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Carotenoid synthesis: A progress report

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Abstract - The present review covers the progress in chemical synthesis of carotenoids over the period 1990 - 1996 and is a continuation of the review given at the 9th International Symposium on Carotenoids held in Kyoto. Highlights presented at previous symposia will be reported briefly and some reflections on possible future developments in the field are made.

HIGHLIGHTS PRESENTED AT PREVIOUS CAROTENOID SYMPOSIA

At the 1st Symposium in Trondheim, the birthplace of the Carotenoid Symposia in 1966, Mayer presented the remarkable first total synthesis of rhodoxanthin, the red pigment of *Taxus baccata L.* In his lecture at the 2nd Symposium in Las Cruces, New Mexico, Weedon discussed the acetylenic carotenoids such as alloxanthin, crocoxanthin and diatoxanthin and presented the total synthesis of optically inactive (9*Z*,9'*Z*)-alloxanthin, a geometrical isomer of the natural (all-*E*)-alloxanthin. At the 3rd Symposium in Cluj in 1972, the first synthesis of an optically active xanthophyll, namely (3*S*,5*R*,3'*S*,5'*R*)-capsorubin, was reported, again by Weedon. The starting material selected was (+)-camphor, which was transformed *via* camphoric acid to the desired end group and the target molecule. This represents a very elegant example of a synthesis "*ex* chiral pool" in which a chiral natural product as starting material is wholly or partially built into the target molecule. At the 4th Symposium in Berne in 1975 the total synthesis of (3*R*,3'*R*)-zeaxanthin was reported by the Roche group. For the synthesis of the desired end group a new strategy was applied, namely introduction of chirality biochemically by fermentative reduction with baker's yeast. At the 5th Symposium in Madison, Mayer presented the first, very elegant, total synthesis of (3*S*,3'*S*)-astaxanthin and its (3*R*,3'*R*)- and (3*R*,3'*S*)-isomers. In extension of their previous work the Roche group reported, at the 6th Symposium in Liverpool in 1981, the total synthesis of several of the ten optical isomers of tunaxanthin and also of (3*R*,3'*R*,6'*R*)-lutein and its isomers. In 1984 in Munich at the 7th Symposium, Widmer from the Roche group presented the synthesis of 38 carotenoids with cyclic end groups, starting from the very versatile synthon 6-oxoisophorone. As a contribution from our laboratories the total synthesis of optically active cyclic C_{50}-carotenoids, *e.g.* C.p. 450 and decaprenoxanthin, was reported at the 8th Symposium in Boston. The achievement of Ito's group in synthesizing optically active peridinin, reported at the 9th Symposium in Kyoto, was a highlight. This nor-carotenoid bears five asymmetric carbon atoms plus a chiral axis in the allenic structure. Three years ago at the 10th Symposium, again Ito presented the first total synthesis of optically active fucoxanthin, and this marks another milestone in the history of the carotenoids.
These examples clearly demonstrate both the importance of the Symposium and the steady progress in the synthesis of carotenoids, and it is sure that highly remarkable syntheses will be presented also at this 11th Symposium in Leiden. This review covers progress in chemical synthesis of carotenoids over the period 1990 - 1996, and is a continuation of the review given at the 9th Symposium in Kyoto (ref. 1).

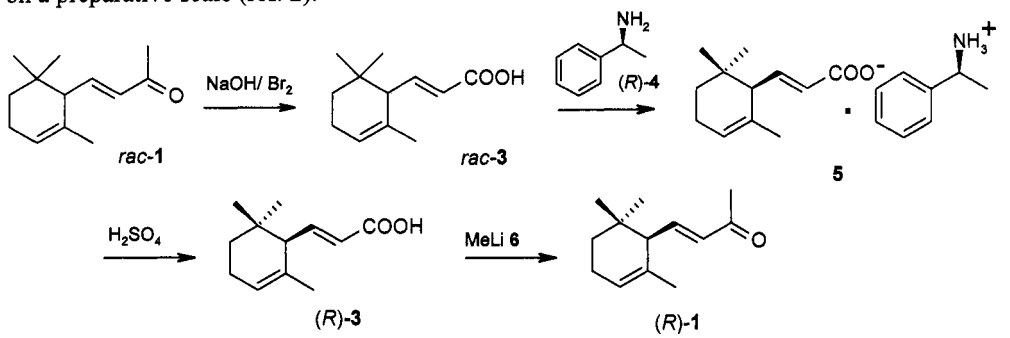
PROGRESS BETWEEN 1990 AND 1996

Normal C_{40}-carotenoids

The ε end group

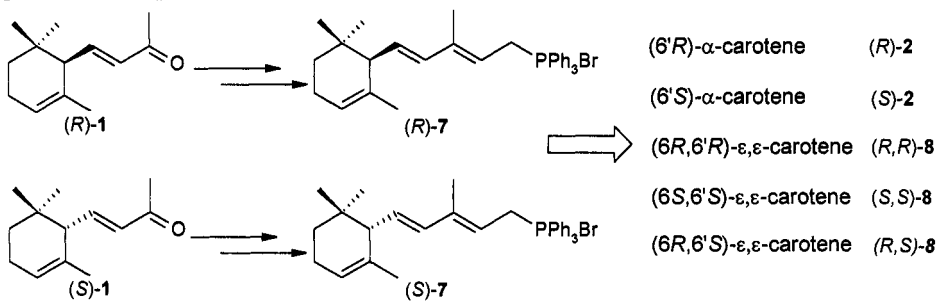
By use of the enantiomeric (*S*-(-))- and (*R*-(+))-α-ionones ((*R*)-**1** and (*S*)-**1**) the naturally occurring (6'*R*)-α-carotene ((*R*)-**2**) and its enantiomer were synthesized in 1957 by the school of Karrer. This constituted the first synthesis of an optically active carotenoid. The enantiomers of α-ionone ((*R*)-**1** and (*S*)-**1**) were

obtained by resolution of the racemate *via* menthylhydrazones. At the 10th Symposium in Trondheim Bernhard and Hengartner reported on an improved route to the enantiomerically pure α-ionones ((*R*)-**1** and (*S*)-**1**) on a preparative scale (ref. 2).



Scheme 1

The procedure, which is based on the separation of diastereoisomers, is described with all the experimental details as a 'Worked Example' in '*Carotenoids' Vol.2* (ref. 3). Racemic α-ionone (*rac*-**1**) was converted into the C_{12}-acid *rac*-**3** and afterwards (*R*)-(+)-1-phenylethylamine ((*R*)-**4**) was added . The resulting salt **5** was recrystallized ten times and, by this procedure, an e.e. of 99.2% was obtained. By treatment with sulphuric acid, the optically active C_{12}-acid (*R*)-**3** was obtained which was converted with MeLi (**6**) into optically active (*R*)-(+)-α-ionone ((*R*)-**1**) in an overall yield of 14.5%. For the synthesis of (*S*)-(-)-α-ionone ((*S*)-**1**), the same protocol was applied but (*S*)-(-)-1-phenylethylamine ((*S*)-**4**) was used (Scheme 1).

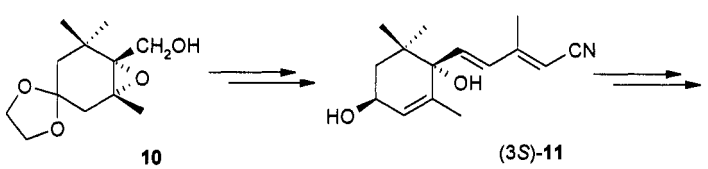


Scheme 2

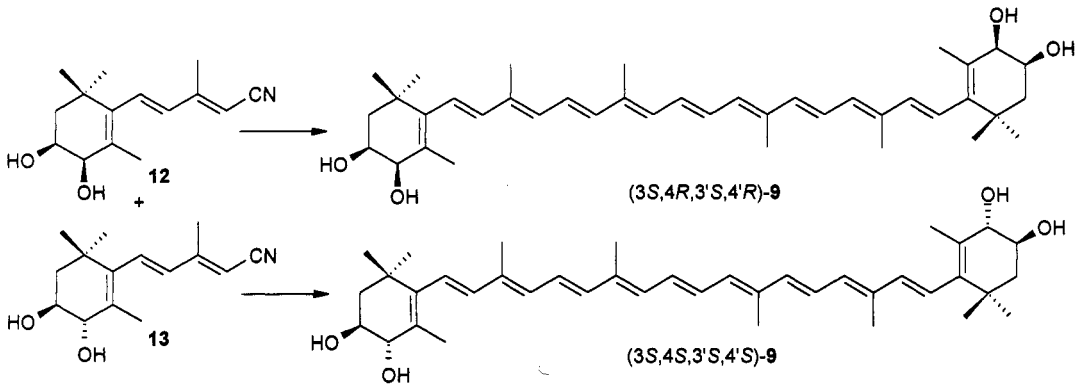
The optically active α-ionones ((*R*)-**1** and (*S*)-**1**) were elongated by standard procedures to the corresponding C_{15}-phosphonium salts (*R*)-**7** and (*S*)-**7** and, with these synthons, (6'*R*)- and (6'*S*)-α-carotene ((*R*)- and (*S*)-**2**) as well as the three stereoisomers of ε,ε-carotene ((*R,R*)-, (*S,S*)- and (*R,S*)-**8**) were synthesized (Scheme 2). The significance of the procedure lies in the fact that gram amounts can be obtained. This is of great importance in view of the need to elucidate the largely unknown biological properties of the dietary α-carotene. However it must be pointed out that an efficient total synthesis of optically active α-ionone is still lacking.

The 3,4-dihydroxy-β end group

The 3,4-dihydroxy-β end group is best known in the tetrol crustaxanthin (**9**) which contains 4 asymmetric carbon atoms. Two stereoisomers, namely the (3*S*,4*R*,3'*S*,4'*R*)- and the (3*S*,4*S*,3'*S*,4'*S*)-isomers have been synthesized in 1990 by the school of Eugster (ref. 4,5).



Scheme 3a

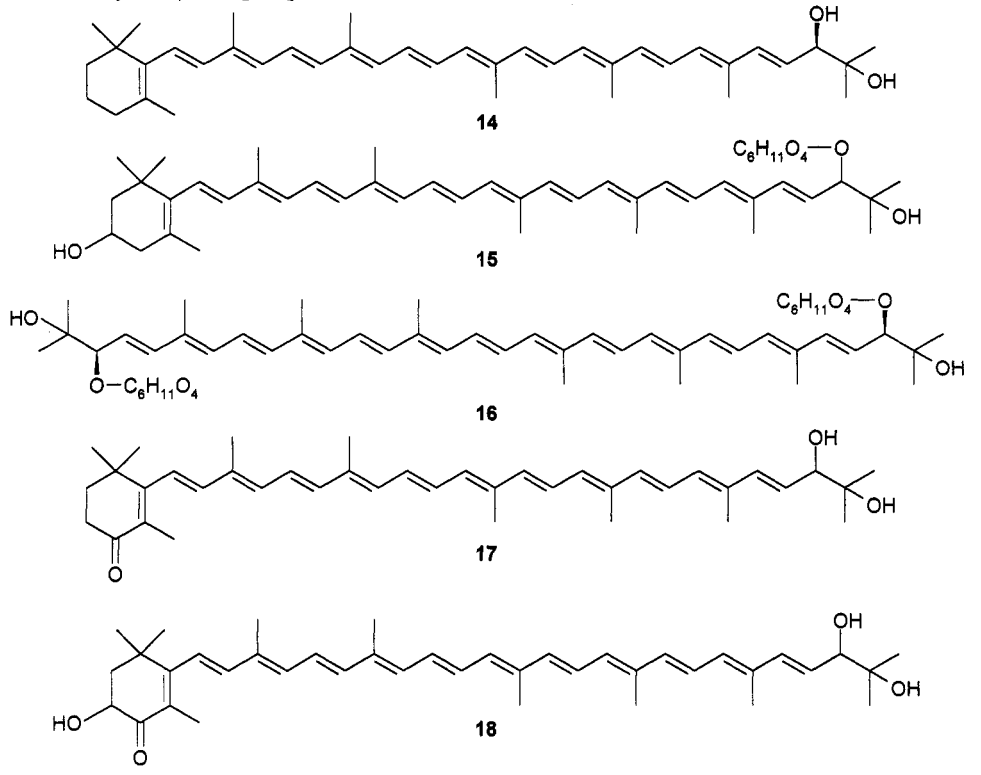


Scheme 3b

For this synthesis the C_{10}-synthon **10**, that has previously been used for the synthesis of violaxanthin, was chosen as starting material, and was converted into a mixture of (3*S*)- and (3*R*)-C_{15}-nitrile, (3*S*)- and (3*R*)-**11**, which were separated. Allylic rearrangement of (3*S*)-**11** gave a mixture of the *cis*- and *trans*-diols **12** and **13** which were separated by chromatography. By standard procedures, applying the $C_{15} + C_{10} + C_{15} = C_{40}$ strategy with an inverse olefination, the two stereoisomers of crustaxanthin, (3*S*,4*R*,3'*S*,4'*R*)- and (3*S*,4*S*,3'*S*,4'*S*)-**9**, were obtained (Scheme 3).

The (2R)-1,2-dihydroxy-3,4-didehydro-1,2-dihydro-ψ end group

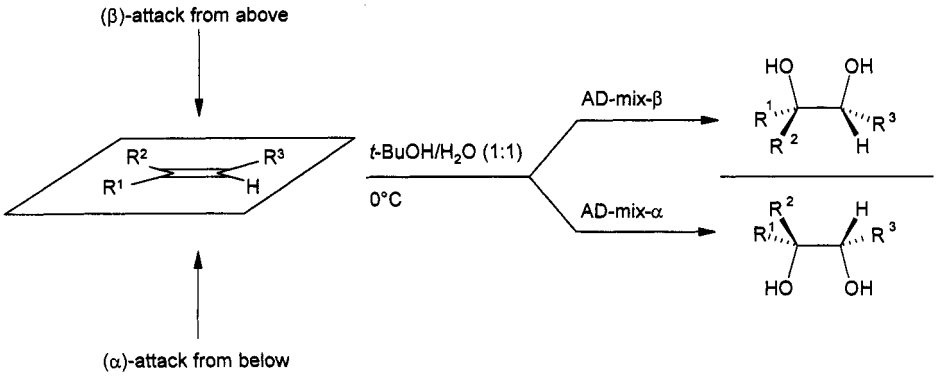
According to the *Key to Carotenoids* (ref. 6) almost 20 carotenoids containing the 1,2-dihydroxy-3,4-didehydro-1,2-dihydro-ψ end group are known.



Scheme 4

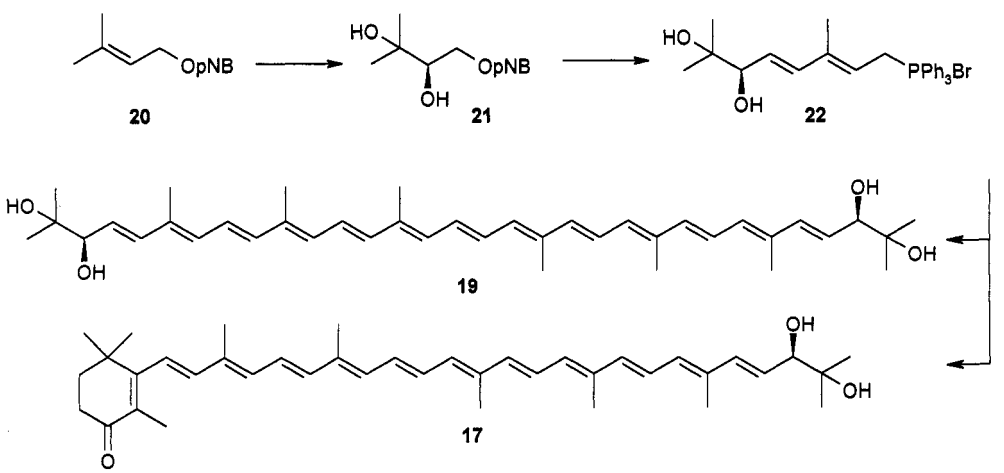
These include plectaniaxanthin (**14**) with the (2'*R*)-configuration, the glycosides of myxol (**15**) with partly unknown stereochemistry, oscillaxanthin (**16**) etc. Furthermore, at the Trondheim Symposium Böhlendorf (ref. 7) presented the isolation of 3-deoxy-2'-hydroxyflexixanthin (**17**) and 2'-hydroxyflexixanthin (**18**)

(Scheme 4). Earlier we reported the synthesis of (2'*S*)-plectaniaxanthin ((*S*)-**14**) starting from L-serine (ref. 8). This approach - *ex* chiral pool - is not suitable for the synthesis of **14**, due to the low availability of D-serine as starting material, and therefore a different strategy was investigated. A method that has successfully been developed recently by Sharpless, an osmium-catalysed asymmetric dihydroxylation, was applied (ref. 9).



Scheme 5

In this reaction, mono-, di- and trisubstituted olefins react with AD-mix-α or AD-mix-β in *t*-BuOH/H_2O to give the corresponding diols in yields of 80 to 98% and an e.e. generally >95% (Scheme 5).



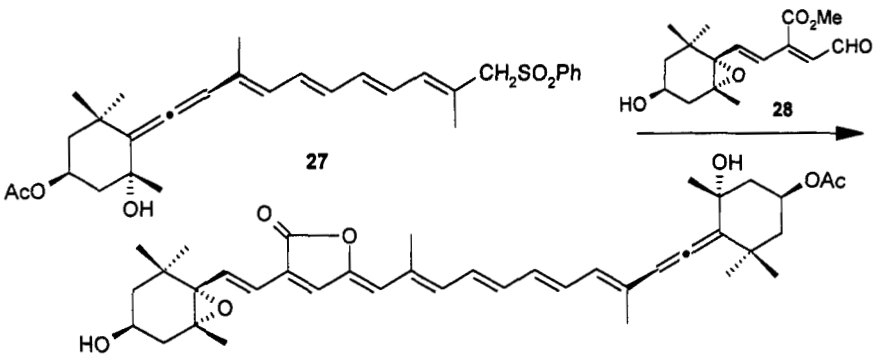
Scheme 6

For the synthesis of (2*R*,2'*R*)-oscillol (**19**) and (2'*R*)-3-deoxy-2'-hydroxyflexixanthin (**17**), prenol was chosen as starting material, and transformed to the corresponding *p*-nitrobenzoyl ester **20**. The Sharpless dihydroxylation gave the corresponding diol **21** which was afterwards converted in six steps into the desired C_{10}-phosphonium salt **22**. With this synthon (2*R*,2'*R*)-oscillol (**19**) and (2'*R*)-3-deoxy-2'-hydroxyflexixanthin (**17**) have been synthesized (Scheme 6) (ref. 10 - 13).

The (3S,5R,6R)-6,7-didehydro-5,6-dihydro-3,5-dihydroxy-β end group

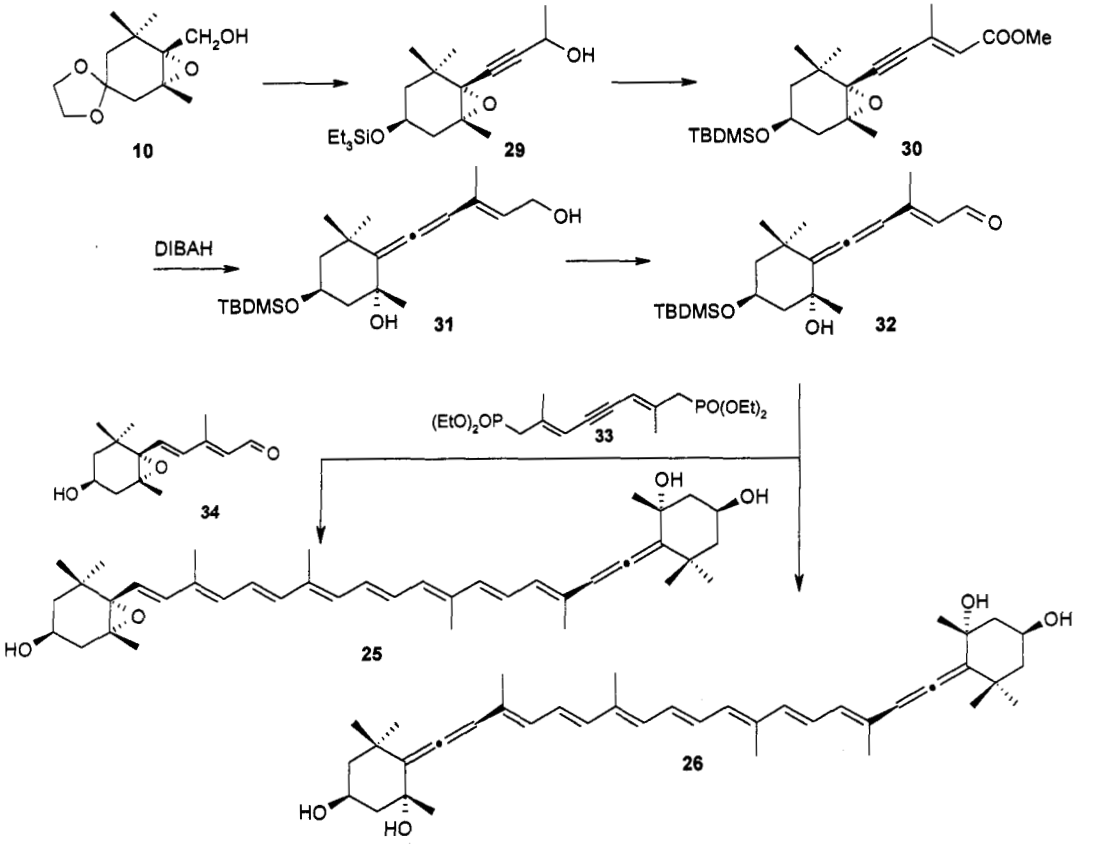
This end group and its 3-acetoxy-derivative occur as characteristic partial structure in important and very widespread carotenoids. Prominent examples are fucoxanthin (**23**), peridinin (**24**), neoxanthin (**25**) and mimulaxanthin (**26**). As mentioned before, the synthesis of optically active peridinin (**24**) was achieved by Ito's group (ref. 14 - 18).

In the final step, the condensation between the (all-*E*) allenic sulphone **27** and the formyl ester **28**, under the conditions of the sulphone method, furnished a mixture of optically active peridinin (**24**) and its (11'*E*)-isomer and these were clearly separated by preparative HPLC in the dark (Scheme 7).



Scheme 7

The school of Eugster developed the total synthesis of neoxanthin (**25**) and mimulaxanthin (**26**) (ref. 19 - 22).



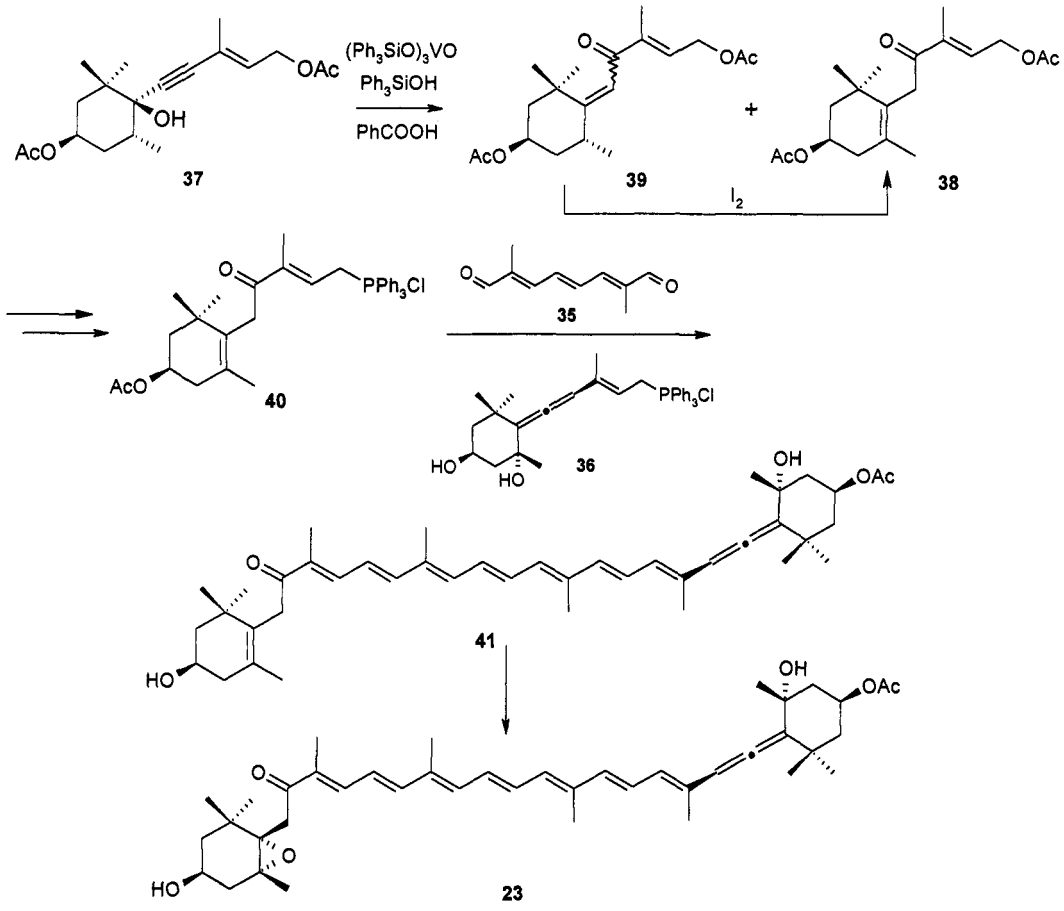
Scheme 8

As starting material the versatile protected C_{10}-epoxyalcohol **10,** which has already been used for the synthesis of optically active crustaxanthin (**9**), was selected. Starting with this synthon the acetylenic C_{13}-epoxyalcohol **29** was obtained in 6 steps. The C_{15}-epoxyester **30** was prepared in four steps and was reduced with DIBAH in the key step to the allenic C_{15}-diol **31**, which was afterwards oxidized to the corresponding hydroxyaldehyde **32**. The double inverse Wittig-Horner condensation of this C_{15}-aldehyde **32** with the acetylenic diphosphonate **33** gave, after partial hydrogenation, mimulaxanthin (**26**), whereas use of the violaxanthin end group **34** and the diphosphonate **33** gave, after partial hydrogenation, optically active neoxanthin (**25**) (Scheme 8). The total synthesis of optically active neoxanthin (**25**) is of special

importance and a milestone. As mentioned before, the first total synthesis of an optically active carotenoid goes back to 1957. The synthesis of optically active neoxanthin marks the end of a progressive development because now all the most important and widespread carotenoids such as α-carotene, lutein, zeaxanthin, violaxanthin, astaxanthin, fucoxanthin, peridinin, have been synthesized. This work took almost forty years of intuition, imagination, creativity, but especially hard work. Furthermore, it is remarkable that this development was begun at the University of Zürich by the school of Karrer and was completed at the same place by Prof. Eugster, the successor of Prof. Karrer.

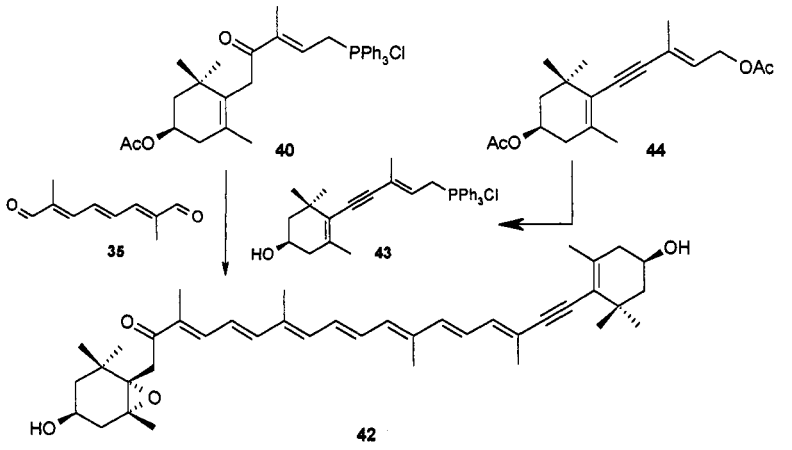
The (3S,5R,6S)-5,6-epoxy-3-hydroxy-8-oxo-5,6-dihydro-β end group

The synthesis of fucoxanthin (**23**), reported by Ito, is clearly a highlight in the field of synthesis of carotenoids (ref. 18, 23, 24).



Scheme 9

The carotenoid was synthesized according to the strategy $C_{15} + C_{10} + C_{15} = C_{40}$ with the C_{10}-dialdehyde **35** as central unit. As the allenic C_{15}-end group **36** had previously been prepared for the synthesis of peridinin, the emphasis was on the preparation of the 3-hydroxy-8-oxo end group. The key step of the synthesis is the rearrangement of the α-acetylenic alcohol **37** into the unsaturated carbonyl compound **38**. This rearrangement was carried out with tris(triphenylsilyl)vanadate, triphenylsilanol and benzoic acid to give a mixture of the isomers **38** and **39**. The latter was converted by iodine catalysis into the desired isomer **38**. This key intermediate was afterwards transformed into the C_{15}-phosphonium salt **40** by standard procedures. The Wittig olefination of the C_{10}-dial **35** first with the fucoxanthin end group **40** and then with the peridinin end group **36** gave, in five steps, the C_{40}-carotenoid **41**. Finally the epoxidation of this compound resulted in optically active fucoxanthin (**23**) and its (*5S,6R*)-isomer (Scheme 9).
In an analogous way also the acetylenic carotenoid halocynthiaxanthin (**42**) has been synthesized.

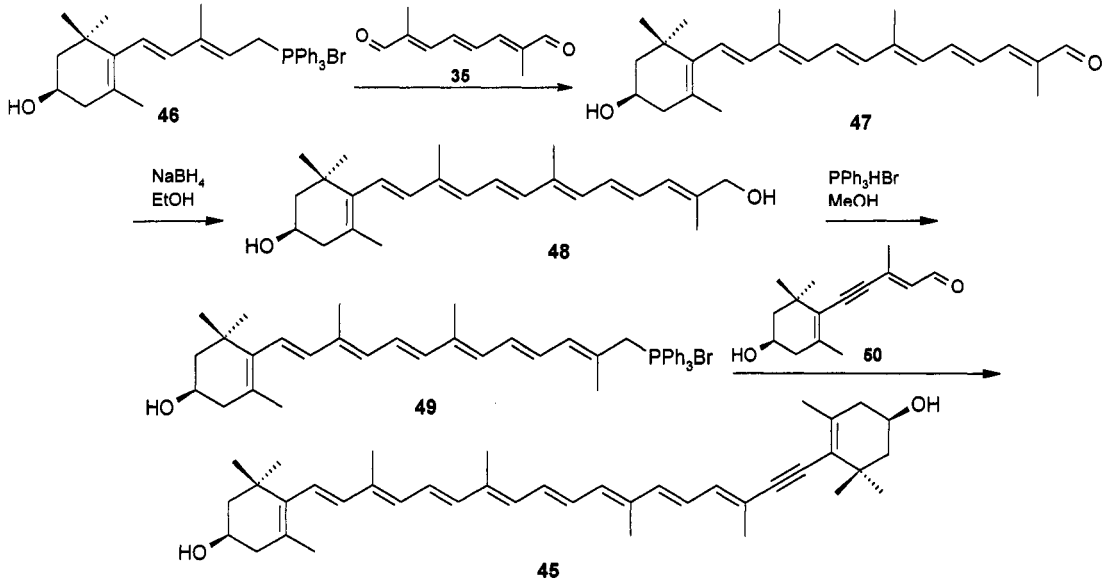


Scheme 10

Instead of the allenic end group **36** the acetylenic C_{15}-phosphonium salt **43** was used. The latter was prepared easily from the acetylenic C_{15}-diacetate **44** (Scheme 10).

The (3R)-3-hydroxy-7,8-didehydro-β end group

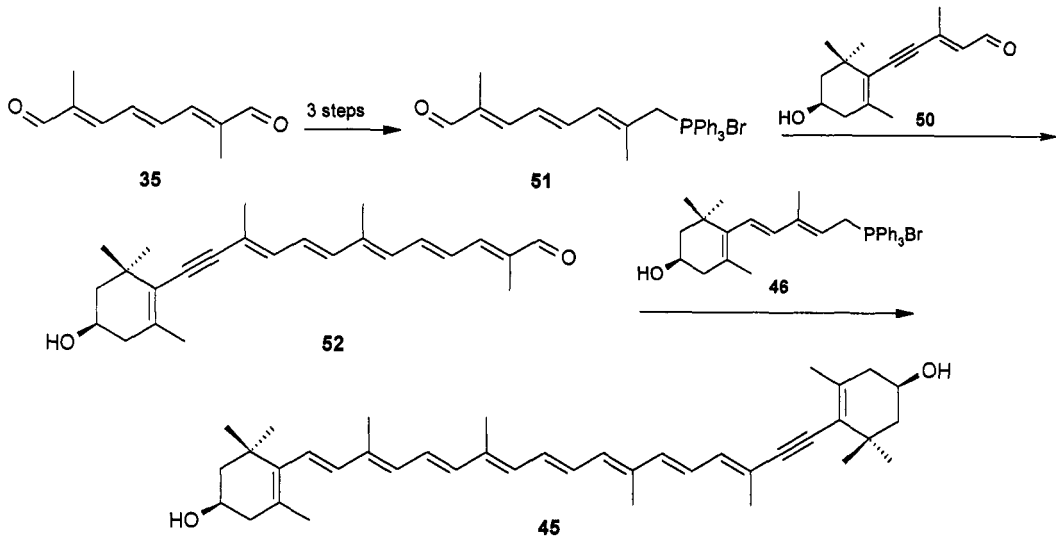
According to the '*Key to Carotenoids*' (ref. 6) more than twenty different naturally occurring acetylenic carotenoids are known. Hitherto three monoacetylenic carotenoids, namely crocoxanthin, 7,8-didehydroastaxanthin and pyrrhoxanthin, as well as two diacetylenic carotenoids, namely alloxanthin and 7,8,7',8'-tetradehydroastaxanthin, have been prepared by total synthesis either as a mixture of optical isomers or partly as pure optical isomers. In addition, some partial syntheses of acetylenic carotenoids have been reported. Problems have been associated with the construction of the (9*E*)- and (9'*E*)-double bonds because an acetylenic C_{15}-phosphonium salt intermediate results in the formation of the thermodynamically more stable (9*Z*)-isomer in the subsequent Wittig reaction.



Scheme 11

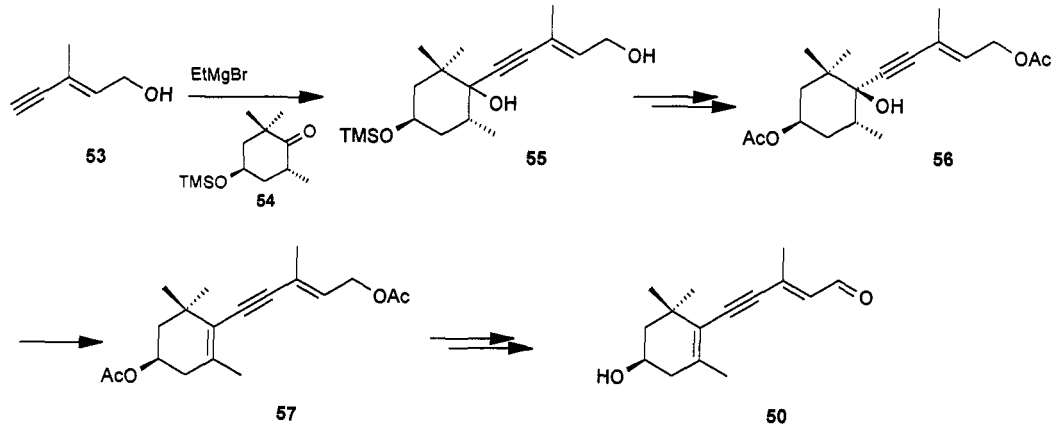
Recently major progress in the field of the total synthesis of acetylenic carotenoids has been made by Haugan and Liaaen-Jensen (ref. 25 - 27), who reported the total synthesis of (all-*E*,3*R*,3'*R*)-diatoxanthin (**45**) as well as its (9*Z*)-isomer ((9*Z*)-(**45**)). For the synthesis of (all-*E*)-diatoxanthin the strategy $C_{15} + C_{10} + C_{15} = C_{40}$ was chosen and two different routes were investigated.

In the first procedure the C_{15}-hydroxyphosphonium salt **46** was converted, by a Wittig reaction with the C_{10}-dial **35**, into the well-known C_{25}-hydroxyaldehyde **47** which was reduced to the diol **48**, which was then converted into the corresponding phosphonium salt **49**. The second Wittig reaction with the acetylenic C_{15}-end group **50** gave the desired optically active diatoxanthin (**45**) as a mixture of geometrical isomers with 63% of the (all-*E*)-isomer. The pure (all-*E*)-isomer was obtained by recrystallization. This total synthesis represents a final proof for the structure, including the (3*R*,3'*R*)-configuration, of natural diatoxanthin (**45**) (Scheme 11).



Scheme 12

In the second route the C_{10}-dial **35** was first converted into the monophosphonium salt **51** which was then reacted with the acetylenic C_{15}-end group **50** to give the acetylenic C_{25}-hydroxyaldehyde **52**. Wittig reaction with the C_{15}-hydroxyphosphonium salt **46** gave (all-*E*,3*R*,3'*R*)-diatoxanthin (**45**) (Scheme 12). Comparison of the two routes shows that the first one is a 13-step synthesis with an overall yield of 22% which is highly remarkable, whereas the second pathway includes 14 steps with an overall yield of 6%.



Scheme 13

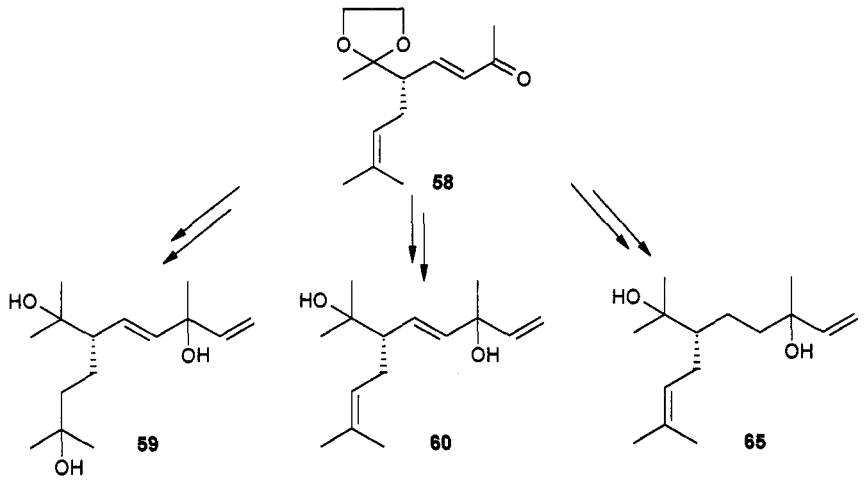
For the synthesis of the acetylenic C_{15}-end group **50** the acetylenic C_6-synthon **53** was used and was reacted with EtMgBr and the protected C_9-hydroxyketone **54** to give the C_{15}-diol **55**. Basic deprotection, recrystallization and subsequent peracetylation gave the protected triol **56** in optically pure form, and the subsequent dehydration afforded the diacetate **57**. Deprotection followed by oxidation with MnO_2 gave the desired end group **50** (Scheme 13).

In an analogous way also (9*Z*,3*R*,3'*R*)-diatoxanthin ((9*Z*)-(**45**)) was prepared. The desired stereochemistry at C(9) of the carotenoid was introduced by using the (*Z*)-isomer of the acetylenic C_6-synthon **53** to give (9*Z*)-(**55**) and subsequently (9*Z*)-(**50**).

Higher carotenoids - acyclic compounds

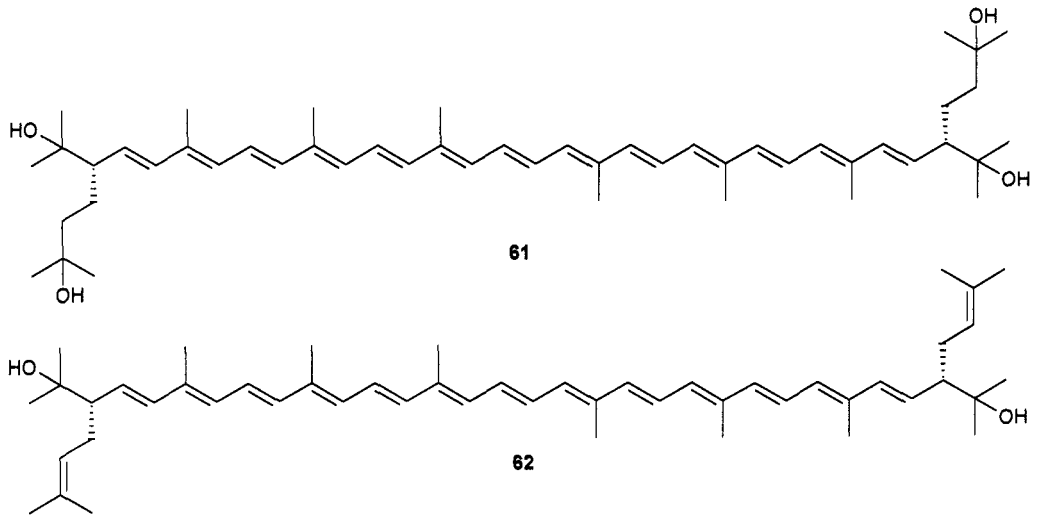
The (2R)-1-hydroxy-2-(3-methylbut-2-enyl)-1,2-dihydro-ψ end group

It is characteristic of higher acyclic carotenoids that the additional isoprenoid units are linked at the C(2) and C(2')-positions of the C_{40}-skeleton and therefore a common synthetic strategy can be applied for the different end groups and carotenoids.

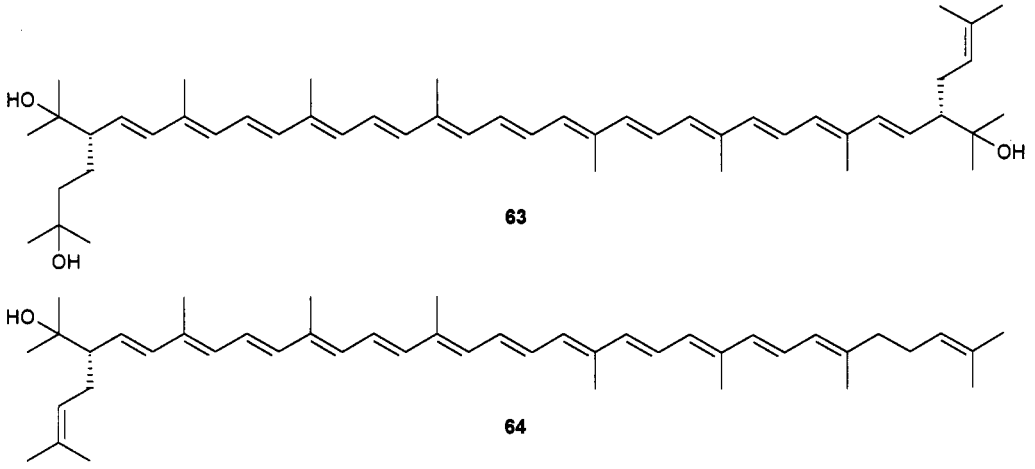


Scheme 14

As starting material, (3*S*)-3-hydroxybutyric acid was chosen and was stereoselectively alkylated and transformed to the common C_{12}-synthon **58**. The subsequent transformations to the C_{15}-end groups **59** and **60**, characteristic of bacterioruberin (**61**) and bisanhydrobacterioruberin (**62**), respectively, were achieved without major problems and in satisfactory yields (ref. 28, 29) (Scheme 14).

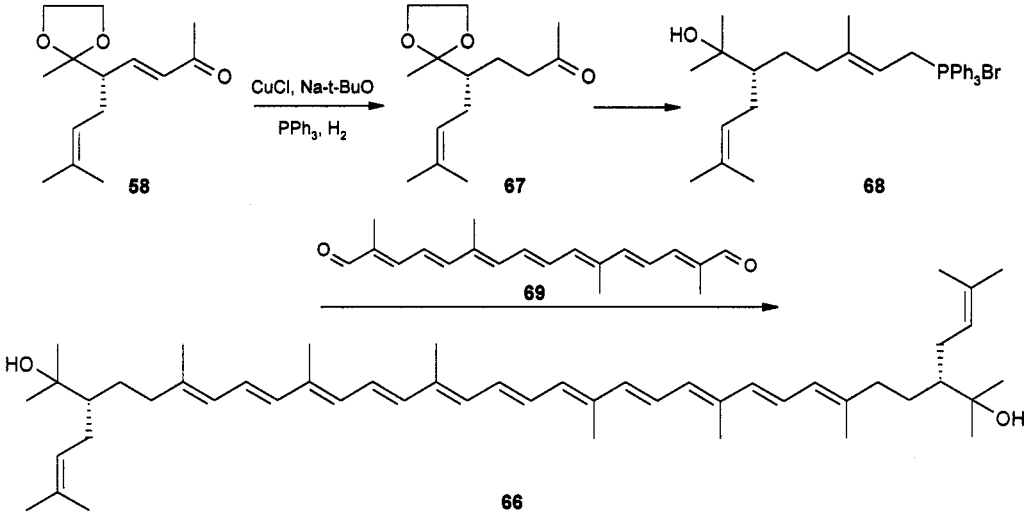


Scheme 15a



Scheme 15b

Previously we reported the synthesis of (2*S*,2'*S*)-bacterioruberin (**61**), (2*S*,2'*S*)-bisanhydrobacterioruberin (**62**), (2*S*,2'*S*)-monoanhydrobacterioruberin (**63**) and the C_{45}-carotenoid (2*S*)-2-isopentenyl-3,4-didehydrorhodopin (**64**) (ref. 30, 31) (Scheme 15).



Scheme 16

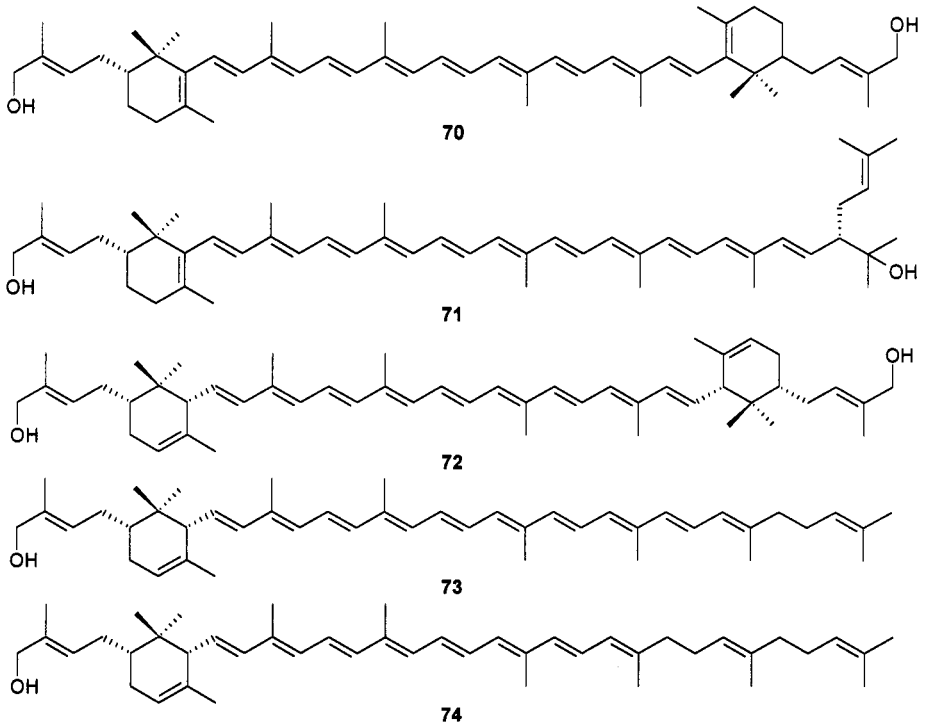
In contrast to the first two end groups the synthesis of the end group **65** (Scheme 14), that contains a single bond at the 3,4-position and is characteristic of 3,4,3',4'-tetrahydrobisanhydrobacterioruberin (**66**), gave major problems. The critical step was the regioselective reduction of the C(3) - C(4) double bond. Several methods were not successful, mainly due to partial racemization at the C(2)-position. Finally the reduction of **58** with triphenylphosphinecopper-(I)-hydride, generated *in situ* from copper chloride, sodium *t*-butoxide, triphenylphosphine and hydrogen, gave the desired building block **67**. As described earlier, the protected ketone was elongated in four steps to the corresponding C_{15}-phosphonium salt **68**. Finally the Wittig reaction with crocetindialdehyde (**69**) gave (2*R*,2'*R*)-tetrahydrobisanhydrobacterioruberin (**66**) (ref. 32, 33) (Scheme 16).

Higher carotenoids - cyclic compounds

The (2R,6R)-(4-hydroxy-3-methylbut-2-enyl)-γ end group

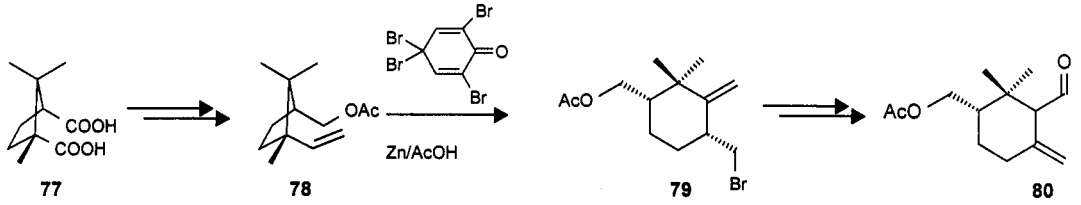
Besides the acyclic compounds, thirteen naturally occurring cyclic C_{45}- and C_{50}-carotenoids have been isolated; as in the acyclic compounds, the additional isoprenoid units are linked to the C_{40}-skeleton at the

C(2)- and C(2')-positions. The compounds differ mainly in the constitution of the cyclic end groups: β and ε end groups are known as well as the γ end group.

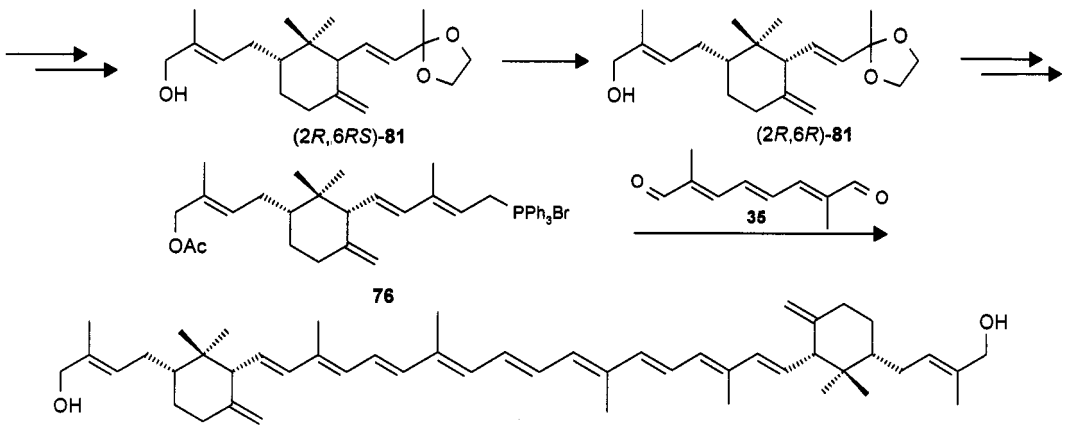


Scheme 17

Previously we reported the total synthesis of optically active C.p. 450 (**70**), C.p. 473 (**71**), decaprenoxanthin (**72**) and the two derivatives 7',8',11',12'-tetradehydrononaprenoxanthin and 11',12'-didehydrononaprenoxanthin ((**73**) and (**74**)) (ref. 34 - 37) (Scheme 17). In continuation of this work we have investigated the total synthesis of optically active sarcinaxanthin (**75**), which contains an exocyclic double bond and two asymmetric carbon atoms in each ring. Previously this carotenoid has been prepared by Férézou and Julia (ref. 38) as a racemate with the correct relative stereochemistry at the ring system. For the synthesis of optically active (all-*E*,2*R*,6*R*,2'*R*,6'*R*)-sarcinaxanthin (**75**), the strategy $C_{20} + C_{10} + C_{20} = C_{50}$ was selected. The optically active C_{20}-end group **76** was prepared starting from (+)-camphoric acid (**77**) which was transformed in six steps into the unsaturated acetate **78**. The key step of the synthesis is the ring enlargement of the acetate **78** with 2,4,4,6-tetrabromocyclohexa-2,5-dienone to the bromocyclohexane derivative **79** containing an exocyclic double bond. Afterwards the double bond was epoxidized and the desired exocyclic double bond at position C(5) was introduced by a basic dehydrohalogenation. Afterwards the epoxide was opened with a Grignard reagent to give the C_{11}-aldehyde **80** that was afterwards converted by standard methods into the protected allylic C_{18}-alcohol **81** which was separated chromatographically into its (6*R*)- and (6*S*)-isomers. Afterwards the optically pure (2*R*,6*R*)-**81** was converted into the corresponding C_{20}-phosphonium salt **76**. Reaction of this end group **76** with the C_{10}-dial **35** gave optically active (all-*E*,2*R*,6*R*,2'*R*,6'*R*)-sarcinaxanthin (**75**) (ref. 39) (Scheme 18).



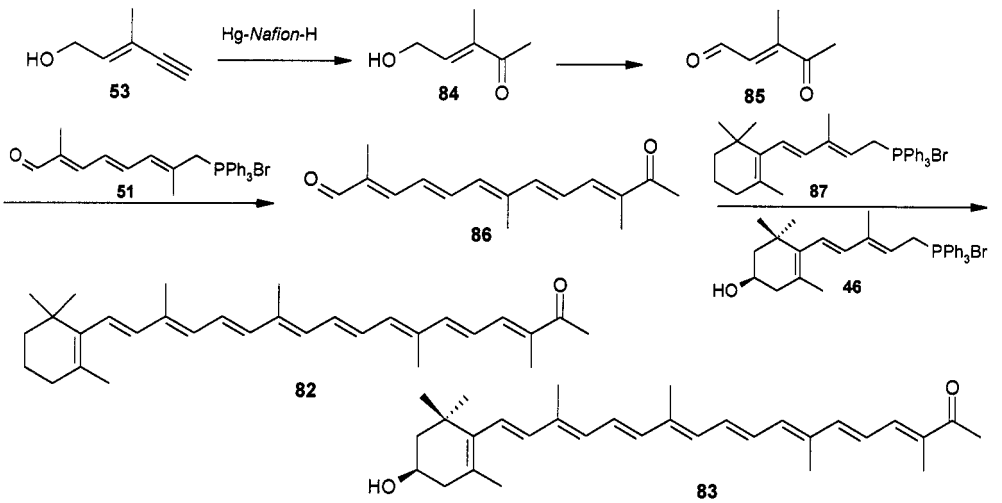
Scheme 18a



Scheme 18b

Apocarotenoids

Among the approximately fifty known apocarotenoids, the methyl ketones are an important group. Examples are the C_{33}-methyl ketones citranaxanthin and reticulaxanthin and the corresponding β-hydroxy ketones which are believed to be isolation artifacts formed by aldol condensation of C_{30}-carotenals with acetone. Further representatives of this group are the C_{31}-compounds including especially sintaxanthin (**82**) and (3*R*)-3-hydroxysintaxanthin (**83**). The isolation of these compounds from various citrus fruits has been reported. A partial synthesis of sintaxanthin has been reported earlier but recently Haugan described the total synthesis of sintaxanthin and of its optically active 3-hydroxy derivative according to the strategy $C_{15} + C_{10} + C_6 = C_{31}$ (ref. 40).



Scheme 19

As starting material, the acetylenic C_6-alcohol **53** was selected and was converted by a mercury-catalysed hydration into the ketoalcohol **84**, which was afterwards oxidized to the ketoaldehyde **85**. The Wittig reaction with the phosphonium salt **51** derived from the well-known C_{10}-dial **35** gave the C_{16}-ketoaldehyde **86** and finally the reaction with the C_{15}-phosphonium salt **87** afforded sintaxanthin (**82**). By using the optically active (3*R*)-3-hydroxy-β end group **46** in the last step, (3*R*)-hydroxysintaxanthin (**83**) was prepared (Scheme 19).

A LOOK INTO THE FUTURE

To answer the question about the future of carotenoid synthesis it may help to answer another question: "*Why synthesis?*" First of all, the synthesis of a new molecule is a true *scientific challenge*, especially if new structural elements must be constructed. New structural elements sometimes require new methods, new reagents and sometimes it turns out that these developments can be applied generally in organic chemistry.

Today the total synthesis of a carotenoid for *structure elucidation* is often no longer necessary because of advances in high resolution spectroscopic methods but, when only small amounts of a new natural carotenoid are available, full spectroscopic characterization may not be possible, and a total synthesis of the proposed structure then becomes indispensable, especially to establish its stereochemistry.

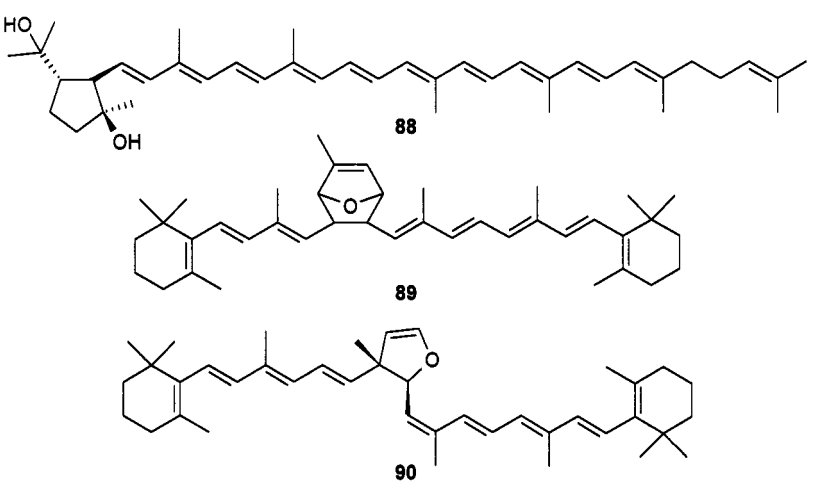
Chemical synthesis has a major part to play in the sophisticated *interdisciplinary studies* that are now needed to study the biological functions and actions of carotenoids. Several carotenoids found in the human diet, especially lycopene, zeaxanthin and lutein, could also be important in giving protection against serious disorders such as cancer and heart disease. Characterization of these effects and elucidation of the mechanism involved require substantial quantities - from g to kg - of pure carotenoids; these materials can only be produced by chemical synthesis.

For the investigation of structure-function relationships, *model compounds* are often highly desirable or even necessary. In this connection also the synthesis of labelled carotenoids has to be mentioned.

The interest in definite *(Z)-isomers* has increased tremendously during the past few years and also in this field total synthesis is indispensable.

Furthermore synthesis of carotenoids is an excellent field for the *training* of synthetic organic chemists. A lot of important reactions can be exemplified with carotenoids and, especially in practical courses, a lot of synthetic expertise can be acquired by the students.

Recent investigations make it clear that the investigation of the biological and chemical properties of metabolites and degradation products, such as **88** which was isolated from human serum (ref. 41), and **89** and **90** which are oxidation products of β,β-carotene with O_2 without any radical inducer (ref. 42), is of utmost importance (Scheme 20). These metabolites and degradation products often show structures that for carotenoids are rather unusual and therefore provide a wide open field for the creative synthetic chemist.



Scheme 20

SUMMARY AND CONCLUSIONS

The seventies and eighties of this century may be called the glorious years of the synthesis of carotenoids. As discussed, many highly remarkable syntheses have been realized and they mark milestones in the history of the carotenoids. During the reviewed period of 1990-1996 the total synthesis of peridinin and fucoxanthin are outstanding achievements in the field and, with the syntheses of neoxanthin, all major carotenoids have been synthesized. Carotenoid synthesis has a long and distinguished history but it has also an exciting future. The old objectives remain valid, but there are new and more diverse challenges as

carotenoid science expands into new areas. And there is another aspect. Let's look at the definition of the term 'Synthesis'. In Kingzeit's Chemical Encyclopaedia 'Synthesis' is defined as 'the building up of elements into compounds, or of compounds into more complex compounds'. However the term 'Synthesis' is used in many contexts far removed from chemistry. In its broadest sense, synthesis means the tying together of individual pieces to construct or create a whole article. These activities of constructing and creating are fascinating, a challenge to the imagination and inherent to mankind. And therefore carotenoid synthesis will, without any doubt, continue to develop.

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