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Vitamins

One Hundred Years of Vitamins—A Success Story of the Natural Sciences

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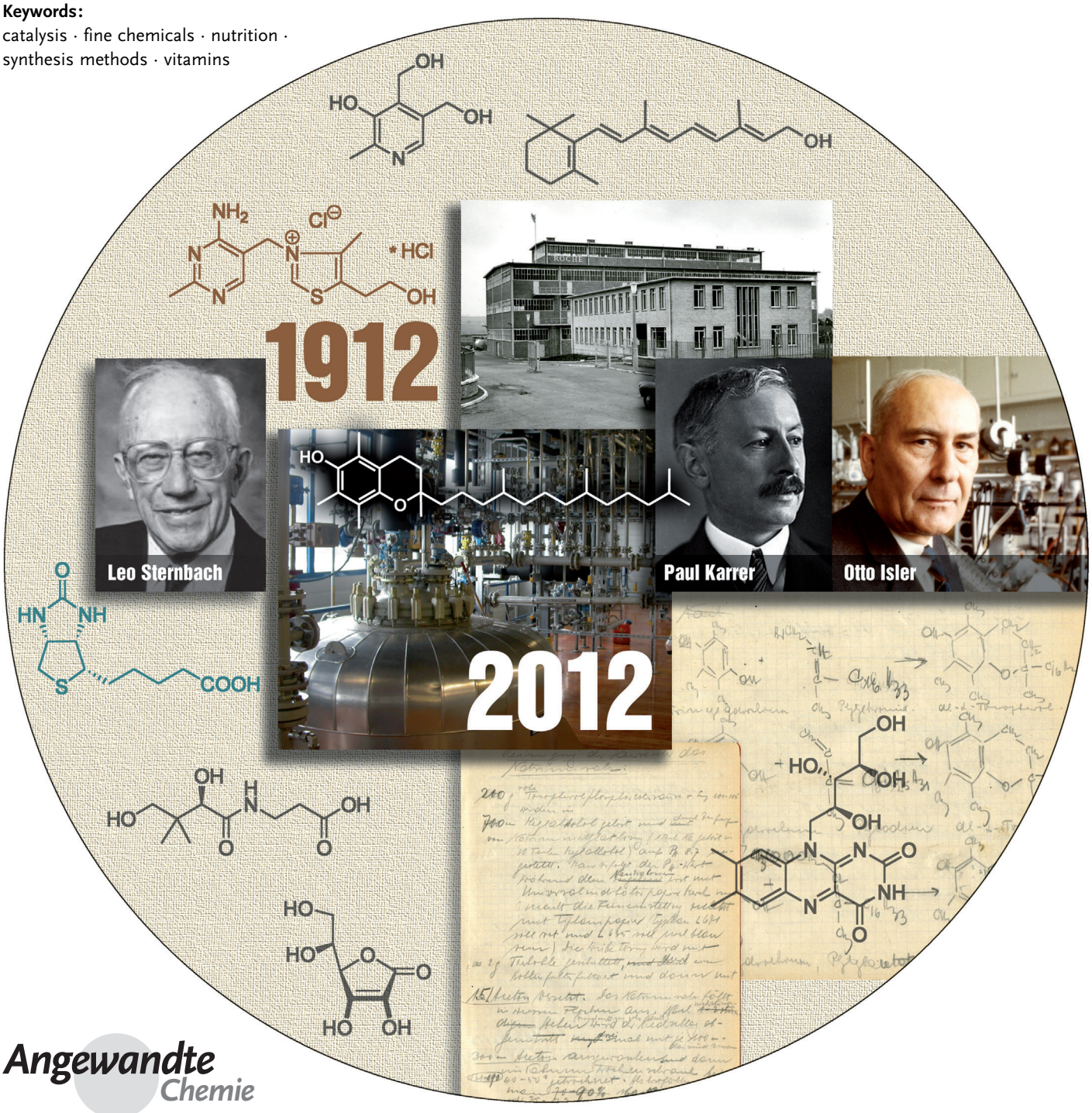

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The discovery of vitamins as essential factors in the diet was a scientific breakthrough that changed the world. Diseases such as scurvy, rickets, beriberi, and pellagra were recognized to be curable with an adequate diet. These diseases had been prevalent for thousands of years and had a dramatic impact on societies as well as on economic development. This Review highlights the key achievements in the development of industrial processes for the manufacture of eight of the 13 vitamins.

From the Contents

1. Introduction

Vitamins are essential organic compounds which are either not synthesized in the human or animal organism, or are formed in insufficient amounts, and therefore must be taken up with the diet as such or as a precursor.[1]

In 1906 Frederick Gowland Hopkins (Figure 1) indicated that "*no animal can live on a mixture of pure protein, fat, carbohydrate, salts, and water*".[2] This started the search for "growth factors" in food. It was the Dutch physician Christiaan Eijkman who found that a constituent of rice bran can prevent a beriberi-like disease in chickens.[3] The credit for being the first scientist to adopt the deficiency theory for the etiology of this disease belongs to Gerrit Gijns. He stated that the disease breaks out when a substance necessary for the metabolism is lacking in the food.[4]

In 1912 the Polish biochemist Casimir Funk (Figure 2) isolated a bioactive substance from rice bran which was at first given the name "vita-amine" (later "aneurin" for "anti-neuritic vitamin" and eventually "thiamin").[5] Funk realized that this substance could cure chickens and humans of beriberi. He published a landmark paper "The etiology of the deficiency diseases" and stated that all deficiency "diseases can be prevented and cured by the addition of certain preventive substances, the deficient substances", for which he proposed the name "vitamins".[6]

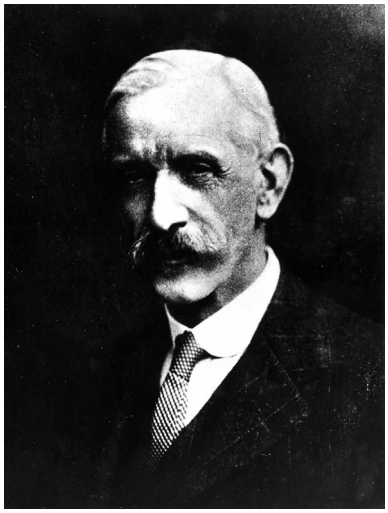

Figure 1. Frederick Gowland Hopkins (source: Roche Historical Archive).

In 1916 the American biochemist Elmer McCollum (Figure 3) introduced the capital letters A–D to differentiate between vitamins.[7] Later, vitamins E and K were added, and it was realized that vitamin B can contain more than one factor, so a further differentiation into vitamins B_1, B_2, and so on was made.

These observations and findings greatly facilitated experimental research in the following years. The next three

Figure 2. Casimir Funk (source: Roche Historical Archive).

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Figure 3. Elmer McCollum (source: Roche Historical Archive).

decades were full of scientific breakthroughs in understanding the role of vitamins, and by 1941 all 13 vitamins had been identified, their structures characterized, and their role for humans and animals defined.[8] A summary of the discovery, isolation, and assignment of the chemical structure and first production of the individual vitamins is given in Table 1 (see also Figure 4).

These scientific breakthroughs were honored with 12 Nobel Prizes to 20 laureates.[9] The first Nobel Prize in chemistry relating to vitamins was given to Adolf Windaus for his studies on the constitution of sterols and their connection with the vitamins.[10] This was followed by the Nobel Prize in Medicine and Physiology in 1929 jointly to Christiaan Eijkman, for the discovery of the anti-neuritic vitamin, and to Sir Frederick Gowland Hopkins, for the discovery of the growth-stimulating vitamins.[11]

The understanding that micronutrients are essential for human and animal growth and health was a major stimulus for nutritional science. It subsequently became clear that breakthroughs in production, formulation, and application would have to be achieved to allow vitamins to be given to humans and animals. This inspired scientists in universities and companies to develop synthetic routes and production technologies. The first commercialized vitamin was ascorbic acid/vitamin C from Merck (Cebion), which was isolated from plant leaves, and became available in 1933.[12] The first industrial-scale chemical production was also of vitamin C and was achieved by F. Hoffmann–La Roche (Roche)[13] in 1934, and was based on a combined fermentation and chemical process developed by Tadeus Reichstein (Figure 5).[14] To commemorate this, the Swiss Chemical Society selected vitamin C for the 100 Rappen Swiss postage stamp for the International Year of Chemistry in 2011 (Figure 6).

In the following years, all of the vitamins became available through chemical synthesis, fermentation, or extraction from natural materials (Table 1), and it was not until 1987 that all the vitamins were accessible by industrial processes. Today,

Manfred Eggersdorfer completed his PhD at the Technical University Munich. After postdoctoral research at Stanford University, working with Carl Djerassi on the isolation and characterization of sterols from marine origin, he joined BASF, Ludwigshafen and worked in different positions including Head of R&D Fine Chemicals. He joined Roche in 1999 as Head of R&D Vitamins and Fine Chemicals, which was acquired by DSM. He is an active member of the Advisory Board of the Johns Hopkins Bloomberg School of Public Health and the Strategy Board of the Institute of Food Science University Hamburg.

Ulla Létinois studied chemistry at the University of Oldenburg, Germany and at the University Champagne-Ardennes, France. After a PhD in organic synthesis and spectroscopy under the co-direction of Stefan Berger (University of Leipzig, Germany) and Patrick Pale (University of Strasbourg, France), and postdoctoral research with Jean-Pierre Sauvage and Bernard Meunier (Toulouse, France) in 2005 she started working in Basel, Switzerland as a laboratory head in DSM Nutritional Products in Process Research.

Dietmar Laudert studied biology and completed his PhD in Plant Physiology at the University Bochum, Germany. He started his industrial career at Scinet Bioproducts GmbH, working as Scientist and project manager on molecular biology contract research. He joined Roche Vitamins/DSM Nutritional Products in 2001, where he has been engaged in several strain and process development activities for the production of water-soluble vitamins such as riboflavin and ascorbic acid. He is currently a Senior Scientist and competence team coordinator in the Biotech Department at DSM Nutritional Products.

Jonathan Medlock studied natural science (chemistry) at the University of Cambridge, UK and stayed there to complete a PhD in organic synthesis with Stuart Warren in 2000. After postdoctoral research in asymmetric catalysis with Andreas Pfaltz (University of Basel) he returned to Cambridge to work for the 'Catalysis and Chiral Technologies' group of Johnson Matthey. In 2009 he moved to the Process R&D department of DSM Nutritional Products in Basel, Switzerland, where he is currently a Senior Scientist and Laboratory Head. His interests cover all aspects of catalysis, especially hydrogenation reactions.

Table 1: Vitamins and their discovery, synthesis, and main biological function.

Vitamin[a]	Discovery	Isolation	Structural elucidation	First Synthesis[a]	Main biological function
vitamin A	1916	1931	1931	1947	retinal, the oxidized metabolite of retinol, is required for the process of vision
vitamin D	1918	1932	1936	1959	bone mineralization, control of cell proliferation, and differentiation, regulation of calcium and phosphate blood levels; modulation of immune system
vitamin E	1922	1936	1938	1938	fat-soluble antioxidant, cell signaling, regulation of gene expression.
vitamin K	1929	1939	1939	1939	blood coagulation, bone metabolism
vitamin B_1	1912	1926	1936	1936	cofactor in energy metabolism and pentose metabolism, nerve impulse conduction, and muscle action
vitamin B_2	1920	1933	1935	1935	precursor for biosynthesis FMN or FAD, cofactors involved in redox reactions
niacin vitamin B_3	1936	1936	1937	1994	precursor for biosynthesis of NAD and NADP, cofactors involved in redox reactions
pantothenic acid vitamin B_5	1931	1938	1940	1940	pantothenic acid, as a constituent of coenzyme A, is involved in metabolism of carbohydrates, proteins, and fats
vitamin B_6	1934	1938	1938	1939	cofactor involved in neurotransmitter biosynthesis
biotin vitamin B_7 vitamin H	1931	1935	1942	1943	cofactor involved in the metabolism of lipids, proteins and, carbohydrates
folic acid vitamin B_9	1941	1941	1946	1946	cofactor involved in amino acid metabolism and synthesis of nucleic acids
vitamin B_{12}	1926	1948	1956	1972	necessary for the formation of blood cells, nerve sheaths, and various proteins; involved in fat and carbohydrate metabolism
vitamin C	1912	1928	1933	1933	involved in collagen synthesis, antioxidant

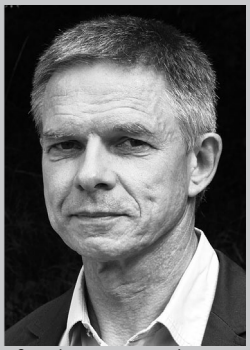
[a] Vitamins A, D, E, and K represent the subgroup of lipid-soluble vitamins, the others belong to the water-soluble ones. For the sake of clarity only one representative of each class is given in Figure 4.

Tom McClymont graduated in chemistry from Glasgow University in 1966. He completed his PhD at Hatfield Polytechnic in 1972, partly on aspects of the Lindlar hydrogenation in the vitamin A synthesis. He joined Roche in 1966 and worked for ten years in vitamins process research (England), then in chemical production and site management (Scotland), and finally in technology strategy (Switzerland) until his retirement from DSM Nutritional Products at the end of 2009.

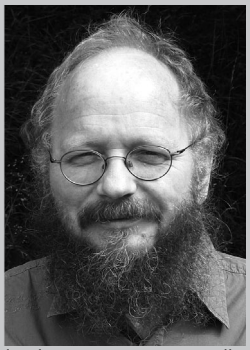
chemical synthesis is still the dominant method on a commercial scale.

1.1. Vitamin Production

Vitamins are organic molecules with complex and quite different chemical structures. The development of industrial production processes required a broad array of scientific and manufacturing expertise. The development of synthetic routes for vitamins was a pioneering phase in chemistry and process development, and the development of industrial



Thomas Netscher studied chemistry at the Universities of Constance and Freiburg i.Br., Germany, where he completed his PhD with Horst Prinzbach. In 1987 he joined F. Hoffmann–La Roche, now DSM Nutritional Products, in Basel (with a stay at the Roche Research Center in Nutley, USA in 1991/92), where he is now a Principal Scientist responsible for isoprenoid chemistry. Together with colleagues from DSM and Solvias he received the Sandmeyer Award 2008, held the Roche Lecture in 1997/98, is currently Lehrbeauftragter of the University of Freiburg i.Br., and a member of the German, the Swiss, and the American Chemical Societies.



Werner Bonrath studied chemistry in Bonn and Münster (Diploma 1985) and completed his PhD in 1988 at the MPI, Mülheim, with Günther Wilke. He joined Hoffmann–La Roche in 1989 and worked in the field of catalysis for fine chemicals, especially vitamins and carotenoids. In 2007 he completed his habilitation at the University Jena, and is a lecturer at the Universities of Jena and Basel. Since the integration of Roche Vitamins into DSM, he is Competence Manager, Heterogeneous Catalysis at DSM Nutritional Products in Kaiseraugst, Switzerland. His interests cover all aspects of catalysis, especially Lindlar-type hydrogenation and ethynylation.

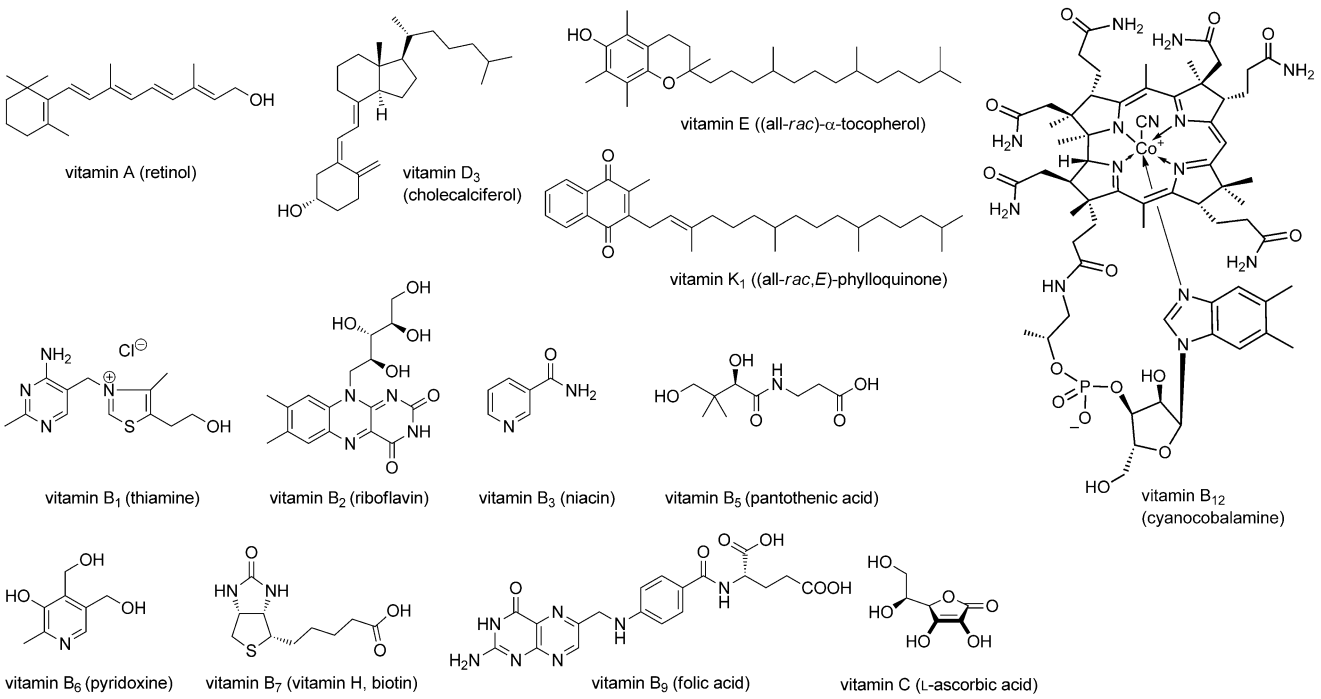


Figure 4. Representative structures of the 13 vitamins.

Figure 5. Tadeus Reichstein (source: Roche Historical Archive).

processes for the production of vitamins can roughly be divided into four phases:

- The pioneering days from 1930 to 1950;
- the scaling-up and engineering phase from 1950 to 1970;
- the period of worldwide production plants followed by consolidation from 1970 to 1990; and
- the period of the rise of new technologies from the 1990s to the present day.

The first phase was characterized by laboratory-scale syntheses to confirm their structures and to provide enough of the bioactive to perform animal and human studies. Practical manufacturing routes for small-scale production were then

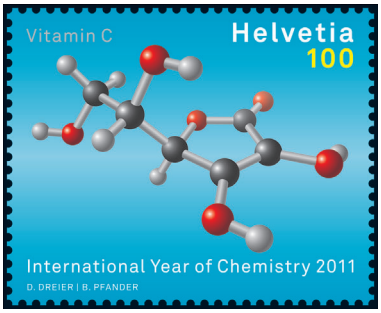


Figure 6. Stamp issued on the occasion of the International Year of Chemistry 2011, depicting a molecule of vitamin C as a symbol of innovation that originated from Swiss chemical research. (© Die Post.)

developed. This was often done in close cooperation between academic and industrial research groups. Examples are the cooperation of Roche Basel with Tadeus Reichstein (ETH Zurich, vitamin C) and Paul Karrer (University of Zurich, vitamins A and E), as well as of Georg Wittig with BASF (vitamin A). This was followed by the construction of small production plants in several countries to enable market development on a local or regional basis.

The growth of the vitamin market continued and required the production of larger volumes, so scaling up and engineering factors characterized the second phase. This presented new challenges, such as recycling of solvents, improving yields, and for the larger volume products even moving from batch to continuous processes. New routes or improved processes were developed at universities as well as in companies. The concept of larger plants triggered a rational process R&D from the laboratory via pilot plants and finally to production. The resulting "economy of scale" enabled

production costs to be reduced significantly. The large companies—especially Hoffmann–La Roche and BASF, who were market leaders—built several plants in different regions for security of supply. The number of companies producing and selling vitamins grew: especially European and Japanese pharmaceutical companies as well as a few chemical companies, such as BASF and Lonza, which had the benefit of backward integration in key raw materials.

The third phase was characterized by an even higher growth in volume, based in particular on market development in animal nutrition. This resulted in the rationalization of production into one single plant. This philosophy was especially promoted by the Vitamins Division of Hoffmann–La Roche (now DSM Nutritional Products). This strategy required a reliable and stable operation of the plant, because a shutdown would have had a major impact on the global supply of the vitamin. Process development became a key competence and differentiating factor. Building a pilot plant was too costly, so "miniplants" were developed which simulated the complete production concept, including recycling of solvents and recovered precursors. A change in the competitive environment also became evident in this phase: China defined supplying its population with vitamins as a key strategy and stimulated local companies to enter the vitamin business.

The fourth phase in vitamin production was characterized by the rise of new technologies and by a dramatic change in the competitive environment. The benefits of "economy of scale" for major producers made smaller producers leave the market. The number of Chinese producers initially increased and then declined because of the increasing role of environmental factors and quality issues.[15] In parallel, general economic trends such as the increase in raw material and energy costs, sustainability, and quality influenced production and required major investments. The number of companies active in vitamin production and marketing changed, and left DSM as the only Western producer with a complete portfolio, BASF with a strong position in vitamins A and E, and a reasonable number of Chinese companies, none of them complete portfolio providers.

Fermentation technology started to gain in importance: vitamin B_{12} is only produced by fermentation, the production of vitamin B_2 shifted from chemical to fermentation technology in the last decade, and promising approaches are in development for the other water-soluble vitamins. We are also experiencing the early phase of a new technology: the overexpression of vitamins in plants by using traditional breeding or genetically modified plants.[16] The first studies on the sweet potato or yellow corn with an increased level of β-carotene (pro-vitamin A) obtained by traditional breeding are in being tested in Africa. A project called "golden rice", involving a genetically modified plant with higher β-carotene, has been announced for the start of 2013.

1.2. Nutritional Role of Vitamins

The World Bank's assessment of fortification of food products such as milk, flour, and juice was: "*probably no other technology available today offers as large an opportunity to improve lives and accelerate development at such low cost and in such a short time*".[17] The synthesis and industrial production of vitamins has resulted in their worldwide availability. Authorities had started to establish dietary standards and nutrient requirements for the optimal and safe intake of vitamins depending on age, gender, and risk groups as early as the 1940s.[18] A number of countries implemented fortification programs of staple food to secure a sufficient intake of vitamins for the full population; today this has been established in more than 50 countries.[19]

Today, as a consequence of results from many human studies, there is a general consensus by scientists about the biological function of vitamins and their impact on health and healthy aging.[20] In addition, new data from national intake surveys reveal that, even in industrialized countries in Europe, US, and others parts of the globe, some segments of the population have a vitamin deficiency, for example, of vitamin D, folate, or vitamin E.[21] Triggered by the analysis of the human genome and building on new science, a renaissance in vitamin research started this century: it allows nutrient–gene interactions to be studied, and the discovery of polymorphism (individual differences in the genome in populations) has allowed specific requirements for vitamins to be identified.[22]

This Review provides an overview of the development of industrial synthetic processes for manufacturing a selected number of vitamins. These examples have been chosen because they represent typical characteristics of the history of science and technical development from identification and characterization to industrial production.

We start with the first industrially synthesized vitamin (vitamin C) and then continue with other members of the water-soluble vitamins group (vitamin B_1, B_2, B_6, pantothenic acid, biotin) and conclude with two lipid-soluble vitamins (A and E).

2. L-Ascorbic Acid (Vitamin C)

2.1. Physiological Functions

Vitamin C is a water-soluble vitamin that is essential for the biosynthesis of collagen, carnitine, and catecholamines. It is also a strong antioxidant that protects molecules from oxidative damage. Vitamin C serves as an electron donor for enzymes involved in the synthesis of collagen, carnitine, and norepinephrine. It is also involved in the metabolism of tyrosine. The clinical syndrome of vitamin C deficiency is scurvy, a condition characterized by bleeding and impaired wound healing.[20]

2.2. History

Scurvy was a common disease among mariners and discoverers until the beginning of the 19th century, with serious symptoms such as collagen instability causing loss of teeth, bleeding of mucous membranes, anemia, and even-

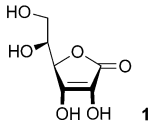


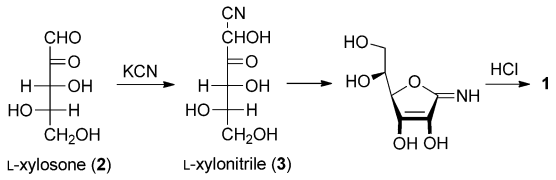
Figure 7. Vitamin C (**1**).

tually death. Medical studies by ship's doctors such as Lind (1717–1794) and Blane (1749–1834) proved that scurvy results from the lack of a nutritional factor in the human diet. This was first designated as the antiscorbutic factor, later L-ascorbic acid or vitamin C.[23] Vitamin C was isolated from plant tissues as well as the adrenal glands of guinea pigs suffering from scurvy, and crystallized by Szent-Györgyi in 1931.[24] Its chemical structure (Figure 7) was elucidated in 1933 and confirmed by a synthetic route developed by Walter Norman Haworth.[25] Shortly after the structural confirmation of L-ascorbic acid and its first synthesis, an industrial process for its manufacture was established by Reichstein, Grüssner, and Oppenauer.[26] L-Ascorbic acid (**1**) was the first industrially produced vitamin. Several processes for the production of vitamin C have since been established.

2.3. First Syntheses

Several overviews on L-ascorbic acid syntheses have been published over the last 50 years.[27] In general, polyhydroxy compounds were used as the starting materials in all the efficient syntheses. Chemical synthesis can start from different sugars, depending on the reaction pathway chosen, whereas biotechnological approaches only use glucose as the starting material.

In Haworth's first synthesis of vitamin C, L-xylosone (**2**) was synthesized from the pentose xylose. The C_1 chain extension was then achieved using potassium cyanide. Lactonization and enolization of the L-xylonitrile (**3**) under acidic conditions resulted in a yield of L-ascorbic acid of around 40 % (Scheme 1).[25a] This procedure was never of commercial interest, since the starting materials are too expensive. A similar synthesis starting from arabinose also found no commercial application.[28]

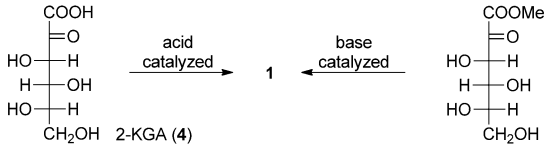


Scheme 1. Synthesis of L-ascorbic acid from xylosone.

The principle of L-ascorbic acid preparation includes either an acid-catalyzed cyclization of 2-keto-L-gulonic acid (2-KGA, **4**) or a base-catalyzed cyclization of the corresponding methyl ester (Scheme 2). These aspects are discussed in more detail below.

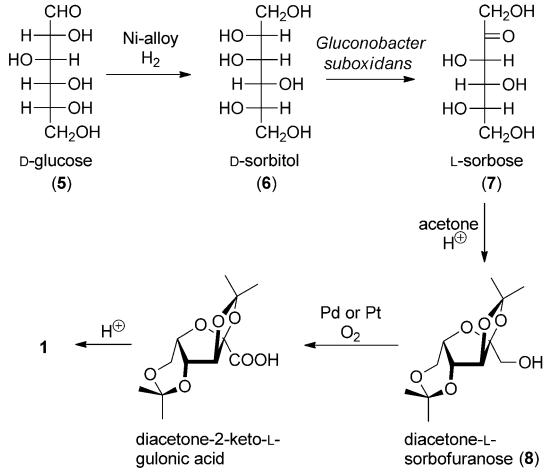
2.4. Industrial Processes

The first industrial preparation of L-ascorbic acid used the Reichstein–Grüssner process. In the classical process D-



Scheme 2. Principle of L-ascorbic acid synthesis through rearrangements.

glucose (**5**; Scheme 3) is hydrogenated over a nickel-alloy catalyst to afford sorbitol (**6**). Microbiological oxidation with *Gluconobacter oxydans* results in the formation of L-sorbose (**7**). An acid-catalyzed reaction with acetone results in the



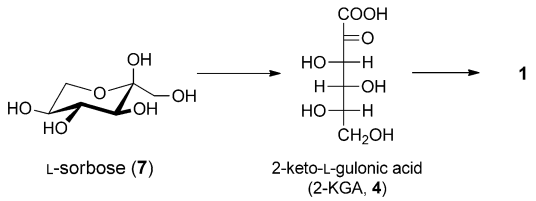
Scheme 3. Reichstein–Grüssner process for the manufacture of L-ascorbic acid.

formation of 2,3,4,6-di-*O*-isopropylidene-α-L-sorbofuranose (**8**), which is oxidized in high yield and selectivity to di-*O*-isopropylidene-2-ketogulonic acid. Acid treatment removes the acetal protecting groups and the resulting 2-ketogulonic acid rearranges to L-ascorbic acid.[27a] The base-catalyzed rearrangement has also been described, and the advantages and disadvantages have been discussed.[29] The oxidation of **8** can be effected by treatment with hypochlorite in presence of a nickel salt, by electrochemistry, or by air-oxidation catalyzed by palladium or platinum on a carrier.[30]

A further attractive approach to L-ascorbic acid is the synthesis of 2-ketogulonic acid (2-KGA, **4**) by direct oxidation of L-sorbose (**7**). This reaction was investigated by several research groups with little success (Scheme 4).[31] The gold-catalyzed oxidation of carbohydrates shows interesting results. Problems in the selectivity of the sorbose oxidation may be solved by these catalysts in the future.[32]

2.5. Biotechnological Production of L-Ascorbic Acid

A two-stage microbial fermentation process developed in China in the late 1960s and early 1970s[33] is generally employed to produce **4** by a biotechnological approach.



Scheme 4. Direct oxidation of L-sorbose (**7**).

Similar to the Reichstein–Grüssner process described above, L-sorbose (**7**) is generated by the *Gluconobacter*-mediated oxidation of D-sorbitol (**6**). However, in contrast to the chemical oxidation, the biochemical oxidation is carried out in a second fermentation step with *Ketogulonicigenium* strains, and **4** is obtained by oxidation of the intermediate L-sorbosone. Efficient fermentation of *Ketogulonicigenium* requires co-cultivation of a helper strain, for example, *Bacillus megaterium*. The underlying supportive mechanism, however, is not understood. For process control, the 2-KGA fermentation process must be separated into two sequential steps, keeping *Ketogulonicigenium* apart from D-sorbitol. In contrast to *Gluconobacter*, *Ketogulonicigenium* would mediate the oxidation of D-sorbitol to glucose, gluconate, 2-ketogluconate, and other oxidation products, which would result in a lower yield of **4**. As in the Reichstein–Grüssner process, **4** is eventually converted by an acid-catalyzed reaction via its methyl ester into L-ascorbic acid. The described two-stage microbial fermentation process is very efficient and can produce up to 130 g L^{-1} **4** with a yield of over 80% based on D-sorbitol. Compared to the Reichstein–Grüssner process, the 2-KGA fermentation process provides a clear cost benefit, since it requires not only less chemicals and energy, but also significantly less investment in production equipment because of the simpler process requirements.

An improved version of the fermentation process to generate **4** involves three oxidation reactions from D-sorbitol to 2-KGA (**4**) in a single process step that is facilitated by a mixed culture of *Gluconobacter suboxydans* IFO3255 and *Ketogulonicigenium vulgare*. *Gluconobacter* can substitute for the *Bacillus* helper strain, thus facilitating *Ketogulonicigenium* growth. It also mediates the oxidation of sorbitol to sorbose at a sufficient rate without allowing *Ketogulonicigenium* to oxidize the sorbitol to glucose and other undesired oxidation products.[34] A single-strain process for 2-keto-L-gulonic acid based on an intensively mutagenized *G. oxydans* strain was developed, but never commercially exploited, probably because of inferior space–time yields.[35]

Alternative microbial routes to 2-keto-L-gulonic acid (**4**) starting from D-glucose via 2,5-diketo-D-gluconate have been developed by employing *Erwinia* and *Corynebacterium* species in a two-step process or by employing genetically engineered *Erwinia* species expressing a gene for a *Corynebacterium* 2,5-diketoreductase.[36] However, as a consequence of poor performance, these processes were not used industrially.

All of the L-ascorbic acid bioprocesses developed to an industrial stage so far result in the formation of the precursor compound 2-KGA (**4**), which is converted in a costly final chemical rearrangement step into ascorbate. Numerous attempts have been made to further reduce the production costs associated with ascorbate and to design microbial routes that directly form L-ascorbic acid. Microalgae such as *Chlorella* species that synthesize L-ascorbic acid in an analogous manner to the plant pathway yielded up to 2 g L^{-1} of the vitamin, although it was mainly associated with the biomass.[37] Although D-glucose (**5**) was used as the fermentation substrate, the reported low productivity rendered a commercial application nonviable.

Another approach tried to utilize the biosynthetic capacity of *Saccharomyces cerevisiae* (baker's yeast), which can synthesize the C_5 L-ascorbic acid analogue D-erythroascorbic acid in nature. Characterization of the *S. cerevisiae* pathway revealed that cells incubated with L-galactose, L-galactono-1,4-lactone, and L-gulono-1,4-lactone led to the direct formation of L-ascorbic acid.[38] The results suggest that the pathway could be exploited for the direct production of ascorbate by a single fermentation step, but so far no commercial process has been established.

Another promising direct route to L-ascorbic acid has been identified by the discovery of dehydrogenases present in *Ketogulonicigenium* sp. and *Gluconobacter* species that convert L-sorbosone, the partially oxidized biosynthetic intermediate of the microbial 2-KGA processes, directly into vitamin C.[39]

3. Thiamin (Vitamin B_1)

3.1. Physiological Functions

Thiamin (**9**, Figure 8) is a water-soluble vitamin that plays an essential role in the metabolism of carbohydrates and branched-chain amino acids. Thiamin, in the form of thiamin pyrophosphate, acts as co-enzyme in the oxidative phosphorylation of α-ketoacids and in transketolase reactions, two processes important to the metabolism of carbohydrates and lipids. Thiamin deficiency is characterized by beriberi, a syndrome that occurs in two principle forms—dry (paralytic peripheral neuropathy) and wet (heart abnormalities and failure)—and by the Wernicke–Korsakoff syndrome.[20]

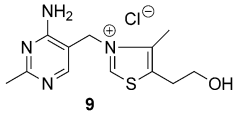


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Figure 8. Thiamin (**9**).

3.2. History

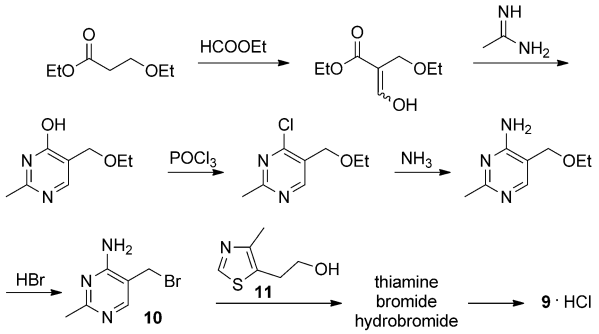
Vitamin B_1 or thiamin (**9**) played a very important part in the early history of the synthesis and commercial manufacture of vitamins. From the end of the 19th century there was intense scientific and medical debate in Europe, Asia, and the USA about the real cause of the wasting disease known as

beriberi. Causes ranging from bacteria, parasites, toxins, to—the ultimately correct—nutritional deficiency were postulated and heatedly defended.[40] In Japan and the Dutch East Indies, the introduction of white ("polished") rice prepared by mechanically removing the outer layers of the grain coincided sometimes with major outbreaks of beriberi. In 1897 Christian Eijkman, a Dutch physician working in Batavia (today's Jakarta), showed that polyneuritis in birds and the related beriberi in humans could be induced by a diet restricted to polished rice, and that this could be reversed by feeding unpolished rice or the "polishings" which had been removed in the processing.[41] Eijkman believed that the harmful component (a bacterium or toxin) was in the rice kernel, and that somehow the husks prevented the disease.

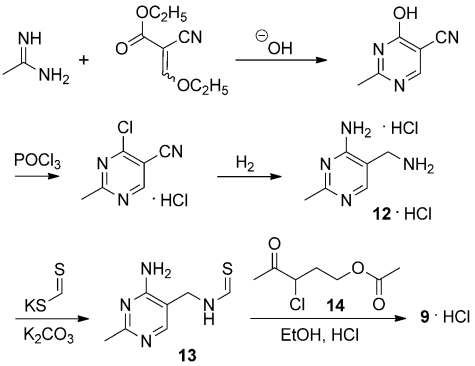
In 1901 Gerrit Grijns, Eijkman's assistant in Java, proposed the correct interpretation: that polyneuritis and beriberi were caused by a deficiency of a nutrient found in the rice husks.[42] In 1911 the Polish chemist Casimir Funk, working at the Lister Institute in London, isolated an impure substance from rice bran that prevented polyneuritis or beriberi, and soon after he coined the term "vita-amine".[6] In 1926, working in Eijkman's institute in Jakarta, the Dutch biochemists Barend Jansen and Willem Donath isolated a tiny amount of pure crystalline substance from several hundred kilograms of rice polishings.[3] Eijkman showed that this substance could cure polyneuritis at a concentration of only 2 ppm. Elucidation of the structure of the molecule proved to be difficult, not least because of the tiny amounts which were available. A major step forward was made by Adolf Windaus in Göttingen in 1932, who first recognized that the molecule contained sulfur and who also correctly proposed $C_{12}H_{18}N_4OSCl_2$ as the molecular formula of the thiamin chloride hydrochloride salt.[43] Working from his fortuitous discovery that the molecule could be quantitatively split into two components—a pyrimidine and a thiazol ring—by treatment with sodium sulfite, the American chemist Robert R. Williams proposed the correct molecular structure **9** for the vitamin in 1934[44] and later the now-accepted name "thiamin".[45] The correct structure of the pyrimidine component was clearly shown by the work of Rudolf Grewe in Göttingen.[46] Several syntheses followed in quick succession in 1936–1937, for example, by Hans Andersag and Kurt Westphal (IG-Farben, Elberfeld);[47] Robert R. Williams and Joseph K. Cline (Bell Labs/Merck, USA);[48] Alexander Todd and Franz Bergel (Univ. Edinburgh/Lister Institute, London).[49]

A characteristic of this pioneering research into thiamin was the speed with which these successful syntheses followed the isolation and structure elucidation. There was intense competition among the various research groups, driven in part by the certain knowledge that the scourge of beriberi, widespread in some countries, could be cured by enrichment of foodstuffs with the vitamin, which implied a ready market for the newly named "thiamin". In contrast, scurvy, known to be curable by L-ascorbic acid (vitamin C), was a relatively rare disease.

Of the synthetic routes to thiamin, the most practical for developing to an industrial scale were those of Williams and Cline (Scheme 5) and of Todd and Bergel (Scheme 6). The



Scheme 5. Synthesis of thiamin by Williams and Cline.

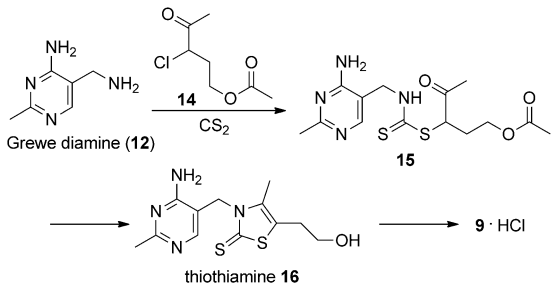


Scheme 6. Synthesis of thiamin by Todd and Bergel.

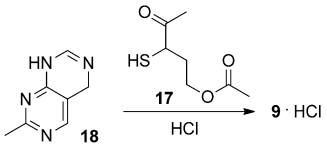
pioneering work of Williams had been generously supported by Merck & Co, and it was natural that the exclusive rights to his synthesis were readily granted to that company, which first produced thiamin in Rahway, New Jersey in 1937. F. Hoffmann–La Roche (Basel) had supported Todd and Bergel,[50] through the friendship of their head of research Markus Guggenheim with Prof. George Barger of Edinburgh University. Roche quickly developed the Todd–Bergel route into a process which could be operated on a scale that would allow the annual production of some hundreds of kilograms.

Merck's industrial-scale version of the Williams synthesis consisted firstly of the production of both the required 4-amino-5-bromomethyl-2-methylpyrimidine (**10**) and the thiazole component **11**. Condensation gave thiamin bromide hydrobromide which was converted by silver chloride or ion exchange into the required thiamin chloride hydrochloride (**9**·HCl, Scheme 5). The Todd–Bergel route (Scheme 6) depended on the formation of a thioformyl derivative **13** of diamine **12** (generally known as "Grewe diamine"),[51] which was condensed with an open-chain chloroketone **14** to give the required thiazole.

This process was eventually replaced by a much more efficient route (Scheme 7), in which Grewe diamine **12** reacts with carbon disulfide and the chloroketone **14** to give a ketodithiocarbamate **15** and then thiothiamin **16**, which is oxidized and transformed to **9**·HCl.[52] Chloroketone **14** can also be replaced by a mercaptoketone **17**, which is then treated, not with **12**, but with dehydrated, bicyclic *N*-formyl Grewe diamine **18** (Scheme 8).[53]



Scheme 7. An industrial synthesis of **9**.



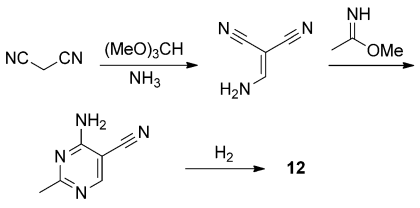
Scheme 8. Coupling of mercaptoketone **17** to **9**·HCl.

In the years immediately before and during World War II, Roche operated small thiamin plants in Basel, Nutley (USA), Welwyn Garden City (UK), and Grenzach (Germany). After 1950, intensive efforts were made by Roche and Merck to improve their processes. The complexity of the multistep synthesis and the many chemical options theoretically available offered great opportunities for significant improvements in the process. Moreover, the rapid progress made by Nathan C. Hindley in improving the yield was the main driving force for the early introduction of process research as a highly regarded discipline within Roche.

3.3. Current Syntheses

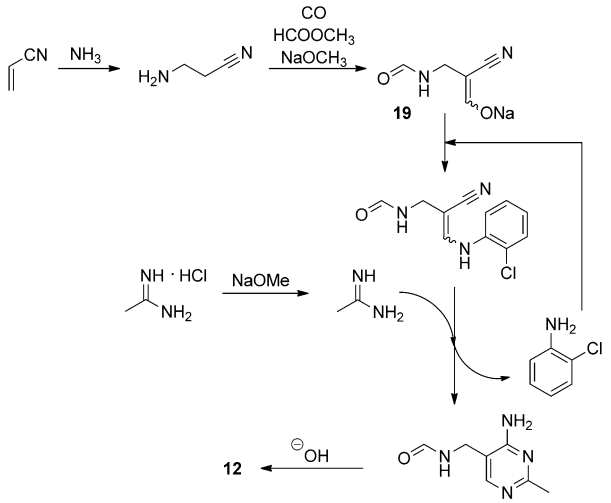
All industrially relevant syntheses of **9** use Grewe diamine **12** as the key building block. The common starting materials (C_3 units) for the synthesis of **12** are acrylonitrile or malononitrile. Malononitrile is transformed with orthoformate into the related aminomethylene malononitrile, which is condensed with an activated acetonitrile, methyl acetimidate, and leads to the 5-cyanopyrimidine (Scheme 9).

Malononitrile is a key cost determinant in the synthesis of **12**. Many routes starting from the cheaper acrylonitrile were investigated over the years to improve the cost efficiency of the process, and several options were developed by the leading manufacturers. Acrylonitrile is functionalized with

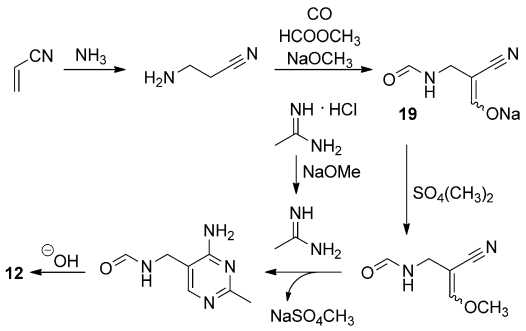


Scheme 9. Synthesis of **12** starting from malononitrile.

ammonia to give aminopropionitrile[54a] or with formamide to give *N*-formylaminopropionitrile,[54b,c] which is reacted to form the corresponding metal enolate **19**. The highly sensitive enolate **19** is converted into an enamine[55] (usually using *o*-chloroaniline;[56] Scheme 10), to an enol alkyl ether (Scheme 11),[57] or to a dialkylacetal (not shown).[58] Both derivatives are condensed with acetamidine to afford **12**.



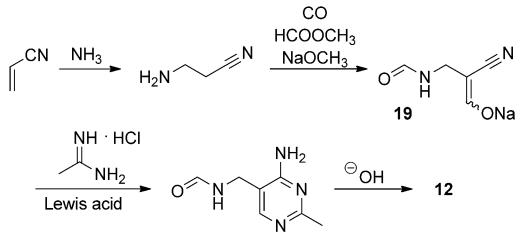
Scheme 10. Synthesis of **12** via an enamine by using *o*-chloroaniline as a derivatizing agent.



Scheme 11. Synthesis of **12** by using dimethyl sulfate as a derivatizing agent.

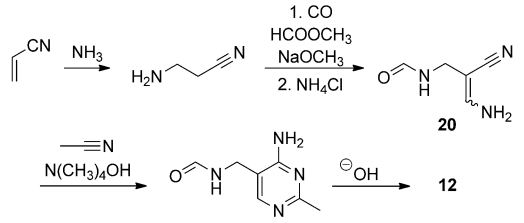
The latter two processes have the disadvantage that highly carcinogenic reactants such as *o*-chloroaniline and dimethyl sulfate are used. The derivatization with dimethyl sulfate leads to stoichiometric amounts of sodium methylsulfate waste. *o*-Chloroaniline is recycled, but traces may possibly be found in the final product **9**. Acetamidine is commercially available as the hydrochloride salt, the free base being not very stable. In both syntheses, acetamidine hydrochloride has to be reacted with a strong base, which leads to additional amounts of salt waste.

Very recent Grewe diamine syntheses involve even shorter routes, which conveniently use metal enolate **19** directly in a Lewis acid catalyzed condensation with acetamidine hydrochloride (Scheme 12).[59] Biphasic hydrolysis of



Scheme 12. Lewis acid catalyzed coupling of enolate **11** with acetamidine hydrochloride.

the *N*-formyl Grewe diamine allows for easy separation and purification of **12**.[60] The compound can be prepared in a three-step synthesis from acrylonitrile. Another recent synthesis avoids the use of acetamidine hydrochloride, but makes use of the primary enamine **20**, which reacts directly with acetonitrile in a base-catalyzed reaction to give **12** (Scheme 13).[61]



Scheme 13. Base-catalyzed enamine–acetonitrile coupling to **12.**

Even today, **12** remains of interest to current process research groups still trying to develop novel routes to highly pure thiamin (**9**).[62] Although cost was always a main driver for process research, developing a process that would reliably produce thiamin of sufficient excellent pharmaceutical quality proved to be a very challenging task. Since the synthesis is complex, there are many opportunities for the formation of by-products which can carry through to the final product. Every process change brings with it the chance that the impurity profile will also change. This aspect of the thiamin synthesis was key to the rapid acceptance of chromatographic techniques (GC, paper, thin-layer, later HPLC etc.) by the main manufacturers.

3.4. Challenges

In addition to the challenge of chemical purity, thiamin chloride hydrochloride sets the chemist, whether in development, production, or formulation, a particular physicochemical challenge in that it exists in several crystal forms.[63] This property was already noted by the early investigators.[49] The normal commercial form is the (nonstoichiometric) monohydrate. This can convert into the thermodynamically preferred hemihydrate, which can then set to a concrete-like mass on liberation of the water.

The main commercially available product forms are thiamin chloride hydrochloride and thiamin mononitrate. Thiamin pyrophosphate (cocarboxylase) was earlier produced as a specialty product, but today plays no significant part in the global thiamin market.

Today, since thiamin is widely used in human nutrition, deficiency is very much less prevalent, but it can still occur in particular groups, for example in patients with congestive heart failure,[64] in those who abuse alcohol,[65] and in famine situations.[66]

4. Riboflavin (Vitamin B_2)

4.1. Physiological Functions

Riboflavin (**21**) is a water-soluble vitamin that is an essential coenzyme for redox reactions in many different metabolic pathways. It is the precursor to the flavoenzymes flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), and is found in nature also in the free form and as the 5′-phosphate derivative (Figure 9). FAD is part of the

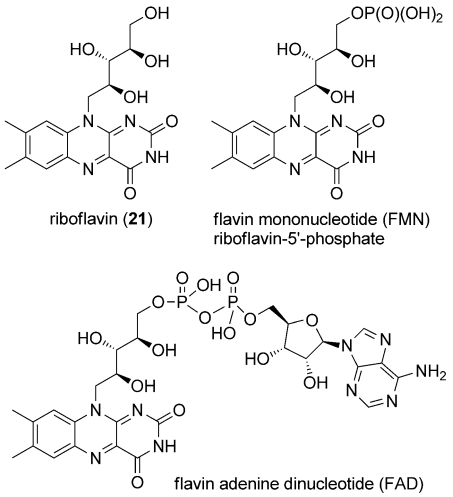


Figure 9. Riboflavin derivatives in nature.

respiratory chain and is central to energy production. Flavoenzymes are involved in one-electron transfers, dehydrogenase reactions, hydroxylations, oxidative decarboxylations, and dioxygenations.[20]

4.2. History

In the past, Vitamin B_2 was often called lactoflavin, ovoflavin, lyochrome, heptoflavin, or uroflavin. Riboflavin is found in all plant and animal cells. In culture media of fungi or bacteria, for example, *Ashbya gossypii*, *Eremothecium ashbyii*, or *Bacillus subtilis*, riboflavin can be accumulated at concentrations over 10 $g\,L^{-1}$.[67]

Riboflavin had already been isolated around 1880 as the yellow pigment from whey by the English chemist Blyth.

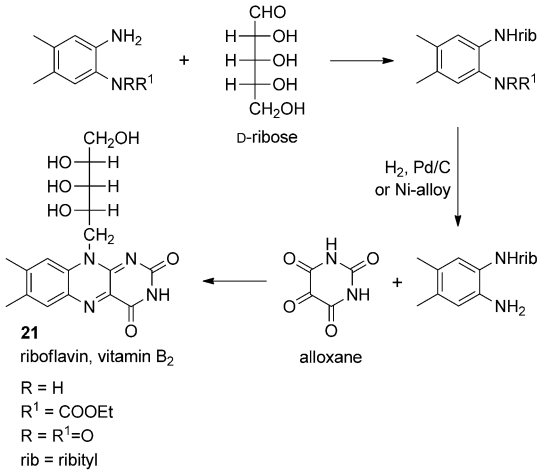
However, he did not recognize its nutritional function.[67] The vitamin B complex was initially discovered in 1917 in extracts of brewer's yeast, and nutritional scientists distinguished two components of the complex: vitamin B_1 or the antineuritic factor and vitamin B_2 or the rat antipellagra factor. Whereas vitamin B_1 turned out to be a unique chemical entity, that is, thiamin **9**, vitamin B_2 consisted of several different components including a yellow, intensively fluorescing compound designated riboflavin. Kuhn, György, and Wagner-Jauregg isolated pure **21** from egg yolk and determined its function as a vitamin.[68] Karrer and Schöpp later isolated **21** from liver and vegetables.[69] The structure of riboflavin was proven by chemical synthesis in the mid-1930s.[70,71] Since the 1950s, the biochemical aspects of flavin research have been the main focus. For a more detailed summary and an insight into the chemistry and biochemistry of flavoenzymes the reader is referred to comprehensive reviews.[72,73]

Chemical production processes were established at Merck, Roche, BASF, ADM, and Takeda in the first decades of vitamin B_2 production. The industrial production process was switched from chemistry to biotechnology around 2000. In a similar way to other water-soluble vitamins, competitors from Asia entered the market around 1990, and applied chemical and biotechnological production procedures to manufacture **21.** Today, DSM Nutritional Products manufactures the vitamin in a plant in Southern Germany, with *Bacillus subtilis* employed in the fermentation process. BASF moved their riboflavin production process based on *Ashbya gossipii* from Germany to Gunsan, South Korea some years ago. The main Chinese producer is Hubei Guangji Pharmaceutical Co. Ltd. of Hubei Province, who also uses *Bacillus subtilis* for the fermentation. The total quantity of riboflavin produced at present by fermentation is more than 4000 t each year. About 70% is used as a feed additive in the form of spray-dried granules, and 30% is required for the fortification of foods and in pharmaceutical applications.[74]

4.3. Chemical Production of Riboflavin

The first chemical synthesis of riboflavin was accomplished by the research groups of Kuhn and Karrer in 1934 and 1935.[70,71] The procedure of Kuhn et al. involved a reductive condensation of 6-nitro-3,4-xylidine with D-ribose, and the resulting nitro compound was reduced catalytically to the phenylenediamine, which was treated with alloxane under acid conditions. The yield was 16% based on ribose.[75] Karrer et al. also obtained **21** starting from D-ribose. Treatment with 2-(ethoxycarbonylamino)-4,5-dimethylaniline was followed by hydrogenation under basic conditions and condensation with alloxane to give riboflavin in 15% yield (Scheme 14).[70a,75]

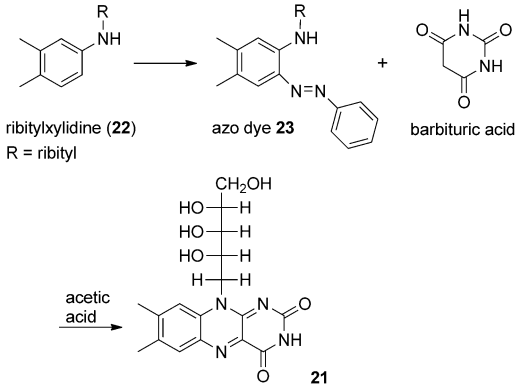
The yield was increased by employing a modification of the route used by Karrer et al., whereby 3,4-xylidine was condensed with D-ribose or its tetraacetate to give *N*-D-ribityl-3,4-xylidine, which was coupled with a diazonium salt. This compound could be reduced and treated with alloxane to yield riboflavin.[76]



Scheme 14. Synthesis of riboflavin by Karrer, Kuhn et al.

4.4. Technical Processes to Riboflavin

Since 1934 many variations and refinements have been introduced to the general syntheses developed by the research groups of Kuhn and Karrer to adapt them to large-scale manufacture. An important step forward in riboflavin synthesis was the direct condensation of barbituric acid with an azo dye in acetic acid. This so-called Tishler reaction gives **21** in 48% yield based on ribose (Scheme 15).[77]

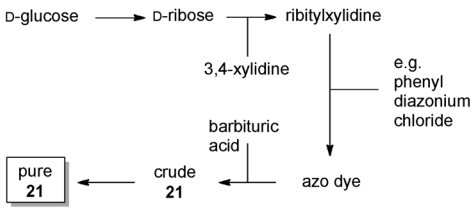


Scheme 15. Riboflavin synthesis by a Tishler reaction.

All subsequent chemical routes to riboflavin followed this principle. In the technical processes D-ribose, ribitylxylidine, and barbituric acid were used as the starting materials. D-Ribose was first synthesized by Emil Fischer and is nowadays produced by microbiological methods from glucose with *Bacillus pumilis* or *Bacillus subtilis*.[78,79] The annual production of D-ribose by using this method is several thousand tons. The key intermediate ribitylxylidine (**22**) is produced from D-ribose and xylidine in high yield, with xylidine itself manufactured from 4-bromo-*o*-xylene and ammonia in the presence of cuprous chloride.[80,81] An alternative method for the synthesis of **22** consists of coupling ribonolactone with xylidine, then converting the resulting anilide into the

chloroimine, which is reduced to ribitylxylidine.[82] The reductive coupling of ribonolactone and 3,4-xylidine[83] and a subsequent dehydration of ribonamide to ribonitrile are followed by condensation with barbituric acid.[84] The product arising from the condensation of ribose and xylidine, after hydrogenation over a nickel-alloy catalyst at a hydrogen pressure of 25–60 bar, is ribitylxylidine **22**.[85] The synthesis of barbituric acid is described in detail in the literature.[86,87]

As mentioned in the previous section, another key intermediate in riboflavin synthesis is the so-called azo dye **23**. The reaction of ribitylxylidine and an aryl diazonium salt (aryl = phenyl or nitrophenyl) was first described by Karrer et al.[10,76] A modified synthesis of **23** from ribitylxylidine and substituted amines, e.g. *o*-anisidine, was described in a patent.[88] Chemical processes for the manufacture of riboflavin may be summarized as shown in Scheme 16.



Scheme 16. Industrial manufacture of riboflavin by chemical processes.

The purification of crude riboflavin by using mineral acids was first patented in 1943.[89] Alternative approaches for purification under basic conditions were not industrialized.[90]

4.5. Biosynthesis of Riboflavin in Microorganisms

Of the water-soluble vitamins, the biosynthetic pathway leading to riboflavin was the most intensively studied. Ground-breaking findings for the elucidation of riboflavin biosynthesis were contributed in the 1950s by the research group of Plaut, and since the 1970s by the research group of Bacher. For more detailed insights into the biocatalytic mechanism of riboflavin biosynthesis the reader is referred to excellent comprehensive reviews.[91,92] The synthetic pathway to **21** in microorganisms has been studied in detail and has been reviewed in detail.[93]

4.6. Biotechnological Production of Riboflavin

The first microbial production processes for riboflavin that were developed in the 1940s used natural overproducing yeast strains such as *Candida famata*, *Eremothecium ashbyi*, and *Ashbya gossypi.* Another riboflavin production process based on the fermentation of the Gram-negative bacterium *Corynebacterium ammoniagenes* was developed at Kyowa Hakko of Japan. However, despite attractive published productivities, the *C. ammoniagenes* production strains were probably never employed for the commercial manufacture of riboflavin. In the early 1970s Merck Sharp and Dohme, USA, developed a riboflavin production process based on an *A. gossypii* which was later purchased by BASF, who implemented it on an industrial scale. After several years of the chemical and microbial processes being used in parallel, the chemical route was abandoned. Over the years steady improvements in the production capabilities of the *A. gossypii* host strain were obtained by classical mutagenesis and selection as well as metabolic engineering.

The riboflavin process based on *A. gossypii* uses vegetable oils as the fermentation feedstock, thus necessitating β-oxidation of fatty acids and subsequent efficient utilization of the acetyl-CoA (CoA = coenzyme A) produced. The metabolic flux through the riboflavin biosynthetic pathway was improved by a rational approach and additional copies of the genes encoding riboflavin biosynthetic enzymes were introduced into the genome of *A. gossypii*.[94–96] *A. gossypii* deposits riboflavin in its vacuole by an active transport process, and intracellular crystals are formed at elevated concentrations.

Riboflavin is released into the medium by heat-induced lysis of the biomass after completion of the fermentation run. Controlled cooling of the fermentation broth promotes growth of the riboflavin crystals and enables separation of the crystals from the biomass by decantation. Further purification of riboflavin is achieved by recrystallization.

A high-performing riboflavin production strain based on *B. subtilis* was developed at Roche and is similar to the production strain developed at the Russian Institute for Genetics and Selection of Industrial Microorganisms.[97,98] A *B. subtilis* mutant designated RB50 was isolated that contained purine-analogue-resistant mutations designed to deregulate the purine pathway and a riboflavin-analogue-resistant mutation in the riboflavin kinase that deregulates the riboflavin biosynthetic pathway.[99] The mutation in the riboflavin kinase resulted in drastically reduced levels of FMN formed, thus leading to low FMN levels in the cell. Since FMN, but not riboflavin, acts as an effector compound that triggers the riboswitch-based riboflavin repression system in *B. subtilis*, the mutants overproduce and secrete riboflavin. Genetic engineering was applied to further enhance expression of the *rib* gene by making use of strong, constitutive promoters and by increasing the dosage of the *rib* gene. This procedure was optimized, and a production strain was established.[100] Riboflavin accumulates during the fermentation and crystallizes in the fermentation broth. The long needle-shaped crystals can be easily recovered and separated from the biomass by decanting. Treatment of the recovered riboflavin crystals with acid at elevated temperatures followed by intensive washing resulted in isolation of a 96% pure product. Food/pharma-grade riboflavin of over 99% purity can be obtained by recrystallization. Since 2000, DSM Nutritional Products has been producing riboflavin exclusively by the microbial process based on *B. subtilis*. For more details on the microbial production of riboflavin the reader is referred to an excellent review by Hohmann and Stahmann.[101]

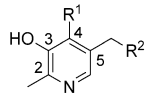
5. Pyridoxine (Vitamin B_6)

5.1. Physiological Functions

Vitamin B_6 consists of pyridoxal (PL), pyridoxine (PN), pyridoxamine (PM), and their 5′-phosphate derivatives (PLP, PNP, and PMP, respectively). PLP is involved in many different enzymatic reactions in the body that affect immune function, erythrocyte metabolism, gluconeogenesis, formation of niacin, and hormone modulation.[102] Vitamin B_6 deficiency is characterized by nonspecific findings of seborrheic dermatitis, microcytic anemia, convulsions, and depression.

5.2. History

The six chemically closely related compounds of the vitamin B_6 complex were identified by György and Birch, and called adermin.[103] Their isolation from rice bran and yeast as well as their structural confirmation were achieved in 1938 independently by several research groups.[104] Two syntheses of pyridoxine, in the hydrochloride form, were published in 1939.[105] They are similar in the structural element 2-methyl-3-hydroxypyridine, only the substituents in positions 4 and 5 are different (Figure 10). It was demonstrated by microbiological methods that the six compounds with vitamin B_6 activity are interconvertible.[106]



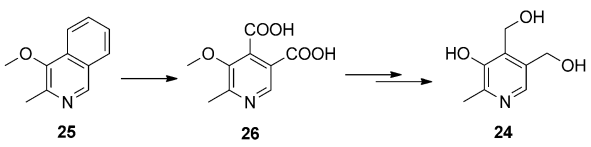
$R^1 = CH_2OH$, $R^2 = OH$, pyridoxine , **24**
$R^1 = CH_2OH$, $R^2 = OPO_3H_2$, pyridoxine-5'-phosphate
$R^1 = CHO$, $R^2 = OH$, pyridoxal
$R^1 = CHO$, $R^2 = OPO_3H_2$, pyridoxal-5'-phosphate
$R^1 = CH_2NH_2$, $R^2 = OH$, pyridoxamine
$R^1 = CH_2NH_2$, $R^2 = OPO_3H_2$, pyridoxamine-5'-phosphate

Figure 10. Compounds with a vitamin B_6 function.

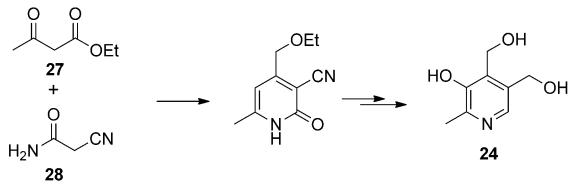
5.3. Principal Methods for the Synthesis of Pyridoxine Hydrochloride

Up to now, five principally different routes have been developed for the synthesis of pyridoxine. Several variants of all of those schemes exist. Review articles summarizing these developments have been published.[107,108] Pyridoxine was synthesized for the first time starting from substituted isoquinolines or quinolines, for example, 2-methyl-3-methoxyisoquinoline, by degradation (Scheme 17).[105b] The main disadvantages of this procedure are the limited availability of the starting materials and the expensive methods for reducing the intermediate diacid **26** into the diol **24**.

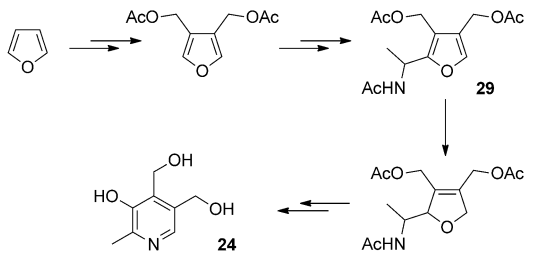
The first commercial process for the preparation of **24** started from aliphatic precursors such as ethyl acetylacetate (**27**) and cyanoacetamide (**28**) or malononitrile (Scheme 18).[105a,109,110] The advantage of this route was the easy availability of the starting materials. The disadvantages of this sequence are a high number of reaction steps including problems with the yields of individual transformations and the rather low overall yield. Several approaches following this concept were described over many years.[111] The *N*-acetyl compound **29** was synthesized from furan in a multistep reaction sequence and then further transformed into pyridoxine by an anodic electrolytic oxidation in methanol followed by a saponification (Scheme 19).[112] However, the overall yield of the process is low and not competitive with other approaches.



Scheme 17. Pyridoxine from isoquinolines.



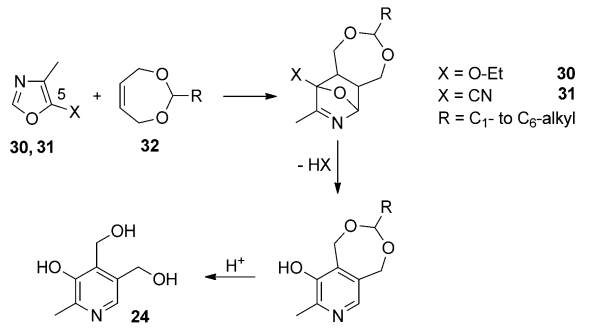
Scheme 18. Synthesis of pyridoxine by a Knoevenagel reaction.



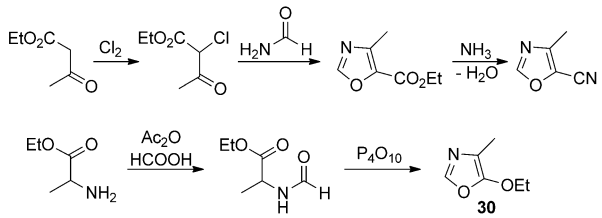
Scheme 19. Furan approach to pyridoxine.

Kondrateva demonstrated the potential of oxazoles in the synthesis of pyridine rings by Diels–Alder reactions. Based on this fundamental study, the synthesis of pyridoxine was realized.[113] This concept resulted in a considerable number of patent applications on this topic. A real breakthrough was the introduction of a leaving group in position 5 of the methyloxazole.[114] The diene compound in the industrial production of pyridoxine is 5-cyano-4-methyloxazole or 5-ethoxy-4-methyloxazole.[108] Commercial syntheses of pyridoxine carried out by Takeda, Merck, Daiichi, BASF, and Roche followed this Diels–Alder concept, but differed in the type of diene used (Scheme 20).

Several routes are known for the production of 5-ethoxy-4-methyloxazole (**30**, Scheme 21). The starting material is D,L-alanine ethyl ester, which is formylated and dehydrated in



Scheme 20. The Diels–Alder approach for the synthesis of a pyridoxine.



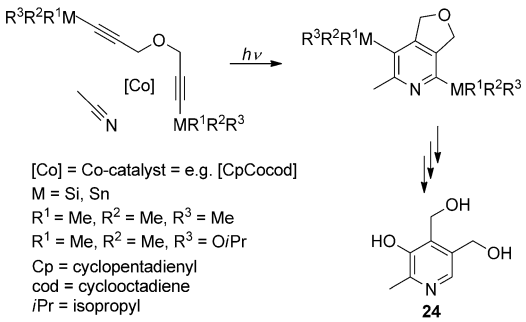
Scheme 21. Synthesis of oxazole derivatives.

the presence of phosphorus pentoxide.[115] Alternative routes to alkoxyoxazoles start from maleic anhydride,[116] which is transformed by treatment with ammonia to D,L-aspartic acid, followed by N-formylation, dehydration, saponification, and decarboxylation. Furthermore, oxalic ester derivatives of D,L-alanine can be transformed to oxazole derivatives.[117] During recent years, several modifications of this approach hav been established by changing the reaction sequence and applying basic conditions. This has led to lower waste formation and an increased yield.[118] An alternative synthesis of alkoxyoxazole derivatives is based on isonitriles, produced from alanine by formylation, dehydration, and thermal treatment, but has not been industrialized up to now.[119]

Since ethoxyoxazoles are very expensive from an industrial viewpoint, alternative oxazole derivatives from cheaper starting materials are of great interest. Moreover, oxazoles with an improved thermal stability would be beneficial. Therefore, 4-methyl-5-cyanooxazole (**31**) is a useful diene for the Diels–Alder reaction. For example, 4-methyl-5-carboxyoxazol esters are available starting from ethyl acetoacetate (from ethanol and diketene) by chlorination and reaction with formamide. Treatment of the ester with ammonia and dehydration form the 4-methyl-5-cyanoxazole.[107] The dehydration is carried out in the presence of phosphorus pentoxide/quinoline.[120] Several other dehydration methods which are more environmentally friendly have been described,[108,121] for example, using cyanuric chloride, sulfur trioxide amine complexes, silicon tetrachloride, or gas-phase reactions.

The following general statements can be made about the dienophiles which can be used in the Diels–Alder reaction leading to pyridines: derivatives of maleic and fumaric acid are rather reactive in this reaction. Their disadvantage is that the reduction of the carboxylic acid functionality needs costly hydride reagents. None of the vitamin B_6 syntheses presently in operation makes use of it. The theoretically ideal reaction partner of 4-methyloxazoles would be (*Z*)-butynediol. This dienophile, however, reacts in the presence of oxazoles in an alternative reaction pathway with formation of furans in good yields.[122] The best dienophiles reported so far are cyclic acetals of (*Z*)-butenediol.[114b] In general, the oxazole compound in this cycloaddition reaction should have rather little steric hindrance and high thermal stability to achieve good results. Today, more than 60 years after Kondrateva's first publication on the synthesis of pyridines by a Diels–Alder reaction with oxazoles as dienes, it can be stated with a very high degree of certainty that all present-day industrial vitamin B_6 syntheses use this basic reaction in their key step.

A different approach to the synthesis of pyridine derivatives by employing a cobalt-catalyzed [2+2+2] cycloaddition was established by Parnell and Vollhard[123] as well as by Geiger et al. (Scheme 22).[124] Acetonitrile and α,ω-diynes



Scheme 22. Cobalt-catalyzed [2+2+2] cycloaddition on the way to vitamin B_6.

could be transformed into pyridoxine. However, the selectivity of this reaction was moderate due to competitive formation of carbocycles. The replacement of the trimethylsilyl group by an aromatic OH group limited the yield (only 17% for this step), thus resulting in a disappointingly low overall yield of 3–7%. The moderate selectivity of the cobalt-catalyzed [2+2+2] cycloaddition could be enhanced by applying a modified Co catalyst under irradiation, whereas the introduction of the OH group can be achieved in an acceptable yield by using a different silicon protecting group.[125]

In contrast to the situation of other water-soluble vitamins, DSM (formerly Roche) is the only one of the early companies still producing vitamin B_6. Since the 1990s the picture has changed in such a manner that producers from Asia (in particular China) have entered the market and increased their production volumes. Since the 1960s all producers of pyridoxine have been using the Diels–Alder approach. Whereas the producers in Asia use ethoxyoxazole as the diene component, those in Europe use cyanooxazole.

6. Pantothenic Acid (Vitamin B_5)

6.1. History and Physiological Functions

Pantothenic acid (vitamin B_5, **33**; Figure 11) was identified in 1931 as a growth factor and isolated in 1938 from sheep's liver.[126] This factor prevents chicken dermatitis and was essential for the growth of rats.[127] Pantothenic acid is widely distributed in foods, thus pantothenic acid deficiency is rare.[20]

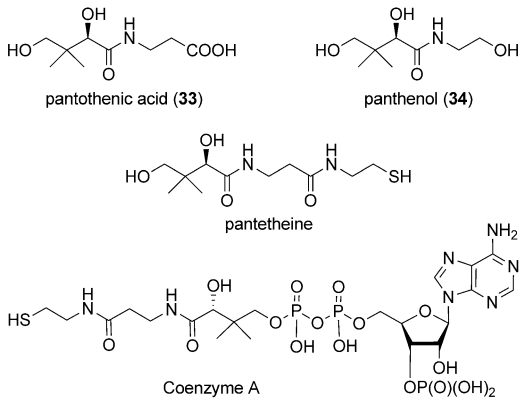
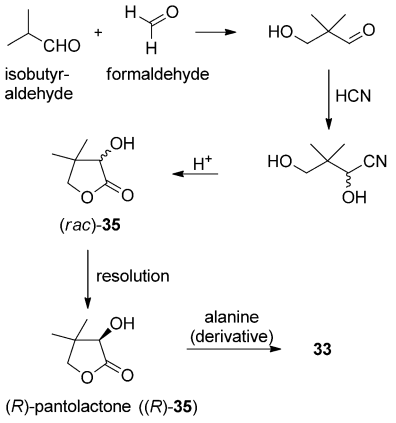


Figure 11. Pantothenic acid and derivatives.

Pantothenic acid is an acid- and a base-sensitive hygroscopic oil, and thus it is sold commercially as its calcium or sodium salts or as the primary alcohol derivative panthenol (**34**). In nature, pantothenic acid is part of coenzyme A and is found, for example, in the liver, kidney, corn, yeast, and green plants. The ubiquitous distribution of **33** is also reflected in its name pantothenic acid, which comes from Greek and means everywhere.[128] Lipman recognized co-enzyme A as a cofactor of the enzymatic acyl transferase reaction.[129] A pantothenic acid unit was also identified in pantetheine, a secondary growth factor in lactic acid bacteria.[130] The biosynthesis of **33** starts from pyruvic acid, which is transformed in a complex pathway to vitamin B_5.[131] Pantothenic acid and also pantolactone (**35**), the key intermediate of its synthesis, occur in nature in the *R* configuration. Therefore, a milestone in the history of pantothenic acid was the determination of its absolute configuration by Hill and Chan.[132] The X-ray analysis of calcium–pantothenate complexes was described in 1979.[133]

6.2. Synthesis of Pantothenic Acid

One stereogenic center, an ω-peptide linkage, a carboxylic moiety, and a primary as well as a secondary hydroxy group are found in pantothenic acid. The synthesis of **33** and of most of its derivatives starts from (*R*)-pantolactone ((*R*)-**35**). Pantolactone is synthesized in racemic form from isobutyraldehyde and is later resolved to give the *R* isomer. The (*S*)-pantolactone is separated, transformed into the sodium salt, and racemized. Condensation of **35** with alanine or derivatives thereof affords pantothenic acid or derivatives (Scheme 23).



Scheme 23. Synthesis of pantothenic acid.

The synthesis of the racemic pantolactone involves the aldol condensation of isobutyraldehyde and formaldehyde, followed by treatment with hydrogen cyanide under acidic conditions. The intermediates are not isolated and *rac*-**35** can be obtained after extraction and distillation in a yield of around 90%.[134] Several methods are known for the resolution of *rac*-**35**. The resolution is carried out on an industrial scale by treatment of *rac*-**35** with quinine in methanol. The (*R*)-**35** salt is less soluble then the (*S*)-**35** salt and can be isolated by crystallization.[135] Alternative methods make use of strong bases derived from cinchona alkaloids.[136] Efficient separation of (*R*)-**35** can also be achieved with chiral amines such as dehydroabietylamine (from pine resin) or (+)-3-aminoethylpinane (from (−)-α-pinene).[137] Alternative procedures for the synthesis of (*R*)-**35** starting from 2-oxopantolactone, synthesized by oxidation of *rac*-**35**, and enantioselective hydrogenation in the presence of a chiral rhodium catalyst or microbiological methods have been reported, but not scaled-up into production.[31a,138]

A different concept follows the oxynitrilase-catalyzed synthesis of cyanohydrin. Aldehydes, for example, 3-hydroxy-3,3-dimethylpropanal, are treated with hydrocyanic acid in the presence of such an enzyme and then hydrolyzed to give (*R*)-**35** in high optical purity.[139]

Calcium and sodium pantothenates are manufactured by the addition of calcium or sodium β-alaninate to (*R*)-**35** in methanol.[140] Depending on the reaction conditions, products are obtained in different forms as a result of polymorphism.[141]

7. Biotin (Vitamin B_7, Vitamin H)

7.1. Physiological Functions

(+)-Biotin (vitamin H or vitamin B_7; **36**) is a member of the water-soluble B vitamins. It functions as a coenzyme in bicarbonate-dependent carboxylation reactions in lactate and pyruvate metabolism, leucine degradation, and propionate metabolism.[142] Biotin deficiency, described in individuals on a prolonged diet of raw egg whites and in those on total parenteral nutrition that lacks biotin supplementation, is

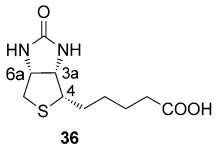


Figure 12. (+)-Biotin (**36**).

characterized by dermatitis, conjunctivitis, alopecia, and central nervous system abnormalities. An adult human needs about 0.03–0.1 mg (+)-biotin per day. Biotin possesses three stereogenic centers. The only isomer exhibiting full biological activity is the one with the configuration 3a*S*,4*S*,6a*R*, namely D-(+)-biotin (**36**, Figure 12).[143]

7.2. Introduction to the Chemistry and Overview of the Industrial Production of (+)-Biotin

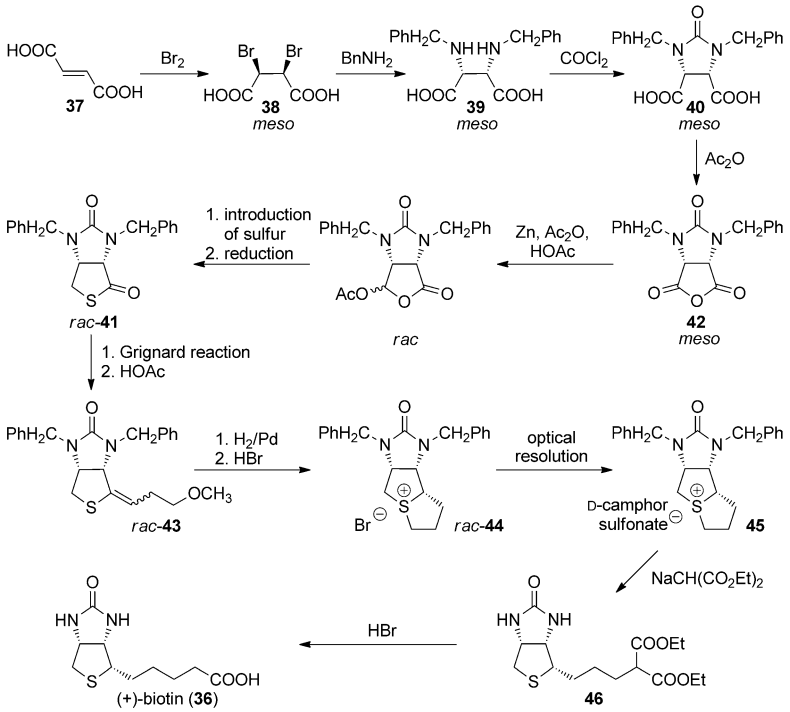
The history of biotin starts with the publications of the first total synthesis of racemic biotin and its subsequent optical resolution by Harris, Folkers et al. at Merck in 1943.[144] Goldberg and Sternbach of Hoffmann–La Roche applied for patents on the first commercially applicable biotin synthesis in 1946 (publication in 1949).[145] Since then, the optimum total synthesis of biotin (or, alternatively, a biotechnological method) has attracted the interest of many industrial and academic research laboratories. Companies who made considerable developments in this field were Merck & Co. (Research Laboratory, Rahway) and Merck (Darmstadt), Hoffmann–La Roche (with several research groups in Nutley, Paris, and Basel), Lonza, Sumitomo Chemical Co., Takeda Chemical Industries, BASF, Lederle Laboratories (Pearl River), Parke–Davis, Syntex Research (Palo Alto), and Pfizer Central Research.

The general production method still applied today is a multistep chemical synthesis. The world market for **36** is about 100 t per year. Since several companies stopped production, the current manufacturers of (+)-biotin (**36**) are DSM and several Chinese producers.

From a chemical and, in particular, from a production point of view, the following general problems accompanied with efficient routes to **36** have to be solved in an economically and ecologically satisfactory manner: The introduction of nitrogen and sulfur functionalities to form the highly functionalized bi-heterocycle, introduction of the C_5 side chain, and generation of the three stereogenic centers of the all-*cis*-thiophane ring. Excellent reviews on approaches to biotin, covering about 40 original full total syntheses with discussion and comparison of synthetic strategies, were published by De Clercq[146] and Seki.[147]

7.3. Commercial Routes to (+)-Biotin: The Goldberg–Sternbach Concept

Although the Goldberg–Sternbach concept described in the patents dates back to 1946 (publication in 1949),[145] this lactone–thiolactone approach is still valuable today. The cyclic anhydride **42** was obtained by starting from readily available fumaric acid (**37**) via the *meso* compounds **38**–**40** (Scheme 24). After several functional-group transformations with racemic thiolactone *rac*-**41** as an intermediate, *rac*-**43** was



Scheme 24. The Goldberg–Sternbach concept.

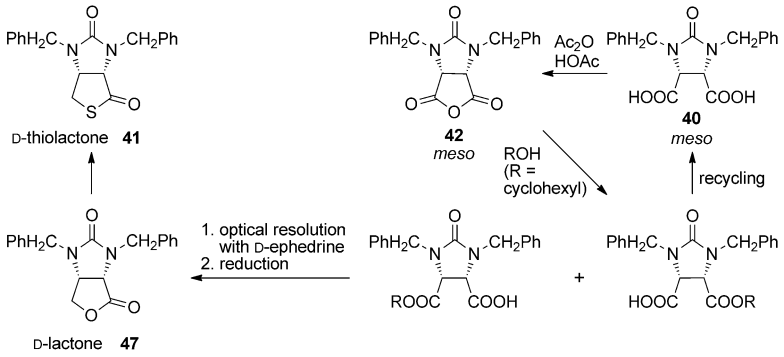
transformed to the racemic sulfonium salt *rac*-**44**. The early optical resolution (on the racemic sulfonium salt *rac*-**44**) was desirable and not a drawback, since the "wrong" isomer was used as a pharmaceutically active compound for another product stream at that time. (+)-Biotin (**36**) was produced by a C_2 elongation (→**46**) and decarboxylation sequence. Optical resolution by use of D-camphorsulfonic acid delivered the chiral salt **45**.

This concept is undoubtedly the origin of commercial production by total synthesis. Several features are contained in this scheme, which were used in later synthesis sequences developed by other research groups: the thiolactone intermediate, the generation of the all-*cis* configuration by catalytic hydrogenation of an exocyclic olefin, and the use of the *N*-benzyl protective groups and their removal by hydrogen bromide. Thus, this process has been designated "*a landmark accomplishment in the context of biotin synthesis*" by De Clercq.[146]

7.4. Further Developments and Other Total Syntheses

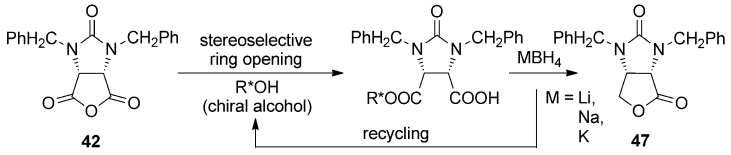
The original Goldberg–Sternbach concept was improved significantly by Gerecke, Zimmermann, and Aschwanden.[148] They found that (chiral) lactone **47** can be directly converted with potassium thioacetate into (chiral) thiolactone **41**

(Scheme 25). The optical resolution step, which takes place advantageously at a relatively late stage, delivered D-lactone **47** after reduction and cyclization of the crystalline ephedrine salt of the diastereomeric half-ester intermediate. The undesired enantiomer was recycled by acid hydrolysis back to diacid **40**. This procedure was operated on a commercial scale until the 1990s.



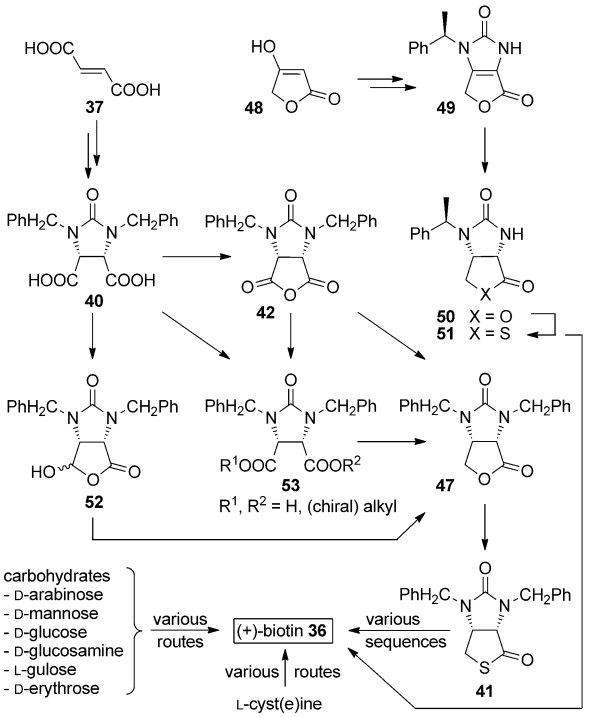
Scheme 25. The improved Goldberg–Sternbach concept: Direct conversion of a lactone into a thiolactone and late optical resolution.

A further improvement was made by Pauling and Wehrli. They used a diastereoselective ring opening of anhydride **42** with a chiral alcohol (Scheme 26)[149] to replace the optical-resolution step. D-Lactone **47** was thus obtained by reduction of the selectively formed diastereoisomeric half-ester by treatment with a complex hydride and ring closure.



Scheme 26. The Pauling–Wehrli concept of diastereoselective ring opening.

One central question has to be answered in all commercially attractive synthesis schemes: At which stage should chirality be introduced? Classical optical resolution and the use of chiral auxiliaries (including enzymes) have been evaluated as methods to achieve this (Scheme 27). Routes involving chiral starting materials available from natural sources were also investigated thoroughly.[146,147] Particularly attractive were cheap carbohydrates such as D-mannose and D-glucose which had been selectively derivatized to introduce the nitrogen and sulfur functionalities. Of the other carbohydrates, L-cysteine (L-cystine) was studied extensively for its suitability in industrially feasible routes.[147] Up to now, however, none of the approaches starting from chiral pool materials could be transferred to large-scale production. The advantage of even very cheap stereochemically defined chiral starting materials is often lost by lengthy sequences, requiring protection and deprotection transformations because of the high degree of functionalization in the respective intermediates.



Scheme 27. Selected strategies used for the introduction of optical activity in routes to (+)-biotin.

An analysis of processes generating (+)-biotin (**36**) operated on an industrial scale (see Scheme 27, upper part) clearly shows that D-lactone **47** (or its equivalent **50**) is the most commonly used chiral intermediate. That is, transformations yielding **47** are the most preferred methods for the introduction of chirality. Several reaction sequences have been used in the past to achieve this:

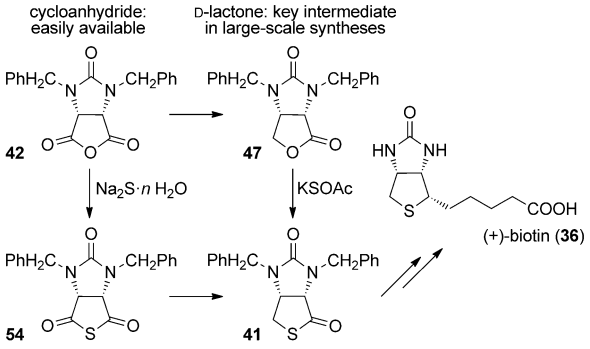
- Ring opening of anhydride **42** by (achiral) alkanols delivers half-esters **53** (R^1 or $R^2 = H$), which are resolved by the formation of diastereoisomeric salts with chiral amines such as D-ephedrine (see Scheme 25);
- diastereoselective ring opening with chiral alcohols yields diastereoisomeric esters (see Scheme 26);
- derivatization to chiral imides is also described;
- lipase-catalyzed esterification of diacid **40** as well as the hydrolysis of diesters **53** (R^1 and $R^2 =$ alkyl) have been applied;
- diastereoisomeric acetals formed from hydroxylactones **52** give D-lactone **47** after reduction and cyclization.

All these routes to D-lactone **47** have, unfortunately, the common disadvantage that several steps are required from the precursors **40** or **42**, and recycling of the undesired stereoisomer(s) and/or the (expensive) chiral auxiliary is necessary.

7.5. Latest Developments Based on Catalytic Asymmetric Synthesis

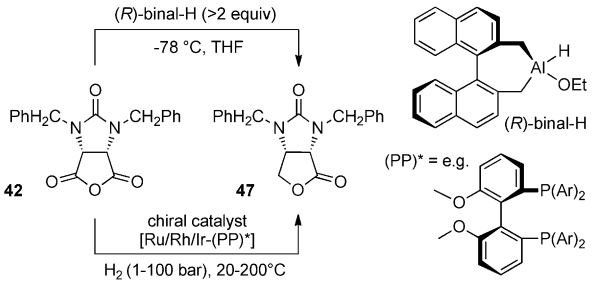
A highly diastereoselective Rh^{I}-catalyzed asymmetric hydrogenation was the key step in a very short route to (+)-biotin developed by researchers at Lonza together with colleagues from the catalysis group of the former Ciba–Geigy.[150,151] Tetronic acid (**48**, Scheme 27), prepared from diketene, served as a cheap starting material. The selectivity of the heterogeneous diastereoselective hydrogenation of intermediate **49** could be improved to >99:1 when the diphosphane josiphos2 was used as a ligand. The production of biotin via lactone **50** and thiolactone **51** was performed on multiton scale, but had to be terminated due to a severe drawback with this approach: the final deprotection step involving hydrogenation of an intermediate olefin followed by HBr treatment destroys the chirality of the (expensive) auxiliary used for protection of the nitrogen atom, thus leading to a dramatic increase in the overall production cost.

Nonetheless, the potential of asymmetric catalysis has been further exploited. When analyzing the key steps described in the preceding paragraphs, the following conclusion can be drawn: Based on the easy availability of cyclic anhydride **42** as a precursor and the use of D-lactone **47** as a preferred chiral intermediate, it becomes apparent that a direct reductive transformation of cyclic *meso*-anhydride **42** to D-lactone **47** in a catalytic enantioselective manner (Scheme 28, upper part) would be a further breakthrough. An alternative would be the reduction of thioanhydride **54** to D-thiolactone **41**.



Scheme 28. Preferred direct key steps for introducing chirality into commercial (+)-biotin syntheses.

Despite the rapid development of organic synthesis methods, however, environmentally friendly and efficient protocols for some functional-group transformations are still lacking. Such an example is the direct reduction of cyclic *meso*-anhydrides to optically active lactones. Only a few studies on this topic are reported in the literature. Matsuki et al. have described the stereoselective reduction of **42** to **47** with Noyori's binal-H (Scheme 29, upper part).[152] Over-stoichiometric amounts of the expensive chiral reagent, however, had to be used at low temperature (−78 °C) to achieve acceptable results (76 % yield, 90 % *ee*). Although the direct highly enantioselective reduction and concomitant



Scheme 29. Direct reduction of cyclic anhydride **42** to D-lactone **47** by a stoichiometric transformation and by catalytic asymmetric hydrogenation.

desymmetrization could be achieved in a single step for the first time, a large-scale application is problematic and costly due to the extensive use of the chiral auxiliary. The method has, however, been applied successfully to the (laboratory-scale) reduction of thioanhydride **54** to D-thiolactone **41**.[153]

The overall synthesis of (+)-biotin based on the original Goldberg–Sternbach approach, which had already been assessed as being highly efficient,[146] could also be improved considerably by using the tools of today's highly sophisticated asymmetric catalysis: In an intercompany collaboration between DSM Nutritional Products and Solvias, the dream reaction depicted in Scheme 29 (lower part) could be achieved with high chemoselectivity and optical induction (>95 % *ee*) at full conversion.[154,155] Furthermore, this method can be applied to the preparation of a variety of (achiral) lactones, which are valuable materials in the fine chemicals area.[156]

8. Vitamin A (Retinol)

8.1. History and Physiological Functions

Vitamin A (**55**), or retinol, is a lipid-soluble diterpene; it is one of a family of compounds called the retinoids, which all have similar biological activity. Other members of the family include the corresponding aldehyde (retinal) and acid (retinoic acid), and they are only found in animal tissue. Vitamin A plays an important role in the process of vision. Vitamin A deficiency affects an estimated 190 million pre-school children in developing countries worldwide and accounts for a large proportion of morbidity, mortality, and blindness in young children in these countries.[157] The related compounds in plants are the carotenoids, especially β-carotene (**56**, provitamin A), which can be oxidatively degraded in the animal to give vitamin A and its derivatives.[158] Although it was originally isolated from liver oil, almost all of the vitamin A produced nowadays is derived from chemical synthesis.[159] Since vitamin A itself is unstable, the major commercial product is vitamin A acetate (**57**), with the propionate **58** and palmitate **59** being used for specialist applications (Figure 13).

The use of certain foods rich in vitamin A (e.g. liver) has been known since Egyptian times to cure night blindness. Vitamin A was part of the vital lipid-soluble substances

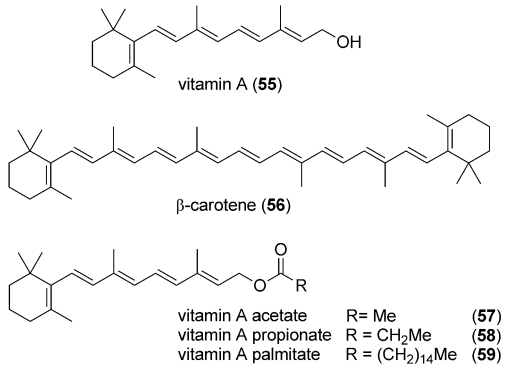
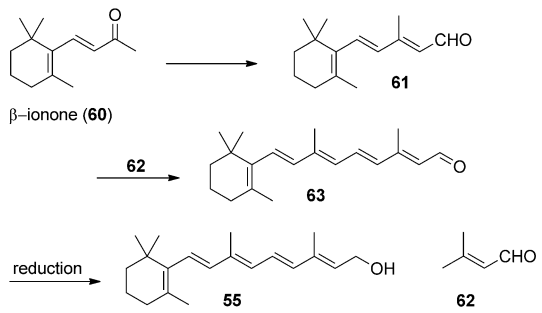


Figure 13. Vitamin A derivatives.

isolated from milk by Stepp in 1909,[160] and was differentiated into "fat-soluble A" by McCollum and Kennedy in 1916 and later into vitamin A.[7a] In 1931 Karrer and co-workers isolated almost pure retinol from the liver oil of mackerel,[161] and Karrer was awarded the Nobel Prize in 1937 for his work.

8.2. First Synthesis of Vitamin A

Vitamin A can be isolated from the liver oils of a number of different marine animals, and this was the main method of production in the 1930s and 1940s. However, the amount of vitamin A present varied from animal to animal,[159] and being from natural sources had supply constraints. The first synthesis of vitamin A was reported by Kuhn and Morris in 1937 (Scheme 30).[162] Starting from β-ionone (**60**), a C_2 extension



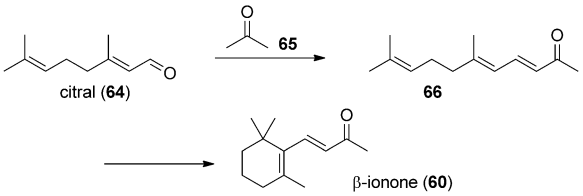
Scheme 30. First synthesis of vitamin A by Kuhn and Morris.

gave the C_{15} aldehyde **61**, which was then condensed with 3-methylcrotonaldehyde (**62**), to give vitamin A aldehyde (**63**). A Meerwein–Ponndorf–Verley reduction with isopropanol gave a yellow oil that had a vitamin A content of 7.5%.

Despite the low yield, the preparation of synthetic vitamin A had been demonstrated, and this provided the incentive for other academic and industrial laboratories to start or continue work in this area. Several unsuccessful attempts were made to repeat the Kuhn synthesis.[163,164] It would be another ten years before vitamin A was synthesized again, although the outbreak of the Second World War almost certainly interfered with progress. The key building block for the synthesis by Kuhn and Morris, as well as all future vitamin A syntheses, is β-ionone (**60**). Therefore, it is worthwhile considering its synthesis before continuing with the preparation of vitamin A.

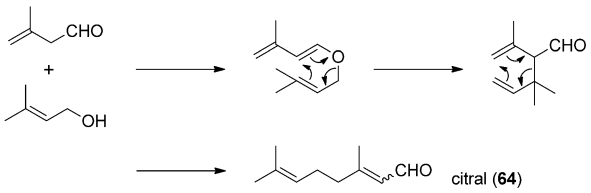
8.3. Synthesis of β-Ionone

β-Ionone (**60**) was known in the 19th century as a component of perfume, and could be prepared from lemongrass oil (which is predominantly citral, **64**).[159] Condensation of **64** with acetone (**65**) gave pseudoionone (**66**), which cyclizes in the presence of strong acid to β-ionone (**60**, Scheme 31).



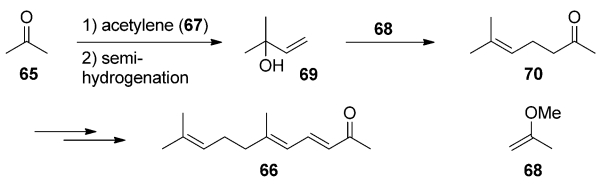
Scheme 31. Synthesis of β-ionone from citral.

From the 1940s onwards, synthetic routes to citral (**64**) were developed by Roche and others which allowed the large-scale production of β-ionone for the synthesis of vitamin A. One of these routes is still used by BASF and most other suppliers. The modern, efficient route to citral developed by BASF and starts from isoprenal and prenol (Scheme 32).[31a]



Scheme 32. Synthesis of citral (**64**) from isoprenal and prenol.

Roche developed an efficient synthesis of pseudoionone (**66**) avoiding citral by using a series of C_2 and C_3 elongations with acetylene (**67**) and isopropenyl methyl ether (IPM, **68**) (Scheme 33). The route delivers methylbutenol (MBE, **69**), which then undergoes chain elongation to give methylheptenone (**70**). This process to yield pseudoionone (**66**) is still in operation today.[31a,165]



Scheme 33. Synthesis of pseudoionone (**66**) by C_2 and C_3 elongations.

8.4. Subsequent Syntheses of Vitamin A

The synthesis of vitamin A methyl ether (**71**, Figure 14) was reported by Milas,[166] who used an acetylenic Grignard coupling to build up the polyene side chain. Although successful, there was no method for the conversion of the methyl ether into the alcohol, and the biological activity of **71** was found to be significantly lower than that of natural vitamin A.

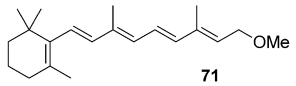


Figure 14. Vitamin A methyl ether (**71**).

Meanwhile, a research group at Hoffmann–La Roche in Basel, Switzerland, led by Otto Isler (Figure 15) was trying to develop an industrially viable route to vitamin A. In fact, the

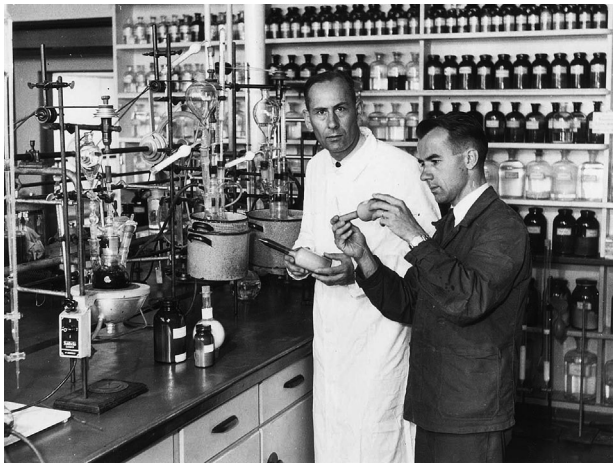
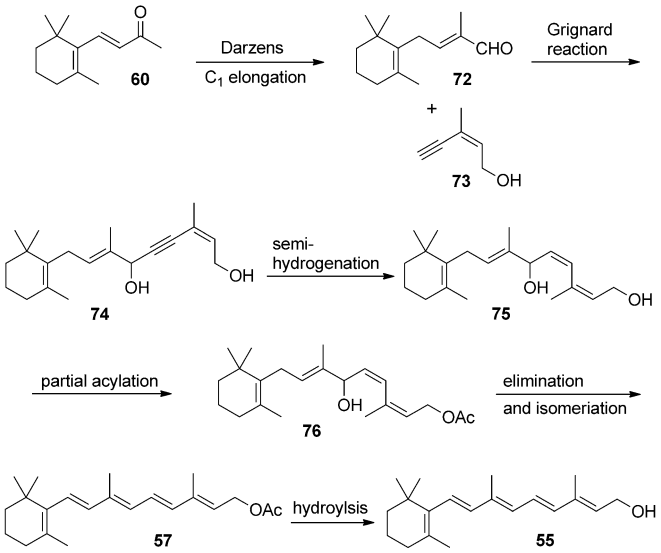
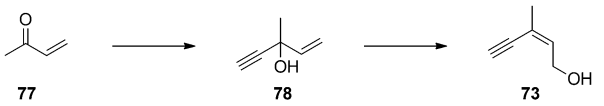


Figure 15. Otto Isler (left) with his co-worker Gody Ryser (source: Roche Historical Archive).

Roche group had even prepared vitamin A methyl ether (**71**) by an identical acetylenic Grignard strategy.[159] This successful "model experiment" led to further development of the Grignard step and allowed the use of 3-methylpent-2-en-4-yn-1-ol (**73**), rather than the methyl ether. Addition of the Grignard reagent derived from **73** to the C_{14} aldehyde **72** resulted in the formation of diol **74**, which could be partially hydrogenated to give tetraene **75**. Partial acylation to monoacetate **76**, elimination, and isomerization gave vitamin A acetate (**57**). Hydrolysis of the acetate yielded small quantities of synthetic *crystalline* vitamin A (**55**) for the first time (Scheme 34).[167] The C_6 unit **73** can be prepared in two steps from methyl vinyl ketone (**77**) by addition of acetylene to give 3-methylpent-1-en-4-yn-3-ol (**78**), which then undergoes rearrangement to give the required compound **73** (Scheme 35). A conceptually similar approach had been proposed by Heilbron et al.,[163,168] who used β-ionone, acetylene, and a protected butanone, but the planned route was not investigated because of the unavailability of β-ionone.



Scheme 34. Roche synthesis of vitamin A.



Scheme 35. Synthesis of C_6 building block **73**.

Several steps of the Roche synthesis merit further discussion. The semihydrogenation of alkyne **74** to alkene **75** was initially achieved using a poisoned palladium on charcoal catalyst or palladium on calcium carbonate. Whilst this process was successful, it was exceedingly difficult to avoid over-hydrogenation, which led to impurities that were difficult to separate. A significant improvement was made by Lindlar who developed a lead-doped palladium on calcium carbonate catalyst.[169] The use of an additional catalyst poison (usually an amine such as quinoline) allowed the hydrogenation reaction to be easily stopped after one equivalent of hydrogen had been consumed, thereby giving the desired alkene in high yield.

The elimination and isomerization of monoacetate **76** is a very sensitive step and must be carefully controlled to avoid decomposition. It was originally performed with iodine, and the process was improved by the use of phosphorus oxychloride. However, the best procedure involves the use of strong acid at low temperature and results in a yield of vitamin A acetate (**57**) of over 90%.[159]

Both steps in the synthesis of **73** have undergone significant optimization (Scheme 35). The original addition of acetylene to methyl vinyl ketone (**77**) resulted in moderate yields, the formation of large amounts of waste, and high energy usage. The optimization of the reaction conditions in combination with improved engineering methods resulted in a significant increase in the yield as well as to lower usage of raw materials and less waste.[170] The rearrangement of 3-hydroxy-3-methyl-pent-1-yn-4-ene (**78**) to **73** was originally

carried out with dilute sulfuric acid;[167] more efficient processes have recently been developed that use biphasic conditions and heterogeneous catalysts to result in higher yields and allow recycling of the catalyst multiple times.[171]

The Roche synthesis described in Scheme 34 was implemented on an industrial scale, initially in Roche's plants in Basel (Switzerland) and Nutley (USA; Figure 16). In 1957

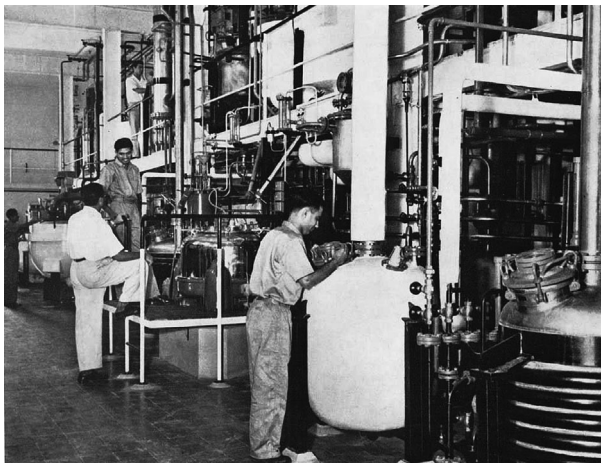


Figure 16. Early production of vitamin A at Roche Nutley, USA (source: Roche Historical Archive).

a third production facility was opened in Dalry (Scotland). Worldwide demand for vitamin A acetate increased every year in the 1960s, and the production at Roche's facilities ended the decade six times greater than at the start. To cope with the increased demand it was decided to consolidate the majority of the production at one new plant in Switzerland; as this plant came on-stream, production at other sites was slowly wound down.

Following the successful production of vitamin A by Roche, a number of other companies started production by alternative routes. A series of possible disconnections of vitamin A acetate are shown in Figure 17. The route of Kuhn and Morris (Scheme 30) used a $C_{15}+C_5$ approach, forming

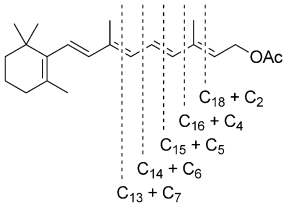
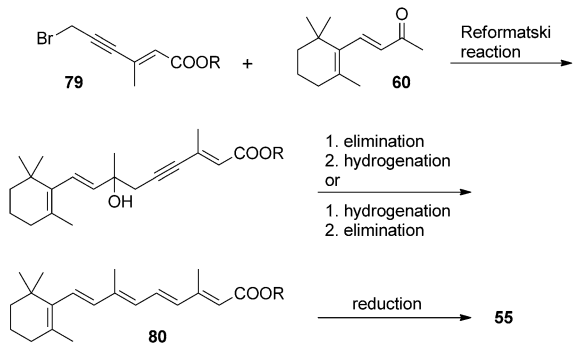


Figure 17. Synthetic strategies for the synthesis of vitamin A.

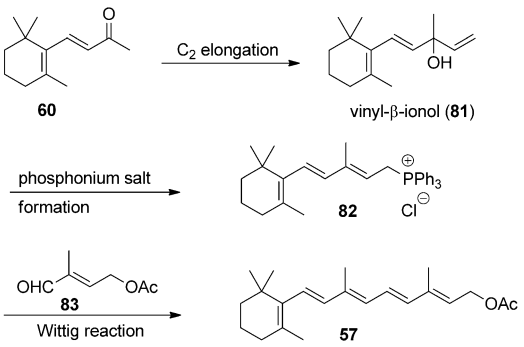
a carbon–carbon double bond, whereas the Roche route (Scheme 34) used a $C_{14}+C_6$ approach whereby the two subunits were coupled through formation of a carbon–carbon single bond. Routes that have been implemented on an industrial scale are: $C_{15}+C_5$ (BASF, Sumitomo, and Rhône–Poulenc), $C_{16}+C_4$ (DPI, Glaxo), and $C_{18}+C_2$ (Philips and AEC).[172] Of these, the most industrially important ones are the Roche route described above, the BASF $C_{15}+C_5$ route involving a Wittig reaction, and the Rhône–Poulenc $C_{15}+C_5$ route involving a Julia reaction.[173]

In the 1950s, at the time they started work on the synthesis of vitamin A, BASF had close contact with Georg Wittig. They quickly realized that the use of what was to become the "Wittig reaction" could have a significant impact on the synthesis of polyenes such as vitamin A.[174] However, their first successful synthesis[175] involved a Reformatski reaction between the propargyl bromide **79** and β-ionone (**60**, Scheme 36). Semihydrogenation of the alkyne to the alkene and dehydration could be performed in either order and gave the ester **80**. Reduction with an aluminum hydride reagent gave vitamin A (**55**) in good yield.



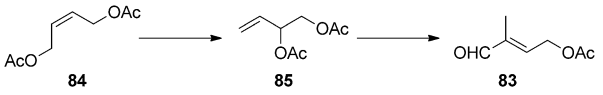
Scheme 36. First BASF route to Vitamin A.

Greater success was achieved with the Wittig reaction; during the course of the 1950s, BASF investigated the possible combinations $C_{10}+C_{10}$, $C_{13}+C_7$, and $C_{15}+C_5$ with either the phosphonium salt as the $C_{10}/C_{13}/C_{15}$ unit or as the $C_{10}/C_7/C_5$ unit.[176] The most successful process to date is the $C_{15}+C_5$ approach with the phosphonium salt **82** and the aldehyde **83** (Scheme 37).[177] β-Ionone (**60**) was converted into vinyl-β-ionol (**81**) by a C_2 extension. This extension can be done either by direct addition of a vinyl Grignard[178] or a two-step addition of acetylene followed by semihydrogenation.[179] Vinyl-β-ionol (**81**) can be converted into the phosphonium salt **79** either by treatment with triphenylphosphine and HCl gas or direct treatment with triphenylphosphonium hydro-



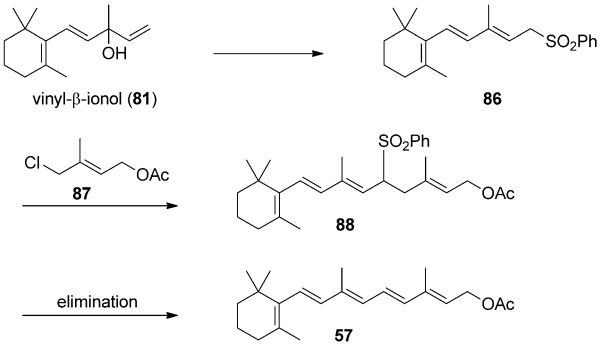
Scheme 37. BASF route to vitamin A by using a Wittig reaction.

chloride.[177] A Wittig reaction with aldehyde **83** gives vitamin A acetate (**57**) directly.[174] The C_5 aldehyde **83** is readily accessible from butene diacetate **85** by hydroformylation.[180] In turn, this is available by rearrangement from the symmetrical diacetate **84** (Scheme 38).[181]



Scheme 38. Formation of aldehyde **83**.

The third industrially interesting approach to vitamin A was developed by Rhône–Poulenc. In a similar way to BASF's collaboration with Georg Wittig, the Rhône–Poulenc approach used sulfone chemistry developed in collaboration with Marc Julia for the formation of a carbon–carbon double bond. A $C_{15} + C_5$ approach was also used, and the key starting material was again vinyl-β-ionol (**81**), although other combinations were investigated. Treatment of **81** with the anion of phenylsulfinic acid resulted in the allylic sulfone **86** (Scheme 39).[182,183] The sulfone could be deprotonated with a number of bases and then treated with the allyl chloride **87**.



Scheme 39. Rhône–Poulenc synthesis of vitamin A.

The resulting C_{20} sulfone **88** could then undergo elimination to give vitamin A acetate. A wide variety of bases could be used, but the most successful were potassium alkoxides.[184] Alternatively, the same sulfone condensation could be performed with the allyl bromide **89** (Figure 18), which,

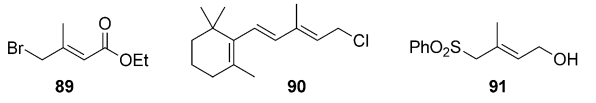


Figure 18. Alternative building blocks towards vitamin A.

after elimination of the sulfinic acid, gave vitamin A ethyl ester.[185] The opposite coupling of a C_5 sulfone **91** and C_{15} halide **90** was reported by a group from Roche in 1976;[186] however, this route was not commercialized.

The main producers of vitamin A at present are DSM and BASF, with lower volumes being produced by Adisseo, Kingdomway, Zhejiang NHU, and Zhejiang Medicine Co. Ltd. To the best of our knowledge, the current manufacturing conditions only differ from the originally reported steps as a result of incremental improvements in the process that have been implemented over the past 65 years. Isler states in his review of 1979[159] that "*Each of the known manufacturing procedures leaves something to be desired. The ideal synthesis, which is not yet invented, should start of cheap reagents and use catalytic reactions which cut down the amount of pollutants.*" Despite over 30 years having passed, this summary is still valid today!

9. Vitamin E (α-Tocopherol)

9.1. Physiological Functions and History

Vitamin E is the most important lipid-soluble antioxidant in biological systems. The term vitamin E covers all tocol and tocotrienol derivatives that exhibit qualitatively the biological activity of α-tocopherol (**92**),[189] which is the most relevant compound for human health. Vitamin E functions as a chain-breaking antioxidant that protects polyunsaturated fatty acids in membranes and plasma lipoproteins against the propagation of free-radical reactions.[187] Vitamin E also plays a role in immune function[188] as well as non-antioxidant functions in cell signaling, gene expression, and regulation of other cell functions.

All naturally occuring substances of this group are single-isomer products (Figure 19). The group of α-, β-, γ-, and δ-tocopherol (**92–95**) possess a 2*R*,4′*R*,8′*R* configuration; the corresponding tocotrienols (**96**) are found as 2*R*,3′*E*,7′*E* isomers.[165,190,191]]

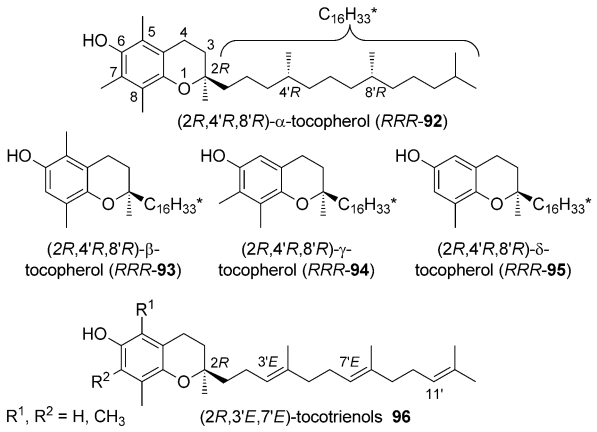
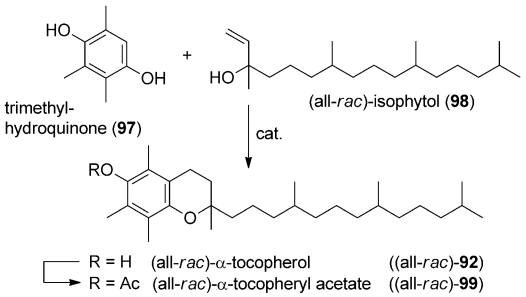


Figure 19. Tocopherols and tocotrienols, the naturally occuring vitamin E compounds.

Vitamin E was discovered by Evans and Bishop in 1922 as a dietary factor essential for reproduction.[192] Its isolation from wheat germ oil[193] enabled its structural elucidation by Fernholz.[194] Rich sources of active vitamin E compounds are edible oils originating from sunflower, soybeans, and palm oil. Vitamin E plays an essential role in the reproduction of

various animal species. While *RRR*-**92** shows the highest specific vitamin E activity of all the stereoisomers or homologues determined experimentally,[195] the economic importance of vitamin E is based on the fact that all such compounds differ only quantitatively in this respect. Thu, (all-*rac*)-α-tocopherol ((all-*rac*)-**92**), an equimolar mixture of all eight stereoisomers manufactured from trimethylhydroquinone (**97**) and (all-*rac*)-isophytol (**98**) (Scheme 40), is today's industrially most relevant product.



Scheme 40. Industrial synthesis of (all-*rac*)-α-tocopherol.

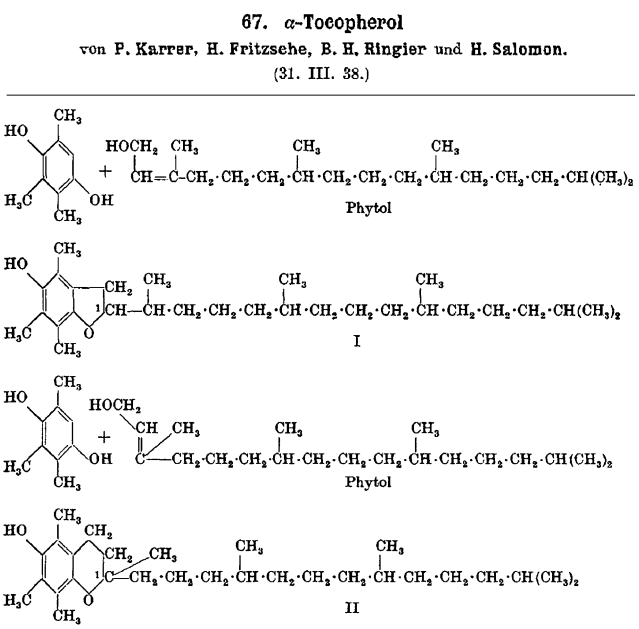
9.2. The First Syntheses, Biological, and Economical Significance

The first successful chemical synthesis of α-tocopherol was published in 1938 by Karrer et al. at the University of Zurich.[196] In the same year, Karrer was contracted as a consultant by Roche. From the note added in proof in the original publication (Figure 20) it is apparent that Isler had identified a similar synthesis for α-tocopherol. This fruitful collaboration between academia and industry resulted in the launch of the acetate derivative (all-*rac*)-**99** under the name Ephynal in 1939. Although this was already a technical synthesis, only a few kilograms were initially produced per year. Interestingly, natural (optically active) phytol extracted from hundreds of kilograms of stinging nettles was used as the side-chain component in the synthesis on this scale, since isophytol (**98**) was not yet industrially available.[197]

9.3. Synthesis of (all-rac)-α-Tocopherol

The main producers of (all-*rac*)-**92** today are BASF, DSM, and some Chinese companies, while Eisai and Adisseo (former Rhône–Poulenc) stopped production several years ago. The large-scale industrial synthesis of this "synthetic vitamin E" exceeds 30000 t per year world wide, and consists of three major parts:[31a,190,198,199] the preparation of the aromatic building block (trimethylhydroquinone, **97**), the production of the side-chain component ((all-*rac*)-isophytol, **98**, or a corresponding C_{20} derivative), and the condensation reaction (Scheme 40).

Selected routes to 2,3,5-trimethylhydroquinone (**97**) are shown in Scheme 41. *m*-Cresol (**100**) is catalytically methylated to trimethylphenol **101**, which is transformed by oxidation to quinone **103** and subsequently reduced to hydroquinone **97**. Alternative processes start from mesitol



67. α-Tocopherol

von P. Karrer, H. Fritzsche, B. H. Ringier und H. Salomon.

(31. III. 38.)

Phytol

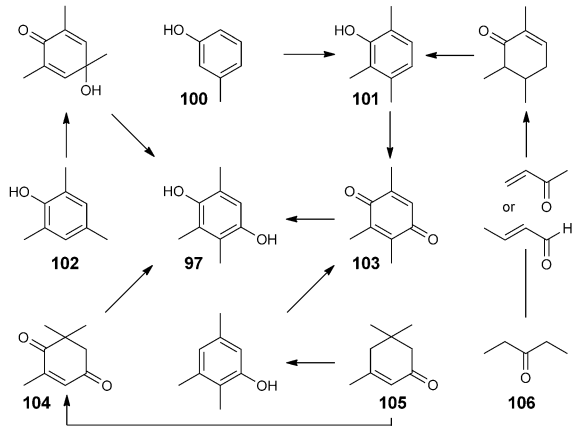
I

Phytol

II

Anmerk. b. d. Korrektur: Bei einem von Herrn Dr. *Isler* im Laboratorium der Chemischen Fabrik *F. Hoffmann-La Roche & Co. A.G.*, Basel aus 3-Brom-hydrophytylbromid und Trimethyl-hydrochinon analog hergestellten Kondensationsprodukt, das nicht einheitlich ist, aber die in dieser Abhandlung beschriebene Cumaranverbindung enthält, konnte die biologische Prüfung im pharmakologischen Laboratorium der *F. Hoffmann-La Roche & Co. A.G.* bereits zu Ende geführt werden. Dieses synthetische Produkt besitzt Vitamin-E-Wirkung.

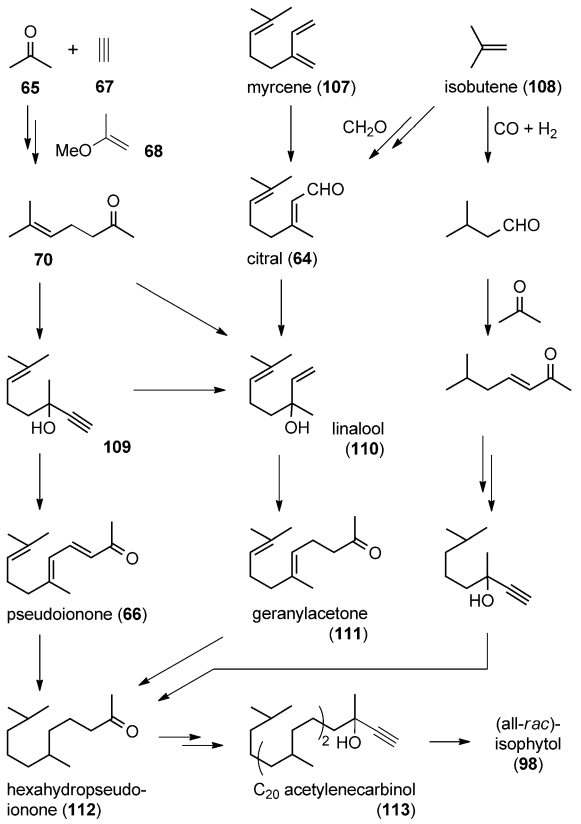
Figure 20. The first publication about a successful synthesis of α-tocopherol by the Karrer research group in 1938[196] (copyright Verlag Helvetica Chimica Acta). The text below the reaction scheme says: "*Note added in proof: An analogously prepared condensation product was obtained by Dr. Isler in the laboratory of the chemical factory F. Hoffmann–La Roche & Co. A.G., Basel, from 3-bromo-hydrophytyl bromide and trimethylhydroquinone, which is not homogeneous, but the biological testing could already be finalized in the pharmacological laboratory of F. Hoffmann–La Roche & Co. A.G. This synthetic product exhibits vitamin E activity.*"



Scheme 41. Selected routes to 2,3,5-trimethylhydroquinone (**97**).

(**102**, oxidation and rearrangement), isophorones (**104**, **105**, oxidation/hydrogenation/isomerisation sequences), snd diethyl ketone (**106**, condensation reaction with methyl vinyl ketone or crotonaldehyde).[31a,190,200]

Various synthetic strategies are applied for the preparation of (all-*rac*)-isophytol (**98**), which is used preferentially as the side-chain building block.[31a,190,191,200] Representative pathways are outlined in Scheme 42. A repeated $C_2 + C_3$



Scheme 42. Manufacture of isophytol by various routes (*E*/*Z* isomerism of olefins is omitted here).

homologation sequence starts from acetone (**65**) and acetylene (**67**) or the vinyl-Grignard compound. The C_3 elongation of the isoprenoic chain is achieved by treatment of the acetylenic alcohol with methyl acetoacetate or isopropenyl methyl ether (**68**) as an activated acetone equivalent to yield the C_8 unit methylheptenone (**70**), which is further transformed to dehydrolinalool or linalool (**109**, **110**, C_{10}) and C_{13} compounds (pseudoionone, **66**, which is transformed also to vitamin A, geranylacetone (**111**), and hexahydropseudoionone (**112**)). Subsequent chain elongations in combination with hydrogenation/rearrangement reactions lead to C_{15} (nerolidol), C_{18}, and C_{20} intermediates (e.g. acetylenecarbinol **113**), which finally yield (all-*rac*)-isophytol (**98**).

A different approach is the prenol–prenal route[201,202] starting from inexpensive isobutene (**108**, C_4) and formaldehyde (C_1) to give citral (**64**, C_{10}), which is then further processed. Myrcene (**107**, C_{10}) from natural sources has been alkylated by a rhodium-catalyzed process in the presence of a water-soluble phosphine ligand[173,203] to generate hexahydropseudoionone (**112**) after subsequent decarboxylation and hydrogenation.

Special features of this area of isoprenoid chemistry, such as the ethynylation of ketones, the methods for C_3 elongation by the acid-catalyzed Saucy–Marbet and Carroll reactions, aldol condensation, the Prins reaction (preparation of isoprenol), complete hydrogenation, Lindlar-type hydrogenation (which selectively reduces C≡C bonds to the corresponding *Z*-configured C=C bonds),[169] and various types of rearrangement reactions of allylic and propargylic alcohols (or derivatives) have become important reactions in the large-scale production of isoprenoids.[31a,204] Multiphase catalysis is a valuable concept towards the elaboration of efficient (continuous) processes in such pathways.

The final step in the manufacture of (all-*rac*)-α-tocopherol ((all-*rac*)-**92**) by condensation of trimethylhydroquinone (**97**) with isophytol (**98**, Scheme 40) was improved considerably by the discovery of alternative and more-efficient Brønsted acids. Novel acidic catalysts allowed catalyst loadings of less than 1 mol%, thus replacing conventional reagents, such as $ZnCl_2$ in combination with mineral acids, BF_3, Fe/HCl, $AlCl_3$, or other reagents that have been used in stoichiometric or at least relatively high catalytic amounts, and result in higher selectivity and yield.[205–211]

9.4. Synthesis of (2R,4′R,8′R)-α-Tocopherol

(all-*rac*)-α-Tocopherol ((all-*rac*)-**92**) is industrially the most important product. Nevertheless, the naturally occurring stereoisomer (2*R*,4′*R*,8′*R*)-α-tocopherol (*RRR*-**92**; Figure 19) exhibits the highest specific vitamin E activity.[195] Thus, many years ago it was already considered that this vitamin E component should be made accessible on a large scale. The first synthesis of *RRR*-**92** (and of the 2*S*,4′*R*,8′*R* epimer) was published by the research group of Isler in 1963 (Figure 21).[212] Further developments will be mentioned below.

Today about 10% of the total amount of vitamin E produced industrially is isomerically pure (2*R*,4′*R*,8′*R*)-α-tocopherol (*RRR*-**92**) prepared by semisynthesis for pharma (human) applications. Soya deodorizer distillates (SDD), a waste stream from the production of that vegetable oil, are applied as starting materials. The mixture of the four homologous tocopherols ("mixed tocopherols", *RRR*-**92** to *RRR*-**95**, Figure 19) is isolated by a combination of several separation methods. It is then upgraded to the biologically more active α-tocopherol (*RRR*-**92**), of which there is only 5% in the original mixture. Permethylation reactions such as chloro-, amino-, or hydroxymethylation reactions can be used to achieve this.[191,213,214] This semisynthetic approach still has the general problem of a (given) limited availability of starting material (SDD) from natural sources, which prevents an increasing demand of *RRR*-**92** from being satisfied above a certain level. The possibility of improving the α-tocopherol content in agricultural crops by genetically manipulating the vitamin E biosynthetic pathway has also been investigated and discussed.[215]

Considerable efforts have been directed during the last four decades at the development of stereoselective syntheses of *RRR*-**92** and of corresponding building blocks to overcome

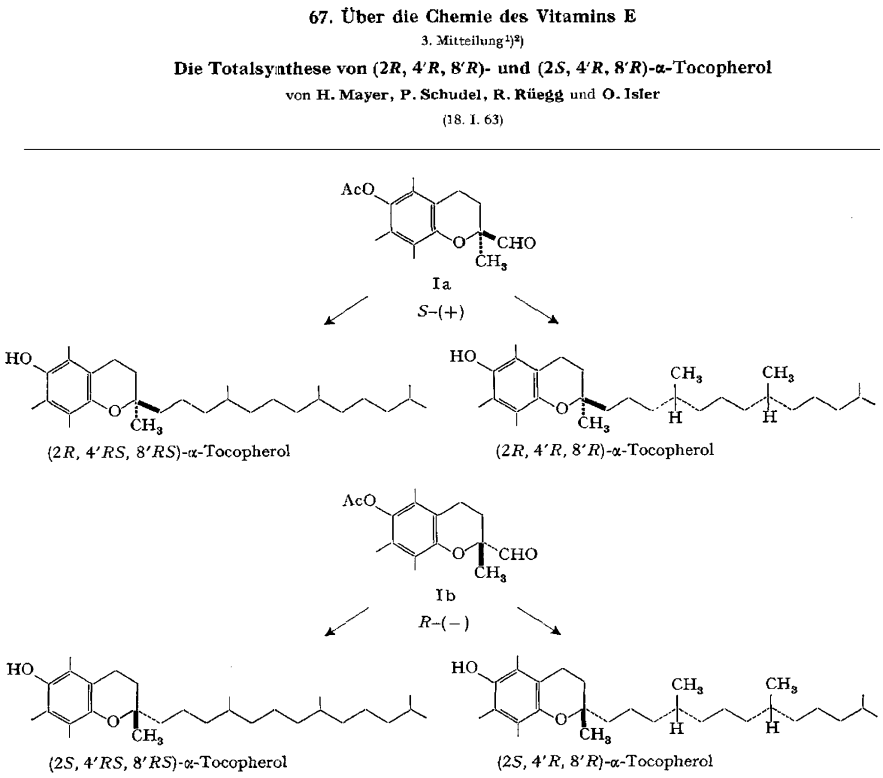


Figure 21. The first synthesis of (2*R*,4′*R*,8′*R*)-α-tocopherol and its 2 epimer published in *Helv. Chim. Acta*[212] (copyright Verlag Helvetica Chimica Acta).

the shortage of starting material from natural sources.[190,191,199,216–219] General routes are based on classical optical resolution, biocatalysis (by microorganisms and isolated enzymes), chiral-pool starting materials, the application of stoichiometric and catalytic amounts of chiral auxiliaries, and asymmetric catalysis (Figure 22). Significant efforts were undertaken in the research centers of Roche at Basel and

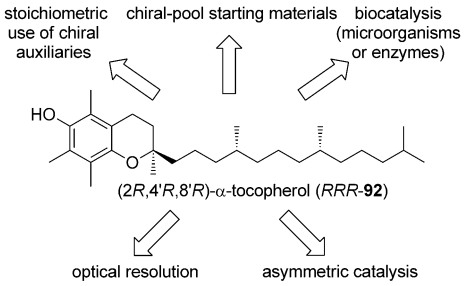
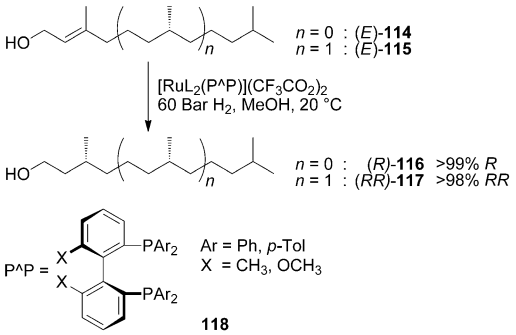


Figure 22. General strategies used in the synthesis of (2*R*,4′*R*,8′*R*)-α-tocopherol.

Nutley, as well as in university laboratories between 1970 and 2000. Many of the methods developed, however, are not suitable for large-scale applications because they suffer from complexity, limited space–time yield, and formation of excessive amounts of waste material. The goal of an economic industrial total synthesis of *RRR*-**92** has still not yet been reached by any of the methods described.

In particular, industrially applicable methods for the construction of the chiral chroman bicycle and the coupling of chroman and side-chain building blocks are still lacking. Considerable progress has been made in key transformations by the use of exceptionally efficient new asymmetric hydrogenation techniques. Based on the seminal work of Noyori and coworkers in the 1980s, the homogeneous asymmetric hydrogenation of allylic alcohols catalyzed by ruthenium complexes was performed at Roche in Basel on a pilot scale with substrate/catalyst ratios of up to 150000:1 (Scheme 43). For example, the C_{10} building block (*E*)-**114** was transformed into (*R*)-**116** with > 99% selectivity by using (*S*)-MeOBIPHEP (**118**, Ar = Ph, X = OCH_3) as a ligand. The hydrogenation of (*E*)-**115** under similar conditions with the catalyst derived from (*S*)-*p*-Tol-BIPHEMP (**118**, Ar = *p*-Tol, X = CH_3) gave (*R*,*R*)-**117** (> 98%).[219]

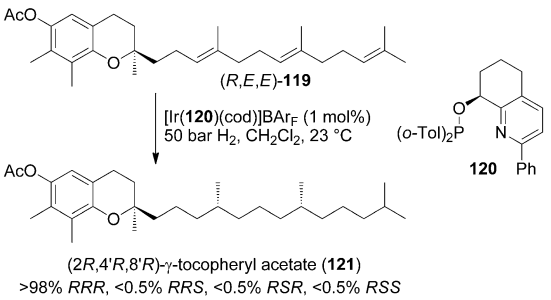
The concomitant introduction of two chiral centers by the reduction of



Scheme 43. Asymmetric hydrogenation of allylic alcohols in isoprenoid chemistry.

unfunctionalized trialkyl-substituted olefins in the presence of Ir-BAr_F complexes containing chiral P,N ligands opened the way to a completely different retrosynthetic concept (Scheme 44). Asymmetric hydrogenation of γ-tocotrienol derivative (*R*,*E*,*E*)-**119** with pyridyl phosphinite **120** developed in a collaboration between the Pfaltz research group and DSM Nutritional Products furnished (all-*R*)-γ-tocopheryl acetate **121** with excellent stereoselectivity, and with the formation of less than 0.5% of each of the other stereoisomers.[220]

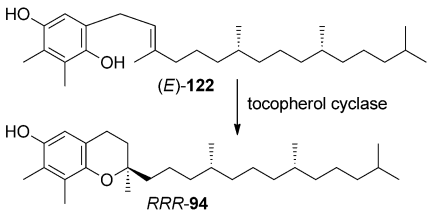
A noteworthy approach is based on the biosynthetic pathway of vitamin E compounds. The mechanism of the ring closure of chromanol catalyzed by the enzyme tocopherol cyclase from cyanobacteria has been investigated by the



Scheme 44. Asymmetric hydrogenation of unfunctionalized trisubstituted olefinic double bonds.

Woggon research group.[221] Tocopherol precursor *E*-**122** yielded (2*R*,4′*R*,8′*R*)-γ-tocopherol (*RRR*-**94**) exclusively, while the corresponding *Z* isomer did not react (Scheme 45).

Biomimetic routes for chromanol cyclization have been developed on the basis of these data.[222,223] Organocata-



Scheme 45. Enzymatic chromanol ring formation to afford (2*R*,4′*R*,8′*R*)-γ-tocopherol.

lytic[224] and other approaches[225–228] based on new synthetic methods have also been published in recent years, thus showing that the synthesis of *RRR*-**92** is still a research topic of current interest.

10. Conclusions

Vitamins have been known now for one hundred years, but the "history of vitamins" has still not come to an end. Manufacturing processes continue to be improved and completely new routes or processes are being developed. Modern trends include the continuing shift from batch to continuous processes and from the use of stoichiometric amounts of reagents to catalysis. In addition, the use of renewable raw materials as key building blocks for the production of vitamins is of growing importance. A constantly increasing number of studies deal with the relevance of vitamins for long-term health and healthy aging, as well as their importance in reducing the risk of noncommunicable diseases. In this regard, we still have to ensure that people all over the globe have access to sufficient vitamins. Science continues to provide new insights into this field, and demonstrates that the identification of the role of vitamins was one of the most important contributions of science to mankind.

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