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CHARACTERISATION, CHEMISTRY AND STEREOCHEMISTRY OF CAROTENOIDS

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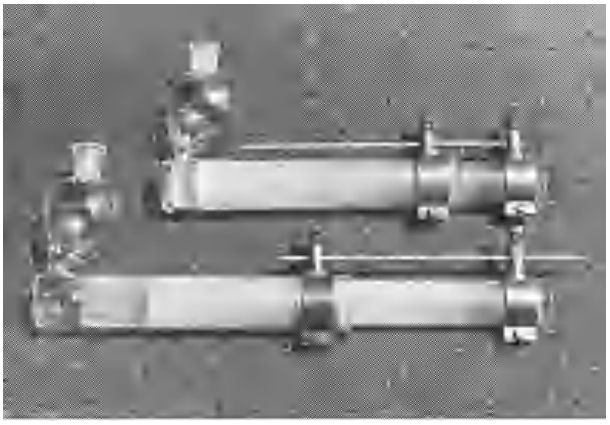
Abstract - A review is presented on progress made since the 4th International Symposium on Carotenoids, Berne, Switzerland, 1975, in the following areas of carotenoid chemistry:
- New structures.
- Important chemical transformations.
- Stereochemistry: new assignments of absolute configuration, and a chemist's approach to a deeper understanding of the biological cyclisation step.
- Carotenoids in rose flowers.

1. INTRODUCTION



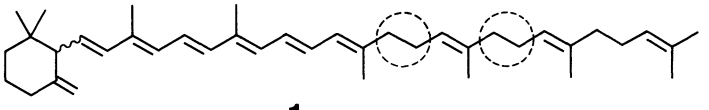
Photograph 1

Only a few amongst you will recognise what is depicted on this photograph: it shows Baly-tubes with variable thickness, with which I recorded my first carotene spectrum - still with photo-plates - in ca. 1947. The whole procedure lasted about a week. My teacher at the time, Professor Paul Karrer, though, procured one of the first Beckman DU as soon as was possible for him. I am sure I don't need to tell any of you what a rapid development the analysis of the carotenoids then underwent. However, my present progress report is not going to begin with the historical 1940's mentioned, but will follow on from the lecture report given in 1975 by Professor S. Liaaen-Jensen in Berne (Ref.1). Properly speaking, the carotene researchers are in the happy position where each year good progress reports appear in the Specialist Reports. I have the privilege, however, of being able to bring you something more comprehensive and also to include newest and unpublished material.

I will speak first about new carotenoids and will go into their characterisation, then mention a few chemical transformations. After this I will discuss the absolute configurations, then go into the problems of the stereochemistry of the cyclisation step in the carotenoids and in the last section say something about the carotenoids in roses.

2. NEW CAROTENOIDS

The graph which Professor Liaaen-Jensen had shown in Berne in 1975 (Ref. 1) has, at the time of report, still scarcely flattened. Numerous new carotenoids have again been discovered, however, no more fundamentally new structures. It must be clearly stated and contrasted with the speedy advances in other terpenoid classes, e.g. with the sesqui- or diterpenes. Here, it is indeed still possible for a small and active group to isolate and clarify one hundred or more new substances in a period of five to ten years! Perhaps the transition of main activity from the plant world to that of the insects or marine animals will again bring something new. Examples are found on:



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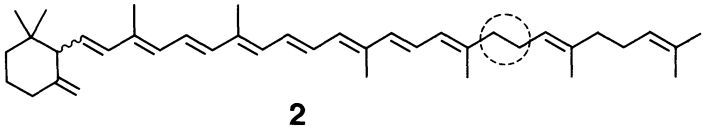

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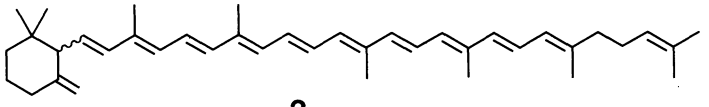

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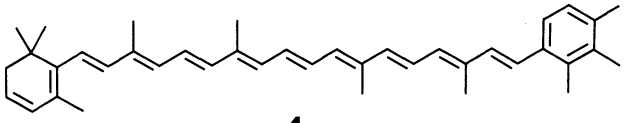

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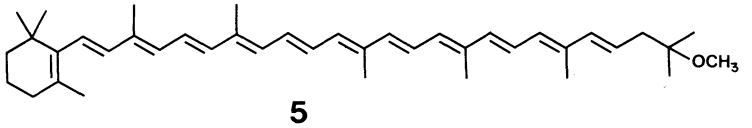

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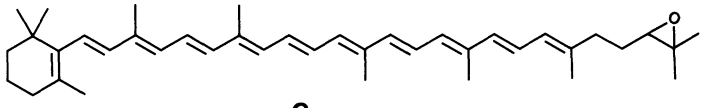

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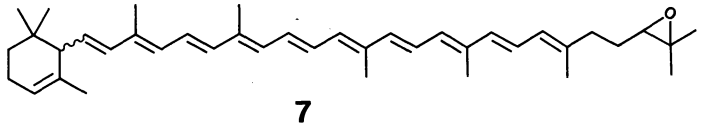

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Scheme 1

Hydrocarbons

The 3 γ,ψ-carotenes 1, 2, 3 have been isolated by Britton and Goodwin from Coccinella septempunctata (Ladybird beetles) (Ref. 2). The constitution proposals are based on UV/VIS- and mass spectra. The absolute configuration remains open, presumably until again such a sensational mass occurrence of ladybird beetles arises as we had in Europe in 1976. Britton and Goodwin postulate that the cyclisation step possibly takes place in the animal. Because of the pronounced rarity of the γ-terminal group one should, in this connection, be reminded of the occurrence of γ,γ-carotene in aphids (Ref. 3). From the chemical point of view, the γ-types should actually occur much more frequently - I will return to this point later. A poly-(Z-)-β,ψ-carotene has been ascertained in fruits of tangerine tomatoes (Ref. 4). It may be closely related to the "pro-β,ψ-carotene" isolated and crystallised by Zechmeister and Schroeder (Ref. 5) from fruits of Butia capitata and Pyracantha angustifolia, whose structure is still open. For both (Z)-isomers, stronger absorption on $Ca(OH)_2$ and MgO than the all-(E)-β,ψ-carotene is quoted. Both furnish on I_2 isomerisation a little all-(E)-β,ψ-carotene.

I am convinced that the time has now arrived, for these and other (Z)-isomeric carotenes to be isolated and structurally elucidated by modern methods. They are, probably, more widespread than one has hitherto assumed. The (Z,E)-isomerism is really one of the most inherent phenomena of the carotenoids. It stands - at least on this scale - almost alone in the chemistry of natural substances. I shall return later to one special aspect of this characteristic.

A new carotene is tethyatene (4) (3,4-didehydro-β,χ-carotene), which has been isolated from the orange-red sea-sponge Thethya amamensis (Ref. 6).

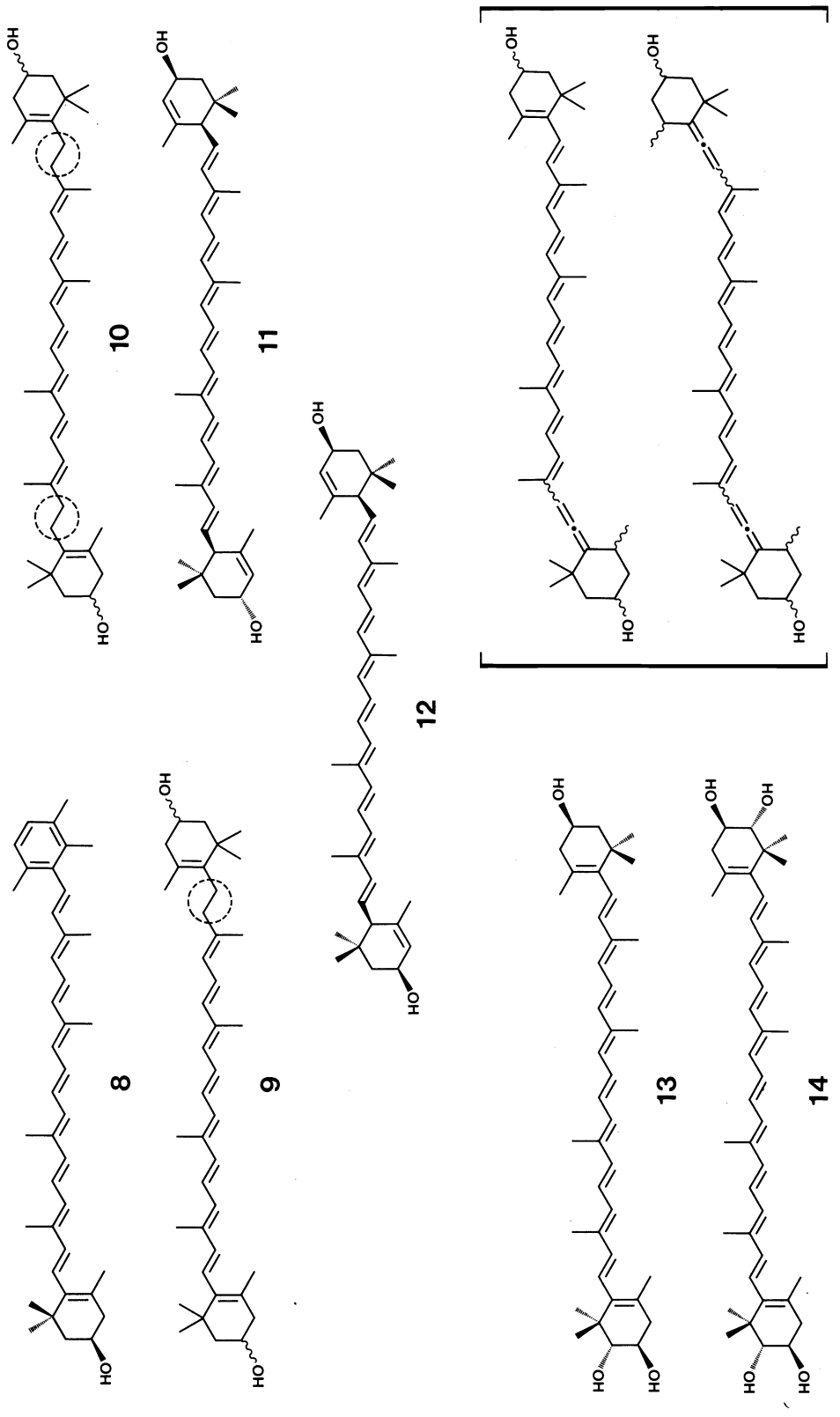
Methylethers and Epoxides

I will now mention a few newly discovered carotene methylethers and epoxides. The methoxylated β,ψ-carotene 5 (1'-methoxy-3',4'-didehydro-1',2'-dihydro-β,γ-carotene) was isolated by Britton et al. (Ref. 7) as trace carotenoid from cultures of Rhodomicrobium vannielii. The new substance is interpreted as being a link in the biogenesis pathways to β-carotene on the one hand, and spirilloxanthin on the other. The same authors, in their search for new carotene epoxides (Ref. 8) in extracts from the tomato mutant "δ", then came across traces of 6 (1',2'-epoxy-1',2'-dihydro-β,ψ-carotene) and 7 (1',2'-epoxy-1',2'-dihydro-ε,ψ-carotene). The derivation of constitution is essentially based on comparative UV/VIS- and mass spectra and comparative chromatograms. The elucidation of the chirality at C(6) in 7 should no longer present problems today; it is more difficult to prove that of the epoxide group. I must state that, hitherto, it is still not known for any carotenoid with a terminally-placed epoxide group. Should these epoxides play a role in the ring-closing reactions, then the elucidation of the chirality of this terminal group is, of course, of importance.

New hydroxycarotenes

Agelaxanthin A (8) ((3R)-β,φ-caroten-3-ol) was isolated from the sea-sponge Agelas schmidtii (Ref. 9). I will return to its absolute configuration in section 4. For parasiloxanthin and dihydroparasiloxanthin, two carotenoids isolated from skin and fins of Parasilurus asotus (Ref. 10), the constitutions 9 and 10 are given: (7',8'-dihydro-3,3'-dihydroxy-β,β-carotene and 7,8,7',8'-tetrahydro-3,3'-dihydroxy-β,β-carotene, respectively). Argumentations for these constitutions are based essentially on comparison with the properties of 3-hydroxyzeacarotene; unfortunately there are no chiroptical data quoted in the work. This shortcoming befalls not only this but also numerous other works. Particularly for such rare and difficultly accessible carotenoids, that is very regrettable. In section 4, I will go into more detail about chiriquixanthin A (11) and B (12), isolated from the skin of a frog. As derivatives of ε,ε-carotene they both offer particular interest. The possible identity with the so-called tunaxanthin (from fish) is still not definitely clarified.

A very significant and in many ways also instructive structure revision has arisen for the hydroxycarotenoids 13 and 14. I have put the old suggestions in brackets next to the new ones. We are dealing with carotenoids from the algae Anacystis nidulans, which on recent investigation (Ref. 11), on the basis



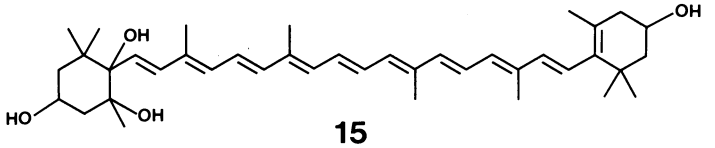
Scheme 2

of UV/VIS- and mass spectra immediately turned out to be tri- and tetrahydroxy carotenoids, respectively, of the β,β-type. The constitutions proposed on the strength of insufficient microtests (Ref. 12) were thus immediately dropped. Primary hydroxyl groups are absent on the grounds of the ^{1}H-NMR-spectrum, secondary, allylic as well as tertiary -OH's are also lacking, which follows from the stability of the compound in HCl/chloroform. Since dioxolane formation occurs with acetone, vicinal hydroxyls exist on C(2)/C(3), C(2')/C(3') respectively. From $^3J_{2,3}$ = 10.5 Hz, a quasi-equatorial position of the OH-groups in the β-ring was deduced and, from the obvious C_2-symmetry, also of those in the β'-ring. The OH-group on C(3') of 13 is certain on the basis of ^{1}H-NMR comparisons. Nostoxanthin 14 is completely different from crustaxanthin in the IR- and ^{1}H-NMR-spectra. For derivation of the absolute configuration see section 4. The transformations demonstrated thin-layer chromatographically by Stransky and Hager (Ref. 12):

nostoxanthin (14) $\xrightarrow{LiAlH_4}$ caloxanthin (13) + zeaxanthin

zeaxanthin $\xrightarrow{H_2O_2}$ caloxanthin + nostoxanthin

thus necessitate verification. In this connection, the "Pigment IV" and "Pigment II" (Ref. 13) isolated in very small amounts, from cultures of Rhizobium lupini should also be mentioned, for which analogous constitutions to 13 and 14 (that is, without stereochemistry) are given.



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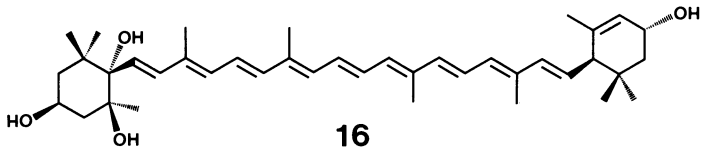

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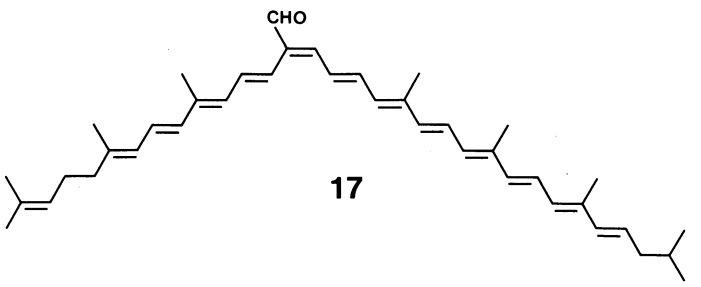

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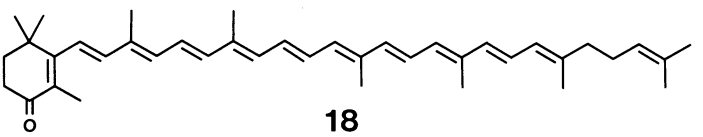

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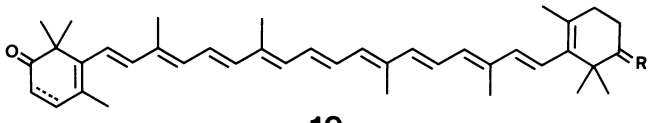

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Scheme 3

The constitution 15 is given for a tetrahydroxy carotene from the juice of Valencia oranges (Ref. 14). The arguments are: λ_{max} 474, 445, 424 (solvent ?). The glycol 95 with analogous chromophoric system shows λ_{max} 476, 448, 425 (ethanol); see section 4; formation of a diacetate and conversion into mutatoxanthin by sufficiently long treatment with HCl. Chiroptical data are unfortunately not communicated. The formation of 15 from antheraxanthin is likely. The stereochemistry of the epoxide hydrolysis is of interest in view of the analogous cases mentioned in sections 3 and 4.

From an older sample of "taraxanthin" (see Note a), which had been isolated by Karrer et al. from Ranunculus acer, a glycol was also isolated; which according to Ref. 16 is assigned structure 16 (argumentation for the absolute configuration see section 4).

Carotenoids with carbonyl groups

A new lycopenal (17); 13-(Z)-3',4'-didehydro-1',2'-dihydro-ψ,ψ-caroten-20-al; possibly also 3,4-didehydro-1,2-dihydro-structure) has been found in addition to neurosporene, lycopene, 1,2-dihydroneurosporene, 1,2-dihydrolycopene, 1,2-dihydro-3,4-dehydrolycopene and 13-(Z)-ψ,ψ-caroten-20-al in cultures of Rhodopseudomonas viridis (Ref. 18).

β,ψ-Caroten-4-one 18 was isolated as the main pigment from an Arthrobacter sp. (Ref. 19). A whole series of 2-oxo-, 2,2'-dioxo-, 2-oxo-2'-hydroxy-β,β-carotenes (19) including some with 3,4-didehydro structures are reported to occur in the insect Carausius morosus (Ref. 20).

Two Japanese teams, evidently independently of each other and in mutual unawareness of the results, have been working on the carotenoids from the sea-sponge Tedania digitata. According to Okukado (Ref. 21), the main pigment is named tedanin and on the basis of extensive investigations assigned structure 20 (2,3-didehydro-3-hydroxy-β,χ-caroten-3-one) (see Scheme 4). Since Okukado's isolation included a saponification step, it is possible that the known dehydrogenation of the original keto to the enolised diketone has occurred. From the same species, Tanaka et al. (Ref. 22) obtained an also crystalline carotenoid, which they called tedaniaxanthin and assigned structure 21. The striking end group was not commented upon in the work of the authors. A carotenoid named clathriacine, isolated by Tanaka and Katayama from the sea-sponge Clathria frondifera, was assigned structure 20 (Ref. 23). The esters of 20 are named "Clathriaxanthin" by these authors. Thus, the tedanin from Okukado and the clathriacine from Tanaka and Katayama are synonymous.

The compounds 22 and 23 are 4-oxo-β,β-carotene derivatives, which have been discovered in cultures of Rhizobium lupini (Ref. 13). The trans-configuration for the glycol grouping was deduced on the basis of the ^{1}H-NMR-spectra. The absolute configuration is still unknown.

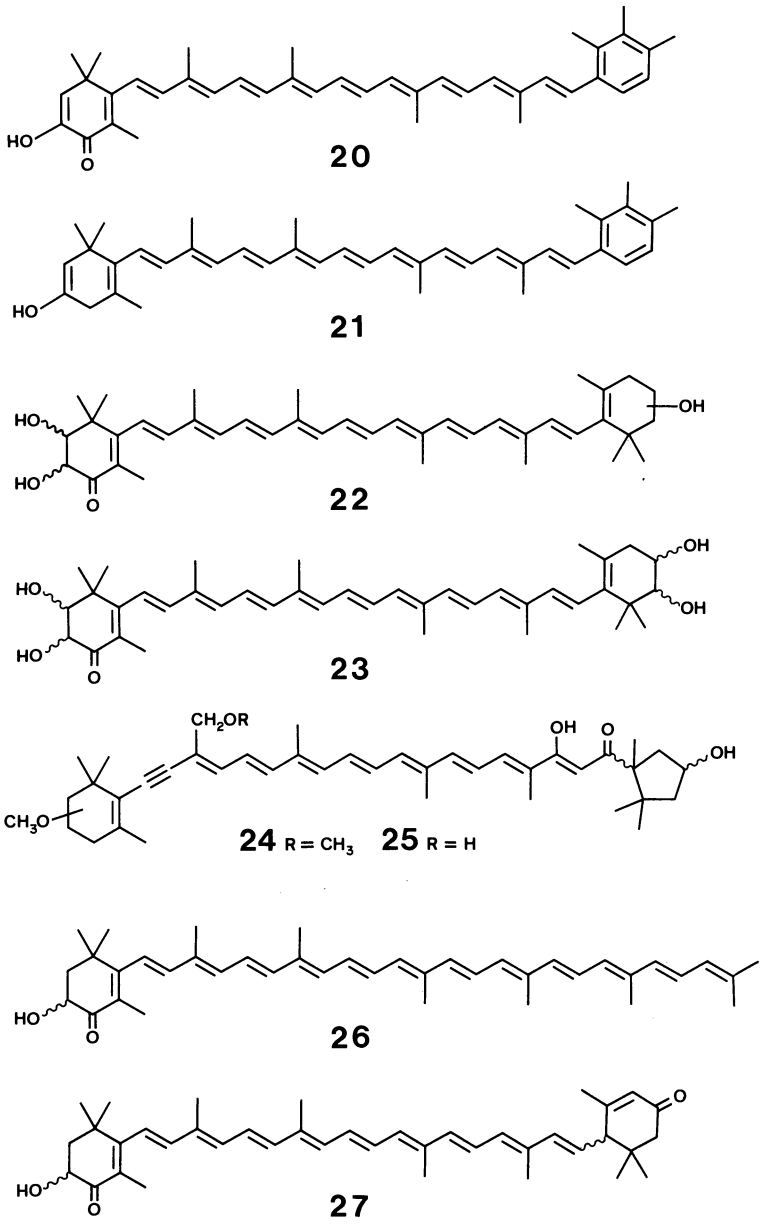
Fritschiellaxanthin is a new carotinoid with a 4-oxo function (109); see section 4 (Ref. 24).

The constitution 25 was proposed for agelaxanthin C from the previously mentioned sea-sponge Agelas schmidtii, whilst agelaxanthin B (24) possibly represents the 19-O-methylether of agelaxanthin C (Ref. 9); for the absolute configuration of the $\varkappa$-terminal group see the comments in section 4. Besides 8, 24 and 25, this sponge also contains α-carotene, isorenieratene, zeaxanthin and trikentriorhodin.

From the red "fermenting yeast" Phaffia rhodozyma, 3-hydroxy-4-oxo-torulene (26; 3-hydroxy-3',4'-didehydro-β,ψ-caroten-4-one) was isolated in slight amounts (Ref. 25). The 7,8-didehydroastaxanthin ester (110) from starfisch (Ref. 26) may well be identical with asterinic acid (see section 4).

Note a. The "taraxanthin" from R. Kuhn and E. Lederer (Ref. 15), a nicely crystalline substance, is not, as is maintained in several newer works, identical with lutein epoxide but is a mixture of lutein epoxide/flavoxanthin/chrysanthemaxanthin (73:13:14 ex Taraxacum officinale) (Refs. 16 & 17).

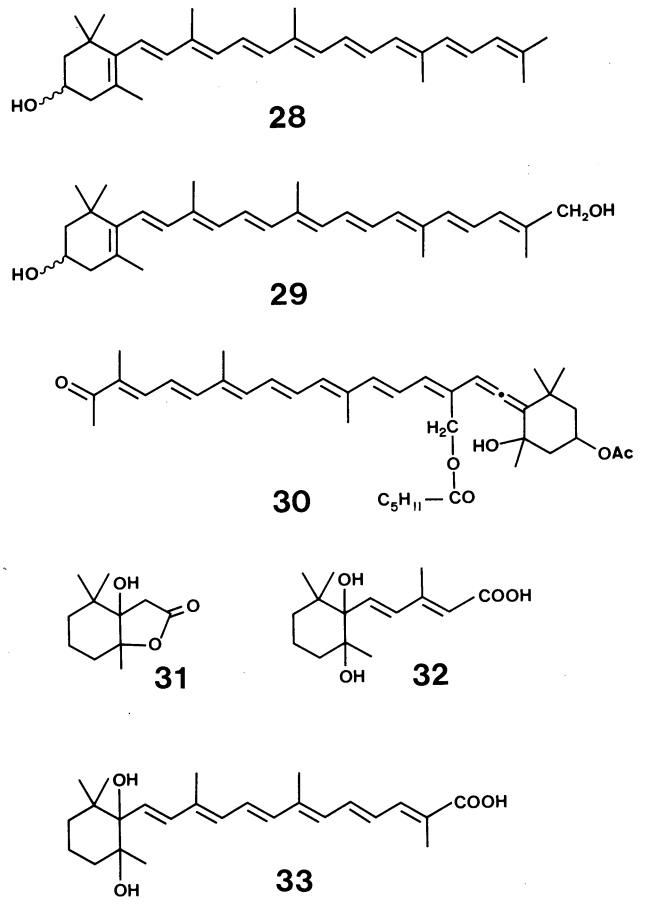
Finally, the carotene 27, named papilioerythrinone isolated from integuments of pupae of Papilio xuthus (swallow-tail) and carapaces of crab (Paralithodes brevipes) should be mentioned (Ref. 27). It occurs besides papilioerythrin (3'-OH instead of CO), canthaxanthin, astaxanthin, etc. (swallow-tail). Chiroptical data are missing in this work. Therefore the biogenetic sequence proposed by the authors must be regarded with caution.



Scheme 4

Apocarotenoids

One knows today, that carotenoids are transformed in plant organs into very many fragments, which scarcely show any further connection with carotenoids. I draw your attention here to flavours from rum, whisky, wine, tea, tobacco etc. This is not the point here, I will rather limit myself to substances, which still show a more distinct connection with carotenoids.

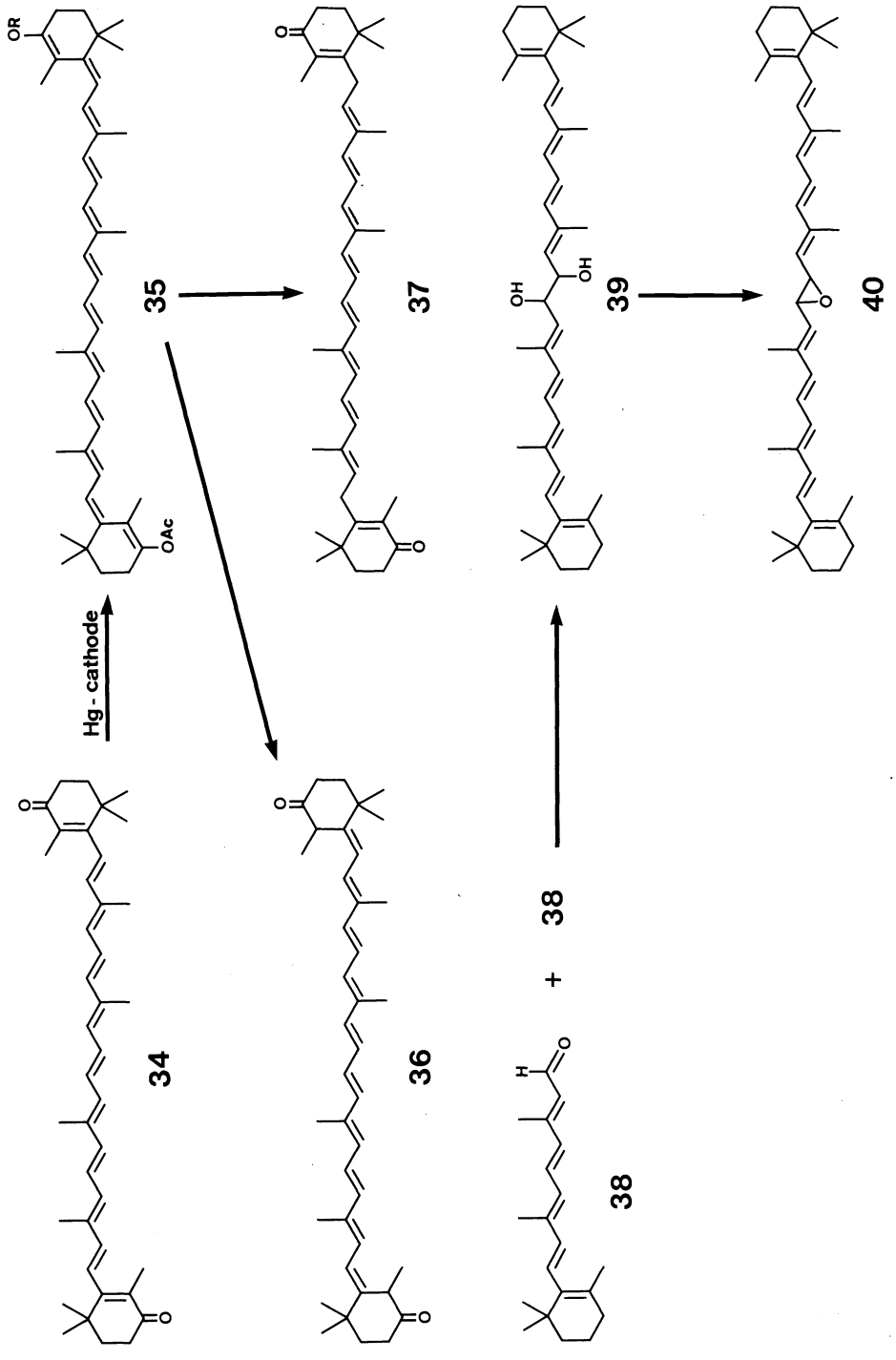


Scheme 5

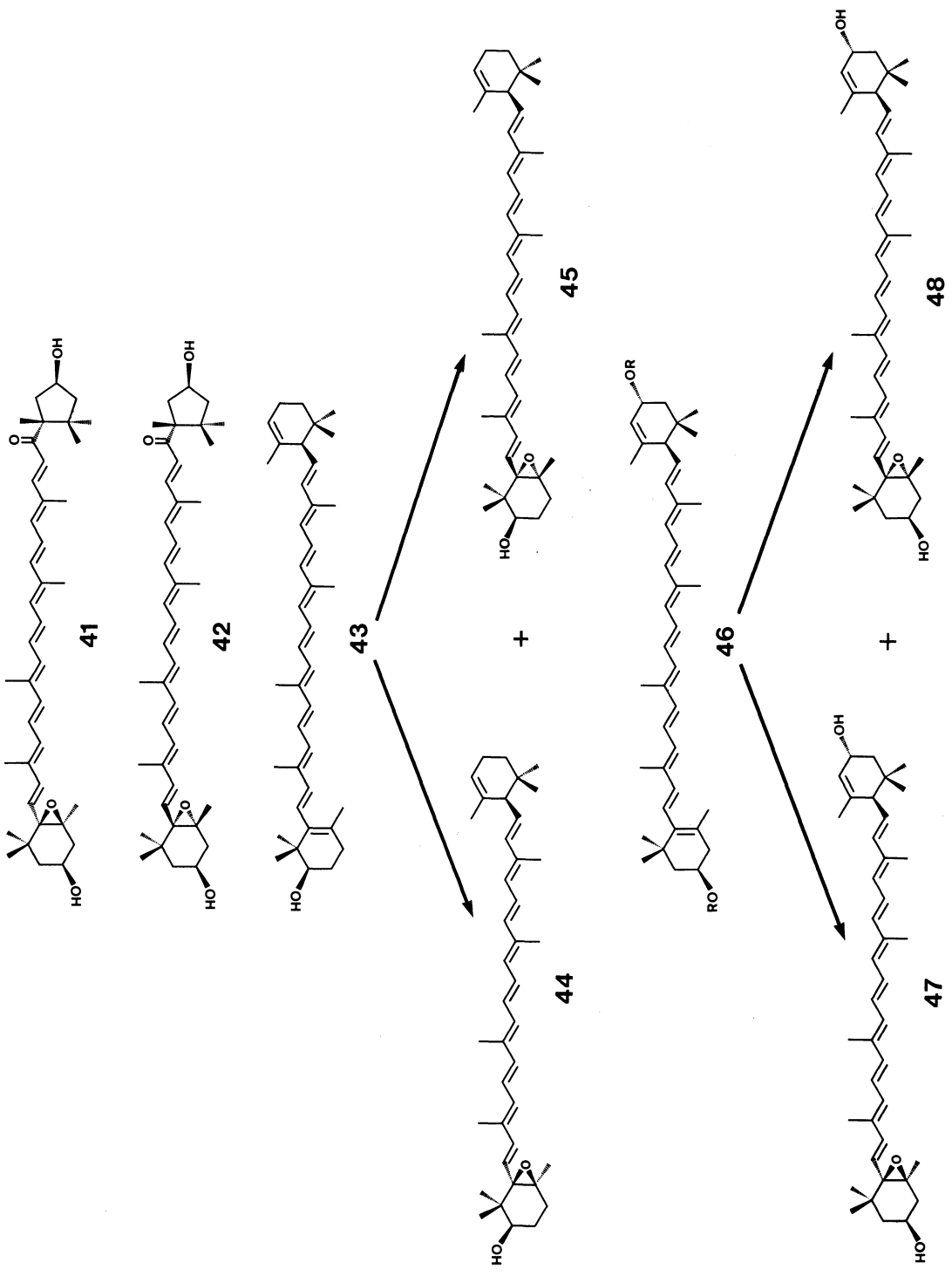
β-Citraurinine (28) and β-citraurol (29) were isolated from citrus fruits (oranges, mandarines) (Ref. 28). The hydrocarbon is very unstable in the crystalline state and quickly discolourises. No reproducible ^{1}H-NMR-spectra could be obtained. 29 is also unstable. To date, 7 naturally occurring 8'-apocarotenoids are known, of which 5 originate from citrus fruits. For this reason, the authors take one particular biogenetic pathway into consideration. 19-Hexanoyloxy-paracentrone (30) was isolated, in addition to 19'-hexanoyloxy-fucoxanthin, from Coccolithus huxleyi (Ref. 29).

In well documented works, Kulkarni et al. (Ref. 30) have isolated and clarified a whole range of apocarotenic acids from the parasitic Aeginetia indica (Orobanchaceae). Compound B (aeginetic acid) has constitution 32, according to the ^{1}H-NMR- and mass spectra. A trans- (diaxial) position of the vicinal OH-groups was concluded from the negative periodate cleavage, as well as from pyridine-induced-NMR-shifts in conjunction with a conformational argument. In my opinion, however, the lastly-mentioned conclusions are not conclusive, because not only the axial but also the equatorial CH_3 at C(1), together with CH_3-C(5), experience practically the same large paramagnetic shifts. However, the derivation of the configuration of the glycol grouping can be upheld by other means: comparison with the chemical shifts on natural azafrin ester (Ref. 31) and "cis-OH-azafrin ester" (Ref. 32) (not carried out by the Indian authors) shows that only a trans-diaxial configuration comes into consideration. Also, the compound B has a different melting point to the racemic compound prepared by Tamura et al. (Ref. 33).

Compounds D and E (33) appear to be dimorphous. They both exhibit very similar ^{1}H-NMR-spectra to compound B, with regard to the ring protons, and show in the mass spectrum the fragmentation behaviour described by Enzell (Ref. 34) on azafrin. Compound F is an azafrin type, possibly a stereoisomer of azafrin. Besides these compounds, the lactone 31 (aeginetolide) was also isolated.



Scheme 6



Scheme 7

3. SELECTED CHEMICAL REACTIONS ON CAROTENES AND CAROTENOIDS

At the time of report, new experiments on the functionalisation of easily obtainable carotenes, such as β-carotene, canthaxanthin etc. have been made, which could gain significance for future synthetic work. They are mentioned in the form of an extract in this section. In addition, interesting reaction modes have been discovered during structure elucidation.

Reductions

Electrochemical reduction under acetylation conditions on canthaxanthin (34) gave the retro-compound 35 (R = Ac) in addition to traces of retro-monoacetate (35, R = H) and 37. From 35, after hydrolysis, the compounds 36 and 37 (5,5'-dihydrocanthaxanthin and 7,7'-dihydrocanthaxanthin, respectively) were formed concurrently (Ref. 35). In this connection, the analogous electrochemical reduction of β-carotene should be mentioned (Ref. 36), in which 65% 7,7'-dihydro-β-carotene was formed. These reactions therefore proceed, very similarly to the older chemical reductions of polyenes and polyene-ketones with the metal/acid combination; e.g. with sodium amalgam/ether/H_2O (Refs. 37, 38, 39) or zinc/pyridine/glacial acetic acid (Ref. 40).

Pinacolisation

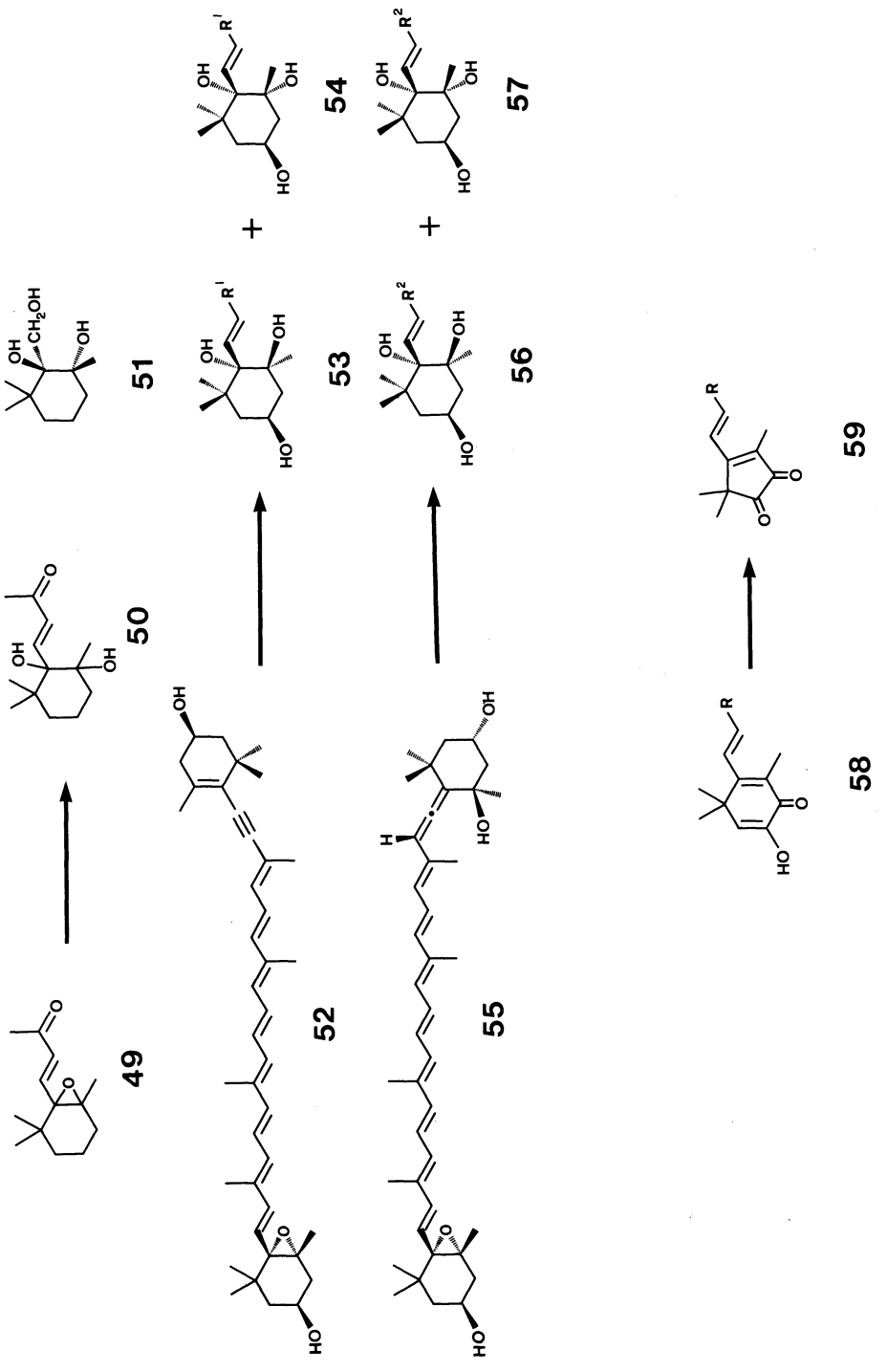
Work on these reactions has repeatedly been done in recent times. Thus vitamin A-aldehyde (38) could be converted into 15,15'-dihydro-15,15'-dihydroxy-β,β-carotene (39) in a yield of 10% by controlled potential electrolysis at a mercury cathode (Ref. 41). Substantially better yields are obtainable by chemical means according to Ref. 42 (zinc amalgam, zinc-copper couple in pyridine). Principally it concerns the same methods which had been applied by Kuhn and Winterstein (Ref. 43) for the first time in the polyene series. We have likewise obtained good yields of glycol 39 by this method (Ref. 46). The low valency complexes of Ti (prepared from $TiCl_4/LiAlH_4$ or $TiCl_4/Zn$ according to Ref. 44, or $TiCl_4/LiAlH_4$ (Ref. 45)), which were used by these authors for a new synthesis of β-carotene in yields of 85-90%, also give the pinacol 39 under suitable conditions (-70°) (Ref. 46). The main product 39 has C_2-symmetry according to the ^{1}H-NMR-spectrum and is thus the racemic form. From 39, the epoxide 40 can be prepared (Ref. 46) with the sulfurane according to Ref. 82.

Epoxidation reactions

I would now like to mention a few epoxdiation reactions, which have recently been carried out. The team in Cluj (Rumania) has made extensive investigations on in-chain epoxides of canthaxanthin (Ref. 47). The following epoxides were characterised: mono-9,10, di-9,10,9',10', mono 13,14, mono-11,12. The rearrangement to furanoid epoxides and their behaviour towards $BH_4^{\ominus}$ and $LiAlH_4$ was also examined. Researchers in Pécs (Hungary) have published similar reactions on capsanthin (Ref. 48). The isolated epoxides (capsanthin epoxide A (41; 3S, 5S, 6R) and B (42; 3S,5R,6S)) were formed in the ratio 3:1. The two epimers could be well separated on $CaCO_3$ with benzene; whereby 41 adhered better than 42. The almost enantiomeric CD-curves of the two compounds in the region of 200-370 nm is noteworthy. Their acid-catalysed rearrangement resulted in the furanoid capsochromes A + A' and B + B' respectively. Somewhat different ratios were found (Ref. 49) on epoxidation of β,ε-caroten-2-ol (43). The epoxides 44 and 45 were formed in the ratio 3 : 2. With this pair, the trans-epoxide (OH··· epoxy-group) adhered better. For lutein (46), the situation is more extreme: The usual epoxidation methods always lead to almost pure cis-epoxide (47) (ratio 47:48 = ca. 19:1) (Refs. 50 & 51).

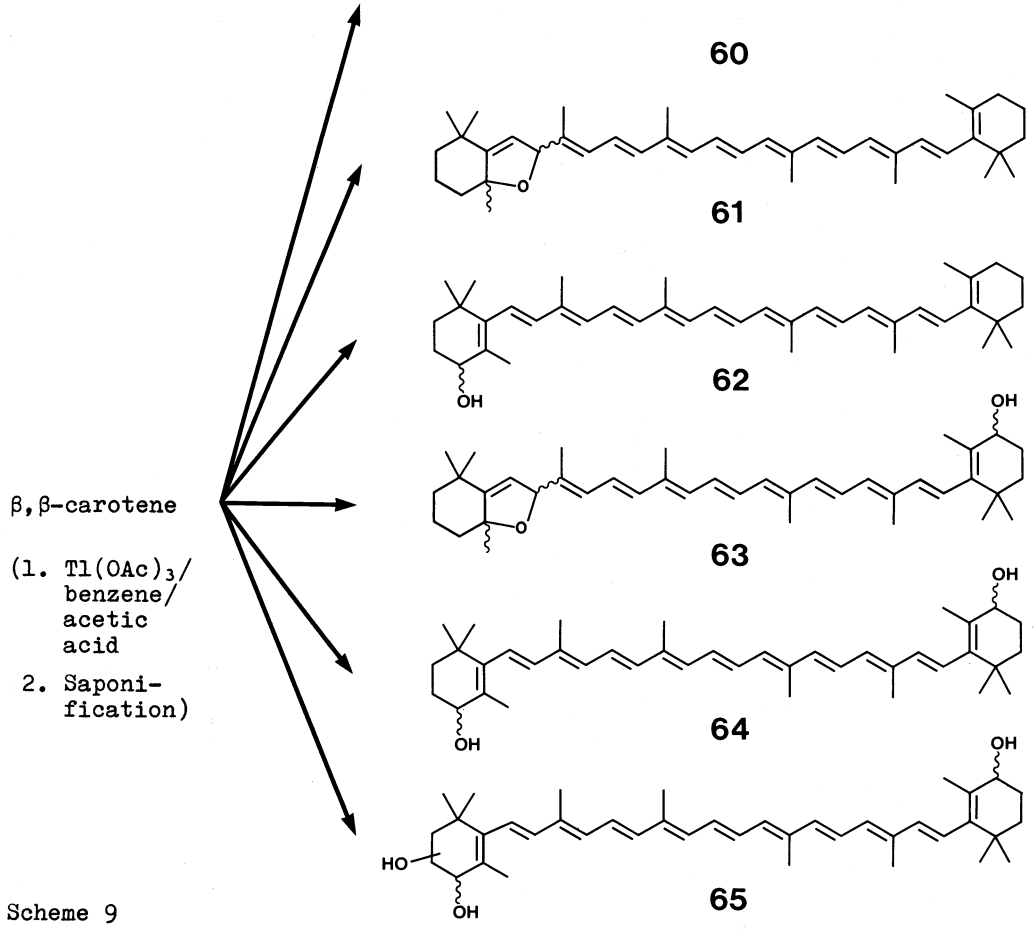
Epoxide hydrolyses

In connection with the elucidation of the configuration of natural carotenoid-5,6-glycols, the question of their origination from 5,6-epoxides and formation therefrom in vitro has, in recent times, received increased consideration. Karrer and Stürzinger (Ref. 52) converted β-ionone-5,6-epoxide (49) (carotenoid numbering!) into the crystalline glycol 50 for the first time. Its configuration, plausible for mechanistic reasons, was, however, proved by X-ray of the related (racemic) compound 51 (Ref. 53). This method of hydrolysis is likewise successful with typical carotenoid epoxides, provided that one works with aqueous mineral acids with the admixture of dioxane, tetrahydrofurane, etc.

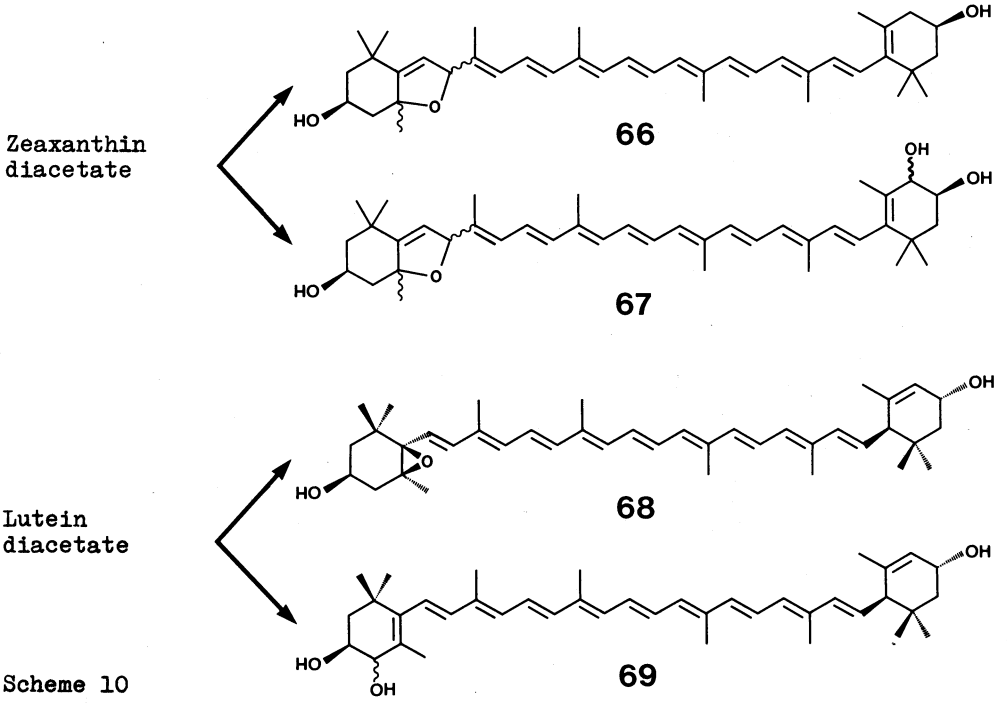


Scheme 8

Didehydro-β,β-carotene, m.p. 138-139°



Scheme 9



Scheme 10

The main hydrolysis products in the reactions hitherto known are, however, always furanoid epoxides, which in non-aqueous medium are known to constitute the only products. The following glycols were prepared: from diadinoxanthin (52; absolute configuration see section 4) 2 tetraols arose, the more polar of which proved to be identical with heteroxanthin (Ref. 54). Since the two epimers strongly differ in the IR-spectrum, structure 53 was assigned to that possessing the stronger intramolecular H-bonding (heteroxanthin), and structure 54 to the C(5)-epimer. It is noteworthy that, under the conditions stated, no furane oxide is formed from the tetraols 53 and 54 (compare also the reaction on 15). Thus an inversion at C(6) is improbable.

Finally, two very polar pentaols could be isolated by chromatography from neoxanthin samples originating from Trollius europaeus ("Trollixanthin"). These could also be synthesised from neoxanthin 55 with aqueous acid. They show the same chemical and spectral differences as 53 and 54, and thus have structures 56 and 57 (Ref. 54).

Oxidations with $KMnO_4$ and MnO_2

These oxidations belong, as you know, to the classical method by which the structure elucidation of β,β-carotene was carried out. Recently, researchers from Pécs (Ref. 55) were able to show that, under suitable conditions, this degradation of caroten-5,6- and 5,8-epoxides leads to 8'- or 10'-apocarotenals. Thus, 5,6-epoxy-apo-10'-β-carotenal was formed from 5,6-epoxy-β,β-carotene, 5,6-epoxy-β,ε-carotene respectively, and 5,6,5',6'-diepoxy-β,β-carotene. From aurochrome, the 10'- and from mutatochrome the 8'-apocarotenal were synthesised. Interesting is the observation by Coman et al. (Ref. 56) that diosphenols of the astacene type (58) can be converted into 2-nor compounds of the (blue) violerythrin type (59) with MnO_2 in acetone.

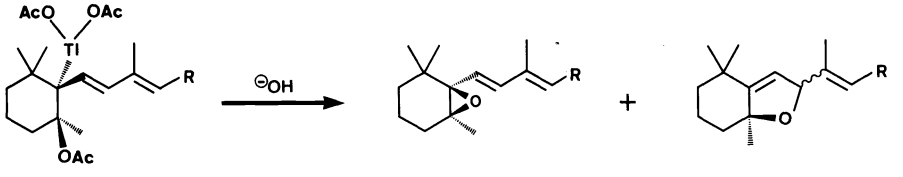
Oxidations with O_2 in alkaline solution

K-t butylate/O_2 permits the conversion of 4-oxocarotenes into diosphenols of the astacene type. If the diosphenol system is first reduced with borohydride to the glycol and then selectively oxidised at the allylic hydroxyl group with MnO_2 (or by Oppenauer), a synthesis of (±)-astaxanthin can be realised (Ref. 57). The same authors prepared analogously: (±)-3-hydroxy-canthaxanthin, (±)-3-hydroxyechinenone and the corresponding (±)-15,15'-didehydro analogues. In this connection attention is drawn to the evidently unexpected easily occurring air oxidation of β-carotene, which was observed on microcell C chromatograms (Ref. 58).

Oxidations with $Tl(Ac)_3$

A study on the reaction of selected carotenes and carotenoids (Ref. 59) resulted in a number of reaction products of which the following have hitherto been cristallised and identified: from β,β-carotene - a didehydro-β,β-carotene (60) of still unknown structure; (±)-mutatochrome (61), (±)-isocryptoxanthin (62); (±)-4'-hydroxymutatochrome (63); (±)-isozeaxanthin (64); a (±)-hydroxyisozeaxanthin (65). Zeaxanthin gave mutatoxanthin (66) and 4-hydroxymutatoxanthin (67), and from lutein the cis-epoxide (68) was formed as well as a 4-hydroxylutein (69).

The results show that the expected allylic oxidation predominantly occurs. The epoxides may have been formed from an unstable thallium compound (70) on saponification of the reaction products, e.g.



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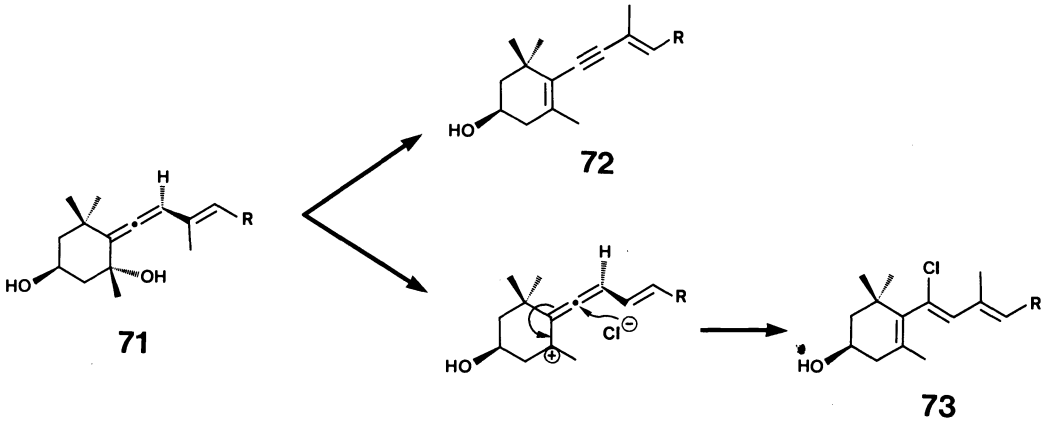
Scheme 11

Halogenations of the side chain with NBS

Since in recent times various carotenoids with oxygenated methyl groups have come to light as natural products, new procedures for the rational synthesis of such compounds must be developed. A first access was found by the Norwegian team (Ref. 60) in the radical bromination of crocetindial with NBS, in which both in-chain-methyls are preferentially attacked. Mono- and di-substituted products arose, which after hydrolysis gave the corresponding alcohols. From this ψ,ψ-caroten-20-ol, rhodopin-20-ol and rhodopin-20'-ol have now been prepared according to the usual procedures (Ref. 61).

HCl reactions on carotenoids

The reaction of zeaxanthin, isozeaxanthin and lutein with chloroform/HCl was investigated by Pfander & Leuenberger (Ref. 62) with regard to the products. It led to the foreseeable substitution and elimination products. More interesting is the corresponding reaction of allenyl alcohols of the neoxanthin type (71):



Scheme 12

A careful study (Ref. 63) now confirmed an earlier finding (Ref. 64) according to which, in this reaction, elimination occurs with the formation of the C(7)/C(8)-acetylene bond giving 72, whereby though considerable amounts of 7-chloro-substituted carotenoids (73) are also formed.

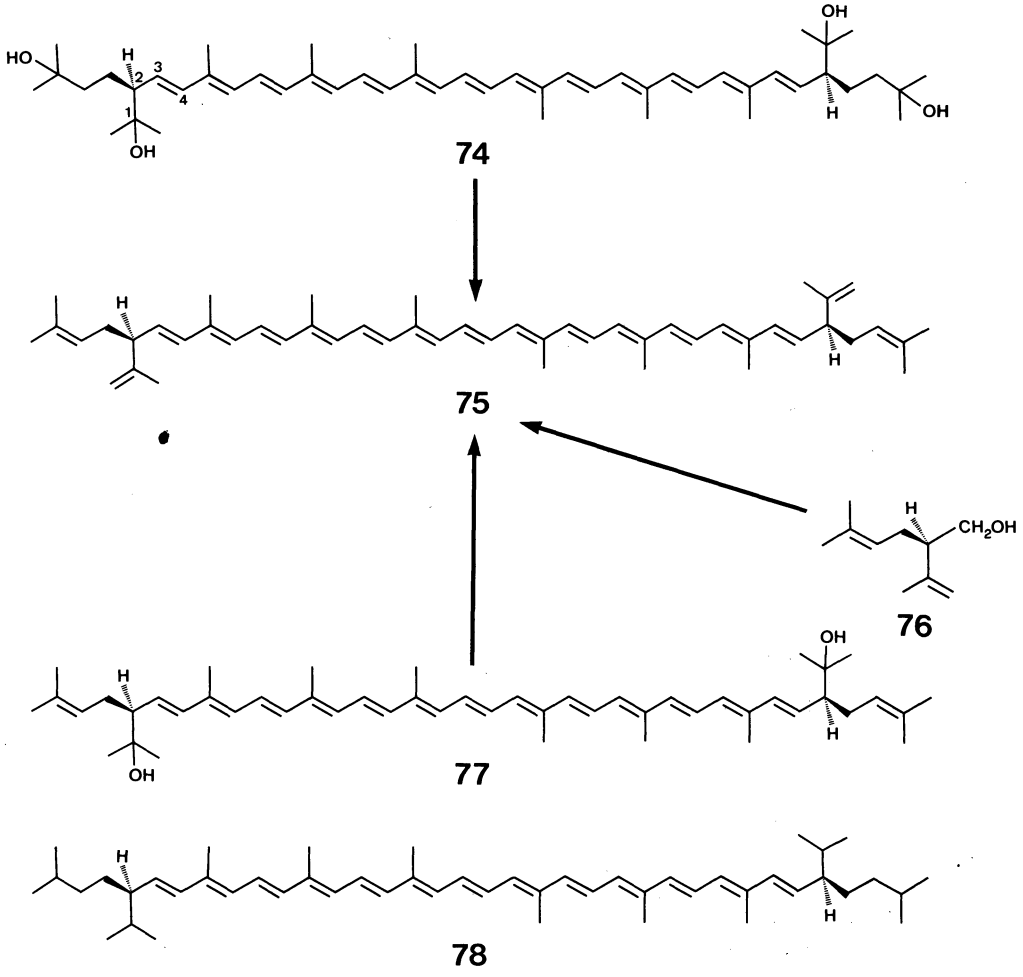
4. STEREOCHEMISTRY: ABSOLUTE CONFIGURATIONS

Since the carotenoid symposium in Berne (1975), at which Professor Liaaen-Jensen summarised the situation on the configurational findings of carotenoids at that time (Ref. 1), a considerable number of absolute configurations have again been established. The methods developed earlier have proved very fruitful and the basis for numerous correlations by means of chiroptical methods has turned out to be quite reliable. The contributions again came almost exclusively from the laboratories of Liaaen-Jensen, Weedon and Eugster. It should be remembered that the carotenoids represent one of the last great groups of natural products where this work was still to be achieved: with amino-acids, sugars, steroids, terpenoids, etc. this work had, essentially, already been accomplished earlier. The specific difficulties in the carotenoid chemistry are due to the fact that the relative configurations were also still unknown, so that the determination of a single centre could not almost automatically lead to the absolute configuration of the whole molecule.

I would like to classify the new chirality determinations, taking the hydrocarbons as a basis, and discuss them in this sequence.

Acyclic carotenoids

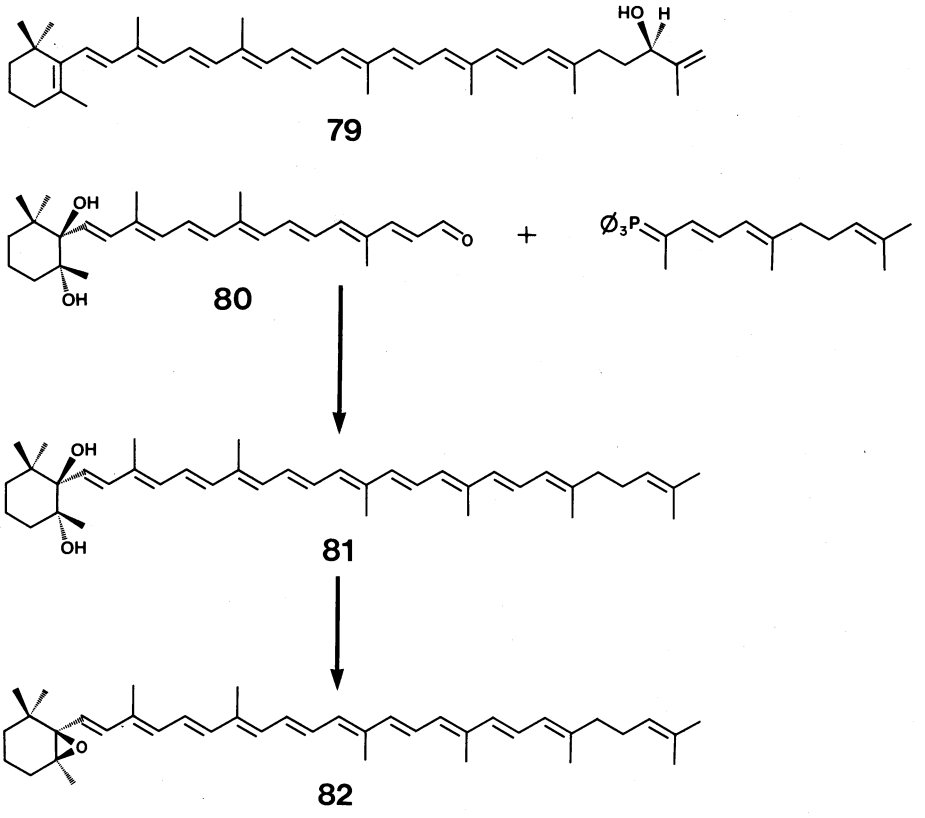
In contrast to an earlier publication (Ref. 66), Johansen and Liaaen-Jensen (Ref. 65) have guaranteed the (2S,2'S)-configuration of bacterioruberin (74) and bisanhydrobacterioruberin (77) by synthesis of tetraanhydrobacterioruberin (75) using (-)-(R)-lavandulol (76) as starting material. 75 can be prepared by elimination reactions from 74 and 77. Remarkable is that comparison of the CD-curves of 74 and 77 with those of 78 had given a different result, since they are almost enantiomeric. Thus it follows anew that such chiroptical comparisons only allow conclusions on the absolute configurations when the most similarly built molecules are compared with the most similar functional groups. Evidently, the conformational equilibria in the case of 74, 75, 77 and 78 are partially different. The absolute configuration at C(2) in 74 and 77 corresponds to that in decaprenoxanthin, sarcinaxanthin and C.p. 450.



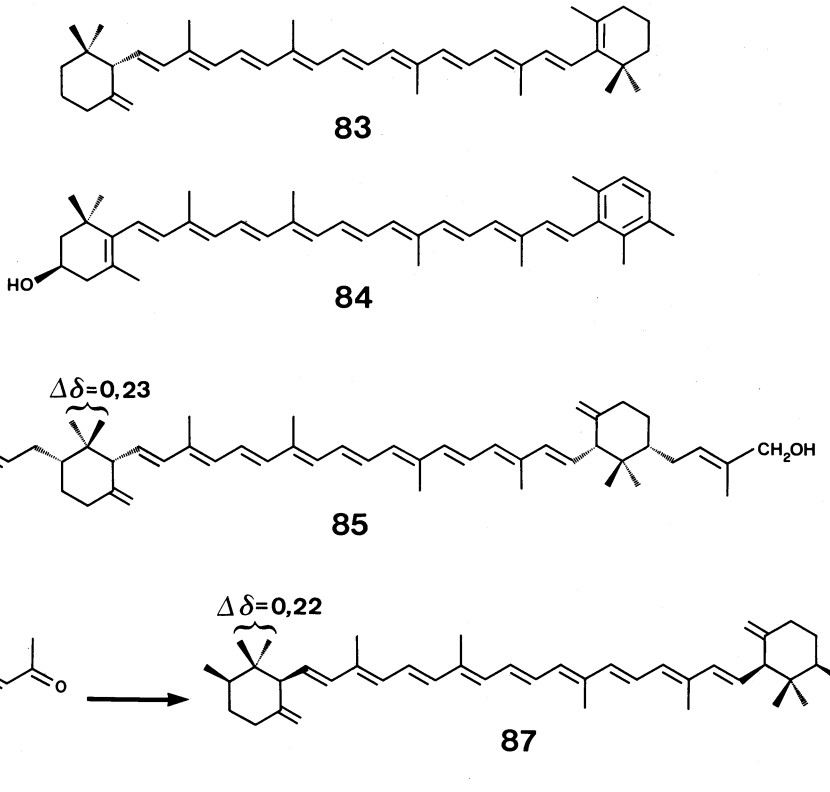
Scheme 13

Monocyclic carotenoids

The (2'R)-chirality for aleuriaxanthin (79) (Ref. 68) followed on the basis of Horeau experiments with the gas-chromatographic modification according to Ref. 67 and on the assumption that 2-propenyl >CH_2. At RT, the Cotton effects are extremely weak in 79. For the synthesis of (5S,6R)-5,6-epoxy-5,6-dihydro-β,ψ-carotene (82, = γ-carotene epoxide), which is so far unknown as a natural substance, Eschenmoser and Eugster (Ref. 69) used azafrinal (80) as condensation partner for the Wittig salt on ψ-ionol. The crystalline (5R,6R)-5,6-dihydro-β,ψ-caroten-5,6-diol (81) was hereupon converted into the crystalline epoxide (82) with sulfurane according to Ref. 82. The glycol 81 shows very weak Cotton effects, with the epoxide they are substantially more pronounced.



Scheme 14



Scheme 15

Bicyclic carotenoids

The β,γ-carotene 83 isolated from Caloscypha fulgens has (6'S)-chirality (Ref. 70), which follows from a comparison of the CD-curves with the synthetic product ent 83, prepared from enriched (R)-γ-ionone (see Note b). The agelaxanthin A already mentioned in section 2 has structure 84, as a result of the agreement of the CD-spectrum with (-)-zeaxanthin (3R,3'R); consequently it is (3R)-β,φ-caroten-3-ol (Ref. 9). There have now been numerous arguments published (Ref. 75) which clarify the absolute configuration of sarcinaxanthin (85) and its mono-β-D-glucoside: CD- and ^{1}H-NMR-comparisons with the (2R,6S,2'R, 6'S)-2,2-dimethyl-γ,γ-carotene (87) synthesised from cis-γ-irone 86 suggest that C(6) and C(6') have (R)-chirality in 85 and that the C(2)-substituent is cis to the side-chain, provided the substituent at C(2) has no essential influence on the CD effect. However, doubts about this line of reasoning are still possible because the published CD-curves of 85 and 87 as well as of 2'-methyl-β,γ-carotene deviate quite clearly from that of the unsubstituted β,γ-carotene (Ref. 70).

From this must be concluded that the substituent at C(2) exerts a considerable influence on the conformation of the γ-ring and thus on the CD-effect. The cis-position of the C(2)-C(6) substituents derived from the ^{1}H-NMR-spectrum should, moreover, be confirmed by synthesis of the analogous trans-compound and comparison with its ^{1}H-NMR-spectra.

In section 2 I have already mentioned the two ε,ε-carotendiols chiriquixanthin A (88) and B (89) (Ref. 76). According to the ^{1}H-NMR-spectra B has C_2-symmetry and one ring in A shows analogous chemical shifts to lutein and is consequently trans-3,6-disubstituted (compare Ref. 77), whereas the other must therefore be cis-3,6-disubstituted. The same was also concluded from the ^{1}H-NMR-spectra for both rings in B. The absolute configuration at C(6) and C(6') was derived from comparison of the CD-curves with configurationally guaranteed compounds of the ε-series. In the last analysis, it is based on that of ε,ε-carotene itself (Refs. 71 & 72).

The absolute configuration of decaprenoxanthin (90) was previously derived in Berne (Ref. 1). Since then, the full publication has appeared (Ref. 78) and the following arguments must be appended: the absolute configuration, as given in 90, is based on the one hand on chiroptical comparisons with the synthetic cis- and trans-dimethyl-ε,ε-carotenes 91 and 92, which were synthesised from the optically active α-irones (absolute configuration see Ref. 79), and on the other hand on ^{1}H-NMR-data. Since 91 and 92 respectively show opposite and the same CD spectra compared with the chiroptical standard ((6S,6'S)-ε,ε-carotene (Refs. 71 & 72)), it follows that the C(2) substituent in this case makes no essential contribution to the Cotton effect. From this, the chirality of 90 with respect to C(6) and C(6') ensues. For the determination of chirality at C(2) and C(2') shift arguments in the ^{1}H-NMR-spectra served, see Scheme 16. The not obvious equalisation of the influence of hydroxy-isopentenyl and methyl on the chemical shift of the geminal methyl groups was ultimately confirmed by stereospecific synthesis of (±)-2,6-trans-decaprenoxanthin, which was carried out by Chopra et al. (Ref. 80).

Carotene epoxides are very widespread in nature, however still nothing is known about their absolute configuration. In connection with the determination of the absolute configuration of azafrin and azafrinal (80; see below) Eschenmoser and Eugster then first synthesised (5R,6R)-5,6-dihydroxy-β,β-caroten-5,6-diol (95) and (5R,6R, 6'R)-5,6-dihydroxy-β,ε-caroten-5,6-diol (97), respectively (Refs. 69 & 81) with the aid of the corresponding Wittig salts 93 and 94. These were then converted into the epoxides with the sulfurane reagent of

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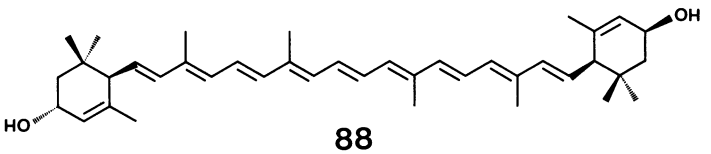
Note b. Regarding the determination of chirality of (-)-γ-ionone by correlation with (-)-(S)-α-ionone see Refs. 71, 72 & 73. In the recently published correction by Ohloff & Vial (Ref. 74) of their rotation value for dihydro-γ-ionone (not of the chirality!), the derived absolute configuration of γ-ionone in the joint publications (Refs. 71 & 72) is not dealt with: (-)-(S)-γ-ionone is connected with (-)-(S)-α-ionone and (-)-(S)-dihydro-α-ionone; the catalytic hydrogenation of (-)-(S)-γ-ionone yields (+)-(S)-dihydro-γ-ionone and not (-)-(S)-dihydro-γ-ionone as previously stated.



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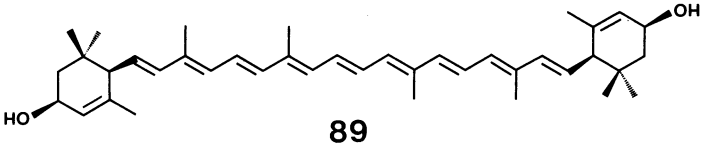

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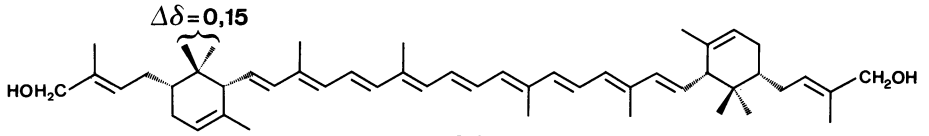

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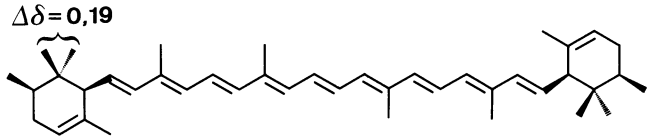

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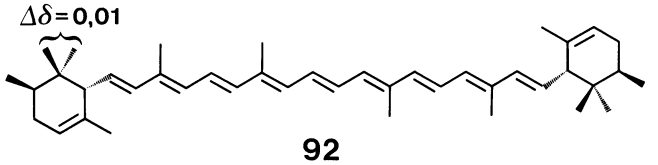
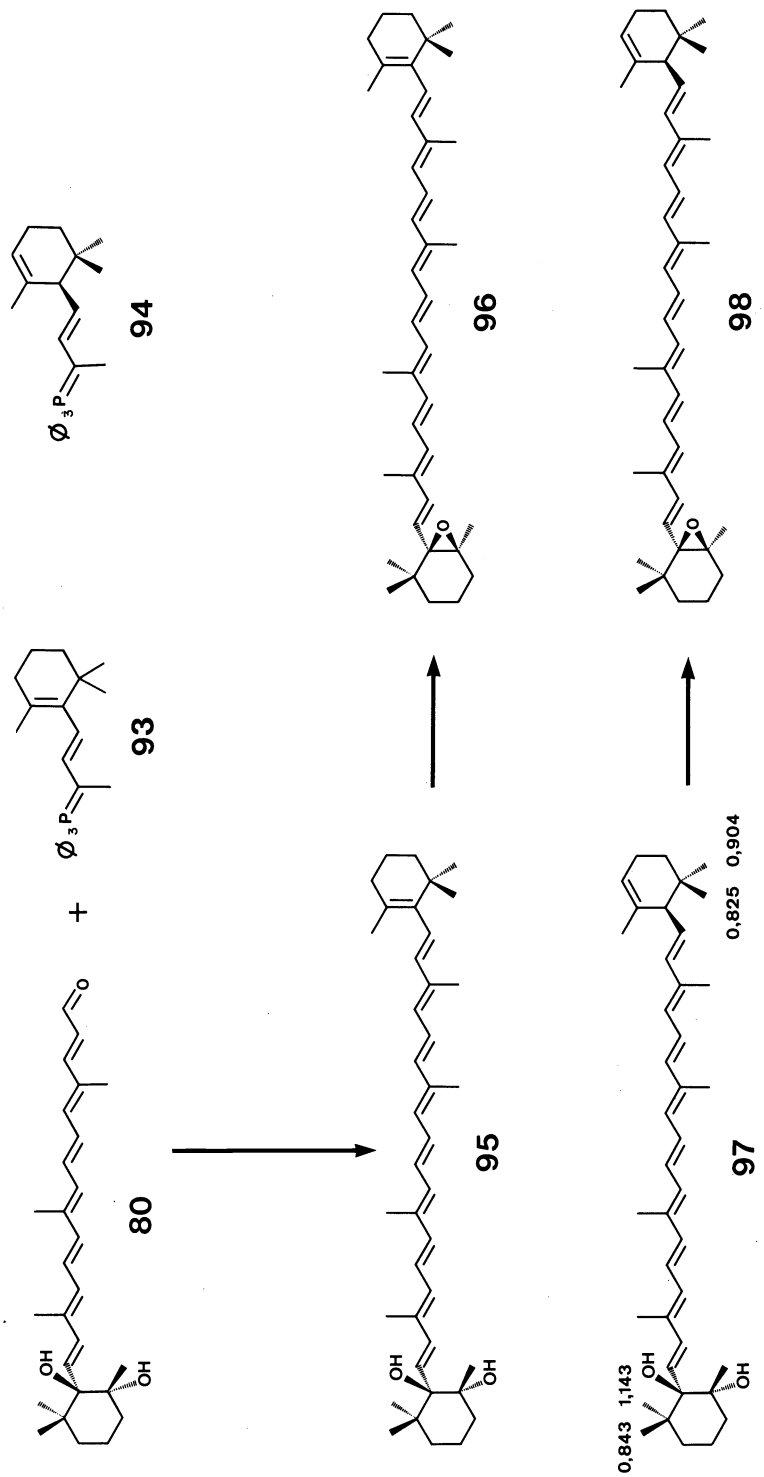


92

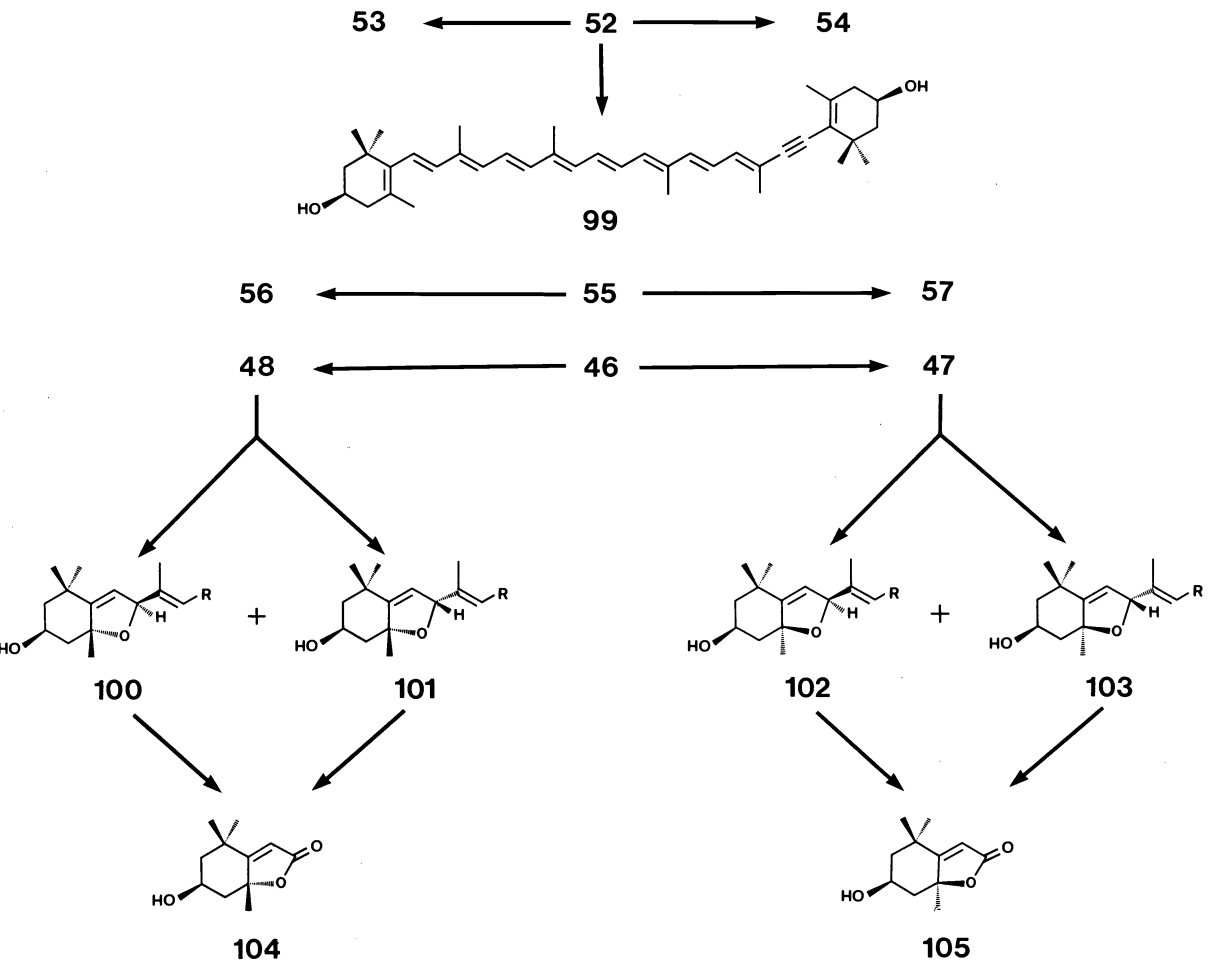
Scheme 16

Martin (Ref. 82). The glycols 95 and 97 are still unknown as natural products. However, they show such unexpected properties with regard to their solubility and chromatographic behaviour that they have possibly been overlooked up to now. Their properties lie much closer to the hydrocarbons than to the usual xanthophylls in spite of the diol grouping present. One must attribute this to the ditertiary nature of the trans-glycol grouping, which is in addition strongly hindered sterically by the neighbouring methyl groups. The CD-curve of 95 shows only weakly pronounced maxima, as expected; that of 97 is determined by the centre of chirality at C(6'). The Cotton effects of the two epoxides 96 and 98 are very much more strongly pronounced. With these data, the chiralities of the natural products can now be clarified. Strangely enough, apparently still no chiroptical properties of β- and α-carotene epoxides, respectively, have been published.

In connection with the discussion on compounds 81, 95, 97 a few further glycols should be named, whose absolute configurations have been published at the time of reporting (Refs. 83 & 54). It deals with heteroxanthin (53) and the tetra- and pentahydroxy compounds 53, 54, 56, 57 and 16 (see sections 2 and 3). On the one hand, diadinoxanthin (52) could be converted into diatoxanthin (99) of known configuration (Ref. 50) by lithium aluminium hydride reduction of the silyl ether, whereby the configuration at C(3) and C(3') was determined (the configuration at the epoxide grouping resulted from ^{1}H-NMR-spectra of diadinochrome and comparison with data from 3,5-cis- and 3,5-trans-isomeric furane oxides (Ref. 84). On the other hand, epoxide hydrolysis in a protic solvent (see section 3) gave the glycols 53 and 54, of which 53 proved identical with heteroxanthin. Consequently, diadinoxanthin (52) has the (3S,5R,6S,3'R)- and heteroxanthin the (3S,5S,6S,3'R)-configuration. (The cis- and trans-configuration, respectively of C(3)/C(5) was established by IR-spectroscopy; see section 3.)



Scheme 17



Scheme 18

The glycols 56 and 57 were also prepared by protic hydrolysis, this time of neoxanthin (see section 3). The absolute configuration of the tetraol 16 from Ranunculus acer is not entirely certain, it is based on the assumption that we are dealing with a protic hydrolysis product of lutein epoxide (48). With regard to the absolute configuration of 48, the arguments of Professor Weedon's team and those from Zurich are now in agreement (Refs. 51 & 84). However, for the furanoid epoxides flavoxanthin and chrysanthemaxanthin derived therefrom, they differ with respect to the configuration at C(8) (Refs. 17 & 84) and also concerning the assignment of the ^{1}H-NMR-signals for H(7) and H(8) and whether the $^3J(7,8)$-coupling of 2 Hz is due to the cis- or trans-compound (100, 101 respectively). In our opinion it is due to the cis-compound 100. This is, however, chrysanthemaxanthin and not flavoxanthin (101). The matter has a certain significance in carotenoid chemistry, since furanoid epoxides are widespread and flavoxanthin/chrysanthemaxanthin can represent the basis for further chiroptical correlation. The two epimers can easily be differentiated in the CD-spectrum, see Fig. 1. For our work on flavoxanthin/chrysanthemaxanthin, my co-workers have collected, extracted and chromatographically worked up about 140 kg of dandelion flowerheads.

On rearranging synthetic lutein epoxide 47 (cis) with acid under aprotic conditions, one obtains the C(5)-epimeric furane oxides. We have also clarified their absolute configurations and assigned structure 103 to 5-epi-flavoxanthin and structure 102 to 5-epi-chrysanthemaxanthin (Ref. 85). The nickel peroxide degradation of 100/101 leads to (-)-loliolide, and of 102/103 to (+)-isololiolide.

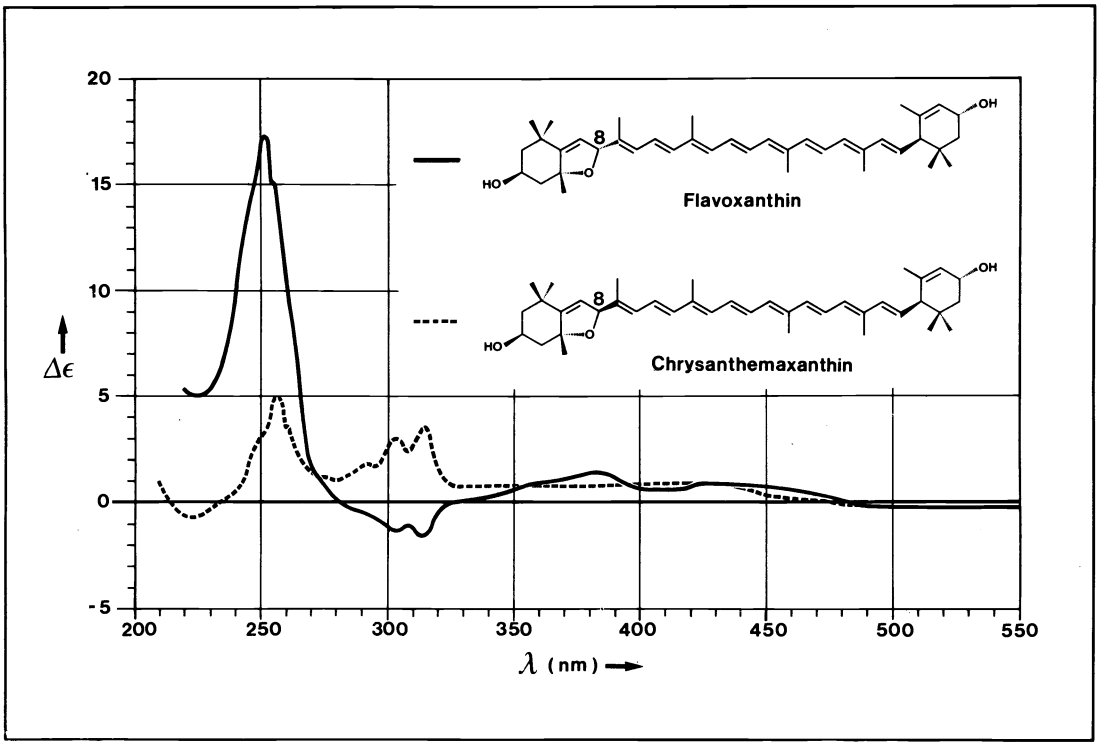


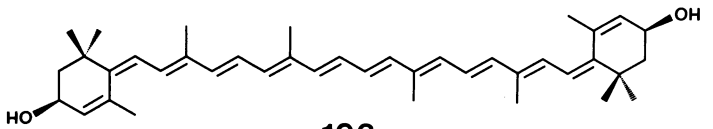
Fig. 1

The carotenoids caloxanthin (13) and nostaxanthin (14) have already been mentioned in section 2. The absolute configurations given there (Ref. 11) result from application of Mills' rule: The preferred conformation of the β-ring can be inferred from the CD and this itself is determined by the substituent at C(3). Furthermore, the ^{1}H-NMR-spectra reveal a trans-configuration for the glycol group. Thus caloxanthin is (2R,3R,3'R)-β,β-caroten-2,3,3'-triol (13) and nostoxanthin is (2R,2'R,3R,3'R)-β,β-caroten-2,2',3,3'-tetraol (14).

In a publication dating back relatively far, Entschel and Karrer (Ref. 86) had been able to connect (-)-zeaxanthin with (+)-escholtzxanthin (106) as follows:

(-)-zeaxanthin ⟶ physalien $\xrightarrow[2.\ \text{N-ethylmorpholin}]{1.\ \text{NBS/chlorof./-18}^{\circ}}$

di-O-palmitoyleschscholtzxanthin ⟶ (+)-eschscholtzxanthin (106)



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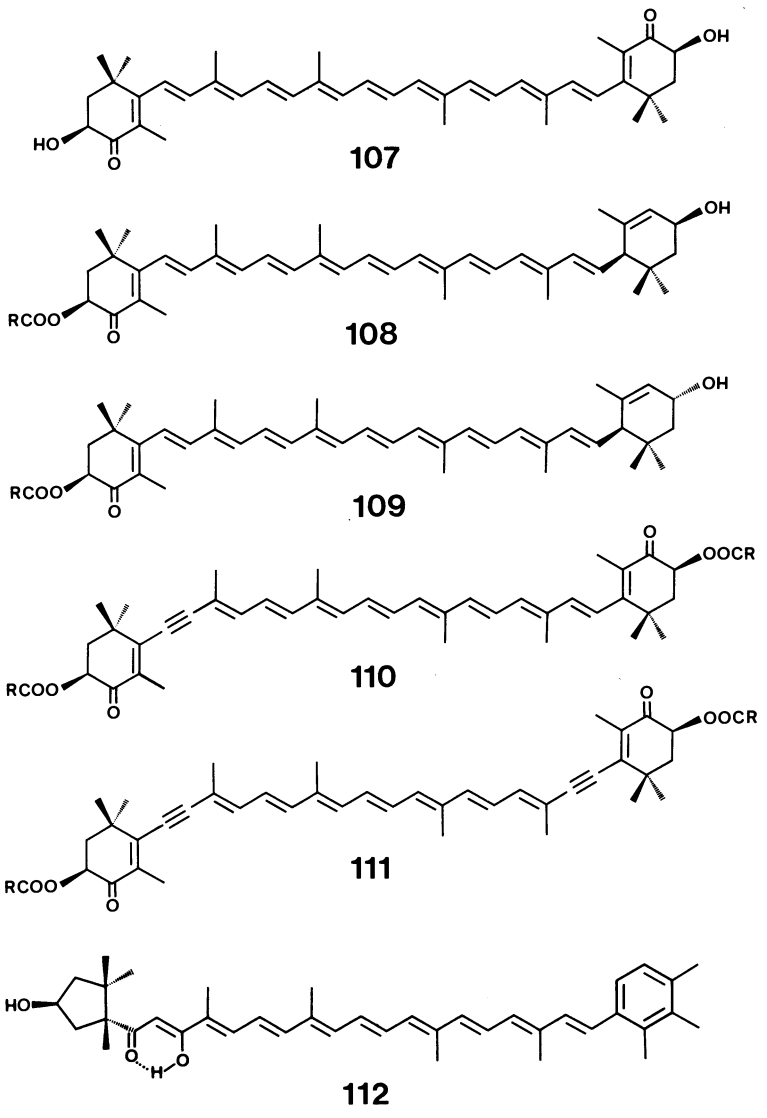
Scheme 19

With the clarification of the absolute configuration of (-)-zeaxanthin (Ref. 50), that of eschscholtzxanthin thus also followed - which has been overlooked in several newer reviews.

Ketocarotenoids

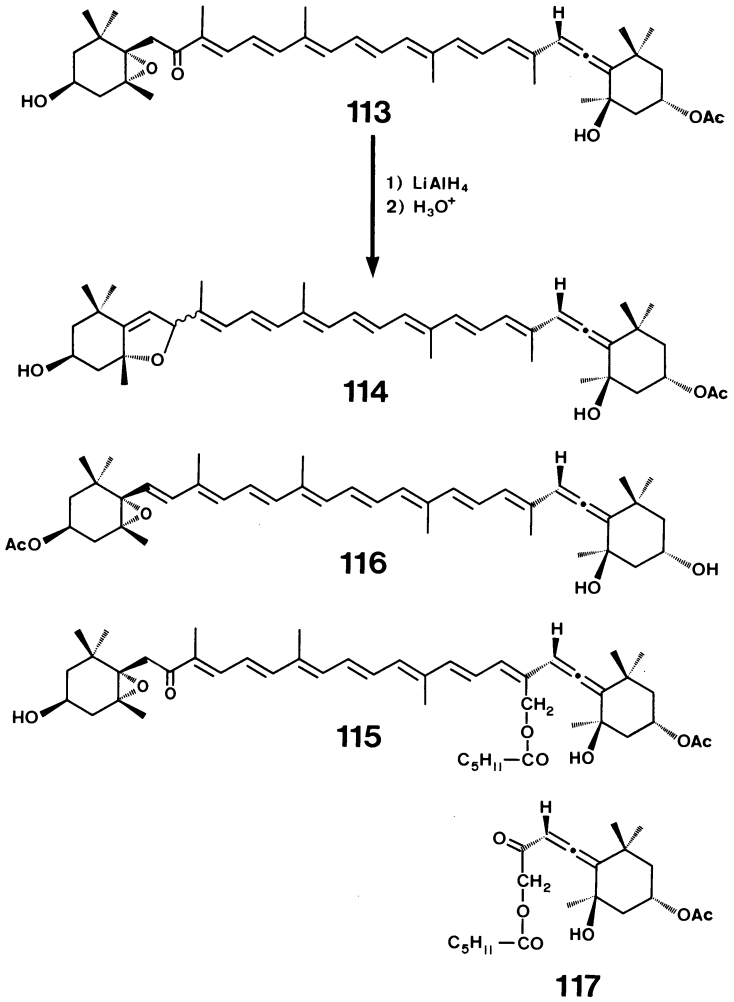
All preparations of astaxanthin (Hommarus, Halocynthia, Haematococcus, Schizonobia (Ref. 87), goldfish (Ref. 24), Fritschiella (Ref. 24)) isolated up till recently have (3S,3'S)-chirality (107) with the striking exception of a



Scheme 20

carotenoid recently isolated from Phaffia rhodozyma (Ref. 88), for which (3R, 3'R)-chirality was derived on the basis of CD-spectra. In this connection, attention should also be drawn to the syntheses of all-(E)-(3S,3'S)- and 15, 15'-(Z)-(3S,3'S)-astaxanthin by Englert et al. (Ref. 89), where it was shown that alteration in the geometry of the C(15)-C(15')-double bond leads to an almost complete reversal of the Cotton effects.

The so-called α-doradexanthin, which has been ascertained in fish and insects, is interpreted as being an intermediate in the biogenetic pathway to astaxanthin. Its absolute configuration was hitherto unknown. Dr. Buchecker will furnish evidence for it in his lecture in terms of 108 (Refs. 24 & 90). It is thus 4-keto-3'-epilutein ((3S,6'R,3'S)-3,3'-dihydroxy-β,ε-caroten-4-one). On the other hand, the so-called α-doradexanthin which has been isolated from the terrestrial green-algae Fritschiella tuberosa (Ref. 91) is epimeric at C(3') and accordingly a new carotenoid. We name it fritschiellaxanthin (Ref. 24) (109; (3S,6'R,3'R)-3,3'-dihydroxy-β,ε-caroten-4-one). In connection with these works, the "3'-ketolutein" ((3S,6'R)-3-hydroxy-β,ε-caroten-3-one) has also been prepared in larger amounts and precisely characterised. These data (Ref. 24) may be valuable for the structure elucidation of philosamiaxanthin and similar ketocarotenoids.



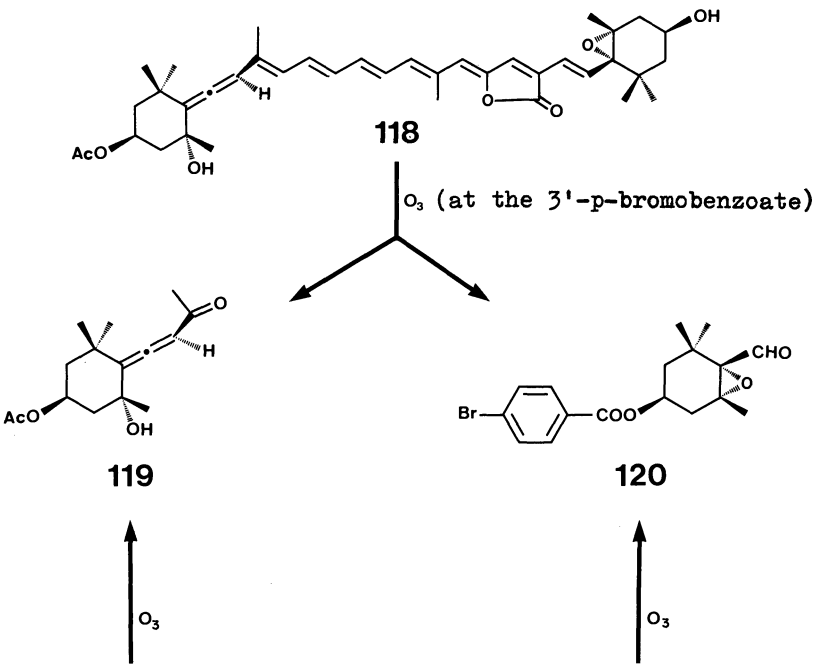
Scheme 21

According to Berger et al. (Ref. 92), asterinic acid (110 and 111) has (3S,3'S)-chirality - as does astaxanthin. This conclusion was derived from chiroptical comparisons of the $NaBH_4$-reduction products with the corresponding tetraols from 107: C(4)- and C(4')-OH-groups provide no essential contribution to the Cotton effect. Moreover the CD-curves of the configurationally-certain carotenoids diatoxanthin (99) and alloxanthin (7',8'-didehydro-99) were compared and almost identical curves ascertained; the acetylene bonds in the polyene chain thus only led to a flattening out of the CD-maxima.

Chopra et al. (Ref. 93) have prepared trikentriorhodine (112) from (+)-camphor by a synthesis based on the Claisen reaction (compare Ref. 94). The product obtained, however, only showed weak Cotton effects. Comparison with the trikentriorhodine isolated by Buchecker et al. (Ref. 9) from Agelas schmidtii shows that the synthetic product is largely racemised or epimerised:
Ref. 93: $\Delta\varepsilon$ 262 (-0,05), 303 (+0,06), 370 (-0,06) (solvent unknown)
Ref. 9: $\Delta\varepsilon$ 264 (-1,1), 301 (+1,3), 360 (-0,7) (in ether/hexane 1:1)

Allenic carotenoids

The (5R,6S)-chirality in fucoxanthin (113) was hitherto acknowledged as being provisional. Bernhard et al. (Ref. 95) have now proved it by conversion of 113 into 114: The 3,5-trans position of the O-functions can easily be recognised in the ^{1}H-NMR-spectra.



Scheme 22

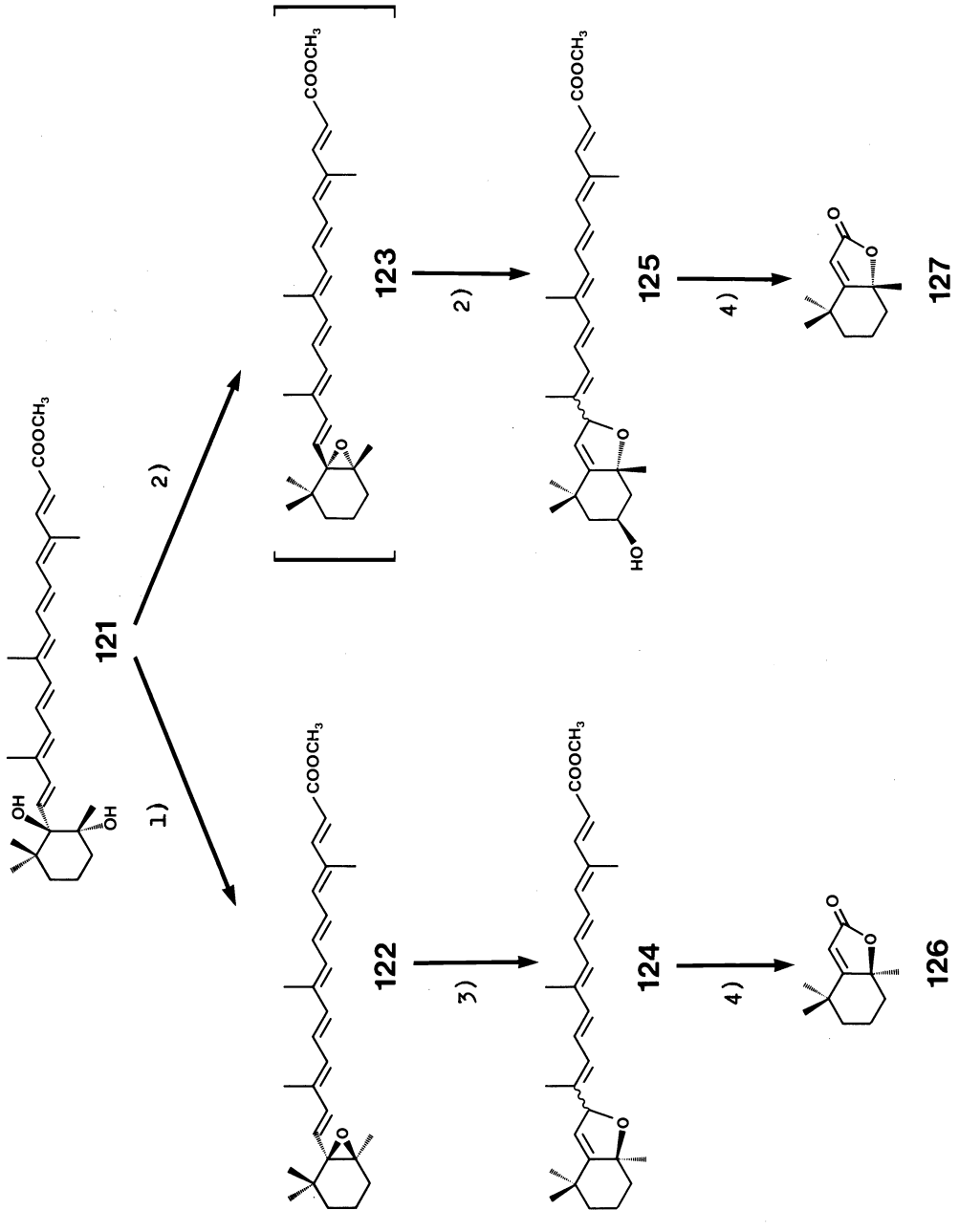
19'-Hexanoylfucoxanthin, whose constitution had been communicated in 1975 (Ref. 1), has now been completely characterised (Ref. 97). Since it only shows weak Cotton effects which allow no conclusion whatever as to the absolute configuration (its saponification and reduction products also show the same behaviour), the compound was degraded by ozonolysis to 117. With the exception of the signals due to the hexanoyl residue, this presented identical ^{1}H-NMR- and CD-spectra to the corresponding degradation product 119 from fucoxanthin. And so the structure of the allene side was clarified. Identical ^{1}H-NMR-signals in 115 and 113 with regard to CH_3(16),(17),(18) and CH_2(7) point to a similar relative configuration at the epoxide ring. The absolute configuration expressed at this ring in structure 115 is, however, not proven.

As Hertzberg et al. (Ref. 96) demonstrate, dinoxanthin has the structure 116 and is 3-O-acetylneoxanthin. Saponification, acid rearrangement to furanoxide and chromatographic separation of the C(8')-epimers gave products which each show well-concurring CD-spectra with the corresponding epimers of neochrome. From the available data, probably similar absolute configurations of dinoxanthin and neoxanthin may be concluded.

Apocarotenoids

On the basis of ^{1}H-NMR-comparisons of the signals due to CH_3(1), (5), (9), H-C(8) and the CH_3CO-group of peridinin (118) with fucoxanthin and neoxanthin, the same relative configuration at the allene end group in the two compounds can be concluded (Ref. 97). The ozonolysis furnished clear evidence for both ends: degradation ketone 119 with the allene grouping proved to be identical in ^{1}H-NMR- and CD-spectra with the known degradation product from fucoxanthin (Ref. 98); the same is true for the epoxide end 120, which for comparison was synthesised from the di-p-bromobenzoate of violaxanthin.

The arguments communicated at the 4th International Carotenoid Symposium for the absolute configuration of azafrin ester in terms of structure 121 (Ref. 99) have now been published (Refs. 31, 81, 100). The decisive experiment was the use of complementary- and regioselective-acting reagents, which allowed the preparation of the enantiomeric pairs 122/123 and 124/125, respectively, from a



Scheme 23

1) sulfurane according to Ref. 82; 2) $TiCl_4$/benzene/ether; 3) H_3O^+; 4) NiO_2

pure stereoisomer. From this, (+)-(S)-dihydroactinidiolide (126) was synthesised on the one hand, and (-)-(R)-dihydroactinidiolide (127) on the other in very good yield. On the plausible assumption, verified in many examples, that $TiCl_4$ attacks the allylic hydroxyl and that sulfurane attacks the sterically less hindered C(5)-OH group, the rearrangment and degradation products obtained can easily be construed.

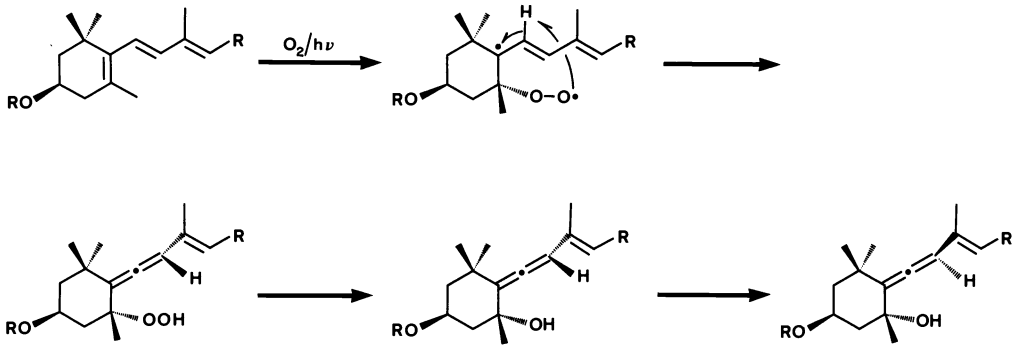
Azafrin shows only weakly pronounced Cotton effects, as do all other carotenoid glycols (81, 95, 53, 54, 56, 57); however when the epoxides, e.g. 122 are at issue they are much stronger.

(Z,E)-isomeric carotenoids

The ^{13}C-NMR-method has proved to be the most important modern technique for determining the position of (Z)-double bonds in polyenes (Refs. 101 & 102). Attention is drawn equally here to the extensive syntheses of phytoenes with (E,E,E)-, (E,Z,E)-, (E,E,Z)- and (E,Z,Z)-configurations in the triene part and of model substances by Khan et al. (Ref. 103). Accordingly, the main phytoene isomer isolated from carrot oil, commercial tomatoes, Phycomyces blakesleanus and Chlorella vulgaris has been shown to have the (E,Z,E)-configuration, whereas phytoene from diphenylamine-inhibited cultures of Flavobacterium dehydrogenans consists principally of the (E,E,E)-isomer. In addition to these two isomers, a third isomer was found in Rhodospirillum rubrum inhibited by 2-hydroxybiphenyl and in Mucor hiemalis inhibited by fluoren-9-one to which Granger et al. (Ref. 104) attribute the (E,E,Z)-configuration. The stereochemistry of this new isomer has been reexamined by Barlow et al. (Ref. 105) by using comparative ^{13}C-NMR-data. It is suggested that it could also be (Z,E,Z)-configurated instead of (E,E,Z).

Neocapsorubin A and neozeaxanthin A are the (Z)-13-, neocapsorubin B and neozeaxanthin B are the (Z)-9-isomers (Refs. 102 & 106). Violeoxanthin is (Z)-13-violaxanthin (Refs. 102 & 107). Isomerisation of violeoxanthin to violaxanthin gave a product with identical CD-spectra. From this as well as from ^1H-NMR-spectra of the furane oxides, analogous absolute configuration of the stereoisomers is indicated. According to Ref. 107, tareoxanthin from dandelion flowers (Ref. 108) is a mixture of neolutein epoxide A + neolutein epoxide B + a little cis-violaxanthin.

Fucoxanthin stereoisomers: when all-(E)-fucoxanthin is isomerised with $I_2/h\nu$, 4 new isomers arise which were chromatographically separated (Ref. 109). All the isomers showed CD-spectra different from that of the all-(E)-form. On the basis of IR-, UV/VIS- and ^1H-NMR-spectra, the (Z)-13- and (Z)-13'-geometries, respectively, are assumed for the isomer pairs I and II. Isomer III showed no cis-peak, but a hypsochromic shift by 2 nm of the longwave band. Significant shifts of CH_3(16'), (17') as well as of H-C(8') in the ^1H-NMR-spectrum suggest stereoisomerism of the allene bond. This isomer was ascertained earlier in up to 6% in crude fucoxanthin from Fucus serratus. This finding supports the suggestion by Isoe (Ref. 110) for the formation of the allene grouping; see also Ref. 111. The following reaction sequence is postulated:



(R = acyl or H)

Isomer-III (unstable)

Fucoxanthin (113)

Scheme 24

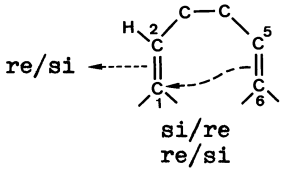
As a very important outcome of newer CD-measurements on (Z,E)-isomeric carotenoids, the fact should be mentioned that the geometry of the double bonds can exert an unexpectedly large influence on the course of the curve; in isolated cases the curves run almost enantiomerically! The following examples are worthy of mention:

all-(Z)-astaxanthin and (Z)-15,15'-astaxanthin (Ref. 89):	CD-curves qualitatively enantiomeric
fucoxanthin (all-(E)-8'-(R))(Ref. 109):	227 (+0,44), 265 (-0,55), 331 (+0,29)
(13-(Z))	(-0,75) (+1,50) (-1,00)
(13'-(Z))	(-0,65) (+0,15) (-0,50)
(8'-(S))	(-1,70) (+1,60) (-0,45)
violaxanthin/violeoxanthin (Ref. 107):	CD-curve qualitatively enantiomeric in the region 200-350 nm; in VIS the same; ORD up to 350 nm enantiomeric.
all-(E)-neoxanthin and 9-(Z)-neoxanthin (Refs. 50 & 112):	a few samples of different origin show different CD-curves; including a pair of almost enantiomeric ORD-curves in the region 200-350 nm.
mono(Z)-lutein, mono-(Z)-zeaxanthin and mono (Z)-diatoxanthin (Ref. 1):	almost all maxima enantiomeric to those of the all-(E)-compounds.

These few examples show that systematic investigations are essential on optically active polyenes with regard to the correlation between geometrical isomerism and CD. The danger exists that wrong conclusions are made from the CD-curves as to the underlying configuration.

CYCLISATION REACTION

I will now come to the problem of the stereochemical course of the biological carotene cyclisation. A few years ago, Goodwin (Ref. 113), Britton (Ref. 114), Davies (Ref. 115) and Porter (Ref. 116) adequately summarised the general state of knowledge. The first model conceptions (e.g. in Ref. 117) were naturally still very tentative. Since then, they have been continually modified and refined. More recently, important impetuses have come from the determination of the absolute configuration of natural (+)-α-carotene (Refs. 71 & 72) and trisporic acids (Ref. 118). From this and also from extensive incorporation studies by different teams, above all by Goodwin et al., the opinion is steadily gaining ground that the C(1) methyl groups of lycopene and neurosporene retain their identity during the cyclisation; i.e. according to the conformational folding, the (E)-methyl group becomes the pro-(R)- or pro-(S)-methyl group on the cyclohexene and vice-versa. Unequivocal proof for this, however, is hardly yet at hand. If one studies the schemata proposed so far for the cyclisation step, one notices that they are still incomplete and have hitherto disregarded one important aspect of carotenoid chemistry. I am thinking here of the really facile (E,Z)-isomeriation of conjugated double bonds which occurs under completely different influences. If we examine the following factors for the cyclisation of a 1,5-diene system, namely

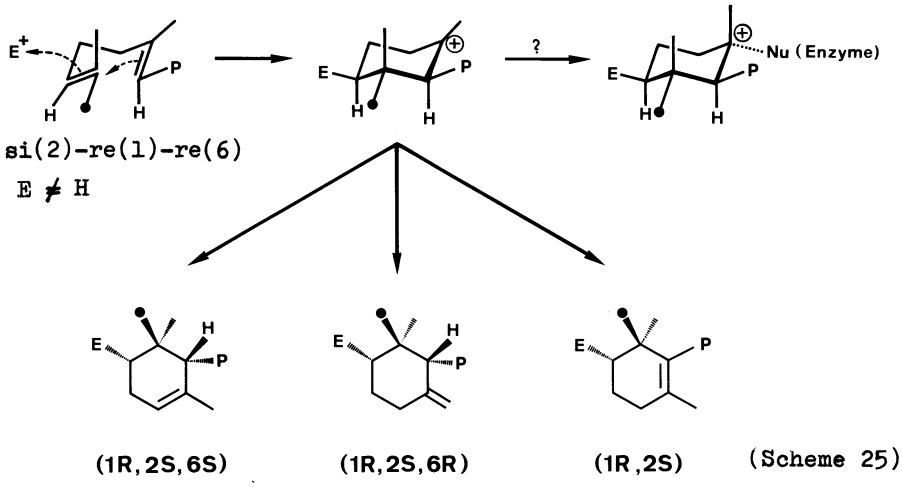


1) Chair or boat folding;
2) Geometry of the C(1)-C(2), C(5)-C(6) double bond resp. - also in view of the individuality of the C(1)-methyl groups;
3) Pro-chirality of the -ene surfaces.

8 possibilities follow schematically:

Enantiomeric chair foldings:

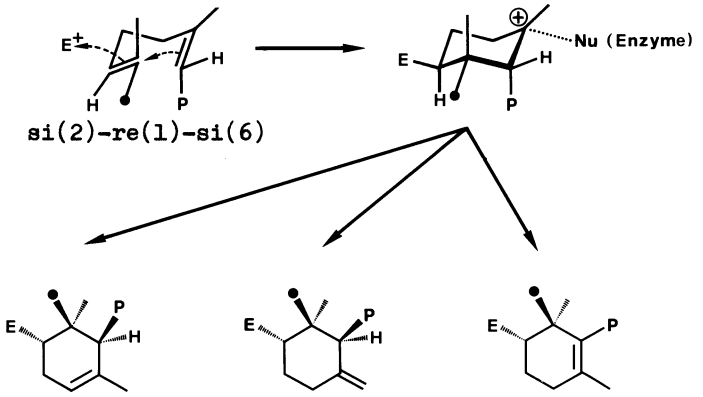
C_1(E,E)



(1R,2S,6S) (1R,2S,6R) (1R,2S) (Scheme 25)

In vitro, the cyclisation is an overall trans-addition. In vivo, however, one finds only the products of an elimination reaction. The products formed are given.

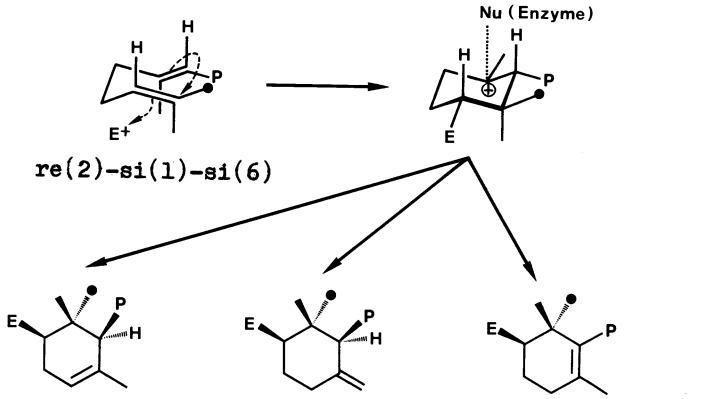
C_1(E,Z)



(1R,2S,6R) (1R,2S,6S) (1R,2S) (Scheme 26)

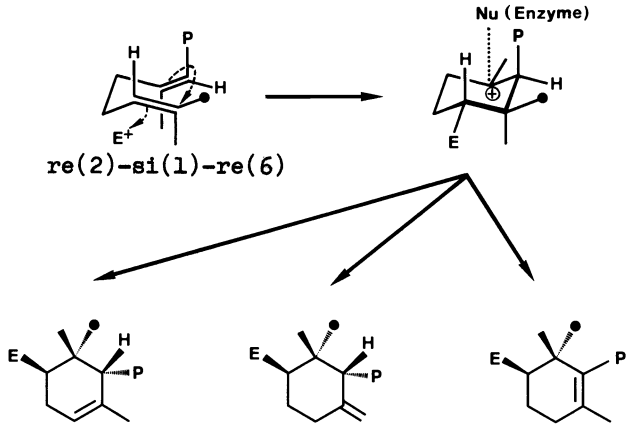
In this second case, we change the configuration of the C(5)-C(6) double bond: the resulting products are given. I would like to point out that the diastereomeric cations don't necessarily have to lead to the same products (ε, γ or β).

C_2(E,E)



(1S,2R,6R) (1S,2R,6S) (1S,2R) (Scheme 27)

$C_2(E,Z)$

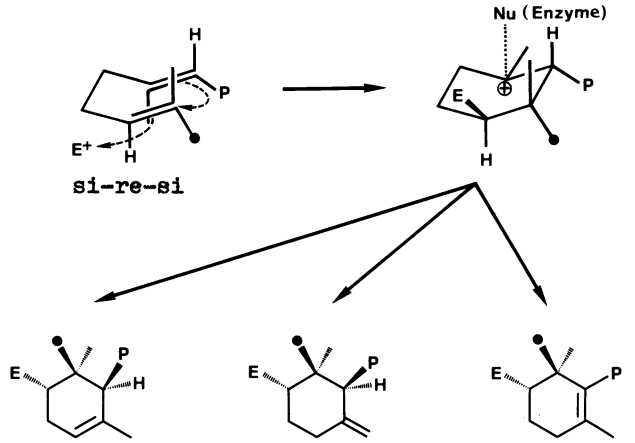


(1S,2R,6S) (1S,2R,6R) (1S,2R) (Scheme 28)

Now the electrophile assumes a β-position, the (E)-methyl group, however, an α-position and the configuration of the C(5)-C(6) double bond again determines the configuration at C(5)

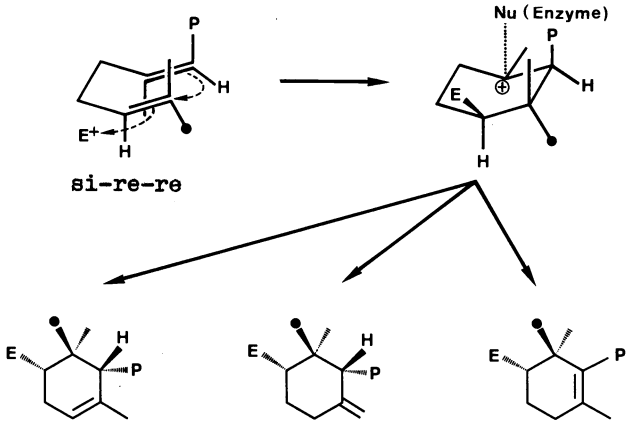
enantiomeric boat foldings:

$B_1(E,E)$



(1R,2S,6R) (1R,2S,6S) (1R,2S) (Scheme 29)

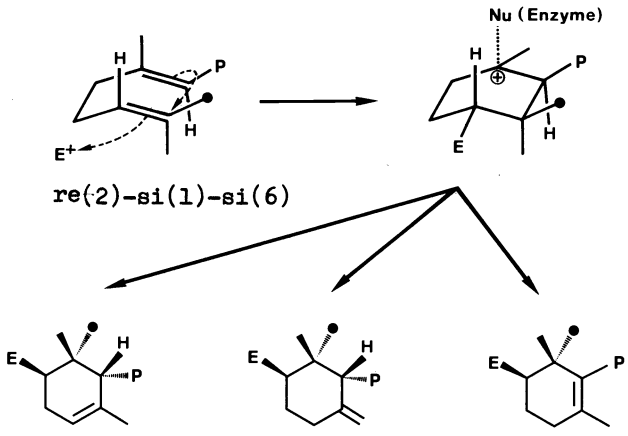
$B_1(E,Z)$



(1R,2S,6S) (1R,2S,6R) (1R,2S) (Scheme 30)

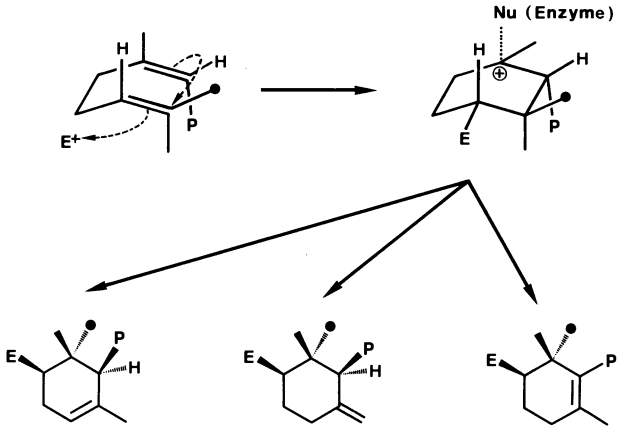
Both foldings result in products, which have already been found with the chair foldings; the same also applies to the enantiomeric B_2 foldings.

$B_2(E,E)$



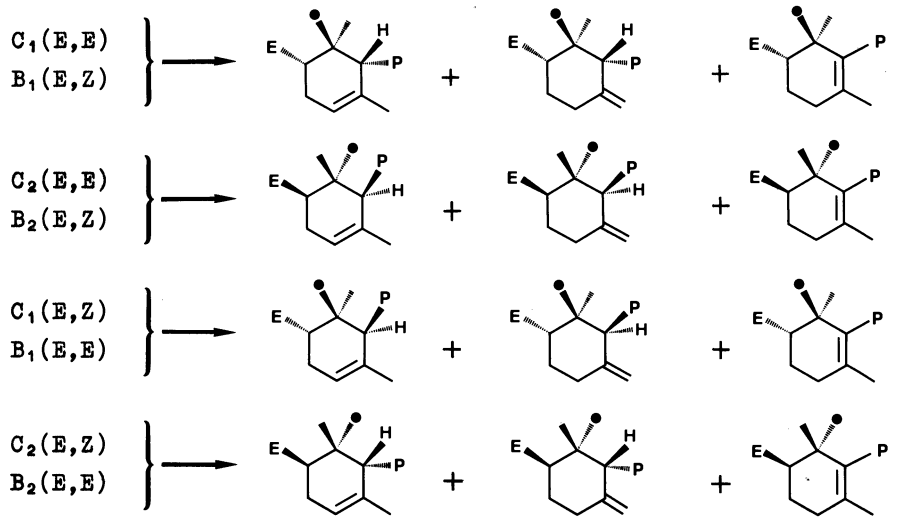
(Scheme 31)

$B_2(E,Z)$



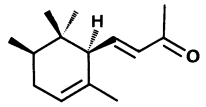
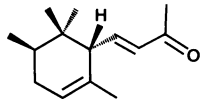
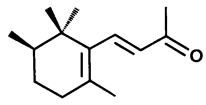
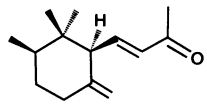
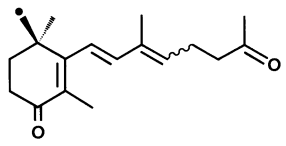
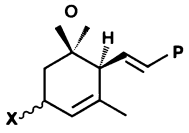
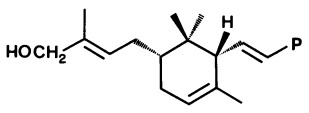
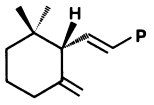
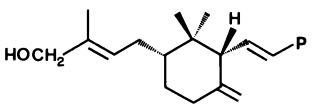
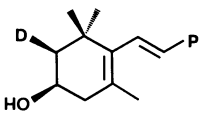
(Scheme 32)

Summary of the 8 possibilities

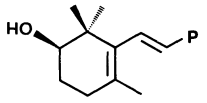


(Scheme 33)

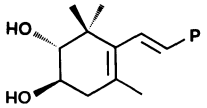
From this comparison, several conclusions can be drawn. I will discuss a few of them. To begin with, can we conclude anything from the hitherto known absolute configurations with regard to the stereochemistry of the cyclisation step ?

	(+)-cis-α-irone	(Ref.79)	from C_2(E,E), B_2(E,Z)
	(-)-trans-α-irone	(79)	C_2(E,Z), B_2(E,E)
	(+)-β-irone	(79)	C_2(E,Z), B_2(E,E) C_2(E,E), B_2(E,Z)
	(+)-cis-γ-irone	(79)	C_2(E,E), B_2(E,Z)
	trisporic acid	(118)	C_1(E,E), B_1(E,E) C_1(E,Z), B_1(E,Z)
	α-carotene, X=H	(71,72)	C_1(E,Z), B_1(E,E)
	α-zeacarotene, X=H	(119)	C_2(E,E), B_2(E,Z)
	δ-carotene	(120)	
	ε-carotene, X=H	(120)	
	semi-α-carotenone, X=H	(121)	
	lutein, X=α-OH	(77)	
	fritschiellaxanthin, X=α-OH	(24)	
	chiriquixanthin A, X=α-OH	(76)	
	chiriquixanthin B, X=β-OH	(76)	
	α-doradexanthin, X=β-OH	(24)	
	decaprenoxanthin	(78)	C_1(E,E), B_1(E,Z)
	β,γ-carotene	(70)	C_1(E,E), B_1(E,Z) C_2(E,Z), B_2(E,E)
	sarcinaxanthin	(75)	C_1(E,E), B_1(E,Z)
	2β-^{2}H-zeaxanthin	(122)	C_2(E,E), B_2(E,E) C_2(E,Z), B_2(E,Z)

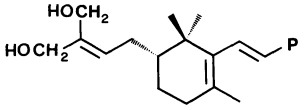
(cont.)



2β-OH-β-carotene (Ref.123) from $C_2(E,E)$, $B_2(E,E)$
$C_2(E,Z)$, $B_2(E,Z)$



nostoxanthin (11) $C_1(E,E)$, $B_1(E,E)$
caloxanthin (11) $C_1(E,Z)$, $B_1(E,Z)$

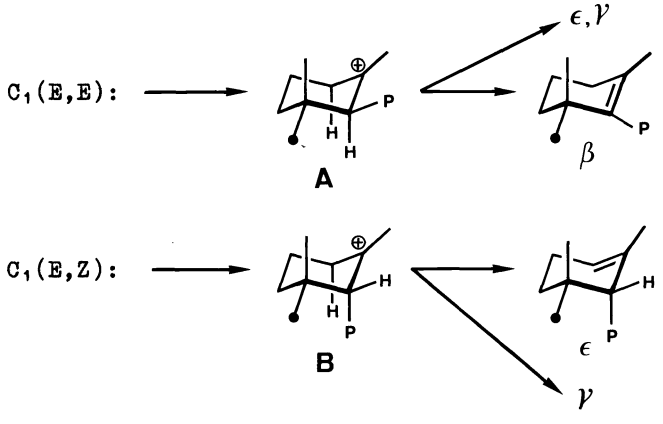


c.p. 450 (1,78) $C_1(E,E)$, $B_1(E,E)$
$C_1(E,Z)$, $B_1(E,Z)$

Scheme 34

As a simplification, it is assumed that each substituent at C(2), i.e. CH_3, OH, isopentenyl, corresponded to the cyclisation inducing electrophile analogous to H^+, D^+. Even if one leaves the biogenetically not particularly clear irones out of consideration, one immediately comes to the result that none of the hitherto established absolute configurations suffices to enable a certain conclusion regarding the stereochemistry of the cyclisation step. The nearest one comes to it (the certain conclusion!) is in the case of decaprenoxanthin and sarcinaxanthin, where it must concern the C_1- or B_1-folding. The survey also shows quite clearly, however, that there is more than one type of folding which is made use of by the different organisms. But there is still no recognisable connection with carotene types (β-, α- or γ-carotenes, i.e. β-, ε- or γ-series) or with the organisation level of the organisms (bacteria, fungi, higher plants).

I would now like to make a few speculations about the ε-, γ- and β-trichotomy. These series are not, according to what is known (Ref. 113), biologically interconvertible. The origin of the 3 different series has hitherto remained unsolved. It follows, however, quite simply - at least in part - if one postulates that the configuration at C(6) of the formed cyclohexane ring decides which series arises, and one can furthermore connect this configuration with the geometry of the C(5)-C(6) double bond and the conformation of the folding.

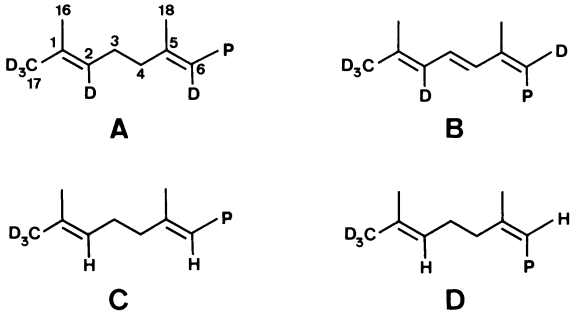


Scheme 35

Looking at the cations formed from the $C_1(E,E)$- and $C_1(E,Z)$-foldings, it follows that different situations are at hand for the elimination of a proton: if an anti-H is removed as proton, which is probable for stereo-electronic reasons, then the product from A will be different to the product from B! Further speculation is forbidden by the sparse experimental facts available to date. However, I would like to emphasise again that I postulate that this problem (i.e. the transition into the ε- or β-series) is connected with the geometry of

the C(5)-C(6) double bond in the acyclic precursor as lycopene or neurosporene. Experimental investigations in this direction are still lacking.

Future biochemical investigations with suitably configurated or labelled carotenes must give an insight into the problems outlined of the stereochemistry of the biological ring-closure. Suitable molecules for such investigations would have to possess the following end groups:



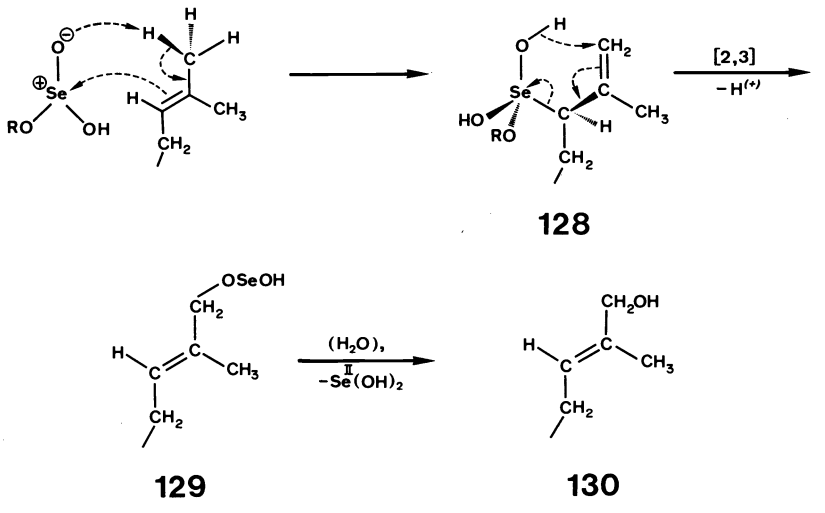
Scheme 36

Since the stereochemistry at C(2) can be clarified by the elegant technique of Britton et al. (Ref. 122) and the chirality at C(6) in the ε- and γ-series is well known, we have contented ourselves for the time being with synthesising the d_3-type (C). Thereby, we are of course aiming at the determination of configuration at C(1) in β-, ε- and γ-carotenes.

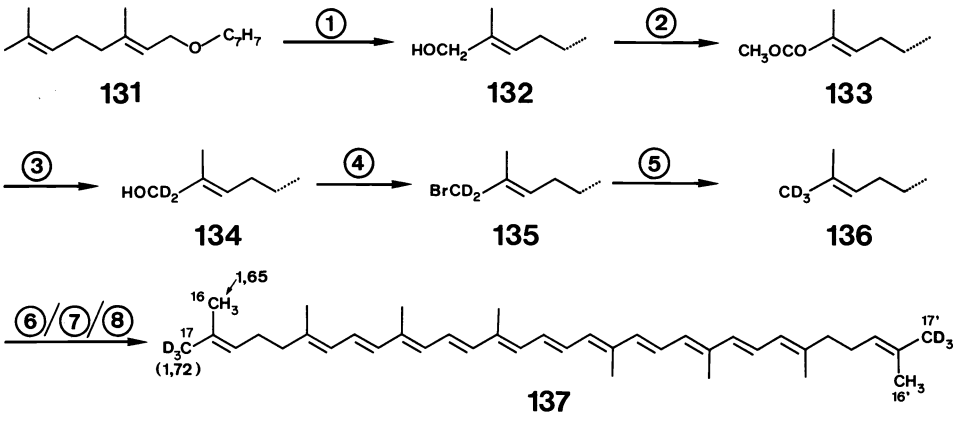
Synthesis of 17,17,17',17',17',17'-d_6-lycopene (Ref. 124)

Deuterated lycopenes have already been synthesised by different teams (Refs. 125, 126, 127). For our objective, however, none of the techniques employed in the works cited came into consideration (e.g. catalytical deuteration of triple bonds, $LiAlD_4$-reductions of carbonyl groups, base catalysed H⇌D-exchange of azide protons, syntheses with d_3-vinyl chloride etc.).

For the selective conversion of CH_3(17) into CD_3(17) we employed the following reaction, namely between an allylic system and selenious acid to give an allylic seleninic acid (128) (Ref. 128) which is today interpreted as ene-reaction. This very quickly undergoes a [2,3]-sigmatropic rearrangement and is then



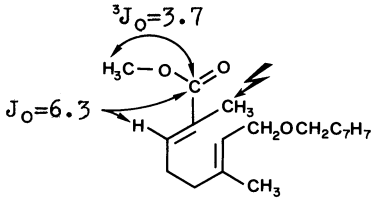
Scheme 37



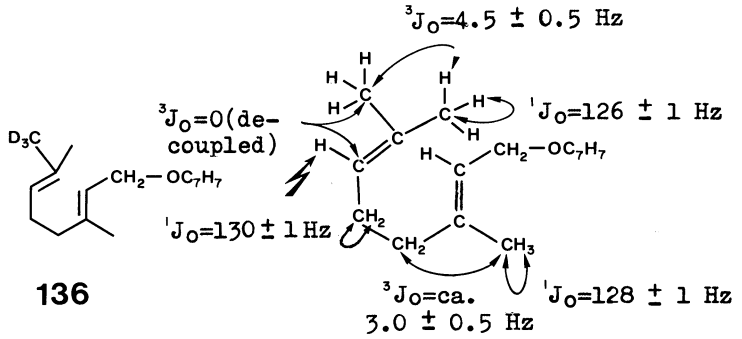
(1) SeO_2/ethanol; 30-60°. (2) MnO_2/ethyl acetate; Ag_2O/NaOH; CH_2N_2; 20%. (3) $LiAlD_4$/ether; 90%. (4) PBr_3/CaH_2/hexane. (5) $LiAlD_4$/ether; 30%, based on 134. (6) Li/$HN(Et)_2$, -78°; 49-56%. (7) PBr_3/py; $P(C_6H_5)_3$; 47%. (8) $NaOCH_3$; crocetindial; 44-61%.

Scheme 38

hydrolytically cleaved. The regioselectivity attains more than 90%. Application to geranyl-O-benzylether (131) (Ref. 129) gave first of all the alcohol 132, which was then converted in several stages into the d_3-compound 136 and then by conventional steps into d_6-lycopene 137. The (E)-configuration of the C(1) double bond was preserved in all steps. This was verified by detailed ^{13}C-NMR-analysis of the ester 133 and d_3-geranylbenzylether (see Note c). In this way with the help of decoupling experiments e.g. on 133, the ^3J-coupling constants of the carbonyl C with the methoxyl group were determined ($^3J_{red}$ =



133



136

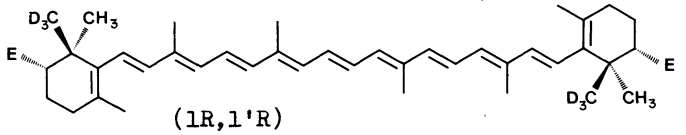
Scheme 39

Note c. We are indebted to Dr. Ulrich Vögeli from the group of Prof. W. von Philipsborn for extensive measurements and help in interpretation.

2.96 Hz; ^3J_o = 3.7 Hz) and those to the methine proton measured ($^3J_{red}$ = 6.08 Hz; ^3J_o = 6.3 Hz). Since the range of 6.5 - 7.6 Hz is typical for a cis-relationship whilst it amounts to 12.8 - 14.5 Hz for a trans-arrangement (Ref. 130), the stereochemistry at the double-bond is clarified. A similar process was carried out for the compound 136. Finally, the signal of the methyl group absorbing at lowest field is missing in the ^{1}H-NMR-spectrum of the d_6-lycopene obtained.

With sufficient amounts of d_6-lycopene 137 at hand (we have about 0.5 g), incorporation studies with carotene cyclases can now be started. I refer to relevant works by Porter, Goodwin and Davies. When β,β-carotene is formed one can expect:

β,β-carotene:

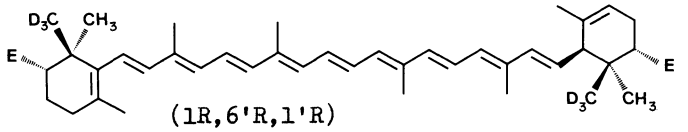


(1R,1'R) (from C_1, B_1)

or: (1S,1'S) (from C_2, B_2)

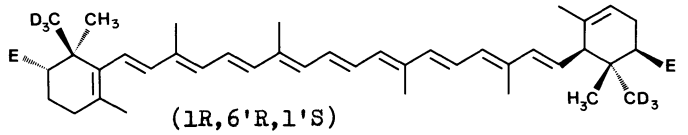
(presuming analogous cyclisation steps at both ends)

β,ε-carotene:



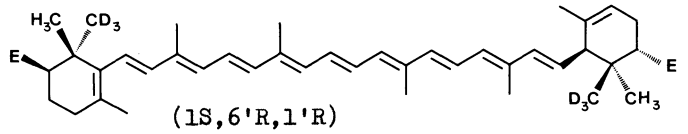
(1R,6'R,1'R) (β-ring from C_1 or B_1, ε-ring from C_1(E,Z) or B_1(E,E))

or:



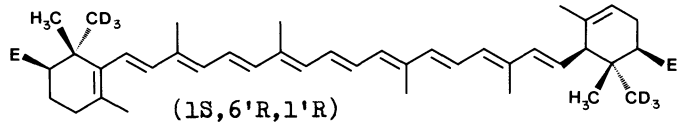
(1R,6'R,1'S) (β-ring from C_1 or B_1, ε-ring from C_2(E,E) or B_2(E,Z))

or:



(1S,6'R,1'R) (β-ring from C_2 or B_2, ε-ring from C_1(E,Z) or B_1(E,E))

or:

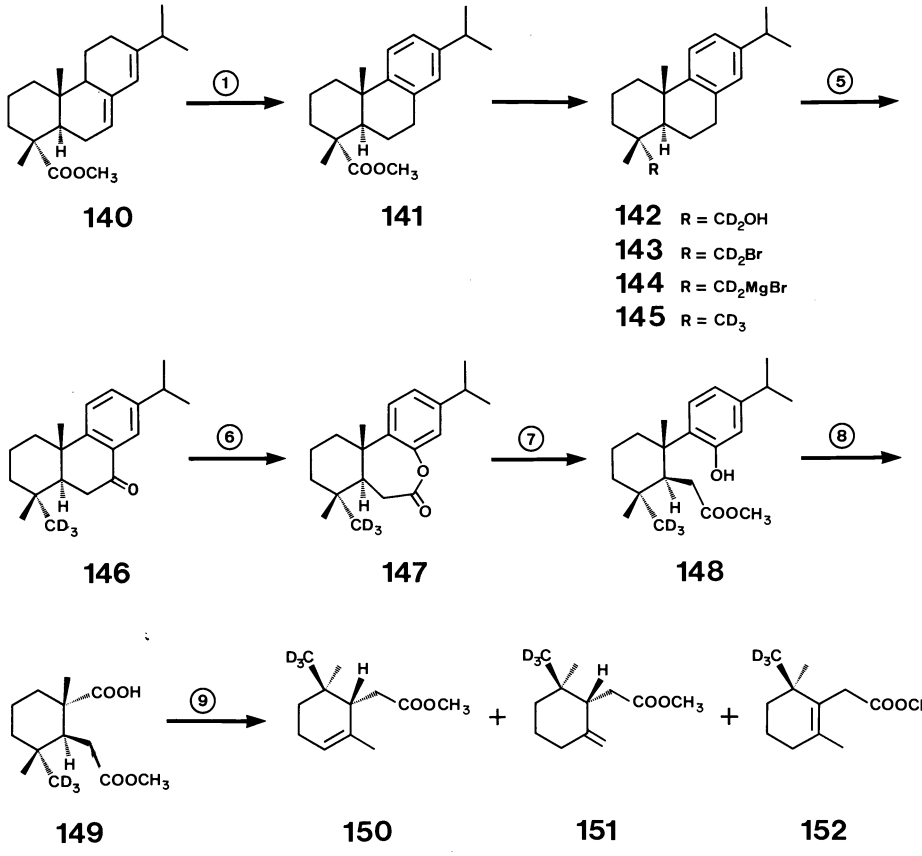


(1S,6'R,1'R) (β-ring from C_2 or B_2, ε-ring from C_2(E,E) or B_2 (E,Z))

Scheme 40

The decision between the various possibilities thus requires that the configuration of the products formed at C(1) and C(1') in β,β-carotene, and at C(1), C(1') and C(6') in β,ε-carotene can be diagnosed. For C(6') chiroptical methods are reliable; for C(1') in β,ε-carotene we have considered the ^{1}H-NMR-method, above all because today it is applicable to sub-milligram quantities. The geminal methyl groups in the ε-ring do, of course, have different chemical shifts, yet, still no assignment of originals has hitherto been made.

Synthesis of (-)-(1R,6S)-10,10,10-d_3-homo-α-cyclogeranic acid (Ref. 131)
We started with ca. 1 kg of configuratively known abietic acid (140) and degraded it in a time-consuming but lucid way to the double-bond isomeric d_3-homo-cyclogeranic acids 150, 151 and 152:



140 **141** **142** R = CD_2OH **143** R = CD_2Br **144** R = CD_2MgBr **145** R = CD_3

146 **147** **148**

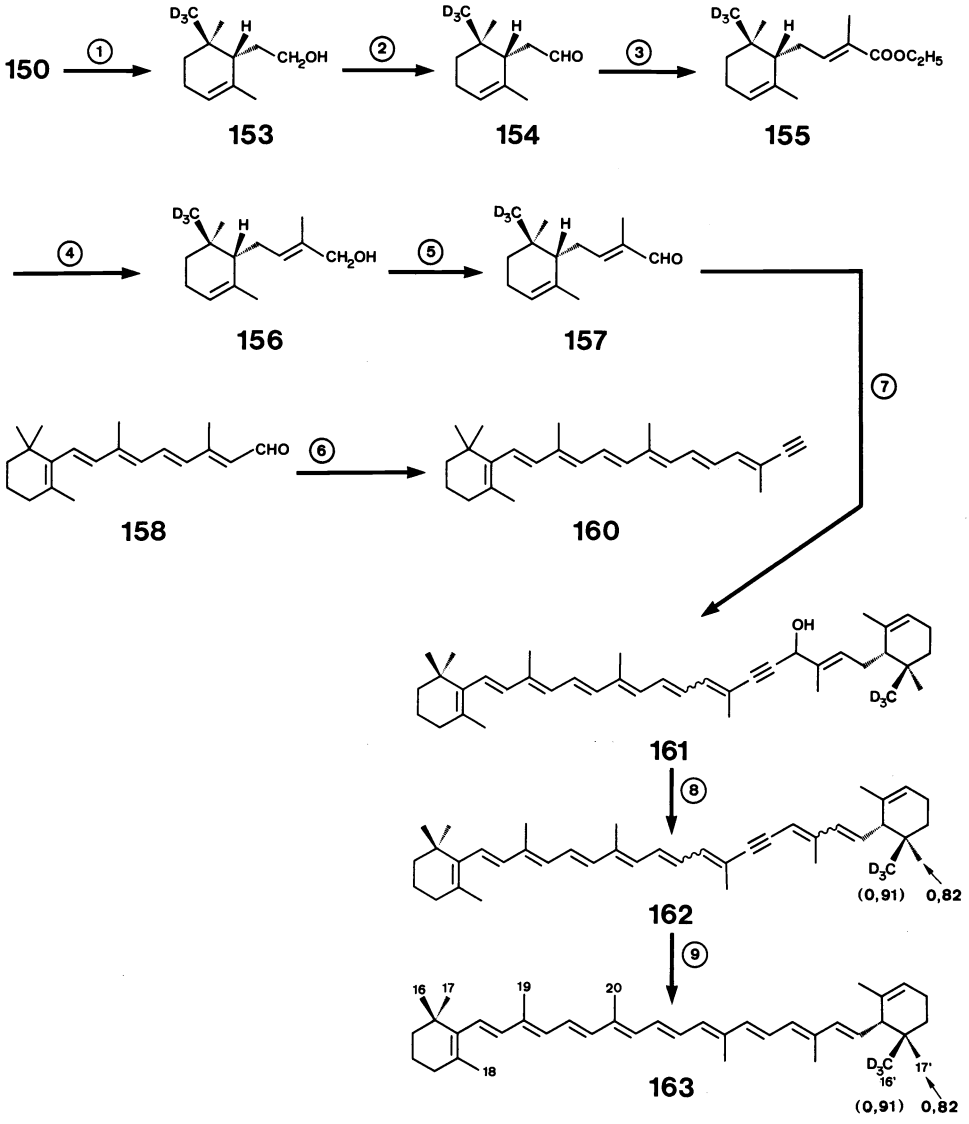
149 **150** **151** **152**

(1) 1. NBS/$BaCO_3$; 2. NaOAc/HOAc (Ref. 132). (2) $LiAlD_4$/ether; 98%. (3) C_6H_5P/NBS/THF; 80-90%. (4) 1. Mg; 2. D_2O or $Li(Et_3BD)$/THF; 90-95%. (5) CrO_3/acetone/H_2SO_4 according to Jones; 95%. (6) CH_3COOOH/Na_2HPO_4; 65-70% based on 146. (7) CH_3OH/HCl. (8) $O_3/CHCl_3$ MeOH; Pd/$BaSO_4/H_2$ or $KMnO_4/MgSO_4$/acetone; 40%. (9) $Pb(OAc)_4/h\nu$ >300 nm/benzene; separation by HPLC on $SiO_2/AgNO_3$; Σ 150, 151, 152 45-50% from 149; obtained 150 : 151 : 152 = 1 : 1.4 - 1.6 : 0.3 - 0.4 (GC).

Scheme 41

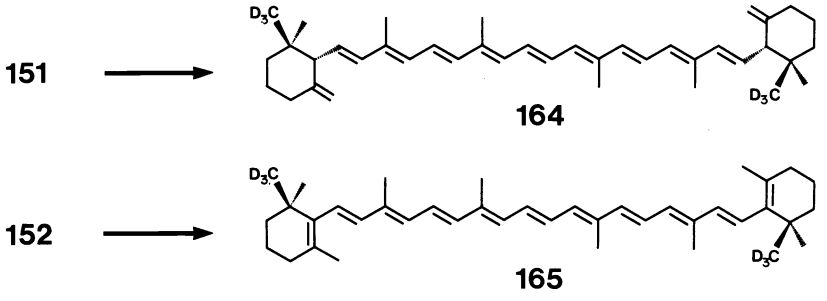
Subsequently we first of all synthesised the important β,ε-carotene 163 as follows (Ref. 131):

Synthesis of (1'R,6'S)-16',16',16'-d_3-β,ε-carotene (see Scheme 42)
The crystalline d_3-β,ε-carotene 163 obtained has practically the same CD-spectra as the non-deuterated compound. In the ^{1}H-NMR-spectrum, the signal at 0.91 ppm for the C(16')-CH_3 is missing, whilst that at higher field (0.82 ppm) is unchanged. Thus for the first time an assignment of these signals can be made: that at highest field is cis to the side chain. One must not, however, apply this fact to all intermediates, for in one case the signals reverse. Thus - assuming successful incorporation of 137 - the chirality at C(1') in β,ε-carotene can now be spectroscopically determined. Corresponding syntheses of d_6-γ,γ-carotene 164 and d_6-β,β-carotene 165 are in progress but not yet completed.



(1) $LiAlH_4$; 95%. (2) Pfitzner-Moffat oxidation with DCCD on Merrifield-Polymer/DMSO/py/benzene/CF_3COOH (Ref. 133); 85%. (3) Wittig with φ_3-P=C(CH$_3$)COOEt, benzene; 75-82%. (4) $LiAlH_4$; 95%. (5) MnO_2/ethyl acetate; 95%. (6) Wittig with φ_3-P=CH-CH=C(CH$_3$)C≡CH (159) (Ref. 134); 40-45%. (7) 160 + BuLi + 157; 80% based on 157. (8) HBr (48%)/CH_2Cl_2/2.5 min -50°; 80%. (9) Lindlar/H_2; isomerisation; cryst.; 37%.

Scheme 42



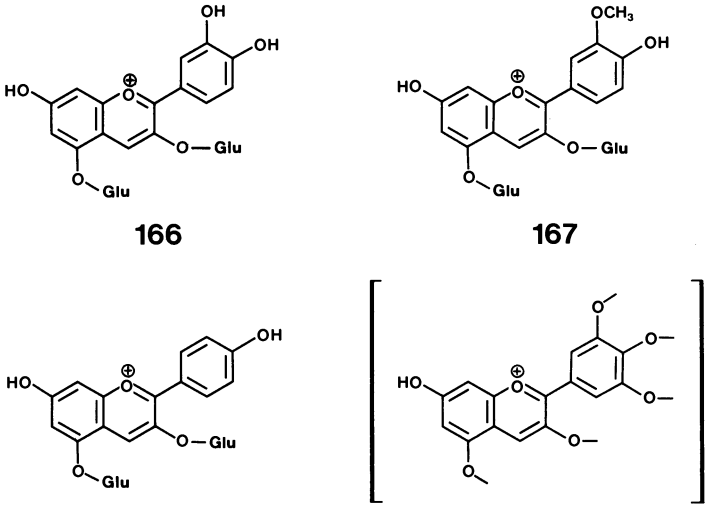
164 165

Scheme 43

I believe that with the syntheses just outlined, a contribution from the chemical side has been achieved which, together with biochemists, can successfully help to solve the problem of the stereochemistry of the biological ring-closure in carotenes.

5 CAROTENOIDS IN ROSE FLOWERS

In conclusion, I would briefly like to refer to one aspect of the carotenoid chemistry which has an eminently aesthetic character. By that, I mean the only most recently discovered fact that carotenoids are essential flower pigments in yellow-, orange-, salmon- or copper-coloured garden roses. Hitherto it was assumed that it concerned flavonoids. Up till now the following have come to light as typical rose pigments:

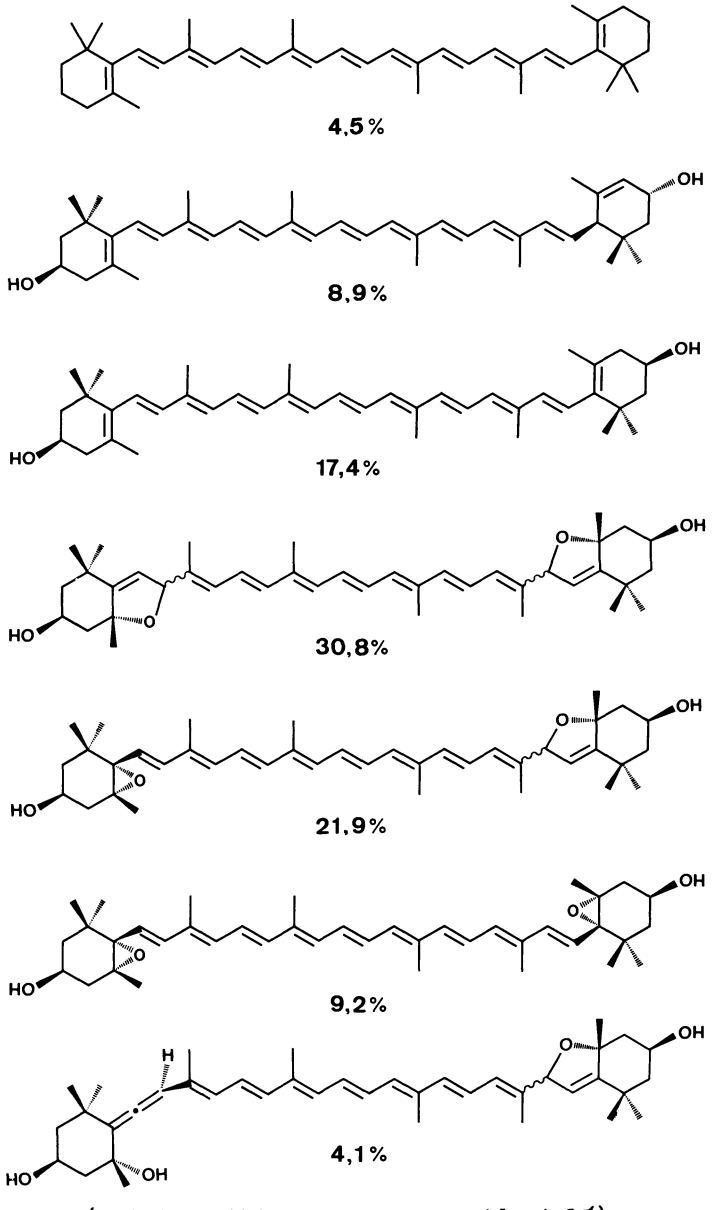


166 167 168 169

Scheme 44

When cyanin 166 predominates, then the flowers exhibit a deep red tone (e.g. Rosa gallica,"Papa Meilland", "Arturo Toscanini", "Mr. Lincoln", "Reine des Violettes", etc.). With peonin (167) as the main pigment, the flowers are deep pink (e.g. Rosa rugosa,"Conrad Ferdinand Meyer", "Queen Elizabeth", "Roseraie de l'Hay"). When pelargonin (168) is the predominant pigment, we have the modern geranium-, scarlet- and brick-red tones. This colouration has only become prominent since about 1950. We find it for example in "Gloria mundi", "Princess van Orange", "Independence", "Baccara", "Tropicana", "Sarabande",

"Radar". There can be no true blue roses, since the corresponding anthocyanin delphinin (169) does not occur in roses. Few rose admirers know that yellow garden roses (teahybrids, polyantha, floribunda) have also only fairly recently come into being (see Note d). They can all be traced back with two exceptions (namely "Gottfried Keller" and "Poulsen's Yellow") to "Soleil d'Or", which originated from crossing the violet-red hybrid perpetual "Antoine Ducher" with pollen from the yellow Rosa foetida persiana. We therefore decided to investigate this very influential R. foetida more closely. Sacrificing two year's blossoms from my garden - it flowers only once a year - gave the following results (Ref. 135):



(mutatoxanthin + apocarotenoids 4.1%)

Scheme 45

Note d. Among other rose classes, yellow roses were found above all amongst tea roses (e.g. "Safrano", "Gloire de Dijon", "Madame Levet") and amongst noisette roses (e.g. "Marechal Niel", "Alister Stella Gray", "Chromatella"). They owe their emergence to intercrossing of the yellow china rose "Parks Yellow Tea-scented China" (R. x odorata ochroleuca) in the first half of the 19th century.

70% of carotenoids consist of epoxides. Valadon and Mummery (Ref. 136) have also ascertained a similarly high percentage of epoxides in modern yellow tea hybrids ("Sutters Gold", "Allgold", "Jan Spek", "Gold Crown", "Gold Gleam", "Bossa Nova", "Zambra"). Yellow roses thus owe their colouration mainly to carotenoids, blends, e.g. "Piccadilly", "Masquerade", possess mixtures of carotenoids and anthocyanins.

One can conclude, therefore, that by intercrossing Rosa foetida, the ability to produce and store carotenoids in high concentration in the petals has for the first time become a hereditary characteristic. Accordingly, carotenoids occur not only in (rose-)hips, which was of course known a long time ago, but are also essential constituents of the yellow-, salmon-, apricot- and copper-coloured hybrids. This extension of the carotenoid chemistry into horticultural areas holds an especial fascination for some of us.

Acknowledgement - I thank the Swiss National Funds for the generous support of our work in the carotenoid field. Substantial contributions were made by the following co-workers: Dr. Richard Buchecker, Walter Eschenmoser, Arnold Hofer, Hanspeter Märki, Gérald Werner, Mrs. Edith Märki-Fischer, Nikolas Vergos, Herbert Cadosch, Dr. Peter Rüedi and Dr. Ulrich Vögeli.

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