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Large-Scale Production of Bioactive Ingredients as Supplements for Healthy Human and Animal Nutrition

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Abstract: In this review, synthetic strategies and the development of environmentally benign methods for the production of economically important vitamins, carotenoids, and nutraceuticals used as food and feed supplements are illustrated by selected examples. The application of efficient catalytic transformations in multi-step chemical syntheses of such natural products enables technically feasible and cost-effective processes. For the preparation of fat-soluble (isoprenoid) vitamins A and E and the water-soluble vitamin (+)-biotin, homogeneous metal catalysis, including enantioselective transformations, heterogeneous and enzymatic catalysis serve as key methodologies. In the area of carotenoids, general building concepts and coupling methods for the total synthesis of β-carotene and astaxanthin are discussed. Biotechnological methods and isolation from natural sources are also employed successfully, as exemplified for the xanthophyll lutein and the antioxidant (–)-epigallocatechin gallate. Lastly, key steps of the chemical synthesis of the polyphenol resveratrol are highlighted.

Keywords: Carotenoids · Catalysis · Chemical synthesis · Nutraceuticals · Vitamins

1. Introduction

A fundamental role of nutrition is to ensure an adequate intake of macro- and micronutrients, permitting the smooth operation of metabolic processes.[1] In order to supply such ingredients for nutrition in sufficient amounts and satisfactory quality, efficient production methods are needed. In the present review we illustrate synthetic strategies and production processes towards selected bioactive substances used as food and feed supplements, namely the economically important classes of vitamins, carotenoids and nutraceuticals.[2]

In the fine chemicals industry (bio-) chemical transformations are often based on stoichiometric organic reactions, where significant amounts of by-products and waste are formed.[3,4] For the production of vitamins, carotenoids and nutraceuticals, the development and application of efficient catalytic methods in multi-step synthesis is of central importance and has been elaborated into a competence platform.[2,3] According to Sheldon's definition,[5] most vitamins are considered fine chemicals with production volumes of about 100 to 10'000 tonnes per annum. In this area, the main focus of research and development is directed towards sustainable chemistry, aiming for the reduction of waste, the combination of unit operations and, as a consequence, the reduction of production costs. One possibility to achieve these goals is adherence to the twelve principles of 'green chemistry',[6–8] which includes the concept of atom economy,[9] the use of less toxic reagents and solvents, and improved energy efficiency, among others.

Besides chemical total (and partial) syntheses as well as enzymatic and fermentative (biotechnological) transformations, the isolation, separation and purification of compounds from natural sources, for example by extraction (often in combination with distillation or adsorption) is another important methodology in the field of producing nutritional supplements. In this context the use of food-approved solvents, including supercritical fluids such as $scCO_2$, is of high interest.[10,11]

2. Vitamins

Vitamins are essential organic compounds, which are either not synthesized in the human or animal organism, or not formed in sufficient amounts. They must be consumed with the diet either as such or as precursors, the so-called pro-vitamins, which can be converted to the corresponding vitamin *in vivo*. A representative example for the latter is the pro-vitamin β-carotene which is transformed biochemically into vitamin A.[12] The classification of vitamins is based on their biological activity, and the historical terms 'water soluble' and 'fat soluble' are related to their physical properties. The term 'vitamin' was coined in the literature by Funk[13] and originates from the combination of the words 'vital' and 'amine', describing essential compounds. Upon under-supply to the human body, diseases like beri-beri, a nervous disease, could arise. The thirteen compounds denominated as vitamins cover a large structural variety. An overview of the vitamins and their functions is compiled in Table 1.

For the manufacture of vitamins several key technologies have been developed over the last years. This progress is based on a long tradition of natural product syntheses performed by chemists in both Swiss academia and industry. L-Ascorbic acid is the vitamin produced on the largest volume worldwide. A molecular model of this compound has been chosen by the Swiss post as a theme on a special issue stamp on the occasion of the International Year of Chemistry 2011 (Fig. 1), acknowledging the great impact of chemical research and innovation in Switzerland.

Selected examples of the large-scale production of such fine chemicals which were established during the last five to ten

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Table 1. Selected data on fat and water soluble vitamins

Vitamin	Year of discovery	Main function	Solubility
A (retinol)	1909	vision process	fat soluble, lipophilic
D (calciferol)	1918	calcium and phosphate metabolism	fat soluble, lipophilic
E (tocopherol)	1922	intracellular antioxidant	fat soluble, lipophilic
K (phylloquinone)	1929	blood aggregation (biosynthesis of prothrombin)	fat soluble, lipophilic
B_1 (thiamin)	1897	decarboxylation, phosphate donor	water soluble, hydrophilic
B_2 (riboflavin)	1920	hydrogen or electron transport in metabolism	water soluble, hydrophilic
B_3 (niacin)	1936	hydrogen or electron transport	water soluble, hydrophilic
B_5 (pantothenic acid)	1931	transfer of acyl groups	water soluble, hydrophilic
B_6 (pyridoxine)	1934	transfer of amino groups	water soluble, hydrophilic
B_7 (H, biotin)	1931	transfer of carboxyl groups	water soluble, hydrophilic
B_9 (folic acid)	1941	transfer of formyl groups	water soluble, hydrophilic
B_{12} (cobalamin)	1926	1,2-hydrogen shift	water soluble, hydrophilic
C (ascorbic acid)	1912	hydroxylation	water soluble, hydrophilic

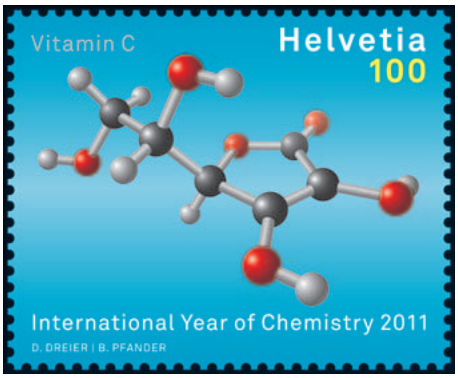


Fig. 1. Stamp issued on the occasion of the International Year of Chemistry 2011, depicting a molecule of vitamin C as a symbol of innovation that originated from Swiss chemical research (© Die Post).

years[2] are described in this section. At DSM Nutritional Products, a major part of the corresponding processes is located in production facilities in Sisseln (Rhine valley) and Lalden (Rhone valley), Switzerland.

Isoprenoid units (C_5) are found in all fat-soluble vitamins and carotenoids. The principle of manufacturing key building blocks used in the total synthesis of vitamins A and E (**1** and **2**, Fig. 2) is exemplified below (Scheme 1). (all-*rac*)-α-Tocopherol (**2**), the industrially most relevant representative of the group of vitamin E compounds (biologically active, essential, and fat-soluble anti-

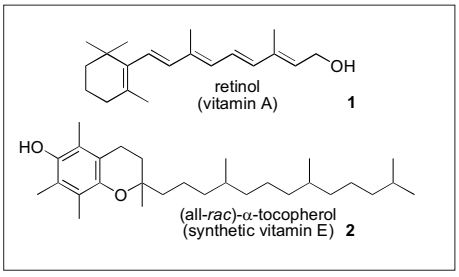
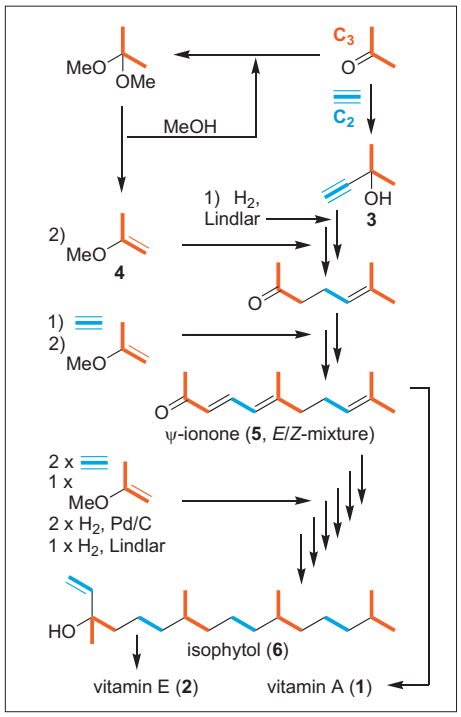


Fig. 2. Retinol (vitamin A, **1**) and (all-*rac*)-α-tocopherol (synthetic vitamin E, **2**).



Scheme 1. Reaction sequence for the manufacture of isoprenoid building blocks.

oxidants derived from 6-chromanol[12,14]), is produced in over 30'000 tonnes per annum, and mainly used in animal nutrition (feed) applications.[2] The C_{20} isoprenoid isophytol (**6**) is built up by a repeated C_2 (acetylene) + C_3 (acetone) homologation sequence, using essentially two types of C-C bond forming reactions.[2,3]

Key technologies for the construction of isoprenoid building blocks are acid- and base-catalyzed addition and condensation reactions, as well as various noble metal catalyzed hydrogenation reactions. Chemically, the C_5-units are usually formed by sequential C_2- (base-catalyzed ethynylation, for example in the transformation of acetone to methylbutynol, **3**) and C_3-elongation reactions (acid-catalyzed Saucy-Marbet[15] or Carroll reaction), while the Kimmel-Sax reaction (ketene chemistry) is less efficient. In some applications, aldol condensation with acetone is used for C_3-elongation, for example in the preparation of ψ-ionone (**5**) from citral. The formation of significant amounts of by-products (self-condensation of starting materials) are, however, often observed when using such procedures.

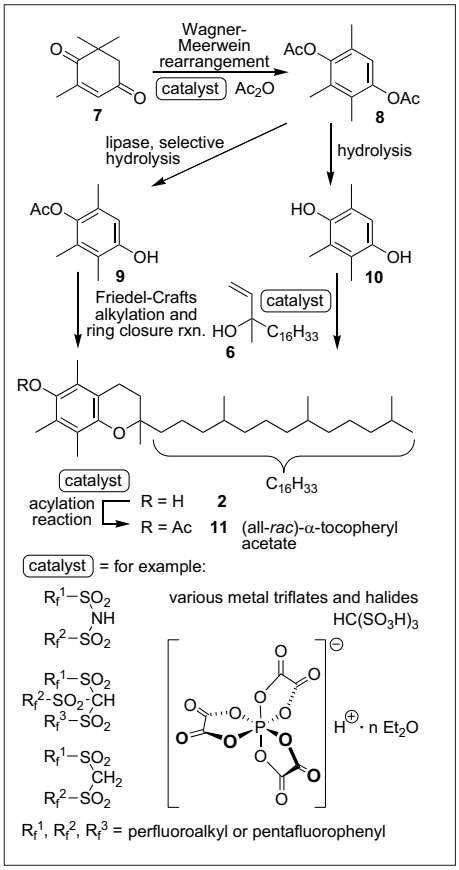
For an acid-catalyzed C_3-elongation, the Carroll reaction (rearrangement of a β-keto allyl ester) exhibits a less favorable atom economy due to the loss of CO_2. The most efficient process is based on the Saucy-Marbet reaction, which is usually carried out under acid catalysis. By using the activated acetone equivalent isopropenyl methyl ether (**4**) as a C_3-building block, the corresponding ketones can be obtained in high selectivity and yields, such as ψ-ionone (**5**), a central intermediate for the synthesis of both vitamins A and E. Modern trends in acid-catalyzed reactions aim for the replacement of regular Brønsted acids by solid acids, for example ion-exchange resins or zeolites. This technology allows continuous processing and benefits from waste reduction, since an often necessary neutralization step can be avoided, that would otherwise result in additional salt formation. Multi-phase catalysis is another valuable concept towards the elaboration of efficient (continuous) processes.

The ethynylation of ketones is a base-catalyzed reaction and has replaced previous stoichiometric Grignard additions. The catalytic reactions are carried out in presence of ammonia and a base, for example KOH, at 0–25 °C at a substrate-to-catalyst ratio of >200.[16] Recent improvements of solid base catalysts for ethynylation reactions are based on new types of macroreticular resins, which have an extended lifetime and can be reused several times.[17]

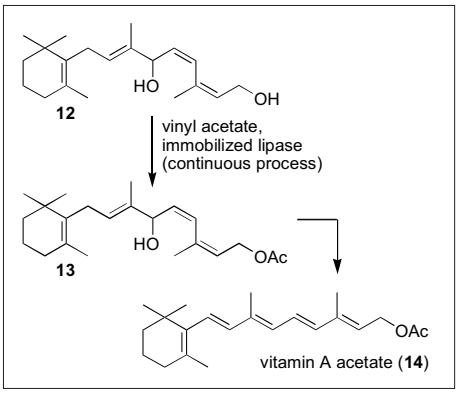
Besides the heterogeneous catalytic hydrogenation of olefins to saturated hydrocarbons, the Lindlar-type hydrogenation, which selectively reduces C≡C triple bonds

to the corresponding *Z*-configured C=C double bonds, has proven to be an important technology in the large-scale production of isoprenoids. In the past, Lindlar hydrogenations have been carried out discontinuously in slurry type reactions.[18] The development of new types of catalysts (Pd-nanoparticles on an oxide sinter metal fiber) allows immobilization and thus continuous processing in a fixed bed reactor.[19]

The discovery of alternative and more efficient Brønsted acids for the synthesis of (all-*rac*)-α-tocopherol not only improved the condensation reaction of trimethylhydroquinone (**10**) with isophytol (**6**) considerably, but also had a strong impact on other key steps in vitamin production, as outlined in Scheme 2. In the final step of the manufacture of (all-*rac*)-α-tocopherol (**2**), higher selectivity and yield could be achieved by the use of novel acidic catalysts, replacing conventional reagents like $ZnCl_2$ 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. Very effective catalysts are various metal triflates[20] and halides,[21] perfluoro-substituted imides,[22] methides,[23] and tris(oxalato)phosphorus acid[24] with catalyst loadings of below 1 mol%. In this context, also the use of supercritical fluids for this condensation reaction is worth a mention.[25]



Scheme 2. Brønsted acid catalysis in the synthesis of vitamin E.



Scheme 3. Lipase catalyzed mono-acetylation of a vitamin A intermediate.

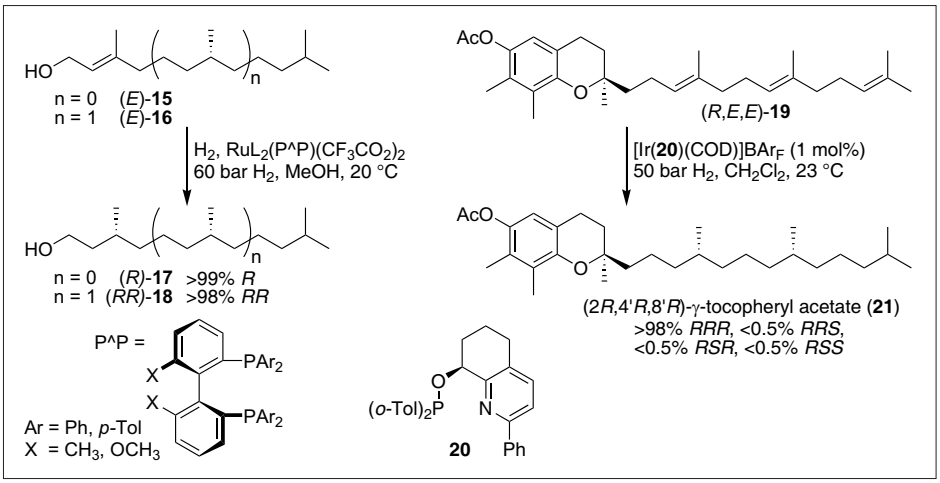
The application of such catalysts in other reactions was also successful, as for example in the Wagner-Meerwein rearrangement/isomerization of ketoisophorone (**7**) to diacetate **8,** an intermediate in the synthesis of hydroquinone **10**, as well as in the acylation of phenol **2** to (all-*rac*)-α-tocopheryl acetate (**11**), the vitamin E derivative primarily used for feed applications. The concept behind these research activities is the application of a single, readily available catalyst to several reactions of a synthesis sequence. One example is the use of methanetrisulfonic acid (easily accessible from acetone and oleum) in truly catalytic amounts (0.04–1.0 mol%), which catalyzes three different types of reactions in the synthetic route outlined in Scheme 2: **7** → **8**, **10** + **6** → **2**, and **2** → **11**.[26] A highly selective condensation of monoacetate **9** with isophytol (**6**) to acetate **11** can be accomplished by carefully chosen reaction parameters, including type and amount of catalyst, preventing a considerable saponification of starting material and product.[27]

Remarkably, enzyme catalysis can be used cost-effectively not only for high-value products like enantiopure drugs, but also for the large-scale preparation of low-cost achiral or racemic bulk products. Lipase-catalyzed mono-saponification of diacetate **8** to **9** suppresses any formation of the regioisomeric mono-acetate or hydroquinone **10**.[28] In the synthesis of vitamin A acetate (**14**, Scheme 3), the yield of the final step can be considerably improved by using pure mono-acetate **13** prepared by an enzymatic, regioselective mono-acetylation of diol **12** in >97% selectivity for the primary hydroxy group.[29]

In the development of stereoselective processes one example is relevant to the preparation of the single-isomer product (2*R*,4'*R*,8'*R*)-α-tocopherol,[14] which is so far only available in limited amounts by partial synthesis. Mixtures of mainly lower homologues of the biologically most active α-tocopherol (so-called mixed tocopherols) are isolated from a side stream of soybean processing, and chemically upgraded. Significant efforts have been directed towards an economical total synthesis of this natural product during the last decades, with the aim to by-pass the shortage of the natural source starting material.

Although an economic total synthesis of (2*R*,4'*R*,8'*R*)-α-tocopherol could not be accomplished to date, considerable progress has been made for key transformations by the use of exceptionally efficient new asymmetric hydrogenation technologies. Based on the seminal work of Noyori and colleagues in the 1980s, ruthenium-catalyzed asymmetric hydrogenation of allylic alcohols was performed on pilot scale with substrate-to-catalyst ratios of up to 150'000 (Scheme 4). Using (*S*)-MeOBIPHEP (Ar = Ph, X = OCH_3) as ligand, C_{10}-building block (*E*)-**15** was transformed into (*R*)-**17** with >99% selectivity, and hydrogenation of (*E*)-**16** gave (*R*,*R*)-**18** (>98% *RR*) with the catalyst derived from (*S*)-*p*-Tol-BIPHEMP (Ar = *p*-Tol, X = CH_3).[30]

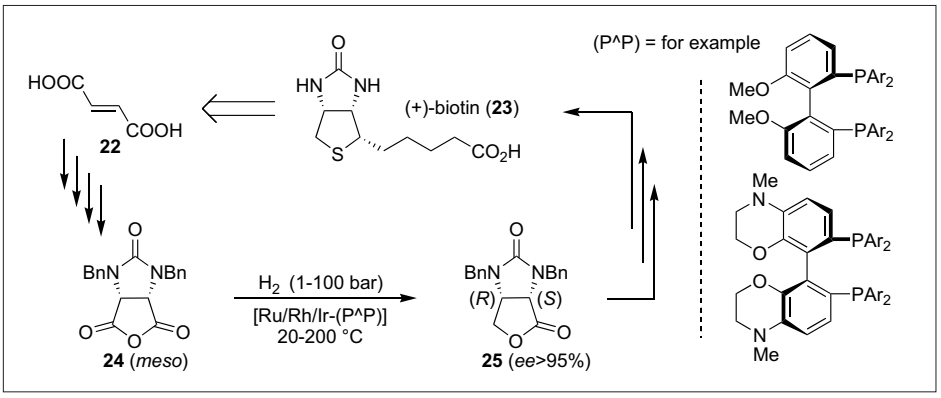
The concomitant introduction of two chiral centers by the reduction of unfunctionalized trialkyl substituted olefins in the presence of Ir-BAr_F complexes con-



Scheme 4. Asymmetric hydrogenation towards (2*R*,4'*R*,8'*R*)-tocopherols.

taining chiral P,N-ligands opened the way to a completely different retrosynthetic concept. Asymmetric hydrogenation of γ-tocotrienol derivative (*R*,*E*,*E*)-**19** with pyridyl phosphinite **20** developed in a collaboration of the Pfaltz group (Uni Basel) with DSM Nutritional Products furnished (all-*R*)-γ-tocopheryl acetate **21** with excellent stereoselectivity and formation of less than 0.5% of each of the other stereoisomers.[31]

Another fantastic reaction solved a long-standing problem in the industrial synthesis of (+)-biotin (**23**), an important water-soluble B-vitamin (Scheme 5). *N*-Benzyl protected key building blocks, in particular D-lactone **25**, are on the one hand easily accessible from fumaric acid (**22**) and are used in all commercial processes, but need on the other hand the application of expensive reagents in multi-step procedures. In contrast, homogeneous catalytic enantioselective hydrogenation of *meso*-anhydride **24** mediated by a metal phosphine complex proceeded with high optical induction and excellent yield. This direct desymmetrization yields D-lactone **25** with an *ee* of >95%, which can be upgraded to >99% by simple recrystallization.[32]



Scheme 5. The dream reaction: Catalytic asymmetric hydrogenation of a (+)-biotin intermediate.

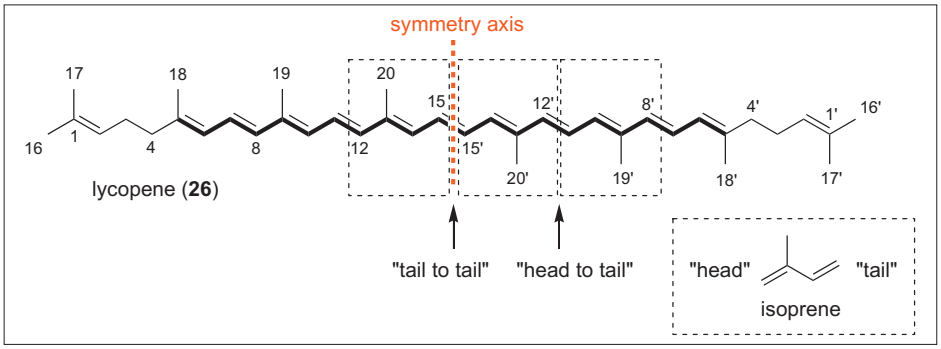


Fig. 3. Carotenoids derived from isoprene units, illustrated for lycopene (**26**).

3. Carotenoids

Carotenoids are plant pigments that naturally occur in fruit and vegetables, easily recognizable by their yellow to red color. They function as strong antioxidants, play an important role as micronutrients in the human diet, *e.g.* protecting against some types of cancer and cardiovascular diseases, stimulate the immune system and have beneficial effects for skin health. The most prominent carotenoids in the human blood plasma are the nutritionally most important ones, such as β-carotene (**27**), lycopene (**26**), β-cryptoxanthin, as well as (all-*R*)-lutein (**31**) and its isomer (*R*,*R*)-zeaxanthin (**28**). The latter two occur in the human eye and are believed to reduce the risk of age-related macular degeneration (AMD),[33,34] which is a leading cause of blindness in the US and Western World.

From a chemical perspective, carotenoids belong to the class of terpenoids and are built of isoprene units (Fig. 3). Most carotenoids are tetra-terpenoids and consist of a symmetric C_{40}-carbon skeleton with a conjugated polyene chain.[35] Due to different chain lengths they absorb light of different colors. Carotenoids are lipophilic and insoluble in water, thus formulation is an important factor for applications in aqueous media.

There are more than 600 known naturally occurring carotenoids, nine of which are sold commercially (Fig. 4).[36] Carotenoids are mainly produced by chemical synthe-

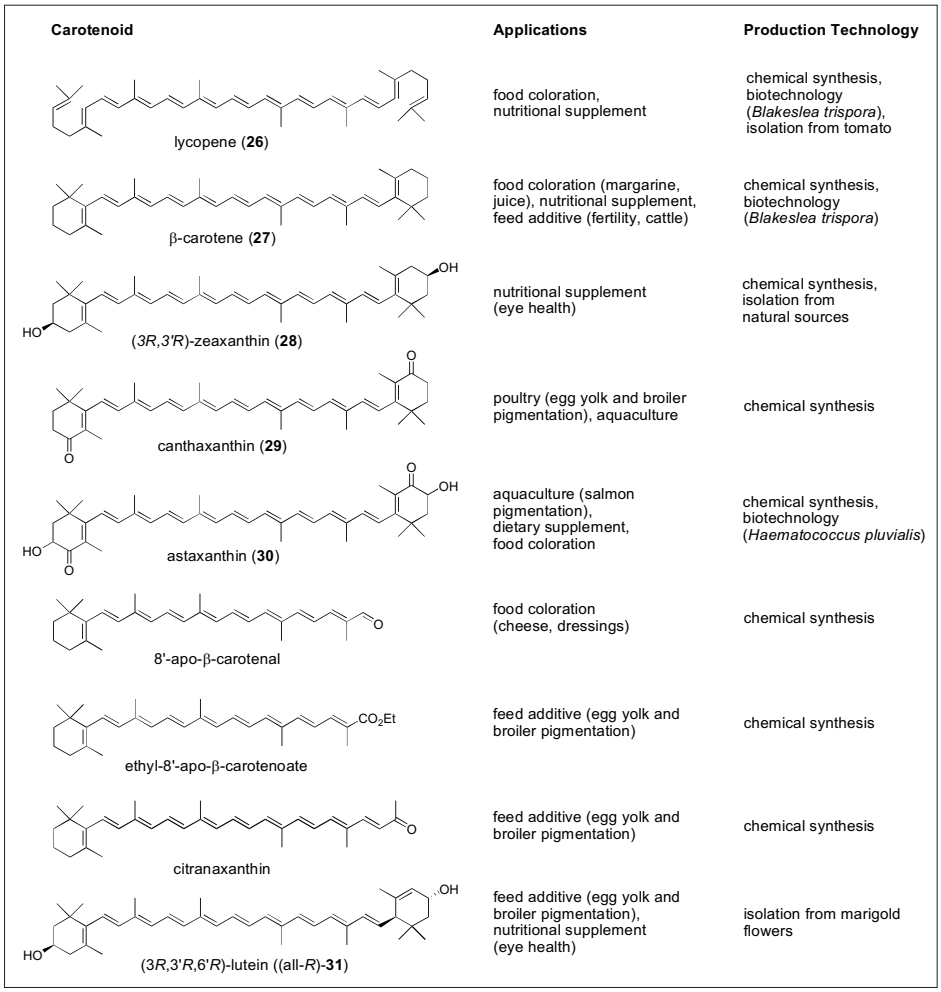
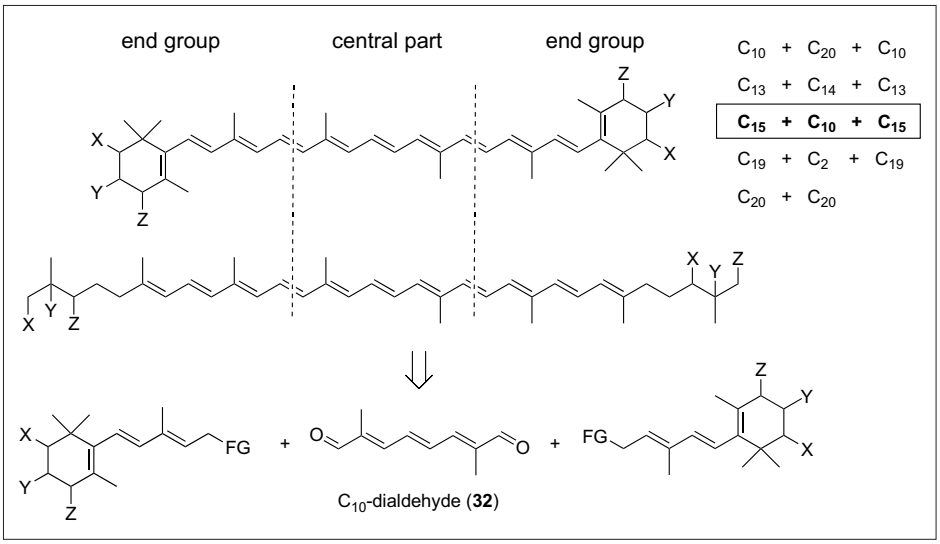


Fig. 4. Industrially produced carotenoids.

sis, but also by biotechnology and isolation from natural sources, *e.g.* lutein.[37]

For the chemical synthesis, several building concepts are possible; however, on industrial scale only few of them have been applied successfully. The most widely used synthesis concept is the C_{15} + C_{10} + C_{15} approach with C_{10}-dialdehyde **32** as central building block (Scheme 6).[37]

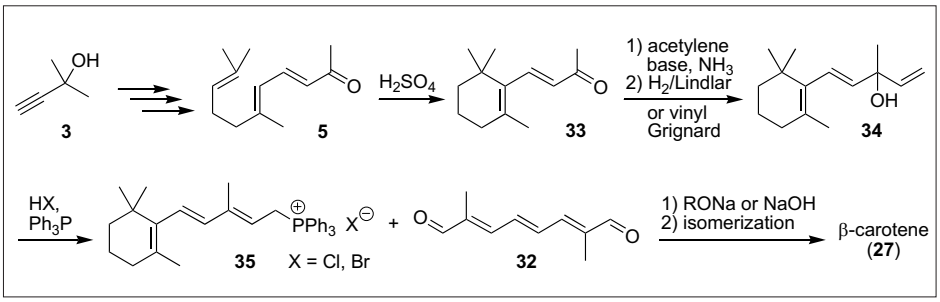
For the final assembly of end groups and the central part only a limited range of coupling methods have been applied in technical processes: a) Wittig olefination, b) Horner-Wadsworth-Emmons olefination, and c) Julia olefination. An interesting alternative to these olefination methodologies is the dienol ether condensation.[38,39] The building block of choice for the central part of the carotenoid scaffold is the C_{10}-dialdehyde **32**, which can be accessed from a C_4-building block, *e.g.* butadiene.[40] Examples of carotenoid syntheses used in industrial production will be described in more detail below.



Scheme 6. Synthetic strategies towards the C_{40}-skeleton of carotenoids.

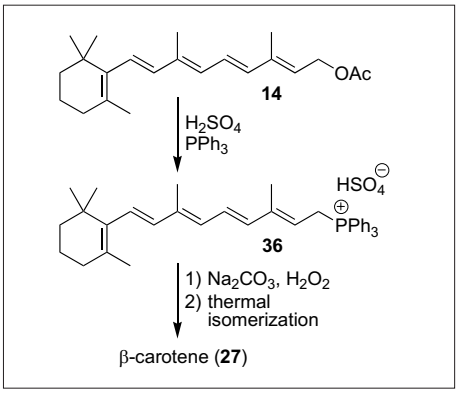
3.1 β-*Carotene (27)*

Several syntheses for the large-scale production of β-carotene (**27**) have been developed.[37] The first synthesis that was realized on industrial scale in the 1950s followed the C_{19} + C_2 + C_{19} strategy, making use of dienol ether condensations to extend the polyene chain followed by a double Grignard coupling of acetylene and two C_{19}-aldehydes.[39] Additional advances in the same decade allowed the synthesis of β-carotene on technical scale *via* a double Wittig reaction according to the C_{15} + C_{10} + C_{15} coupling strategy (Scheme 7).[41,42] A common intermediate in both these syntheses is β-ionone (**33**), which is prepared efficiently *via* iterative acetylene additions, Lindlar hydrogenations and Saucy-Marbet rearrangements followed by an acid-catalyzed cyclization of ψ-ionone (**5**).[15] Vinyl-β-ionol (**34**) is then obtained by one additional iteration of acetylene addition/Lindlar hydrogenation, or a vinyl Grignard reaction. Transformation of vinyl-β-ionol (**34**) into the Wittig salt **35** followed by double condensation with C_{10}-dialdehyde **32** furnishes (all-*trans*)-β-carotene (**27**) after thermal isomerization. In a similar fashion, lycopene (**26**, ψ,ψ-carotene) can be prepared from the corresponding acyclic phosphonium salt derived from ψ-ionone (**5**) and dialdehyde **32**.[43]



Scheme 7. Synthesis of β-carotene (**27**) using a double Wittig reaction (C_{15} + C_{10} + C_{15}).

Another important synthesis of β-carotene (**27**) builds on the structural similarity to vitamin A (**1**):[44,45] Vitamin A acetate (**14**) is transformed into the corresponding phosphonium salt **36** (Scheme 8). Half of this salt is then oxidized with basic H_2O_2, releasing retinal, which subsequently reacts with the remaining phosphonium salt **36** in a Wittig reaction to β-carotene (**27**). Furthermore, β-carotene (**27**) is the starting material for the production of canthaxanthin (**29**, $C_{40} \rightarrow C_{40}$), which can be obtained under oxidative conditions using *e.g.* sodium chlorate/iodine.[46]



Scheme 8. Synthesis of β-carotene (**27**) *via* vitamin A acetate (**14**).

3.2 *Astaxanthin (30)*

This important commercial xanthophyll is used mainly in aquaculture as a feed additive for salmon and trout. It is responsible for the pink color of salmon (see Fig. 5) and usually taken up through the natural feed chain. Since astaxanthin is not part of the salmon biosynthesis, the pink color can only be achieved under aqua farming conditions by supplying feed material enriched with astaxanthin.

Astaxanthin is mainly produced by chemical synthesis. A smaller part is isolated from the fresh water alga *Haematococcus pluvialis*, producing (3*S*,3'*S*)-astaxanthin, mainly in form of fatty acid esters. The two main synthetic routes for astaxanthin are the C_{15} + C_{10} + C_{15} and the C_{10} + C_{20} + C_{10} pathways. The C_{15} building block in the C_{15} + C_{10} + C_{15} route is prepared by a C_9 + C_6 approach starting from ketoisophorone (**7**, Scheme 9). Epoxidation and subsequent hydrolysis affords 4-hydroxy-6-oxo-isophorone (**37**). Catalytic reduction of the less hindered keto group with a Nickel alloy catalyst leads to 3,4-dihydroxyketone **38**. This ketone is protected as an acetal followed by alkynylation with C_6-alkyne **39** and dehydration, furnishing the C_{15}-alkyne **40**. Semi-hydrogenation delivers the C_{15}-alkene **41**, which is converted into phosphonium salt **42**. Finally, double Wittig reaction of phosphonium salt **42** with C_{10}-dialdehyde **32** provides (3*RS*,3'*RS*)-astaxanthin ((all-*rac*)-**30**).[47]

A 'Wittig-free' route to astaxanthin (**30**) is the novel C_{20} + C_{10} + C_{20} approach

Fig. 5. Salmon colored by astaxanthin (© Alexstar – Fotolia.com).

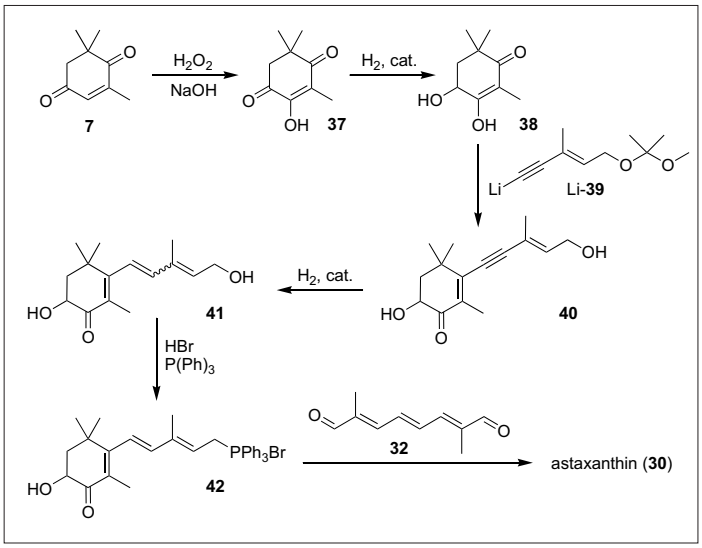
using a double dienol ether condensation, which is catalyzed by Lewis acids. In the key step, dienol ether **43** is condensed with crocetin dialdehyde dimethyl acetal (**44**), furnishing intermediate **45**, which is converted into astaxanthin (**30**) with an aqueous mineral acid (Scheme 10).

The corresponding C_{10}-building block **43** is obtained starting from trimethylcyclohexenone **38**. Reaction with paraformaldehyde in the presence of an acid gives the protected ketone **46**, which is converted to the desired C_{10}-dienol ether **43** by means of a Peterson olefination (Scheme 11).[38]

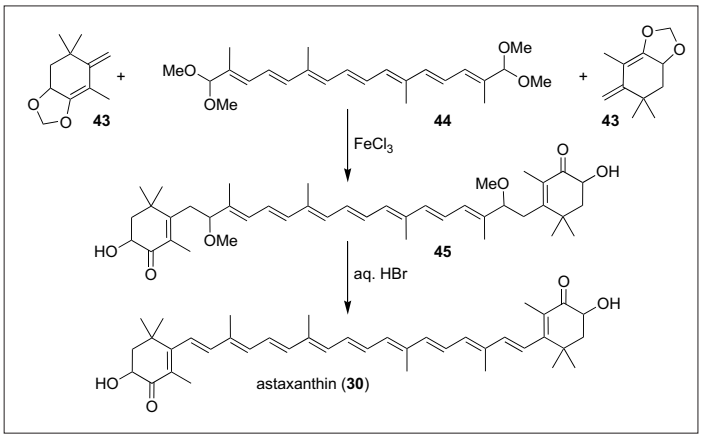
3.3 *Lutein (31)*

This xanthophyll is found in broccoli, green leafy vegetables, yellow and green pepper and pumpkin,[33] and is used as a yellow colorant for applications in poultry products, *e.g.* in egg yolk or broiler pigmentation. Lutein is isomeric with zeaxanthin (**28**) and differs only in the position of one double bond. Due to its non-symmetrical chiral structure, a total synthesis of (3*R*,3'*R*,6'*R*)-lutein is rather complex and challenging to apply on technical scale. However, lutein esters naturally occur in marigold flowers (*Tagetes erecta*, Fig. 6)[48] and can be isolated from the dried marigold petals by extraction (Scheme 12). Saponification of the resulting oleoresin containing xanthophyll esters followed by crystallization affords natural (3*R*,3'*R*,6'*R*)-lutein in high purity.[49]

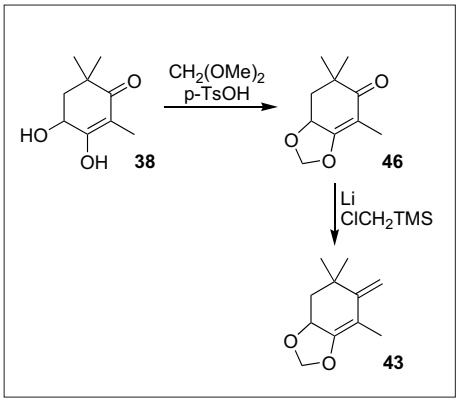
On laboratory scale, the first total synthesis of the natural product (3*R*,3'*R*,6'*R*)-lutein ((all-*R*)-**31**) was reported in 1980.[50] Recent chemical investigations by Khachik and Chang were directed towards the synthesis of the other seven lutein stereoisomers to provide material with defined stereochemistry for metabolic studies, for example on AMD. Their approach uses an enzyme-mediated acylation to resolve the racemic mixture of the hydroxy aldehydes (3*R*,6*R*)-**47** and (3*S*,6*S*)-**47** *via* the acetate **48** (Scheme 13),[51] important building blocks for the synthesis of (3*R*,3'*R*,6'*R*)-lutein and its stereoisomers.



Scheme 9. Synthesis of astaxanthin (**30**).



Scheme 10. Synthesis of astaxanthin (**30**) *via* dienol ether condensation.



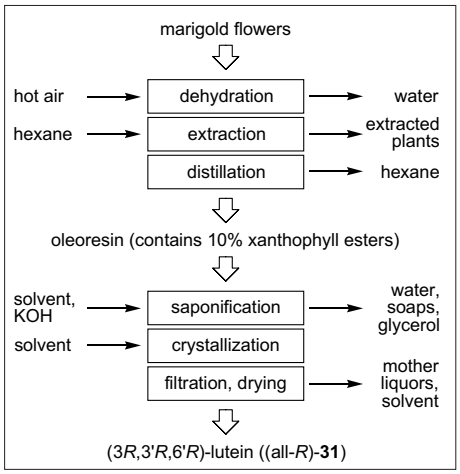
Scheme 11. Preparation of C_{10}-dienol ether **43**.

Fig. 6. *Tagetes erecta*, starting material for the isolation of natural (3*R*,3'*R*,6'*R*)-lutein ((all-*R*)-**31**) (photo by M. Hugentobler).

4. Nutraceuticals

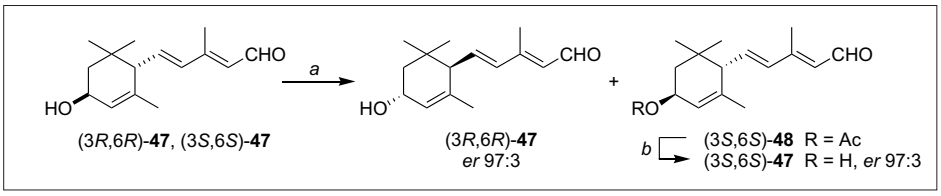
The term 'nutraceuticals' describes naturally occurring compounds that have a beneficial effect on human health, which goes beyond the influence of a well-balanced diet.[1,52] Examples of such nutraceuticals are antioxidants like *n*–3 long-chain fatty acids, probiotics, phytosterols, and polyphenols. The latter are reported to play important roles in long-term health protection[53] and represent an important class of industrially produced compounds like resveratrol **49,** (–)-epigallocatechin gallate (EGCG, **50**), and genistein (**51**) (Fig. 7).

Polyphenols can be found for example in green tea. The consumption of green tea has been associated with health benefits such as cholesterol reduction, the prevention of certain degenerative diseases like Alzheimer's disease, Parkinson's disease, arteriosclerosis, and other aging related disorders.[54] The main polyphenols of green tea are epicatechin, epicatechin gallate, and epigallocatechin gallate (**50**, EGCG) of which EGCG is most abundant and exhibits the strongest antioxidant activity.



Scheme 12. Process for isolation of natural lutein from Marigold.

A highly purified and caffeine-free green tea extract with a minimum content of 94% EGCG is available on the market under the brand name Teavigo®. It is sold as functional food ingredient to the dietary supplement and food industry. Teavigo® is produced starting from commercial green tea extracts with an EGCG content of around 30%. The enrichment of EGCG is achieved by an adsorption/desorption process using polymeric adsorption resins, resulting in a caffeine-free white powder with an EGCG content of >94% (Fig. 8).[55] As an alternative, tea catechins can also be extracted by using high-pressure carbon dioxide with co-solvent addition.[56]



Scheme 13. Lutein synthesis by Khachik and Chang [(*a*) i. Lipase AK *Pseudomonas fluorescens*, vinyl acetate, pentane, reflux, 48 h, 43% conversion; ii. Separation by column chromatography; (*b*) KOH/methanol (10% w/v), 0 °C, 2 h, 97%].

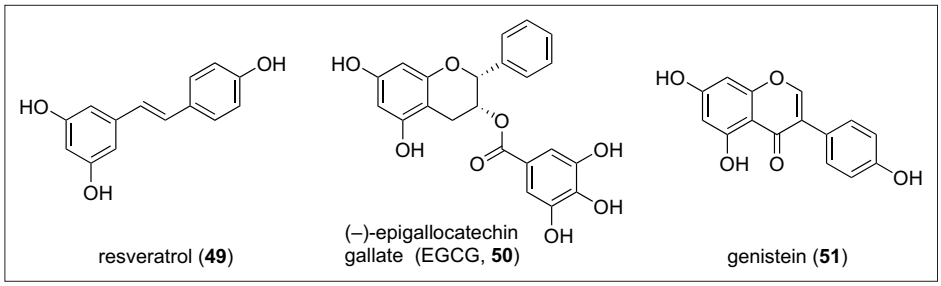


Fig. 7. Examples of commercially available polyphenols.

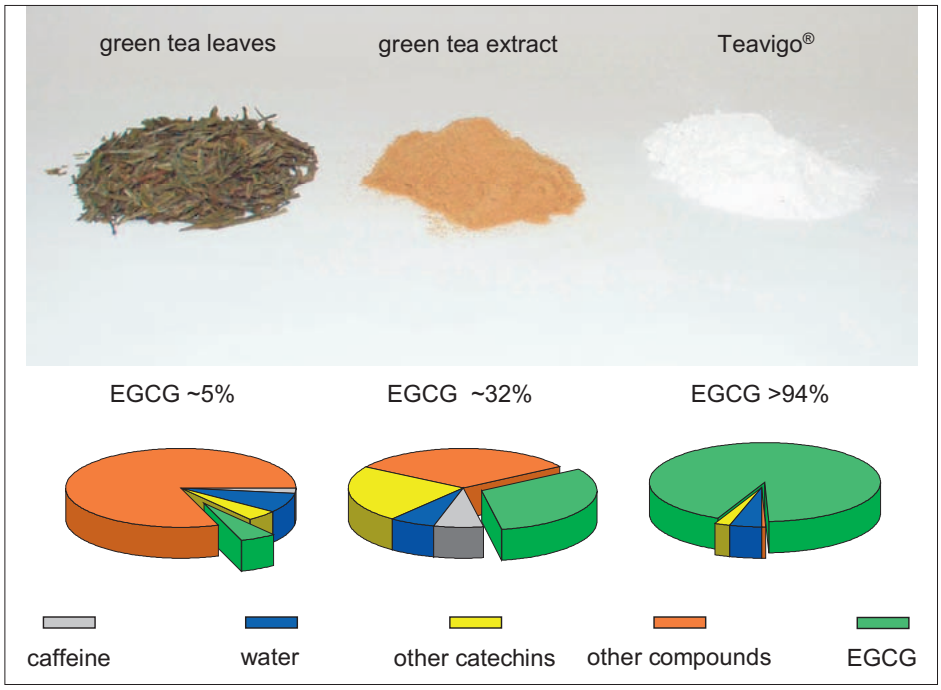


Fig. 8. Isolation of EGCG (**50**) from green tea leaves.

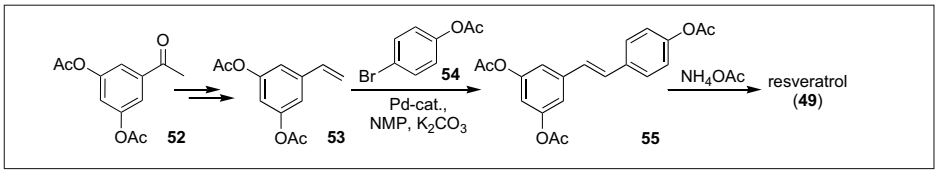
Resveratrol (**49**), another polyphenol, can be found in various plants where it acts as phytoalexin,[57] as well as in fruit (especially grapes, Fig. 9) and vegetables[53] and was first isolated from the roots of white hellebore (*Veratrum album*) in 1940 and later from the roots of *Polygonum cuspidatum* in 1963.[58] It mostly occurs as (*E*)-3,4',5-trihydroxystilbene (resveratrol, **49**). It has been shown to significantly extend the life-span of yeast,[59] worms and fruit flies,[60] as well as fish[61] and counteracts the detrimental effects of a high-fat diet in mice.[62] It has also been associated with the French paradox.[63] Upon moderate consumption of red wine, the dose of **49** taken up is considered to be the origin of protection of heart and blood vessels from arteriosclerosis. Extraction of resveratrol (**49**) from plants is feasible,[64] but laborious due to both the low concentration and the occurrence of structurally related anthraquinones, stilbenes, flavonoids and phenols.[65]

The first chemical synthesis of resveratrol trimethyl ether was reported in 1941.[66] *p*-Methoxyphenylacetic acid was condensed with 3,5-dimethoxybenzaldehyde in the presence of acetic anhydride. After decarboxylation the mixture of (*Z*)- and (*E*)-stilbene was treated with HCl in methanol leading to the isomerically pure (*E*)-stilbene. Such Perkin-type reactions[67] as well as Wittig and Wadsworth-Horner-Emmons type reactions are industrially relevant approaches to

Fig. 9. Grapes and wine contain resveratrol (**49**) (© Sandra Cunningham – Fotolia.com).

resveratrol.[68] Recent synthetic approaches to electron-rich stilbenes including **49** cover a broad range of C–C bond forming reactions.[69]

An attractive access to resveratrol, which does not require cumbersome deprotection of methyl ethers as in the synthesis described above, starts from 3,5-diacetoxyacetophenone (**52**), which is converted to styrene **53** *via* hydrogenation, bromination and subsequent elimination of HBr (Scheme 14).[70] Styrene **53** is then coupled in a Mizoroki-Heck reaction[71] with bromophenyl acetate **54** to resveratrol triacetate **55**, favoring the (*E*)-isomer. The reaction is catalyzed by a tailor-made palladium complex, which mediates the coupling of very electron-rich compounds like diacetoxy styrene **53** and bromophenyl acetate (**54**). Finally, hydrolysis of the acetoxy groups is achieved under mild conditions using ammonium acetate, furnishing resveratrol (**49**).



Scheme 14. Industrially attractive Mizoroki-Heck reaction for the synthesis of resveratrol (**49**).

5. Conclusions

The development of efficient, sustainable low-cost processes is the basis for providing high-quality products for daily life applications in human and animal nutrition. The translation of sophisticated science into valuable, ecologically benign and competitively advantageous processes for the manufacture of nutritional products demonstrates the success story of modern industrial chemistry. This has been illustrated in the present article by highlighting synthetic aspects of representative and important food ingredients such as vitamins, carotenoids and nutraceuticals.

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