Industrial Syntheses of Vitamins

Introduction

Goal – provide an overview of the history of vitamin production with an emphasis on the details pertinent to organic synthesis. Preparations of vitamins B_3, B_5, B_9, B_{12}, D, and K are omitted.

Vitamin – Essential organic compounds that are not synthesized in sufficient amounts, or at all, in the human or animal organism, and must be consumed in the diet as such or as a precursor.

Guiding References

- Eggersdorfer, M.; Laudert, D.; Létinois, U.; McClymont, T.; Medlock, J.; Netscher, T.; Bonrath, W. One Hundred Years of Vitamins—A Success Story of the Natural Sciences. *Angew. Chem. Int. Ed.* **2012**, *51*, 12960 – 12990.
- Wüstenberg, B.; Stemmler, R. T.; Létinois, U.; Bonrath, W.; Hugentobler, M.; Netscher, T. Large-Scale Production of Bioactive Ingredients as Supplements for Healthy Human and Animal Nutrition. *Chima*, **2011**, *65*, 420 – 428.

Early History and Timeline

1897: Christiaan Eijkman observes that removing the outer husks of rice induces beriberi; the husks cure or prevent beriberi.

Four Phases of Vitamin Production

1930 – 1950: Pioneering days (laboratory-scale)

1950 – 1970: Scaling-up and engineering (pilot and larger plants)

1970 – 1990: Worldwide production plants and consolidation

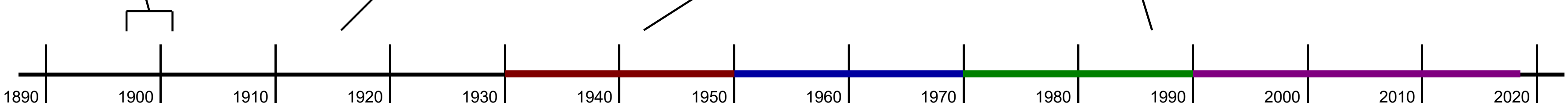
1990 – present: Rise of new technologies

1901: Eijkman's assistant, Gerrit Grijns, proposes that beriberi is caused by the deficiency of a nutrient in the rice husks.

1916: Elmer McCollum introduces capital letters A–D to differentiate between hitherto identified vitamins.

1941: All 13 vitamins identified, characterized, and nutritional roles defined

1987: All vitamins accessible by industrial processes.



1906: "No animal can live on a mixture of pure protein, fat, carbohydrate, salts, and water." – Frederick Gowland Hopkins

1912: Casamir Funk isolates a bioactive substance from rice husks, names it "vita-amine" or "vitamine."

1933: First commercialization of a vitamin (vitamin C).

1934: First industrial process of a vitamin (vitamin C, by F. Hoffmann–La Roche)

Nobel Prizes Awarded for Vitamin Research

1928, Chemistry:
Windaus- sterols and their connection with the vitamins

1929, Physiology or Medicine:
Hopkins - discovery of the growth-stimulating vitamin
Eijkman - discovery of the antineuritic vitamin

1937, Physiology or Medicine:
Szent-Györgyi - discovery of vitamin C (and other achievements)

1937, Chemistry:
Haworth - investigations on carbohydrates and vitamin C
Karrer - investigations on carotenoids, flavins, vitamins A and B_2

1938, Chemistry:
Kuhn - work on carotenoids and vitamins

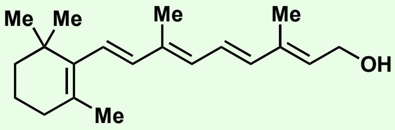
1943, Physiology or Medicine:
Doisy - discovery and chemical nature of vitamin K
Dam - discovery of vitamin K

Industrial Syntheses of Vitamins

Structures, Function, and Important Dates Corresponding to the 13 Vitamins

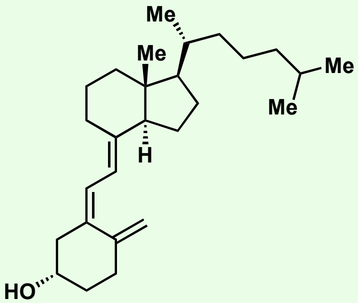
solubility

fat soluble, lipophilic | water soluble, hydrophilic



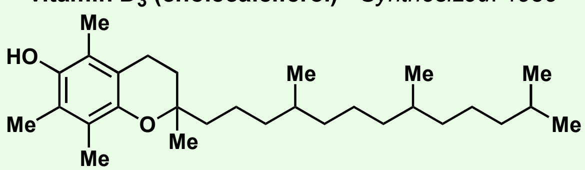
vitamin A (retinol)

Function: precursor to retinal, required for vision
Discovered: 1916
Isolated: 1931
Characterized: 1931
Synthesized: 1947



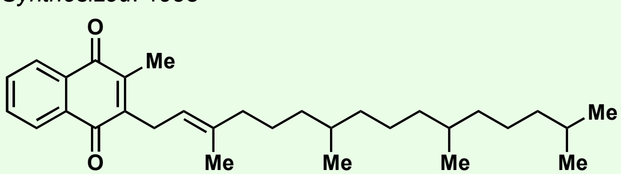
vitamin D_3 (cholecalciferol)

Function: bone mineralization, cell proliferation and differentiation, regulation of calcium and phosphate blood levels; modulation of immune system
Discovered: 1918
Isolated: 1932
Characterized: 1936
Synthesized: 1959



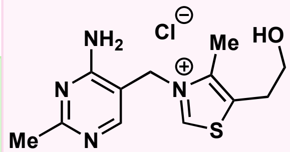
vitamin E ((all-*rac*)-α–tocopherol)

Function: antioxidant, cell signaling, gene expression
Discovered: 1922
Isolated: 1936
Characterized: 1938
Synthesized: 1938



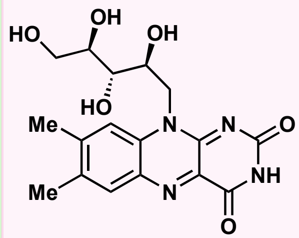
vitamin K_1 ((all-*rac,E*)-phylloquinone)

Function: blood coagulation, bone metabolism
Discovered: 1929
Isolated: 1939
Characterized: 1939
Synthesized: 1939



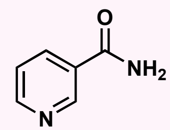
vitamin B_1 (thiamin)

Function: energy, pentose metabolism, nerve impulse conduction, muscle action
Discovered: 1912
Isolated: 1926
Characterized: 1936
Synthesized: 1936



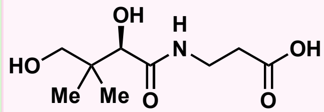
vitamin B_2 (riboflavin)

Function: precursor for biosynthesis of FMN or FAD, cofactors in redox reactions
Discovered: 1920
Isolated: 1933
Characterized: 1935
Synthesized: 1935



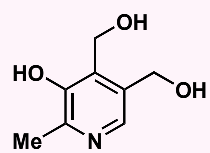
vitamin B_3 (niacin)

Function: precursor for biosynthesis of NAD and NADP, redox reactions
Discovered: 1936
Isolated: 1936
Characterized: 1937
Synthesized: 1994



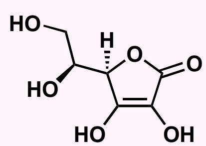
vitamin B_5 (pantothenic acid)

Function: metabolism of carbohydrates, proteins, fats
Discovered: 1931
Isolated: 1938
Characterized: 1940
Synthesized: 1940



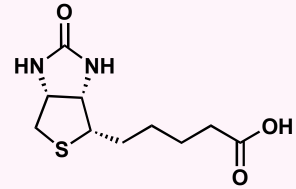
vitamin B_6 (pyridoxine)

Function: neurotransmitter biosynthesis
Discovered: 1934
Isolated: 1938
Characterized: 1938
Synthesized: 1939



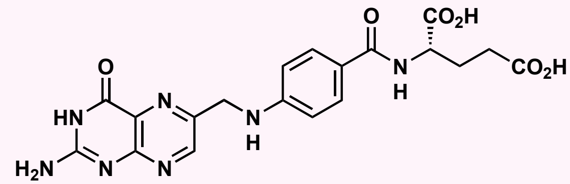
vitamin C (L-ascorbic acid)

Function: collagen synthesis, antioxidant
Discovered: 1912
Isolated: 1928
Characterized: 1933
Synthesized: 1933



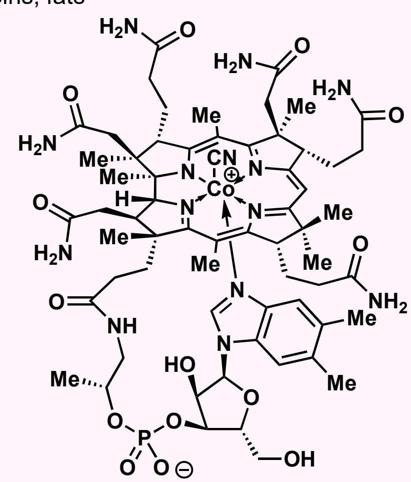
vitamin B_7 (vitamin H, biotin)

Function: metabolism of lipids, proteins, carbohydrates
Discovered: 1931
Isolated: 1935
Characterized: 1942
Synthesized: 1943



vitamin B_9 (folic acid)

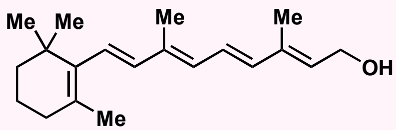
Function: amino acid metabolism, synthesis of nucleic acids
Discovered: 1941
Isolated: 1941
Characterized: 1946
Synthesized: 1946



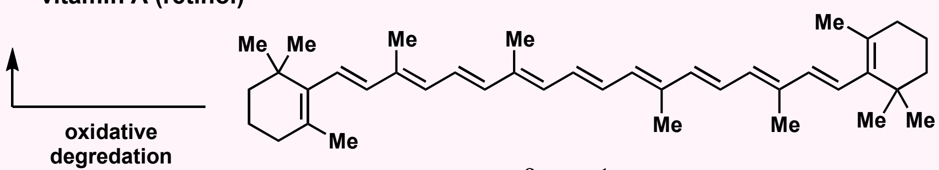
vitamin B_{12} (cyanocobalamine)

Function: formation of blood cells, nerve sheaths, proteins; fat and carbohydrate metabolism
Discovered: 1926
Isolated: 1948
Characterized: 1956
Synthesized: 1972

Industrial Syntheses of Vitamins



vitamin A (retinol)



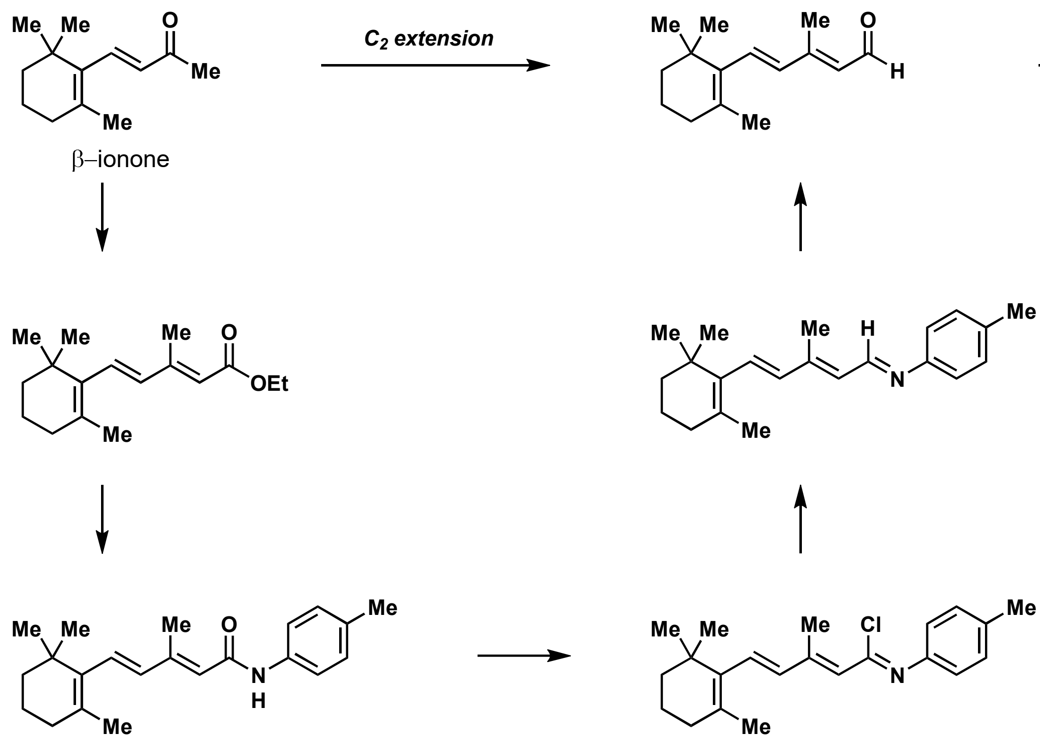
β–carotene

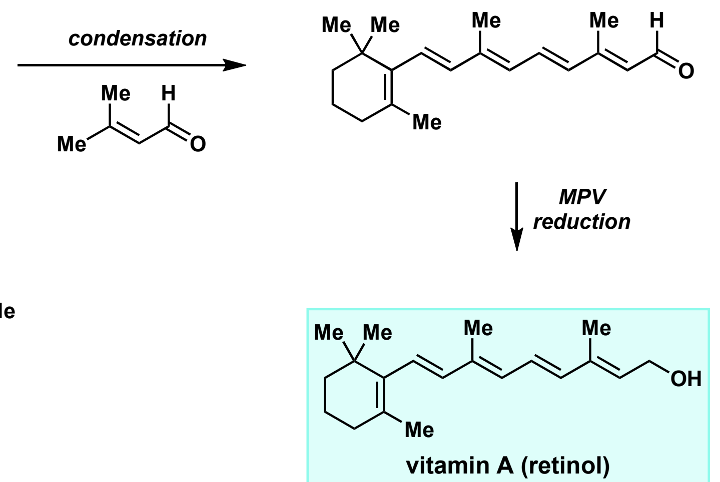
Medicinal Importance
- plays an essential role in vision
- deficiency affects ~190 million pre-school children in developing countries; accounts for a large proportion of morbidity, mortality, and blindness in these children

Discovery
- The use of certain foods now known to be rich in vitamin A (liver) were known to cure night blindness as early as ancient Egyptian times.
- Part of lipid soluble substances isolated from milk by Stepp in 1909.
- Identified as "fat-soluble A" by McCollum and Kennedy in 1916.
- Isolated nearly pure by Karrer and co-workers in 1931.

General Information
- part of retinoid class, including retinal and retinoic acid
- related to carotenoids, including β–carotene (provitamin A)
- unstable, most often commercialized as the acetate, or the propionate or palmitate in certain cases

First Synthesis (Yields and Conditions Noted If Available)
- Kuhn, R.; Morris, C. J. O. R. *Ber. Dtsch. Chem. Ges.* **1937**, *70*, 853.



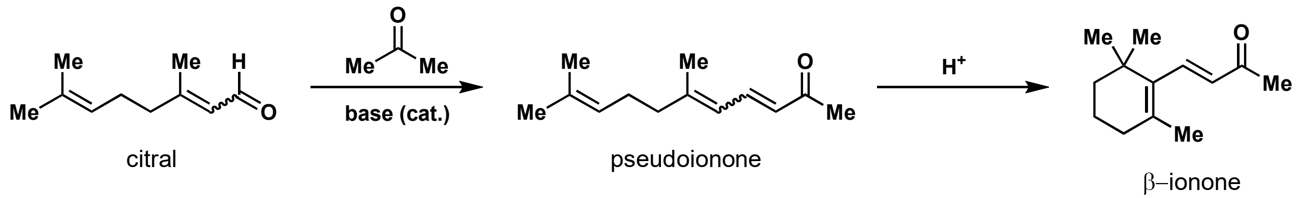


- Isolated as an oil containing 7.5% vitamin A.
- Synthesis was not reproducible by other groups
– β–ionone was established as a key builing block for the vitamin A synthesis

Industrial Syntheses of Vitamins

β–Ionone synthesis

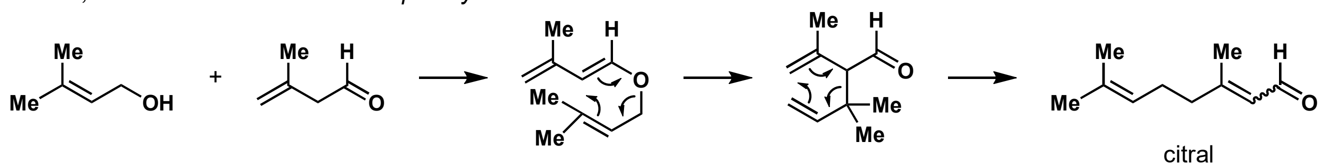
- Known as a perfume component in the 19th century
- Prepared from lemon grass, also containing citral (geranial/neral mixture), which could be converted to β–ionone



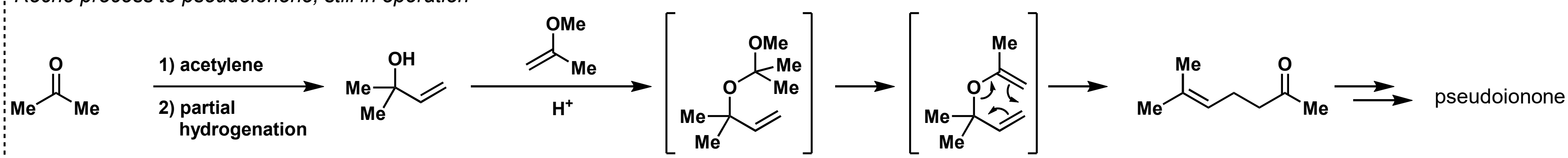
- An industrial process for vitamin A required an industrial process for β–ionone; an industrial process for β–ionone required an industrial process for geranial.

- Roche and others developed routes to citral that are still used today

Modern, efficient route to citral developed by BASF

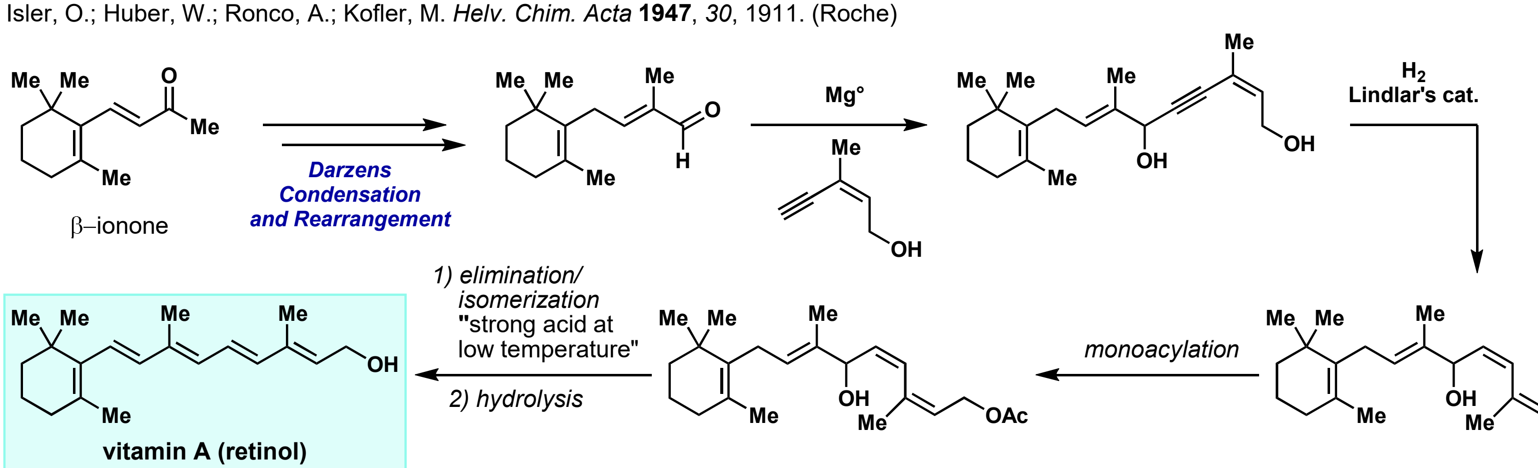


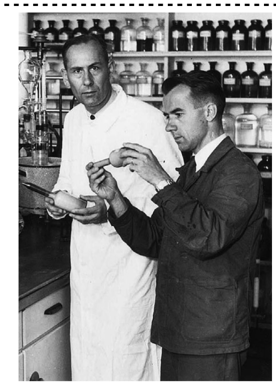
Roche process to pseudoionone, still in operation



First Synthesis of Crystalline Retinol, Later Implemented on the Industrial Scale

- Isler, O.; Huber, W.; Ronco, A.; Kofler, M. *Helv. Chim. Acta* **1947**, *30*, 1911. (Roche)



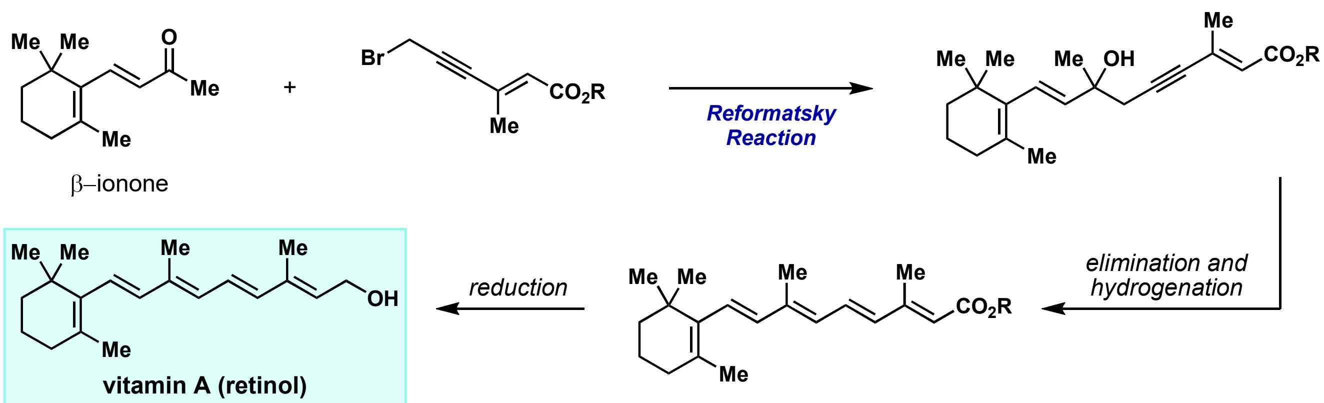


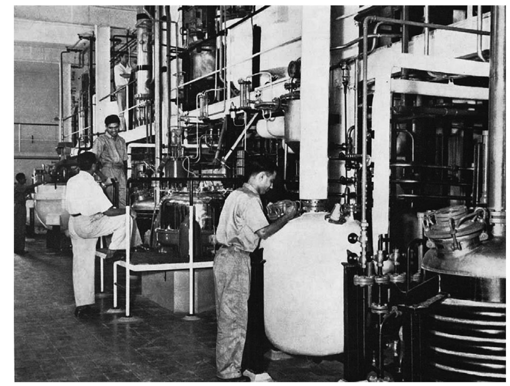
Otto Isler (left)

Industrial Syntheses of Vitamins

Supply and Demand of Retinol
- The Roche synthesis was able to satisfy early worldwide demands at plants in Basel (Switzerland) and Nutley (USA).
- Demand in the 1960's grew to the point that Roche consolidated nearly all vitamin A syntheses to a single plant in Switzerland.
- At this point, other companies began production *via* alternative routes.

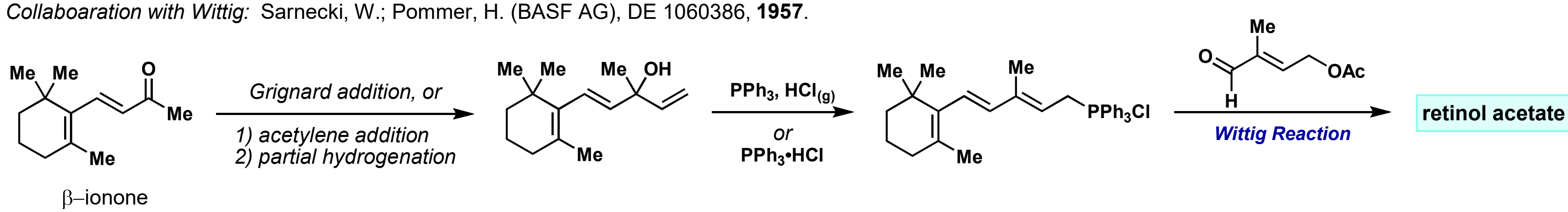
BASF synthesis of Retinol
- *First approach:* Pommer, H. (BASF AG), DE 950551, **1956**.



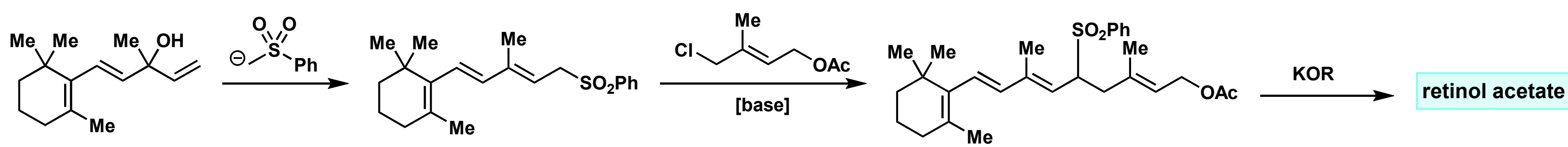


Vitamin A production at Roche Nutley

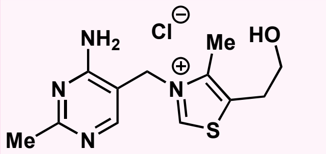
- *Collaboaration with Wittig:* Sarnecki, W.; Pommer, H. (BASF AG), DE 1060386, **1957**.



- *Collaboaration between Rhône–Poulenc and Julia:* Julia, M.; Arnould, D. *Bull. Soc. Chim. Fr.* **1973**, 743.



Industrial Syntheses of Vitamins

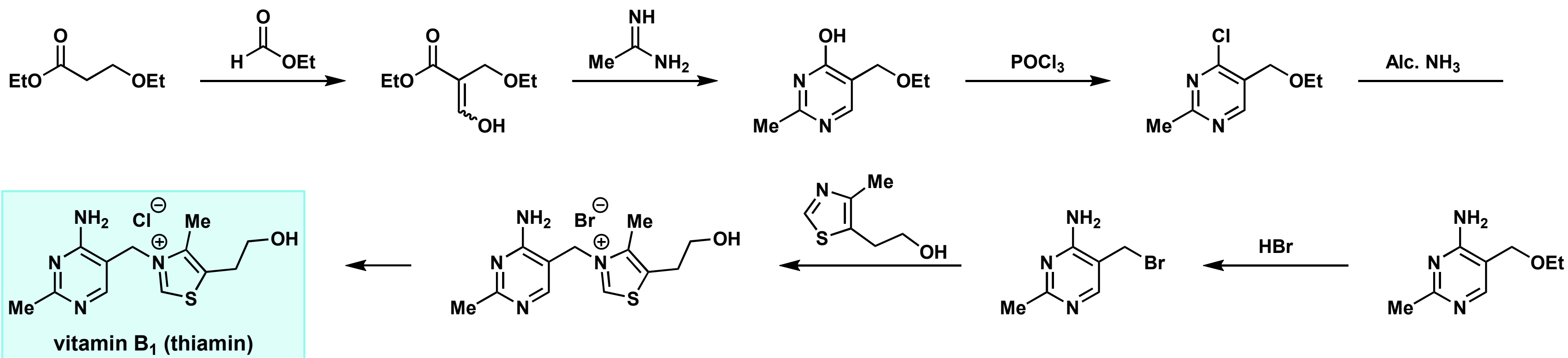


vitamin B_1 (thiamin)

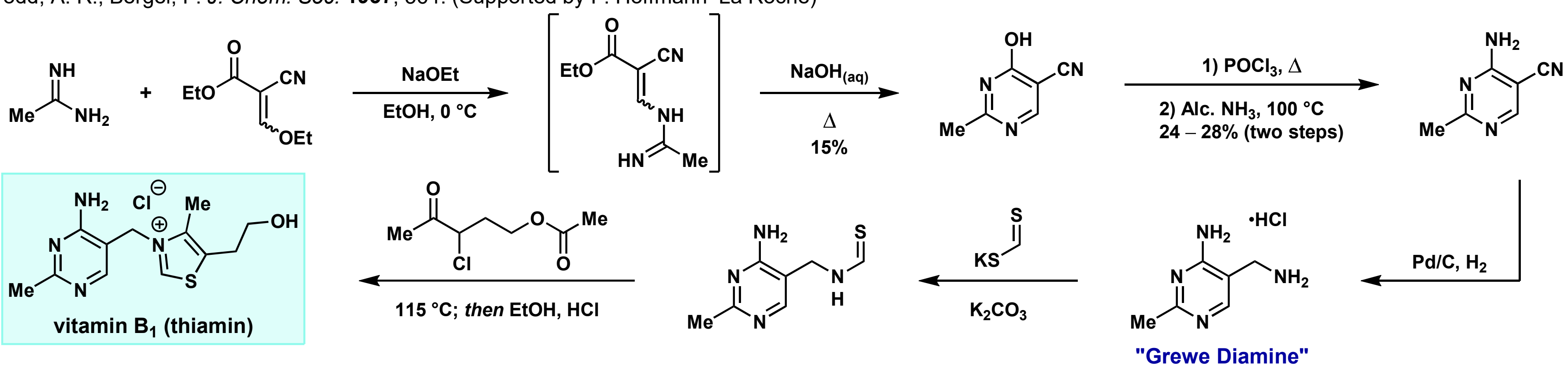
Medicinal Importance
- plays an essential role in metabolism of carbohydrates and branched amino acids
- as thaimin pyrophosphate, acts as a co-enzyme in the oxidative phosphorylation of α–ketoacids and in transketolase reactions
- deficiency causes beriberi in two forms:
  dry beriberi - paralytic peripheral neuropathy
  wet beriberi - heart abnormalities and failure

Discovery
- In 1897, Eijkman showed that polyneuritis in birds and beriberi in humans could be induced by a diet of "polished" rice, or rice with the outer husk of the grain removed. These conditions were reversed by introducing unpolished rice, or the husks, into the diet.
- Eijkman believed a toxin was in the rice kernel; Grigns proposed in 1901 that a nutrient was in the rice husks.
- In 1912, Funk isolated crude thiamin; In 1926, Jansen and Donath isolated pure thaimin that was shown to cure polyneuritis in concentrations as low as 2 ppm.
- In 1932, Windaus proposed the correct molecular formula; In 1936, Williams proposed the correct molecular structure

Notable Early Syntheses (Yields and Conditions Noted If Available)
- Williams, R. R.; Cline, J. K. *J. Am. Chem. Soc.* **1936**, *58*, 1504. (Supported by Merck & Co)



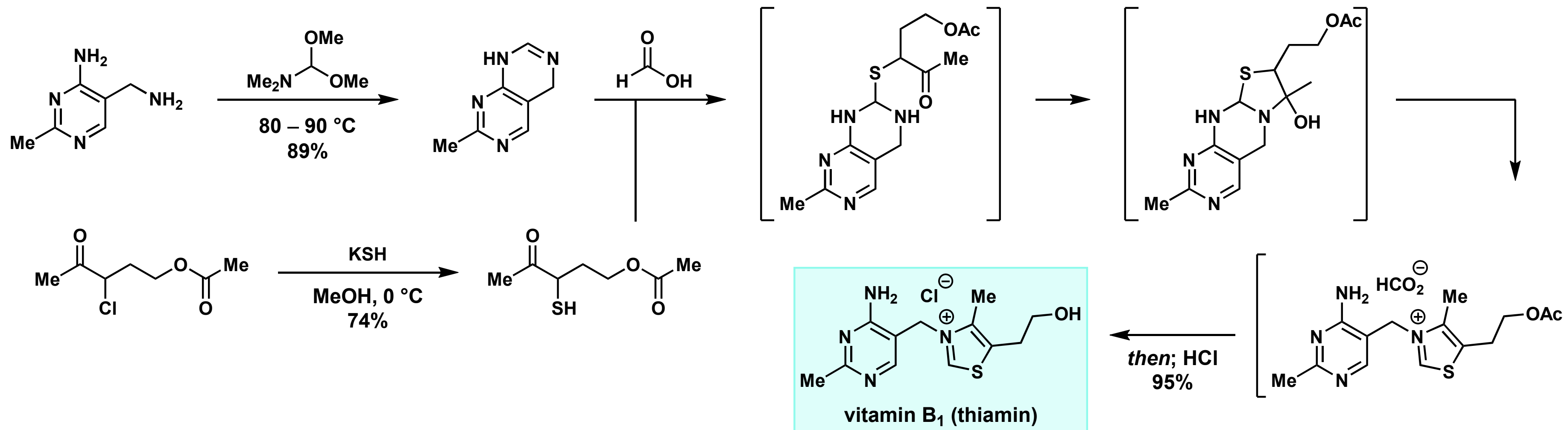
- Todd, A. R.; Bergel, F. *J. Chem. Soc.* **1937**, 364. (Supported by F. Hoffmann–La Roche)



Industrial Syntheses of Vitamins

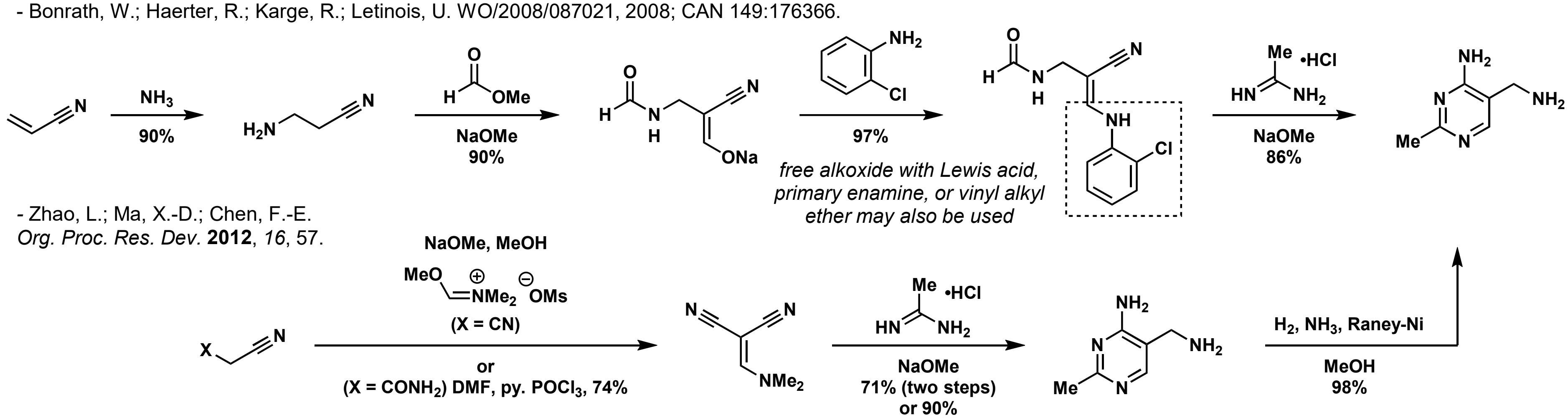
Improvements on Use of Grewe Diamine

- Contant, P.; Forzy, L.; Hengartner, U.; Moine, G. *Helv. Chim. Acta.* **1990**, *73*, 1300. (F. Hoffmann–La Roche)



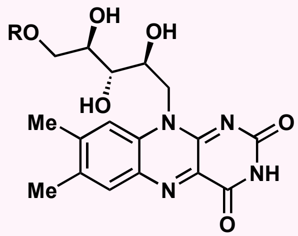
Modern Industrial Syntheses of Grewe Diamine

- Generally, synthetic routes proceed through similar acrylonitrile intermediates with differing substitution at the β–position.
- Maruyama, T; Mikami, I; Lmaoka, K. DE 2323845, 1973; CAN 80:37195.
- Bewert, W.; Littmann, W. DE 2748153, 1979; CAN 91:74645.
- Ernst, H; Littmann, W; Paust, J. DE 3431270, 1986; CAN 105:60313.
- Karge, R.; Letinois, U.; Schiefer, G. WO/2010/010113, 2010; CAN 152:191852.
- Bonrath, W.; Haerter, R.; Karge, R.; Letinois, U. WO/2008/087021, 2008; CAN 149:176366.



- Zhao, L.; Ma, X.-D.; Chen, F.-E. *Org. Proc. Res. Dev.* **2012**, *16*, 57.

Industrial Syntheses of Vitamins

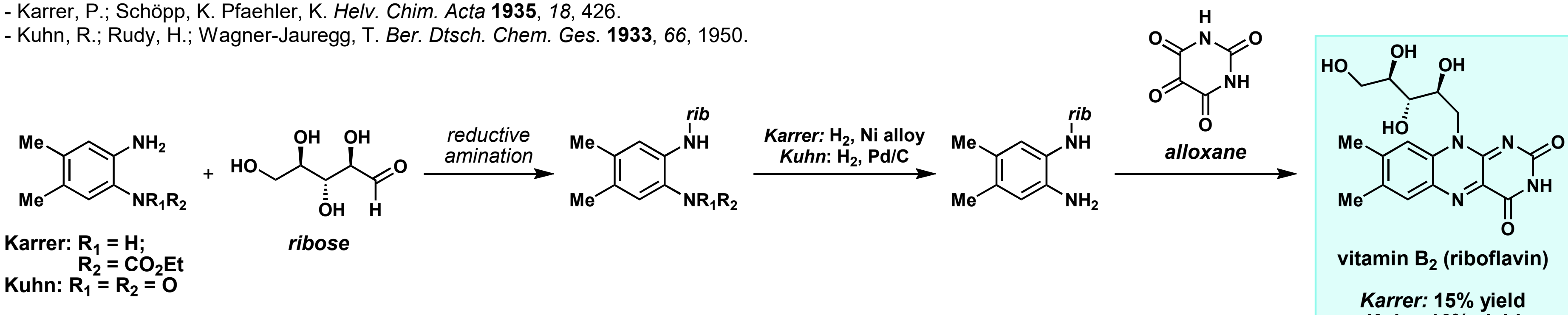


R = H: vitamin B_2 (riboflavin)
R = $P(O)(OH)_2$: FMN
R =P(O)(OH)OP(O)(OH)adenosine: FAD

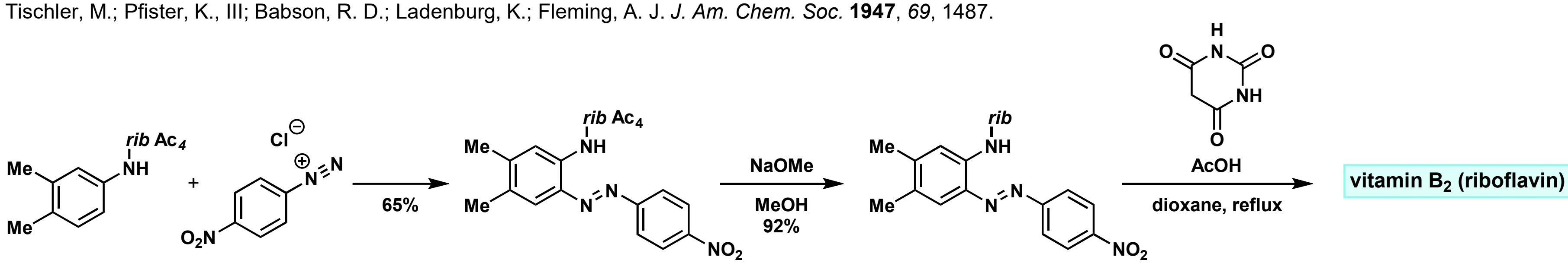
Medicinal Importance
- Essential coenzyme for redox reactions in many metabolic pathways
- Precursor to flavin mononucleotide (FMN, also found in nature) and flavin adenine dinucleotide (FAD)
- FAD is part of the respiratory chain, central to energy production
- Flavoenzymes are involved in single electron transfers, dehydrogenase reactions, hydroxylations, oxidative decarboxylations, and dioxygenations

Discovery and History
- Isolated around 1880 as a yellow pigment by Blyth but not recognized for its nutritional value
- Identified in 1917 when isolated from yeast as a mixture of several compounds.
- Subsequent isolations from egg yolk, liver, and vegetables prompted exploration of its biological function.
- Structure proven by synthesis in 1930.
- Chemical production switched to biotechnology around 2000 using *Bacillus subtilis* or *Ashbya gossippi.*

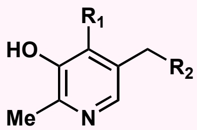
First Syntheses
- Karrer, P.; Schöpp, K. Pfaehler, K. *Helv. Chim. Acta* **1935**, *18*, 426.
- Kuhn, R.; Rudy, H.; Wagner-Jauregg, T. *Ber. Dtsch. Chem. Ges.* **1933**, *66*, 1950.



Second Generation Synthesis, Foundation for Future Syntheses
- Tischler, M.; Pfister, K., III; Babson, R. D.; Ladenburg, K.; Fleming, A. J. *J. Am. Chem. Soc.* **1947**, *69*, 1487.



Industrial Syntheses of Vitamins



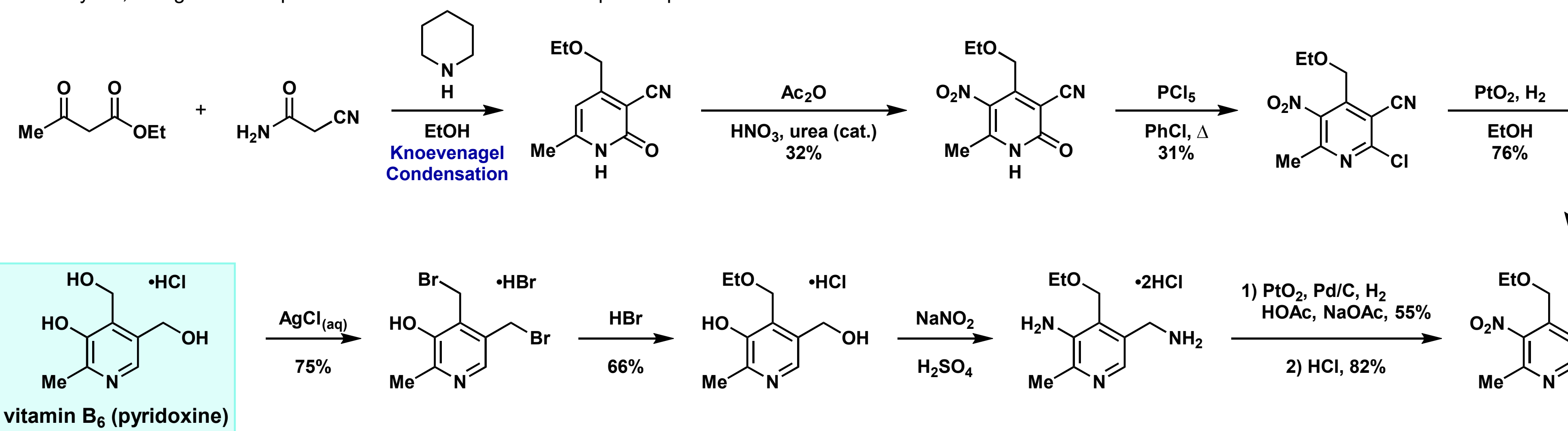
Vitamin B_6 Complex:

R_1 = CH_2OH; R_2 = OH: vitamin B_6 (pyridoxine)
R_1 = CH_2OH; R_2 = OPO_3H_2: pyridoxine-5'-phosphate
R_1 = CHO; R_2 = OH: pyridoxal
R_1 = CHO; R_2 = OPO_3H_2: pyridoxal-5'-phosphate
R_1 = CH_2NH_2; R_2 = OH: pyridoxamine
R_1 = CH_2NH_2; R_2 = OPO_3H_2: pyridoxamine-5'-phosphate

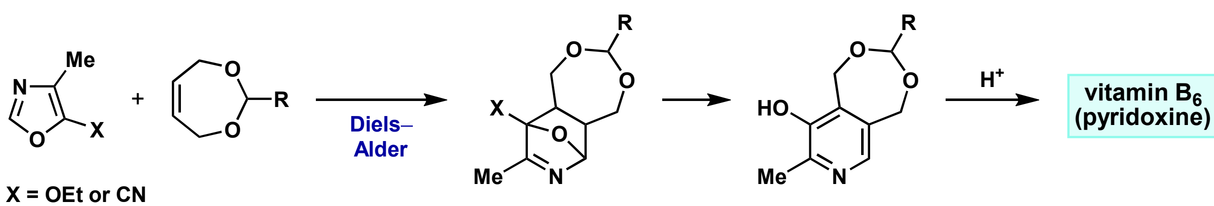
Medicinal Importance
- Pyridoxine-5'-phosphate is involved in reactions that affect immune function, erythrocyte metabolism, gluconeogenesis, niacin formation, and hormone modulation
- Deficiency is related to seborrheic dermatitis, microcytic anemia, convulsions, and depression.

Discovery and History
- Identified as the vitamin B_6 complex in 1934 by Györgi and Birch
- All six compounds with vitamin B activity are interconvertable
- Isolation and structural confirmation was achieved in 1938
- Synthesis was achieved in 1939 by two groups

First Process
- Harris, S. A.; Folkers, K. *J. Am. Chem. Soc.* **1939**, *61*, 1245. (Merck & Co.)
- Low yield, though some improvedments were made in subsequent reports

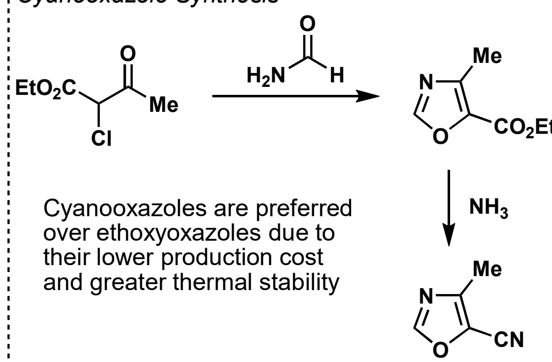


Diels–Alder Oxazole Approach
- Kondrateva, G. Y. *Khim. Nauka Prom-st.* **1957**, *2*, 666.
- Variations were developed into process routes by Takeda, Merck, Daiichi, BASF, and Roche
- All producers of pyridoxine have been employing the Diels–Alder strategy since the 1960s



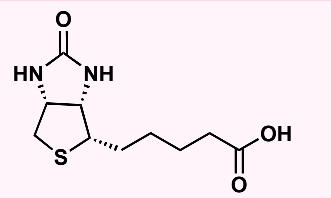
X = OEt or CN
R = C_1 to C_6 alkyl

Cyanooxazole Synthesis



Cyanooxazoles are preferred over ethoxyoxazoles due to their lower production cost and greater thermal stability

Industrial Syntheses of Vitamins



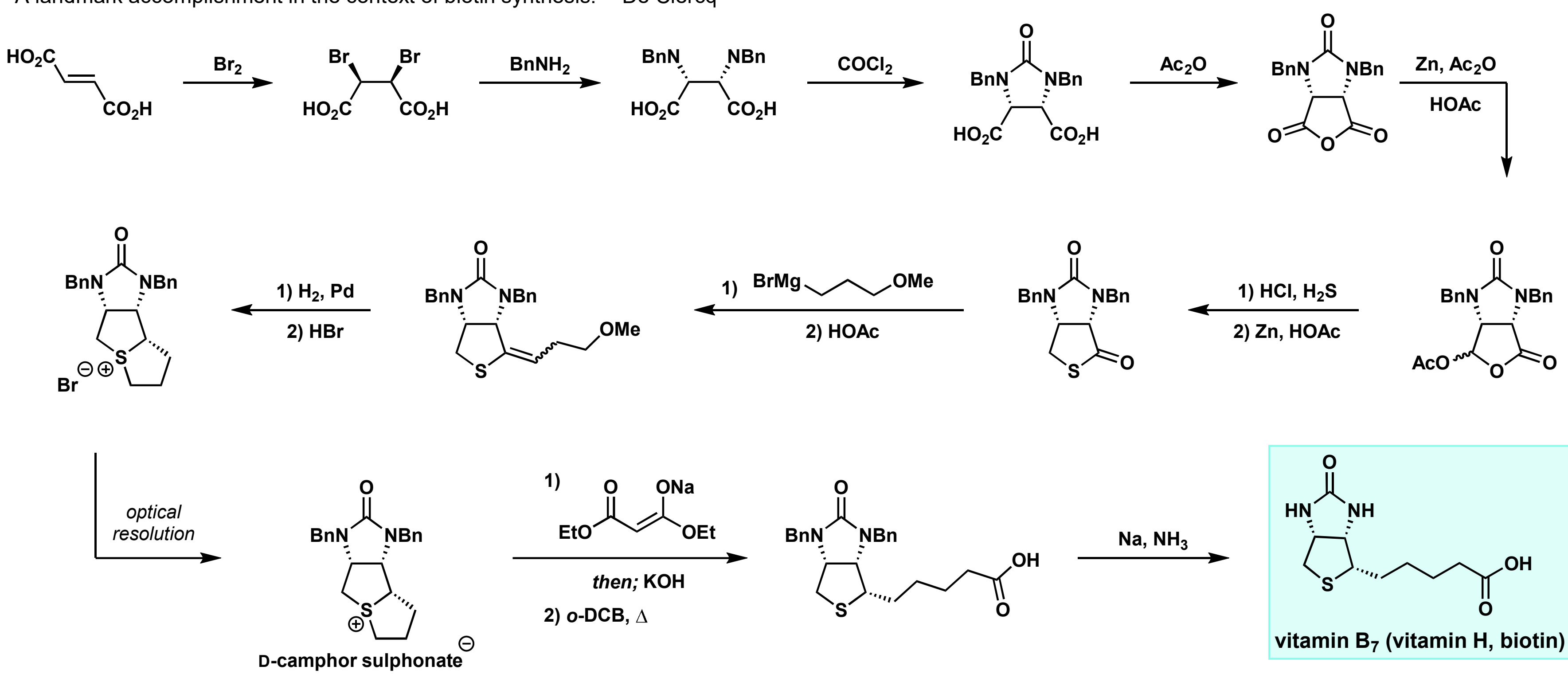
vitamin B_7 (vitamin H, biotin)

Medicinal Importance
- Co-enzyme in bicarbonate-dependent carboxylation reactions in lactate and pyruvate metabolism, leucine degredation, and propionate metabolism
- Deficiency is characterized by dermatitis, conjuctivitis, alopecia, and central nervous system abnormalities
- Adult humans require only 0.03 to 0.1 mg per day

Discovery and History
- Isolated by multiple researchers in the 1920s and was given various names (bios, vitamin H, protective factor x)
- In 1927, Boas demonstrated that rats that developed rashes, alopecia, and paralysis due to a diet high in raw eggs were cured by biotin.
- In 1940, Du Vigneaud discovered that these various substances were all the same compound, and determined its structure.

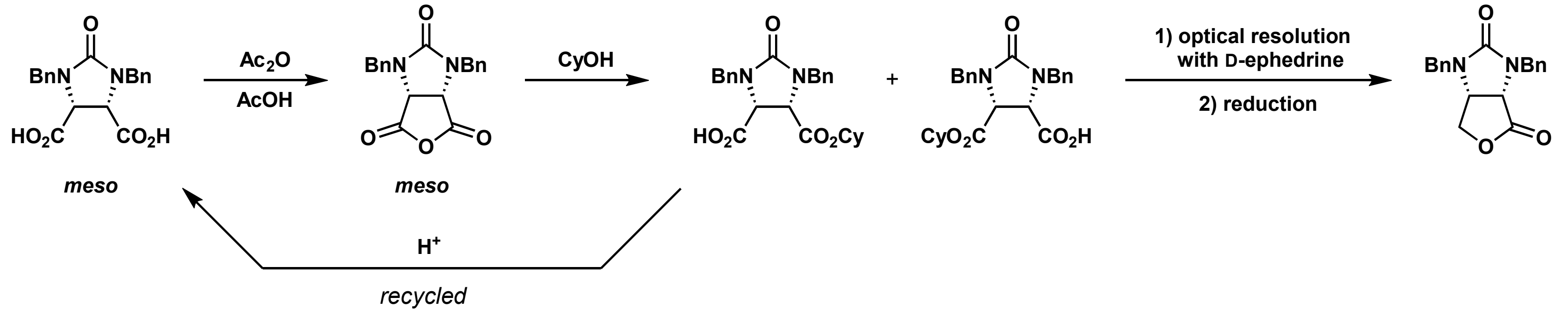
Biotin Synthesis
- First total synthesis accomplished in 1943 by Harris, Folkers, *et al*. at Merck
- First commerical route patented by Goldberg and Sternbach of Hoffmann–La Roche in 1946
- Approximately 40 total syntheses of biotin exist

Goldberg–Sternbach Concept
- Goldberg, M. W.; Sternbach, L. H. (Hoffmann–La Roche Inc.), IS 2489232, **1949**.
- "A landmark accomplishment in the context of biotin synthesis." - De Clercq



Industrial Syntheses of Vitamins

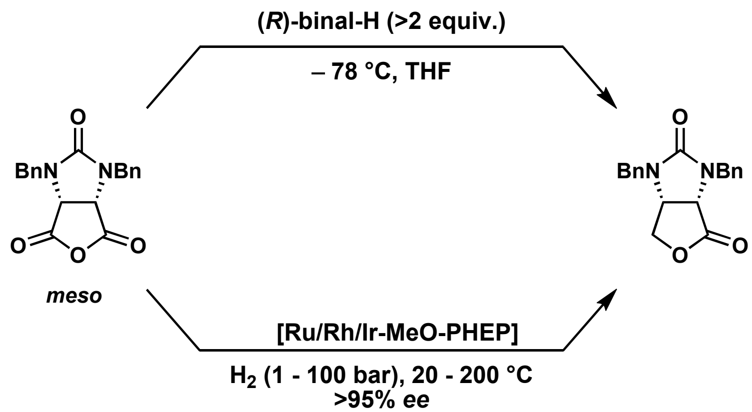
Improvements to the Goldberg–Sternbach Concept
- Gerecke, M.; Zimmerman, J.-P.; Aschwanden, W. *Helv. Chim. Acta* **1970**, *53*, 991.
- Used commercially until 1990
- Alternatively, a chiral alcohol could be used to desymmetrize the *meso* cyclic anhydride.
  (Pauling, H.; Wehrli, C. (F. Hoffmann – La Roche & Co. AG), EP 0161580, **1985**.

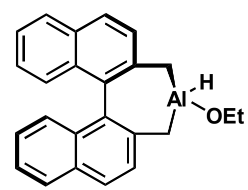


- Generally, companies working to improve the Goldberg–Sternbach Concept were driven to introduce chirality at a later stage. Earlier introduction of chirality by chiral auxiliaries or chiral pool starting materials often resulted in lengthy sequences that precluded large scale production.
- The transformation of the *meso* cyclic anhydride and the chiral lactone became the preferred stage for the introduction of chirality.

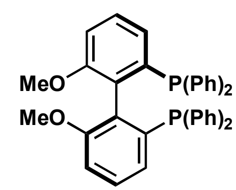
- Matsuki and co-workers developed an asymmetric reduction of the cyclic anhydride using Noyori's binal-H, though the use of a stoichiometric chiral reagent that required low temperatures to achieve desired results was not an attractive pathway.
  Matsuki, K.; Inoue, H.; Takeda, M. *Tetrahedron Lett*. **1993**, *34*, 1167.

- A catalytic, enantioselective reduction would be the most modern strategy to affect this conversion, and has been accomplished in an effort between DSM Nutritional Products and Solvias.



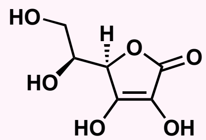


(*R*)-binal-H



(*R*)-MeO-PHEP

Industrial Syntheses of Vitamins

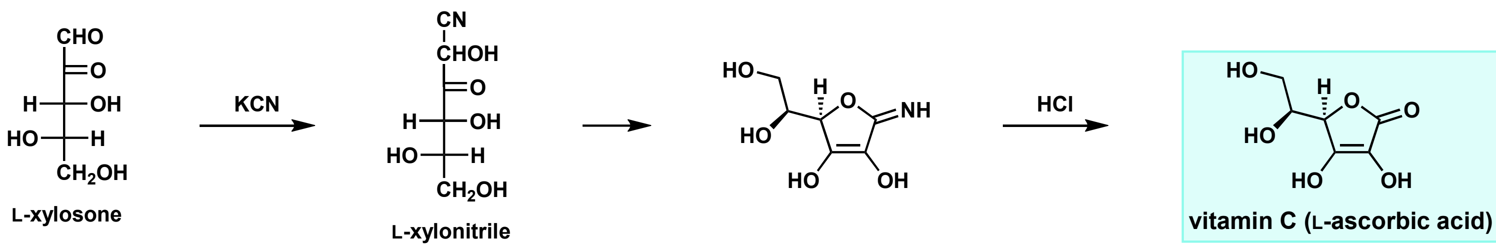


vitamin C (L-ascorbic acid)

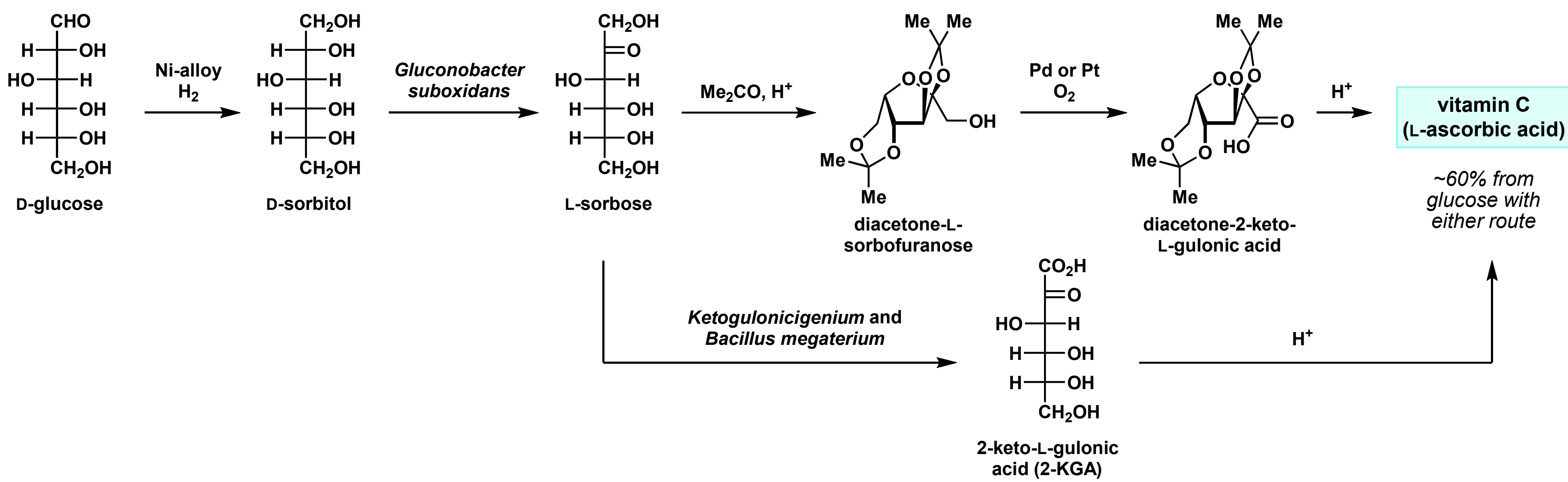
Medicinal Importance
- Essential for the biosynthesis of collagen, carnitine, and catecholamines, and functions as an electron donor in these processes
- Strong antioxidant
- Metabolism of tyrosine
- Deficiency is characterized by scurvy (bleeding and impaired wound healing, eventual death)

Discovery and History
- In the late 18th century and early 19th century, ship doctors Lind and Blane determined that the nutritional factor, "the antiscorbutic factor," was responsible for scurvy.
- In 1931, L-ascorbic acid was first isolated from the adrenal glands of guinea pigs and crystallized by Szent-Györgyi.
- In 1933, the chemical stucture was elucidated and confirmed by synthesis by Walter Norman Haworth.
- Shortly after, an industrial process was developed by Reichstein, Grüssner, and Oppenauer, making vitamin C the first vitamin to be industrially produced.

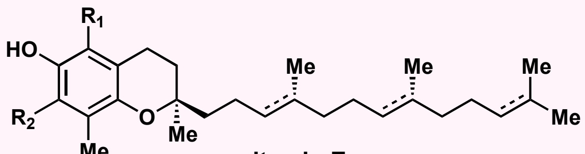
First Synthesis
- The first (and most syntheses) of vitamin C start with sugars
- Haworth, W. N. *Chem. Ind.* **1933**, *52*, 482.



Reichstein–Grüssner Process, and Improved Biotechnological Process



Industrial Syntheses of Vitamins



vitamin E

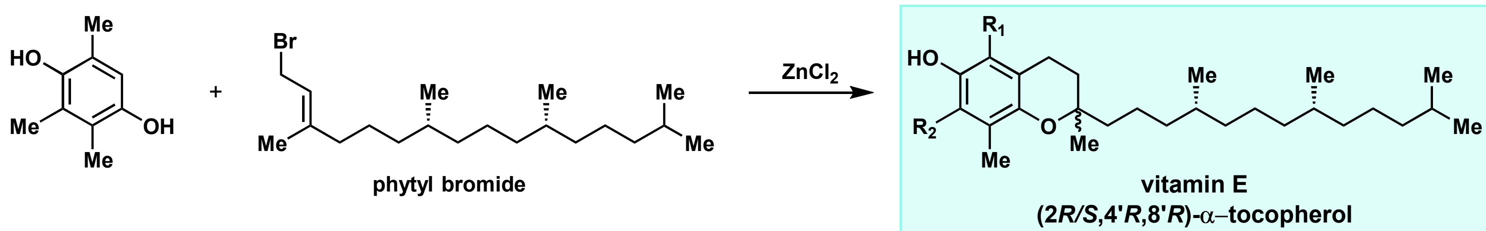
$R_1 = R_2$ = Me: (2*R*,4'*R*,8'*R*)-α–tocopherol
R_1 = Me; R_2 = H: (2*R*,4'*R*,8'*R*)-β–tocopherol
R_1 = H; R_2 = Me: (2*R*,4'*R*,8'*R*)-γ–tocopherol
$R_1 = R_2$ = H: (2*R*,4'*R*,8'*R*)-δ–tocopherol

triene: (2*R*,3'*E*,7'*E*)-tocotrienols

Medicinal Importance
- "Vitamin E" refers to all tocopherol and tocotreinol derivatives that exhibit activity similar to (2*R*,4'*R*,8'*R*)-α–tocopherol (the most active).
- Chain-breaking antioxidant that protects poly-unsatured fatty acids in membranes and plasma lipoproteins against radical reactions
- Plays a role in immune function, non-antioxidant functions in cell signaling, gene expression, and regulation of other cell functions

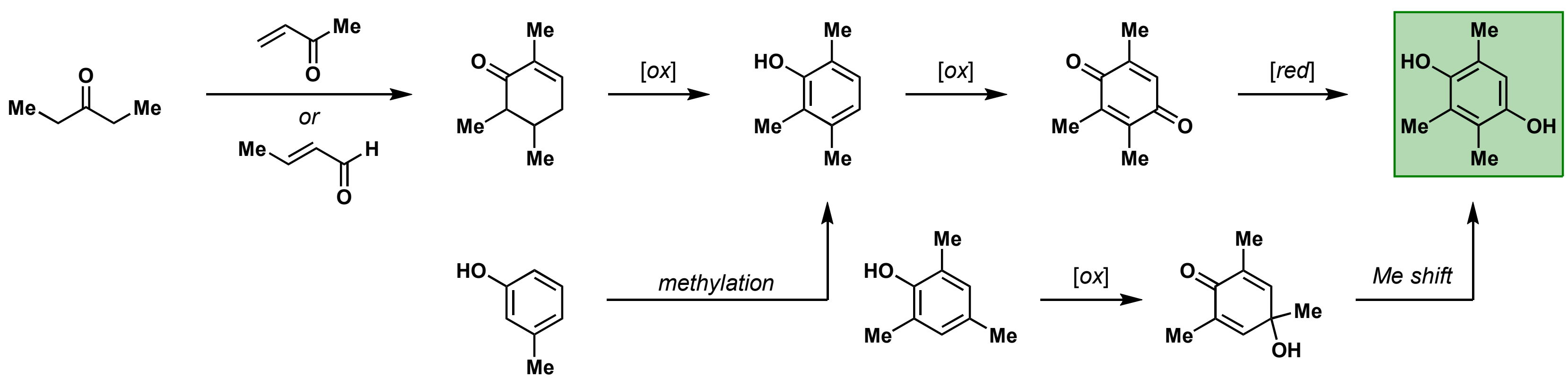
Discovery and History
- Discovered by Evans and Bishop in 1922 and identified as a dietary factor essential for reproduction
- Isolated from what germ oil by Fernholz, which enabled structural elucidation
- Since the difference in activity between the stereoisomers is minimal, (all-*rac*)-α–tocopherol is the most relevant commercial product

First Synthesis
- Karrer at University of Zurich and Isler at Roche synthesized α–tocopherol independently *via* similar methods at nearly the same time. This led to a collaboration between Karrer and Roche.
- Karrer, P.; Fritzsche, H.; Ringier, B. H.; Salomon, H. *Helv. Chim. Acta* **1938**, *21*, 520.
- Karrer, P.; Fritzsche, H.; Ringier, B. H.; Salomon, H. *Nature* **1938**, *141*, 1057.



Industrial Syntheses
- Major producers are BASF and DSM
- Industrial syntheses consist of three parts: preparation of the aromatic building block; preparation of the side chain, and the condensation reaction

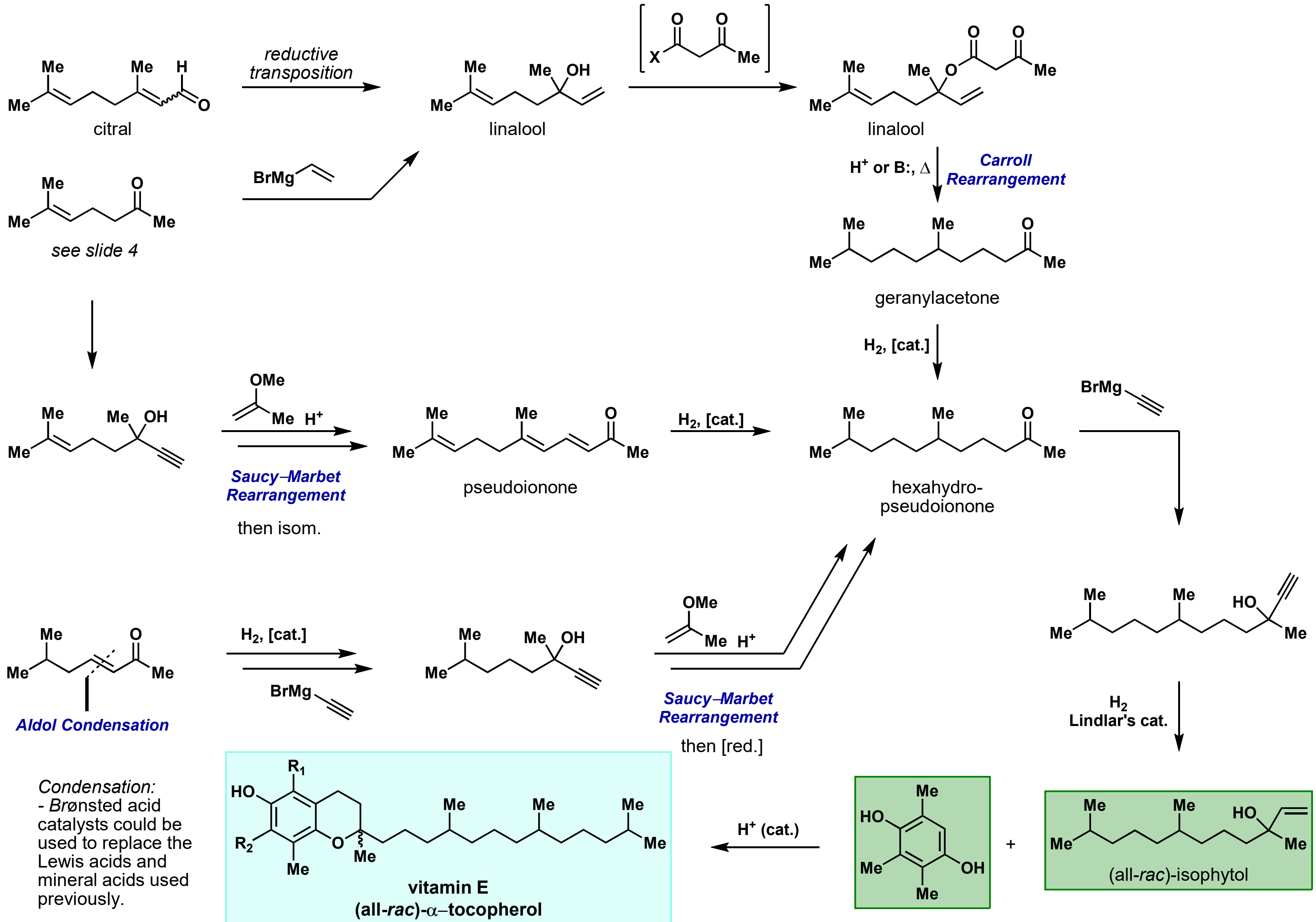
Selected routes toward trimethylhydroquinone



Industrial Syntheses of Vitamins

Selected routes toward (all-rac)-isophytol, the preferential side chain building block

- Critical to all routes are the Saucy–Marbet and Carroll rearrangements, Grignard reagent additions, and hydrogenation (both full and partial)



Condensation:
- Brønsted acid catalysts could be used to replace the Lewis acids and mineral acids used previously.

Industrial Syntheses of Vitamins

Production of (2R,4'R,8'R)-α–tocopherol

- A waste stream from vegetable oil, soya deodorizer distillates (SDD), contains tocopherols that can be reacted and manipulated to produce pure (2R,4'R,8'R)-α–tocopherol
- First synthesized by Isler in 1963
- No methods have been applicable for an industrial process, though many efforts have been made.
- Noyori asymmetric hydrogenation of allylic alcohols provides a promising and scalable pathway toward the desired phytol side chain
  Netscher, T.; Scalone, M.; Schmid, R. *Asymmetric Catalysis on Industrial Scale* (Eds.: H.-U. Blaser, E. Schmidt), Wiley-VCH, Weinheim, **2004**, pp. 71 – 89