INDUSTRIAL SYNTHESIS OF TERPENE COMPOUNDS*

H. POMMER and A. NÜRRENBACH

BASF AG, 6700 Ludwigshafen, GFR

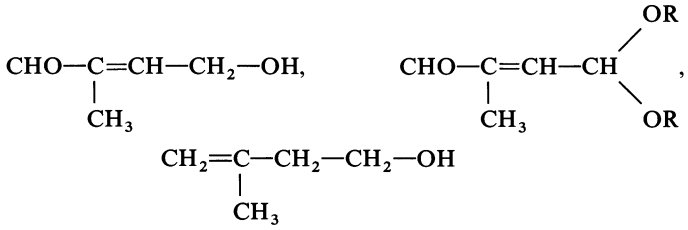
ABSTRACT

The translation of new organic syntheses carried out on a laboratory scale into plant practice is a problem which is as old as industrial chemistry itself. The worldwide growth of chemistry necessitates today the production of, *inter alia*, compounds of complex structure on a scale which has hitherto been reserved for commercial syntheses. This has placed great demands on the chemist working in industry. The chemist's own knowledge of other scientific disciplines and his working together with physicists and engineers as a team are essential pre-requisites for economic success.

The problems arising in connection with the scaling up of new reactions into chemical processes, say, for the production of 1000 tons/year of a vitamin will be described in more detail, referring to a few examples which, for the sake of simplicity, will be restricted to problems in terpene chemistry.

The reaction discovered by Wittig in the 'fifties and named after him, namely the introduction of a double bond using phosphoranes, will be explained with reference to the syntheses of vitamin A, carotenoids and terpenes. With the aid of a flow sheet it will be shown how the problems occurring in the translation of these strongly exothermic reactions into industrial processes can be solved without taking risks, how triphenylphosphine which is required for the Wittig reaction can be safely produced on a commercial scale from phosphorus trichloride, sodium and chlorobenzene and how the triphenylphosphine oxide formed in the Wittig reaction can be reconverted into triphenylphosphine.

It is possible with these basic reactions which can be mastered industrially, the reduction of triphenylphosphine oxide to triphenylphosphine being of great economic importance, to develop from suitable building blocks, mainly C_5 compounds having functional groups, such as



or from methyl heptenone a large number of hitherto difficultly accessible

* Owing to the indisposition of Professor Pommer, this lecture was delivered by Dr Nürrenbach.

terpenoids, such as heptaminol, hydroxycitronellal, citral, menthol, pear ester, lavandulol, juvenile hormone, sinensal, ionones and irones. Examples of the industrial synthesis of methylheptenone from acetone, formaldehyde and isobutylene and of isoprene will also be given.

INTRODUCTION

To discuss the problems encountered in the industrial synthesis of terpenes, I have selected examples from one of BASF's new activities. I shall outline the technical synthesis of methyl heptenone which uses simple, generally accessible chemicals, such as isobutylene, acetone and formaldehyde. I shall also describe the conversion of this intermediate into more sophisticated products, some of which are indicated in *Figure 1.*

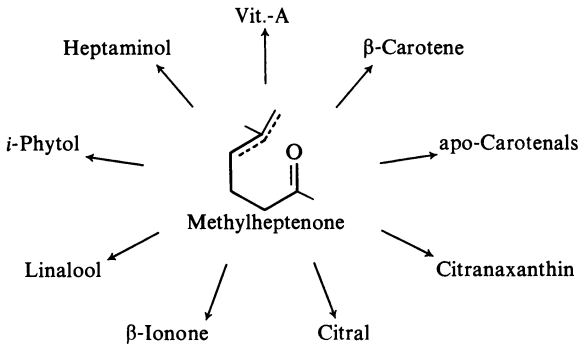


Figure 1

The demand for these types of natural substances amounts to thousands of tons a year in some cases. Industry is therefore faced with the task of developing processes which enable the required amounts to be produced at competitive costs and in a consistent quality. For this it is necessary to tread new paths of industrial synthesis and take advantage of the great advances which have been made in process engineering and process chemistry as the result of the expansion in petrochemistry, e.g. to develop continuous fully automated processes. Evolving such processes initially in the laboratory, then in a pilot plant and finally scaling them up to the desired industrial level, is one of the most attractive tasks for somebody engaged in research.

It takes five to ten years before this can be achieved and during this time a chemist has to endure failures, recognize false trails and, if necessary, make a new start. He must possess the virtue of being able to wait for success. He must be capable of cooperating with colleagues from other scientific disciplines, such as physicists, mathematicians and engineers, and last but not least with businessmen.

After these introductory remarks I would now like to describe some such developments. I have already mentioned that many years are needed before a new process can be realized commercially. It will not surprise you therefore if I cannot offer you much that is new in the way of pure chemistry. My

subject simply does not allow me to deal with the latest laboratory work and my main objective is to give you a picture of the development of a recent activity in industry.

If you are confronted with the task of producing terpenoid or, specifically, isoprenoid compounds, the question immediately arises as to how big the individual building blocks are going to be. Today more than ever before, you will want to know which starting materials are readily accessible and how expensive they are. A further question will be the linking of these building blocks to the required product, in other words to find out which reaction is most suitable and, later, industrially feasible. If the building blocks are too small, large molecules have to be built up via many stages, and this raises great problems regarding yield, purity and, later in the commercial realization, capital expenditure. If the building blocks are too large, flexibility is lost. The C_5 unit seemed to us to be the optimum building block. Nature too uses the C_5 unit for building up a large number of compounds—adaptation to the variety of natural compounds should not therefore be difficult. The build-up can then be achieved in sufficiently large steps so that the end product can be obtained in relatively few reaction stages.

There may, however, be other ways of producing the basic portion of the molecule, especially if specific efficient steps lead to it. As an example I would like to discuss the synthesis of methyl heptenone. This compound used to be produced by the circuitous route of reacting acetone with acetylene to give methyl butynol, hydrogenating to methyl butenol and chain lengthening with ethyl acetoacetate according to Carroll. Each of the three stages means a separate plant, a separate process, losses, purification—in brief—a relatively expensive synthesis.

Therefore, to simplify matters, an elegant one-stage synthesis of this C_8 unit has been developed in the last few years at BASF from simple petrochemical raw materials and scaled up for commercial operation:

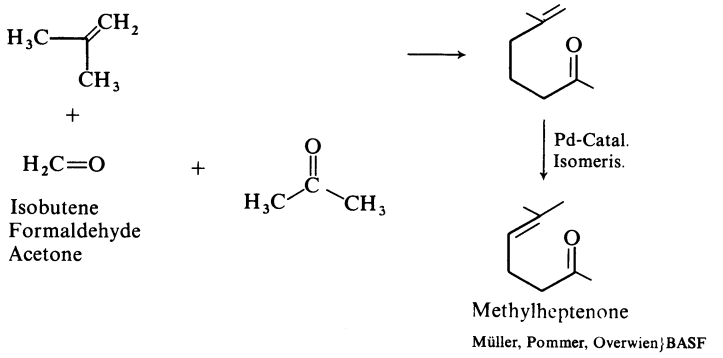


Figure 2

Methyl heptenone can be produced from isobutene, formaldehyde and acetone in a single step. The double bond in this compound is shifted as compared with that of the natural substance, although this has its advantages

later on. Methyl heptenone as it occurs naturally can be easily obtained by isomerization with a noble metal catalyst.

The reaction of acetone, isobutene and formaldehyde to form methyl heptenone is carried out at about 200–300°C and some hundred bars. It is surprising that methyl heptenone is obtained in a commercially attractive yield by means of this reaction because at these temperatures and pressures the three reactants may react not only with each other but also with themselves to form a great variety of varied chemical compounds:

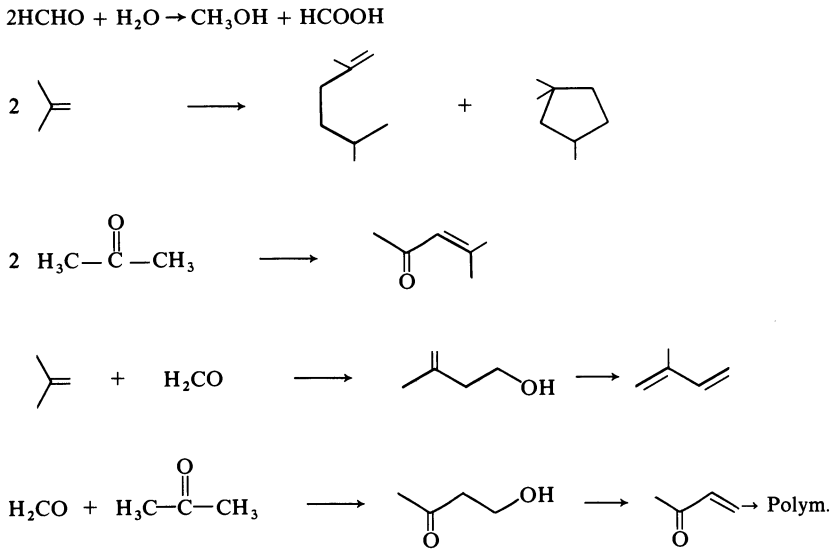


Figure 3

For example, formaldehyde is subject to the Cannizzaro reaction, and isobutene may react with itself to form dimethylhexene and trimethylcyclopentane. Under the conditions acetone affords mesityl oxide. Other reactions include the formation of 3-methylbuten-3-ol-1, which is easily dehydrated to isoprene. Formaldehyde can react with the acetone to form ketobutanol which in its turn can easily form methylvinylketone. Suitable reaction control can substantially suppress these reactions in favour of the production of methyl heptenone. Details of the industrial synthesis are shown in the flow sheet (*Figure 4*).

The three components isobutene, acetone and aqueous formaldehyde solution are separately brought to the required temperature in preheaters and then pumped into the high pressure reactor proper. Excess isobutene and acetone are distilled off through pressure columns and recycled to the reaction, while the reaction product is distilled through several columns.

It was naturally a great advantage in the development of the methyl heptenone synthesis for us at BASF to be able to fall back on our extensive experience in high pressure chemistry. There were therefore a considerable

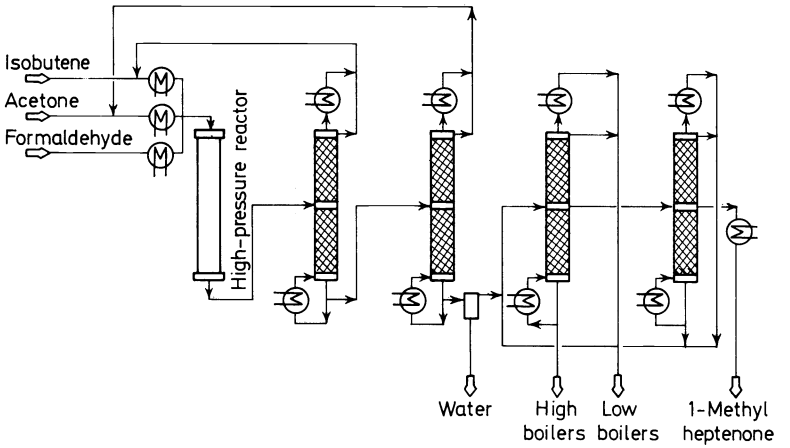


Figure 4. Industrial synthesis of methyl heptenone

number of spin-offs from the work on this compound. As I have already mentioned, one of the byproducts which occurred was 3-methylbuten-3-ol-1 or isoprenol. If isobutene is allowed to react with formaldehyde under the conditions of the methyl heptenone synthesis, isoprenol is obtained in excellent yield. In combination with a specially developed water-eliminating process, we believe that this is the best way of synthesizing isoprene. The actual process is carried out as follows (*Figures 5* and *6*).

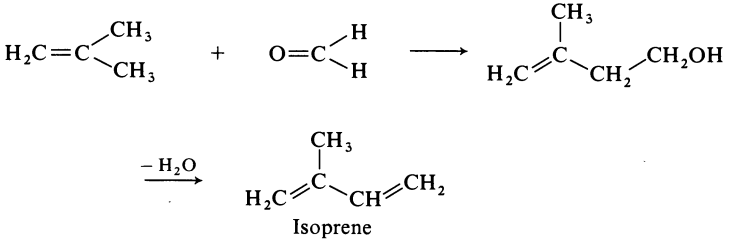


Figure 5

Excess isobutene is reacted with an aqueous formaldehyde solution continuously in a reactor at about 200–300°C and elevated pressure. After the reactor discharge has been cooled, it is freed of isobutene in a separating stage. In a second rectification stage the product is separated from water and byproducts, and fed to a vessel as distillate. After the addition of a catalyst solution the continuous elimination of water takes place here to form isoprene which is obtained through a column in an extremely pure form and advantageously fed straight to the polymerization reaction.

With this example I wanted to show how often new reactions not only lead to the desired compounds but also fertilize other fields of activity. Starting from isobutene, a link was established here between isoprene—a

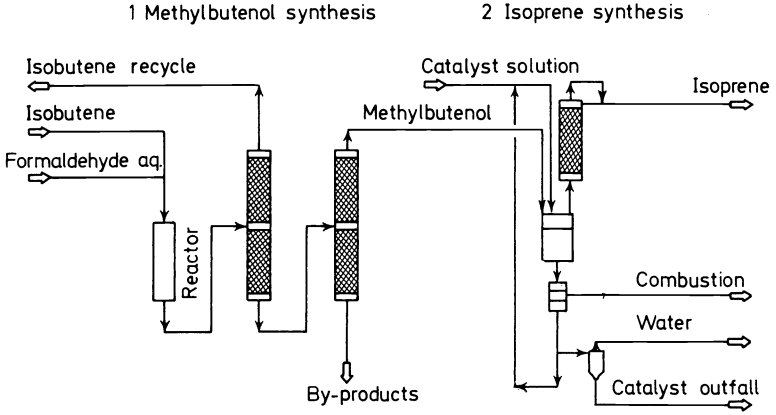


Figure 6. Isoprene synthesis

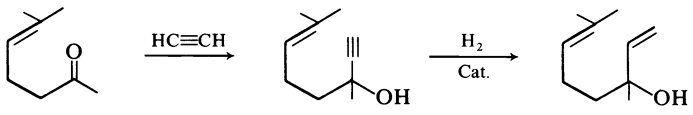
bulk plastics intermediate—and the naturally occurring intermediate methyl heptenone. The latter is a basic product for building up a range of highly sophisticated products.

With the synthesis of methyl heptenone we have built up eight carbon atoms of the desired 'double isoprene unit' with ten carbon atoms. Since our initial postulate was that a C_5 building block is the optimum one for a flexible build-up of higher isoprenoid compounds, we must add two more carbon atoms. Let me therefore go into the three standard linking reactions used for the processes which are the subject of this lecture in somewhat more detail.

REACTION OF CARBONYL COMPOUNDS WITH ACETYLENE

(I) C_2 units are added by reacting carbonyl compounds, generally ketones, with acetylene, followed if necessary by partial hydrogenation of the triple bond to the double bond.

Δ^2-Series:



Methyl heptenone Dehydrolinalool Linalool

Δ^1-Series:

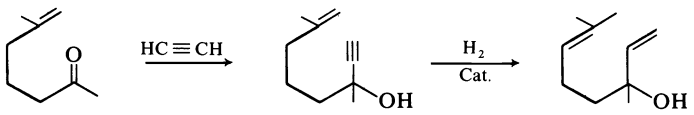


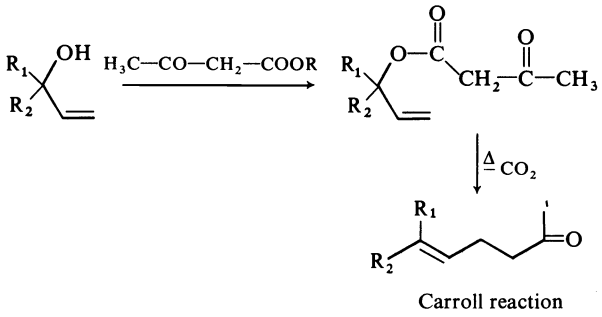
Figure 7

When we apply this to our methyl heptenone we obtain Δ^1- or Δ^2-dehydrolinalool and, after partial hydrogenation, Δ^1- or Δ^2-linalool both of which are high-grade perfumes. Several thousand tons of linalool are manufactured each year.

I do not want to go into details of the industrial ethynylation reaction. It requires a lot of know-how, which was and is available at BASF as the result of decades of experience with industrial acetylene pressure reactions. The same applies to the partial hydrogenation of the triple bond to the double bond on an industrial scale.

THE CARROLL REACTION

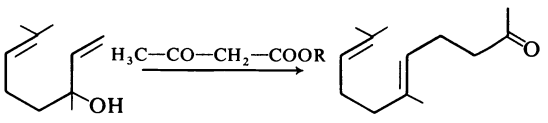
(II) C_3 units are added by the thermal reaction of tertiary propargylic or allylic alcohols with ethyl acetoacetate, a reaction known by the name of its discoverer Carroll. The reaction yields ketones (*Figure 8*). Lack of time prevents me from going into details of the industrial process, which presents no difficulties. The synthesis of geranyl acetone and pseudoionone is illustrated briefly in *Figures 9* and *10* by way of example.



Carroll reaction

Figure 8

Δ^2-Series:



Linalool — Geranyl acetone

Δ^1-Series:

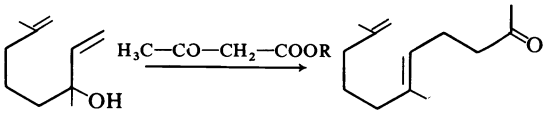


Figure 9

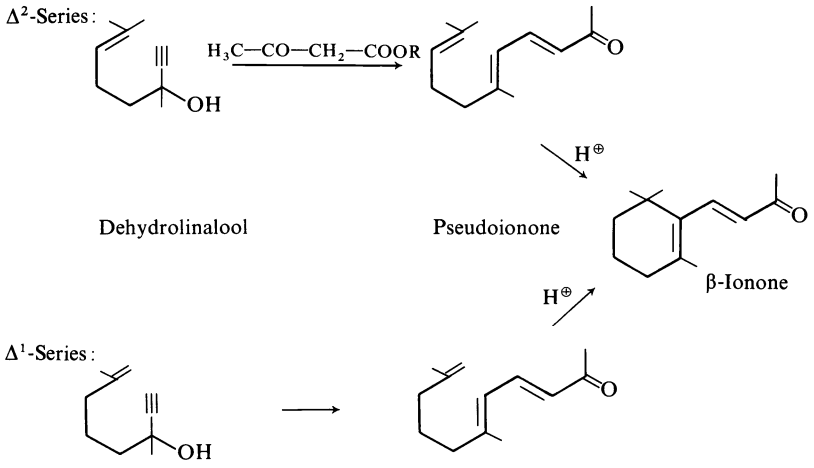


Figure 10

It should be mentioned that the Carroll reaction produces substantially better yields with Δ^1-dehydrolinalool than with Δ^2-dehydrolinalool. The cyclization of the isomeric pseudoionone to the β-ionone, which is of importance for any vitamin A or carotene synthesis, poses no technical problems giving yields of over 80 per cent.

THE WITTIG REACTION

(III) We use the so-called Wittig reaction for linking the isoprene units. This reaction, which was discovered by Wittig and Geisler at the beginning of the 'fifties, has since become indispensable to chemistry. Easy as it is to handle in the laboratory, it was most difficult to translate into plant practice especially because of the stringent criteria of safety, economics and the availability of the starting material triphenylphosphine on a 1000 ton scale.

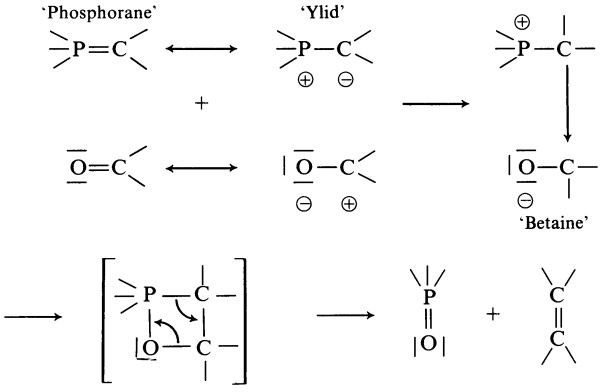


Figure 11

There is traditionally a close contact between the German universities and the chemical industry and Professor Wittig had been discussing his new reaction with BASF long before the publication of his work in this field. At the time we were engaged in the development of industrial vitamin A and β-carotene syntheses and very quickly realized the significance of the Wittig reaction for the synthesis of this type of compound.

It is therefore understandable that, in agreement with Professor Wittig, we began work with the object of scaling up the Wittig reaction specifically for carotenoid syntheses. When we succeeded in replacing the original organo-lithium compounds by other proton acceptors, for example metal alcoholates, we had made a big step forward towards commercial realization. We also found a series of industrially utilizable solvents for the new reaction, such as methanol or dimethylformamide. The control of the exothermic reaction proved relatively difficult. Even when carefully contrived safety measures are observed, a Wittig reaction with sensitive compounds is still critical to carry out in a reactor. We then found an industrial solution by choosing a continuous process which proceeds adiabatically.

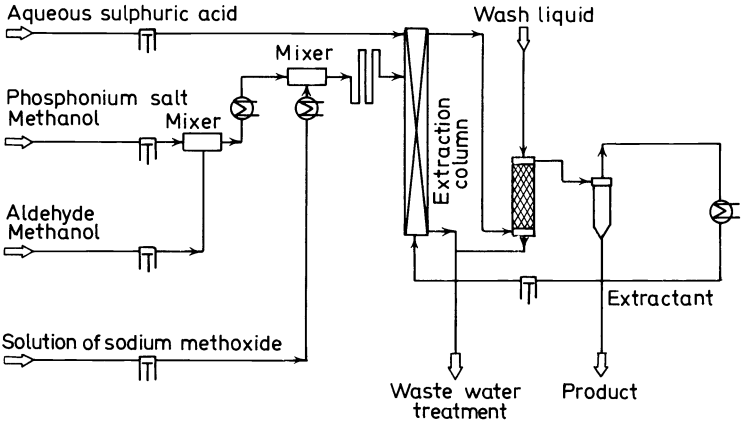


Figure 12. Continuous Wittig synthesis

Figure 12 shows the diagram of a commercial plant for the Wittig reaction of the type existing at BASF in Ludwigshafen which is used, for example, for the production of vitamin A and other carotenoids.

The solution of the triphenyl phosphonium salt in methanol is mixed continuously in a reactor with a methanolic solution of the carbonyl compound to be used and the mixture is cooled down to −30°C in a precooler. At the same time a solution of a proton acceptor is cooled in another precooler and the two solutions are supplied by means of appropriately cooled metering pumps to a nozzle where they react. Normally the reaction starts straightaway and is over after a very short period of time. The temperature rises but is kept below the decomposition point of the phosphorane by an adiabatic heat control. The mixture of reaction product and triphenylphosphine oxide —the mixture is gel-like due to the salt formed—is fed to an extractive

column where the desired reaction product, after having been acidified with sulphuric acid, is extracted with hydrocarbons in a countercurrent flow. The hydrocarbon extract is continuously scrubbed in a second column with aqueous alcohol to remove the last remaining traces of triphenylphosphine oxide. After the extract has been evaporated in a falling-film evaporator under mild conditions, the desired product is obtained. The distillate is returned to the extraction cycle.

In this process the Wittig reaction was used for the first time in industry, at BASF, for linking isoprenoid building blocks. The most representative, vitamin A, is manufactured on a scale of many hundreds of tons a year. However, before it could be utilized industrially, many obstacles had to be overcome.

One of the biggest problems arose from the fact that triphenylphosphine was required, a chemical which was not industrially available at that time. Admittedly, the substance was used in small quantities in 'Reppe chemistry' as a ligand of complex metal carbonyl catalysts, that is to say it was available in small amounts, but the overriding question was whether it could be successfully manufactured on a commercial scale so economically that its use in tons could be envisaged. This auxiliary is after all used in molar amounts in the linking reaction and leaves the reaction as triphenylphosphine oxide. Although the synthesis of the product from phosphorus trichloride, chlorobenzene and metallic sodium had been known for a long time, its scale-up to a commercial process presented an extremely difficult engineering problem. It is evident from the equation that, in the event of disturbances, a large batch is like a time bomb. Consequently, considerable thought and attention had to be paid to safety matters in view of the large amounts of triphenylphosphine involved.

$$3C_6H_5Cl + 6Na + PCl_3$$

$$\rightarrow (C_6H_5)_3P + 6NaCl$$

$$\Delta H \approx -460 \text{ kcal}$$

Figure 13

In the first stage of development triphenylphosphine was manufactured batchwise in stirred vessels. Metallic sodium in 200 kg lots was suspended in an inert solvent such as toluene. The reaction was then carried out at a temperature of 40 to 70°C with cooling by adding phosphorus trichloride and chlorobenzene, the addition thereof being controlled by the temperature. After separation of the precipitated sodium chloride in a centrifuge, the solvent was evaporated and the crude triphenylphosphine isolated. Of course the whole reaction had to be carried out under an inert gas atmosphere. Although we were producing hundreds of tons of product by this process, enlargement of the plant appeared to us to be too big a safety risk. Based on our experience with the batch method we therefore built a larger plant employing a continuous process a few years ago. The critical phase of the reaction—the reaction of metallic sodium with phosphorus trichloride and chlorobenzene—could thus be restricted to a small, readily controllable

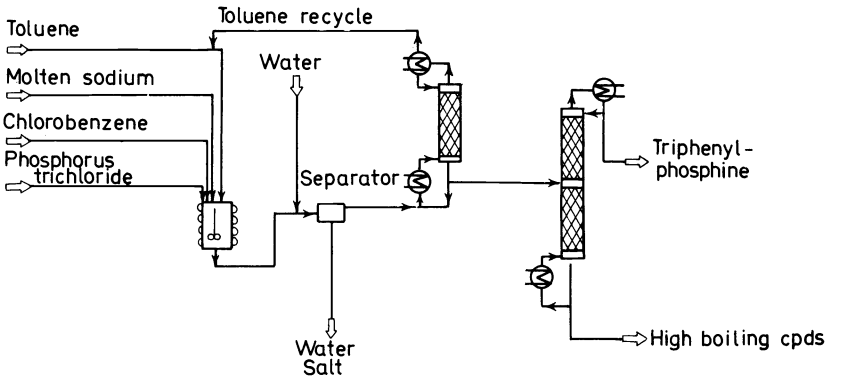


Figure 14. Synthesis of triphenylphosphine

reaction volume. The plant has been in operation for several years and is, as far as we know, the only plant at the present time which manufactures triphenylphosphine by this process.

I have made this little excursion to show you the kind of secondary problems that have arisen as a result of the decision being made to carry out the Wittig reaction on an industrial scale. The chemistry of this reaction has been known for almost a century through the work of Michaelis *et al.* Pre-requisites for enabling the substance triphenylphosphine to be used in industry were the need for it—in the Wittig reaction—and sophisticated process modifications and safety precautions. Today we can look back upon about ten years of experience in the production of triphenylphosphine and see our hopes regarding the reliability of the process confirmed.

In this connection I would like to mention another problem. As is well known, in the Wittig reaction triphenylphosphine oxide is formed as a byproduct in equimolar amounts. What can be done with this product? It does not have a large market. The only thing that can be done is to burn it. However, it is a shame to see such a highly refined substance being processed into ordinary phosphoric acid.

A number of ways of regenerating the phosphine from its oxide were known from the literature at the time. However, all of these methods have the following in common:

(i) The cost of the reducing agents, which leave the reaction as useless byproducts or byproducts that are difficult to purify, is too high.
(ii) The way in which the reaction has to be conducted is difficult and sometimes dangerous.
(iii) The yields of triphenylphosphine are low and consequently the economics are poor.

This was the situation we were facing when we started our work in this field. We were looking for a process in which the formation of useful byproducts compensated for any loss of triphenylphosphine. Since, as has been pointed out above, triphenylphosphine is produced from phosphorus trichloride, chlorobenzene and sodium, the desired byproduct was phosphorus trichloride. The question was how to arrive at this product. We converted

triphenylphosphine oxide, using a method which had been patented by BASF a few years before, to triphenylphosphine dichloride in which the phosphorus is also present in the pentavalent oxidation state. The desired products, namely triphenylphosphine and phosphorus trichloride, both contain phosphorus in the trivalent state. It ought therefore to be possible to arrive at trivalent phosphorus by symproportionation of pentavalent phosphorus with zerovalent phosphorus.

Triphenylphosphine dichloride does in fact behave appropriately in the presence of elementary phosphorus.

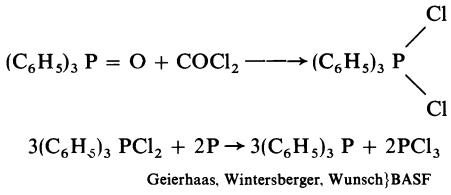


Figure 15

The new process therefore comprises two stages. In the first stage triphenylphosphine oxide is reacted with phosgene to form triphenylphosphine dichloride and in the second stage the triphenylphosphine dichloride obtained is reduced with phosphorus.

Triphenylphosphine oxide can be chlorinated with phosgene directly in the melt as well as in polar inert solvents such as chlorinated hydrocarbons. Triphenylphosphine dichloride is a colourless, hygroscopic crystal powder. It exhibits a number of interesting reactions, a few of which I would like to present to you.

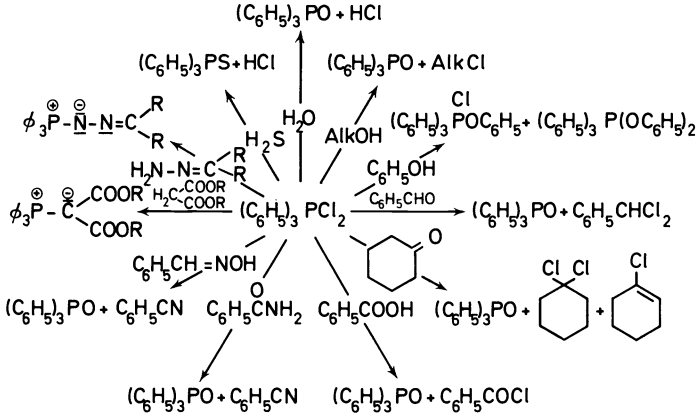


Figure 16. Key compounds obtained from triphenylphosphine dichloride.

Both the red and white forms of phosphorus are suitable for the reaction, if different temperatures are applied. The phosphorus trichloride which

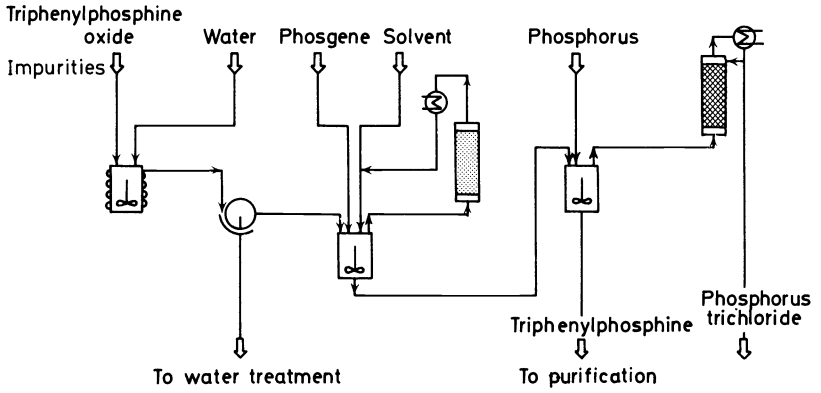


Figure 17. Recovery of triphenylphosphine from triphenylphosphine oxide

forms is continuously distilled off from the mixture, so that it cannot initiate any side reactions.

We thus have at our disposal an industrial process employing the new Wittig reaction which, so to speak, serves as a cement for bonding together the isoprene building blocks discussed earlier.

For the industrial synthesis of vitamin A operated by us we start from a C_{15} building block which we link to a C_5 building block with the aid of the Wittig reaction. The now well-known reaction scheme is shown in *Figure 18.*

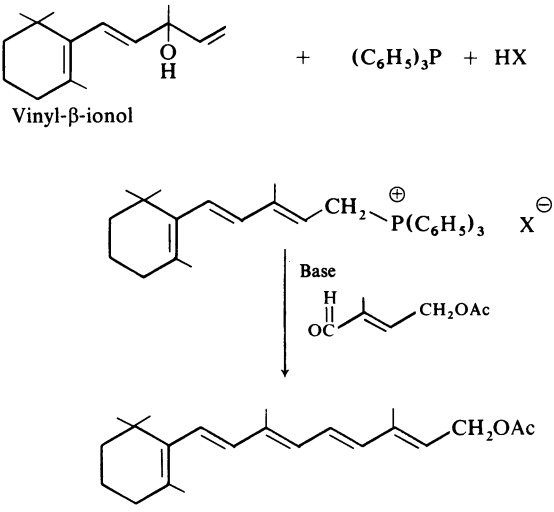
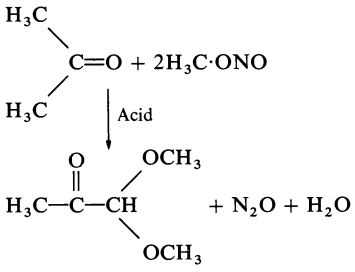


Figure 18. Vitamin A acetate

It is now time for me to say a few words about the industrial synthesis of C_5 building blocks. The C_3 compound methylglyoxal dimethylacetal, for

which we developed a commercial process starting from acetone, turned out to be a key compound for gaining access to this series.

Whereas oxidations are usually carried out industrially with oxidizing agents such as air, oxygen and nitric acid or chromium compounds, in this case none of these oxidizing agents attacked the acetone in the desired manner. Only the reaction with nitrogen–oxygen compounds was successful. The gross reaction is the sum of various individual reactions and can be represented as follows:



Pasedach, Maschke}BASF

Figure 19

To carry out the reaction on a commercial scale, acetone, methanol and nitrosating agent are supplied continuously to a reactor. The N_2O formed

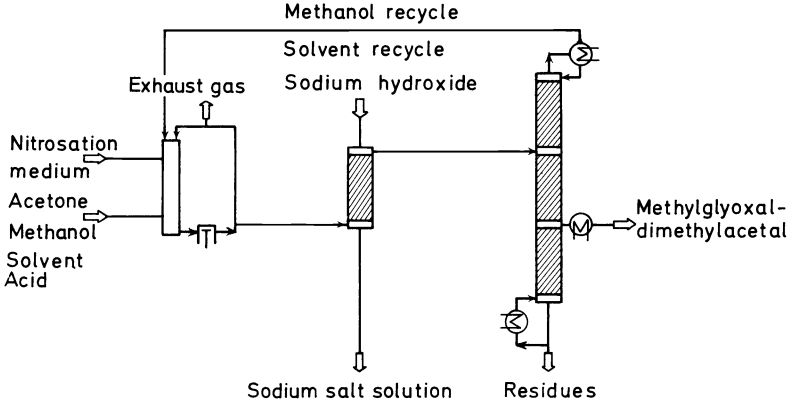
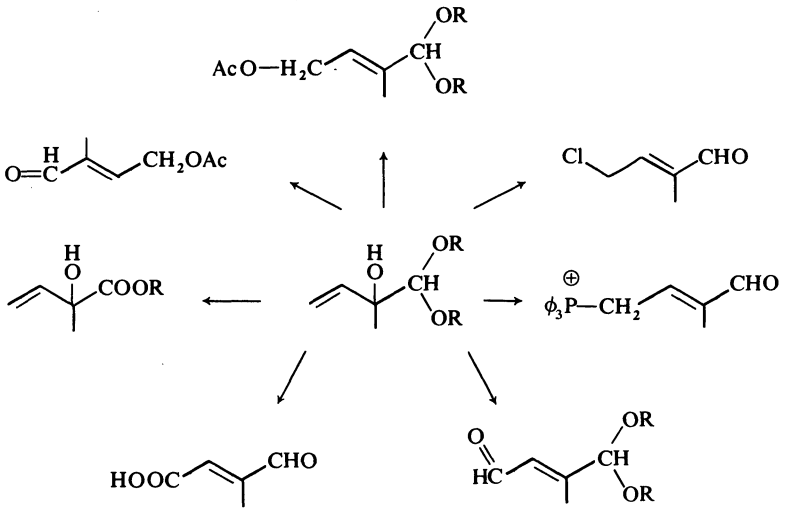


Figure 20. Synthesis of methylglyoxal dimethylacetal

in the reaction escapes as exhaust gas and is destroyed. The reactor discharge passes through a scrubber where the acid portions are removed with dilute aqueous caustic solution. Distillation yields pure methylglyoxal dimethylacetal. Numerous problems connected with corrosion, the formation of deposits and safety matters had to be solved before the plant could operate in the form shown above. This highly reactive and interesting compound thus became industrially accessible for the first time. I will not deal with the numerous syntheses employing methylglyoxal acetal as starting material

which are also of industrial interest but will restrict myself to the industrial synthesis of C_5 building blocks with the aid of methylglyoxal acetal.

By simple ethynylation with acetylene and subsequent partial hydrogenation one of the basic types of the C_5 building blocks sought by us is obtained, namely the vinyl acetal, which, for simplicity's sake, I will refer to as C_5 alcohol. As you can see in *Figure 21*, starting from this compound a number



Freyschlag, Grafen, Nürrenbach, Paust, Pommer, Reif}BASF

Figure 21

of different C_5 building blocks are accessible which merely differ from one another in the functional groups or in the position of the functional groups. There can be no doubt that these are key compounds which provide access—by formal analogy to nature—to a large number of isoprenoid compounds. The β-formylcrotyl acetate required for the industrial synthesis of vitamin A is readily accessible from C_5 alcohol. Let me therefore explain the industrial synthesis of this compound in more detail before I pass on to other C_5 building blocks. As *Figure 22* shows, β-formylcrotyl acetate, which we call C_5 acetate for short, can be obtained easily by acetylation of C_5 alcohol and copper-catalysed allylic rearrangement. *Figure 23* shows how the process has been realized commercially.

C_5 alcohol is acetylated in a reactor with acetic anhydride while simultaneously removing the acetic acid formed. The reaction product is purified by distillation and subjected, with heating, to allylic rearrangement in the presence of a copper catalyst. After hydrolytic cleavage of the acetal group the product is separated into an aqueous and an organic phase. The latter is supplied to a column and pure β-formylcrotyl acetate is isolated as a side-stream.

It is clear that we have tried again and again to manufacture a key

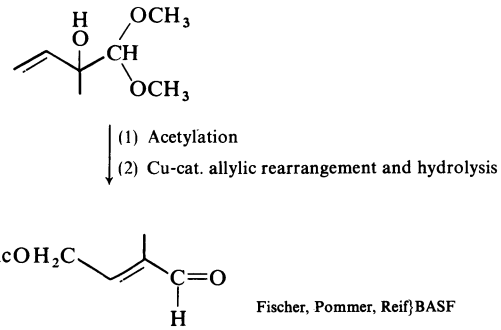


Figure 22

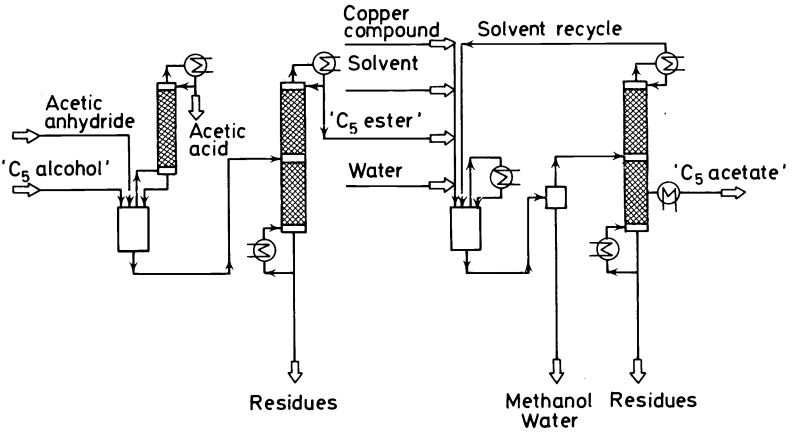


Figure 23. Synthesis of β-formylcrotyl acetate (C_5 acetate)

compound of such industrial importance as β-formylcrotyl acetate by different and simpler methods. I would like to take this opportunity to disclose our latest development to you and hope that this example will show how major fields of activity of a chemical company can benefit one another. A different, original and novel route for manufacturing this compound was devised by a completely different branch, namely high-pressure chemistry. Starting from butynediol—a product which is available in large quantities by Reppe's process, by reaction of acetylene with formaldehyde—butenediol is manufactured by partial hydrogenation. Butenediol, a commercially available product, is used mainly for the production of insecticides, vitamin B_6 and a few pharmaceutical specialities. By analogy to conventional processes, 1-butene-3,4-diol can be obtained by metal-catalysed allylic rearrangement. This compound can, after esterification, be hydroformylated preferentially in the 2-position with a mixture of carbon monoxide and hydrogen if the high-pressure reaction is catalysed with rhodium compounds and not with cobalt salts, as is customary. Since traces of rhodium in the p.p.m. range are satisfactory for the reaction, it is exceptionally attractive from the industrial point of view, see *Figure 24*.

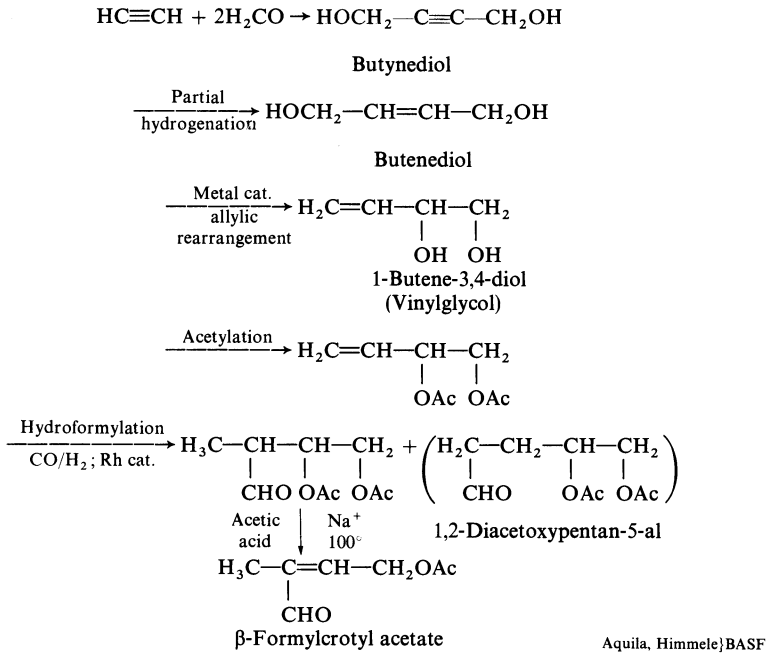


Figure 24

The linear compound 1,2-diacetoxypentan-5-al formed as byproduct is very difficult to separate from the desired compound because of its very similar structure. The boiling points are close together and the mixture is also heat-labile. This problem was solved by the development of a process for selective deacetylation.

When the mixture is treated in the presence of a salt-like catalyst, the selective elimination of acetic acid with the formation of the desired unsaturated compound takes place after heating for a short period. The desired unsaturated compound can be separated easily, for example, by distillation from the diacetoxypentanal which, after hydrogenation and saponification, as a triol, is a useful precursor for lubricants.

In view of BASF's experience in the fields of partial hydrogenation, catalytic allyl rearrangements and particularly hydroformylation at high pressures, expenditure for the development of a commercial process was relatively low.

May I take this opportunity to remind you that one of our commercial-scale syntheses of acetic acid from methanol and carbon monoxide is carried out at a pressure of 700 bars.

The procedure for carrying out the industrial synthesis of this C_5 building block is indicated in *Figure 25*.

In the process, 1-butene-3,4-diol diacetate is mixed with the rhodium catalyst. At high pressure and a temperature of about 100°C the reaction proceeds continuously. After the pressure has been released, the reaction mixture is distilled and continuously deacetylated. Simple distillation is then

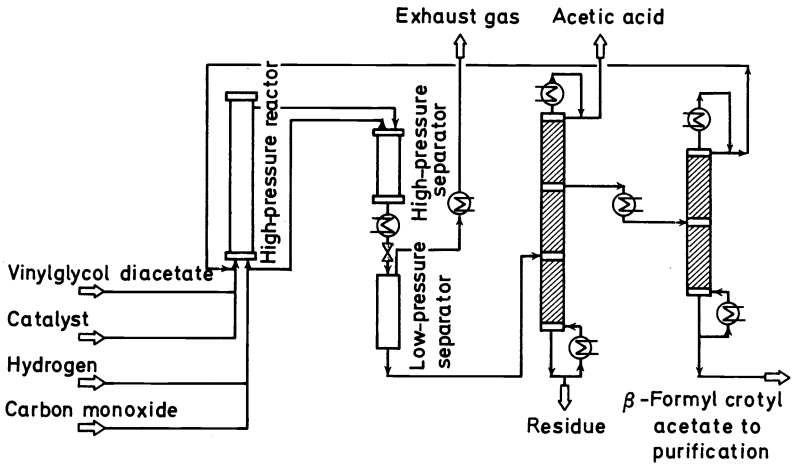
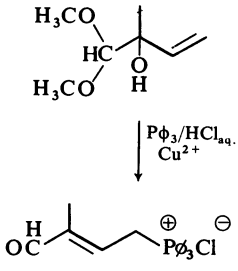


Figure 25. Synthesis of β-formylcrotyl acetate.



Fischer, Pommer, Reif}BASF

Figure 26.

employed to separate the mixture into the linear compound and the desired β-formylcrotyl acetate which may, if necessary, be purified by crystallization.

Starting from butynediol, one of BASF's own products, we have found a novel and economical commercial process for the production of β-formylcrotyl acetate which can also be applied to other compounds.

For building up carotenoids, for example apo-carotenals and citranaxanthin, we need bifunctional C_5 units. One of these compounds can be manufactured in an extremely simple manner by reacting C_5 alcohol with triphenylphosphine and aqueous hydrochloric acid in the presence of catalytic amounts of copper ions (*Figure 26*). This compound is distinguished by two interesting functional groups, both of which are predestined for the Wittig reaction. A compound which we call C_5-ylenal is formed by reaction with proton acceptors. Compounds each having a precisely defined number of isoprene radicals in the molecule can be obtained by reaction with appropriate carbonyl compounds one or more times (*Figure 27*).

A similar effect can be achieved with the aid of the C_5-dialdehyde which can be obtained by allyl rearrangement of C_5 alcohol, followed by an oxida-

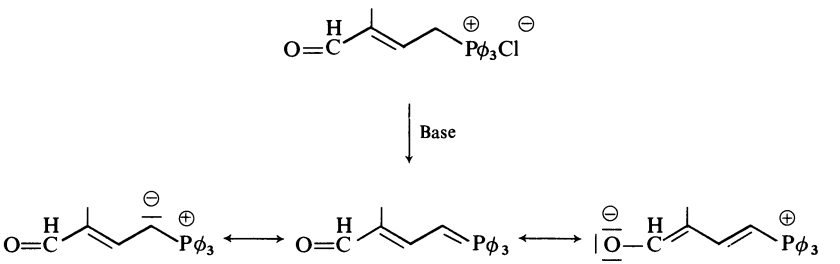


Figure 27

tion step as shown in *Figure 28*. The stepwise reaction of these compounds opens up a convenient route to the apo-carotenal series and citranaxanthin. Citranaxanthin is a carotenoid occurring in citrus fruit which, like β-carotene, is of importance as a food colour. We manufacture it on a commercial scale using the above-described equipment for linking the necessary C_5 building blocks by the Wittig method. The route is shown in *Figure 29*.

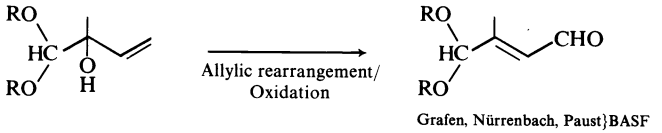


Figure 28

Vitamin A is reacted with triphenylphosphine and a proton donor, for example hydrochloric acid, to form the retinyl phosphonium salt which is then reacted by the Wittig method with the C_5 building block. The resulting β-apo-12′-carotenal (C_{25}) reacts with the above-mentioned C_5-ylenal to form β-apo-8′-carotenal (C_{30}) which is condensed with acetone in a conventional manner to yield citranaxanthin. The analogous reaction with switching round of the functional groups is of course possible. The starting product in this case being the vitamin A aldehyde, as *Figure 30* shows.

Before closing, I would like to describe the synthesis of an important naturally occurring perfume, sinensal. The necessary laboratory work has been completed and scaling-up from this stage to the full-scale plant has started.

Figure 31 shows the structural formula of sinensal which occurs in nature as a mixture of the α and β forms. May I draw your attention to its formal similarity to nerolidol.

By allylic rearrangement of the C_5 alcohol described earlier in the presence of hydrochloric acid β-formylcrotyl chloride is obtained which, after acetalization, is reacted with sodium methyl acetoacetate. The resulting β-ketocarboxylic ester is hydrolysed and decarboxylated (*Figure 32*). Sinensal is then synthesized in a sequence of reactions of the type discussed above, such as vinylations and the Carroll reaction, starting from this C_8 building block (*Figure 33*).

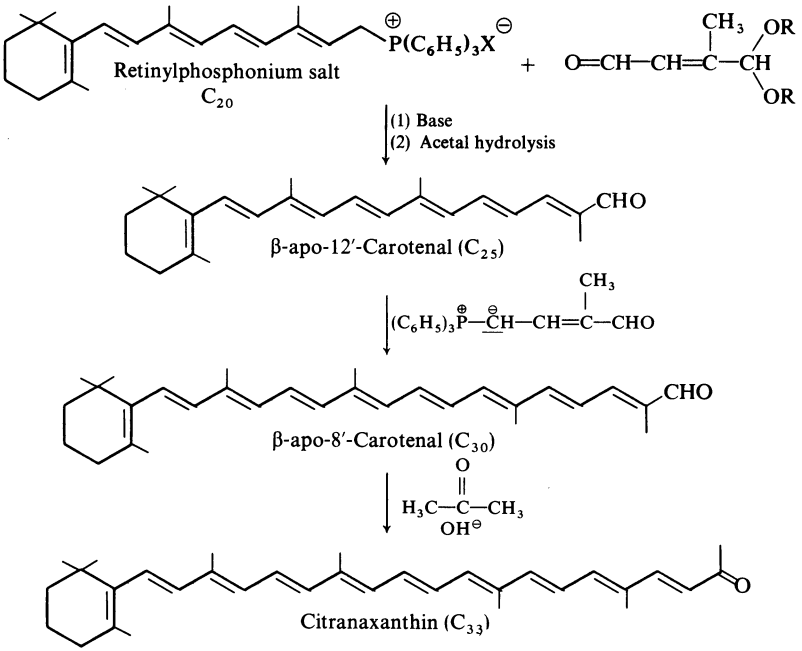


Figure 29.

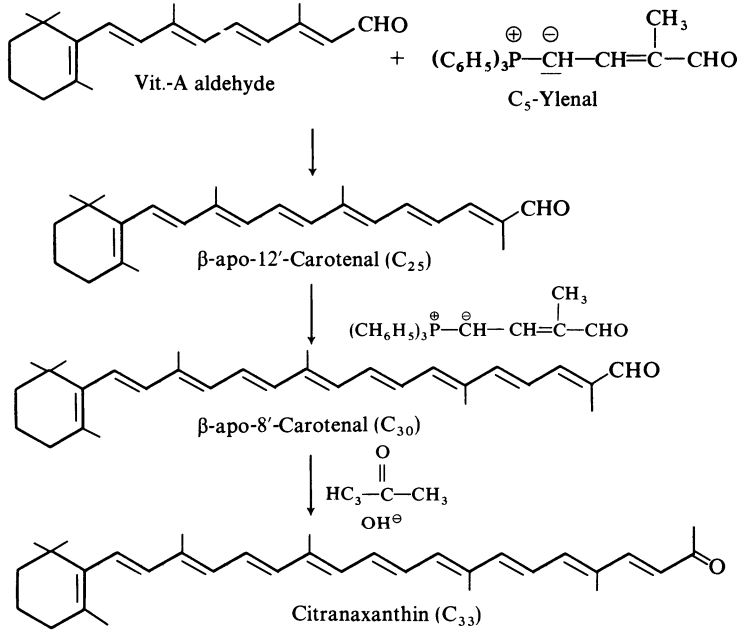


Figure 30.

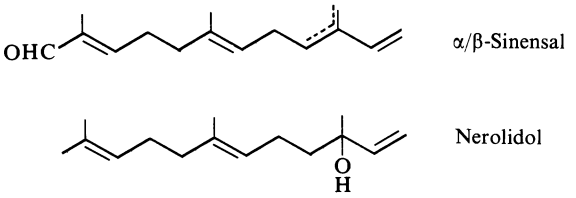


Figure 31

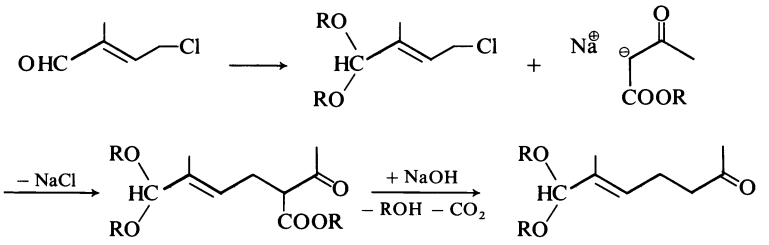


Figure 32

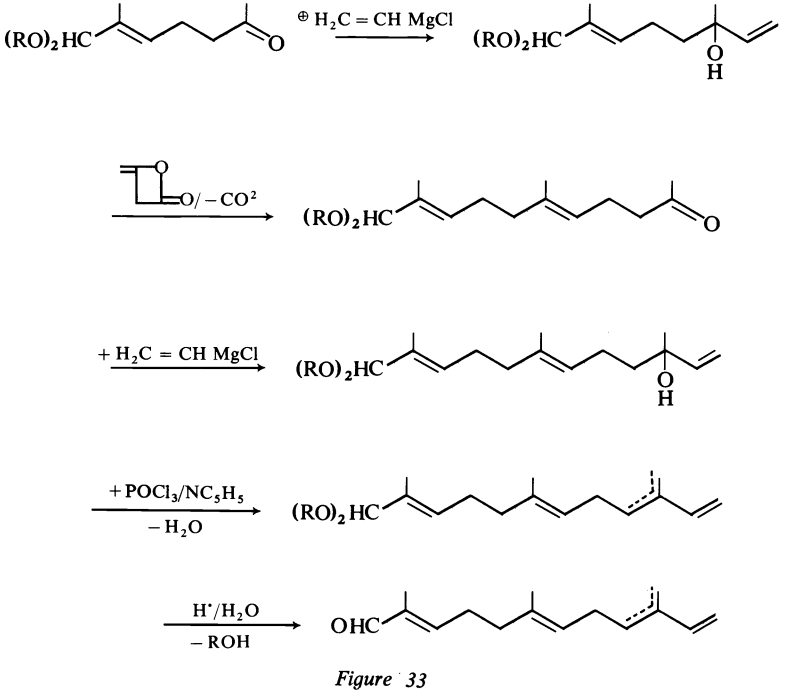
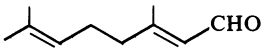
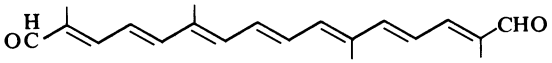
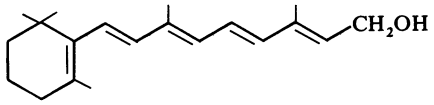
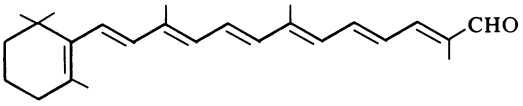
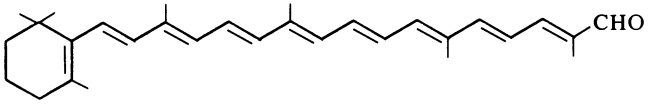
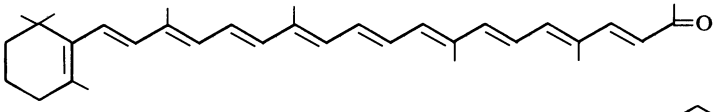
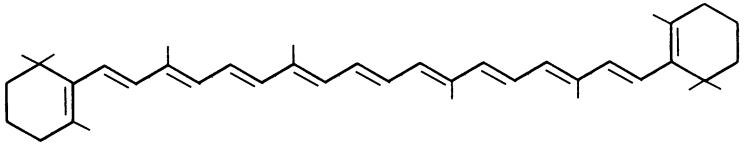
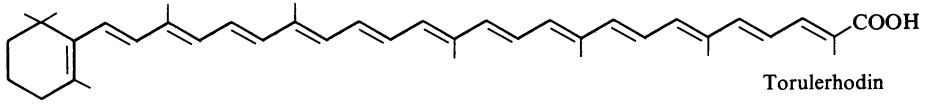
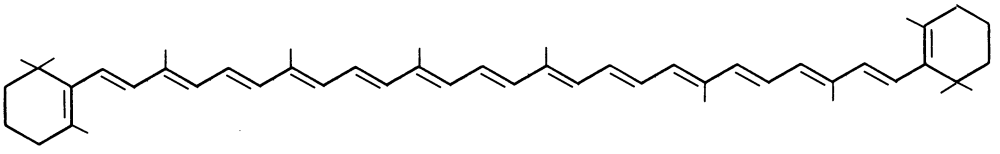
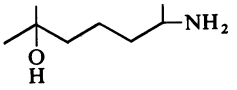


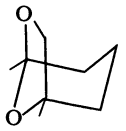
Figure 33

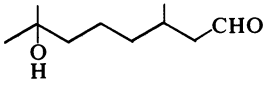
These two examples are intended to illustrate by way of specific products how the combination of the reactions and building blocks presented to you is carried out in practice. *Table 1*, which follows, sets out a list of compounds which we synthesize on a semi-commercial or commercial scale, or whose production is planned.

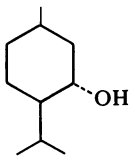
Table 1

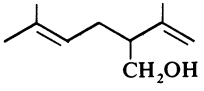
C_{10}		Citral
C_{20}		Crocetinaldehyde
C_{20}		Retinol
C_{25}		β-Apo-12′-carotenal
C_{30}		β-Apo-8′-carotenal
C_{33}		Citranaxanthin
C_{40}		β-Carotene
C_{40}		Torulerhodin
C_{50}		

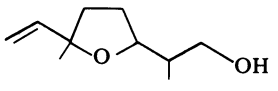
C_8  Heptaminol

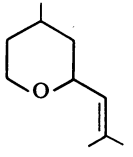
C_8  Frontalin

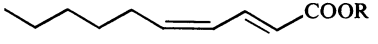
C_{10}  Hydroxycitronellal

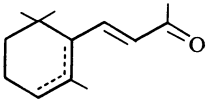
C_{10}  Menthol

C_{10}  Lavandulol

C_{10}  Lilac alcohol

C_{10}  Rose oxide

C_{10}  Pear ester

C_{13}  α/β-Ionone

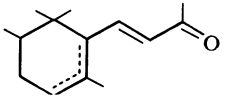
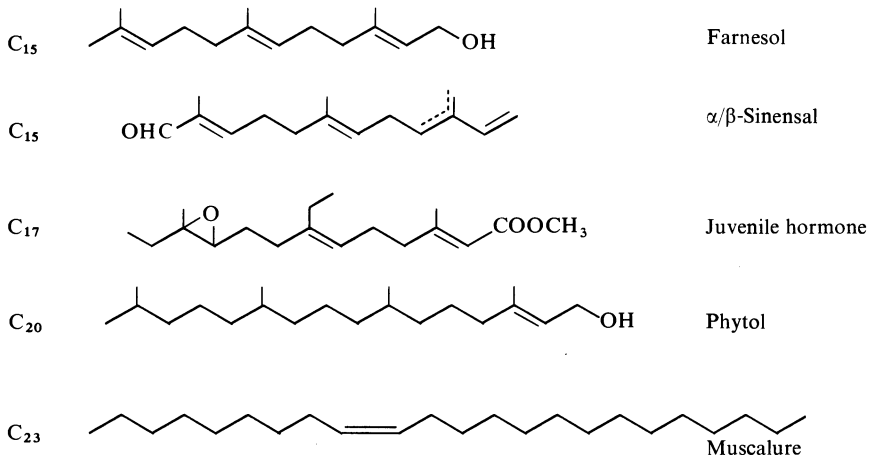
C_{14}  α/β-Irone

Table 1 (contd.)



I cannot discuss the details of this table, but I believe that this survey will give an indication of the variety of compounds which are accessible using the building blocks and reactions described above. I trust that this will show how the persistent investigation of possible uses of new reactions, while paying strict attention to economic aspects, can open up new territory for a company.

Finally I should like to acknowledge those who have collaborated on this work which I have described:

Chemists

Aquila, Bittler, R. Fischer, Fliege, Freyschlag, Geierhaas, Grafen, Grassner, Himmele, Hoffmann, Köhl, Maschke, H. Müller, Nürrenback, Overwien, Pasedach, Paust, Reif, Sarnecki, Stübinger, Werner and Wunsch.

Engineers

Burst, Francke, Holder, R. Müller, Rühle, Scheiper, Schliesser, Seid, Vogel and Waibel.

REFERENCES

R. Fischer and H. Pommer, *DBP 1297597* (1967).
H. Freyschlag, A. Nürrenbach, W. Reif and H. Pommer, *Belg. P. 695116* (1967).
H. Freyschlag, W. Reif and H. Pommer, *DBP 1227000* (1965).
H. Freyschlag, W. Reif, A. Nürrenbach and H. Pommer, *DBP 1211616* (1963).
H. Freyschlag, W. Reif, A. Nürrenbach and W. Sarnecki, *DBP 120832* (1963).
W. Himmele and W. Aquila, *DBP 1941632* (1969).
W. Himmele, W. Aquila and R. Prinz, *DBP 1918694* (1969).
W. Hoffmann, *DBP 2108649* (1971).
W. Hoffmann, *DBP 2143991* (1971).
W. Hoffmann, *DBP 2161084* (1971).
W. Hoffmann, H. Pasedach, H. Pommer and W. Reif, *Liebigs Ann. Chem.* **747**, 60 (1971).

A. Maschke and H. Pasedach, *DBP 1252193* (1966).
H. Müller, *DAS 2031921* (1970).
H. Müller and W. Körnig, *DOS 2031900* (1970).
H. Müller, H. Köhl and H. Pommer, *DBP 1267682* (1967).
H. Müller, H. Overwien and H. Pommer, *DBP 1643729* (1967).
H. Müller and A. Stübinger, *DAS 2050095* (1970).
A. Nürrenbach, W. Sarnecki and W. Reif, *DBP 1203264* (1963).
J. Paust and H. Schumacher, *DOS 2225612* (1972).
H. Pommer, *Angew. Chem.* **72**, 811 and 911 (1960).
H. Pommer, H. Müller and H. Overwien, *DBP 1259876* (1966).
H. Pommer, H. Müller, D. Mangold and H. Overwien, *DBP 1643709* (1967).
W. Reif, R. Fischer and H. Pommer, *DBP 1952649* (1969).
W. Reif and H. Grassner, *Chem.-Ing. Tech.* **45**, 646 (1973).
W. Sarnecki, A. Nürrenbach and W. Reif, *DBP 1158505* (1962).
A. Stübinger and H. Müller, *DBP 2007535* (1971).
G. Wunsch, K. Wintersberger and H. Geierhass, *DBP 1247310* (1966).