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Synthesis of optically active carotenoids: a review

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Abstract - Advances in the field of the synthesis of optically active carotenoids are reviewed. It is shown that the main end-groups or at least precursors of them have been synthesized and that many carotenoids have been prepared in enantiomerically pure form. For the introduction of the centers of chirality selective reduction with baker's yeast, the selection of easily available, naturally occurring, optically active compounds as starting material and the Sharpless epoxidation were applied. It is also shown that many problems are still unsolved.

INTRODUCTION

Today, one of the main tasks of synthetic organic chemistry is the synthesis of enantiomerically pure compounds with important biological activities, particulary in view of the possibility of industrial application.
In 1978 at the symposium in Madison, Dr. Mayer gave an excellent review of the synthesis of optically active carotenoids (ref. 1). The present paper is a continuation of this overview, whereby unsolved problems are also discussed; thus the work in this field during the last decade is reviewed.
From the more than 560 naturally occurring carotenoids (ref. 2) about 370 are chiral and are therefore targets for synthesis in enantiomerically pure form. This includes the synthesis of carotenoids with a relative simple structure such as α-carotene bearing only one chirality center, and also of neoxanthin or fucoxanthin which have five asymmetric carbon atoms plus the allenic structure.
The synthesis of a carotenoid in optically active form consists mainly of the synthesis of an *optically active end-group* or an appropriate building block, even though the synthesis of the whole carotenoid molecule may sometimes cause major problems. Therefore the main emphasis in this paper is on the synthesis of the individual end-groups.

Before discussing the synthesis of or the approaches to the different end-groups, it must be pointed out that, for many natural occurring carotenoids, the structure, and this term includes the stereochemistry, is still unknown or at least uncertain and in all these cases a re-isolation, followed by structural elucidation with all the modern spectroscopic methods, especially high-resolution NMR-spectroscopy, is absolutely necessary.

THE SYNTHESIS OF THE CHIRAL END-GROUPS

Acyclic chiral end-groups

The three main acyclic end-groups with an asymmetric carbon atom are the *(R)-1,16-didehydro-1,2-dihydro-2-hydroxy-ψ-end-group* of aleuriaxanthin (1), the *(R)*- or *(S)-3,4-didehydro-1,2-dihydro-1,2-dihydroxy-ψ-end-group*, which occurs e.g. in plectaniaxanthin and the *(S)-1,2-dihydro-1,2-epoxy-ψ-end-group*, which is characteristic of 1,2-epoxylycopene.
The synthesis of the naturally occurring *(R)-aleuriaxanthin* (1) and its enantiomer has been described by Eschenmoser et al. (ref. 3) (Fig. 1). Starting with O-acetylgeraniol (2) the introduction of the chirality center was achieved by the enantioselective Sharpless epoxidation (ref. 4). After opening the epoxide, the secondary hydroxyl group was protected and the double bond introduced by treatment with thionyl chloride; by standard reactions both enantiomers were synthesized.

Another approach, starting from a readily available optically active synthon, was investigated in our laboratories for the synthesis of plectaniaxanthin (3) and myxol (4) (Fig. 2). Starting with either D-serine and D-mannitol or L-serine and L-mannitol, respectively, both enantiomers of the C_5-building block 5 were synthesized in high yield and good optical purity (ref. 5) and this synthon was used for the synthesis of the C_{10}-phosphonium salt 6. The Wittig reaction with the appropriate C_{30}-aldehyde gave *(S)-plectaniaxanthin* (3) and *(3R,2'S)-myxol* (4), albeit in very low yields, due to the poor reactivity of the C_{30}-aldehyde (ref. 6). Investigations to improve the synthesis e.g. according to the scheme $C_{10} + C_{20} + C_{10} = C_{40}$ or $C_{20} + C_{20} = C_{40}$ were unsatisfactory (ref.

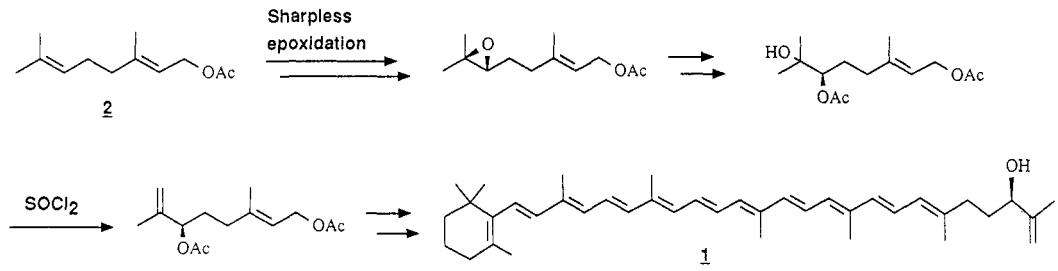


Fig. 1. Synthesis of (R)-aleuriaxanthin

7). As we have reported at the symposium in Boston (ref. 8) the synthesis of *(2R,2'R)-di-O-isopropylideneoscillol* was achieved, but the experiments to remove the protecting groups were unsuccessful, due to the decomposition of the carotenoid. These difficulties have now been overcome by using the acetylenic C_{20}-dialdehyde, whereby the hydroxyl group of the phosphonium salt was not protected for the Wittig reaction. Hydrogenation with Lindlar catalyst, followed by E/Z-isomerization, gave carotenoids with the 1,2-dihydro-1,2-dihydroxy-ψ-end group, e.g. *oscillol*, in satisfactory yields (ref. 9).

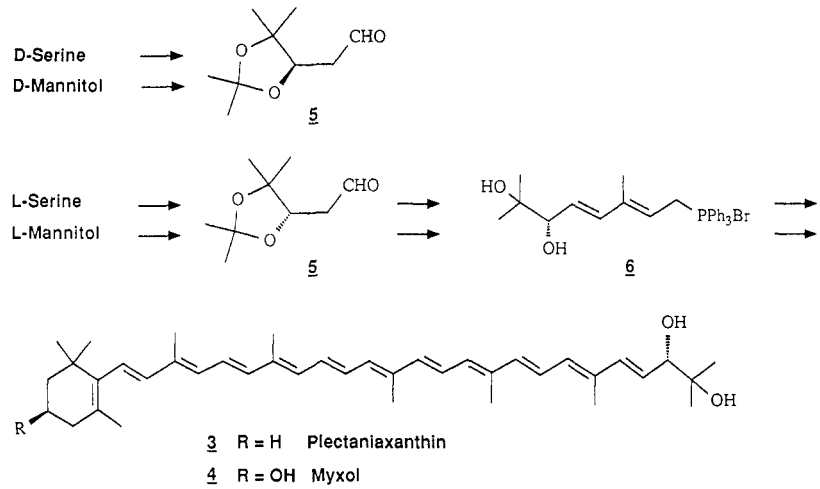


Fig. 2. Synthesis of (S)-plectaniaxanthin and (3R,2'S)-myxol

For the synthesis of the *(S)-1,2-dihydro-1,2-epoxy-ψ-end-group* two different approaches were investigated. On the one hand (Fig. 3) the reduction of the α-hydroxyketone 7 with baker's yeast gave the optically active diol 8, which was converted into the phosphonium

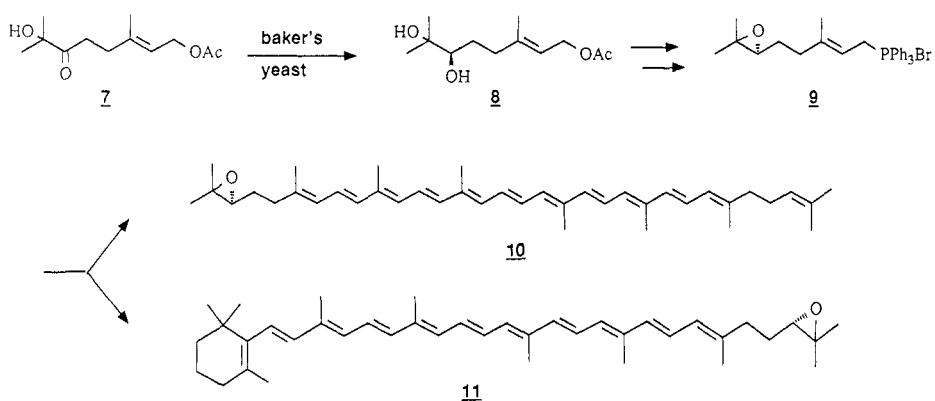


Fig. 3. Synthesis of (S)-1,2-epoxy-lycopene and (S)-1,2-epoxy-γ-carotene

salt 9 and thence into *(S)-1,2-epoxy-lycopene* (10) and *(S)-1,2-epoxy-γ-carotene* (11) (ref. 10). On the other hand (Fig. 4) Sharpless epoxidation of the farnesyl derivative 12, subsequent transformation to the corresponding phosphonium salt 13 and Wittig reaction gave *(S)-1,2-epoxy-ζ-carotene* (14) (ref. 11).

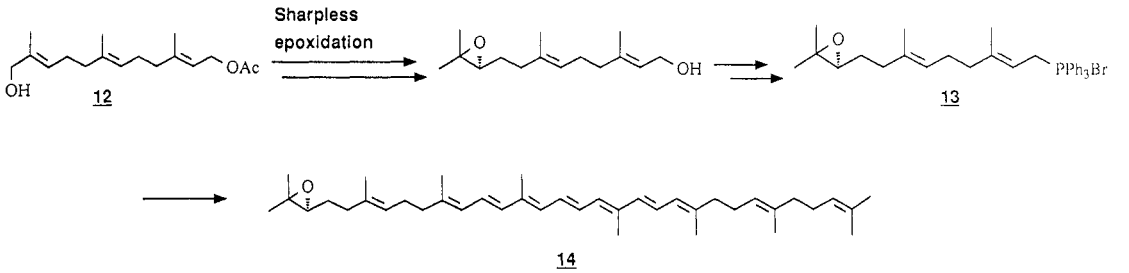


Fig. 4. Synthesis of (S)-1,2-epoxy-ζ-carotene

Cyclic chiral end-groups

The β-end-groups

To date, fourteen carotenoids bearing a *2-hydroxy-β-end-group* have been isolated from green algae, yeasts, insects and crustaceans. Two different ways have been described for the synthesis of this end-group. The regio- and stereospecific reduction of 2-oxo-β-ionone (15) with baker's yeast followed by acetylation gave (S)-2-acetoxy-β-ionone (16) which was converted into *(S)-2-hydroxy-β-carotene* (17) (Fig. 5) (ref. 12). In our laboratories the

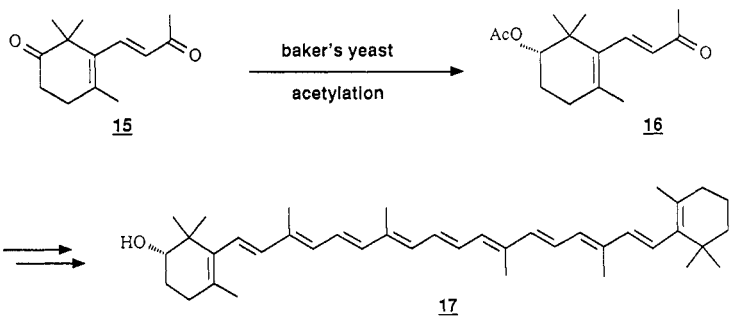


Fig. 5. Synthesis of (S)-2-hydroxy-β-carotene

cyclization of the acetate of optically active (R)-geraniol epoxide (18) was investigated, and it was shown that, through the reaction with BF_3*Et_2O, the synthon 19 can be obtained, although in moderate yield. From this building block, *(R)-2-hydroxy-β-carotene* (20) and *(2R,2'R)-2,2'-dihydroxy-β-carotene* (21) have been synthesized (Fig. 6) (ref. 13).

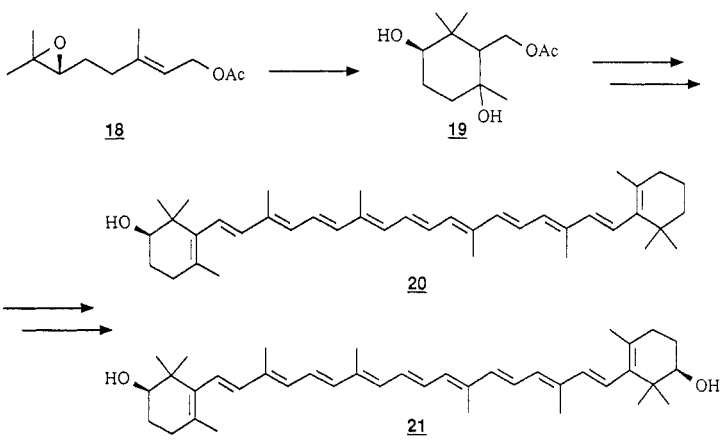


Fig. 6. Synthesis of (R)-2-hydroxy-β-carotene and (2R,2'R)-2,2'-dihydroxy-β-carotene

The *3-hydroxy-β-end-group*, the "*zeaxanthin end-group*", is the most abundant chiral end-group of carotenoids. If one includes also the ethers and esters and the 7,8-acetylenic derivatives more than 80 xanthophylls bear this structural element. Normally the (*R*)-configuration is observed, but (*S*)-enantiomers have also been reported. The synthesis of these end-groups has been studied by the group from Roche (ref. 14), who have reported two different approaches for the introduction of the center of chirality. The enantioselective reduction of oxoisophorone (22) with baker's yeast followed by the diastereo- and regioselective reduction of the resulting diketone 23 gave mainly the hydroxyketone 24 (Fig. 7).

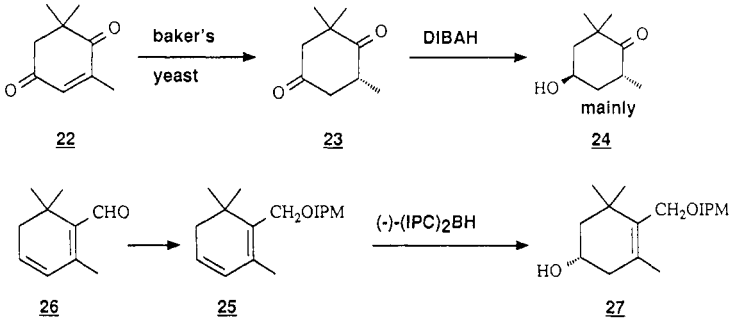


Fig. 7. Synthesis of chiral synthons for the synthesis of the optically active 3-hydroxy-β-end-group

In another reaction sequence, the protected alcohol 25, synthesized from safranal 26, gave, with (+)- or (-)-diisopinocamphenylborane, both enantiomers of the protected 3-hydroxy-β-cyclogeraniol (27). Both synthons were afterwards converted into the corresponding C_{15}-Wittig salt. This compound allowed the synthesis of (*3R,3'R*)-, (*3R,3'S*)- and (*3S,3S'*)-*zeaxanthin* and of other carotenoids with this end-group e.g. *(R)-rubixanthin, (R)-β-cryptoxanthin, (R)-asteroidenone, (R)-β-doradecin, (3S,3'R)-adonixanthin, (R)-reticulaxanthin* (ref. 1) and *(R)-β-citraurin* (ref. 15).

The third monohydroxylated end-group of the β-type, namely the *4-hydroxy-β-end-group*, was synthesized by the school of Eugster (Fig. 8). As starting material, optically active (-)-(S)-α-ionone (28), obtained by resolution of the diastereomeric menthylhydrazones, was epoxidized with monoperphthalic acid; the base-catalyzed opening of the epoxide gave (-)-(R)-4-hydroxy-β-ionone (29) from which *(4R,4'R)-isozeaxanthin* (30) was synthesized (ref. 16). The choice of the protecting group for the hydroxyl group is important for this reaction sequence.

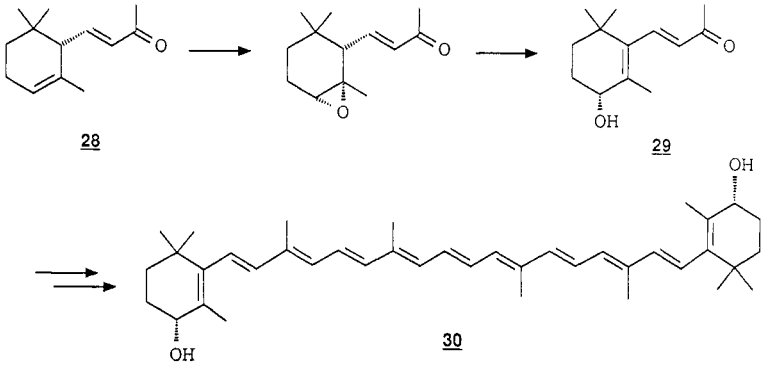
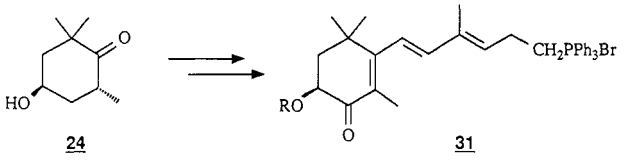


Fig. 8. Synthesis of (4R,4'R)-isozeaxanthin

Two dihydroxy-β-end-groups are known, namely the *2,3-dihydroxy-β-end-group* which occurs e.g. in caloxanthin and nostoxanthin, and for which to our knowledge no synthesis has yet been reported, and the *3,4-dihydroxy-β-end-group*, known from, for example, crustaxanthin and idoxanthin. A possible approach to the synthesis has been reported by Schiedt (ref. 17) for *idoxanthin*. The glycols can be obtained by reduction of the individual stereoisomers of the corresponding 3-hydroxy-4-oxo-compound, i.e. astaxanthin, and subsequent separation of the cis- and trans-glycols by TLC or HPLC.

In a series of publications (ref. 18), the Roche group reported on the synthesis of the *3-hydroxy-4-oxo-β-end-group* and especially of the stereoisomers of *astaxanthin* (Fig. 9), with emphasis on the technical synthesis of this carotenoid. The starting material was again the C_9-hydroxyketone 24 which had been used for the synthesis of zeaxanthin. Through different reaction routes the appropriate C_{15}-phosphonium salt 31 was obtained and several carotenoids have been synthesized e.g. *(3R,3'R)-*, *(3R,3'S)-* and *(3S,3'S)-astaxanthin*, *(R)-hydroxyechinenone*, *(3R,3'R)-* and *(3R,3'S)-adonixanthin*, *(R)-adonirubin* and their antipodes etc. (ref. 19). No synthesis has yet been reported, to our knowledge, for the *(R)-2-hydroxy-4-oxo-* and the *(2R,2S)-2,3-dihydroxy-4-oxo-β-end-groups* which have also been observed in carotenoids.

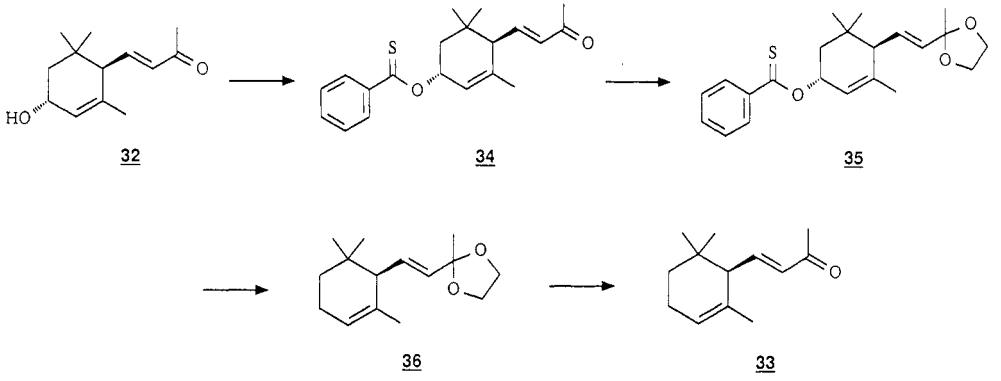


24 31

Fig. 9. Synthesis of the optically active 3-hydroxy-4-oxo-β-end-group

The ε-end-groups

The two most important chiral end-groups in the *ε-series* are the unsubstituted *ε-end-group* e.g. in *α-carotene* and the *(R)-* or *(S)-3-hydroxy-ε-end-group*, the "*lutein end-group*". From the latter also the corresponding *3-oxo-ε-end-group* is accessible. Starting with pure (+)-(R)- and (-)-(S)-α-ionones, the naturally occurring (R)-α-carotene and its enantiomer have been synthesized by the schools of Karrer and Eugster (ref. 20); this represents the first example of a synthesis of a naturally occurring carotenoid in optically active form. However, optically active α-ionone is not readily available. Although this compound is widespread in the plant kingdom, its isolation from natural sources is rather unattractive, especially on a larger scale. Optical resolution of synthetic, racemic α-ionone involves twenty recrystallizations of the diastereomeric menthyl derivatives (ref. 21) and is not very elegant. To our knowledge, no synthesis of optically active α-ionone has yet been reported. The introduction of a center of chirality at C(6) of the ε-ring is, of course, known from the synthesis of lutein and during those investigations the synthesis of optically active (3R,6R)-3-hydroxy-α-ionone (32) was reported. Our investigations were focused on the transformation of this compound to (+)-(R)-α-ionone (33) (ref. 22). For the elimination of a secondary hydroxyl group, a great variety of methods are known, but only the method developed by Barton (ref. 23), which involves the reduction of a thiocarbonyl ester by tributyltin hydride, gave satisfactory results. The radical chain reactions that proceed under neutral conditions are much less subject to steric hindrance and to rearrangement than ordinary ionic reactions. (3R,6R)-3-Hydroxy-α-ionone (32) was quantitatively converted into the corresponding phenylthionocarbonate 34 by reaction with phenylchlorothiocarbonate (Fig. 10). Treatment with 1,2-ethanediol/triethylorthoformate/p-toluenesulfonic acid gave the corresponding acetal 35 and the reaction of this compound with tributyltin hydride and azoisobutyronitrile (AIBN) gave, after flash-chromatography, two compounds, of which the minor product (12%) was the desired deoxygenated compound 36 which was converted afterwards into (+)-(R)-α-ionone (33). Although so far only a moderate yield has been obtained for the key step, we think that this approach is suitable for the synthesis of both enantiomers of α-ionone, which are not only useful starting compounds for the synthesis of carotenoids with the ε-end-group, but also of those with the γ-end-group and of other natural products.

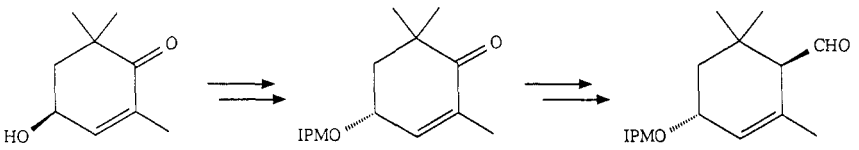


32 34 35

36 33

Fig. 10. Synthesis of (+)-(R)-α-ionone

Considerable efforts have been made to synthesize the *3-hydroxy-ε-end-group*, the "*lutein end-group*". This ring system possesses two chirality centers, giving rise to four different isomers and hence the problem of synthesizing, specifically, one isomer is much more demanding than with a β-ring. The various problems have largely been overcome by the group from Roche, using, as starting material, the C_9-hydroxy-ketone 37 (Fig. 11) that was known from the synthesis of zeaxanthin and astaxanthin. The key step in the introduction of the second chirality center was the diastereoselective epoxidation of the protected ketone 38 with a sulfurylide to give an allylic epoxide and hence the aldehyde 39 with the trans-substituted (3R,6R)-ε-ring (ref. 24). As the stereochemistry at the C(3) position can be inverted through an S_N2-reaction, the (3S,6S)-enantiomer is also accessible. With these building blocks to hand, a number of carotenoids have been synthesized such as *(3R,3'R,6'R)-*, *(3S,3'S,6'S)-*, *(3R,3'S,6'S)-* and *(3S,3'R,6'R)-lutein* and various compounds of the *tunaxanthin group* (ref. 25).
Some special structural elements in the ε-series are the *6-hydroxy-3-oxo-ε-end-group* of sidnyaxanthin, the *3-hydroxy-2-oxo-ε-end-group* of tilefishxanthin IV and the postulated *3,6-dihydroxy-end-group* in trollixanthin. No synthesis has yet been reported for these carotenoids.



37 38 39

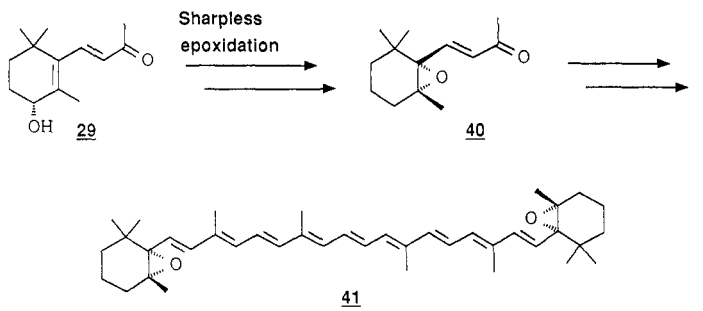
Fig. 11. Synthesis of the (3R,6R)-3-hydroxy-ε-end-group

The γ-end-group

In contrast to α- and β-ionone which have been isolated from natural sources, γ-ionone is known only as a synthetic product. On the other hand the school of Liaaen-Jensen has shown that γ-ionone is a suitable synthon for the synthesis of carotenoids with the γ-end-group, such as β,γ- or γ,γ-carotene. Racemic γ-ionone was partly resolved via its menthylhydrazone, and the enriched (R)- and (S)-enantiomers of β,γ-carotene were prepared (ref. 26). A possible approach to the synthesis of these carotenoids in enantiomerically pure form starts from optically active α-ionone, which can be converted into γ-ionone (ref. 27). This reaction sequence is currently under investigation in our laboratories.

The 5,6-dihydro-β-end-groups

The chemistry of these end-groups, which are hydroxylated and/or epoxidized and which may possess up to three asymmetric carbon atoms giving rise to different stereoisomers, is the domain of Prof. Eugster and, since these results have been presented in several recent publications and in contributions at the previous symposia, they will be summarized only briefly. For the synthesis of the *5,6-epoxy-end-group* (-)-(R)-4-hydroxy-β-ionone (29), synthesized from optically active α-ionone, was epoxidized by the Sharpless method and the product was transformed to (5R,6S)-5,6-epoxy-5,6-dihydro-β-ionone (40) (ref. 28) (Fig. 12).



29 40

41

Fig. 12. Synthesis of (5R,6S,5'R,6'S)-5,6,5',6'-diepoxy-β-carotene

From this synthon, *(5R,6S,5'R,6'S)-5,6,5',6'-diepoxy-β-carotene* (41) was synthesized (ref. 29). With the 5,6-epoxides of defined stereochemistry to hand, the way is also open to the *5,8-epoxides*. This was shown with (5S,6R)-5,6-epoxy-β-carotene, which was obtained by partial synthesis from azafrinal (ref. 30), and rearranged in an acid-catalyzed reaction into the mixture of (5S,8S)- and (5S,8R)-5,8-epoxy-β-carotenes ('mutatochromes') (ref. 31). *Azafrin*, the well known C_{27}-apocarotenoic acid, possesses the *(5R,6R)-5,6-*

dihydroxy-5,6-dihydro-β-end-group. The ester of the *(5S,6S)*-enantiomer 42, has been synthesized (ref. 32); (5S,6S)-5,6-dihydroxy-5,6-dihydro-β-ionone (43) was used as chiral synthon (Fig. 13). The latter was obtained from enantiomerically pure (R)-4-hydroxy-β-ionone (ref. 33).

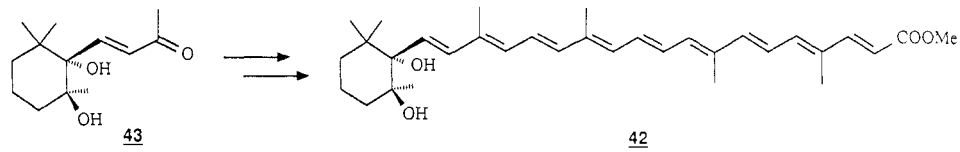


Fig. 13. Synthesis of the methyl ester of (5S,6S)-azafrin

At the last Symposium, Prof. Eugster reported on the synthesis of different isomers of violaxanthin (44) (ref. 34-36). These investigations can be regarded as the most important contribution in the area of the synthesis of optically active carotenoids in the past few years. The key step for the introduction of the chirality centers is the Sharpless epoxidation of the allylic alcohol 45 to the epoxide 46 (Fig. 14). Subsequent oxidation,

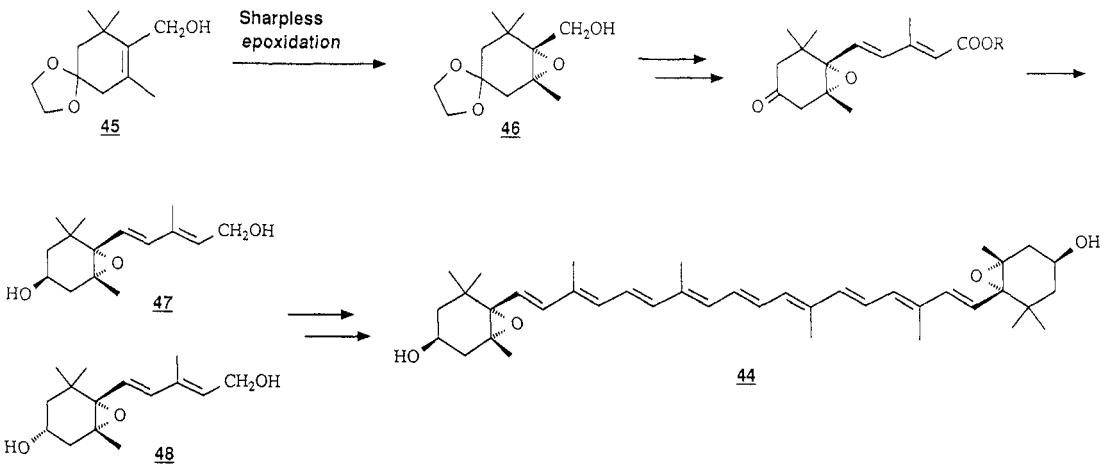


Fig. 14. Synthesis of (3S,5R,6S,3'S,5'R,6'S)-violaxanthin

chain elongation, deprotection and reduction furnished a mixture of the epimeric C_{15}-epoxy-alcohols 47 and 48. *(3S,5R,6S,3'S,5'R,6'S)-Violaxanthin* (44) and its (3R,3'R)-isomer have been prepared from these synthons. Violaxanthin or related compounds with the violaxanthin end-group have been postulated as precursors of several other carotenoids such as mutatoxanthin, heteroxanthin, neoxanthin, diatoxanthin, capsanthin, amarouciaxanthin, renieratinol, cucurbitaxanthin, peridinin and fucoxanthin. The described synthesis of the epimeric C_{15}-epoxyalcohols 47 and 48 opens the way for further investigations of these transformations. In relation to a total synthesis of neoxanthin, a synthesis of the naturally occurring *grasshopper ketone* (49) was reported very recently by Eugster's group (ref. 37); the synthon 50 was used as starting material (Fig. 15). This synthesis

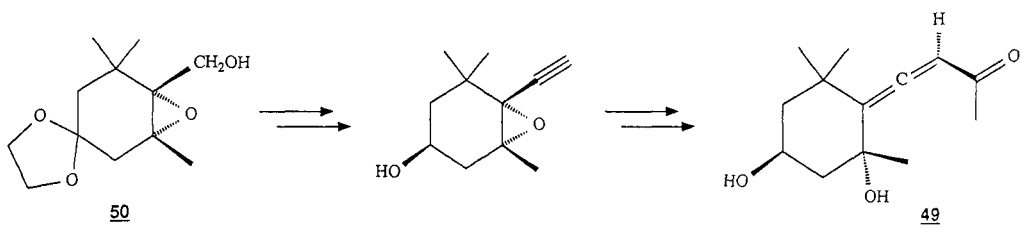
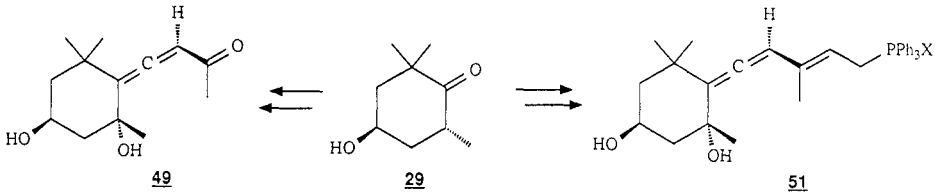


Fig. 15. Eugster's synthesis of the optically active grasshopper ketone

demonstrates the great versatility of this synthon. The first synthesis of the optically active *grasshopper ketone* (49) has been reported by Bernhard (Fig. 16) starting from the well known, optically active C_9-hydroxyketone 24 (ref. 38). In a similar way also the first optically active allenic C_{15}-phosphonium salt 51 has been prepared and used in the synthesis of *mimulaxanthin* and *deepoxyneoxanthin* (ref. 39). This represents the first synthesis of an optically active carotenoid containing an allenic group.



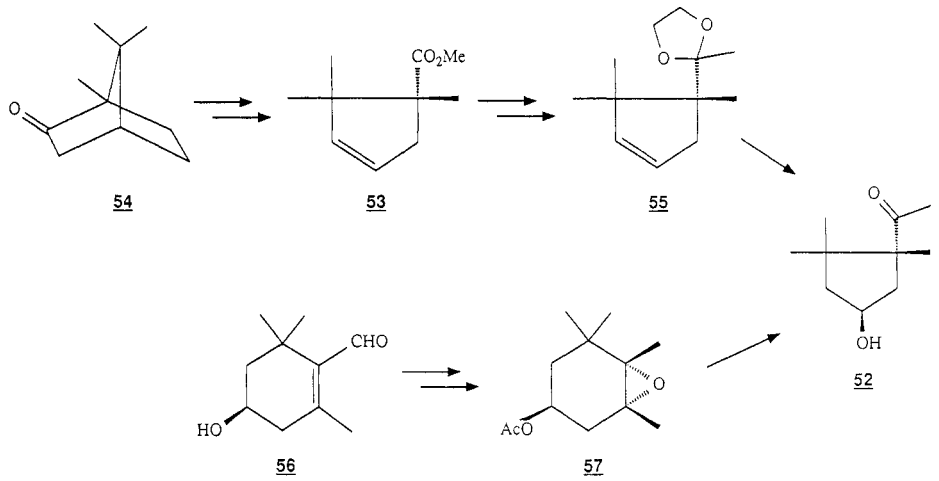
49 29 51

Fig. 16. Bernhard's synthesis of the optically active grasshopper ketone and of mimulaxanthin

A few other end-groups should be mentioned. The synthesis of the *(3R,4S,5R,6R)-5,6-dihydro-3,4-dihydroxy-β-end-group* with four asymmetric carbon atoms, which occurs in *3,4,3',4'-tetrahydroxypirardixanthin* and ophioxanthin was reported by Hengartner (ref. 40). No syntheses have yet been reported for the *(5R,6S)-5,6-dihydro-6-hydroxy-3-oxo-β-end-group* of isomytiloxanthin or for the *(2R,5S,6R)-2'-hydroxy-5,6-epoxy-β-end-group*.

The κ-end-groups

The *(3S,5R)-3-hydroxy-κ-end-group* is characteristic of *capsorubin*, *capsanthin* and *cryptocapsin* isolated from *Capsicum annuum*. Besides these main pigments the corresponding compounds with the *3-oxo-κ-end-group*, namely *capsorubone*, *capsanthone* and *cryptocapsone* are also known. The synthesis of (3S,5R,3'R,5'S)-capsorubin reported in 1973 by Weedon (ref. 41) was the first synthesis of an enantiomerically pure xanthophyll. For this synthesis the C_{10}-synthon 52 was reacted in an aldol condensation with the C_{20}-dialdehyde according to the scheme $C_{10} + C_{20} + C_{10} = C_{40}$. For the preparation of this synthon two different approaches have been described (Fig. 17). In one reaction sequence the cyclopentene derivative 53, which can be obtained from (+)-camphor (54), was selected as starting material. The crucial step in this synthesis is the regio- and stereoselective introduction of the hydroxyl group, whereby the second chirality center is generated. The best results were obtained by hydroboration of the acetal 55 with (+)-diisopinocamphenylborane; with this synthon the carotenoids from red pepper have been synthesized (ref. 42). On the other hand the same synthon 52 can be obtained starting from (R)-3-hydroxy-β-cyclocitral (56). Reduction of the aldehyde, epoxidation, separation of the diastereoisomers and acetylation gave the acetoepoxy compound 57, which, on pinacolic rearrangement, gave the desired compound. A new yet unsolved problem is the synthesis of compounds with a κ-end-group which have an oxidized group at C(17), giving rise to an additional chirality center at C(1).



54 53 55 52 56 57

Fig. 17. Synthesis of the (3S,5R)-3-hydroxy-κ-end-group

The homocarotenoids

The acyclic and cyclic C_{45}- and C_{50}-carotenoids characteristically have an additional C_5-unit at position (2) or at both C(2) and C(2'); the C(2) carbon atom thus becomes asymmetric. At the Liverpool meeting in 1981 we reported on a possible approach to the synthesis of the different acyclic end-groups. The key step is the stereospecific alkylation of optically active esters of (R)-3-hydroxybutyric acid 58 to give the C_9-compound 59. With this synthon the three C_{15}-building-blocks 60-62, which contain the chiral end-groups of the acyclic C_{45}- and C_{50}-carotenoids, have been synthesized (ref. 43) (Fig. 18) and used to prepare *(2S,2'S)-bacterioruberin, (2S,2'S)-bisanhydrobacterioruberin,*

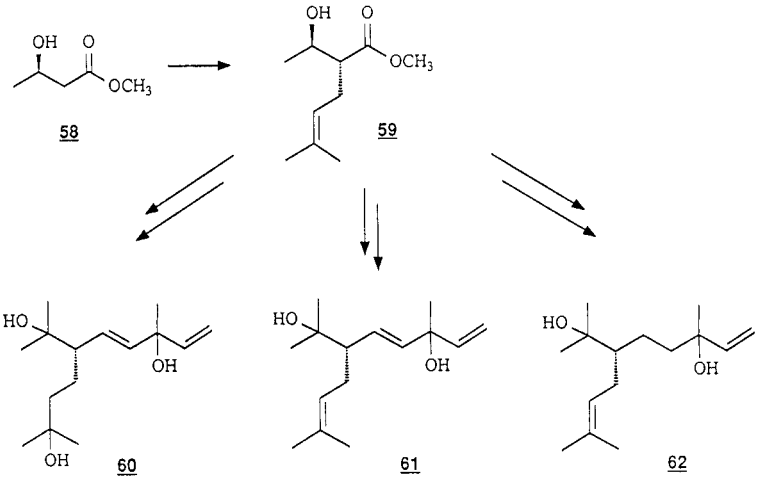


Fig. 18. Construction of optically active end-groups for the synthesis of acyclic C_{45}- and C_{50}-carotenoids

(S)-2-isopentenyl-3,4-didehydrorhodopin and *(S)-trisanhydrobacterioruberin* (ref. 44). For the synthesis of the cyclic C_{45}- and C_{50}-carotenoids we have chosen (-)-β-pinene (64) as starting material. This compound was converted into (-)-verbenol (65) which was pyrolyzed to the optically active aldehyde 66 and thence gave the C_{11}-acetal 67 (Fig. 19). This

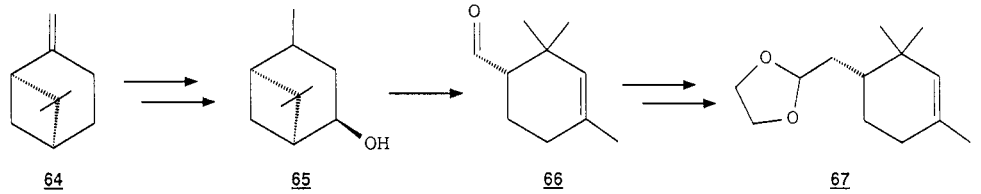
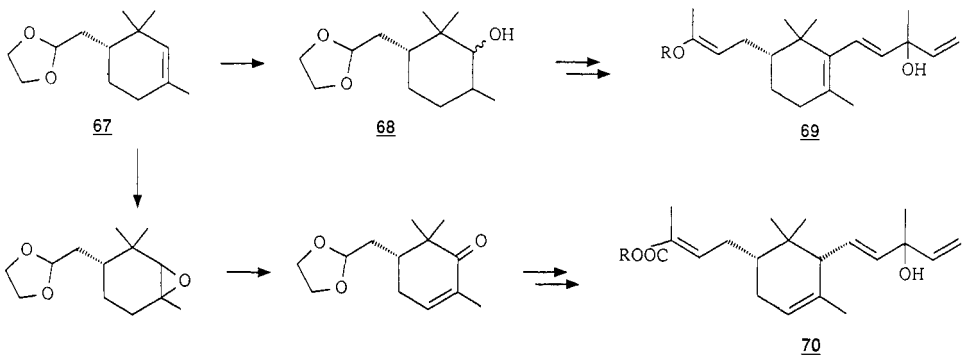


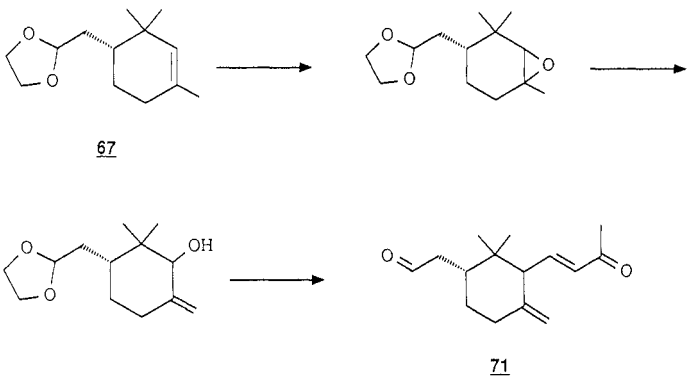
Fig. 19. Synthesis of an optically active synthon for the synthesis of acyclic C_{45}- and C_{50}-carotenoids

synthon was then hydroxylated to 68 (Fig. 20) and elongation of the side-chain and introduction of a C_4- and a C_2-unit, successively, for the polyene chain, gave the optically active C_{20}-building block 69. With this synthon we have synthesized optically active *C.p. 450* and *C.p. 470* (ref. 45). On the other hand the same synthon 67 was epoxidized, a keto group introduced at C(6) and the same approach was then used as in the synthesis of lutein to introduce the chirality center at C(6), i.e. the stereoselective epoxidation. The C_{20}-end-group 70 was obtained and, with this synthon, *decaprenoxanthin, 11',12'-dehydrononaprenoxanthin, A.g. 471* (as a mixture of E/Z-isomers) and the *peracetates* of *decaprenoxanthin mono- and bisglycosides* were obtained (ref. 46). The synthesis of racemic sarcinaxanthin, with the substituted γ-end-group, has recently been reported by the group of Julia (ref. 47). A suitable building block for the synthesis of this carotenoid in enantiomerically pure form is the compound 71, which was again synthesized from the synthon 66 (Fig. 21). The further synthesis of the carotenoid is currently under investigation in our laboratories.



67 68 69 70

Fig. 20. Synthesis of opically active end-groups of cyclic C_{45}- and C_{50}-carotenoids



67 71

Fig. 21. Synthesis of an optically active synthon for the synthesis of sarcinaxanthin

CONCLUSIONS

In 1957 the first carotene was synthesized in optically active form, in 1973 the first xanthophyll followed. What is the state of the art in 1990 - some 20 years later? It is obvious that all the important end-groups have been synthesized or at least promising precursors are available. For the introduction of the centers of chirality different approaches have been used. Selective reduction with baker's yeast gave a synthon from which carotenoids with a zeaxanthin, lutein, astaxanthin or a five-membered-ring-end-group are accessible. Readily available naturally occurring optically active compounds, such as camphor, serine, (-)-β-pinene etc. have been used as starting material. With regard to the chemical reactions, it is obvious that the Sharpless epoxidation is the reaction of choice. With these chiral synthons most of the important carotenoids have been synthesized. The question arises whether the field of the synthesis of optically active carotenoids is exhausted. I am firmly convinced that this is not the case. Although sensational results may not evolve, much work has still to be done. The chiral synthons are ready, they are the tools for the preparation of the many carotenoids that have not yet been synthesized. In this way new and old problems have to be solved. New methods and reactions may be applied and investigated and perhaps further knowledge of synthetic organic chemistry may evolve. Last but not least, one has to bear in mind that carotenoid chemistry is not only chemistry of biologically active molecules with various functions but is also industrial organic chemistry, where other aspects are of interest. Referring to the famous book of Hermann Hesse, Prof. Quinkert recently wrote: "The application of enantiomerically pure active agents is no matter for esoteric players of the "glass-bead" game (ref. 48)."

REFERENCES

1. H. Mayer, Pure Appl. Chem. 51, 535-564 (1979).
2. H. Pfander, Key to Carotenoids, 2nd edition, Birkhäuser Verlag, Basel (1987).
3. W. Eschenmoser, P. Uebelhardt and C.H. Eugster, Helv. Chim. Acta 66, 82-91 (1983).
4. T. Katsuki and K.B. Sharpless, J. Am. Chem. Soc. 102, 5974-5976 (1980); V.S. Martin, S.S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda and K.B. Sharpless, J. Am. Chem. Soc. 103, 6237-6240 (1981).

5. R. Dumont and H. Pfander, Helv. Chim. Acta 66, 814-823 (1983).
6. R. Dumont and H. Pfander, Helv. Chim. Acta 67, 1283-1290 (1984).
7. R. Dumont, Ph. D. Thesis, Berne (1984).
8. H. Pfander, in Carotenoids: Chemistry and Biology (N.I. Krinsky, M.M. Mathews-Roth and R.F. Taylor, eds.), pp. 125-138, Plenum Press, New York (1990).
9. M. Pfister, planned Ph. D. Thesis, Berne.
10. M. Kamber, H. Pfander and K. Noack, Helv. Chim. Acta 67, 968-985 (1984).
11. C. Arm and H. Pfander, Helv. Chim. Acta 67, 1540-1546 (1984).
12. M. Ito, R. Masahara and K. Tsukida, Tetrahedron Letters 2767-2770 (1977).
13. S.Gut, H. Wolleb and H. Pfander, Helv. Chim. Acta 72, 496-501 (1989).
14. H. Mayer, W. Boguth, H.G.W. Leuenberger, E. Widmer and R. Zell, Abstr. 4th. Internat. Carotenoids Symp., p. 43, Berne (1975); H. Mayer, Pure Appl.Chem. 51, 535-564 (1979); R.K. Müller, K. Bernhard, F. Kienzle, H. Mayer and A. Rüttimann, Food Chem. 5, 15-43 (1980); A. Rüttimann and H. Mayer, Helv. Chim. Acta 63, 1456-1462 (1980); E. Widmer, Pure Appl. Chem. 57, 741-752 (1985).
15. H. Pfander, A. Lachenmeier and M. Hadorn, Helv. Chim. Acta 63, 1377-1382 (1980).
16. A. Haag, W. Eschenmoser and C.H. Eugster, Helv. Chim. Acta 63, 10-15 (1980); A. Haag and C.H. Eugster, Helv. Chim. Acta 65, 1795-1803 (1982).
17. K. Schiedt, in Carotenoids: Chemistry and Biology (N.I. Krinsky, M.M. Mathews-Roth and R.F. Taylor, eds.), pp. 247-268, Plenum Press, New York (1990).
18. F. Kienzle and H. Mayer, Helv. Chim. Acta 61, 2609-2615 (1978); R.K. Müller, K. Bernhard and M. Vecchi, in Carotenoid Chemistry and Biochemistry,(G. Britton and T.W. Goodwin, eds.), pp. 27-54, Pergamon, Oxford (1981); E. Widmer, Pure Appl. Chem. 57, 741-752 (1985).
19. K. Bernhard, G. Englert, H. Mayer, R.K. Müller, A. Rüttimann, M. Vecchi, E. Widmer and R. Zell, Helv. Chim. Acta 64, 2469-2484 (1981).
20. C. Tscharner, C.H. Eugster and P. Karrer, Helv. Chim. Acta 41, 32-34 (1958); R. Buchecker, R. Egli, H. Regel-Wild, C. Tscharner, C.H. Eugster, G. Uhde and G. Ohloff, Helv. Chim. Acta 56, 2548-2563 (1973); C. Tscharner, C.H. Eugster and P. Karrer, Helv.Chim. Acta 40, 1676-1677 (1957); C.H. Eugster, R. Buchecker, C. Tscharner, G. Uhde and G. Ohloff, Helv. Chim. Acta 52, 1429-1431 (1969).
21. W. Eschenmoser, P. Uebelhardt and C.H. Eugster, Helv. Chim. Acta 62, 2434-2438 (1979).
22. P. Semadeni, planned Ph. D. Thesis, Berne
23. D.H.R. Barton and S.W. McCombie, J. Chem. Soc. Perkin I 1574-1585 (1974).
24. H. Mayer and A. Rüttimann, Helv. Chim. Acta 63, 1451-1455 (1980).
25. H. Mayer, in Carotenoid Chemistry and Biochemistry, (G. Britton and T.W. Goodwin, eds.) pp. 55-70, Pergamon, Oxford, (1981).
26. M. Hallenstvet, R. Buchecker, G. Borch and S. Liaaen-Jensen, Phytochemistry 16, 583-585 (1977).
27. G. Ohloff and S. Mignat, Liebigs Ann. Chem. 652, 115-126 (1962); T. Oritani and K. Yamashita, Agric. Biol. Chem. 51, 1271-1275 (1987).
28. M. Acemoglu, W. Eschenmoser and C.H. Eugster, Helv. Chim. Acta 64, 2691-2695 (1981).
29. M. Acemoglu and C.H. Eugster, Helv. Chim. Acta 67, 184-190 (1984).
30. W. Eschenmoser and C.H. Eugster, Helv. Chim. Acta 61, 822-831 (1978).
31. W. Eschenmoser, E. Märki-Fischer and C.H. Eugster, Helv. Chim. Acta 67, 170-174 (1984).
32. W. Eschenmoser, P. Uebelhardt and C.H. Eugster, Helv. Chim. Acta 65, 353-364 (1982).
33. W. Eschenmoser, P. Uebelhardt and C.H. Eugster, Helv. Chim. Acta 64, 2681-2690 (1981).
34. C.H. Eugster, in Carotenoids: Chemistry and Biology (N.I. Krinsky, M.M. Mathews-Roth and R.F. Taylor, eds.), pp. 1-20, Plenum Press, New York (1990).
35. M. Acemoglu and C.H. Eugster, Abstr. 8th Internat. Carotenoids Symp., p. 15, Boston (1987).
36. M. Acemoglu, P. Uebelhardt, M. Rey and C.H. Eugster, Helv. Chim. Acta 71, 931-956 (1988).
37. A. Baumeler, W. Brade, A. Haag and C.H. Eugster, Helv. Chim. Acta 73, 700-715 (1990).
38. K. Bernhard, Abstr. 6th Internat. Carotenoids Symp., Liverpool (1981); T. Bjørnland, G. Englert, K. Bernhard and S.Liaaen-Jensen, Tetrahedron Letters 2577-2580 (1989).
39. E. Widmer, Pure Appl. Chem. 57, 741-752 (1985).
40. U. Hengartner, Abstr. 9th Internat. Carotenoids Symp., Kyoto, (1990).
41. B.C.L. Weedon, Pure Appl. Chem. 35, 113-130 (1973).
42. A. Rüttimann, in Carotenoid Chemistry and Biochemistry (G. Britton and F.W. Goodwin, eds.) pp. 71-86, Pergamon, Oxford, (1981); A. Rüttimann, G. Englert, H. Mayer, G.P. Moss and B.C.L. Weedon, Helv.Chim. Acta 66, 1939-1960 (1983).
43. A. Kramer and H. Pfander, Helv. Chim. Acta 65, 293-301 (1982) and 67, 21-28 (1984).
44. J.-P. Wolf and H. Pfander, Helv. Chim. Acta 69, 62-68 (1986); D. Zuber, C. Arm, I. Lakomy, H. Pfander and K. Noack, Helv. Chim. Acta, to be published.
45. H. Wolleb and H. Pfander, Helv. Chim. Acta 69, 646-658 and 1505-1512 (1986).
46. M. Gerspacher and H. Pfander, Helv. Chim. Acta 72, 151-157 (1989) and to be published.
47. J.P. Férézon and M. Julia, Tetrahedron 46, 475-486 (1990).
48. G. Quinkert and H. Stark, Angew. Chem., Int. Ed. 22, 637-655 (1985), referring to H. Hesse: "The Glass Bead Game".