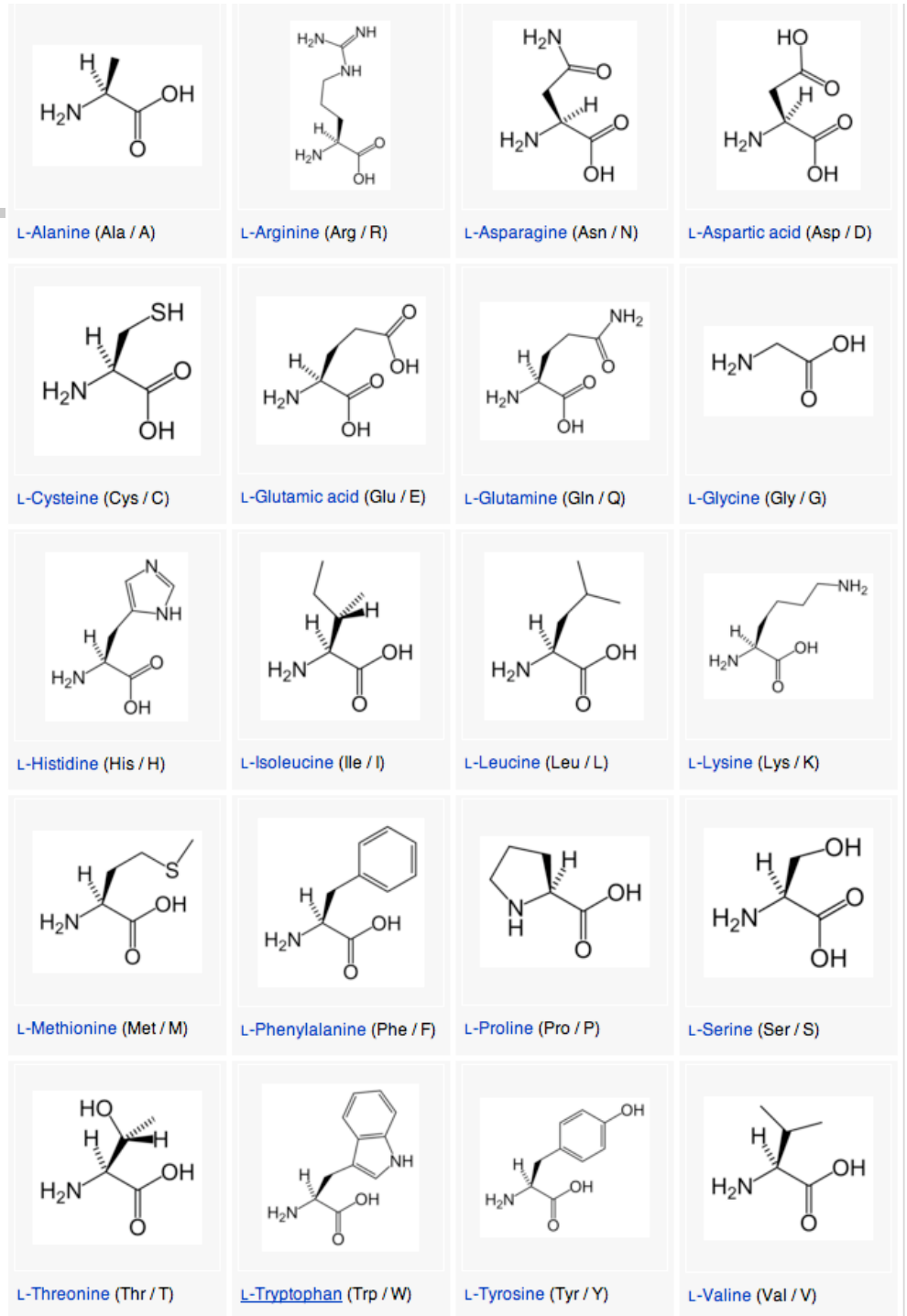
Peptides and proteins

Nobel 1955: Vincent du Vignaud

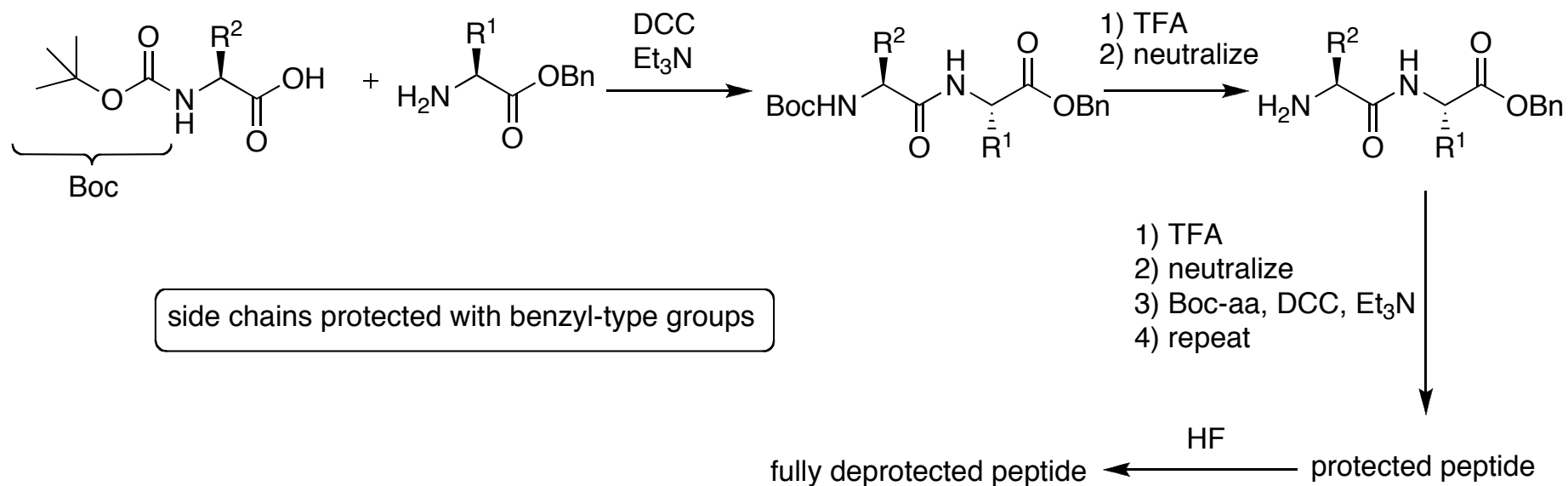
First chemical synthesis of a polypeptide hormone (insulin)

# The 20 natural amino acids

Side chains have varied functional groups for doing different chemistry

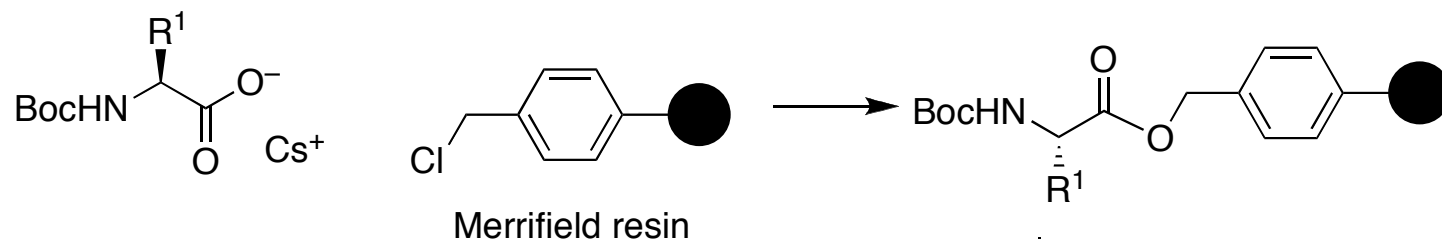


# The Boc/benzyl method of peptide synthesis



need to use pure HF in special teflon vessels to cleanly remove benzyl-type protecting groups

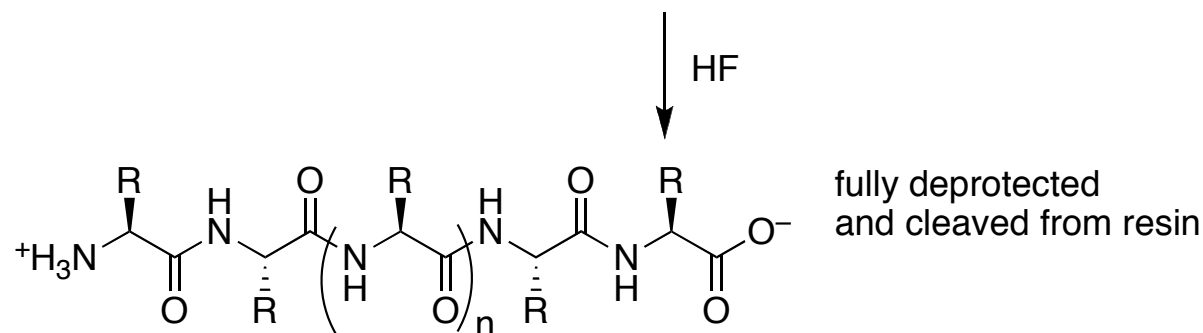
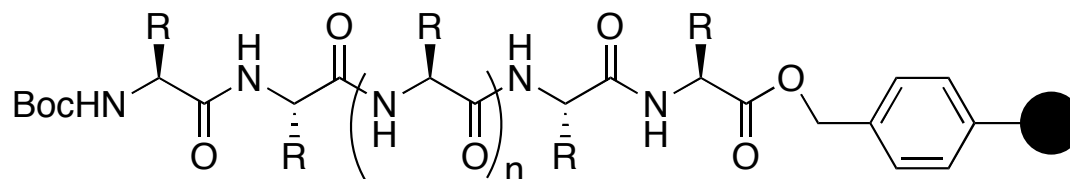
# Solid phase peptide synthesis



Insoluble polymer resin greatly simplifies workup and purification. Just filter to remove excess reagents

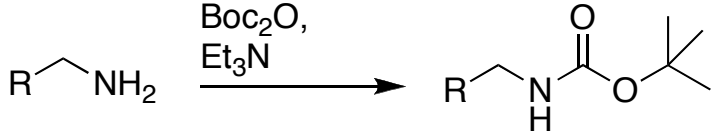
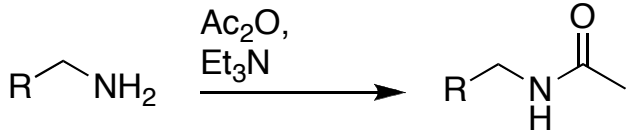
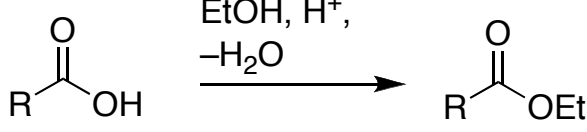
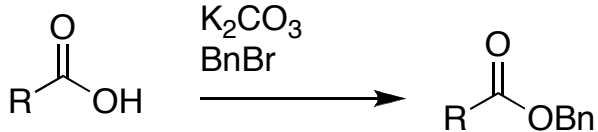
- 1) TFA
- 2) neutralize
- 3) Boc-aa, DCC, Et<sub>3</sub>N
- 4) repeat

Nobel 1984:  
Robert Merrifield





## Protecting groups 2.

Name	Addition	Protects from	Removal
t-butoxycarbamate (Boc)	$\text{R}-\text{NH}_2 \xrightarrow{\text{Boc}_2\text{O}, \text{Et}_3\text{N}}$ 	protects amines from bases, nucleophiles, and electrophiles	TFA or HCl, 25 °C
acetamide	$\text{R}-\text{NH}_2 \xrightarrow{\text{Ac}_2\text{O}, \text{Et}_3\text{N}}$ 	protects amines from bases, nucleophiles, and electrophiles	HBr or HI, heat
alkyl ester	$\text{R}-\text{COOH} \xrightarrow{\text{EtOH}, \text{H}^+, -\text{H}_2\text{O}}$ 	protects carboxylates from anhydrous acids and bases, weak nucleophiles	$\text{HO}^-$ , $\text{H}_2\text{O}$
benzyl ester	$\text{R}-\text{COOH} \xrightarrow{\text{K}_2\text{CO}_3, \text{BnBr}}$ 	protects carboxylates from anhydrous acids and bases, weak nucleophiles	$\text{H}_2$ , Pd/C or $\text{HO}^-$ , $\text{H}_2\text{O}$