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THE TECHNICAL SYNTHESES OF CAROTENOIDS

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Abstract—The various technical syntheses of vitamin A and carotenoids employ only a few key reactions for the formation of the carbon–carbon bond, in particular, the Aldol condensation, the Knoevenagel condensation, the Reformatsky reaction, the Wittig condensation, and the addition of acetylides. Specific industrial examples are given, and the advantages and disadvantages of a particular reaction type are discussed. In the evaluation of a reaction the industrial point of view is emphasized.

Carbon–carbon bond formation using sulfones is discussed in a similar manner although this reaction has so far not found an application in an industrial process.

INTRODUCTION

It is by now well established that the natural pigments belonging to the class of carotenoids are amongst the most important ones responsible for many tantalizing colours in fruits, vegetables, mushrooms, fish, crustaceae, poultry, eggs and dairy products. Their presence is not only desired for aesthetic reasons they also fulfil a vital role as a provitamin A to which their structures are closely related. As a matter of fact β-carotene is our most important source of vitamin A.

In these days of growing populations we have to rely more and more on fast and economic mass production of food. As a result, however, the natural pigments and vitamins are often not present or only in small amounts. To achieve not only quantity but also a high standard in quality the lacking pigments and vitamins have to be supplemented. Of course, natural sources alone could never fill the need. Here the commercial production of these vital compounds is of utmost importance. To devise economic routes feasible on a large scale to these relatively complicated structures has been a great challenge to the organic chemist. As a consequence many new methods or reactions were either discovered or had to prove their real value in carotenoid synthesis, e.g. partial catalytic reductions with Lindlar catalyst or the Wittig-condensation.

The purpose of this paper is to review and evaluate the various key reactions that are being used in technical carotenoid and vitamin A syntheses. Furthermore, in judging the value of a particular process, the reader should get a better understanding of the requirements and conditions employed in industry.

DISCUSSION

Many pathways have been evaluated for the synthesis of vitamin A or more generally of a carotenoid (Fig. 1).

We may start by first preparing the end group (R) and then adding successively small molecular units until we obtain our target compound (route A). We may combine larger sub-units (route B), or we could react a symmetrical central component with two end group-bearing fragments (route C). Within this general framework nearly every combination may be considered. Our final choice of a particular route depends on the following economic considerations: (1) Easily and cheaply available starting materials; (2) high yields in the various reaction steps; (3) minimum amounts of side-products that cannot be recycled and may be the cause of pollution; (4) simplicity of reaction conditions; and (5) energy requirements.

Of the more than three hundred naturally occurring carotenoids only five are at present being manufactured on an industrial scale (Fig. 2). These are β-carotene(I), canthaxanthin(II), ethyl β-apo-8′-carotenoate(III), β-apo-8′-carotenal(IV), and citranaxanthin(V). The structurally related vitamin A acetate(VI) is the compound produced

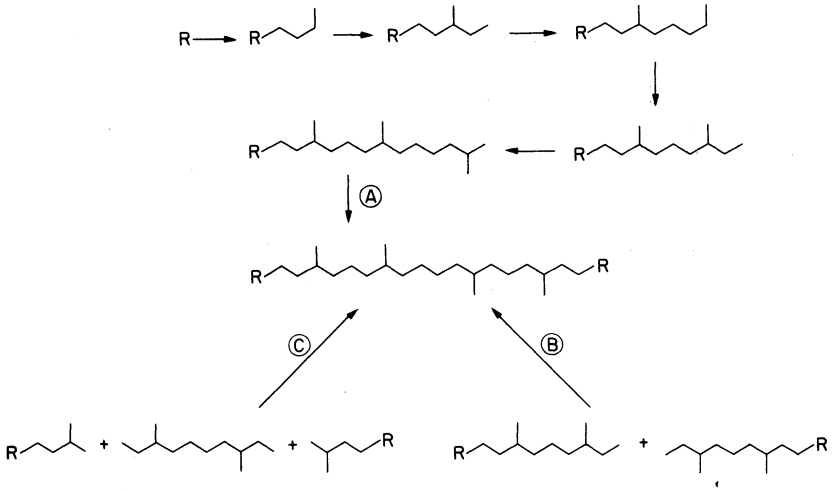


Fig. 1. Generalized scheme of the synthesis of the carbon atom skeleton of a carotenoid molecule.

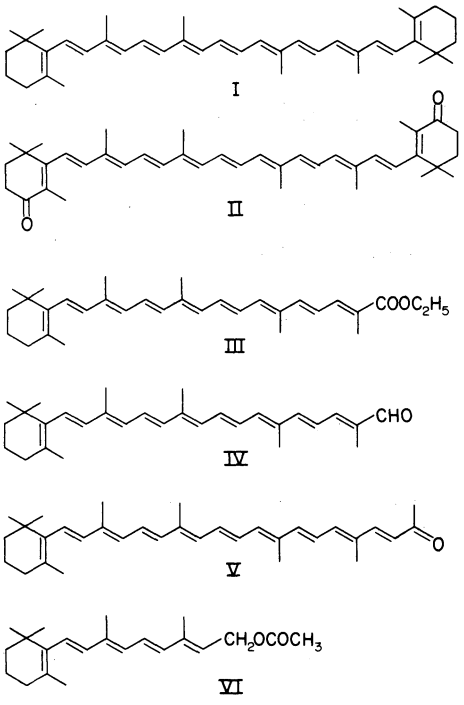


Fig. 2. Commercially synthesized polyenes.

in largest quantities, namely several thousand tons a year. The carotenoids I → IV are being manufactured by Hoffmann–La Roche, I and V by the BASF. For vitamin A acetate we have several producers.

Comparing these compounds we note that they differ in structure only from carbon 14 onward. The exception canthaxanthin is produced by oxidation from β-carotene and not by an independent total synthesis. So we may expect that the commercial syntheses are with regard to intermediate compounds rather similar. And indeed, all commercial processes use as the first key intermediate β-ionone (VII) for which a number of efficient syntheses have been discovered starting essentially with acetone, formaldehyde, and acetylene. From there vitamin A alcohol (VIII) the second common intermediate is obtained. Only the synthesis of β-carotene of Hoffmann–La Roche by-passes VIII (Fig. 3).

To construct vitamin A or more generally the carotenoid from these compounds smaller subunits have to be added. This should occur most desirably in such a way that carbon–carbon bond (σ-bond) formation is immediately followed by olefination (π-bond formation). The number of reactions suitable for this purpose is limited and only a few selected ones have found extensive use in polyene synthesis.

Using common characteristic mechanistic features we may classify these reactions into three major types (Fig. 4). There is type 1 where carbon–carbon bond formation

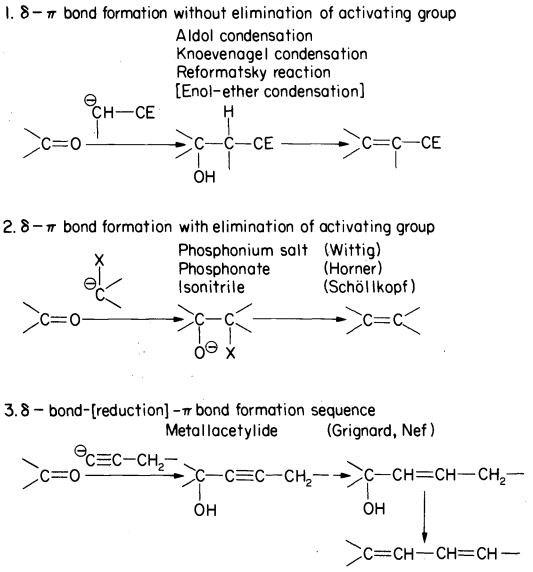


Fig. 4. Classification of olefination reactions.

and subsequent olefination takes place without elimination of the activating group. Included in this type is the Aldol-condensation, the Knoevenagel-condensation, the Reformatsky-reaction, and the enol ether-condensation. The latter does not really belong to that series its reaction mechanism being initially different. However, since a similar intermediate is involved the inclusion may be justified. In type 2 olefination occurs with loss of the activating group. Under this heading we count the Wittig-condensation, the Horner-condensation, as well as the recently published olefination with the help of isonitriles. In the third type a partial reduction after σ-bond formation precedes the introduction of the double bond. Here we may mention the Grignard and Nef reactions with magnesium or alkali acetylides, respectively.

The first general observation one will make is that in all three reaction types *one* substrate is a carbonyl compound. The second observation, although not immediately obvious is that olefin formation is not stereospecific, i.e. mixtures of *cis*- and *trans*-isomers usually arise. From this arsenal of reactions the chemist will select that one most suited for his purpose. Unfortunately not one is applicable in all situations. However, weighing the particular advantages and disadvantages will influence his choice. Although it is difficult to predict the practical outcome for each specific case one can list general observations for these condensation reactions whose considerations prior to experimentations could help establishing priorities. For instance, the Aldol-condensation[1] (Fig. 5), a term applied to the acid or base catalyzed self-condensation or mixed condensation of aldehydes and ketones produces initially β-hydroxy-

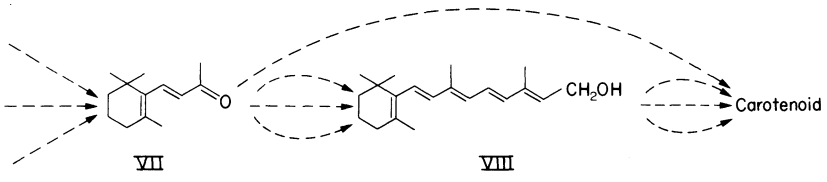
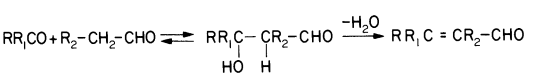


Fig. 3. General scheme for the commercial syntheses of carotenoids.

Aldol-condensation



Advantages
cheap, high yields with acetone condensations,
trans-isomer favoured.

Disadvantages
limited applicability since numerous side-reactions (self-condensation, polymer formation, Cannizzaro reaction, add'n to α,β-unsat. products a.s.o.). First reaction step reversible therefore high yields not always possible. Aldehyde more reactive than ketones.

Industrial examples:

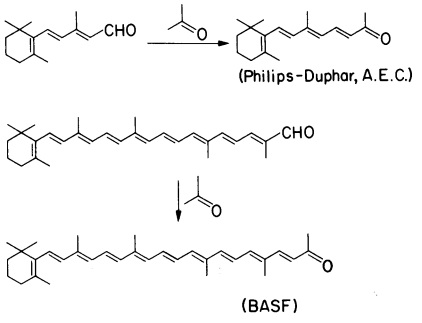


Fig. 5. Evaluation of the Aldol-condensation and its industrial applications.

aldehydes or -ketones. Immediate dehydration results in the isolation of the corresponding α,β-unsaturated carbonyl compound. The reaction is economically attractive especially because of its need for cheap auxiliary chemicals (e.g. alkali hydroxides), however, there are too many disadvantages (Fig. 5) to make it universally applicable. Nevertheless, the examples of its industrial application (Fig. 5) are very satisfying.

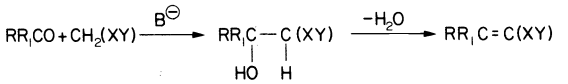
Another reaction which has found extensive use in carotenoid synthesis is the Knoevenagel-condensation[2] (Fig. 6) i.e. the reaction between an aldehyde or ketone and a compound having an activated methylene group in the presence of a base—usually an amine. Although it has the advantage of being applicable to both aldehydes and ketones the disadvantages are considerable to make it really appealing for large scale industrial use. Its major drawback is the fact that it leads to esters or nitriles which for further use have to be reduced to aldehydes or alcohols. So far that reduction is achieved with relatively expensive hydride reagents such as di-isobutylaluminum hydride or lithium aluminum hydride. Despite that the reaction is an essential step[3] in an industrial synthesis of vitamin A.

Similar arguments apply to the reaction between an aldehyde or ketone and an α-haloester in the presence of zinc (Fig. 7) known as the Reformatsky-reaction.[4] It is a valuable procedure for lengthening the carbon chain by two carbon atoms, but besides the disadvantages enumerated in Fig. 7 there is the same drawback already mentioned for the Knoevenagel-condensation, namely that it will lead to acid derivatives that are expensive to reduce. Nevertheless the reaction is applied in one of the key steps of a technical vitamin A synthesis.[3]

An interesting reaction is the condensation of an acetal with an enol ether in the presence of some Lewis acid catalyst (Fig. 8).[5,6] It is a relatively economic method for a two or three carbon extension, however, the disadvantages are in many instances too severe to make it the reaction of choice (Fig. 8). The strongly acidic reaction conditions in the hydrolysis of the intermediate acetal are often the cause for undesired side reactions such as isomerization and decomposition of the product. A successful industrial example is found in the β-carotene synthesis of Hoffmann–La Roche where the method is used twice, first for a two carbon extension and then using a propenyl ether for a chain lengthening by three carbon atoms.

More generally applicable than the reactions of the first type are those proceeding with elimination of the activating group. Here it was notably the Wittig-condensation[7] (Fig. 9), the reaction of an aldehyde or ketone with a phosphorane, which had an enormous impact on polyene synthesis. It has become in most

Knoevenagel-condensation

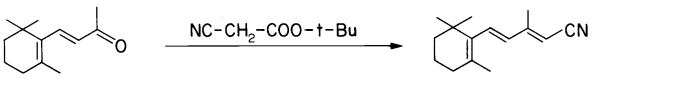


X, Y = NO_2, CN, COOR a.o.

Advantages
applicable to aldehydes and ketones, mild exptl. conditions, high yields possible

Disadvantages
primarily route to α, β-unsaturated acids and nitriles, generally only applicable for the extension by two carbons, side-reactions (Michael add'n)

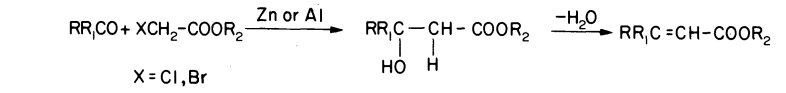
Industrial examples:



(Philips-Duphar)

Fig. 6. Evaluation of the Knoevenagel-condensation and its industrial application.

Reformatsky reaction



Advantages
ketones and aldehydes react, can be applied to the synthesis of α- and β-branched unsaturated acids.

Disadvantages
relatively expensive, side-reactions (coupling of reagents, enolization, aldolization, the Zn-cpd. may add to the CO group of ester).

Industrial examples:

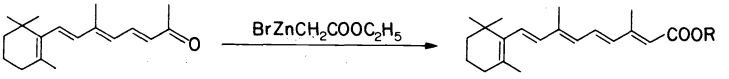


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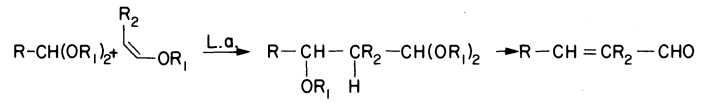
Fig. 7. Evaluation of the Reformatsky-reaction and its industrial application.

situations calling for double bond formation the first reaction to be tried. One knows now of several examples where the reaction is used on a large scale. However, the disadvantages (Fig. 9) may often tip the balance in favour of some of the reactions mentioned before. From an industrial point of view one great drawback is the necessity of recycling triphenyl phosphine. Without that the reaction would be too expensive. A number of efficient processes for that purpose are known.[8] Unfortunately, however, they either are using stoichiometric amounts of expensive reducing agents or are producing large quantities of side-products. Here the discovery of an effective cheap catalytic process would be highly desirable. But even with that reservation the Wittig-condensation is regarded as one of the most efficient and economic reactions in polyene synthesis. Although olefin formation is here, too, not stereospecific. Some control over the stereochemistry is, however, in the realm of possibility.[9-12]

The Horner-reaction which uses phosphonates instead of phosphoranes does not possess some of the disadvantages of the Wittig-condensation. For instance it can be used for the synthesis of tri- and tetra-substituted olefins and the undesired but necessary by-product, a phosphate, is water soluble and therefore easily separated from the product. However, the difficulty associated with the

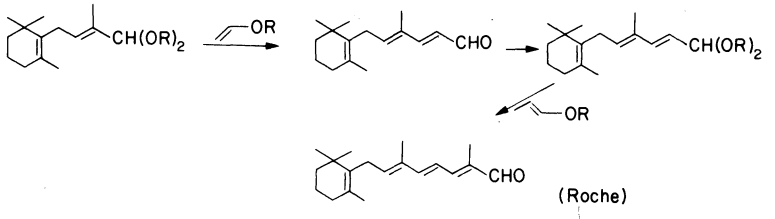
Enol ether condensation



Advantages
good method for 2 or 3-carbon extension, relatively cheap, high yields possible.

Disadvantages
longer extensions e.g. with —OR give lower yields, possibility of further condensation of intermediate acetal with a second molecule of enol ether.

Industrial example:



(Roche)

Fig. 8. Evaluation of the enol ether condensation and its industrial application.

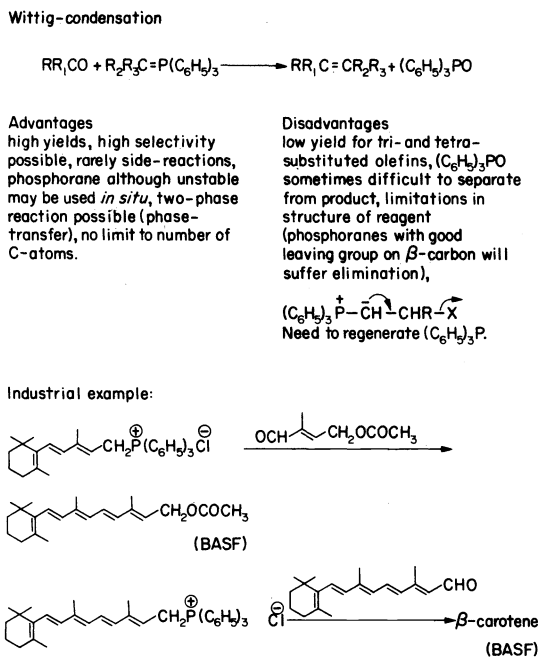


Fig. 9. Evaluation of the Wittig-condensation and its industrial application.

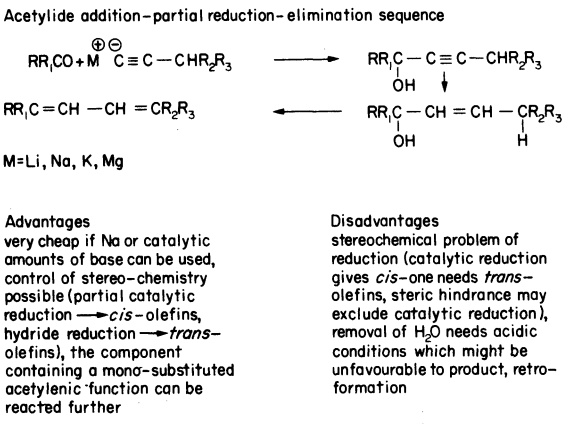


Fig. 10. Evaluation of the acetylide addition.

reconversion of the phosphate into the phosphonate have made this reaction unattractive from an industrial point of view. Therefore no large scale synthesis relies on that reaction.

Just to mention it here in that connection, the carbonyl olefination with isonitriles,[13,14] a reaction also to be counted to the second reaction type, is accompanied by too many side reactions to make it a serious candidate for industrial use.

The third reaction type is also a very important method for carbon–carbon bond formation and olefination.[15] The advantages (Fig. 10) are considerable, but so are unfortunately the disadvantages.

In the industrial examples (Fig. 11) the disadvantages are negligible and the individual steps of the reaction sequence proceed in near quantitative yield.

One reaction which so far has not been commercially exploited is the olefination with the help of sulfones (Fig. 12). The reaction has been known for a while[16–18] but has only recently been used for the synthesis of vitamin A derivatives and carotenoids.[19,19(a–d)]

An obvious advantage of this reaction as compared to the Wittig or Horner olefination is the direct recycling of the sulfinic acid without any chemical modification. However, the need to have activating substituents in the various intermediates is a serious disadvantage. For instance in the absence of additional activation α-alkylation of the sulfone will proceed only in the presence of such strong bases as alkyl lithium or potassium *t*-butoxide. For large scale commercial use these bases are usually too expensive. Alkylation furthermore requires an activated halide such as an allylic halide. Finally in order to split off the aryl sulfinic acid easily the β-proton in the intermediate sulfone should be sufficiently acidic. This again calls for some additional activation possibly through some carbonyl function.

On the other hand there is *one* advantage which will make sulfones very useful for the synthesis of special

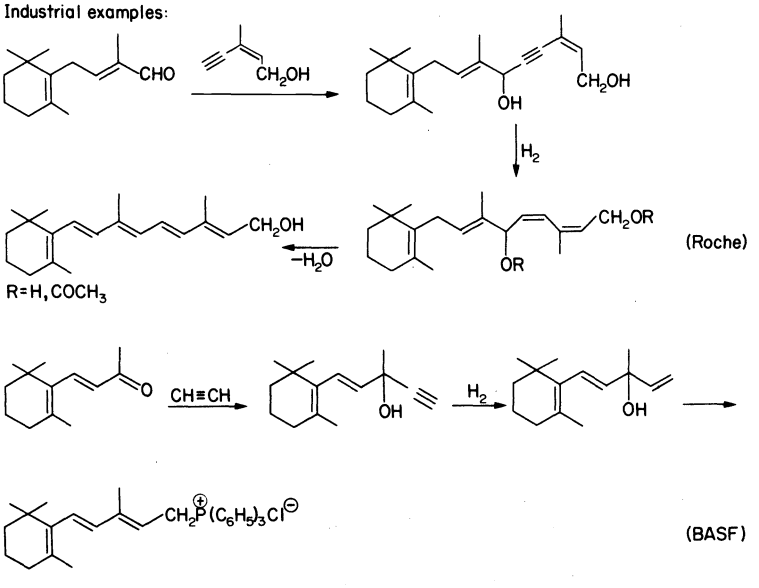
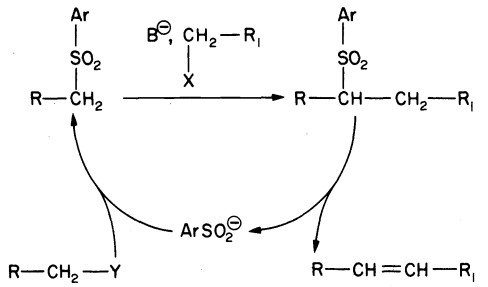


Fig. 11. Industrial application of the acetylide addition.



Advantages	Disadvantages
No need for carbonyl compound, activating group (sulfinic acid) can be recycled.	R and R_1 should be activating, otherwise strong (expensive) bases must be used, side-reactions (e.g if allylic halides are used → allylic substitutions).

Fig. 12. Evaluation of the olefinination with sulfones.

Thus treatment of the ketosulfones IX–XI with lead tetraacetate in benzene furnished the corresponding α-acetoxy compounds.[20] Treatment with selenium dioxide in refluxing dioxane does also not affect the sulfone group as demonstrated with compound XI. A further illustration is the hydride reduction of an ester group to the alcohol and subsequent oxidation of this group to an aldehyde. Again the reactions proceeded without destruction of the sulfone moiety. Phosphonium salts would not withstand such treatment.

Another case where sulfones proved to be superior to phosphonium salts is shown in Fig. 14. Nitromethane addition to the known ketone[21] XIX gave the nitro compound XX in excellent yield. After conversion of the nitro group to an aldehydic function with ozone,[22] followed by introduction of the double bond using 2,3-dichloro-5,6-dicyano-benzoquinone one obtained on sodium borohydride reduction the alcohol XXI. Phosphorous tribromide converted XXI into the corresponding bromide which furnished then the sulfone XXII or the

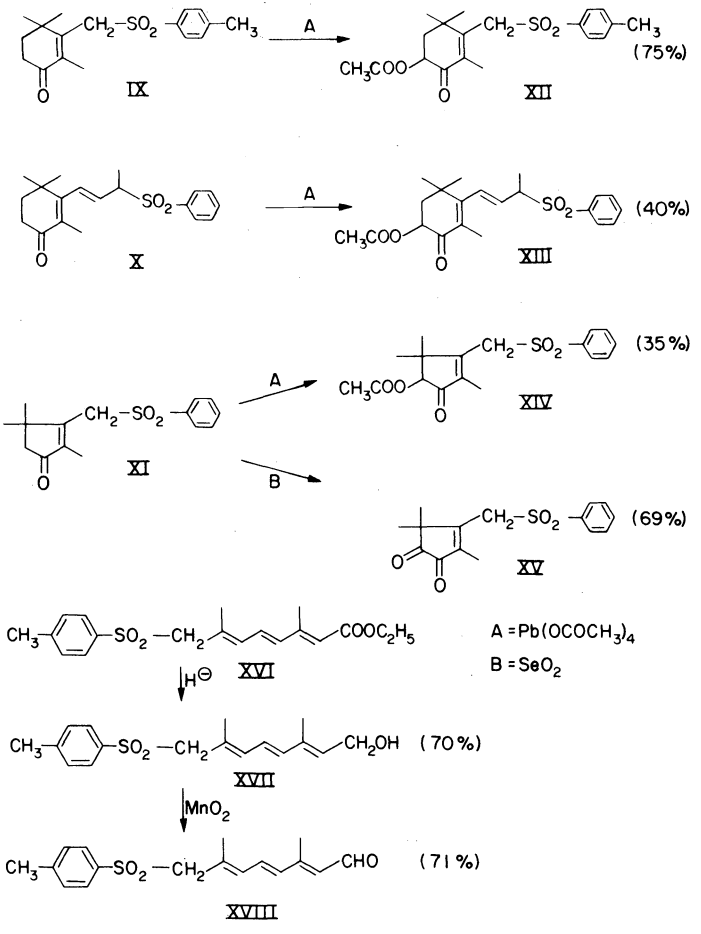


Fig. 13. Reactions on sulfone-bearing molecules. All physical data were in accordance with the proposed structures. Compound, mp: IX, 106–107°; X, 86–87°; XI, 116–118°; XII, 105–106°; XIII, oil; XIV, 118–119°; XV, 135–137°; XVI, 154–156°; XVII, 129–131°; XVIII, 140–142°.

polyenes. Sulfones are chemically relatively inert. It is, therefore, possible to carry out chemical transformations on the sulfone-bearing molecule prior to olefination without destroying the sulfone group. An illustration of this is given in Fig. 13.

phosphonium salt XXIII on treatment with sodium benzenesulfinate or triphenyl phosphine, respectively. Whereas the sulfone XXII could now easily be converted to the acetate XXIV, the corresponding Wittig reaction did not proceed at all. Steric hindrance might explain this

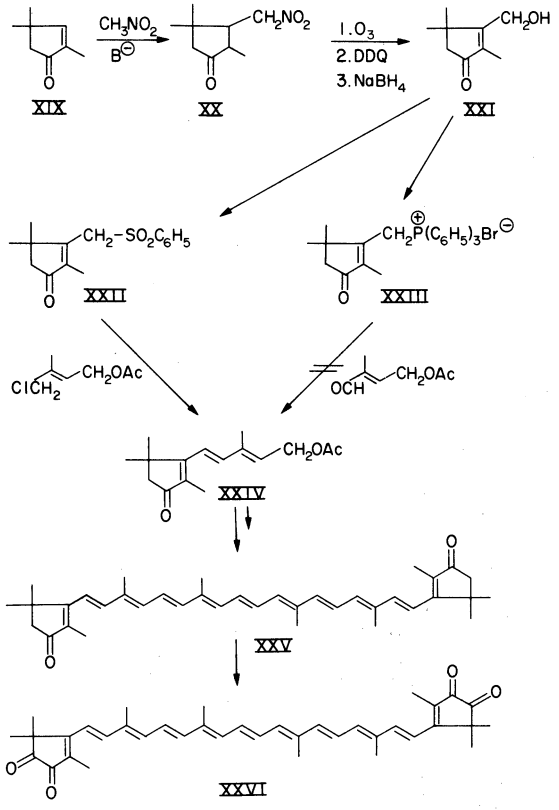


Fig. 14. The synthesis of violerythrin.

failure. Compound XXIV could further be used for the synthesis of 2,2′-di-norcanthaxanthin XXV, which in turn was converted to violerythrin XXVI on treatment with selenium dioxide.[20]

We have now evaluated various key reactions used in polyene synthesis. One disadvantage present in all methods was the non-stereoselective nature of olefin formation. In other words each time a new doublebond is introduced we may encounter *cis*- and *trans*-isomers which have to be separated. Fortunately it is possible in many cases to convert the undesired *cis*-isomer into the *trans*-compound, since the *trans*-isomer is often the more stable one.

An explanation of the difference in stability based on steric arguments has been given by Pauling[23] (Fig. 15). Of course the severity of steric interaction depends on the position of the double bond in the polyene chain and as a consequence some *cis*-isomers are easier to isomerize than others. For instance *cis*-isomers of the 7,8-double bond were until recently[24] not known. The *trans*-compounds are here far more stable. The *cis*-isomers at the 11,12-, 13,14-, and 15,15′-position are also relatively easy to isomerize. Heating in hexane or heptane, or irradiation in the presence of catalytic amounts of iodine is usually sufficient for an effective isomerization. However, a problem to the carotenoid chemist has been the apparent stability of *cis*-compounds at the 9,10-double bond. When for instance the C_{13}-phosphonium salt XXVII is reacted in the presence of base with a C_7-acetoxy aldehyde (Fig. 16) a mixture of *trans*-vitamin A acetate VI and its 9-*cis*-isomer XXVIII is obtained in a ratio of 40 to 60. An isomerization of XXVIII to VI in the usual way is

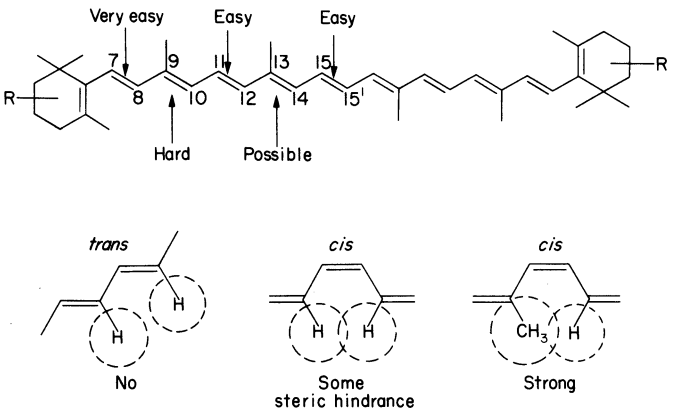


Fig. 15. The isomerization of *cis*-carotenoids into their *trans*-isomers.

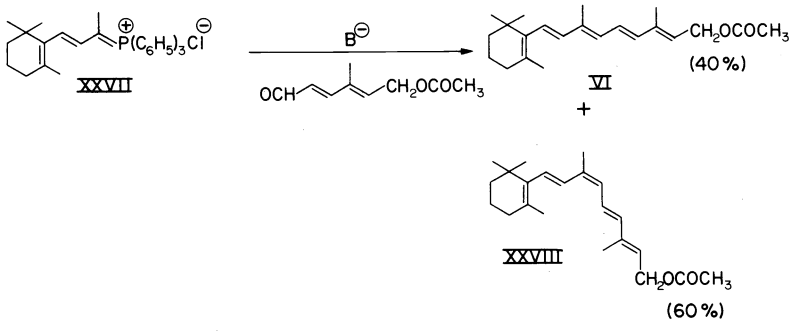


Fig. 16. Ratio of geometric isomers at the 9,10-double bond.

not possible. There are, however, indications in the patent literature[25] that light isomerization in the presence of some sensitizer might be possible.

CONCLUSION

From the foregoing discussion one can deduce that the synthesis of carotenoids with relatively simple structure presents no great problems. The various key condensation reactions seem to be economic enough to make them attractive for large-scale industrial use. However, it is also apparent that each process leaves something to be desired. Therefore, the search for more economic reactions will continue. The pressure of the environmentalist for a decrease in pollution will necessarily stimulate research, too. And clearly, catalytic processes are the ultimate goal. They would be cheap and eliminate the so-far necessary auxiliary chemicals such as acids and bases that are sources for pollution. The possible use of readily available petro-chemicals like ethylene, butadiene, and isoprene as starting materials may be envisaged. Oligomerization and subsequent functionalization[26] may open economic routes to carotenoid building blocks now only accessible by relatively expensive syntheses.

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