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Development of the industrial synthesis of vitamin A

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ABSTRACT

The advances made in chemistry during the last 70 years are excellently illustrated by the development of the industrial synthesis of vitamin A, a diterpene crucial in preventing premature death and visual problems. Arens and van Dorp published the first route in 1946, and critical contributions have been made by a number of scientists since, benefitting from fruitful collaborations between industry and academia. However, these improvements have been mostly incremental, and the work has been performed by a limited number of companies; as yet, there is still no 'ideal' synthesis of vitamin A.

Contents

1. Introduction

Vitamin A (retinol) is an essential micronutrient which humans must ingest from animal or plant sources. Its biological functions include general growth, vision, reproduction and the differentiation of epithelial tissue. Vitamin A deficiency disorders are an important cause of child mortality.[1]

The structure of vitamin A was first elucidated by the Nobel Prize winner, Paul Karrer in 1929–31 after extraction from the liver oils of halibut and mackerel.[2,3] It is a C_{20} diterpenoid containing four isoprene units (Fig. 1). It was isolated and crystallised by Holmes and Corbet from fish liver oils in 1937.[4,5] It is important to note that all vitamin A syntheses must consider stereochemistry, as the side chain of vitamin A has four double bonds. This system can give rise to 16 possible isomers.

Working at Organon International, the Dutch chemists Arens and van Dorp developed the earliest synthesis of vitamin A in 1946–47. In the same year, Isler et al. established a modification to the Arens-van Dorp synthesis which was better suited for industrial scale-up at Hoffmann-La Roche. The synthesis of vitamin A assisted in the advancement of synthetic chemistry, through the work and

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0040-4020/

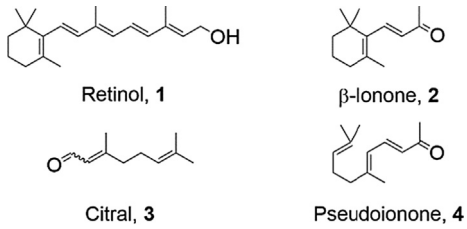


Fig. 1. Structures of vitamin A (retinol) and related compounds.

development of reactions by well-known chemists such as Wittig, Lindlar and Julia. It also led to progress in the synthesis of vitamin E, as the key intermediate, (all-*rac*)-isophytol, shares many synthetic steps with vitamin A, with routes proceeding via citral and pseudoionone (Fig. 1). Citral is an approximately 4:1 mixture of the *E*-isomer, geranial, and the *Z*-isomer, neral. The manufacture of vitamin A has experienced only incremental changes since these early syntheses, and these developments will be illustrated below. Reaction conditions are given where available.

2. Previous work

Kuhn and Morris reported the synthesis of vitamin A in 1937.[6] However, their route provided a sample with only 7.5% biological activity due to the impure intermediate β-C_{15}-aldehyde. It is recorded that the Kuhn–Morris synthesis was repeated by several groups over the following years, unfortunately to no avail.[7,8] Despite this, it is safe to conclude that this first effort provided inspiration and motivation for research into an improved vitamin A synthesis.

This initial study allowed Arens and van Dorp to bridge the gap between earlier attempts at the full synthesis of vitamin A, notably the 1936 paper by Heilbron et al. whose work had included the structure of the key starting material: the C_{18} ketone **5** (Fig. 2) which they believed they had synthesised.[9] However, this compound had an unusually high melting point of 144 °C, which conflicted with Arens and van Dorp's lower boiling point of 138–140 °C. Later, in 1944, Heilbron et al. stated that they had incorrectly assigned the structure of the aldehyde from which the ketone was made, and therefore, Arens and van Dorp concluded that the substance produced did not have the structure of the C_{18} ketone originally proposed.[10]

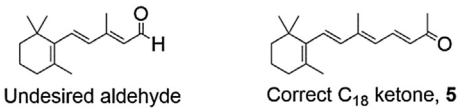
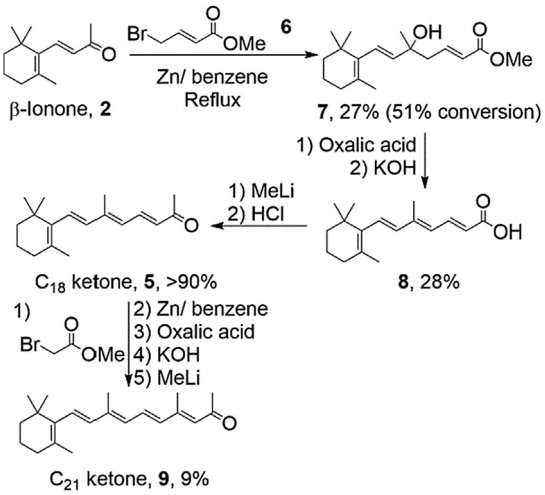


Fig. 2. A key intermediate in the synthesis of vitamin A.

3. Arens-van Dorp synthesis of vitamin A (Organon)

Arens and van Dorp began their investigations into vitamin A by synthesising various compounds with vitamin A activity, namely vitamin A acid.[11] Their work centred on the production of the acid via a linear multistep synthesis starting from β-ionone. Subsequent reactions systematically lengthened the unsaturated carbon side chain through alkylation and interconversion of the functional groups: from esters to carboxylic acids, by saponification; and finally to the corresponding ketone, by the action of excess methyllithium. The synthesis is shown below (Scheme 1).



Scheme 1. Arens-van Dorp synthesis of C_{21} intermediate.

In the synthesis of vitamin A acid by Arens and van Dorp, β-ionone undergoes a Reformatsky reaction. Reformatsky reactions are used in this synthesis to extend the length of the carbon chain; a type of reaction which typically uses zinc and an α-bromo ester to convert ketones into β-hydroxy-esters. However, Arens and van Dorp experimented with reagents other than α-halo esters, as observed in the first step of the reaction when methyl γ-bromocrotonate **6** was reacted with β-ionone producing the hydroxy-ester **7**.[12] In contrast, the reaction of **5** is typical of Reformatsky reactions as it uses methyl bromoacetate, an α-bromo ester, which is reacted with the C_{18} ketone forming a β-hydroxy-ester.

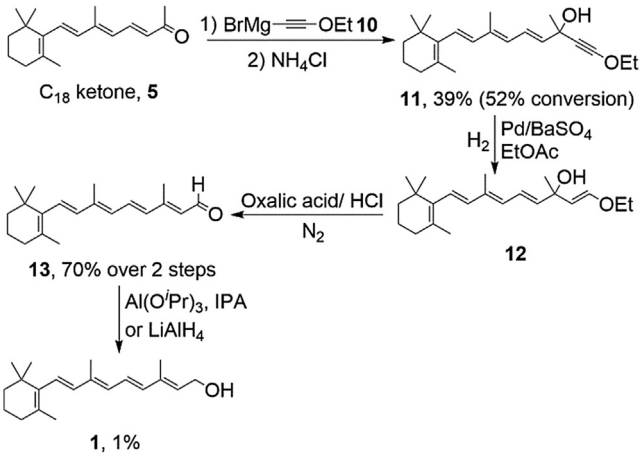
After forming the hydroxy-ester **7** by the first Reformatsky reaction, it was dehydrated using anhydrous oxalic acid to form an ester. Arens and van Dorp found that the Reformatsky reaction produced mainly the hydroxy-ester and a dehydration reaction was necessary to form the desired product.[13] Saponification of the ester formed three crystalline acids of which the main component was ionylidene crotonic acid **8**.

A methylation reaction using methyllithium next converted acid **8** into the C_{18} ketone **5**, found to be a thick yellow oil having a similar structure to vitamin A. From here a repeat of the previous four steps were undertaken: the Reformatsky reaction with methyl bromoacetate; followed by a dehydration using anhydrous oxalic acid; next, ester hydrolysis with potassium hydroxide; and finally the addition of methyllithium to convert vitamin A acid to the C_{21} ketone **9**.

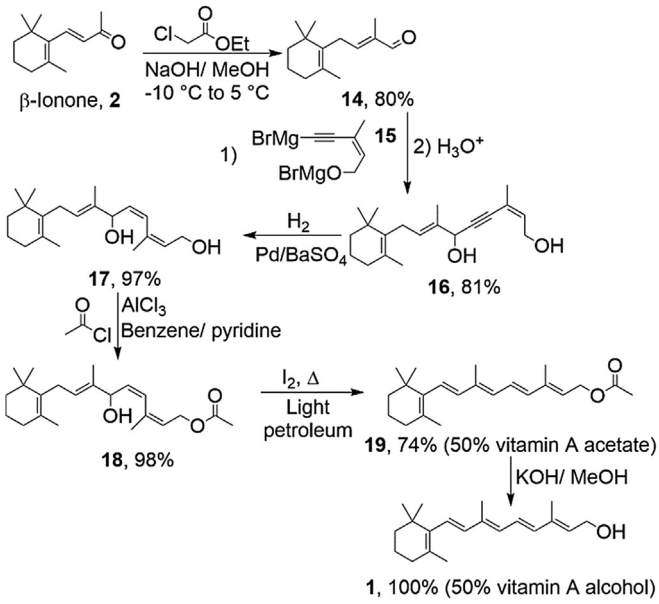
The synthesis of retinol begins from the advanced intermediate C_{18} ketone **5**, which had previously been synthesised in the production of vitamin A acid.[14–17] In the process of synthesising vitamin A, Arens and van Dorp successfully developed a protocol for creating alkoxyethynyl alcohols from ethoxyacetylene and ketones, a procedure subsequently known as the Arens-van Dorp reaction and patented in 1953 (Scheme 2).[18]

The first step in the sequence is a Grignard reaction between the ethoxyacetylene derivative **10** and the C_{18} ketone **5**. Controlled reduction of the triple bond, using a poisoned palladium catalyst under a hydrogen atmosphere, forms **12**. The hydroxy group of **12** is eliminated using aqueous hydrochloric acid upon hydrolysis of the enol ether.

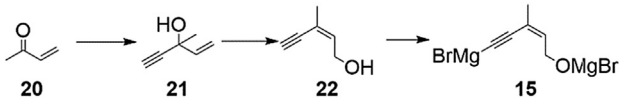
Vitamin A (**1**) can be obtained by reducing the vitamin A aldehyde **13** using aluminium isopropoxide and isopropyl alcohol in a Meerwein–Ponndorf–Verley reduction. Arens and van Dorp found that after chromatography 35% of the material obtained was



Scheme 2. Arens-van Dorp synthesis of retinol.



Scheme 3. Isler synthesis of retinol.



Scheme 4. Synthesis of Grignard reagent.

vitamin A, identified by its biological activity and UV absorption spectrum.

Later, in 1949, Arens and van Dorp found that instead of using aluminium isopropoxide and isopropyl alcohol, the newly-discovered lithium aluminium hydride could be used for the reduction in an improved vitamin A content of 50%.[16] In addition, the article stated that the vitamin A acid could also be converted to vitamin A by reduction with $LiAlH_4$, a route which had also been suggested by Milas.[19] The company DPI also made use of lithium aluminium hydride in 1947 (see below).

However, the use of ethoxyacetylene proved to be ultimately unattractive, as this required extensive time-consuming preparation and was thus not economical for large-scale production.

4. Isler synthesis and modification (Hoffmann-La Roche)

Otto Isler also began research into vitamin A around the same time as Arens and van Dorp, with his first major paper on the subject published in 1947 titled *Synthese des Vitamin A*[20] in agreement with an idea suggested by Heilbron et al. before World War II.[21] Ultimately the Isler modification provided a simpler synthetic route which avoided the preparation of ethoxyacetylene, and thus was suitable for industrial scale-up by Hoffmann-La Roche.[22] The full synthesis of vitamin A by Isler is illustrated below (Scheme 3).

Both the Isler and Arens-van Dorp syntheses start from β-ionone. However, Isler's first stage is a glycidic ester condensation, also known as a Darzens reaction, in which ethyl chloroacetate reacts with β-ionone under basic conditions. An intermediate α,β-epoxy ester is formed, which undergoes hydrolysis with excess NaOH at the carbonyl centre, which is made very electrophilic due to the adjacent electron withdrawing groups. The carboxylate anion undergoes rapid decarboxylation followed by tautomerisation, resulting in an 80% yield of the desired β-C_{14}-aldehyde **14**. Isler commented that the reaction sequence had been studied previously and so worked alongside Lindlar to deduce the optimum conditions for the reduction. It was discovered that the intermediate was heat-sensitive and readily hydrolysed; therefore, it was decided that warming should be avoided during the condensation reaction.

The intermediate aldehyde **14** was next condensed with a Grignard reagent (**15**), generated from 3-methylpent-2-en-4-yn-1-ol and ethyl magnesium bromide. This is followed by aqueous work-up to quench the magnesium salts, thus forming diol **16**. This is the key assembly step which adds length to the carbon chain. The precursor to the Grignard reagent is shown below and is synthesised from methyl vinyl ketone (Scheme 4). Both steps have been improved from the original preparation as a result of optimisation of the reaction conditions and better engineering. This increased the yield and reduced waste. Recent advances by DSM mean that the rearrangement of **21** can now be performed using biphasic conditions[23] or heterogeneous catalysts[24] rather than dilute sulfuric acid. This has improved the yield from 85% to 87% for the biphasic system or 90% for the heterogeneous catalyst.[25]

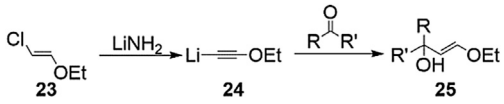
Collaboration between Lindlar and Hoffmann-La Roche led to the development of Lindlar's catalyst, which consists of palladium on calcium carbonate poisoned with lead compounds for the selective hydrogenation of alkynes to alkenes.[26] In this scheme, partial hydrogenation using Lindlar's catalyst reduces the triple bond (**16** to **17**) but leaves the double bonds untouched. Initially a poisoned palladium on charcoal catalyst was used, but this was often hard to control and frequently over-hydrogenated the compound, resulting in impurities which were difficult to remove. This problem was resolved by the use of a lead-doped palladium catalyst on calcium carbonate, further poisoned with an amine which allowed the reaction to be stopped after only 1 equiv of hydrogen had been consumed.[27]

Acetyl chloride or acetic anhydride is used to esterify **17** by selective acetylation of the primary allylic hydroxyl group. Following this, the conjugated system in **18** must rearrange to form the five mutually conjugated bonds of vitamin A. This is achieved by an allylic rearrangement followed by a dehydration reaction, using a small amount of iodine dissolved in light petroleum. This forms vitamin A acetate (**19**) which, by saponification, is converted to vitamin A. The dehydration reaction step was later improved by use of boiling phosphorus oxychloride in pyridine, rather than iodine, and then finally treating with concentrated hydrogen bromide in dichloromethane at a low temperature. However, a better procedure was discovered to be a strong acid at low temperature, which results in a very high yield of over 90% of vitamin A acetate.[28]

Isler's synthetic vitamin A was used by Unilever in their margarines, replacing the use of whale liver oils before 1950.[28]

During the synthesis of carotenoids, Isler identified a further improvement to the Arens-van Dorp synthesis, later called the Isler modification.[29,30] This circumvented the need for ethoxyacetylene, instead starting from β-chlorovinylether (**23**) which was used to synthesise lithium ethoxyacetylene (**24**).

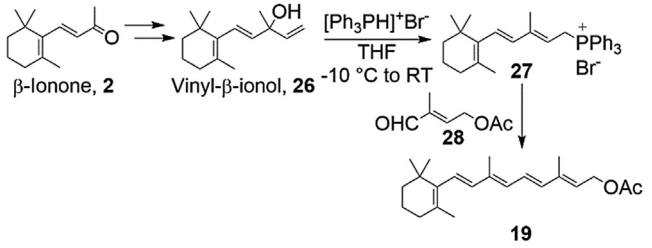
Subsequent reaction with a ketone yielded an intermediate common to the Arens-van Dorp synthesis, allowing synthesis of retinal and reduction to retinol (Scheme 5).



Scheme 5. Isler modification to the Arens-van Dorp synthesis.

5. Wittig reaction (BASF)

BASF first synthesised vitamin A using a Reformatsky reaction between β-ionone **2** and a propargyl bromide, patenting their process in 1956.[31] However, this route was not commercialised due to greater success by Pommer collaborating with Wittig. The newly discovered Wittig chemistry was revolutionary for polyene chemistry. This innovative method allowed synthesis directly from C_{15}-vinyl-β-ionol to vitamin A acetate, by the Wittig reaction with the C_5-aldehyde, β-formylcrotyl acetate **28**. Work to investigate this reaction began at BASF in 1952, and various combinations of phosphonium ylid and carbonyl were considered.[32] The C_{15} phosphonium ylid and the C_5 aldehyde route as shown in Scheme 6 was finally patented in 1957.[33]



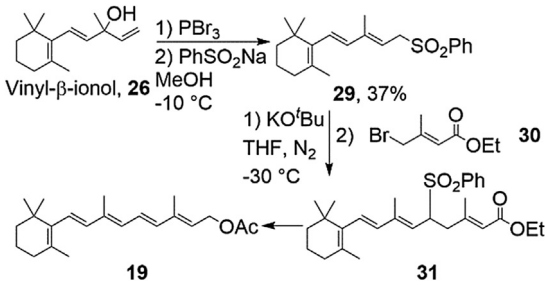
Scheme 6. BASF synthesis of vitamin A acetate.

Vitamin A acetate can be readily converted to retinol by saponification.

6. Julia reaction (Rhône-Poulenc)

In 1974 Rhône-Poulenc (now Adisseo) developed a synthesis of vitamin A that also used the C_{15}+C_5 route which they patented in 1971.[34] Marc Julia collaborated with Rhône-Poulenc to create the Julia reaction which uses sulfone chemistry to form carbon-carbon double bonds; the reaction scheme is shown below (Scheme 7).

The synthesis starts with vinyl-β-ionol (**26**) which is treated with the phenylsulfinate anion producing sulfone **29**. After deprotonation, the intermediate is treated with the allyl bromide **30** shown in Scheme 7 forming the C_{20} sulfone **31**. The C_{20} sulfone undergoes elimination in base, and of those tested, potassium alkoxides were the most effective[35] in forming vitamin A acetate (**19**) in a yield of 86%. It was possible to synthesise retinoic acid

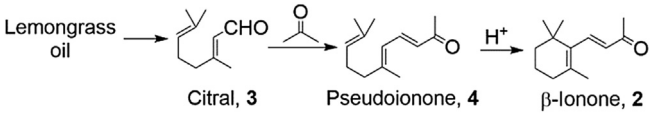


Scheme 7. Rhône-Poulenc synthesis of vitamin A acetate.

derivatives in a similar way.[36] The inverse coupling approach, using a C_{15} halide and C_5 hydroxy sulfone, was subsequently reported in 1976 by Roche but never commercialised.[37]

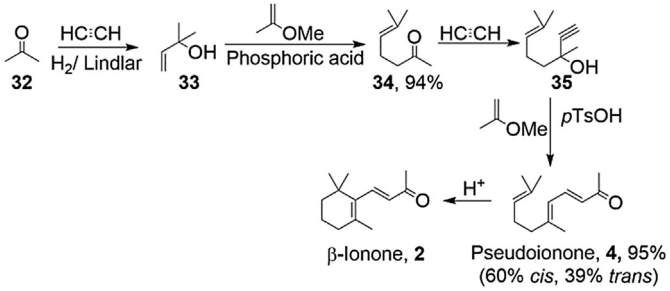
7. Synthesis of β-ionone

The starting material, β-ionone, is the essential starting point for all industrial vitamin A syntheses.[28] In the 19th century, β-ionone was prepared from lemongrass oil which was extracted from the water distillate of *Cymbopogon* sp. which is 70–80% citral and used in the formulation of perfumes.[28] Citral is condensed with acetone to give pseudoionone, and the addition of a strong acid causes cyclisation to β-ionone (Scheme 8).[38]



Scheme 8. Synthesis of β-ionone *via* extraction from lemongrass oil.

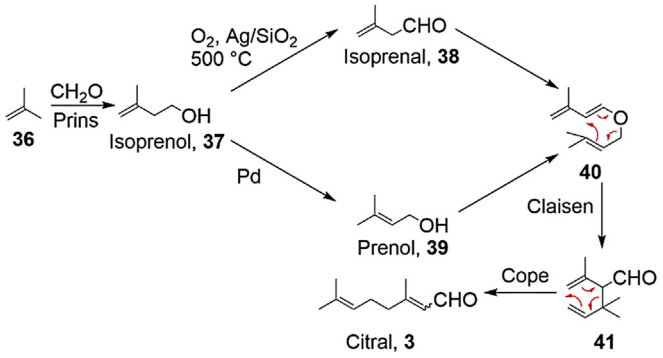
However, lemongrass oil soon became a non-economically viable source of citral due to the increasing cost of production, reduced agricultural area and variability in quantity. During the Second World War, the scarcity of β-ionone slowed research. Roche began work on a total synthesis of β-ionone from acetone in the 1940s (Scheme 9).[28]



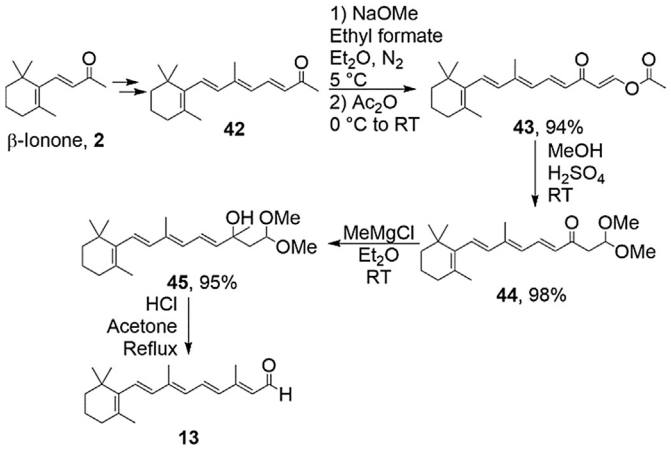
Scheme 9. Roche synthesis of β-ionone.

Acetylene was used to extend the carbon chain length by two, followed by semi-hydrogenation. The reaction of isopropenylether via a sigmatropic rearrangement was developed by Saucy and Marbet.[39–41] This reaction was followed by a further condensation with acetylene, and an additional procedure with isopropenylether gave pseudoionone (**4**), which as stated can be cyclised to β-ionone with the addition of a strong acid.

BASF also developed an alternative route to citral, a key building block in the synthesis of vitamin A (Scheme 10).[42]



Scheme 10. BASF route to citral. More details were not available.



Scheme 11. AEC synthesis of vitamin A aldehyde.

The starting materials are isobutene (**36**) and formaldehyde, which are reacted together in a Prins reaction to give isoprenol (**37**). This can be reacted to give isoprenal (**38**) by oxidation and isomerisation, or prenol (**39**) through the use of a palladium catalyst. Isoprenal and prenol are then combined to give an intermediate **40** which undergoes a Claisen rearrangement, followed by a Cope rearrangement to yield citral (**3**).

8. Industrial developments (post-1954)

In 1979, Isler published an article on the history and industrial applications of carotenoids and vitamin A.[28] Numerous chemical companies have produced different syntheses for vitamin A, yet only a select few were ever commercialised. They can generally be categorised by the final condensation step during the building of the carbon skeleton (Fig. 3).

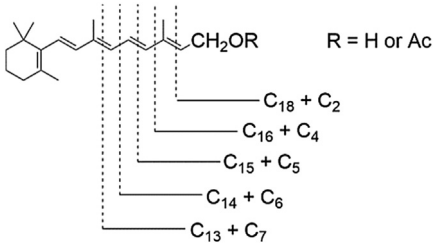


Fig. 3. C–C bond formation during the final construction step.

Those manufacturing processes for syntheses that reached the market are shown in Table 1 below.

As part of these industrial endeavours, Alimentation Equilibré (AEC) developed and patented a higher yielding route to vitamin A aldehyde in the 1960s (Scheme 11).[44,45] The aldehyde retinal **13** can be easily reduced to give vitamin A.

β-Ionone is transformed to the unsaturated methyl ketone **42** by previously described chemistry. The aim of the route from AEC was to avoid the use of the Reformatsky reaction. Instead of targeting the carbonyl group, they reacted at the methyl group to extend the chain with an alkyl formate forming the 1,3-dicarbonyl system. The enol **43** tautomerises to the aldehyde in situ, which is then protected as the acetal **44**, before reductive methylation by a Grignard addition reaction. The presence of acid in the final step enacts dehydration followed by deacetalisation to give the aldehyde product **13**.

In the 1950s, DPI (as part of the Eastman Kodak Company) patented a process for the synthesis of vitamin A from β-ionone where R is an alkyl group (Scheme 12).[46–48]

The first step was the reaction of β-ionone **2** with a propargyl halide in the presence of a metal such as magnesium/mercury amalgam, or zinc. A Grignard reaction with an acetal protected reagent (**47**) gave the alkyne **48** which could be reduced by hydrogen and a palladium or Raney nickel catalyst. A dehydrating agent such as PCl_3, $POCl_3$, BF_3, $AlCl_3$ or PCl_5 was then used to give the conjugated polyene **50**. Treatment with acid simultaneously deprotected the enol ether and induced rearrangement of the double bond architecture to give the aldehyde **51**. A further double bond migration was effected using a basic catalyst such as pyridine, NaOH or $Al(O^iPr)_3$. Finally, the vitamin A aldehyde (**13**) could be reduced to vitamin A by the use of a variety of reducing agents such as $LiAlH_4$ or $Al(O^iPr)_3$.

Both Philips-Duphar and Sumitomo began from the C_{15} compound, β-ionylideneacetaldehyde. Huisman et al. published a series of papers beginning in 1950 upon which the work of Philips-Duphar was based.[49–53] In 1990, the company was sold to Solvay and is now part of Solvay Pharmaceuticals. The synthesis from Sumitomo used the work of Matsumi et al. and focused on the isomerisation of the double bonds to give derivatives of vitamin A acids.[54–56]

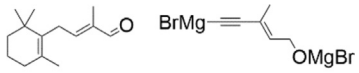
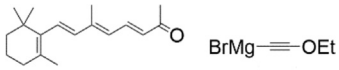
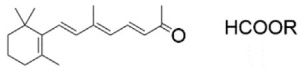
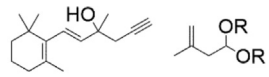
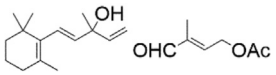
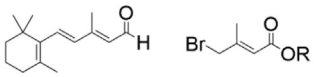
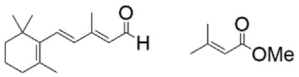
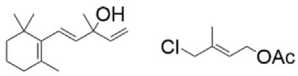
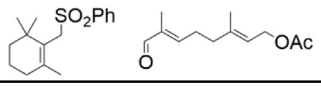
More recently, in the 1980s the Japanese company Kuraray developed an approach to vitamin A acetate using a C_{10}+C_{10} synthesis(Scheme 13).[57]

The addition of sulfone **52** to aldehyde **53** yields the alcohol **54**, which is protected as the THP ether **55**. A double elimination reaction follows and avoids reduction. The second step is a rapid 1,6-elimination of sulfinic acid to give vitamin A acetate in 67% yield. The ratio of isomers as measured by HPLC was all-*trans*:9-*cis*:13-*cis*:11-*cis* 90:2:5:3.

9. Price-fixing (1989–99)

In 2001, the European Commission imposed total fines of €855.22 m on eight companies for their participation in eight distinct market-sharing and price-fixing cartels.[58] Of these, the vitamin A market (worth €150 m in the European Economic Area in 1998) was controlled by Hoffmann-La Roche, BASF and Rhône-Poulenc. Due to its early and full participation in the investigation, Aventis was not fined for its role in the vitamin A cartel; however, Hoffmann-La Roche, the world's largest vitamin producer with 50%

Table 1
Synthetic routes for the synthesis of vitamin A by company

Company	Synthesis	Year published
Hoffmann-La Roche	 $C_{13} + C_7$, $C_{14} + C_6$	1947 (patented 1953)
Organon International	 $C_{18} + C_2$	1946 (patented 1953)
Alimentation Equilibré (AEC)	 $C_{18} + C_2$	Patented 1960, 1964
DPI and GlaxoSmithKline	 $C_{16} + C_4$	Patented 1954
BASF	$C_{15} + C_5$ 	Patented 1957
Philips-Duphar	$C_{15} + C_5$ 	Reported 1950–1961[28]
Sumitomo	$C_{15} + C_5$ 	1962 (patented 1964)[43]
Rhône-Poulenc	 $C_{15} + C_5$	1974 (patented 1971)
Kuraray	$C_{10} + C_{10}$ 	Reported 1986

of the market, and BASF were heavily penalised for their parts in instigating and managing the various cartels. The vitamin A cartel was operational for almost 10 years, starting in 1989.

The high technological barriers to beginning bulk vitamin A production prevented many smaller companies operating. Intermediates such as pseudoionone were not readily available on the market, and thus required synthesis from raw materials. The global vitamin market parallel the boom years of the pharmaceutical industry during the late 20th century. The synthetic pioneers of the vitamin industry still dominated global production well into the 1990s. The cartel of Roche, BASF and Rhône-Poulenc controlled 96% of global vitamin A sales during 1989–1999 whilst the remaining 4% was made up of Chinese, Russian and Indian manufacturers.[59] Roche concluded the sale of its vitamins division to DSM in 2003.

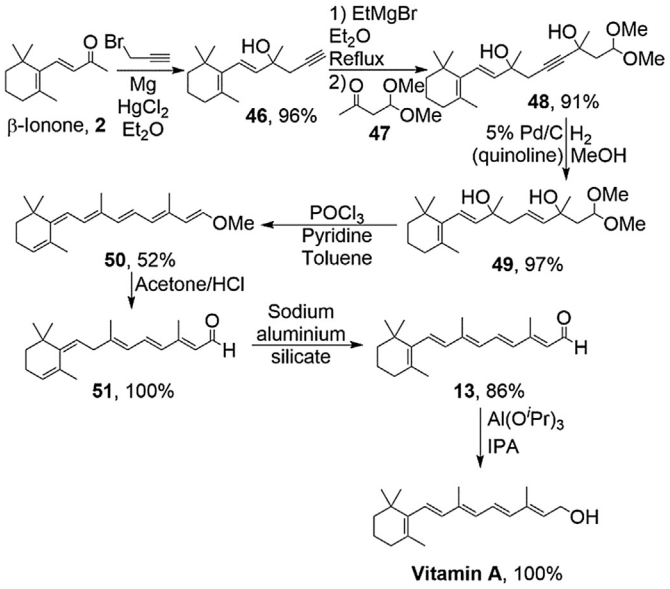
Vitamin A is synthesised for addition into animal feeds, fortified foods, animal products such as meat, poultry, fish, eggs and milk, vitamin supplements and cosmetics. The price-fixing cartel resulted in the over-charging of customers for these products; the world market for vitamin A comprised 87% animal feeds, 6% food and 7% pharmaceuticals from 1987–1998.[59]

10. Conclusions

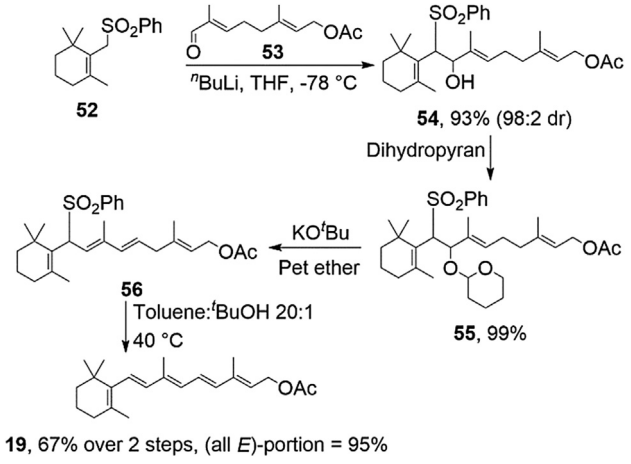
Vitamin A is a lipid-soluble diterpene essential for vision and other biological roles, and vitamin A deficiency is responsible for much mortality and blindness in children in developing countries.

DSM and BASF are the main producers of vitamin A, with smaller amounts manufactured by Chinese companies such as Kingdomway.[43] Whilst the market is still dominated by a small number of large companies, the price of vitamin A is likely to remain stable. However, the increasing cost of raw materials derived from crude oil, such as acetylene and acetone, is likely to have a knock-on effect on the price of vitamin A, whilst demand from developing countries and for animal feed fortification rises. Alternatives to synthesis for use in human nutrition include the over-expression of vitamins in plants, such as the genetic modification of rice to enable biosynthesis of the vitamin A precursor, β-carotene, as part of the 'golden rice' project.[60]

Both DSM and BASF are believed to use syntheses closely related to those described earlier, but with slight modifications made through the adoption of new technology and techniques. Whilst much has changed since 1979, Isler's statement that 'each of the



Scheme 12. DPI synthesis of retinal.



Scheme 13. Kuraray synthesis of vitamin A acetate.

known manufacturing procedures leaves something to be desired' still holds true.

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