Pure & Appl. Chem., Vol.51, pp. 871-886.
Pergamon Press Ltd. 1979. Printed in Great Britain.

NEW APPROACHES TO THE SYNTHESIS OF CANTHAXANTHIN

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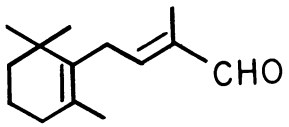
Abstract - The use of sulfur ylides for the chain extention of polyene aldehydes and ketones is described. This work resulted in an approach to synthesizing canthaxanthin via 2,6,6-trimethyl-2-cyclohexen-1-one. The use of a substituted trimethylcyclohexenone or α-ionone for the construction of a C_{15} phosphonium salt and its condensation with a C_{10} dialdehyde for the synthesis of canthaxanthin is also reported.

The work presented in this paper describes our involvement with canthaxanthin as it happened and developed. You will find that it follows a winding road which started with vitamin A and eventually led us to find some old known substrates and reactions that, when connected together, finally resulted in a new synthesis of canthaxanthin.

Our initial introduction into polyene chemistry in 1970 was due to a problem in the present vitamin A synthesis used today at Roche. The two key fragments of this synthesis are compounds 1 and 2 which contain fourteen and six carbons respectively.



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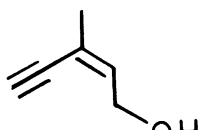

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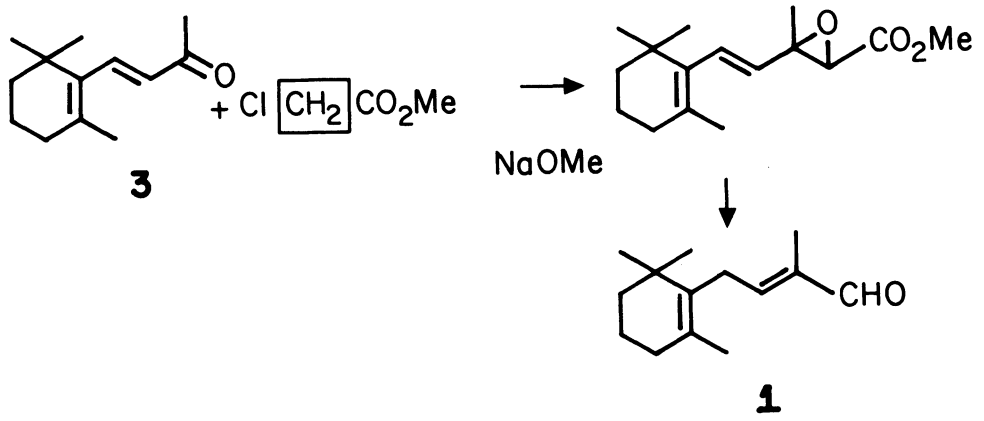
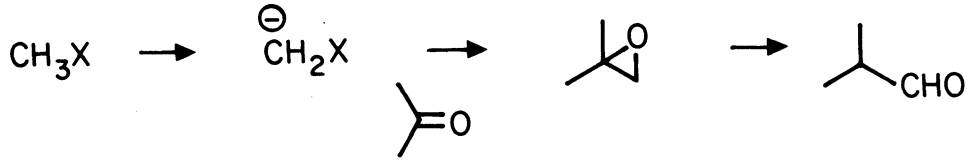
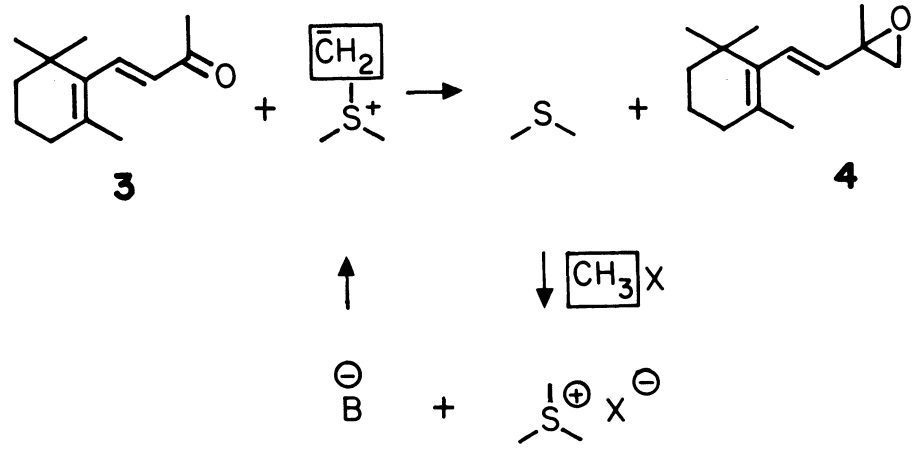
To make vitamin A, the two pieces 1 and 2 are united via a Grignard reaction and subsequently transformed into retinyl acetate by a sequence of reactions employing hydrogenation, acetylation and dehydration. The six carbon unit is obtained from the reaction of acetylene with methyl vinyl ketone followed by an acid isomerization which yields predominantly the cis isomer 2 (Ref. 1). The fourteen carbon fragment 1 is produced from β-ionone by the classic glycidic ester synthesis shown.



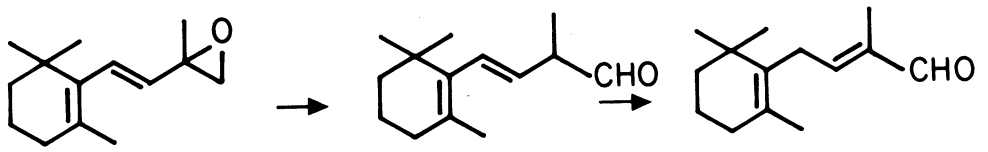
Now while the bulk of the synthesis leading to the final product, vitamin A, is efficient in carbon use, this glycidic ester homologation reaction is wasteful in reagents. What we needed was a reaction sequence which would only employ the one carbon to be inserted and could follow the sequence shown.



The use of sulfur ylides for chain extensions of this type is an old reaction (Ref. 2) and Corey and workers have shown that dimethylsulfonium methylide was a useful reagent for the generation of oxiranes from ketones or aldehydes. Rearrangement of these epoxides can then result in a new aldehyde containing one more carbon. The application of this method to polyene systems has not been extensive and as a one carbon extension it seemed attractive. Formally, the process meets most of the requirements, one carbon is inserted and the waste product, dimethylsulfide, is recycled. The application of this chemistry to β-ionone is as shown and was straightforward, yielding the epoxide 4 in excellent yield.



The isomerization of the epoxide 4 to the aldehyde 5 was not a trivial problem at first and while numerous Lewis acids did give the expected material the yields left much to be desired. However, while we were examining the reactions of epoxide 4 with various Grignard reagents, we observed that the products of the reactions were always derived from the aldehyde 5 and this suggested the use of magnesium bromide as the catalyst for the rearrangement step. This reagent works well in this case and in several other applications and gives no bromohydrins; the rearrangement of 5 to 1 is then carried out with dilute aqueous base in methanol.



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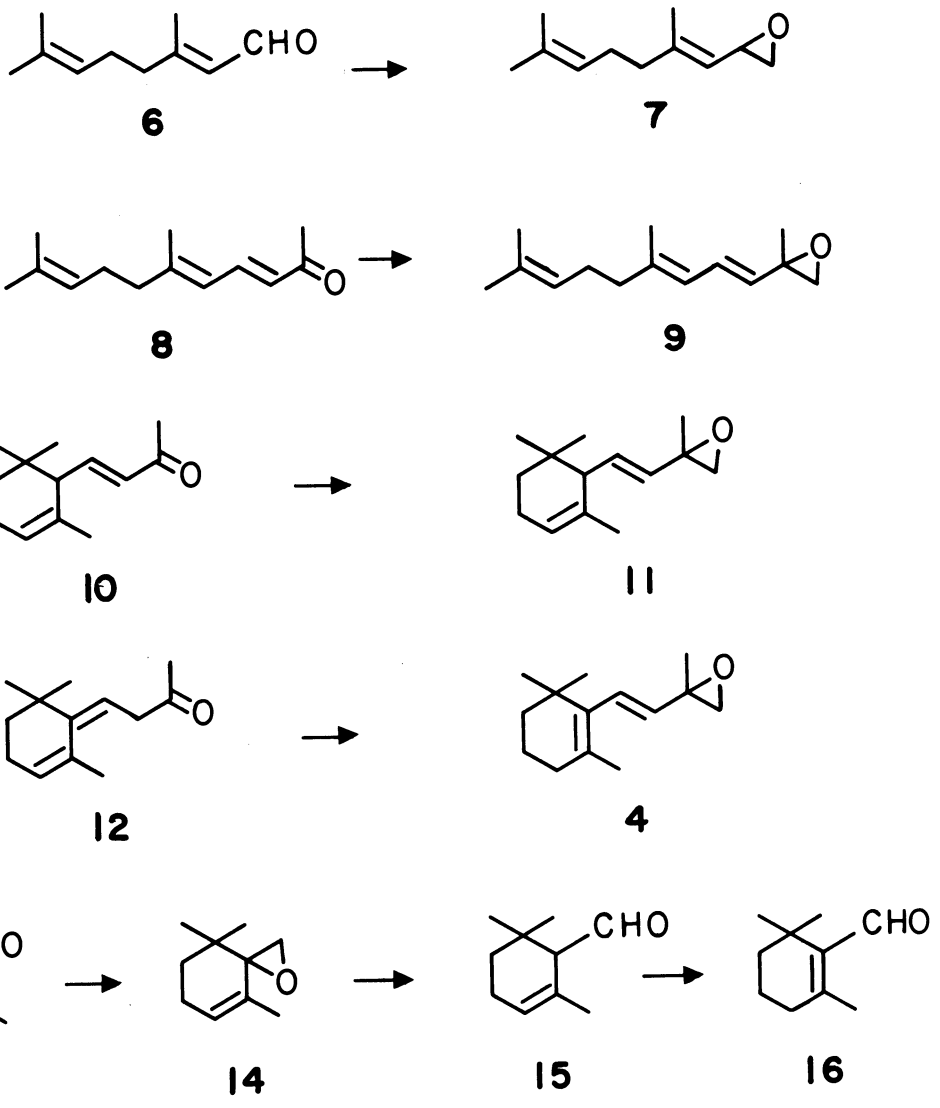
Unfortunately, the Corey method is not practical on a large scale as the ylide, which is of limited stability, has to be generated first and then reacted with the ketone or aldehyde. The use of sodium methylsulfinylmethide as base and anhydrous solvents such as tetrahydrofuran and dimethyl sulfoxide also add substantially to the cost of such a process and make it commercially unattractive. However, on a small scale, the procedure is excellent as the chemical environment is nearly neutral and the reactions are very fast.

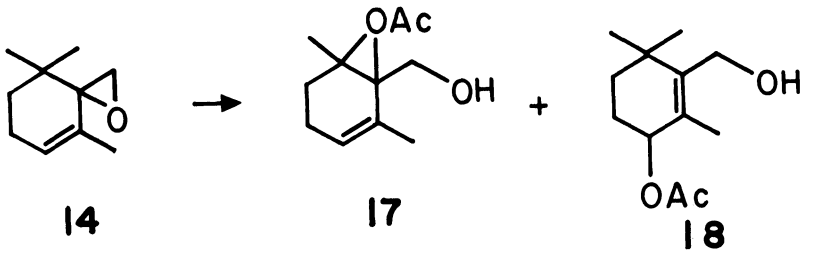
The use of aqueous sodium hydroxide as the base for generating ylides has been employed in the past and in combination with a phase transfer reagent, this system has resulted in some useful procedures for the generation of oxiranes from reactive carbonyl compounds (Ref. 3). Unreactive ketones such as β-ionone do not give epoxides by these reported methods. After working some time in the area of sulfur ylides, it eventually became clear that the counter ion of the sulfonium salt, employed for the generation of the ylide, had a dramatic effect on the outcome of these alkyl transfer reactions. We found that when the counter ion is hard, for example chloride, then even dilute aqueous base gave good yields of oxiranes and with 40% aqueous sodium hydroxide solutions even unreactive ketones such as β-ionone or acetophenone give excellent yields of epoxides. The final reaction conditions we arrived at in connection with the β-ionone system employ a mixture of solid trimethylsulfonium chloride, solid sodium hydroxide, a phase transfer agent (in this case the Makosza catalyst benzyltriethyl ammonium chloride) and dimethyl sulfide as the solvent. To this mixture is added the β-ionone and after stirring at room temperature for several hours the epoxide is produced in near quantitative yield. Subsequent rearrangement with magnesium bromide and then aqueous base results in the desired aldehyde 1 in about 95% yield from β-ionone.

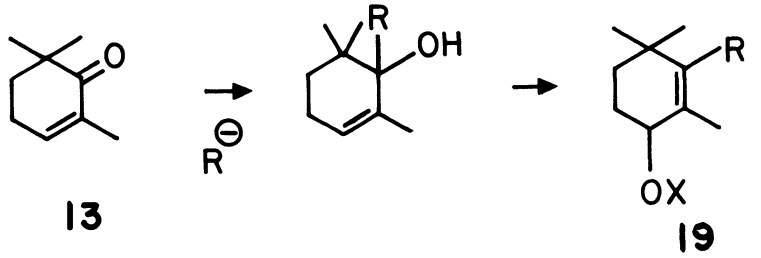
We had now achieved our initial objective for vitamin A in that only one carbon is used in the extension of β-ionone to the aldehyde 1 and that carbon is derived from methyl chloride. The method is also applicable to large scale production as the ylide is generated in situ and is trapped by the ketone while the oxirane formed is protected from the reagents by the nature of the two phase system. Application of this process to a series of aldehydes and ketones gave the following oxides in good yield.



Interestingly retro-ionone 12 gave only the epoxide 4 which is in agreement with the observations we made in connection with the reaction of β-ionone under these conditions. In that case, after partial conversion of 3 to the epoxide 4, one observes the slow build up of retro-ionone in the reaction mixture and, as the reaction proceeds to completion, only the desired epoxide is seen.

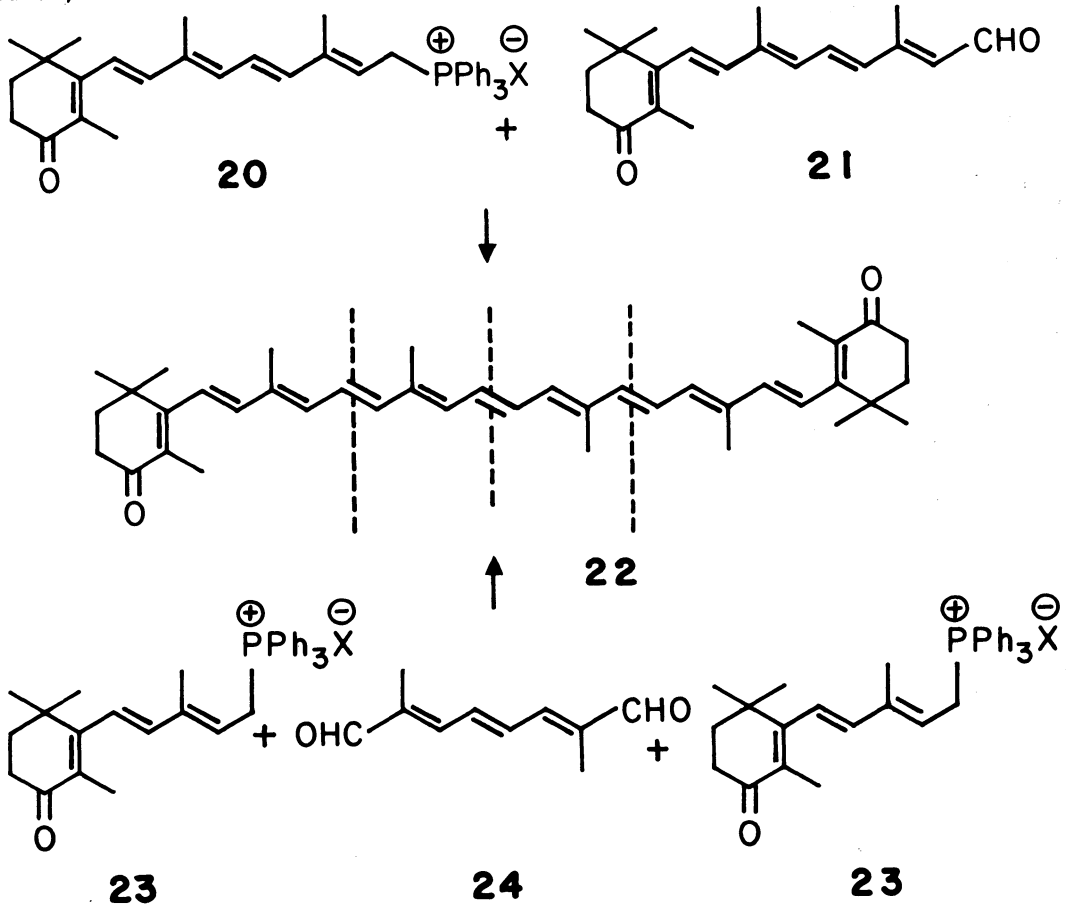
All of these epoxides rearrange to the corresponding β,γ-unsaturated aldehydes on exposure to magnesium bromide in ether, dichloromethane, toluene or dimethyl sulfide. One example of particular interest is the epoxide derived from the trimethylcyclohexenone 13. Rearrangement of this oxirane 14 gives one the option of making either pure α- or β-cyclocitral in high yield (Ref. 4). It was this epoxide 14 which also gave us the first indications that trimethylcyclohexenone 13 could be useful in the synthesis of ring oxygenated carotenoids, canthaxanthin in particular. While investigating the chemistry surrounding 14, we observed that solution of the material in acetic acid resulted in a rapid cleavage of the oxirane system with the formation of two new products 17 and 18, the latter predominating.



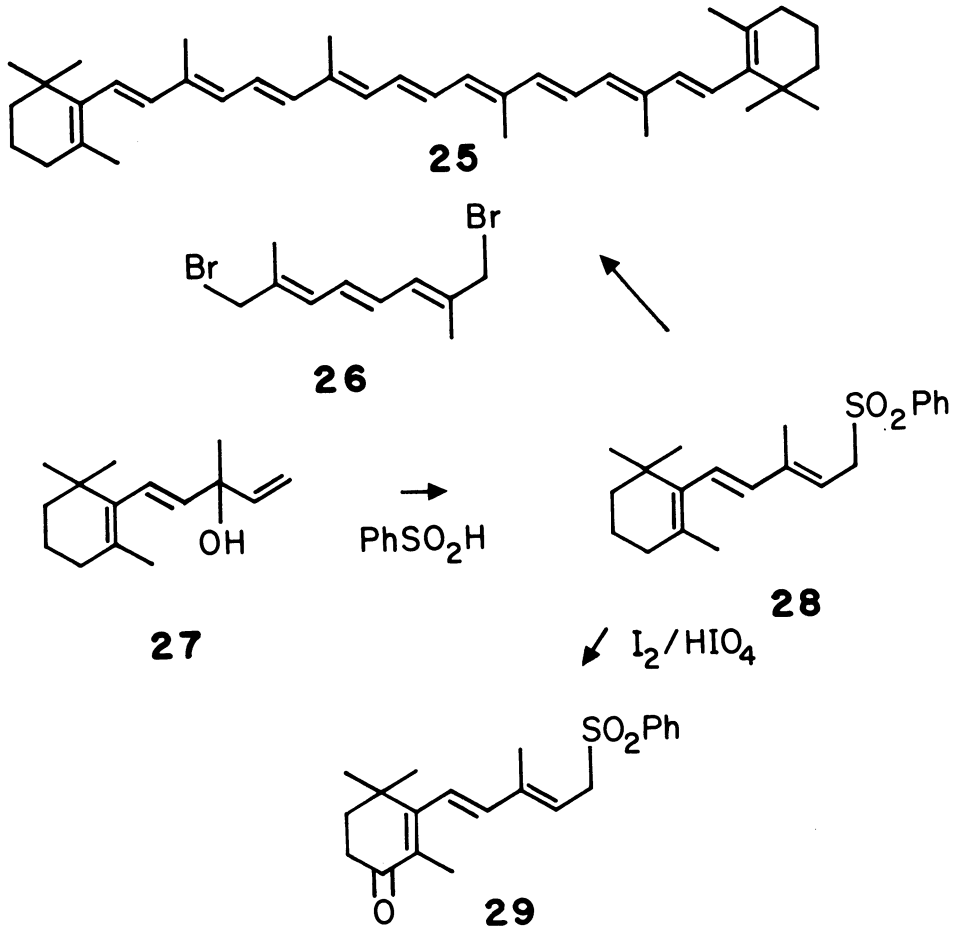


Thus, formally the addition of a suitable group to 13 followed by allylic rearrangement would generate a substrate such as 19 which on oxidation would give the ring functionality required in canthaxanthin.

Presently, canthaxanthin is produced commercially from β-carotene following the lines originally conceived by Karrer (Ref. 5) which employs the allylic bromination of β-carotene followed by solvolysis to the 4,4'-bis acetate and subsequent hydrolysis and oxidation to canthaxanthin. While this procedure is efficient, the possibility of using canthaxanthin as a food colorant in place of the red dyes would place a huge demand on β-carotene production and the oxidation steps leading to the final product. A simpler and more convergent synthesis would therefore be useful. Of the several routes to canthaxanthin, the two shown, based on the similar β-carotene routes, were considered.



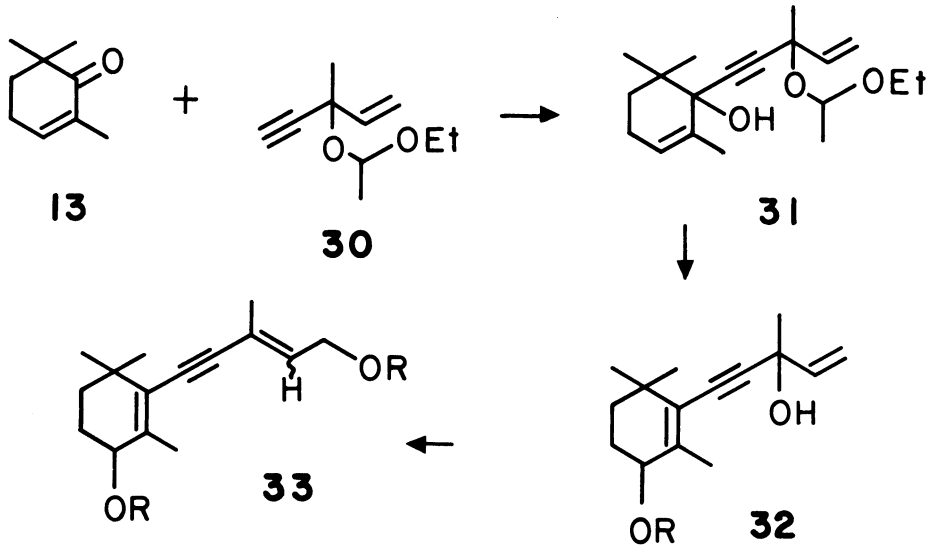
Of these two routes, the one employing the 20+20 construction has been described (Ref. 8) while the process 15+10+15, a popular construction method for carotenoids, has not been employed for canthaxanthin. It was this latter route we favored because the key phosphonium salt 23 seemed more accessable from the trimethylcyclohexenone 13. A simple synthesis of the two twenty carbon units from 13 was also not immediately obvious. It is surprising that the 15+10+15 route to canthaxanthin was not developed previously and to date the only reported material employing this concept must be inferred from the disclosed material in the patents of Rhone-Poulenc (Ref. 6). This chemistry is based on the beautiful work of Marc Julia (Ref. 7) and employs sulfones rather than phosphonium salts in polyene synthesis. An example of the chemistry is shown for the synthesis of β-carotene and commences with the β-ionone derivative 27 which on exposure to a mixture of phenylsulfinic acid in acetic acid yields mainly the all trans sulfone 28. Alkylation of this material with the bromo derivative 26 then gives β-carotene directly. Oxidation of the sulfone 28 is also stated to yield the ketosulfone 29 and one assumes that condensation of this material with 26 would then yield canthaxanthin.



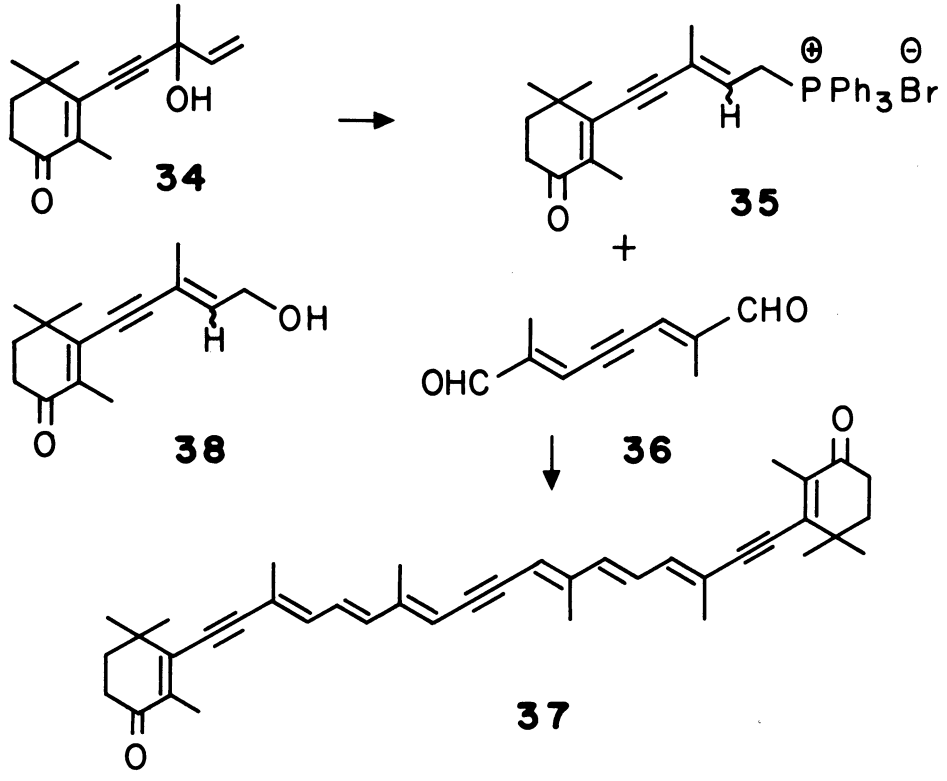
These sulfones have a definite place in polyene synthesis as they are stable materials which regenerate the phenylsulfinic acid when used in a scheme such as the β-carotene synthesis shown. This is a major advantage over the classic Wittig reaction which generates triphenylphosphine oxide which is difficult to recycle.

The symmetrical dialdehyde 24, which we require for our proposed route employing a C_{15} phosphonium salt, is a well-known compound and several good routes to this material have been disclosed (Ref. 8). With this material readily available, we turned our attention to the synthesis of the salt 23 and initially employed the trimethylcyclohexenone 13 and the protected acetylenic carbinol 30. These protected acetylenic alcohols were preferred since their lithium salts were soluble in the reaction medium. Addition of

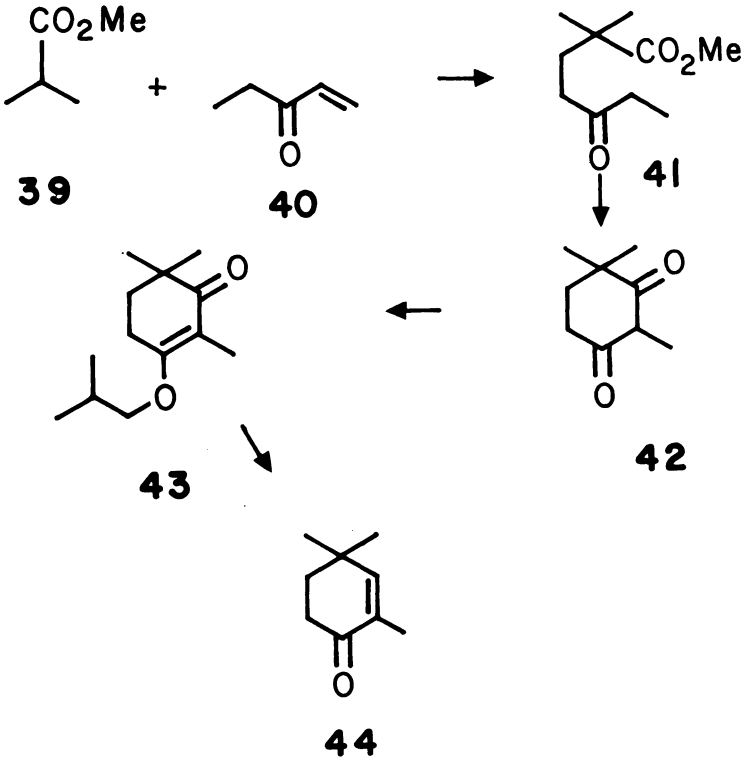
the lithium salt, derived from 30 and n-butyllithium, to cyclohexenone 13 gave an excellent yield of the alcohol 31. Exposure of this compound to acetic acid then resulted in cleavage of the protecting group and allylic rearrangement resulting in the formation of the acetate 32 (R=Ac). Further treatment of 32 with hot acetic acid then results in another allylic rearrangement with the formation of the diacetate 33 (R=Ac) as a mixture of double bond isomers.



Hydrolysis of 32 (R=Ac) with base liberated the diol 32 (R=H) which on oxidation gave the ketone 34. This material, when treated with triphenylphosphine hydrobromide, yielded a phosphonium salt 35 which, when coupled with the dialdehyde 36, resulted in a C_{40} unit 37 as a complex mixture of isomers. While this product 37 was not very useful, it did demonstrate the feasibility of the route. Mild aqueous acid treatment of 34 resulted in the alcohol 38 which was also a mixture of double bond isomers.

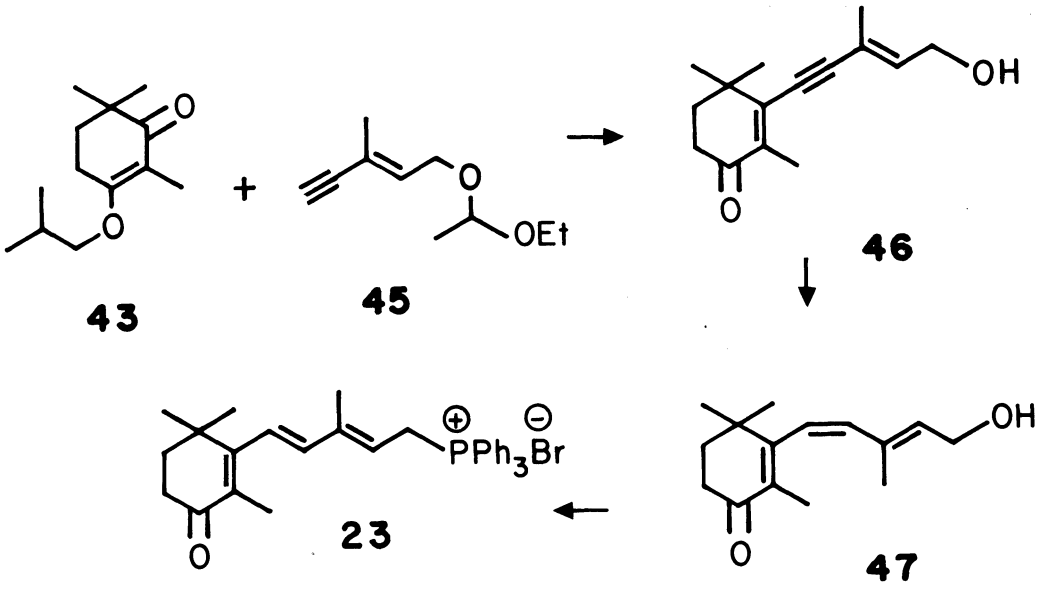


While the initial steps of this synthesis work well, the allylic rearrangement step resulting in compounds such as 38 gives mixtures of isomers and the oxidation of 32 (R=H) to 34 is a poor yield reaction. To avoid this problem, a substituted cyclohexenone was selected which would give the four keto group directly after addition of the substituted acetylene. For this the β-diketone 43 was prepared from methylisobutyrate 39 and ethyl vinyl ketone 40. Addition of the lithium salt, formed from 39 with lithium diisopropylamide, to 40 resulted in a very good yield of the adduct 41 which on cyclization with sodium hydride gave the desired compound 42 in over 80% yield.



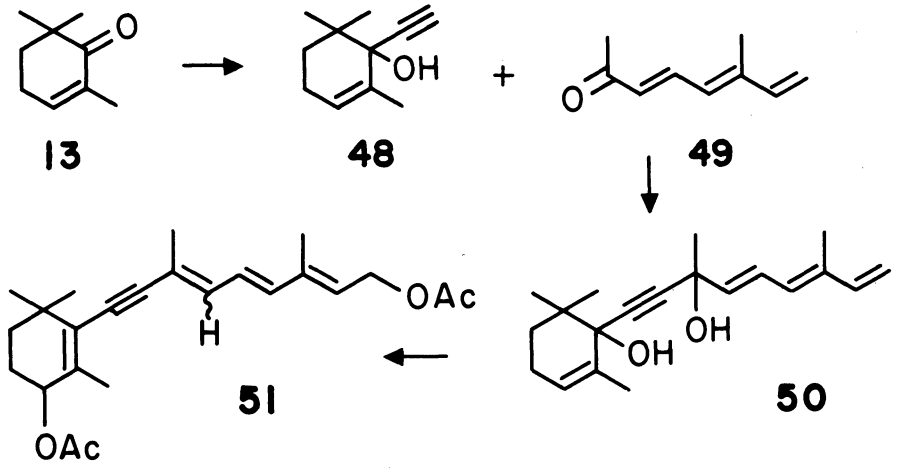
The ketoester 41 had been prepared previously by Weedon and his group (Ref. 9) interestingly enough also in connection with a synthesis of canthaxanthin.

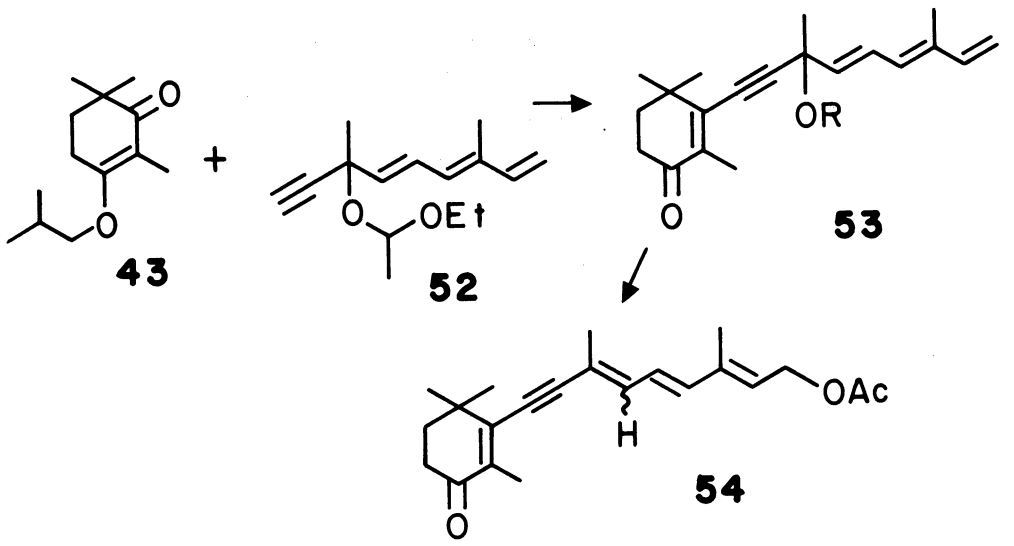
Treatment of 42 with isobutanol and acid then gave one keto enol ether, which as expected had the desired orientation shown in 43. This structure was confirmed by reduction of the material with lithium aluminum hydride which afforded the enone 44 as the sole product. With 43 in hand, the synthesis proceeded smoothly. Addition of the protected acetylene derivative 45 followed by an acid work-up gave the pure trans isomer 46 in over 90% yield.



Selective catalytic hydrogenation of the triple bond resulted primarily in the formation of the cis olefin 47 which after exposure to phosphorus tribromide and then triphenylphosphine yielded the desired phosphonium salt 23,which was greater than 90% trans about the 7,8 double bond. Condensation of this material with the dialdehyde 24 then resulted in pure canthaxanthin 22 in over 80% yield.

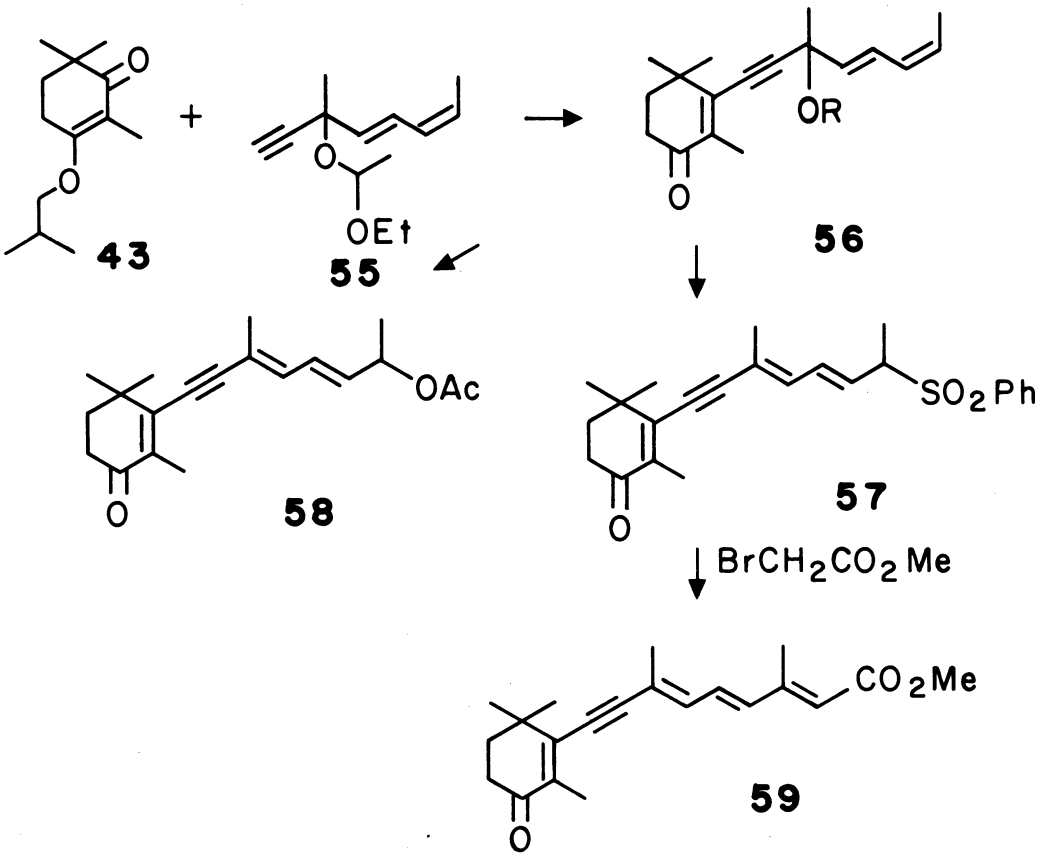
While involved with these various transformations, we examined the possibility of using other side chains and several of these are shown as follows.

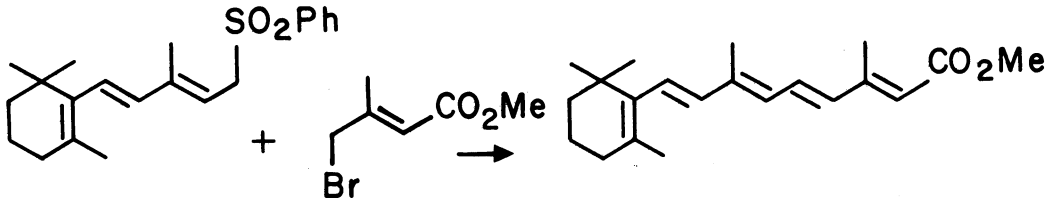




Ethynylation of the ketone group in 13 gave the useful alcohol 48 which as its dilithium salt was condensed with the trienone 49 (Ref. 10) giving the diol 50. This compound was very labile to acid and simply dissolving this material in acetic acid gave the diacetate 51. Similarly, addition of the acetylenic derivative 52 to the ketone 43 gave the product 53 (R=CH(CH_3)OC_2H_5) which on treatment with warm acetic acid gave the acetate 54.

The lithium salt of the shorter side chain 55 also condenses well with the protected diketone 43 and gives the ketone 56. This material was more reluctant to rearrange, but with hot acetic acid, the acetate 58 could be prepared in reasonable yield.

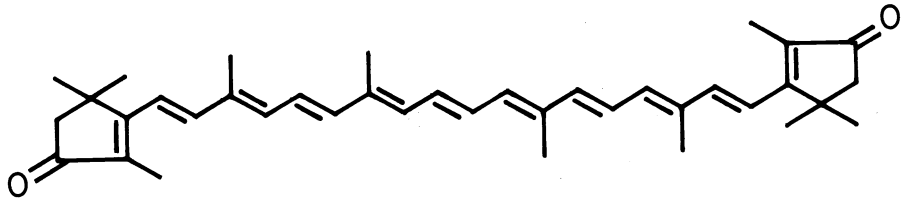




28 60 61

These acetylenic alcohols have been used previously by Attenburrow and later by Olson in their synthesis of vitamin A from 2,6,6-trimethylcyclohexan-1-one (Ref. 10). However, while the reactions are high yield processes, the products are generally mixtures of double bond isomers after acid rearrangement and unless one has a good reduction-isomerization method, these substrates offer few advantages. Compounds such as 56 can also be converted to the sulfones 57 by carrying out the allylic rearrangement in the presence of phenylsulfinic acid. These sulfones in turn can then be homologated by an alkylation-elimination sequence employing methyl bromoacetate. This sequence is very useful and is similar to the method developed by Julia in his work on retinoic acid (Ref. 11). In that case, the sulfone 28 was condensed with the bromo ester 60 to give the ester of retinoic acid 61 in good yield. This type of chain lengthening reaction, alkylation-elimination, will probably find many more uses in the future.

Having found a new method for constructing canthaxanthin, we turned our attention to the dinor compound 62. This material exhibits a deeper red color than canthaxanthin possibly because the polyene chain has more overlap with the planar cyclopentenone units. The reported synthesis of this material, developed by Kienzle at Roche some time ago, was somewhat lengthy and we felt that an approach based on the above work could be useful.



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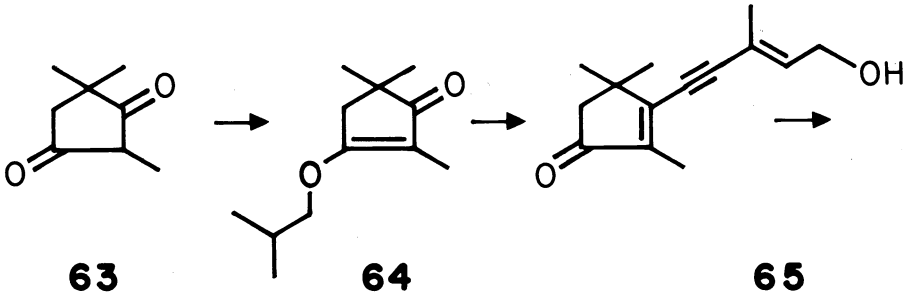
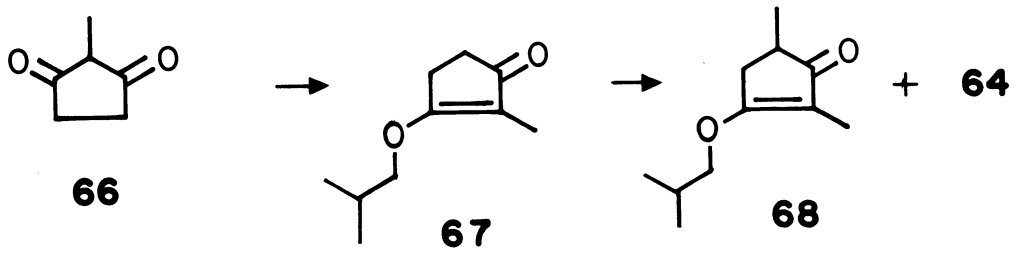
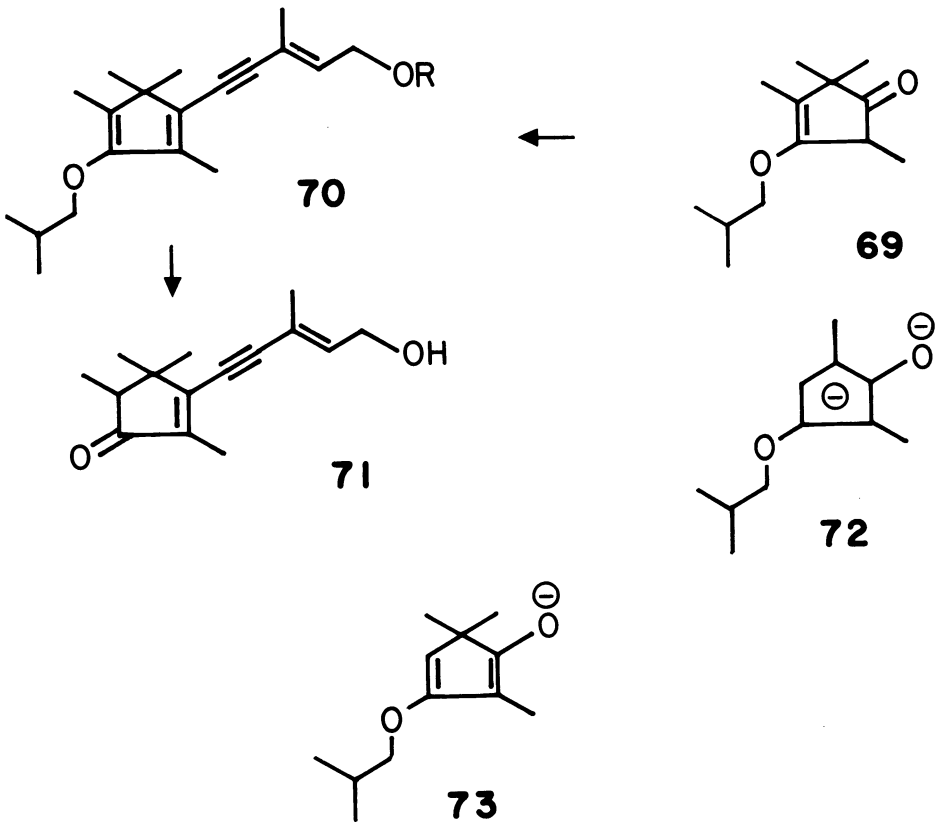


63 64 65

For this, the required C_{14} unit 65 would be constructed as before from a diketone 63. Rather than make the cyclopentan-1,3-dione 63, we chose the simpler way of directly constructing the protected material 64 as follows. The common steroid intermediate 66 was converted to the enol ether 67 in the usual manner and then alkylated to give the desired product. From the work of Stork (Ref. 12) we expected the product of alkylation to be 64.

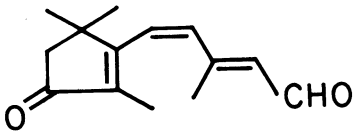


When the lithium enolate of 67 was generated with lithium diisopropylamide at -70° and quenched rapidly with methyl iodide the monomethylated product 68 was the major component of the mixture. If the alkylating agent is added slowly, then the reaction mixture contains equal amount of 67, 68 and 64. This product variation was due to the sudden temperature increase during the rapid quenching conditions, which results in a faster alkylation than proton transfer (cf Ref. 12). Eventually the desired material 64 could be made in a one-pot reaction by the sequential addition of base and methyl iodide with intermittent warming to room temperature. By these means, the desired material could be isolated in 74% yield (glc yield 87%). Also formed in this reaction is a material which was never isolated in a pure form. Its structure rests purely on its chemistry and is tentatively assigned as 69.



The material is possibly a result of alkylation of the dianion 72 rather than γ-alkylation of 73, which would generate a serious 1,2 interaction in the transition state. Why the product 69 prefers the deconjugated arrangement may also be due to the 1,2 methyl interactions. When a mixture rich in 69 was treated with the substituted trans acetylenic derivative as before and worked up with water, the protected alcohol 70 (R=CH(CH_3)OC_2H_5) resulted. Hydrolysis of this product with acid then gave a new hydroxy ketone 71. While both structures 70 and 71 are in agreement with the spectral data, one wonders why the initial acetylenic addition product should eliminate water so readily. Whatever the reason, we were pleased to find that the desired material 65 was readily prepared from 64 and 45 as in the case of canthaxanthin.

Hydrogenation of this material was eventually realized employing a Lindlar catalyst in a mixture of potassium carbonate, quinoline and ethyl acetate. Under these conditions, the cis isomer 74 was formed in reasonable yield together with some over reduction products.



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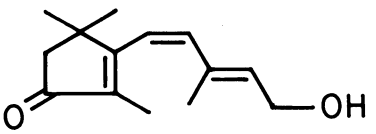

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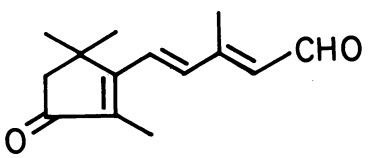

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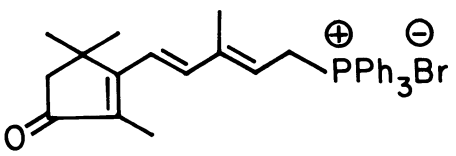

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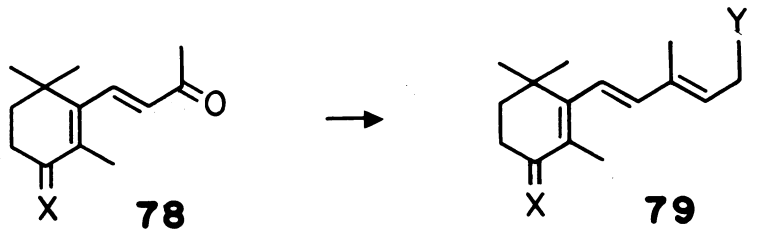
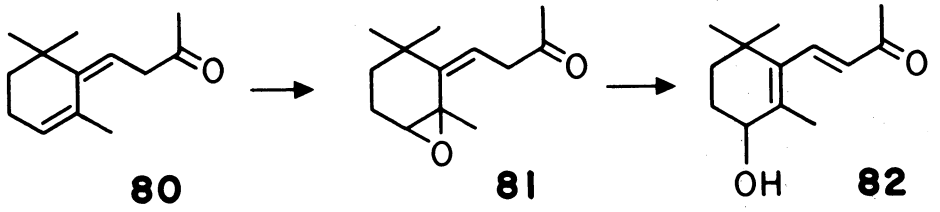
The cis stereochemistry of the 6,7 double bond in 74 was confirmed by oxidation to the aldehyde 75 with manganese dioxide and conversion of this material to the all trans keto aldehyde 76 with iodine.

Careful exposure of the alcohol 74 to phosphorus tribromide gave a very unstable bromo derivative which was immediately converted to the phosphonium salt 77 with triphenylphosphine. Condensation of the salt 77 with the dialdehyde 24 then yielded dinorcanthaxanthin 62 in 65% yield. Unlike the salt 23 used in the construction of canthaxanthin, the ylide derived from 77 was not very stable and if sufficient care is not taken in the Wittig reaction, numerous ylide decomposition products result.

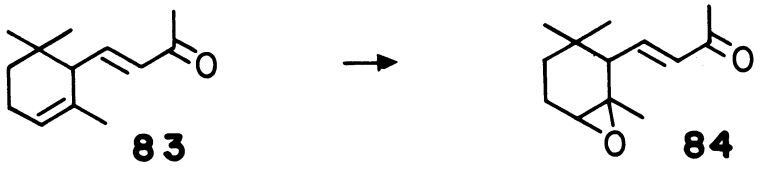
At the end of 1975 when our work on dinorcanthaxanthin was ending, a renewed interest in a better synthesis of canthaxanthin encouraged us to develop a more commercially acceptable route to the key C_{15} phosphonium salt 23. The major practical problems surrounding the scheme presented above result from the use of anhydrous solvents, lithium enolates generated with n-butyllithium and the use of synthons not derived from the traditional chemical family tree from which β-carotene, vitamin E and vitamin A grow. To remove all the above limitations, we planned our new synthesis around an ionone which was then to be elaborated as shown 78 → 79.

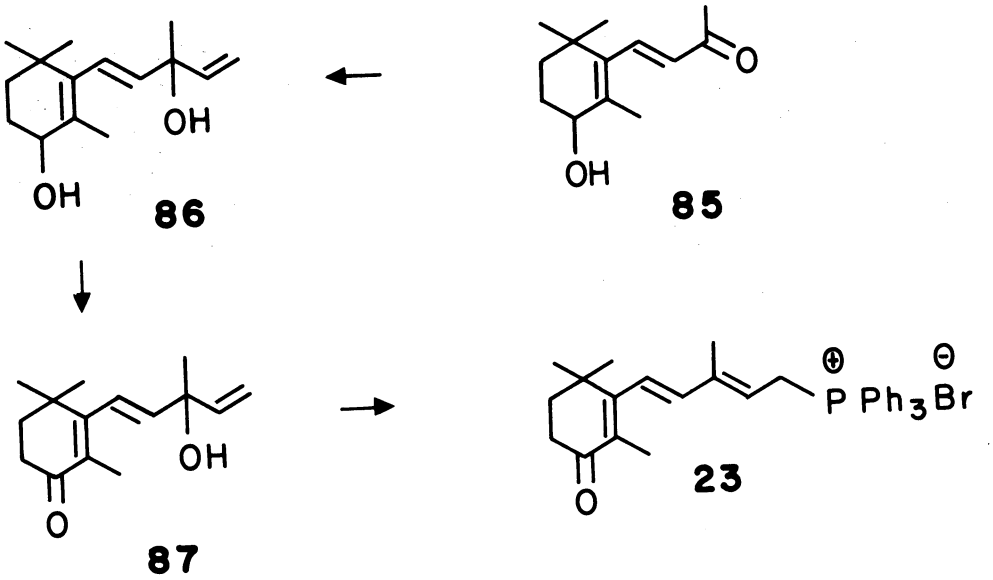


During our work with sulfur ylides, we found a facile procedure for the preparation of retroionone 80 from β-ionone by isomerization with sodium methoxide in dimethyl sulfoxide.



While investigating the chemistry of this material, we observed that oxidation with m-chloroperbenzoic acid gave mainly the oxide 81 which was very labile to base and readily gave the useful hydroxy compound 82. This is an old compound (Ref. 13) and has been made in numerous ways, none of which is attractive. On the basis of this epoxide ring-opening reaction, we conceived of employing α-ionone, a cyclization product of ψ-ionone, for the preparation of the salt 23. Epoxidation of α-ionone 83 with peracetic acid gave the epoxide 84, which had been described by Karrer as far back as 1946 (Ref. 14).

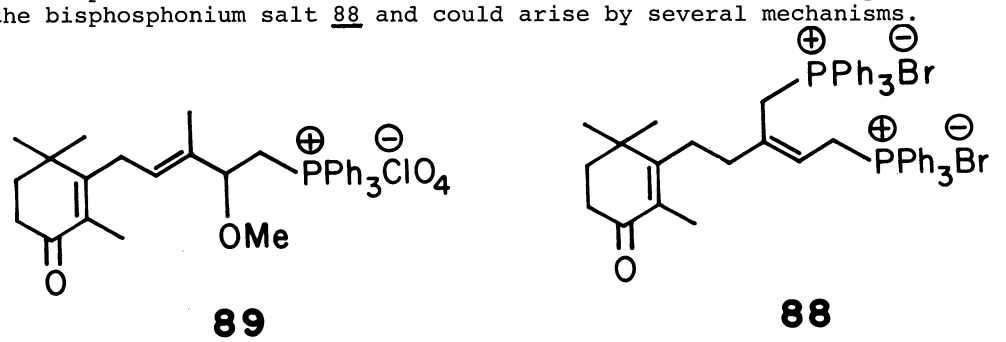




Unlike the epoxide derived from retroionone, compound 84 needed sodium methoxide in refluxing methanol to effect the rearrangement to the hydroxy-ketone 85. Treatment of this compound with an excess of vinylmagnesium chloride then gave the diol 86 which on oxidation with aluminum isopropoxide in an acetone-toluene mixture, yielded the keto alcohol 87 in an overall yield of 64% from α-ionone. Conversion of 87 to the desired salt 23 eventually proved straightforward simply by treatment with triphenylphosphine hydrobromide in dichloromethane. The further transformation to canthaxanthin then follows as before. In this way, one can make the carotenoid in 40% yield from α-ionone employing common chemicals and equipment and involving no unstable intermediates.

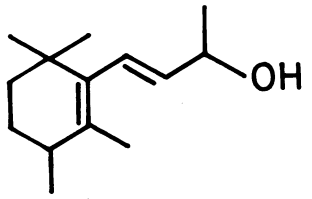
As is often the case in total synthesis, the final solution gives no indications of the problems encountered and even a simple set of transformations as described above for α-ionone have their hidden pitfalls; some of these experiences are as follows.

Initially, in our pilot experiments, the alcohol 87 was converted to the salt 23 in the conventional way employing phosphorus tribromide and then triphenylphosphine. This method worked reasonably well on a small scale but when carried out on a molar scale, a new salt comprising about 20% of the total product mixture resulted. This material was eventually identified as the bisphosphonium salt 88 and could arise by several mechanisms.



One possible rationale for the formation of this salt 88 is due to the excess of hydrogen bromide, generated with the phosphorus tribromide, which leads to dehydration of the alcohol 87. The addition of hydrogen bromide to this dehydration product would then give a dibromide which with triphenylphosphine could afford 88. Noting this problem, we resorted to the use of triphenylphosphine in methanolic sulfuric acid for the formation of salt 23. This is a conventional method employed for the conversion of vinyl-β-ionol to the C_{15} salt employed in the synthesis of vitamin A. Under these reaction conditions, the substrate 87 generated a new product, which was characterized as its perchlorate salt and identified as the methanol adduct 89.

Another side product in our new synthesis of canthaxanthin is the dione 90 which results from the prolonged exposure of the hydroxyketone 85 to the rearrangement conditions. In the sequence of reactions leading to the product 86 from 85, we also observed an unexpected result.



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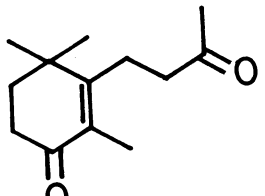

90

For the introduction of the two carbons in the sequence 85→86, the most practical route is clearly via acetylene followed by partial hydrogenation. However, for convenience we originally employed vinylmagnesium chloride in tetrahydrofuran for this transformation. When we substituted the corresponding bromide, the yield of the desired material 86 was poor and the major component was the reduction product 91 formed in at least 50% yield.

In conclusion, it appears that while some general reactions are not always so general, the above work indicates that there are still a lot of old substrates which can be used for the generation of useful processes in the carotenoid field.

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