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SYNTHESIS OF OPTICALLY ACTIVE CAROTENOIDS AND RELATED COMPOUNDS

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Abstract - Syntheses of optically active carotenoids and related compounds reported over the last two decades are reviewed.

The various methods employed for the preparation of optically active building units and their utilization in polyene synthesis are discussed. Some previously unpublished work is described. This includes new routes to (3R,3'R)-, (3S,3'S)- and (3R,3'S)-zeaxanthin, first syntheses of (3S,3'S)-, (3R,3'R)- and (3R,3'S)-astaxanthin, (3S,3'S)-mono- and diacetylenic asterinic acid as well as (3R,3'R)- and (3S,3'S)-actinioerythrol.

Syntheses of optically active forms of some degraded carotenoids, e.g. abscisic acid, xanthoxin, loliolide, dehydrovomifoliol, blumenols A and B, theaspirone and picrocrocin are also reported.

INTRODUCTION

Of the various classes of Nature's pigments, there can be no doubt that the carotenoids are the most widespread and important. They are responsible for many of the brilliant colours in fruit, vegetables, fish, crustacae, eggs and other plants and animals. They probably have the most varied function, and some fulfill a vital role as provitamins A to which their structures are closely related.

According to Straub's list (Ref. 1) of 1976, more than half of the well over 400 naturally occurring carotenoids of known structure possess chiral end groups. That means they occur in optically active forms. The absolute configuration of about 60 has already been established, yet only a few have hitherto been totally synthesized.

It is particularly the total synthesis of optically active carotenoids and related compounds that presents a unique challenge to the skill and ingenuity of the synthetic organic chemist. These compounds not only possess complicated carbon skeletons and functional arrays, but also are usually one of several possible stereoisomers. Thus an ideal synthetic scheme must furnish the correct geometrical and optical isomer as well as the required skeletal and functional group arrangements. The control of the geometry of a double bond incorporated in the polyene chain is not a too difficult process. However, we must face the problem of optical isomerism. The introduction and control of chirality during a synthetic sequence, especially with molecules possessing more than one chiral center, is considerably more difficult and important. Here, the application of new methods and modern physical techniques is an absolute necessity. It is in these areas that substantial progress has been made in recent years.

The tremendous amount of work devoted to the total synthesis of carotenoids and vitamin A was the subject of a comprehensive report (Ref. 2) considering the literature up to 1970. The progress made since then has been reviewed by several authors (Refs. 3-14a). The purpose of this paper is to give a summary up to the middle of 1978 of the main methods for the synthesis of optically active carotenoids and related compounds. As it is impossible in the space of this review to do justice to all the work which has been carried out in this field, a selection of successful synthetic designs will be portrayed and their creation analyzed. Attention will also be directed to some problems that have recently been tackled by a Roche group of scientists. Partial syntheses (change of functionality) will be mentioned briefly only in those cases where this seems appropriate in connection to total syntheses. Some partially synthesized chiral end groups and the corresponding carotenoids are listed in Fig. 42. Similar to the classifications used earlier (Ref. 2), liberal use of building schemes has been made to illustrate the stereochemical outcome of important steps.

DISCUSSION

In designing a synthesis of an optically active carotenoid it is important to consider the following facts: The relatively complex structure of a carotenoid molecule can be constructed only in a multi-step synthesis, best carried out in a convergent manner.

Carotenoids possessing chiral end groups, such as zeaxanthin or astaxanthin, make the situation even more difficult since, most likely, β-ionone or vitamin A alcohol cannot be used as readily available building units. Therefore, completely new routes have to be devised.

In principle, three approaches may be pursued:

1. Utilization of the enantiomers of small chiral components which already possess the desired absolute configuration present in the target molecule.
2. Introduction of chirality into an achiral carotenoid skeleton, such as lycopene, β-carotene or canthaxanthin, as a final step in a synthetic sequence. Obviously, Nature has chosen this elegant pathway, for instance for the formation of ε- or γ-end groups or for the introduction of hydroxyl groups (Ref. 15).
3. A third possibility, namely the resolution of so-called racemic carotenoids - frequently consisting of mixtures of enantiomers and meso-compounds - into enantiomers cannot be followed for practical purposes.

It is the first version that to date has been used exclusively for the synthesis of optically active carotenoids. The desired enantiomers have been obtained by the following methods: a) Isolation from natural sources; b) optical resolution via diastereomeric derivatives; c) enzyme catalyzed processes and d) asymmetric synthesis. To begin in chronological order, the preparation of the important C_{13}-component (+)-(6R)-α-ionone and its utilization for the first synthesis of a natural optically active carotenoid is discussed in the following section.

Alicyclic and acyclic carotenes

One of the most important intermediates for the technical synthesis of vitamin A and certain carotenoids, such as β-carotene and canthaxanthin, is β-ionone (Fig. 1) which is readily obtained by the acid catalyzed cyclization of pseudoionone employing sulfuric acid. It is most interesting to note that this cyclization reaction takes a

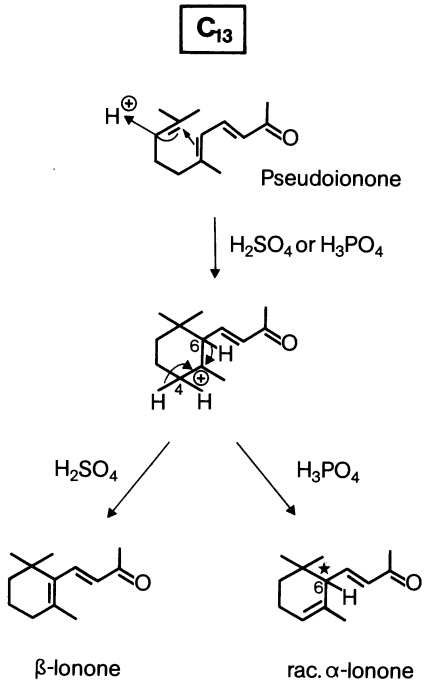


Fig. 1. Synthesis of β- and α-ionone.

completely different course if phosphoric acid is used instead of sulfuric acid as a proton source. In this case, racemic α-ionone is formed as the predominant product. Obviously, one of the protons at C-4 of the intermediate tertiary carbonium ion is abstracted here. The reaction was first studied by German workers in the 1890's (Refs. 16 & 17) and was later covered by many papers and patents (Refs. 18-23). It may well be considered as the first example for the introduction of chirality into the carotenoid field: contrary to β-ionone, α-ionone possesses an asymmetric carbon atom at position 6, making possible two optical isomers.

It was not until 1943, however, that the first successful optical resolution of racemic α-ionone into its enantiomers was reported by Sobotka et al. (Ref. 24) (Fig. 2). It should be noted here that the pure enantiomers show remarkably high optical rotations, as was found in accordance with other workers in the field (Refs. 25-27).

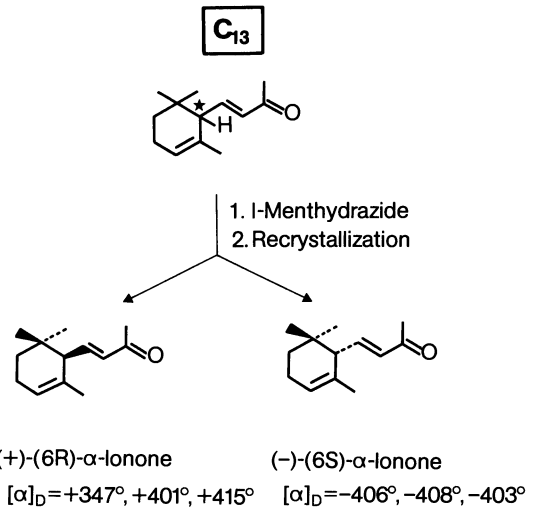


Fig. 2. Resolution of α-ionone.

With the pure (+)-(6R)- and (-)-(6S)-α-ionones at hand, the synthesis of optically active carotenoids having ε-end groups could then be considered and, in fact, both compounds were utilized by the schools of Karrer and Eugster (Refs. 26-29) in their pioneering investigations into the total synthesis of α- and ε-carotene. The task was to devise a suitable route which would provide the desired compounds with retention of configuration. This was done in the following way (Fig. 3): Treatment of the enantiomeric α-ionones with propargyl bromide and zinc in a Reformatzkii reaction afforded

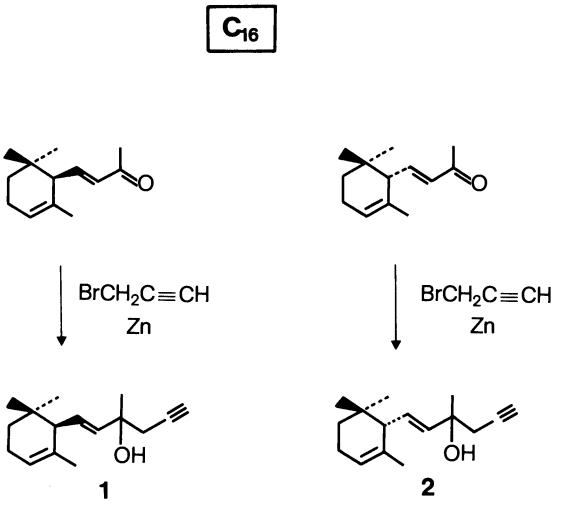


Fig. 3. Synthesis of C_{16}-building units.

the acetylenic C_{16}-carbinols 1 and 2 which could then be reacted with an appropriate central component (Fig. 4). Thus, a mixed Grignard reaction of 1 and the C_{16}-carbinol 3, obtained from β-ionone, with the C_8-diketone 4 first gave a mixture of diastereomeric tetrols 5. Subsequent hydrogenation, dehydration and isomerization afforded (6'R)-β,ε-carotene (α-carotene) which proved to be identical in every respect with the natural compound (Refs. 27-29). This constitutes the first synthesis of a natural optically active carotenoid which can certainly be regarded as a milestone in the field.

Following the same line (6'S)-β,ε-carotene was obtained from the C_{16}-carbinol 2 (Refs. 27-29).

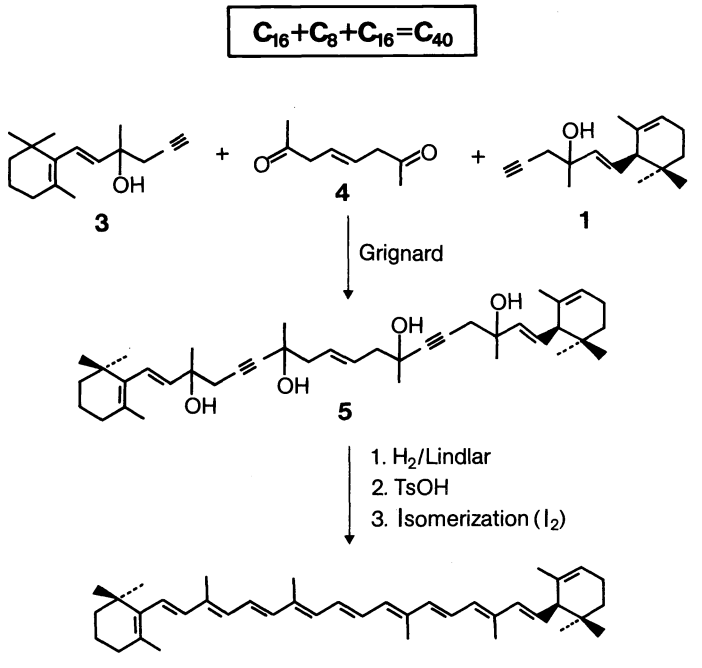


Fig. 4. Synthesis of (6'R)-β,ε-carotene.

A partial synthesis of (6'R)-β,ε-carotene from lutein was reported later (Refs. 30 & 31) in the course of investigations into the absolute stereochemistry of the latter carotenoid.

The symmetrical compound (6R,6'R)-ε,ε-carotene (ε-carotene), identical with the natural compound (Ref. 32), and its enantiomer have been prepared accordingly utilizing two equivalents each of the acetylenic C_{16}-carbinols 1 and 2, respectively (Refs. 26, 27 & 29) (Fig. 5).

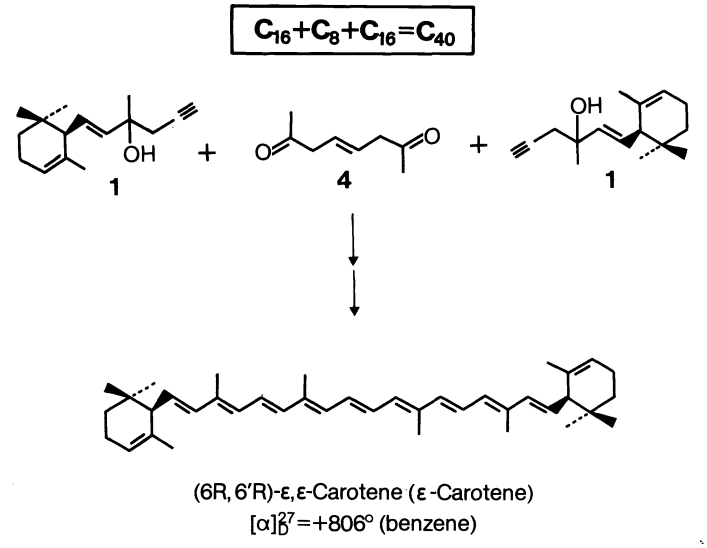


Fig. 5. Synthesis of (6R,6'R)-ε,ε-carotene.

Alternatively, (6'R)-β,ε-carotene could also be prepared according to the scheme $C_{15} + C_{25} = C_{40}$ employing a Wittig reaction (Ref. 33). The C_{15}-phosphonium salt 7 (Fig. 6), obtained from (+)-(6R)-α-ionone via the intermediate vinyl carbinol 6 by standard procedures, was condensed with β-apo-12'-carotenal (8) to give the desired compound.

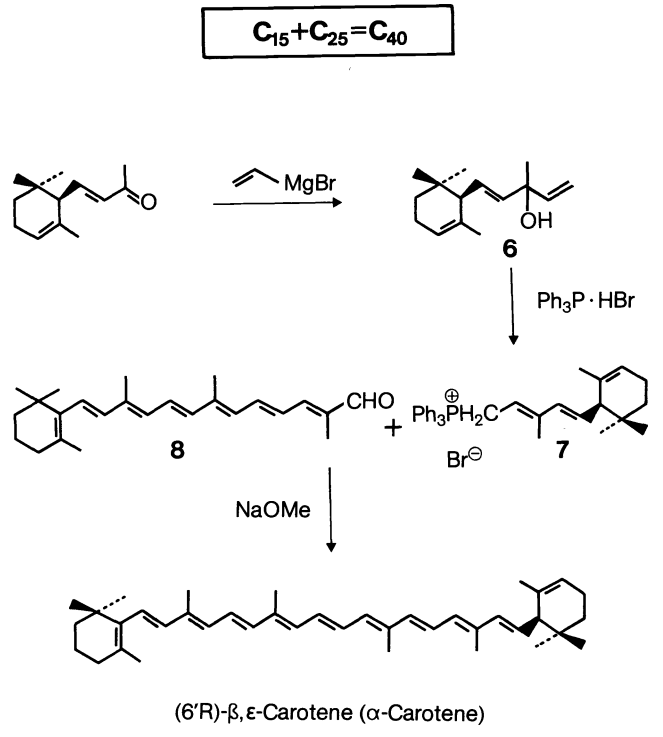


Fig. 6. Alternative synthesis of (6'R)-β,ε-carotene.

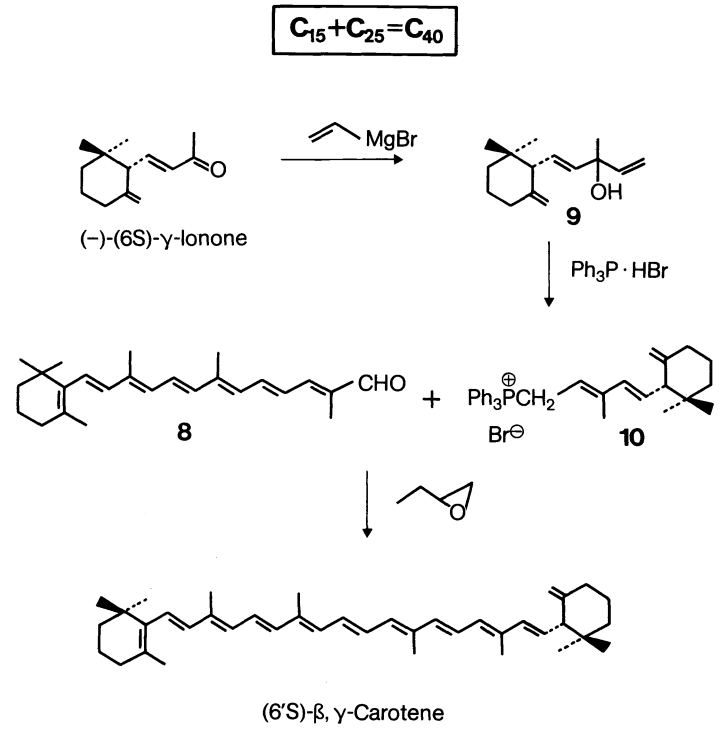


Fig. 7. Synthesis of (6'S)-β,γ-carotene.

Enantiomeric γ-ionones, β- and α-irones have also been successfully used as cyclic C_{13}- and C_{14}-components for the synthesis of optically active carotenes as was recently demonstrated by Liaaen-Jensen and co-workers (Refs. 34-36). Thus, (-)-γ-ionone (Fig. 7) enriched in the (6S)-enantiomer by partial resolution, was first transformed into the C_{15}-Wittig salt 10 via the intermediate vinyl carbinol 9. Condensation with β-apo-12'-carotenal (8) then gave β,γ-carotene enriched in the (6'S)-enantiomer (Ref. 34). β,γ-Carotene enriched in the (6'R)-enantiomer was prepared accordingly. The CD-spectrum of the latter compound was opposite to that of natural β,γ-carotene, thus proving the (6'S)-chirality of the natural product.

(2R,2'R)-2,2'-Dimethyl-β,β-carotene (Fig. 8) has recently been synthesized as a model for CD-correlation and assignment of the (2R,2'R)-chirality to the C_{50}-carotenoid C.p. 450 (Ref. 35). Horner reaction of (+)-(2R)-β-irone, isolated from base-isomerized Iris oil, afforded the C_{16}-ester 11 which on metal hydride reduction provided the corresponding alcohol 12. The Wittig salt 13, obtained by conventional methods, was then condensed with the C_{10}-dialdehyde 14 to give the desired product.

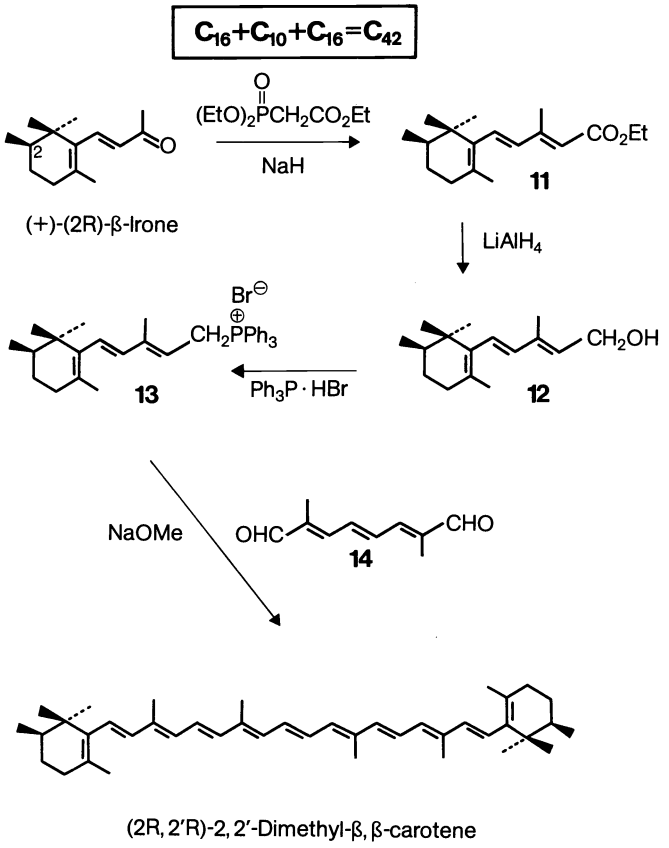


Fig. 8. Synthesis of (2R,2'R)-2,2'-dimethyl-β,β-carotene.

(2R,6S,2'R,6'S)-2,2'-Dimethyl-ε,ε-carotene and its diastereoisomer (Fig. 9) have been synthesized as model compounds for the establishment of the (2R,6R,2'R,6'R)-configuration of decaprenoxanthin (Ref. 36). Employing reactions known to retain stereochemical integrity at C-6 of the ionones, (+)-(2R,6S)-cis-α-irone from Iris oil was converted via the carbinol 15 into the Wittig salt 16 which was then reacted with 14. The (2R,6R,2'R,6'R)-diastereoisomer was prepared in an analogous way starting from (-)-(2R,6R)-trans-α-irone.

Another interesting example for the utilization of natural enantiomers as building units is presented in Fig. 10: (-)-(2R)-Lavandulol proved to be a convenient starting material for the synthesis of acyclic carotenes. Thus, condensation of the C_{15}-Wittig salt 17, prepared with retention of configuration, with crocetindial (18) afforded (2S,2'S)-tetraanhydrobacterioruberin as a model for the assignment of (2S,2'S)-chirality to natural bacterioruberin (Ref. 37).

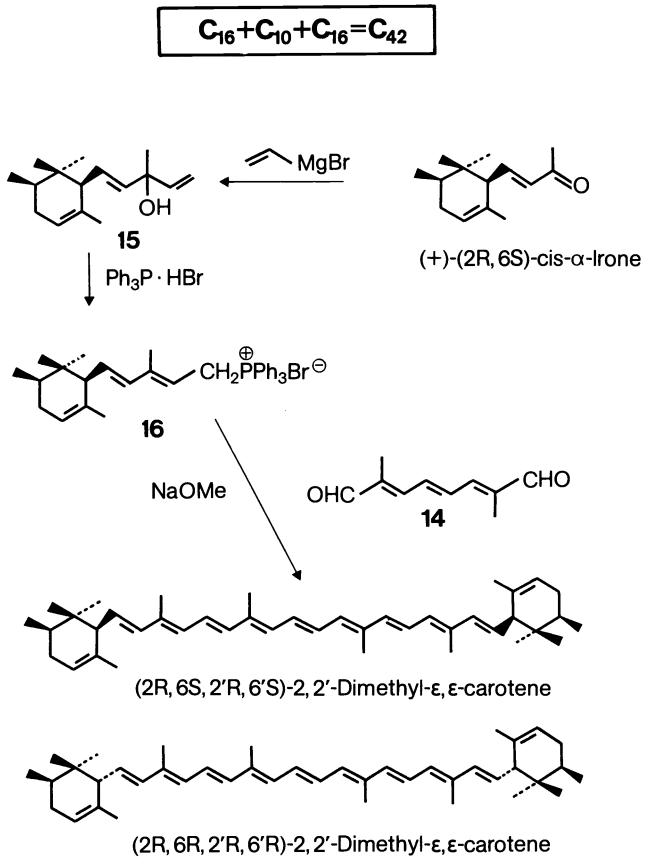


Fig. 9. Synthesis of 2,2'-dimethyl-ε,ε-carotenes.

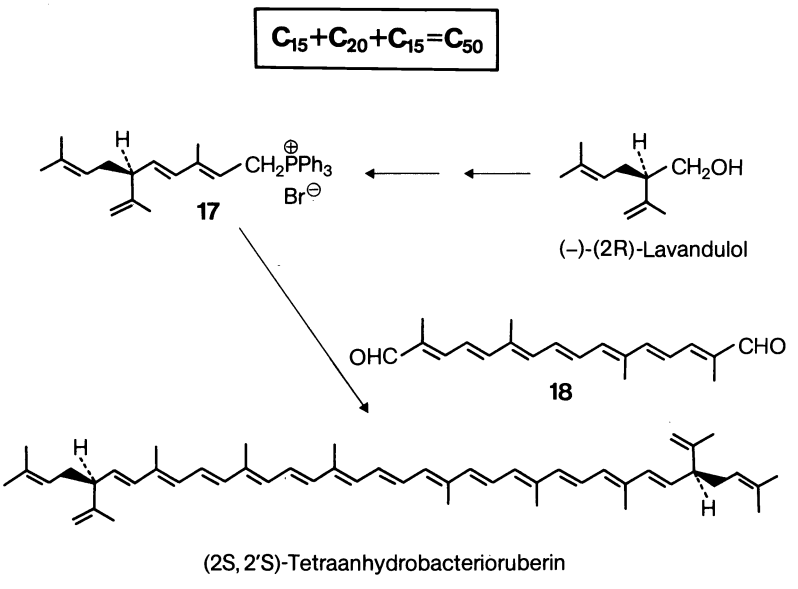


Fig. 10. Synthesis of (2S,2'S)-tetraanhydrobacterioruberin.

Xanthophylls

Four major pigments may be mentioned here representing most of Nature's carotenoid production: fucoxanthin, lutein, violaxanthin and neoxanthin. By comparison, all others are produced in small amounts, though some occur very widely or constitute the principal pigment in a particular organism, such as zeaxanthin and astaxanthin.

The fascinating structures of these compounds have attracted the interest of the synthetic chemist for many years, but it was not until 1972 that the first synthesis of an optically active xanthophyll, capsorubin (Fig. 11), one of the unusual pigments

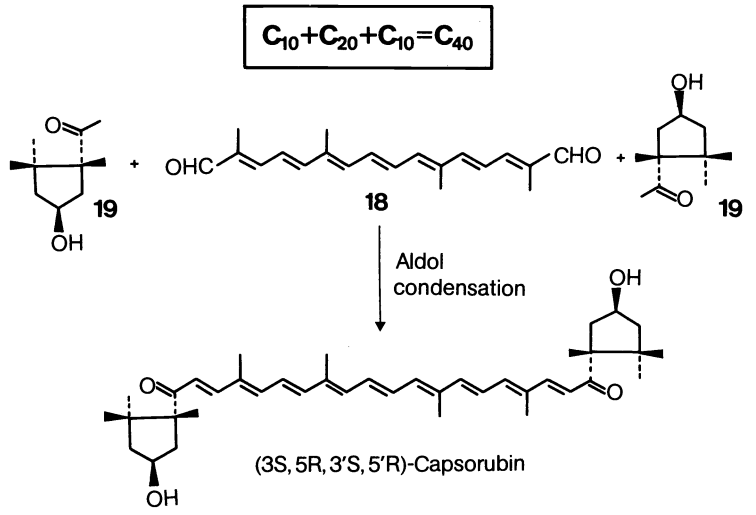


Fig. 11. Synthesis of (3S,5R,3'S,5'R)-capsorubin.

found in red peppers, was reported by Weedon et al. (Refs. 3 & 38). By an aldol condensation, a simple and efficient coupling method, crocetindial (18) was reacted with the appropriate methyl ketone 19 to give (3S,5R,3'S,5'R)-capsorubin possessing the correct natural configuration. The cyclic component 19 was prepared from the ester 20 (Fig. 12) which can be readily obtained from (+)-camphor. Hydroboration gave a mixture of isomeric hydroxy esters 21 and 22. The corresponding cis-isomers could not be detected. Ester 22 was then hydrolyzed to the corresponding acid 23 which was treated with methyl lithium. This is a good example of a diastereoselective, although not regioselective, introduction of a second chiral center into an optically active compound by means of an achiral reagent, in this case a hydroborating agent.

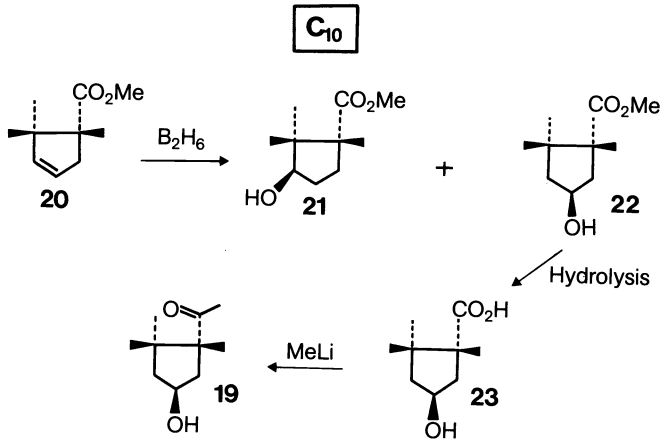


Fig. 12. Synthesis of the five-membered cyclic component.

The total synthesis of (3R,3'R)-zeaxanthin, identical with the natural pigment, was reported at the 1975 Symposium (Ref. 39). Zeaxanthin is very widely distributed. Some plants, such as yellow maize, contain zeaxanthin as the main pigment, accompanied by lutein. It is from this source - besides grass and alfalfa - that zeaxanthin is utilized by the laying hen for egg yolk and skin pigmentation.

Clearly, the molecule possesses two chiral centers at C-3 and C-3' making possible three optical isomers, namely the (3R,3'R)- and the (3S,3'S)-isomer - which together form a racemate - as well as the (3R,3'S)-isomer which, of course, constitutes the internally compensated meso-form (Figs. 22-25). It is this mixture of isomers which is usually obtained in syntheses of the so-called racemate.

Natural zeaxanthin was shown to possess the (3R,3'R)-configuration (Refs. 40 & 41), irrespective of whether the source is higher plants, algae or bacteria (Ref. 42).

Partial syntheses of (3R,3'R)-zeaxanthin from violaxanthin (Refs. 33 & 43), neoxanthin (Ref. 45) and fucoxanthin (Ref. 45) have already been reported.

Our objective was to design a route which would allow the controlled synthesis of all three optical isomers. Here again, the utilization of small optically active building units turned out to be the best strategy for the introduction of chirality into the carotenoid skeleton.

We must acknowledge, however, that this idea had also been expressed earlier by Mori (Ref. 46), who succeeded in synthesizing the protected optically active hydroxy ketone 27. As resolving agent, a steroidal acid chloride was employed to give a mixture of diastereomeric ketones 25 and 26. The diastereoisomer 26 could then be transformed in low yields into the building unit 27 as illustrated in Fig. 13.

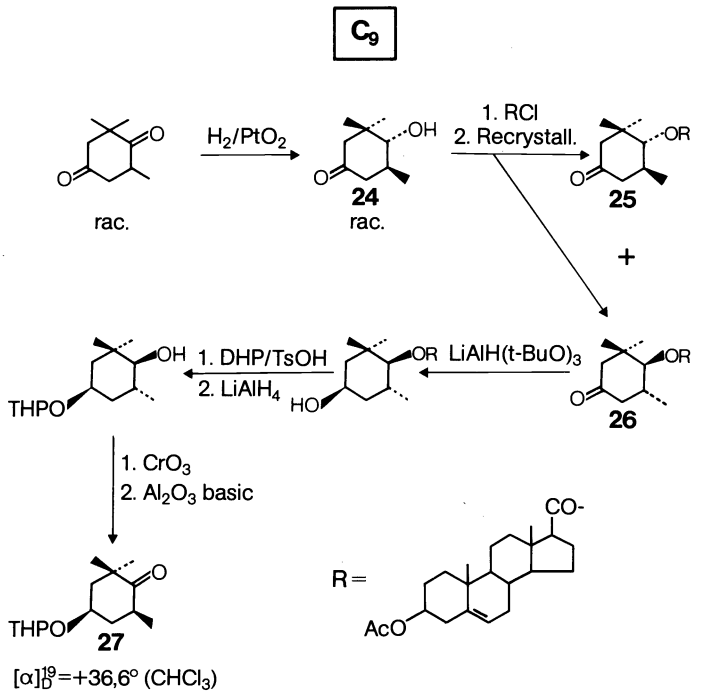


Fig. 13. Synthesis of (4R,6S)-2,2,6-trimethyl-4-(tetrahydropyranyloxy)cyclohexanone.

An efficient technical synthesis of the C_9-hydroxy ketone 30 (Fig. 14), an epimer of 27, has recently been reported by Boguth and co-workers (Ref. 47) utilizing oxoisophorone (28) as a readily available starting material. Chirality at C-6 was introduced by an enantioselective fermentative reduction of the double bond using baker's yeast. Subsequent diastereo- and regioselective reduction of the resulting diketone 29 then gave a 4:1 mixture of epimeric hydroxy ketones 30 and 31 which could be readily separated by Craig-distribution. The hydroxy ketone 30 proved to be an ideal precursor for the synthesis of optically active xanthophylls and related compounds.

Bromination of the acetate 32 (Fig. 15), obtained from 30 by standard procedures, gave a mixture of epimeric bromides 33 which, on dehydrobromination, yielded the unsaturated ketone 34. Subsequent hydrolysis then afforded the unsaturated C_9-hydroxy ketone 35, which turned out to be another very useful building unit (Ref. 48). For comparison of chiroptical properties, 35 was converted into the corresponding benzoate 36 which had already been obtained earlier by Koreeda et al. (Ref. 49) through a different route.

Another efficient entry into the field of chiral components has recently been found by the application of asymmetric hydroboration. Thus, treatment of the protected C_{10}-di-

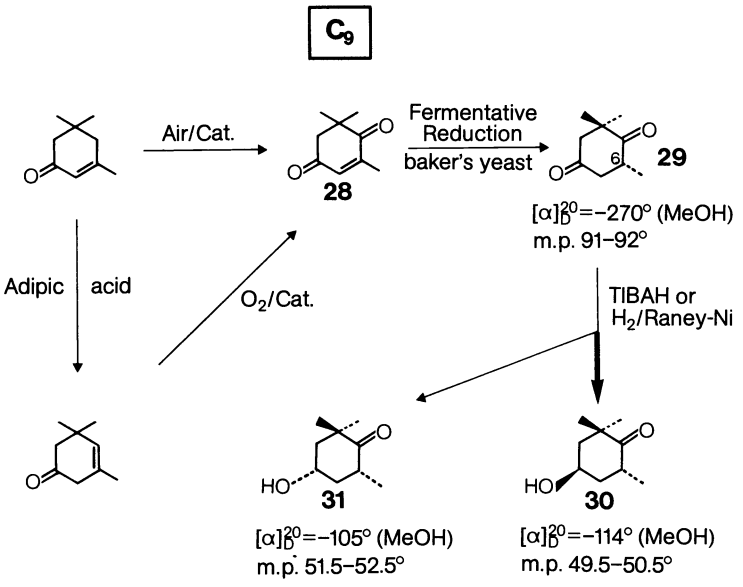


Fig. 14. Technical synthesis of (4R,6R)-4-hydroxy-2,2,6-trimethylcyclohexanone.

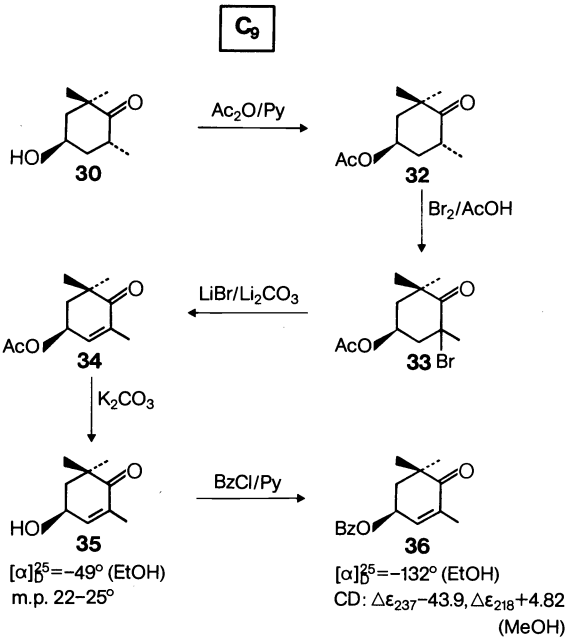


Fig. 15. Synthesis of (4S)-4-hydroxy-2,6,6-trimethyl-2-cyclohexen-1-one.

ene alcohol 37 (Fig. 16) with (+)-diisopinocampheylborane [(+)-(IPC)$_2$BH], readily available from (-)-α-pinene and borane (Refs. 50 & 51), gave the C_{10}-diol 38 in excellent optical yield (Ref. 52). It is interesting to note that in this case chirality is introduced at the prochiral center C-3 with the aid of a chiral hydroborating agent resulting in an enantio- as well as regioselective functionalization of the cyclohexadiene system. Subsequent selective oxidation of the allylic hydroxyl group yielded (3R)-3-hydroxy-β-cyclocitral (39) which had first been obtained by Kuhn and Löw (Ref. 53) from saffron. When (-)-(IPC)$_2$BH was employed, the corresponding enantiomeric compounds 40 and 41 were isolated in an analogous way.

It was also Mori (Ref. 46) who first announced the synthesis of the important C_{13}-in-

termediate (3R)-3-hydroxy-β-ionone (46) starting from the protected hydroxy ketone 27 (Fig. 17). According to a route first disclosed by Weedon and co-workers (Ref. 54) for the synthesis of racemic zeaxanthin, 27 was reacted with protected 3-butyn-2-ol (42) to give after acetylation a mixture of diastereomeric acetates 43 which, after dehydration and subsequent metal hydride reduction of the acetate mixture 44, yielded (3R)-3-hydroxy-β-ionol (45) as a mixture of two epimers at C-9. This product was then oxidized to the desired C_{13}-unit 46 which, in a final step, was converted into the corresponding acetate 47.

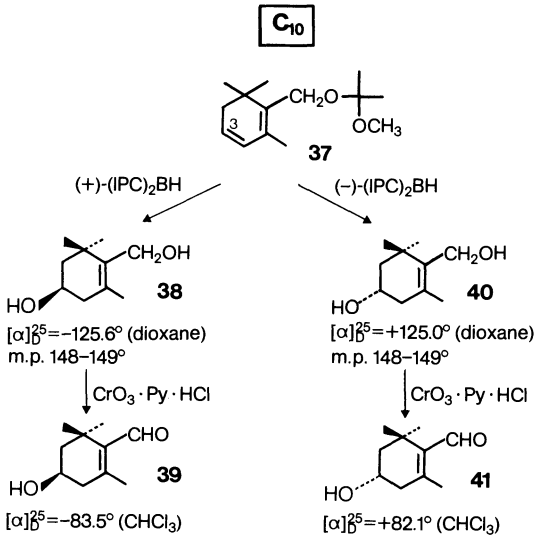


Fig. 16. Synthesis of (3R)- and (3S)-3-hydroxy-β-cyclocitral.

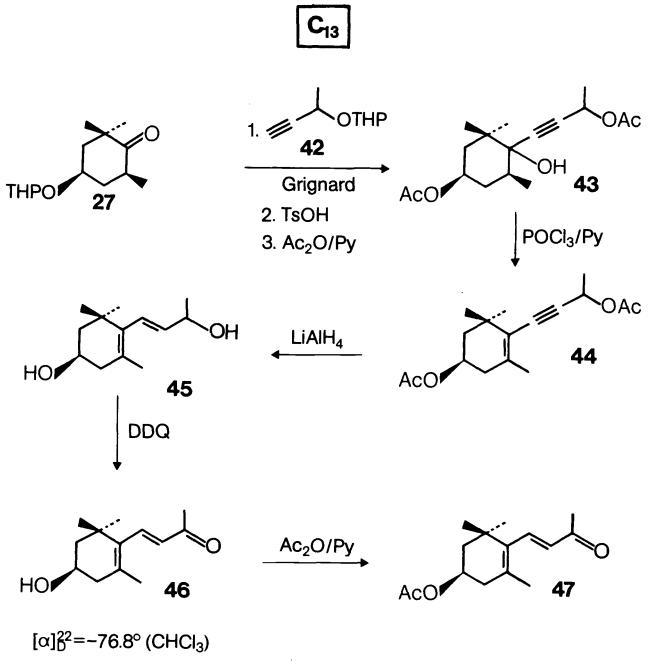


Fig. 17. Synthesis of (3R)-3-hydroxy-β-ionone.

We have followed a similar route (Ref. 39) utilizing the acetonide 48 (Fig. 18) which was readily prepared from the hydroxy ketone 30 by treatment with isopropenyl methyl ether. The reduction of the diacetate 44 was performed with sodium bis-(2-methoxyethoxy)aluminum hydride (SMEAH).

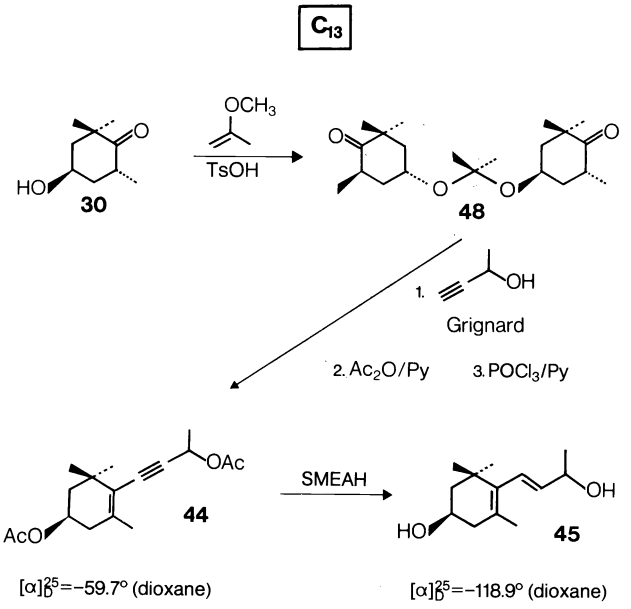


Fig. 18. Synthesis of (3R)-3-hydroxy-β-ionol.

Chain lengthening to C_{13} could also be achieved in a step-wise manner (Ref. 55) (Fig. 19). Thus, ethynylation of the hydroxy ketone 30 gave a mixture of epimeric ethynyl carbinols 48 which, on Si-V-catalyzed rearrangement (Ref. 56), yielded the C_{11}-aldehyde 49. This was smoothly transformed in three steps into the nitro compound 51.

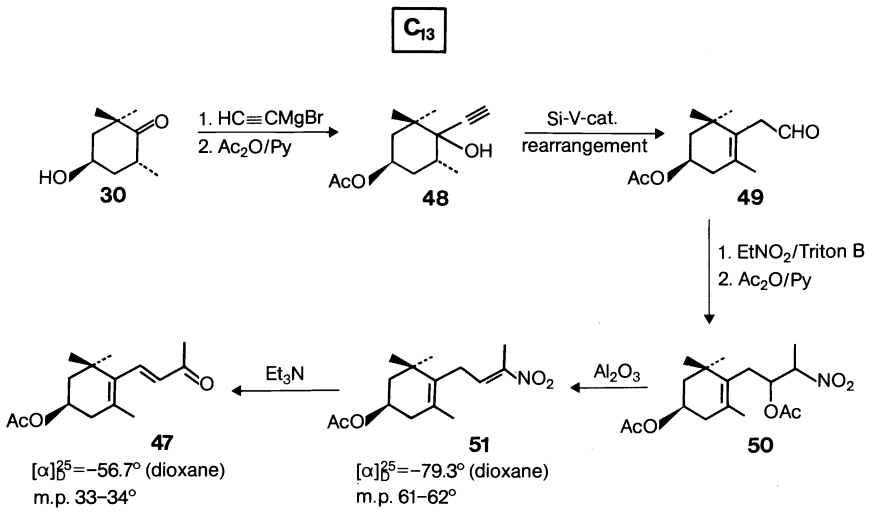


Fig. 19. Synthesis of (3R)-3-acetoxy-β-ionone.

Chain lengthening by two carbon atoms was thereby effected by an aldol-type condensation with nitroethane to give the intermediate nitro compound 50 which readily lost acetic acid on treatment with alumina. In a final step, 51 was converted into the desired (3R)-3-acetoxy-β-ionone (47) by a Nef-type reaction.

A very efficient route affording (3R)-3-hydroxy-β-ionone (46) and various useful intermediates in excellent chemical and optical yields has recently been developed (Ref. 57): Analogous to a method exemplified with 2,6,6-trimethyl-2-cyclohexen-1-one (Ref. 58), the protected hydroxy ketone 52 (Fig. 20) was first reacted with the sulfur ylide 53 to give the allylic epoxide 54 which was readily transformed into (3R)-3-hydroxy-β-cyclocitral (39) via the intermediate aldehydes 55 and 56. Base-catalyzed condensation of 39 or 56 with acetone then furnished 46 which was also converted into the corresponding acetate 47. For structural and CD-correlations 39 and 46 have also been transformed into the corresponding methyl ethers 57 and 58, respectively, which proved to be identical with the known compounds (Refs. 30, 31 & 59). The chirality at C-6

of 55 is being established.

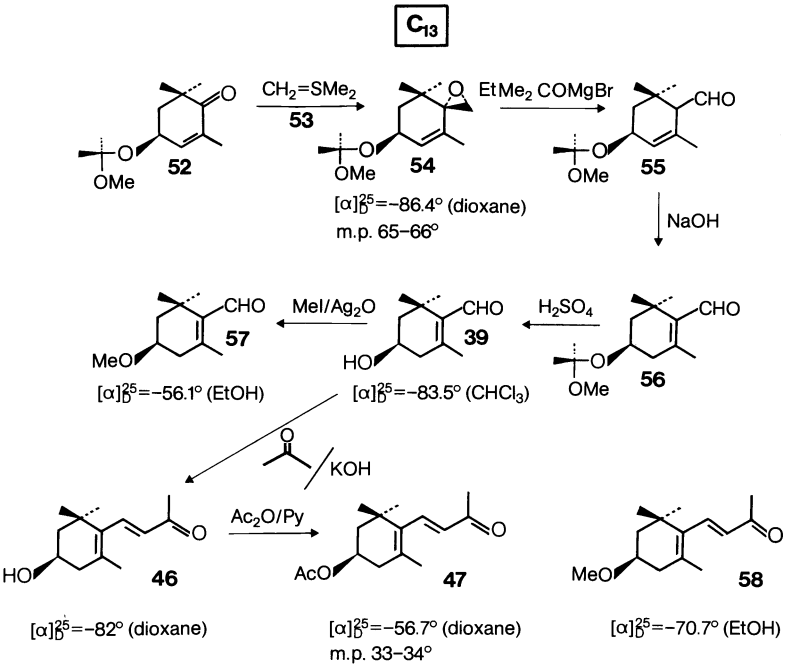


Fig. 20. Technical synthesis of (3R)-3-acetoxy-β-ionone.

(3R)-3-Hydroxy-β-ionol (45), also obtained by reduction of (3R)-3-hydroxy-β-ionone (46), was then converted into a mixture of epimeric C_{13}-Wittig salts 60 and 61, respectively, by standard methods (Fig. 21). The C_{15}-Wittig salts 62 and 63 were prepared according to a method published by Weedon and co-workers (Ref. 54) in the racemic series: Vinylation of 46 gave a mixture of epimeric vinyl carbinols 59 which were treated with triphenylphosphine and a mineral acid (Refs. 39 & 60).

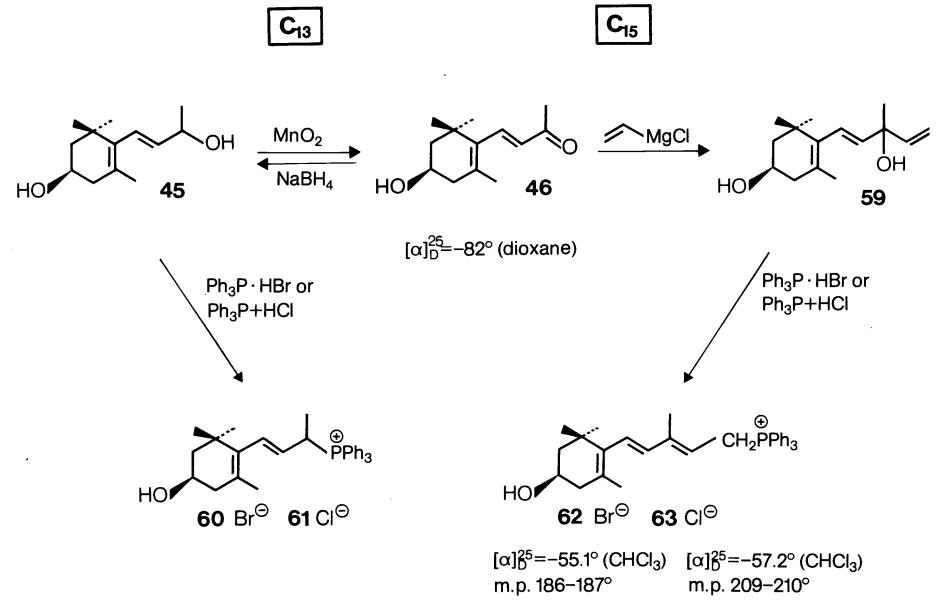


Fig. 21. Synthesis of C_{13}- and C_{15}-Wittig salts.

The synthesis of the C_{40}-carbon skeleton was then achieved according to two symmetrical building schemes. In the first of these (Fig. 22), the C_{13}-Wittig bromide 60 was reacted with the C_{14}-dialdehyde 64 having a central triple bond. The resulting mixture of 15,15'-didehydrozeaxanthin isomers could be isomerized to the all-trans-com-

pound using a special Pd-catalyst in a heterogeneous system. Subsequent partial hydrogenation and thermal isomerization then furnished all-trans-(3R,3'R)-zeaxanthin. When the fully conjugated C_{14}-dialdehyde was used, zeaxanthin was isolated directly in good yield after Pd-catalyzed isomerization (Refs. 39 & 60).

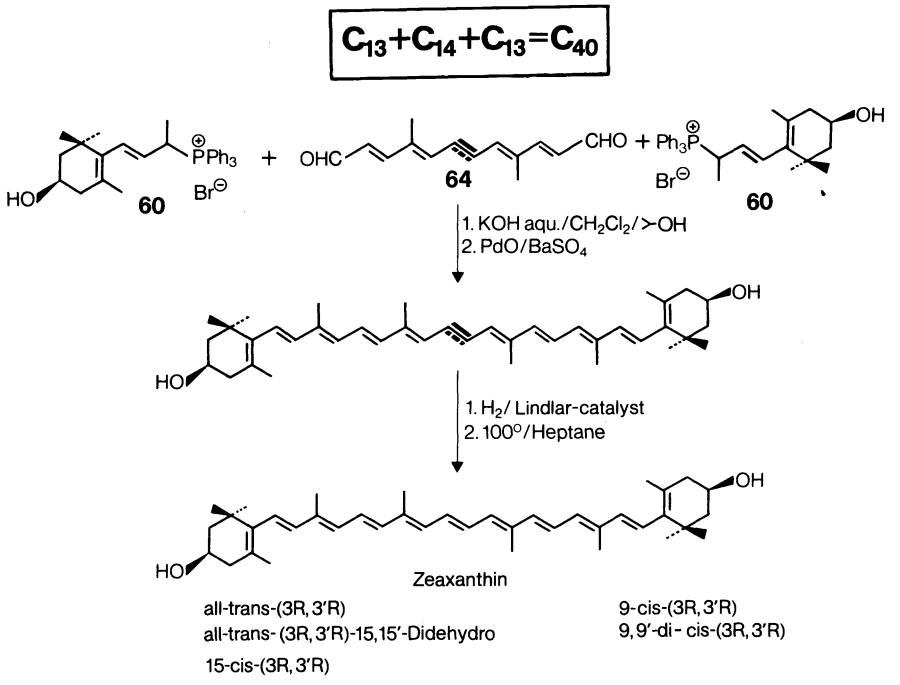


Fig. 22. Synthesis of (3R,3'R)-zeaxanthin.

Besides the all-trans-isomer the following compounds have been isolated in pure form (Ref. 60): all-trans-(3R,3'R)-15,15'-didehydrozeaxanthin, 15-cis-, 9-cis- (Refs. 60a, 61 & 92) and 9,9'-di-cis-(3R,3'R)-zeaxanthin which showed interesting chiroptical properties.

According to the building principle $C_{15} + C_{10} + C_{15} = C_{40}$ (Fig. 23) also first successfully employed by Weedon et al. (Ref. 54) in the racemic series, one can similarly choose the fully conjugated C_{10}-dialdehyde 14 or use one having a central triple bond. The reaction is carried out in a two-phase system, namely CH_2Cl_2/aqueous KOH as the base, furnishing the carotenoids in excellent yields (Refs. 39 & 60).

The knowledge gained in the synthesis of the (R)-configurated compounds could also be applied to the enantiomeric series (Fig. 24). Thus, (3S)-3-hydroxy-β-cyclocitral (41) was transformed into the C_{15}-Wittig salt 65 which was condensed with the C_{10}-dialdehyde 14 to give all-trans-(3S,3'S)-zeaxanthin. The CD-spectrum of this compound was exactly opposite to that of its (3R,3'R)-enantiomer (Ref. 52).

A partial synthesis of all-trans-(3R,3'S)-zeaxanthin from lutein has recently been reported by Andrewes et al. (Ref. 62). We have synthesized this interesting meso-compound utilizing the enantiomeric C_{15}-Wittig salts 63 and 65 (Ref. 52) (Fig. 25). The desired combination of end groups was achieved by first preparing the C_{25}-apo-compound 66 which was then condensed with the Wittig salt 65. As expected, the CD-spectrum of the product showed no optical activity.

Another example of the introduction of chirality by fermentation is presented in Fig. 26. Thus, by using baker's yeast as the biocatalyst, Ito et al. (Ref. 63) were able to achieve the enantio- and regiospecific reduction of 2-oxo-β-ionone (67) to give, after acetylation, (2S)-2-acetoxy-β-ionone (68). The C_{15}-Wittig salt 70, prepared via the ester 69 by standard procedures, was then condensed with β-apo-12'-carotenal (8) affording (2S)-β,β-caroten-2-ol, which proved to be the enantiomer of the natural product (Ref. 64).

Another important xanthophyll is represented by the red pigment astaxanthin which is found in many crustacea, such as the common lobster, in salmon, trout, and in numerous other organisms. Careful consideration of the structure reveals (Figs. 28 & 29) that it contains two chiral α-ketol end groups with two asymmetric centers at C-3 and C-3', making possible three optical isomers similar to zeaxanthin. The (3S,3'S)-configura-

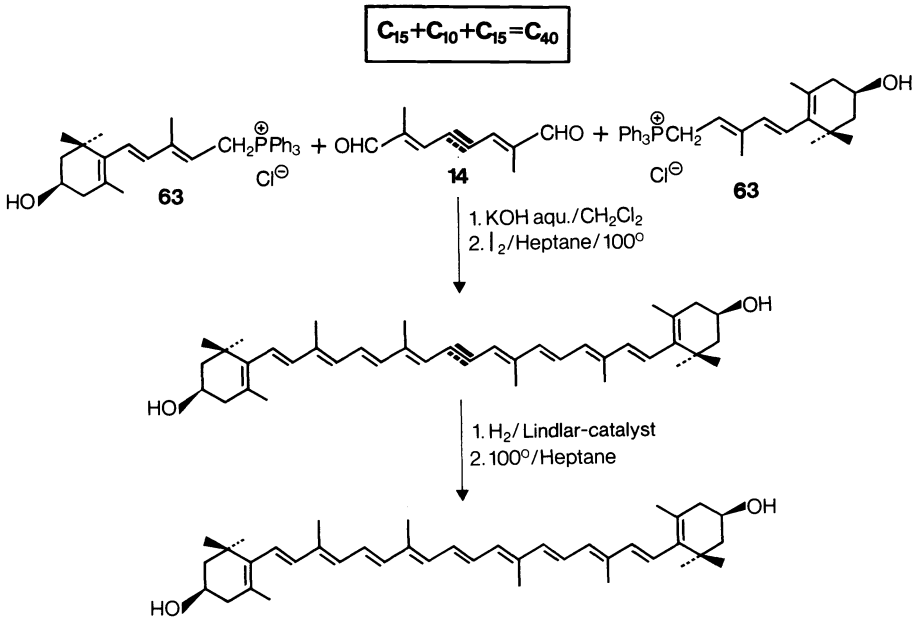


Fig. 23. Technical synthesis of (3R,3'R)-zeaxanthin.

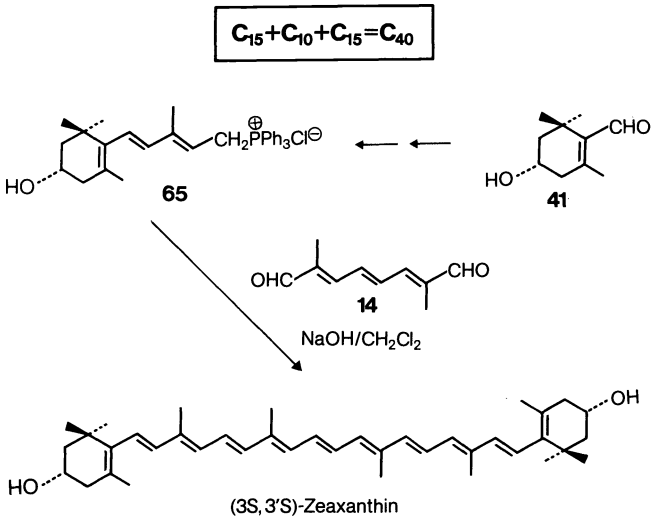


Fig. 24. Synthesis of (3S,3'S)-zeaxanthin.

tion for astaxanthin isolated from different natural sources, such as the common lobster, certain green algae and spider mites, was recently established (Refs. 65 & 66). It is highly interesting to note that the (3R,3'R)-enantiomer has recently been isolated from the red yeast Pfaffia rhodozyma as the first example of a naturally occurring carotenoid biosynthesized in different optical forms (Refs. 67 & 68).

Astaxanthin is known to undergo autoxidation, especially under basic conditions, to give astacene. Moreover, racemization of the α-ketol system may render the preparation of optically pure material impossible. This emphasizes the care that must be given to the reaction conditions employed in a projected synthetic route.

An answer to the problem is presented in Figures 27 and 28 illustrating the first total synthesis of (3S,3'S)-astaxanthin (Ref. 48). A Grignard addition of the protected acetylenic alcohol 72 to the protected hydroxyketone 71 gave a 4:1-mixture of epimeric triols 73 and 74. The introduction of the hydroxyl function into position 4 of the ring was achieved by an acid-catalyzed allylic rearrangement yielding a mixture of cis/trans-triols 75 and 76, the cis-triol 75 predominating. Oxidation of the allylic hydroxyl groups followed by catalytic hydrogenation afforded the C_{15}-ketoaldehyde 77

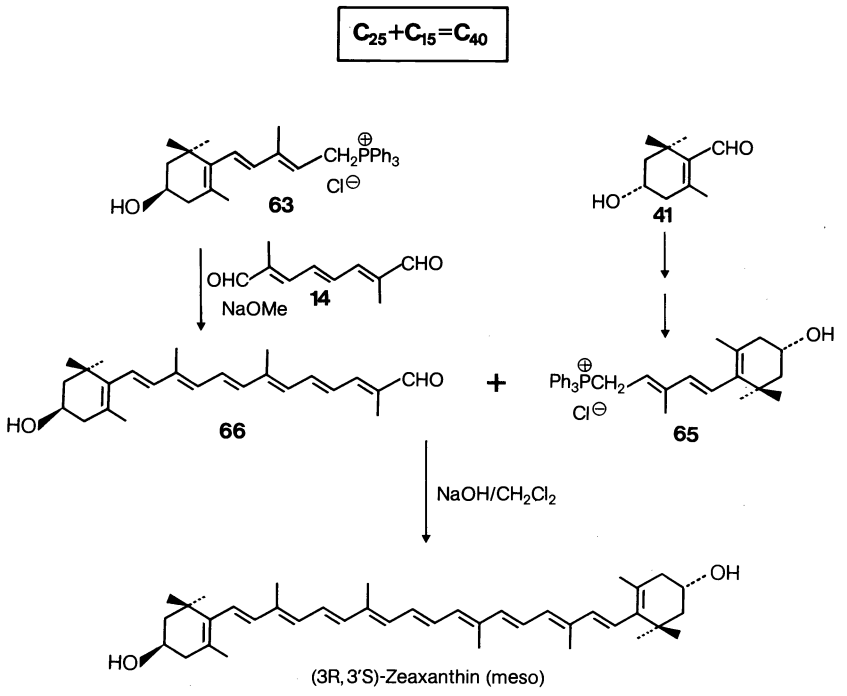


Fig. 25. Synthesis of (3R,3'S)-zeaxanthin.

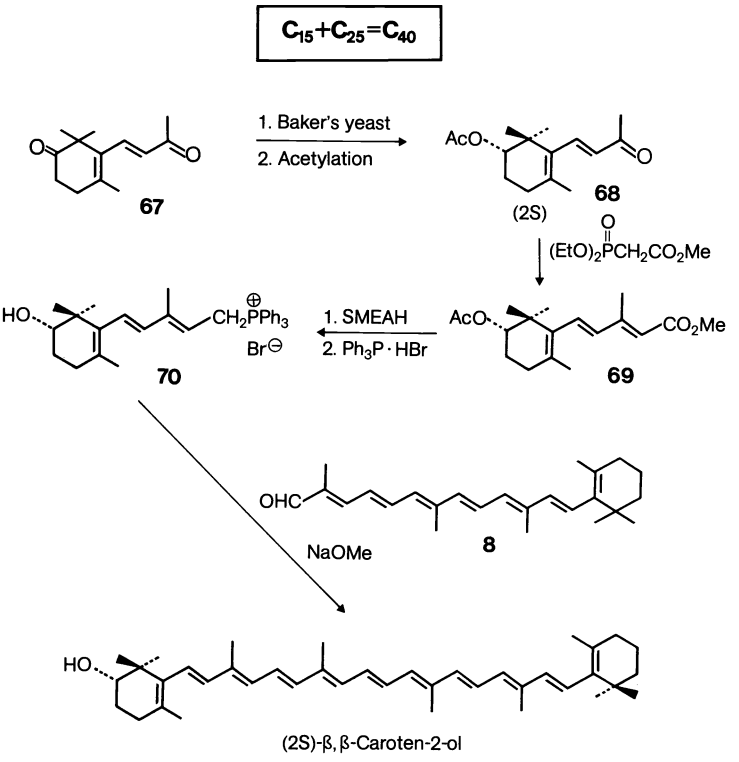


Fig. 26. Synthesis of (2S)-β,β-caroten-2-ol.

whose 7,8-cis-double bond turned out to be surprisingly stable. The protected ketoaldehyde 78 (Fig.28) was then transformed into the C_{15}-Wittig salt 79 by standard procedures. It is interesting to note the selective reduction of the aldehyde group and the all-trans-configuration of 79, the rearrangement obviously taking place during phos-

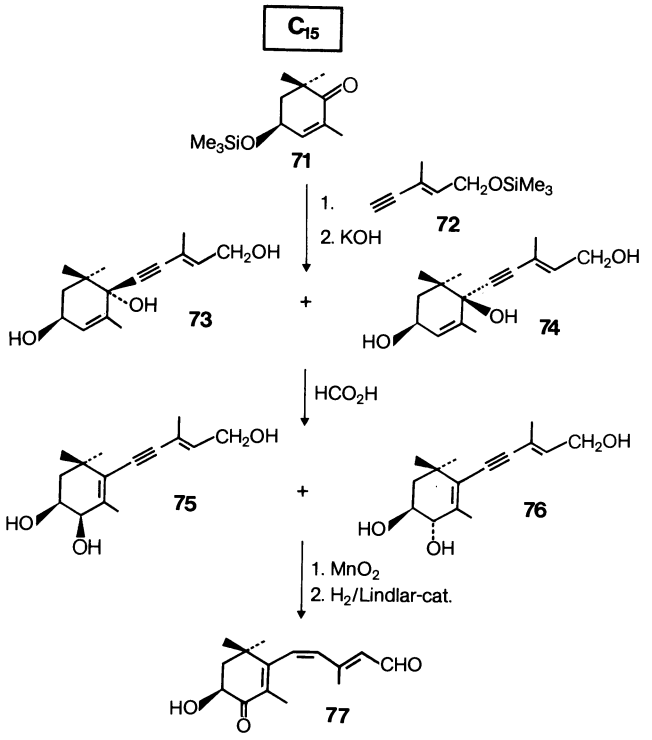


Fig. 27. Synthesis of astaxanthin intermediates.

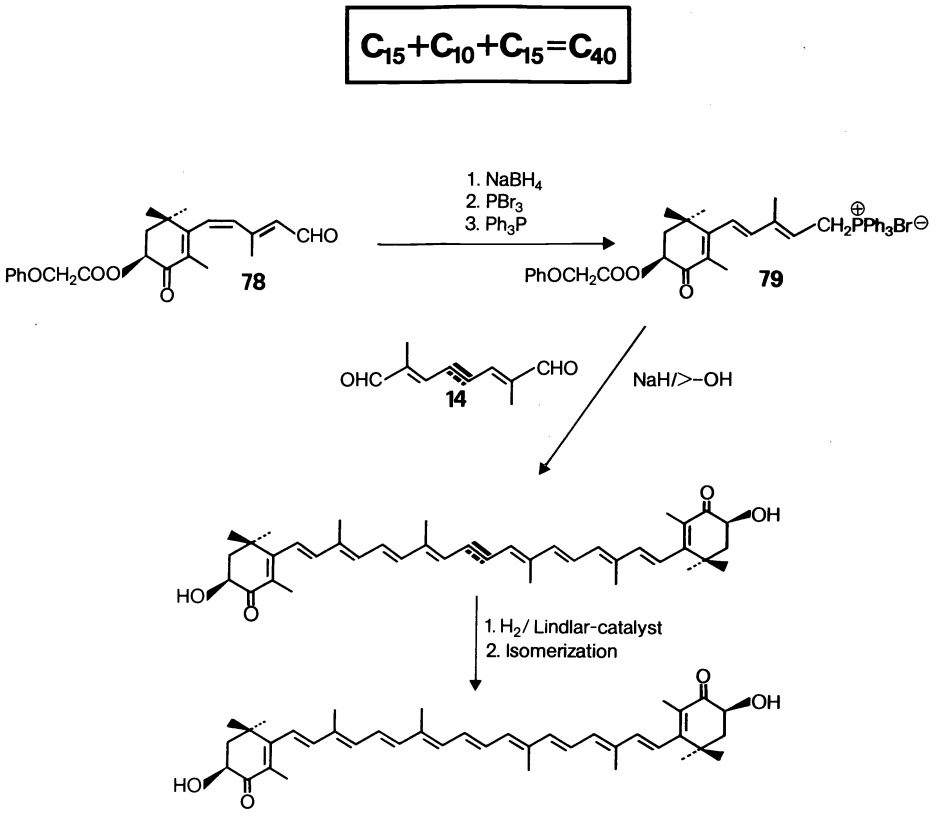


Fig. 28. Synthesis of (3S,3'S)-astaxanthin.

phonium salt formation. In a final step, 79 was condensed with the C_{10}-trienealdehyde 14 to give all-trans-(3S,3'S)-astaxanthin in high yield. Using the C_{10}-dialdehyde with a central triple bond, the corresponding 15,15'-didehydro-compound was formed. This, on hydrogenation, yielded (3S,3'S)-15-cis-astaxanthin which could readily be isomerized to the all-trans-isomer. The physicochemical properties of these compounds have recently been reported in detail (Ref. 69).

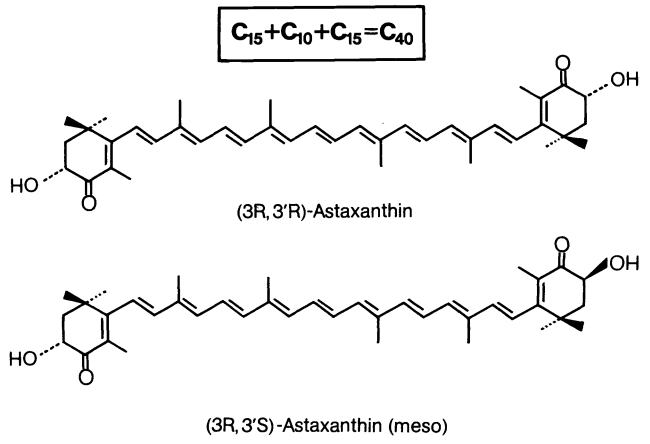


Fig. 29. Synthesis of (3R,3'R)- and (3R,3'S)-astaxanthin.

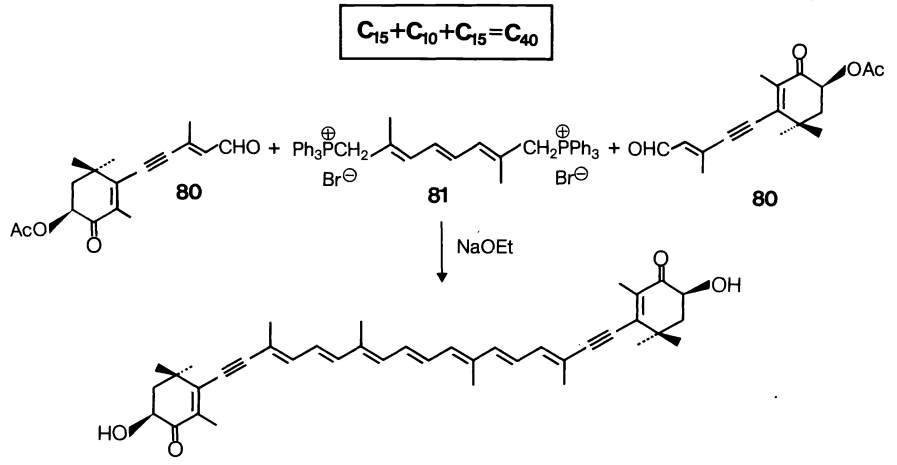


Fig. 30. Synthesis of (3S,3'S)-diacetylenic asterinic acid.

According to the same building principle, $C_{15} + C_{10} + C_{15} = C_{40}$ (Fig. 29), all-trans-(3R,3'R)-astaxanthin has recently been synthesized (Ref. 70). The CD-spectrum of this compound was consistent with that of the (3R,3'R)-isomer isolated from Pfaffia rhodozyma (Refs. 67 & 68), but was exactly opposite in sign relative to that of its enantiomer. The CD-spectrum of the meso-compound, prepared in an analogous way, showed no optical activity (Ref. 70).

The synthesis of all-trans-(3S,3'S)-mono- and diacetylenic asterinic acid (Fig. 30), which are the 7,8-didehydro- and 7,8,7',8'-tetradehydro-analogues, respectively, of astaxanthin, was reported at this meeting (Ref. 71). In this case, special care had to be taken to prevent the formation of 9-cis- and/or 9,9'-di-cis-isomers. A solution for this problem was found by the utilization of the C_{10}-bis-phosphonium salt 81 which was combined with the trans-configurated ketoaldehyde 80. The all-trans-compound thus obtained proved to be identical with the natural product of established

(3S,3'S)-configuration (Ref. 72) isolated from the starfish Asterias rubens (Ref. 72). The corresponding monoacetylenic compound was prepared by a Wittig reaction of the C_{15}-phosphonium salt 79 and the C_{25}-apo-compound 83 (Ref. 71).

Utilizing the appropriate components and building principles (Figs. 31 and 32), the following additional xanthophylls and apo-carotenoids with interesting end group combinations have been synthesized in the course of our investigations (Ref. 73): (3R)-β-cryptoxanthin, (3R)-rubixanthin, (3'R)-asteroidenone, (3'R)-β-doradecin, (3S,3'R)- and (3R,3'R)-adonixanthin, (3S)- and (3R)-adonirubin, the apo-compounds (3S)- and (3R)-82, all-trans- and 9-cis-83, the apo-esters 84 and 85, and (3R)-reticulataxanthin. The chiroptical properties of the synthetic carotenoids β-cryptoxanthin, rubixanthin, and the ketone reticulataxanthin confirm the (3R)-configuration proposed for the natural compounds (Ref. 33). The chiroptical properties of natural asteroidenone, β-doradecin, adonixanthin and adonirubin have not been reported. The apo-compounds 82-85 have been neither totally synthesized before nor isolated from natural material.

Cyclopentyl ketones and nor-carotenoids

Carotenoids possessing five-membered rings have always posed a special challenge to the synthetic chemist. Continuing the discussion started with capsorubin (Fig. 11), three additional carotenoids with chiral five-membered end groups will be discussed briefly. Trikentriorhodin and mytiloxanthin are unique carotenoids owing to the presence of an enolic β-diketone system in which the carbon-carbon double bond of the enol is part of the main polyene chain (Figs. 33 & 34). (3S,5R)-Trikentriorhodin was obtained by a Claisen-type condensation of the protected methyl ketone 86 with the C_{30}-apo-ester 87 (Ref. 38). 9-cis-(3R,3'S,5'R)-Mytiloxanthin was prepared by a Wittig reaction of the C_{15}-Wittig salt 88 with the C_{25}-apo-aldehyde 89 (Ref. 38).

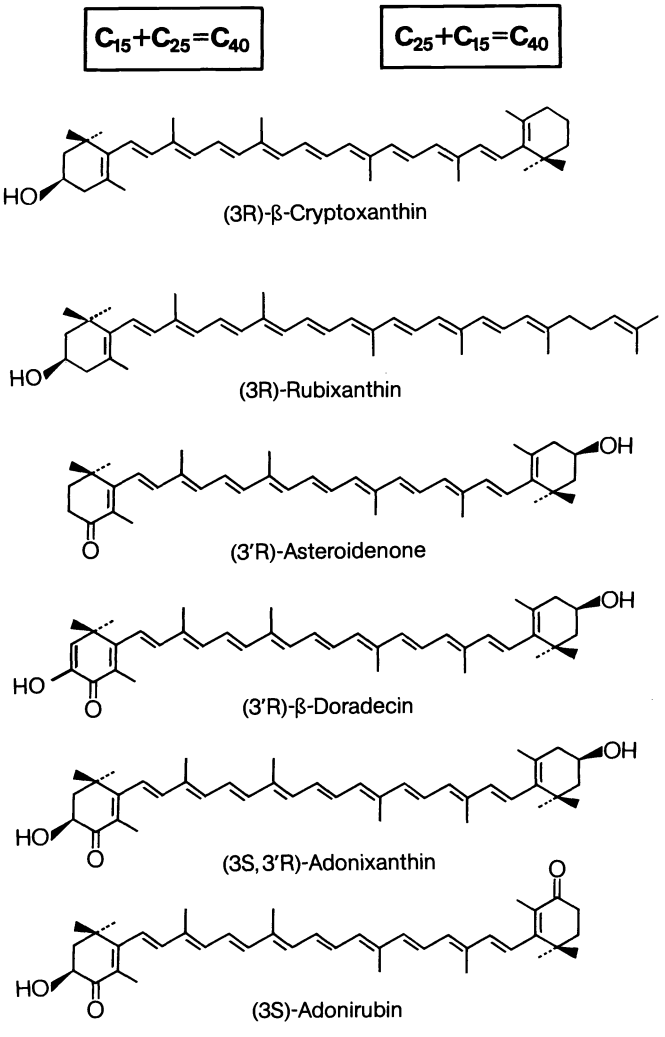


Fig. 31. Synthesis of some xanthophylls.

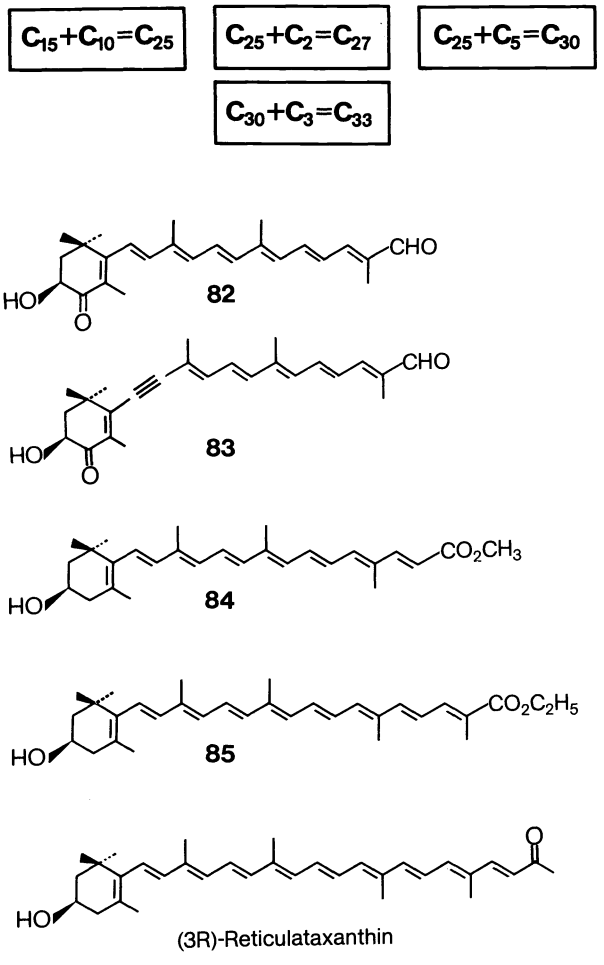


Fig. 32. Synthesis of some apo-compounds.

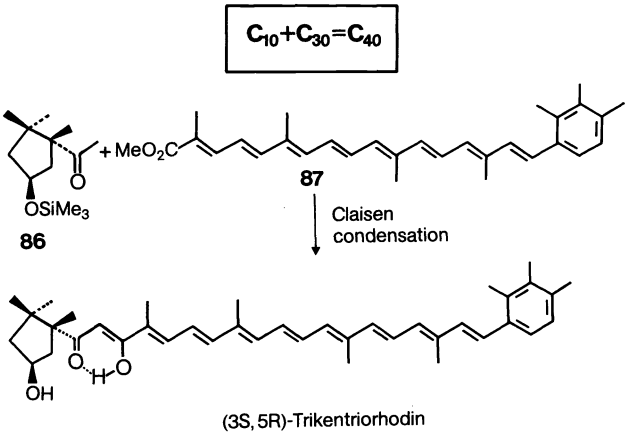


Fig. 33. Synthesis of (3S,5R)-trikentriorhodin.

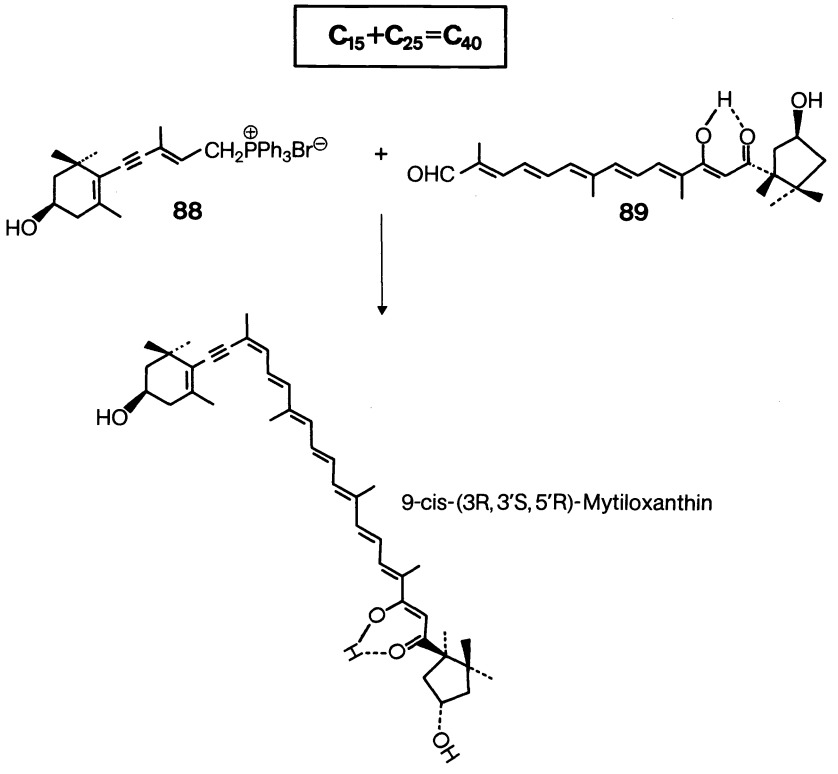


Fig. 34. Synthesis of 9-cis-(3R,3'S,5'R)-mytiloxanthin

Another carotenoid with a unique structure, but with unknown stereochemistry, is actinioerythrin (Fig. 35) which is a naturally occurring diester of the dinor-carotenoid actinioerythrol (Refs. 65 & 74). Solutions of these pigments show a deep brilliant red

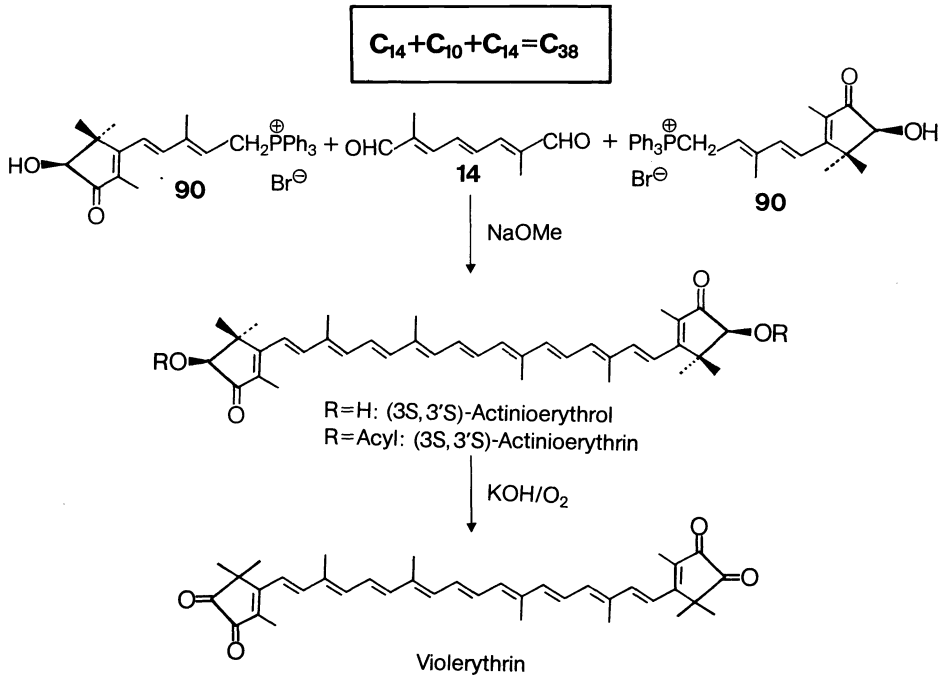


Fig. 35. Synthesis of (3S,3'S)-actinioerythrol and of violerythrin.

owing to a bathochromic shift relative to the corresponding six-membered compounds (Ref. 75). On alkaline oxidation, they are readily converted into the deep blue tetraketone violerythrin (Ref. 74). We have synthesized actinioerythrol (Ref. 75a) and have elucidated its absolute stereochemistry (Ref. 76). Thus, a Wittig reaction of the C_{14}-phosphonium salt 90, possessing the absolute configuration shown, with the C_{10}-dialdehyde 14 gave (3S,3'S)-actinioerythrol and the corresponding diacetate. The (3R,3'R)-enantiomer was prepared accordingly. The CD-spectrum of the diacetate of (3S,3'S)-actinioerythrol proved to be identical in sign to that of actinioerythrin, which has recently been re-isolated from the sea anemone Actinia equina L. (Refs. 65 & 76). This result means that the natural product must have the (3S,3'S)-configuration.

Degraded carotenoids

A large number of interesting compounds can be found among the so-called degraded carotenoids, namely those short chain compounds that are structurally and possibly biogenetically related to the carotenoid molecule. Some selected syntheses will be discussed utilizing the readily available chiral building units mentioned earlier.

The plant growth regulator (+)-(6S)-abscisic acid has been obtained by optical resolution of racemic material (Refs. 49, 77-79) or by a partial synthesis from xanthoxin (Refs. 80 & 81). We have developed a total synthesis (Fig. 36) making this compound and its enantiomer readily available (Ref. 82). Thus, a Grignard reaction of the protected acetylenic cis-alcohol 91 with the protected hydroxy ketone 71 gave a mixture of epimeric triols 92 and 93, which could be readily separated. Metal hydride reduction

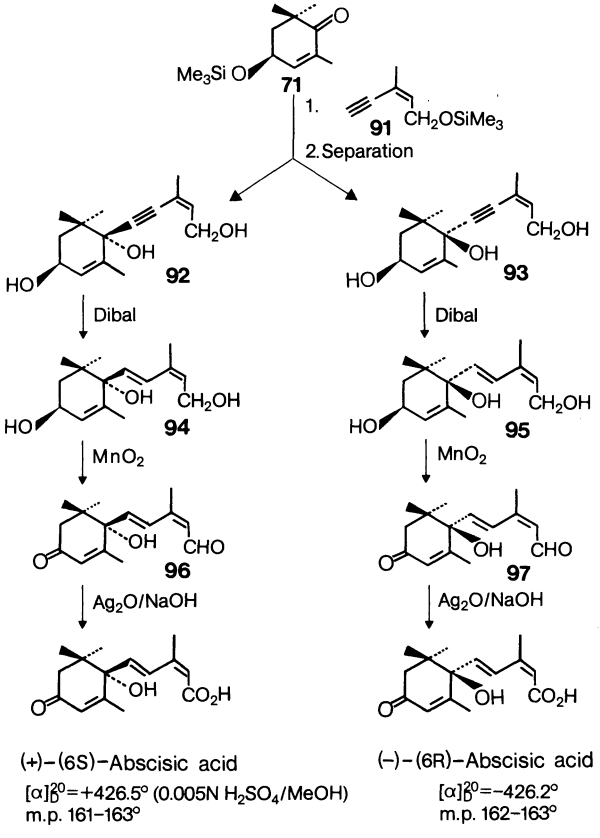


Fig. 36. Synthesis of (+)-(6S)- and (-)-(6R)-abscisic acid.

of the pure triols, followed by MnO_2-oxidation of the intermediate triols 94 and 95, yielded the enantiomeric ketoaldehydes 96 and 97 which were further oxidized to the desired products. It is worth noting that, in this case, chirality was introduced into the target molecule with the aid of the asymmetric center at C-4 of the starting cyclic component 71.

A partial synthesis of the plant growth regulator (-)-xanthoxin has recently been reported (Refs. 81 & 83). In our laboratories, (-)-(3S,5R,6S)-xanthoxin and its (3S,5S,6R)-diastereoisomer were prepared starting from the protected (3R)-3-hydroxy-β-cyclocitral (56) (Fig. 37) (Ref. 82). The desired 9-cis-double bond was introduced by a

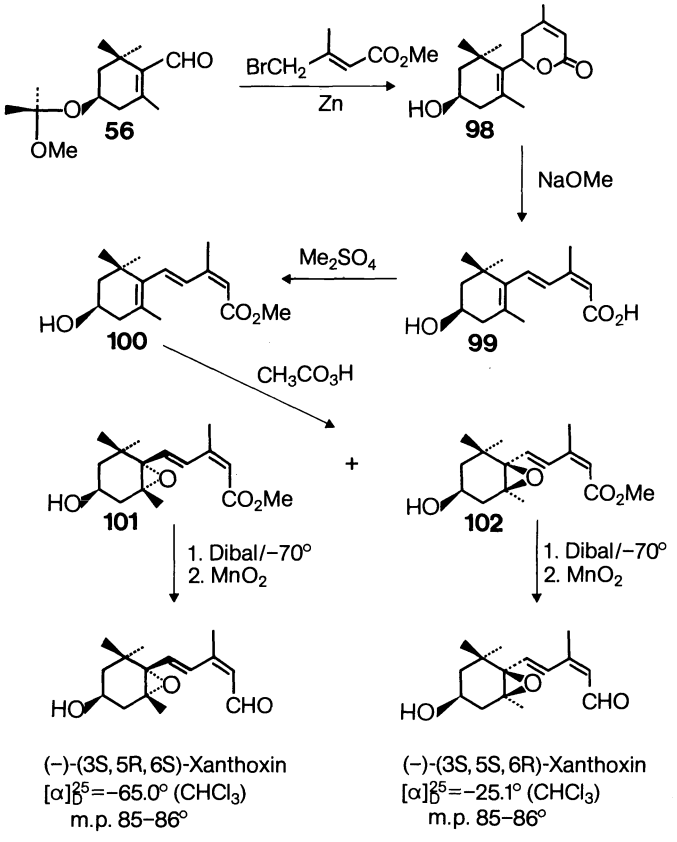


Fig. 37. Synthesis of (-)-(3S,5R,6S)- and (-)-(3S,5S,6R)-xanthoxin.

Reformatzii reaction to give the lactone 98 which, on treatment with base and subsequent esterification, yielded the intermediate C_{15}-ester 100. On epoxidation, this gave a readily separable mixture of epoxy esters 101 and 102 which were converted into the desired xanthoxin isomers by standard procedures.

The flavour constituent (-)-loliolide, earlier obtained from appropriate carotenoid precursors by photo-oxidation (Refs. 80, 84 & 85) or degradation (Ref. 86), was synthesized utilizing the C_{11}-aldehyde 49 (Ref. 82) (Fig. 38). Thus, epoxidation of the corresponding acid 103 gave a mixture of epoxy acids 104 and 105 which, on treatment with BF_3, were converted into the readily separable hydroxy lactones 106 and 107. Subsequent dehydration and hydrolysis of the acetate grouping then yielded (-)-loliolide and its C-5-epimer, respectively. An alternative approach was found by the iodolactonization of acid 103 affording the desired product directly (Ref. 82).

The protected C_9-hydroxy ketone 52 (Fig. 39) also turned out to be a useful starting material for (-)-theaspirone, one of the aroma constituents of black tea, and some of its synthetic precursors (Ref. 87). Thus, chain lengthening with 3-butyn-2-ol first gave the C_{13}-acetylenic triol 108. Subsequent treatment with lithium in liquid ammonia yielded the reduced triol 109 which was oxidized to (+)-(6S)-dehydrovomifoliol (Refs. 46 & 88) and/or (+)-(6S,9R)-blumenol A (Ref. 88). According to a sequence recently reported by Weiss et al. (Ref. 88), the latter compound was then selectively hydrogenated to give (+)-(6S,9R)-blumenol B which, on cyclization, yielded (-)-(6S,9S)-theaspirone.

As a final example, the synthesis of picrocrocin is discussed briefly. Picrocrocin is the bitter essence of the popular yellow spice, saffron, which is obtained from the stigmas and styles of the plant Crocus sativus. The attractive colour is, of course, produced by a number of carotenoids, namely several crocetin mono- and diglucosyl and gentiobiosyl esters (Refs. 89 & 90). Careful consideration of the structure (Fig. 40) reveals that it is sensitive to both acid and base, yielding safranal and glucose by elimination. Bearing this in mind, we tried to avoid acidic reaction conditions and to generate the aldehyde function in a later stage of the synthesis. Thus, reaction of the monoacetate 110 with α-acetobromoglucose gave the pentaacetate 111, which was converted into the corresponding pentol 112 by treatment with alkali. Subsequent selec-

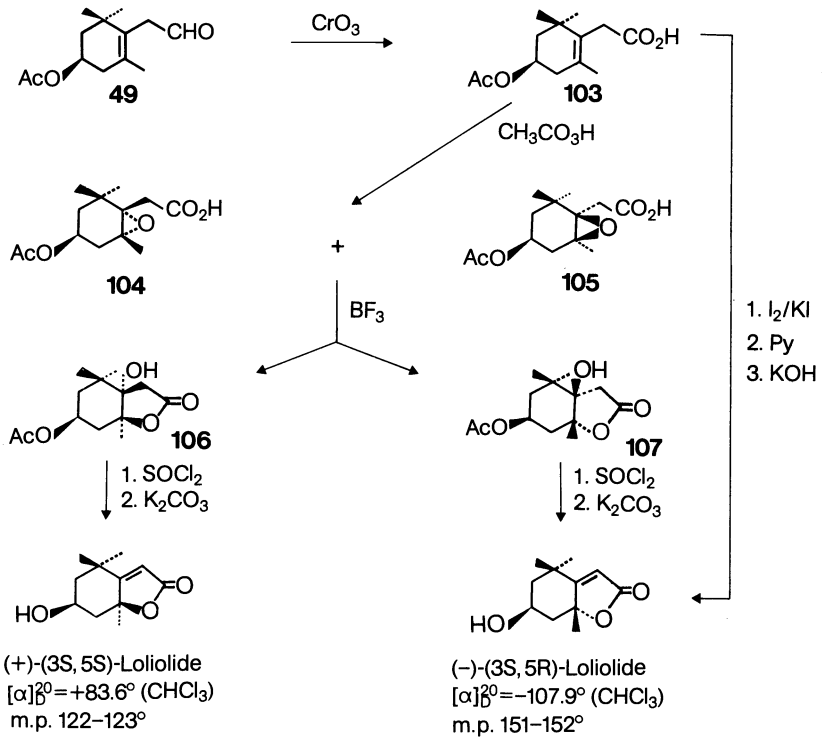


Fig. 38. Synthesis of (+)-(3S,5S)- and (-)-(3S,5R)-loliolide.

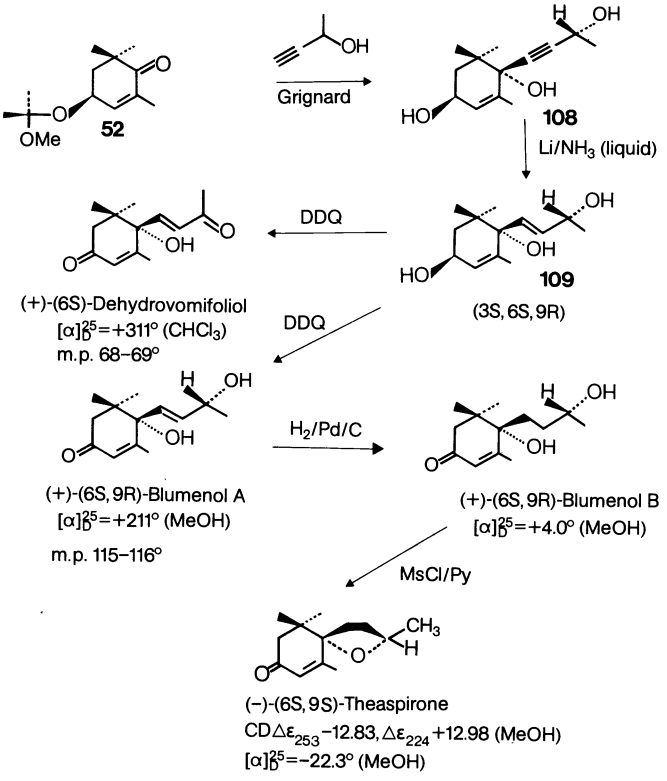


Fig. 39. Synthesis of (+)-(6S)-dehydrovomifoliol, (+)-(6S,9R)-blumenol A, (+)-(6S,9R)-blumenol B and (-)-(6S,9S)-theaspirone.

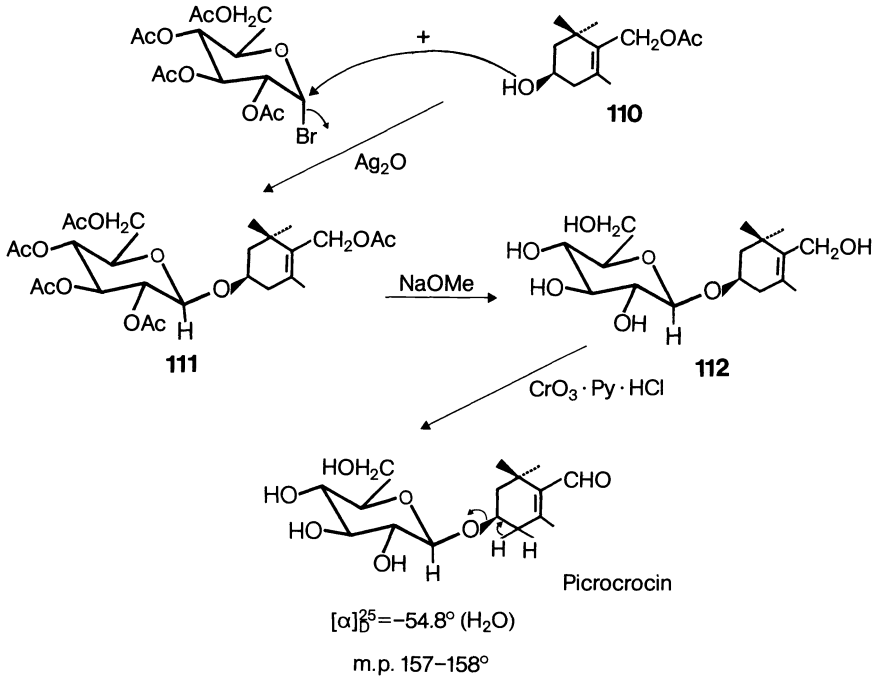


Fig. 40. Synthesis of picrocrocin.

tive oxidation of the allylic hydroxyl group with pyridinium chlorochromate then yielded picrocrocin which proved to be identical with the natural product (Refs. 59, 87 & 91).

CONCLUSION

The foregoing discussion has shown that the total synthesis of optically active carotenoids and related compounds confronts the chemist with a real challenge. It has also

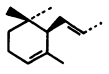
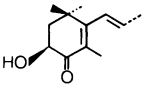
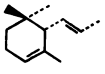
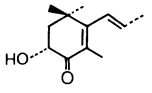
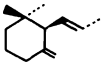
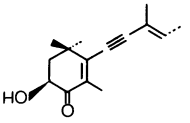
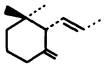
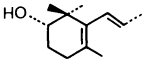
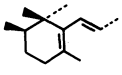
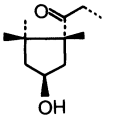
End group	Carotenoid	Refs.	End group	Carotenoid	Refs.
	(6'R)-β,ε-Carotene	27-29 33		(3S,3'S)-Astaxanthin	48
	(6'S)-β,ε-Carotene	27-29		(3R,3'R)-Astaxanthin	70
	(6'R)-β,γ-Carotene	34		(3S,3'S)-Asterinic acid	71
	(6'S)-β,γ-Carotene	34		(2S)-β,β-Caroten-2-ol	63
	(2R,2'R)-2,2'-Dimethyl-β,β-carotene	35		(3S,5R,3'S,5'R)-Capsorubin	3,38

Fig. 41. Totally synthesized chiral end groups and carotenoids.

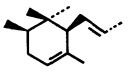
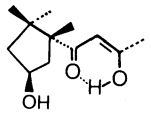
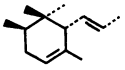
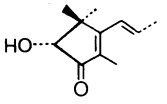
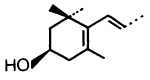
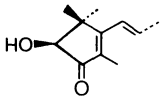
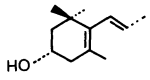
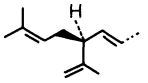
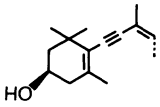
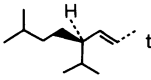
End group	Carotenoid	Refs.	End group	Carotenoid	Refs.
	(2R, 6S, 2'R, 6'S)-2,2'-Dimethyl-ε,ε-carotene	36		(3S, 5R)-Trikentriorhodin	38
	(2R, 6R, 2'R, 6'R)-2,2'-Dimethyl-ε,ε-carotene	36		(3R, 3'R)-Actinioerythrol	76
	(3R, 3'R)-Zeaxanthin	39.60		(3S, 3'S)-Actinioerythrol	76
	(3S, 3'S)-Zeaxanthin	52		(2S, 2'S)-Tetraanhydro-bacterioruberin	37
	9-cis-(3R, 3'S, 5'R)-Mytiloxanthin	38		(2R, 2'R)-Octahydro-tetraanhydrobacterioruberin	37

Fig. 41 (continued). Totally synthesized chiral end groups and carotenoids.

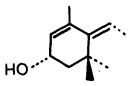
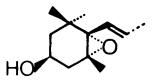
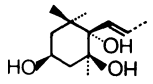
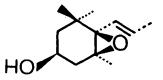
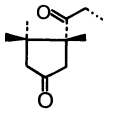
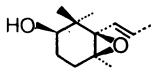
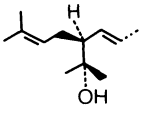
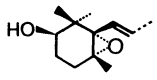
End group	Carotenoid	Refs.	End group	Carotenoid	Refs.
	Eschscholtzxanthin	92,93		Lutein epoxide	86
	Heteroxanthin	92,94		Violaxanthin (semisynthetic)	33
	(5S, 6R)-5,6-Epoxy-5,6-dihydro-β,β-carotene	95		Capsanthinone	97-99
	(2R, 5S, 6R, 6'R)-5,6-Epoxy-5,6-dihydro-β,ε-caroten-2-ol	96		Dianhydrobacterioruberin	100
	(2R, 5R, 6S, 6'S)-5,6-Epoxy-5,6-dihydro-β,ε-caroten-2-ol	96			

Fig. 42. Partially synthesized chiral end groups and carotenoids.

become apparent, however, that the synthesis of even more complex structures possessing the correct absolute configuration lies within the range of possibility. The development of a technical procedure for the synthesis of optically active products represents a problem which is not so easy to solve. In industry priority is given to

nature-identical carotenoidal pigments which are natural constituents of human and animal food whose use is wide-spread. They should either enlarge the presently limited colour range from yellow and orange red to red and blue or have some special field of application. Zeaxanthin, astaxanthin, actinioerythrin and violerythrin may be mentioned here as possible candidates. The work reported indicates that a technical production of (3R,3'R)-zeaxanthin and (3S,3'S)-astaxanthin will most likely be achieved in the near future.

In conclusion, the chiral carotenoid end groups and the corresponding optically active carotenoids that have been totally synthesized to date are summarized in Fig. 41. In Fig. 42 are listed some partially synthesized chiral end groups and the corresponding carotenoids obtained by the appropriate transformations. End groups of established absolute configuration and some carotenoids in which these were shown to be present are compiled in Fig. 43.

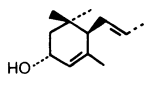
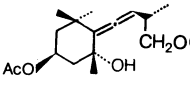
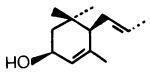
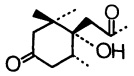
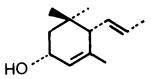
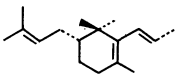
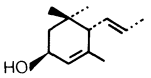
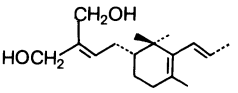
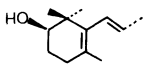
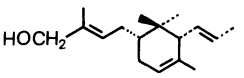
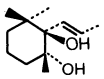
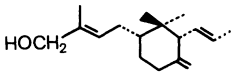
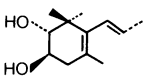
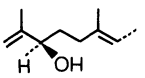
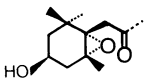
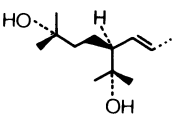
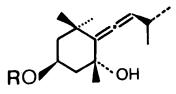
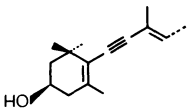
End group	Carotenoid	Refs.	End group	Carotenoid	Refs.
	Lutein	30,31 62,101		19'-Hexanoyloxy-fucoxanthin	111
	Chiriquaxanthin A or B	102		Isomytiloxanthin	3,112
	Tunaxanthin	103		C.p. 450	35
	Tunaxanthin	103		C.p. 450	35
	(2R)-β,β-Caroten-2-ol	64,104		Decaprenoxanthin	113
	Azafrin	105		Sarcinaxanthin	114
	Caloxanthin	106		Aleuriaxanthin	115
	Fucoxanthin	4,107		Bacterioruberin	37
	R = H: Neoxanthin R = Ac: Fucoxanthin	108-110 4,107		Alloxanthin	33,40

Fig. 43. End groups of established absolute configuration, not yet synthesized.

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