

Synthesis of Vitamins & Cofactors

Gaich Group Seminar

17.07.2014, Darius Schwazrer

Cofactor/Coenzyme:

- A nonprotein component of enzymes is called the cofactor. If the cofactor is organic, then it is called a coenzyme. Coenzymes are relatively small molecules compared to the protein part of the enzyme. Many of the coenzymes are derived from vitamins

Protein + Cofactor/Coenzyme = Holoenzyme

Proteinpart of Enzyme = Apoenzyme

Vitamin:

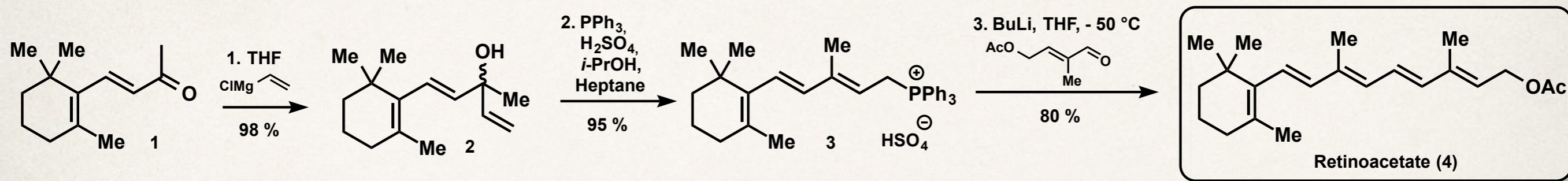
- 1912 Kazimierz Funk defined that the essential substances contain an amine function are called Vita = life; amine

Essential, organic compounds which are not synthesized in the human or animal organism or formed only in insufficient amounts .

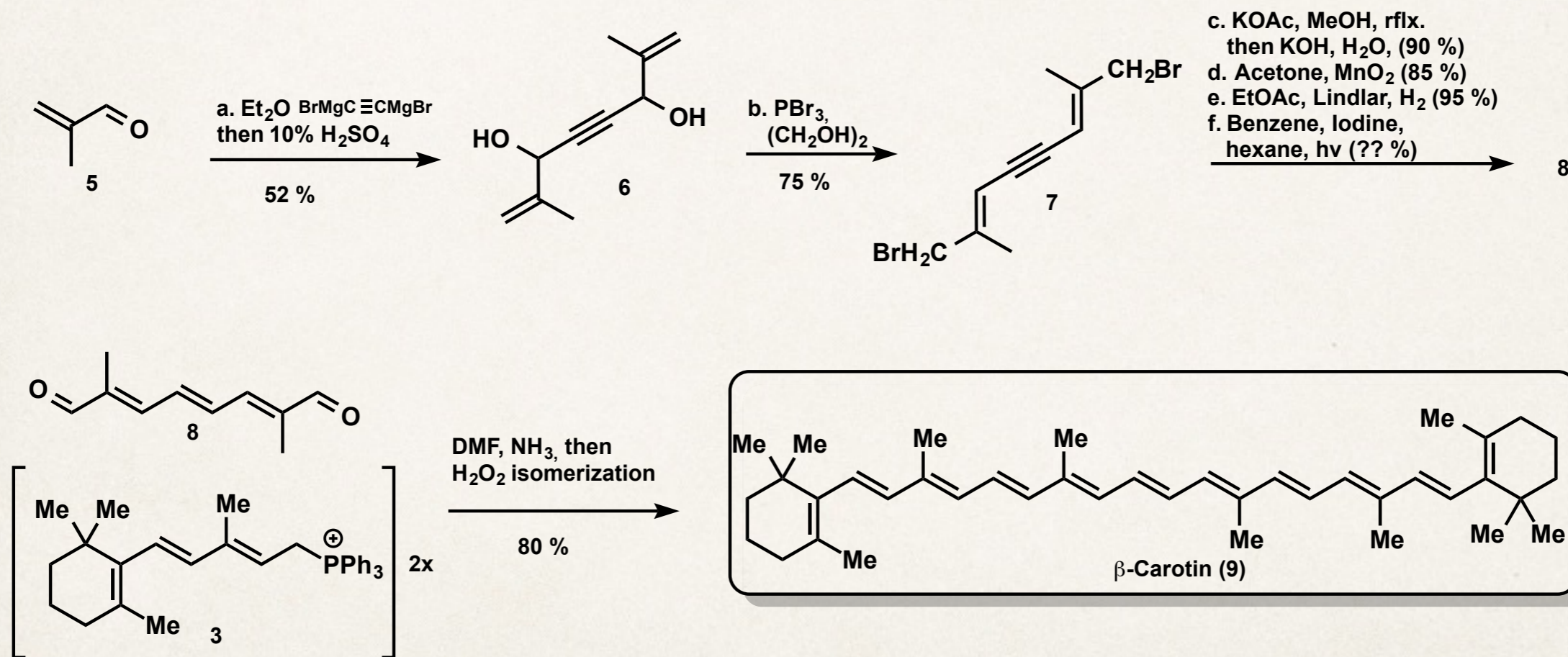
Must be regularly consumed with diet

Vitamin A & β -Carotene

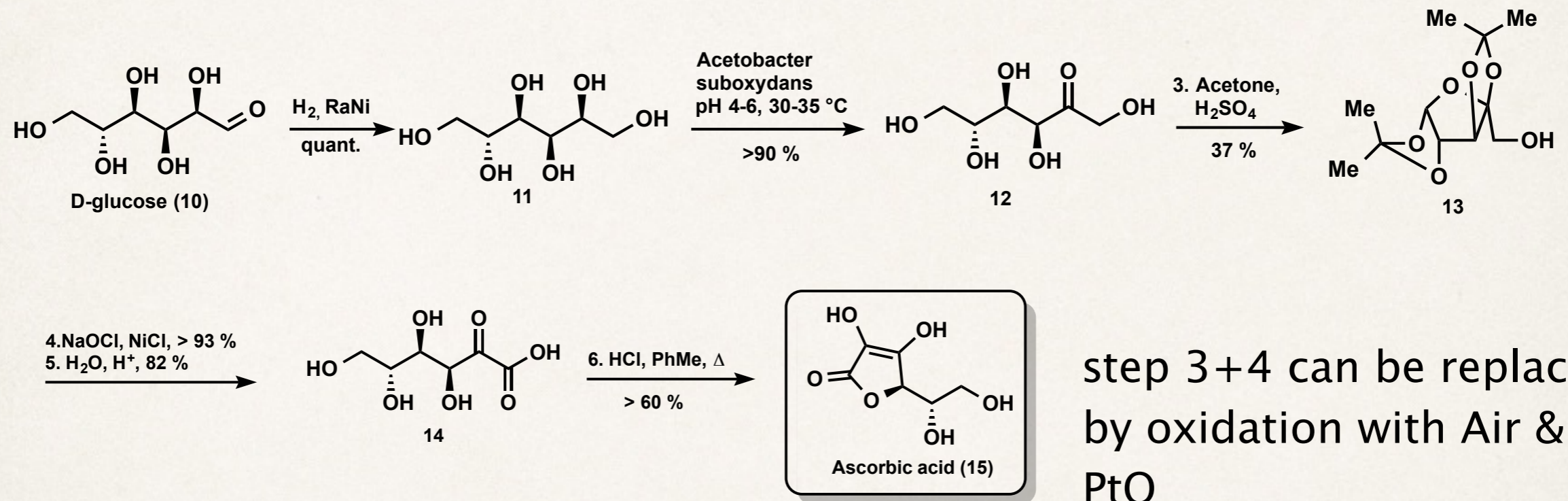
Retinol acetate (BASF)



β -Carotene (BASF)



Vitamin C synthesis by Reichstein process

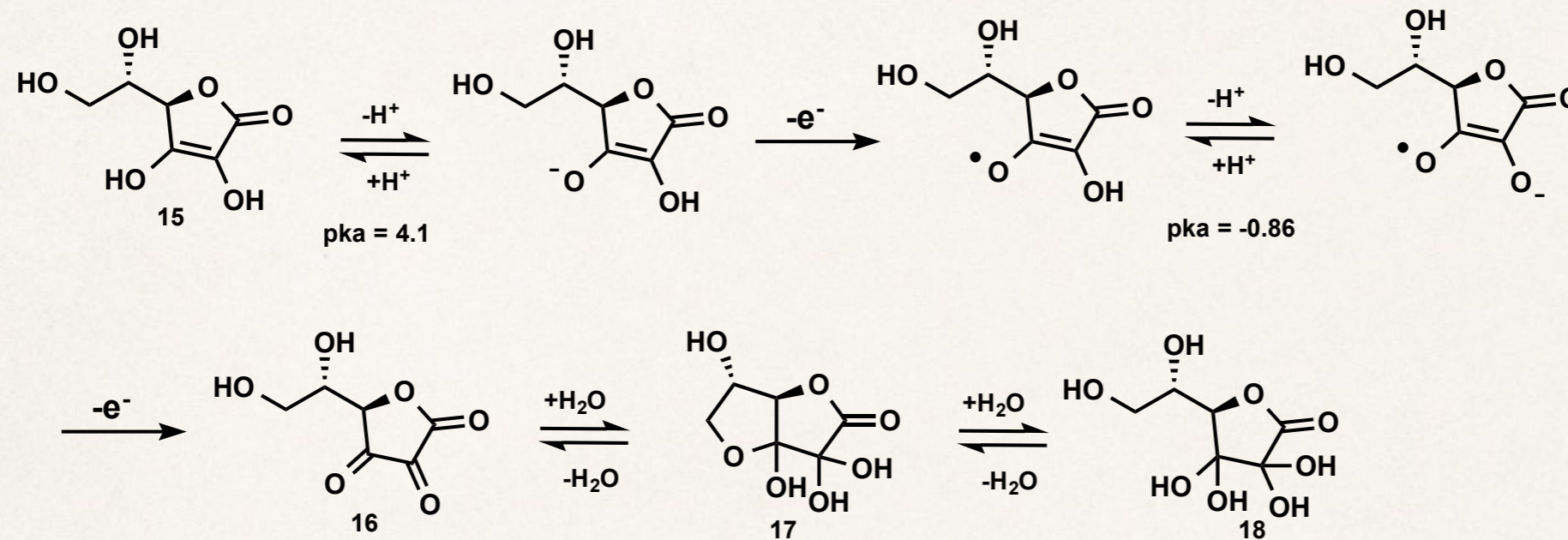


Reichstein synthesis was optimized so that each step gives over 90 % yield

Overall yield from D-glucose is now 60 %

Direct synthesis via microalgae possible, but yield and concentration are too low

Metabolism of Vitamin C



Economic aspects

- production > 600 kt/a
- cost ~3000 €/t

Industrial use

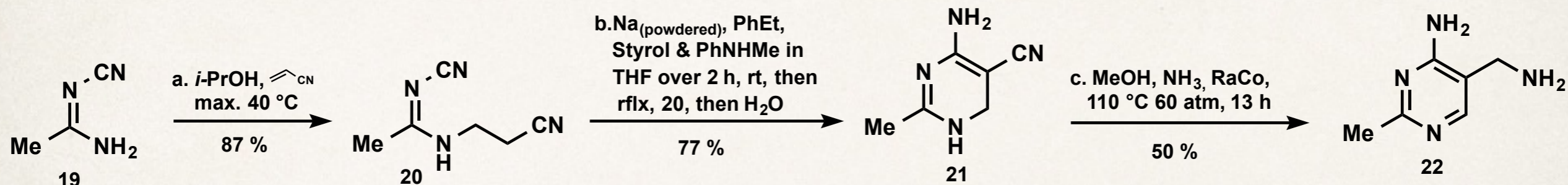
- Inhibition of nitrosamine in cured meat
- Improvement of flour quality
- Increasing of clarity of wine & beer
- protecting fruits from browning

Biological activity

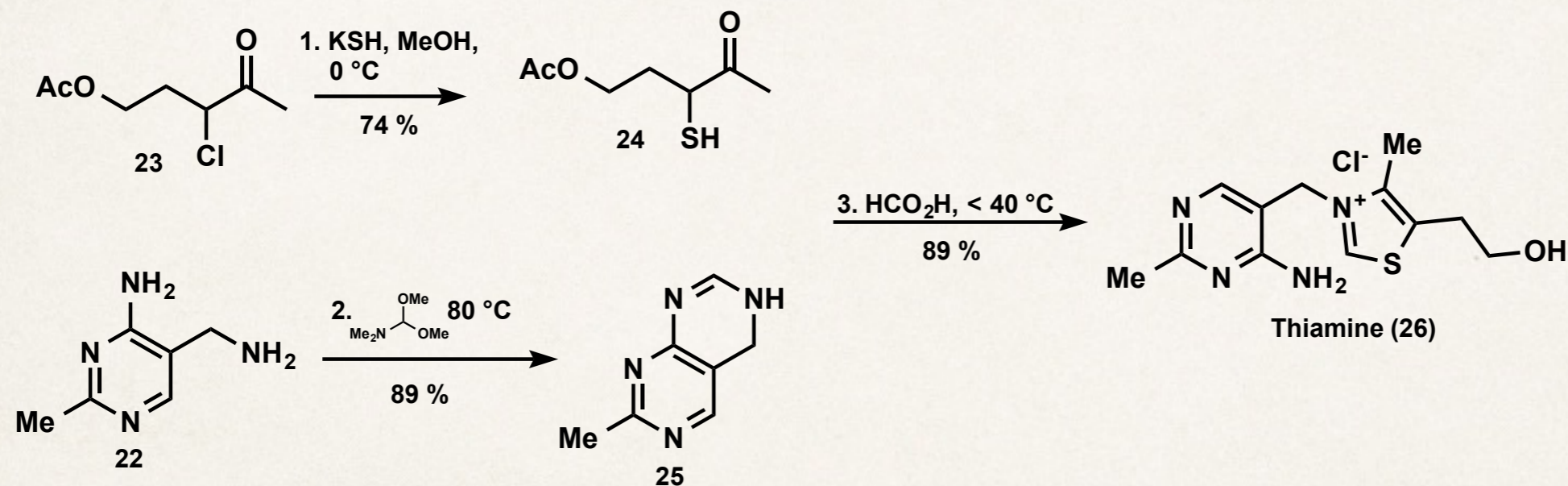
- anti oxidant
- radical scavenger
- electron donator for 8 enzymes (hydroxylases)
- prevents from scurvy

Synthesis of Vitamin B₁

Step 1. Synthesis of 22



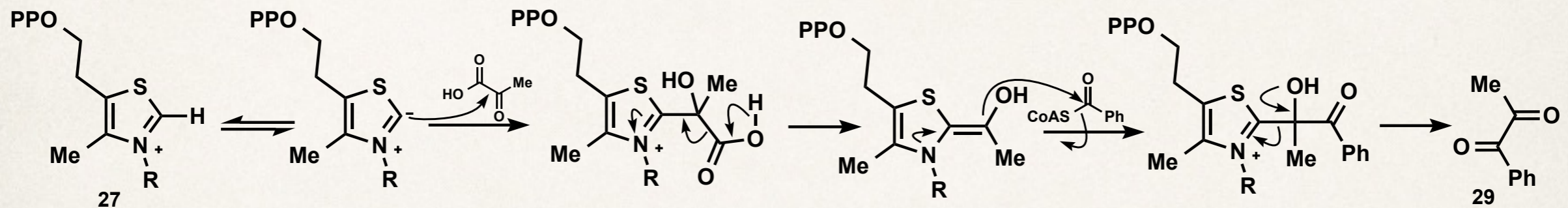
Step 2. Condensation & formation of thiazolium ring



22 and 23 commercially available

Biological activity

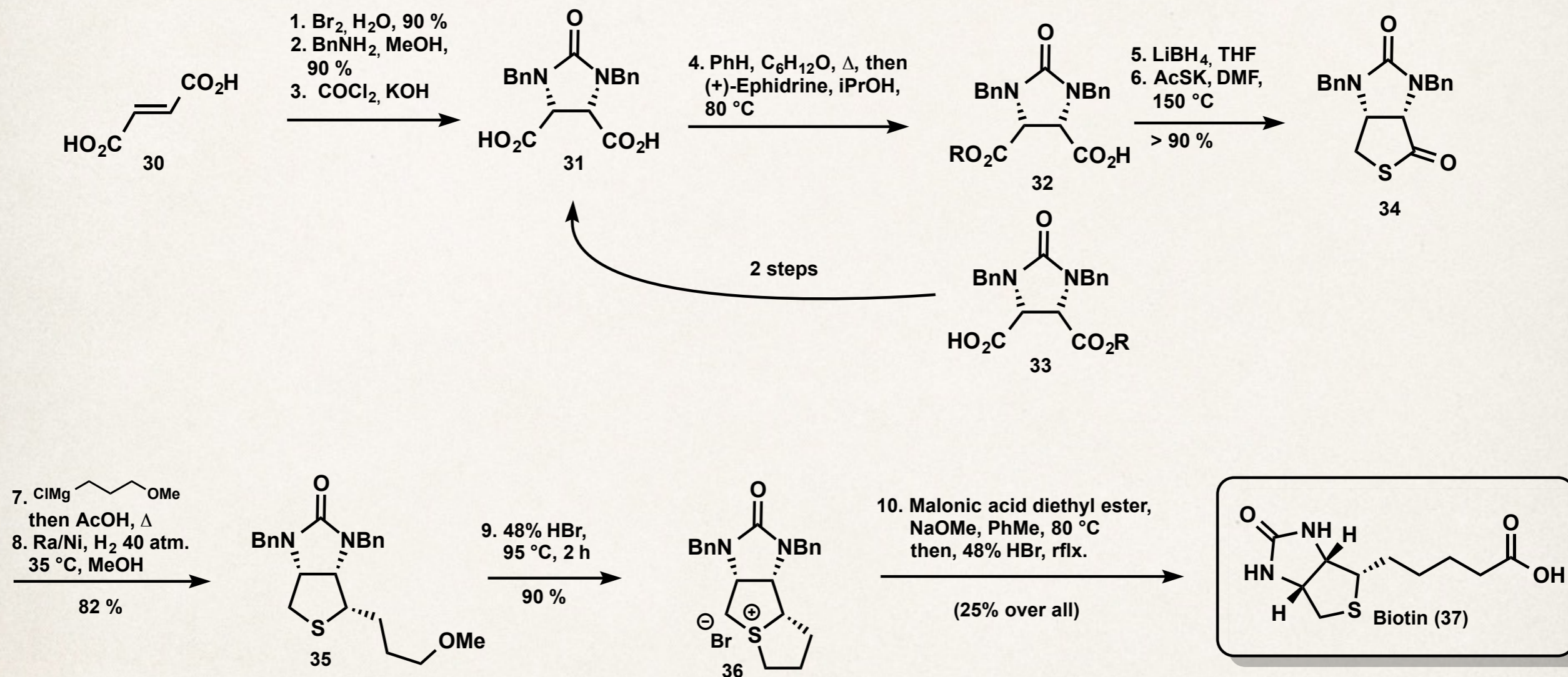
- Thiaminediphosphate (TDP) is the active form
- Essential for carbohydrate & energy metabolism
 - Present in pyruvate dehydrogenase, oxoglutarate dehydrogenase, transketolase, pyruvate decarboxylase, 2-hydroxyphytanoyl-CoA lyase.



Deficiency

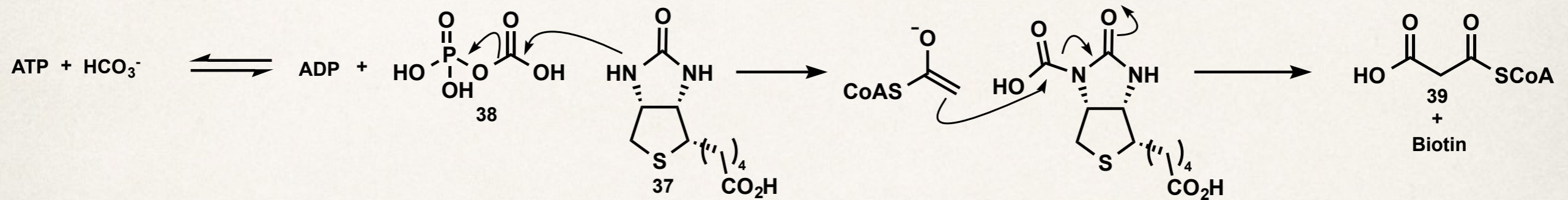
- Beriberi —> effects peripheral nervous system; cardiovascular system,
- Polyneuropathy
- Anemia
- many more

Vitamin B₇ Synthesis by Hoffmann-La Roche



Biological activity

- present in carboxylases (pyruvat-, acetyl-CoA-, propionyl-CoA-, methylcrotonyl-CoA-carboxylase)
- catalyzes carboxylation as a CO₂ carrier
- Formation of malonyl-CoA from acetyl-CoA



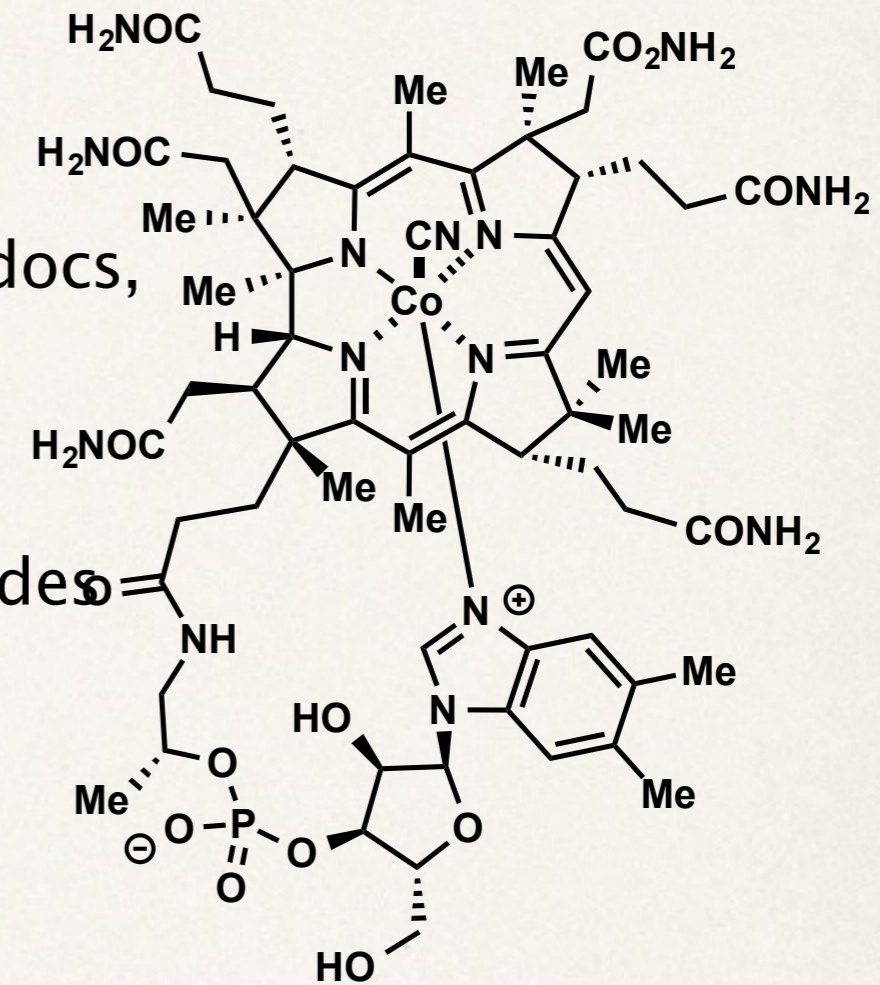
Biotin deficiency causes
Neurological symptoms
(depression, lethargy,
etc.)

Vitamin B₁₂

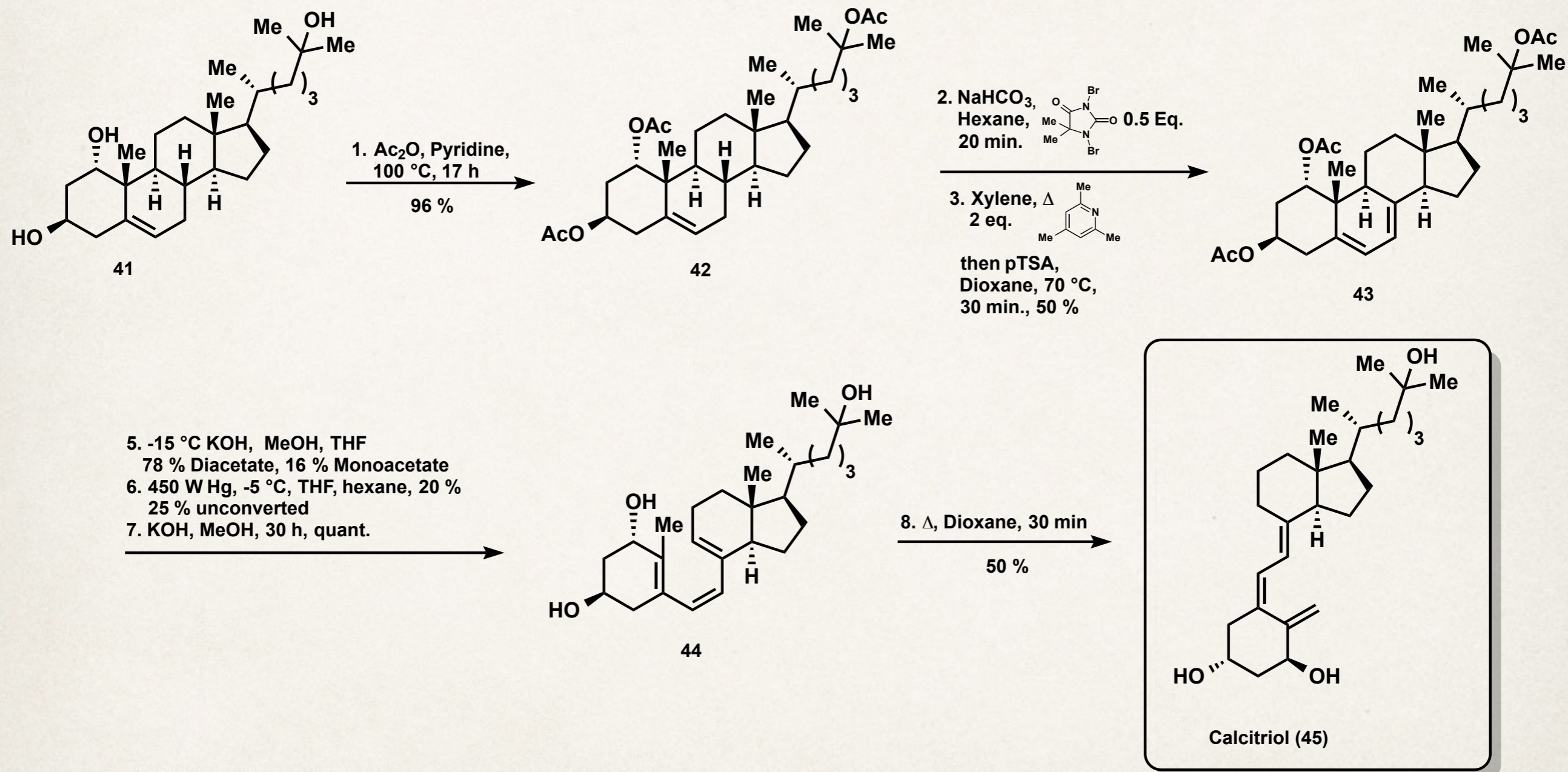
- Synthesis by fermentation
- No industrial total synthesis available
 - Total synthesis with 113 steps, 12 PhD, 91 Postdocs, 17 years
 - optimized to 70 steps
- cobalt can be complexed by CN⁻, SO₃²⁻, OH⁻, halides
- 10t/a; market volume 77*10⁶ EUR

Biological activity

- catalyzes 1,2 H shift
- Coenzyme for Methionin-synthase & Methylmalonyl-CoA-mutase
- Hydroxy-cobalamin —> treatment of cyanide poisoning
- deficiency causes anaemia



Synthesis of Vitamin D₃



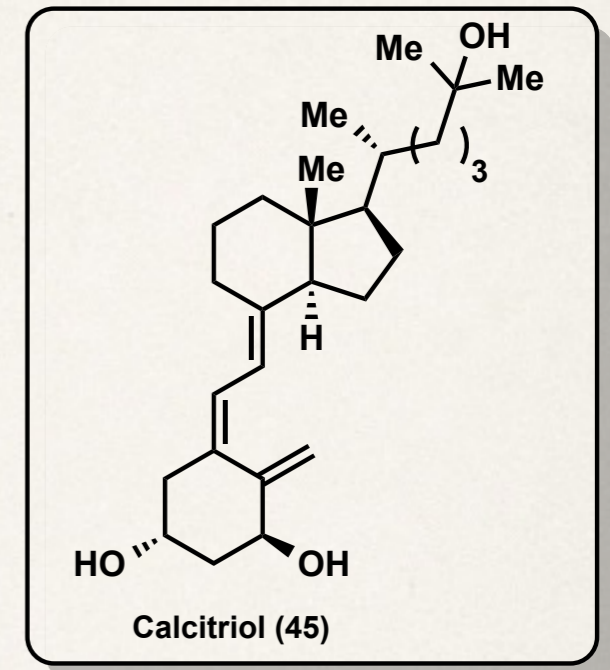
Biological activity of Vitamin D₃

- hormonally active vitamin
- increases the Ca²⁺ concentration in the blood, by increasing the uptake in the gastrointestinal tract
- decreases the probability to get some of up to 17 different cancer diseases

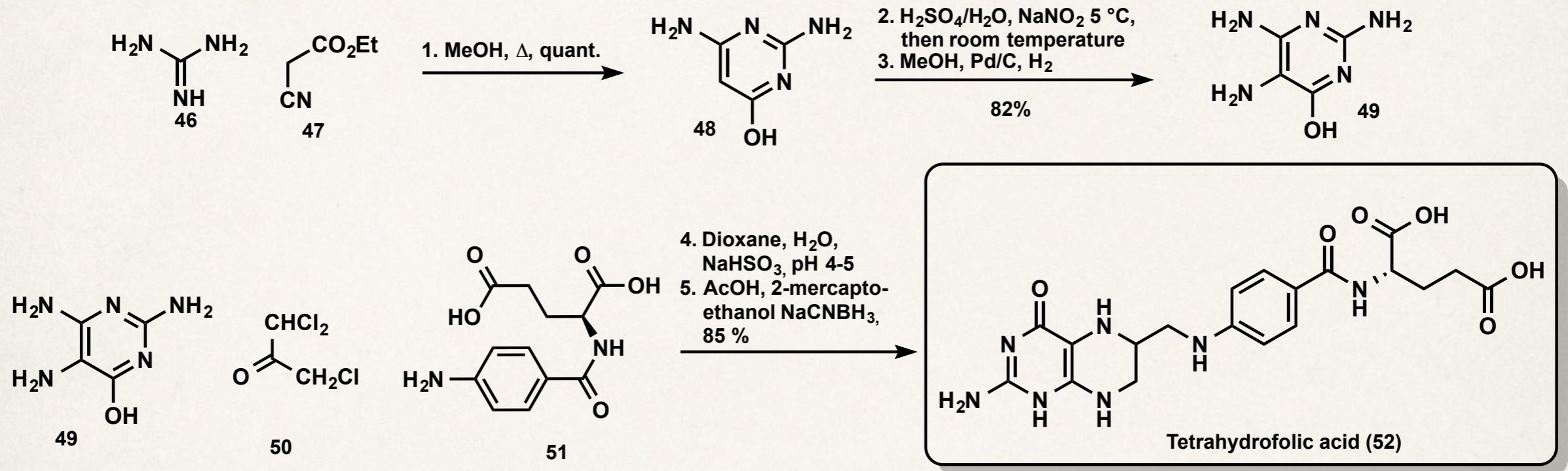
Hypervitaminose causes calcification of tissues and arteries

Production & prize

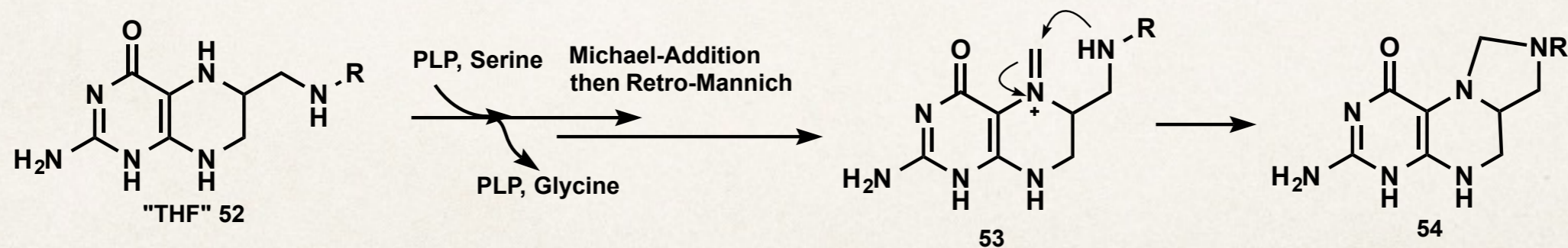
- No t/a given
- cost 50 \$/kg



Vitamin B₉ synthesis

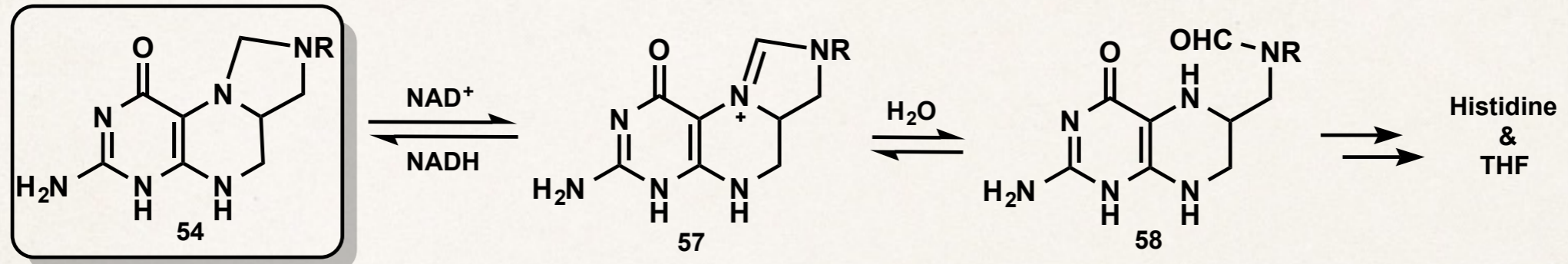


Folic acid is metabolized to „THF“ what is the active compound

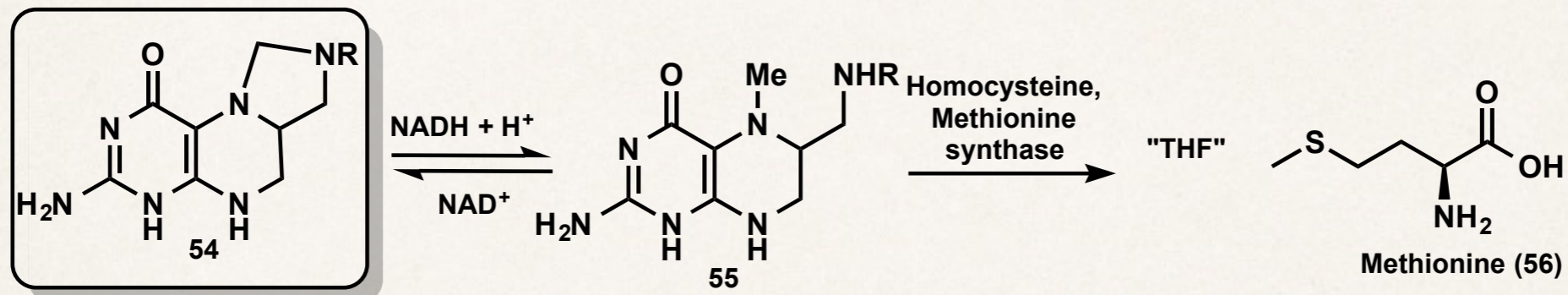


Biological activity of „THF“

Formyl transfer in the Histidine biosynthesis



Methyl transfer in the SAM biosynthesis



Economic aspects

- 400 t/a available as pure crystals
- cost 36 – 77 €/kg
- used for feed enrichment

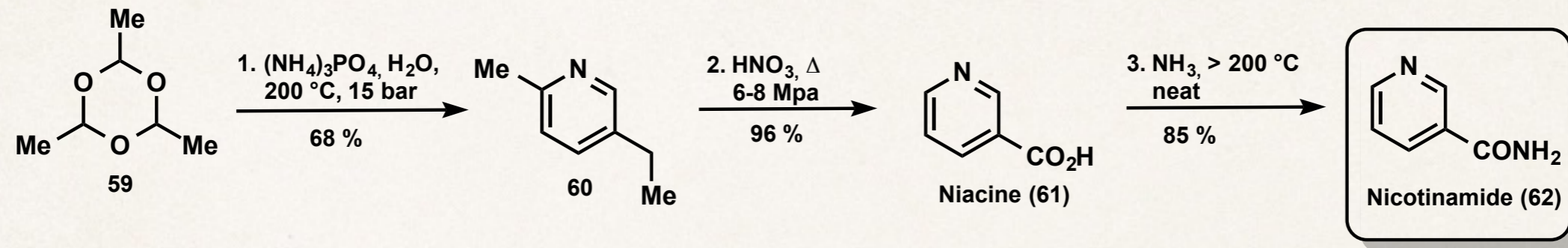
Folic acid & derivatives

(antifolates) are used in anti cancer therapy
Acts as an antidepressant

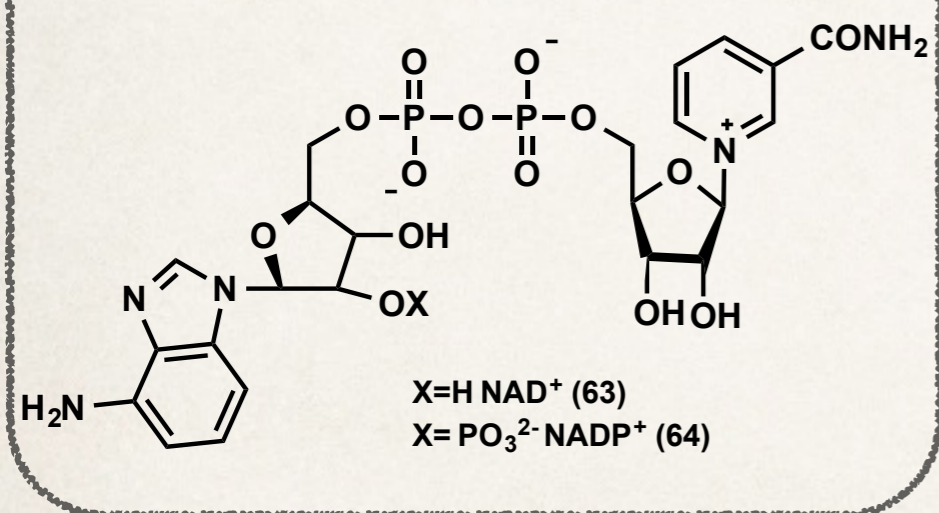
Deficiency

- anaemia
- neural tube defects
- depression

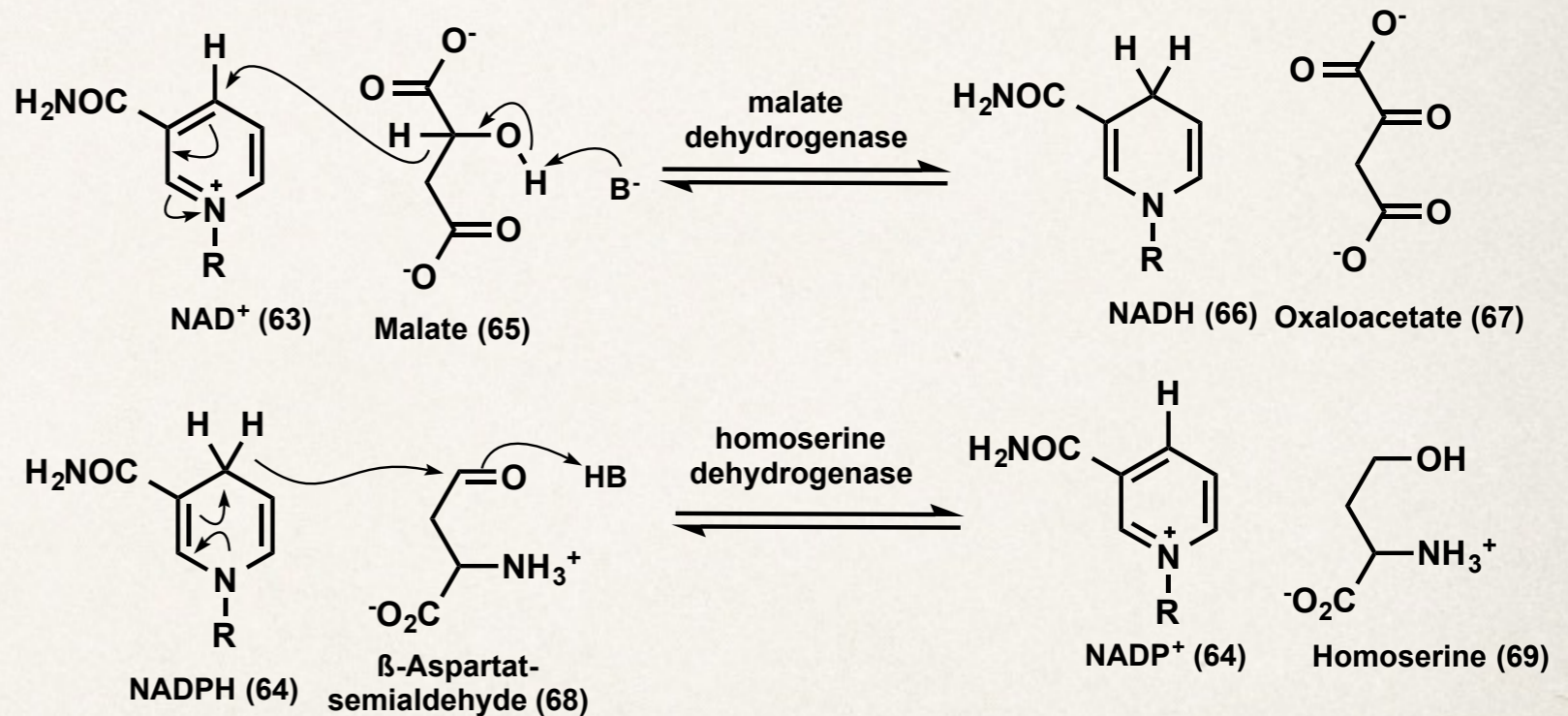
Vitamin B₃ synthesis (Lonza)

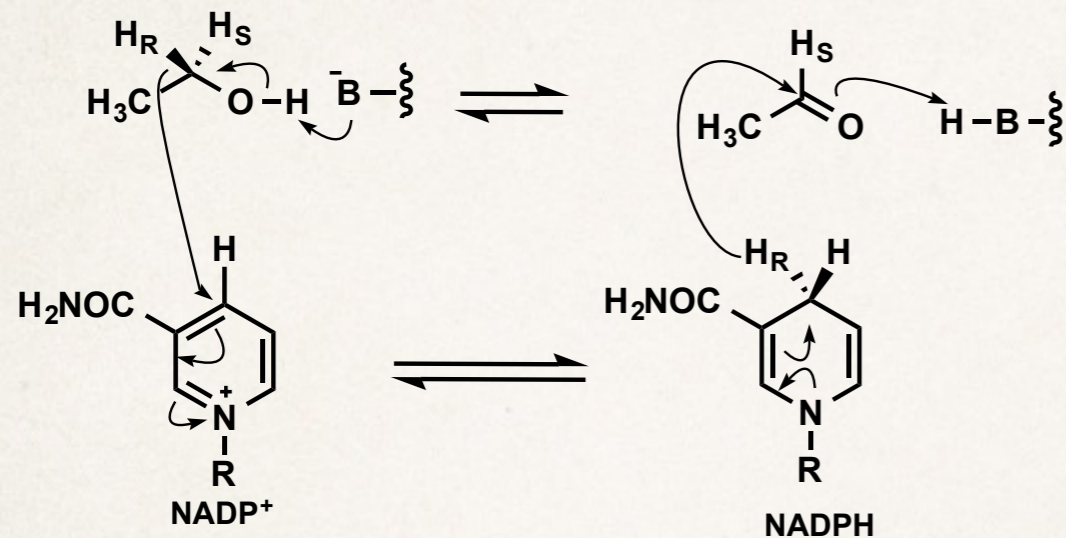


active coenzyme



redox reactions using NAD^+ & NADPH





- re- (pro R) & si- (pro S) specific enzymes
- stereospecific dehydrogenation also possible

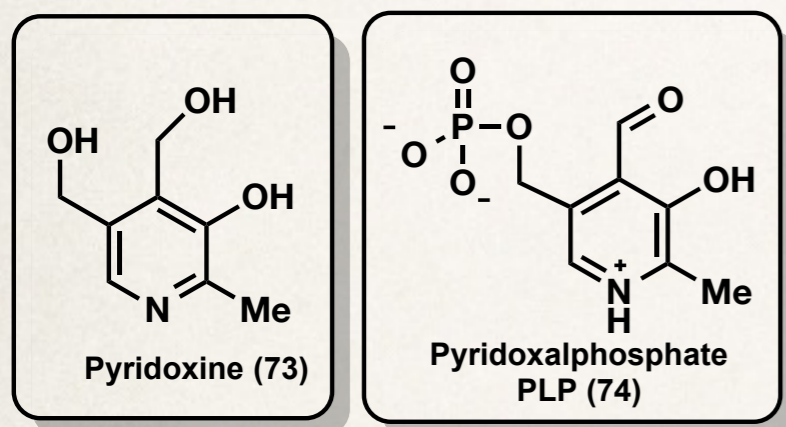
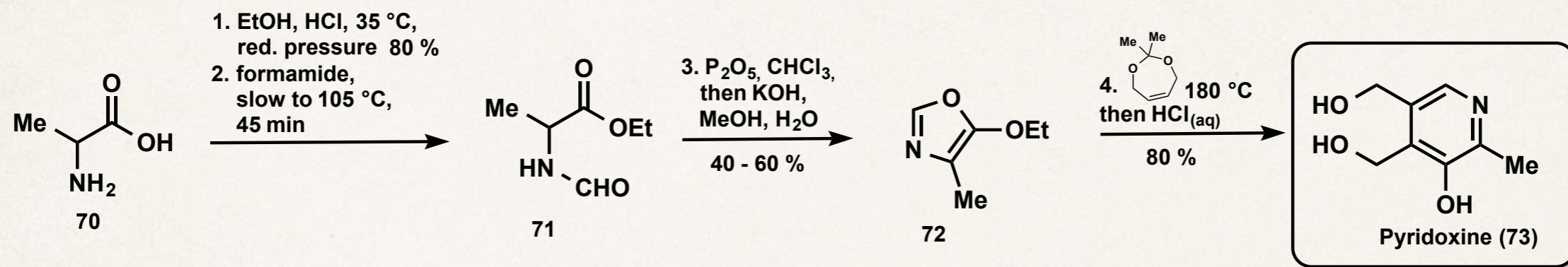
Economic aspects

- world capacity >>22000 t/a
- cost 10-100 \$/kg
- mainly produced in China

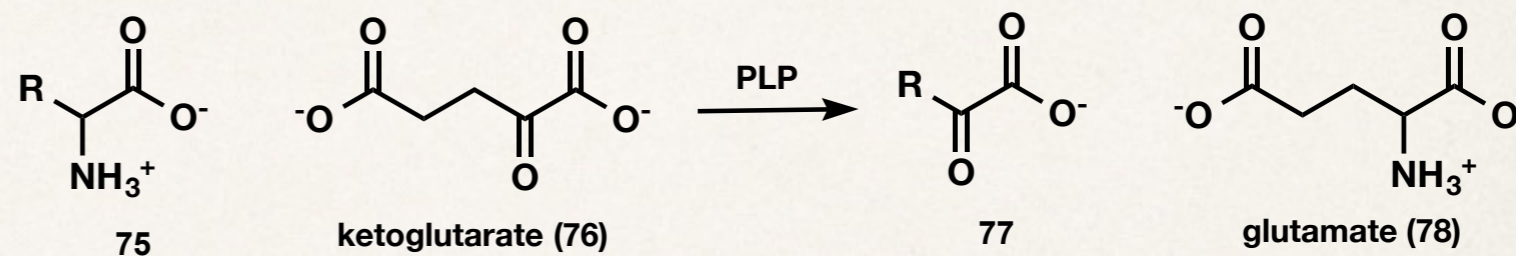
Vitamin B₃ deficiency

- Pellagra
 - diarrhea,
 - dermatitis,
 - dementia, death
- Mental confusion
- Ataxia
- Dilated cardiomyopathy
- peripheral neuritis
- etc.

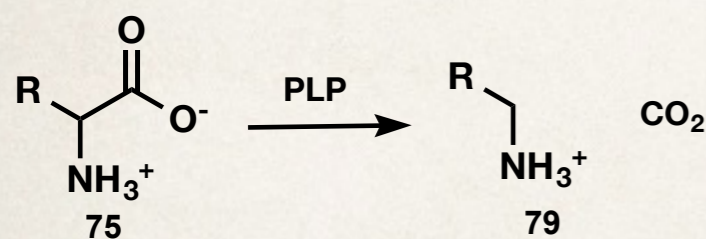
Vitamin B₆ synthesis



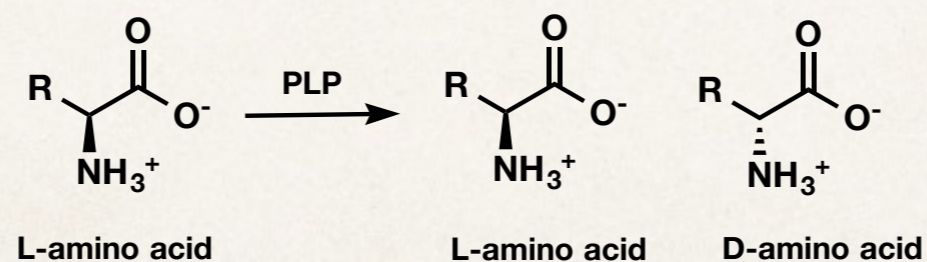
Transamination



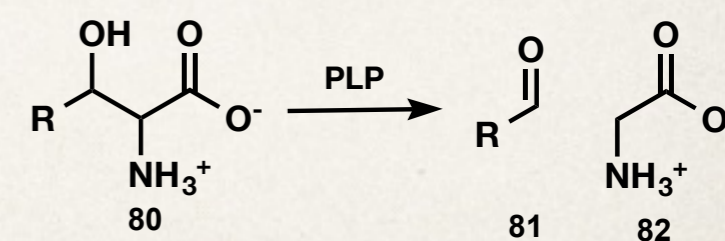
Decarboxylation



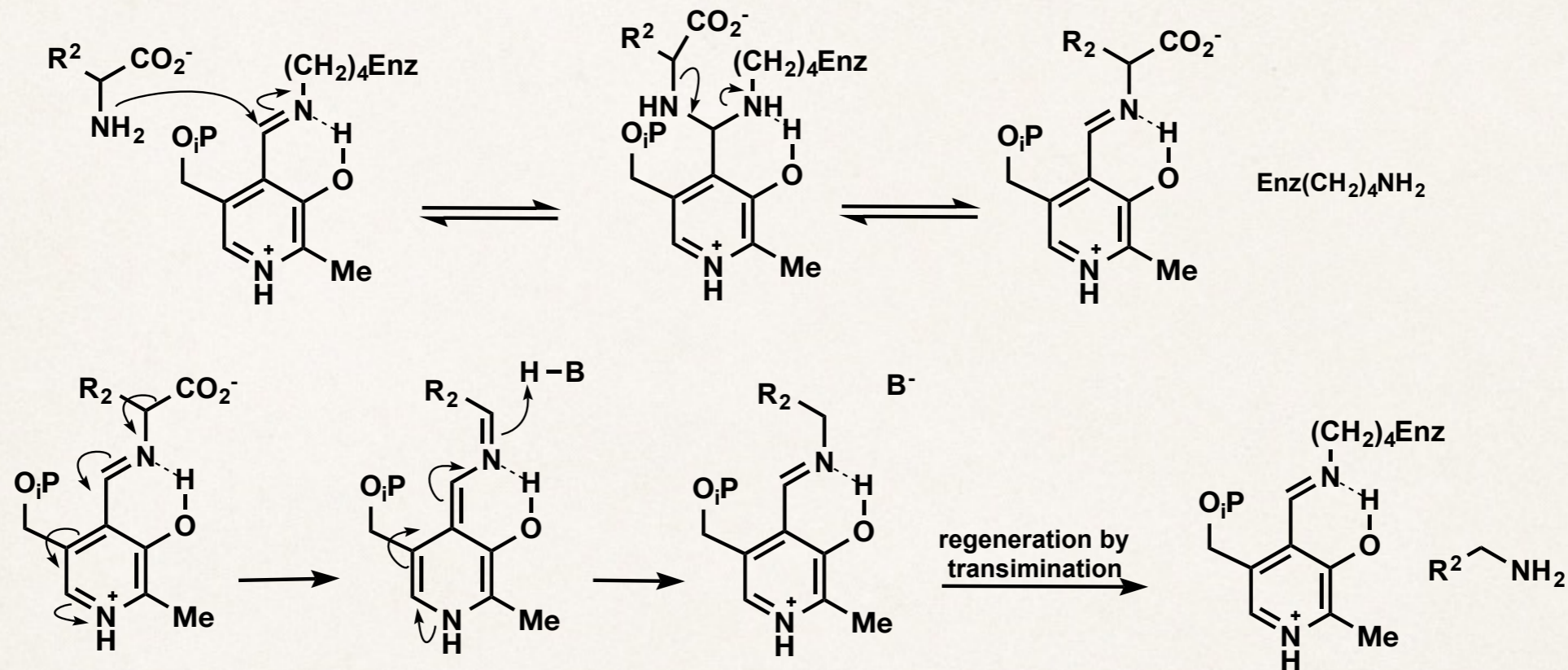
Isomerization



Retro-Aldol



Mechanism for the decarboxylation reaction



Economic aspects

- world capacity >>4100t/a
- cost 50\$/kg
- mainly produced in China

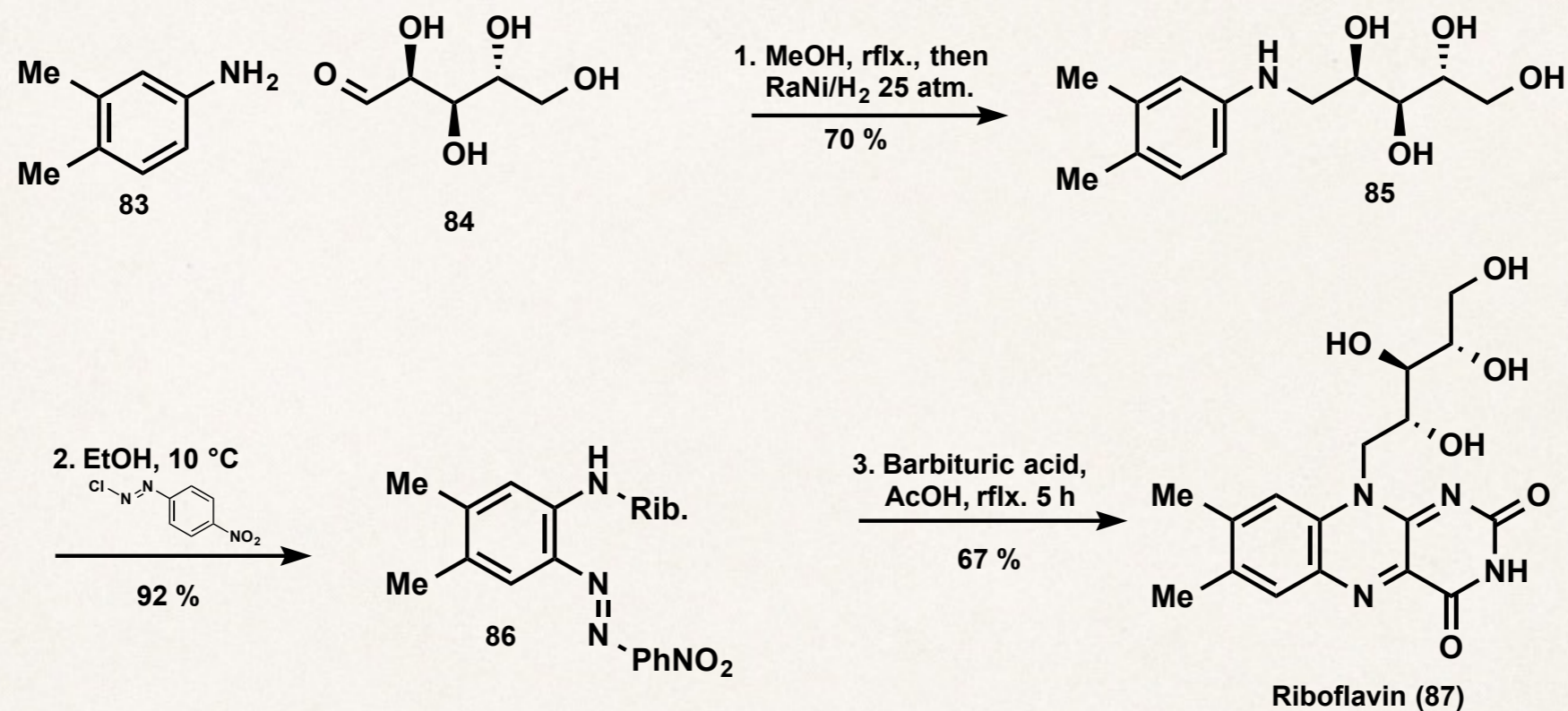
Pyridoxine deficiency causes

- anaemia
- nerve damage
- skin problems

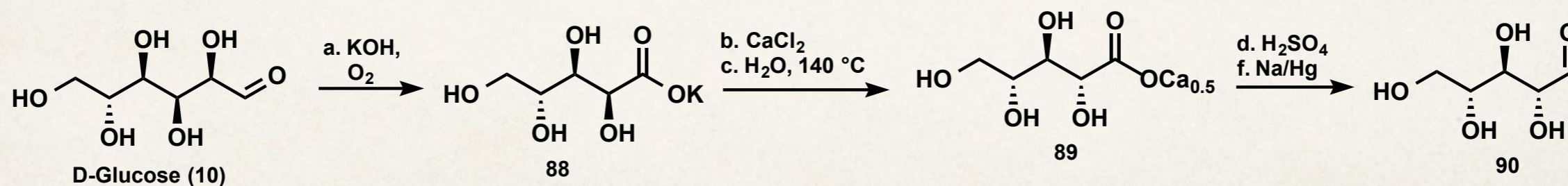
Used for treatment of

Wilson's & rheumatic diseases
carpal tunnel syndrome,
autism, schizophrenia,
mental retardation, etc.

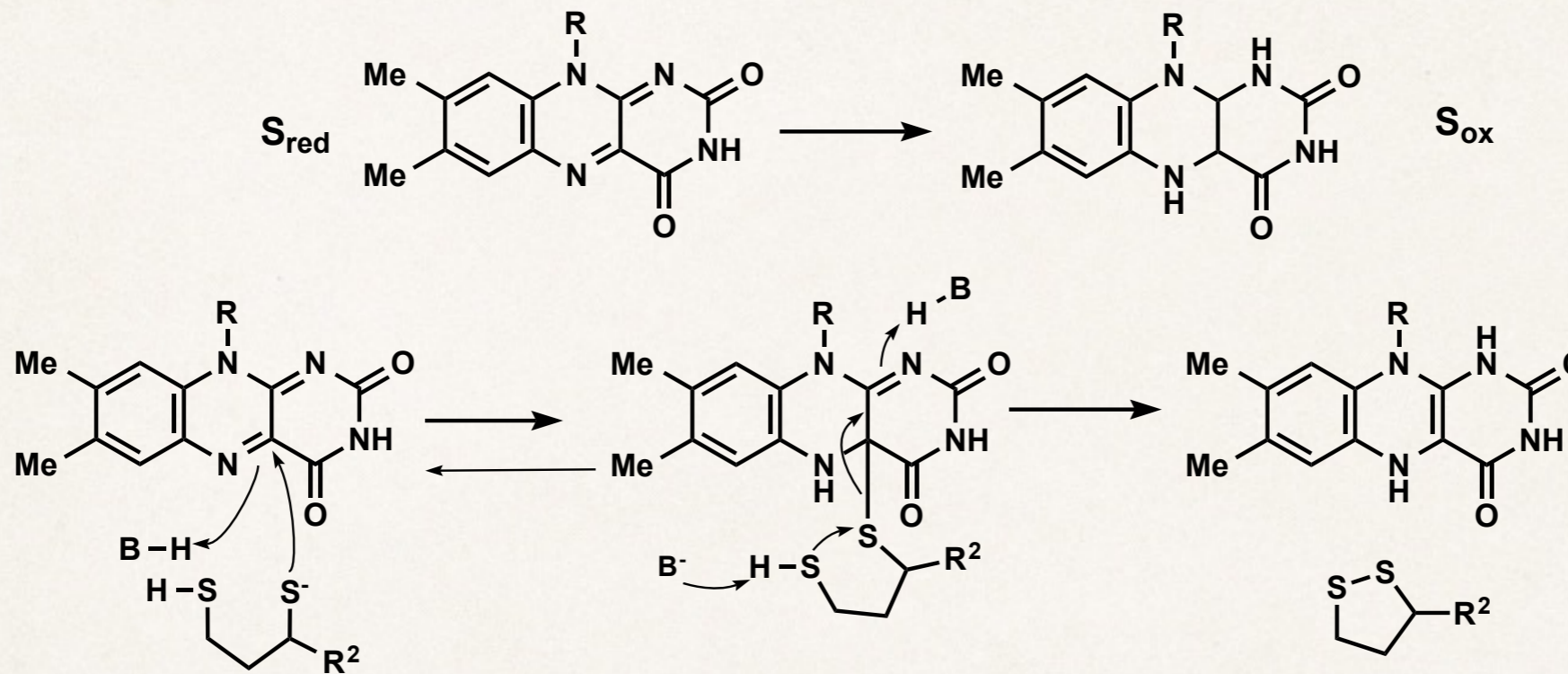
Vitamin B₂ synthesis



An efficient & cheap synthesis of D-ribose (90) is essential for the industrial riboflavin production



Biological activity



- Most reactions follow a radical mechanism
- Is able to form Cl^+ species with oxygen & chloride

Economic aspects

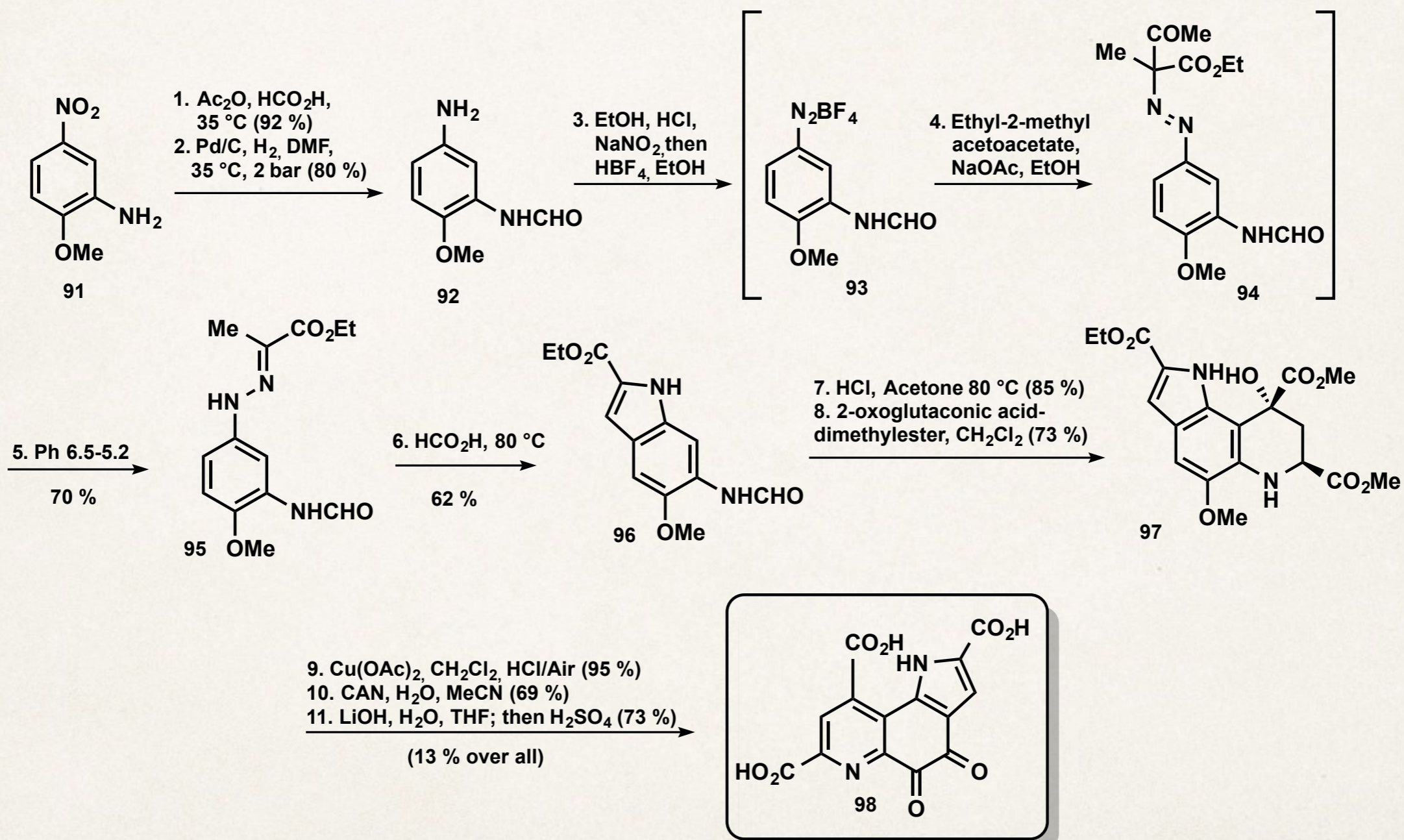
- world capacity 2400t/a
- cost 45–54 €/kg
- produced by HLR, BASF, Takeda, ADM

Deficiency

- atrophic glossitis
- seborrheic dermatitis
- eye problems
(all in all nothing serious)

Synthesis of Methoxatin

- 1st. Synthesis by Corey in 50 mg scale



Thank you for your attention

General Literatur

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