

NEW STRUCTURES

SYNNØVE LIAAEN-JENSEN

Organic Chemistry Laboratories, Norwegian Institute of Technology, University of Trondheim, N-7034
Trondheim-NTH, Norway

Abstract—The paper updates Isler's monograph of 1971 regarding the structures of naturally occurring carotenoids, their chemical reactions and their stereochemistry.

Around ninety new structures are reported, including the new series of C₃₀-carotenoids, enolized β-diketones and several carotenoids with 2-hydroxy β-rings.

Progress in stereochemistry resulting in the configurational assignment of eleven additional chiral carotenoid end groups and the absolute configuration of around thirty carotenoids, including C₅₀-carotenoids, is discussed.

INTRODUCTION

The present paper aims at updating Isler's⁷⁰ comprehensive monograph of 1971, regarding the structures of naturally occurring carotenoids, including their stereochemistry.

As shown in Fig. 1 the number of natural carotenoids with reasonably well established structures has increased at a steady rate also during the past 5 yr. However, the *ca.* ninety new structures reported mainly represent other combinations of previously known structural elements, and relatively few novel structural features have been disclosed. Exceptions are the new series of C₃₀-carotenoids,^{120,121} enolized β-diketones such as mytiloxanthin (11)⁷⁶ and trikentrionrhodin (53)³ and the series of carotenoids with 2-hydroxy β-rings.^{79,96,14,15}

Some new reactions useful for structural studies of carotenoids* will be referred to.

Since 1970 circular dichroism has become a routine tool and a major progress in stereochemistry is characteristic for the period. Of the at present *ca.* 190 chiral carotenoids described, the chirality of 38 carotenoids were included in Isler's⁷⁰ monograph, 4 of which have subsequently been revised. These carotenoids were restricted to 7 different chiral end groups. During the subsequent period the number of carotenoids with known absolute configuration has been approximately doubled, covering the configuration of 11 additional chiral end groups, leaving only few chiral end groups unsolved.

RECENTLY STRUCTURALLY ELUCIDATED CAROTENOIDS

Straub's compilation¹¹⁸ of naturally occurring carotenoids, completed in 1970/71, comprises 284 structures. During the last 4-5 yr *ca.* 90 new structures have been elucidated, and some earlier structures have been revised or abandoned. Only reasonably well documented structures are included here. Space does not permit a discussion of the evidence on which these structures are based, but key references are included. Proposals lacking mass spectral and ¹H NMR evidence must be considered tentative.

C₃₀-Carotenoids

From a strain of *Streptococcus faecium* has been isolated a novel series of C₃₀-carotenes, comprising the C₃₀-analogues 1, 2, 3 and 4 of phytoene, phytofluene, ξ-carotene and neurosporene, designated by a 4,4'-diapo nomenclature.¹²⁰ 4,4'-Diaponeurosporene (4) also occurs as a monool (5) and a D-glucoside (6),¹²¹ Scheme 1.

C₄₀-Carotenoids

New C₄₀-skeletal carotenoids will be summarily referred to in groups of characteristic structural features, following the system used in a previous review.⁸⁷ These structures represent an extension of the compilation by Straub.¹¹⁸

Hydrocarbons, Scheme 2. The monocyclic 7', 8', 11', 12'-tetrahydro-β,ψ-carotene (7) has been isolated from diphenylamine (=DPA)-inhibited cultures of *Phycomyces blakesleeianus*.⁴⁶ θ-Carotene is claimed to be a mixture of ξ-carotene and 7,8,11,12-tetrahydro-ψ,ψ-carotene, and it is recommended that the name θ-carotene be abandoned.⁷⁵ The presence of γ,γ-carotene (8) in aphids⁹ has been proved by total synthesis.¹⁰ Two new acetylenic aryl carotenes 7,8-didehydroeneriatene (9) and 7,8-didehydroisoreneriatene (10) are also documented.^{56,69}

Acetylenic xanthophylls, Scheme 3. Acetylenic bonds are still restricted to the 7(7') position in naturally occurring carotenoids. The occurrence of 4-keto-cynthiaxanthin and 4,4'-diketocynthiaxanthin is recently reported.⁵⁷ However, these are synonyms of the previously known mono- and diacetylenic asterinic acid.⁵¹ Manixanthin is thought to be 9,9'-dicis-alloxanthin.⁴² Mytiloxanthin (11) from edible mussel represents a novel, well documented, enolized β-diketone with cyclopentane end group.⁷⁶ The remarkable isomytiloxanthin (12) also occurs in *Mytilus edulis*.⁷⁶ The structure of heteroxanthin (13) with a cyclic trihydroxy end group has now been established.^{30,39}

Allenic xanthophylls, Scheme 3. Additional allenes have been reported including mimulaxanthin (14)¹⁹ and a revised structure of vaucheriaxanthin (15)³² based on spectral evidence. Dinoxanthin has been shown to be neoxanthin 3-acetate (16)⁷⁵ and the identity of trollixanthin and trolliflor with neoxanthin has been proved.³⁷ The structurally complex 19'-hexanoyloxy-fucoxanthin (17) has been obtained from algal source.^{19,63}

Epoxides and furanoxides, Scheme 4. Additional epoxides of aliphatic carotenes have been reported from tomatoes.²² These now include phytoene-1,2-epoxide (18), phytofluene-1,2-epoxide (19), phytofluene-1',2'-epoxide (20), ξ-carotene-1,2-epoxide (21), lycopene-1,2-epoxide (22) and lycopene-5,6-epoxide (23).²²

A recent reinvestigation of authentic taraxanthin preparations has eventually proved that taraxanthin is a mixture of lutein epoxyde with minor, known carotenoids.¹⁰ The name taraxanthin should therefore be abandoned. Structure 24 has been suggested for trollichrome from orange juice,⁵⁴ *cf.* however, the finding that trollixanthin is identical with neoxanthin.³⁷

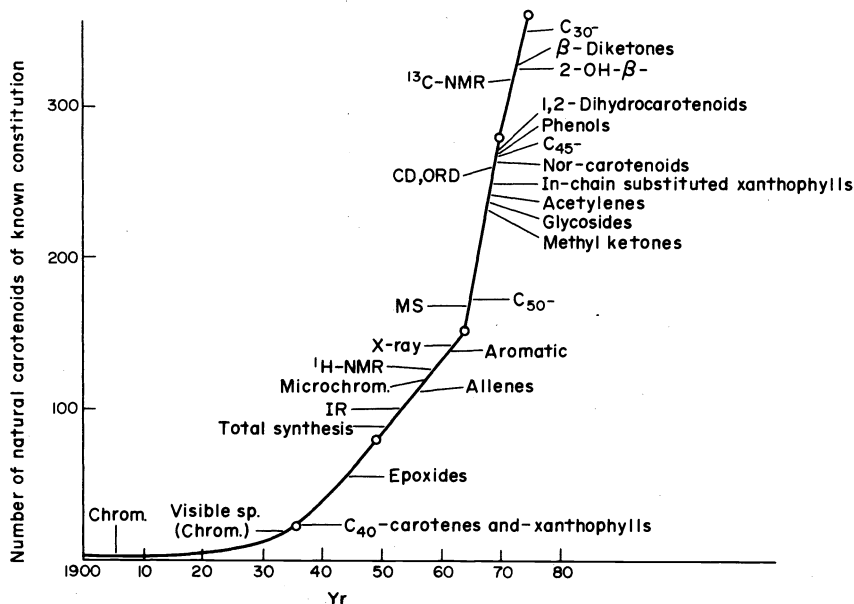
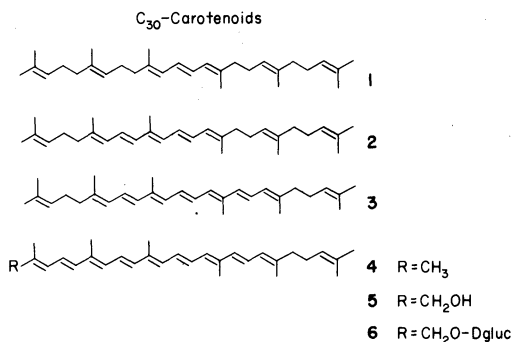
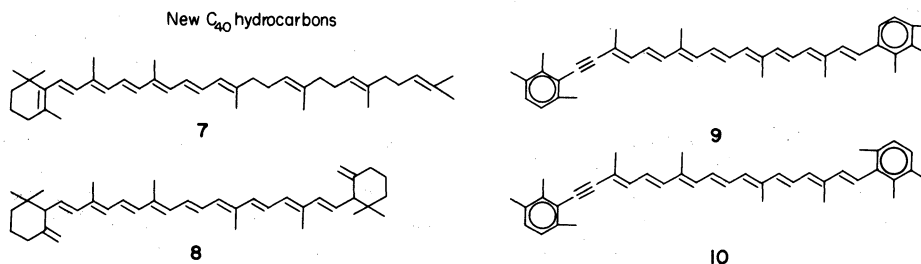


Fig. 1.



Scheme 1.



Scheme 2.

Two additional epoxides **57** and **58**⁹⁶ are mentioned under Alcohols, Scheme 8.

Glycosides, Scheme 5. Several new glycosides have been reported. However, usually they represent aglycones of previously known carotenoids glycosidically bound to glucose or rhamnose. Monocyclic aglycones are present in the tertiary glycosides **25–28**, myxobacton ester (**29**) and myxobactin ester (**30**) isolated from myxobacteria.^{82,84,108} Noteworthy is the esterification of one of the glucosyl hydroxy groups, mainly with C₁₂–C₁₈ unbranched, saturated or monounsaturated acids.⁸⁴ Also obtained from myxobacteria is the acylated acyclic carotenoid glucoside

31.⁸³ From a filamentous gliding organism have been obtained related monocyclic tertiary glycosides: **32** with β,ψ -carotene chromophore, **33** (analogous to the rhamnoside **26**) and the hexoside **34**,⁵⁵ presumably representing myxobacton (**29**) unesterified.

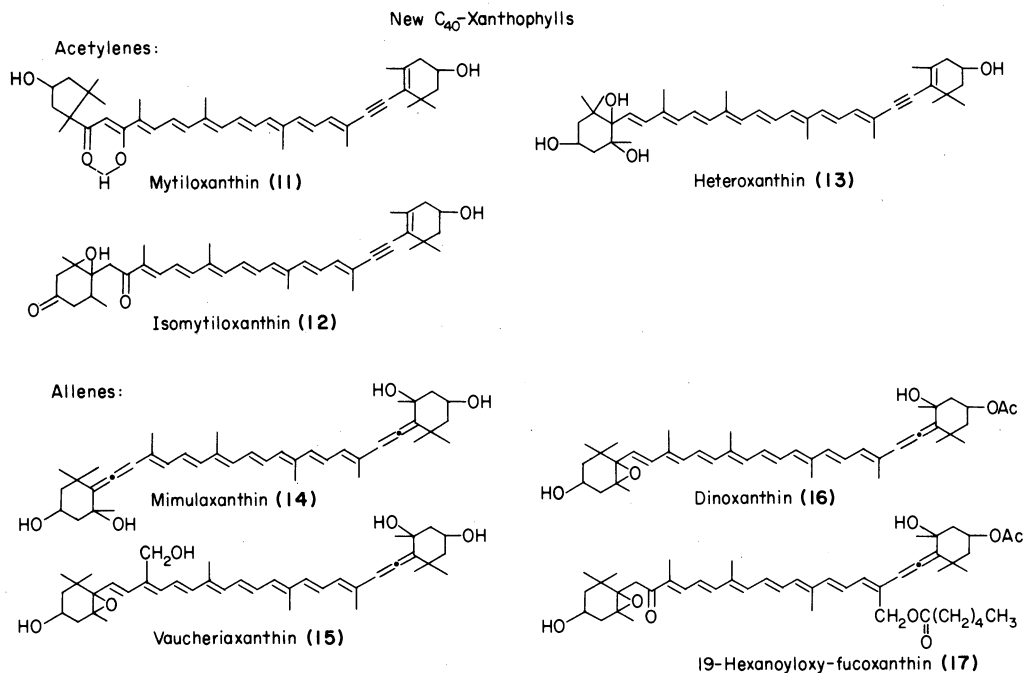
Zeaxanthin is the aglycone of the monorhamnoside **35** and the dirhamnoside **36**, major carotenoids of a coryneform hydrogen bacterium⁹⁹ and a *Corynebacterium* sp.⁶¹ The different, chemical behaviour of secondary, non-allylic glycosides is noteworthy.^{99,104}

Methyl ethers, Scheme 6. Carotenoid methyl ethers are still restricted to photosynthetic bacteria. New representatives have been found in *Thiotheca gelatinosa*: **37**¹¹ with β -ring representing a revision of the previously suggested

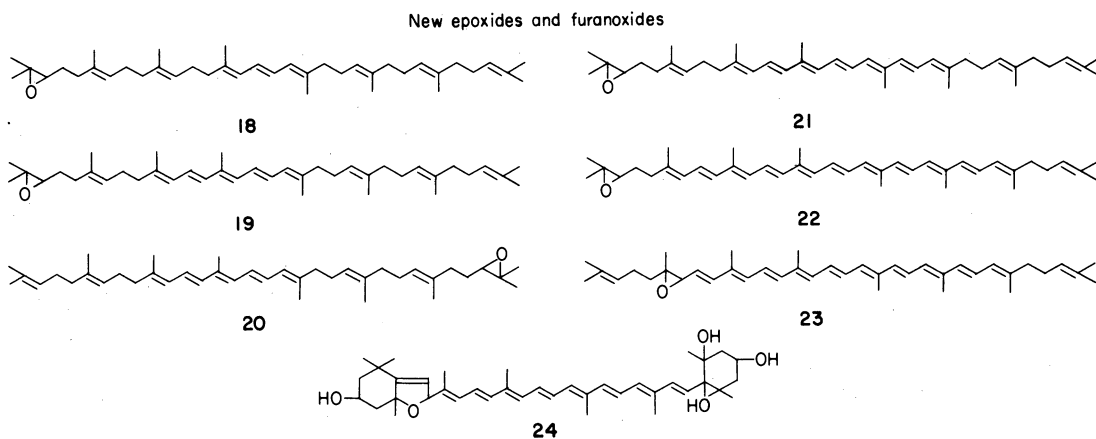
1,2,5-trimethylaryl structure,¹⁰⁵ **38**¹¹ in which an aryl methyl is formally oxidized to a carbomethoxy group and **39**¹¹ which may be the compound considered to be demethylated okenone.¹⁰⁵ Additional aliphatic members come from *Rhodospseudomonas globiformis*; the monoketones **40** and **41** and the diketone **42**.¹¹² Further ketones **43**, **44** and **45** were obtained from DPA-inhibited cultures.¹¹²

From *Rhodospirillum rubrum* cultures grown in the presence of DPA, the monools **46**, **47** and **48** have been isolated.⁴⁷

Aldehydes and ketones, Scheme 7. Those not com-



Scheme 3.



Scheme 4.

mented above include ternstroemiaxanthin (49).⁷⁸ Here a 18-methyl group is formally oxidized to an aldehyde, whereas in 3,4-dehydrolycopene-16-al (50)²⁰ a 16-methyl group has suffered oxidation.

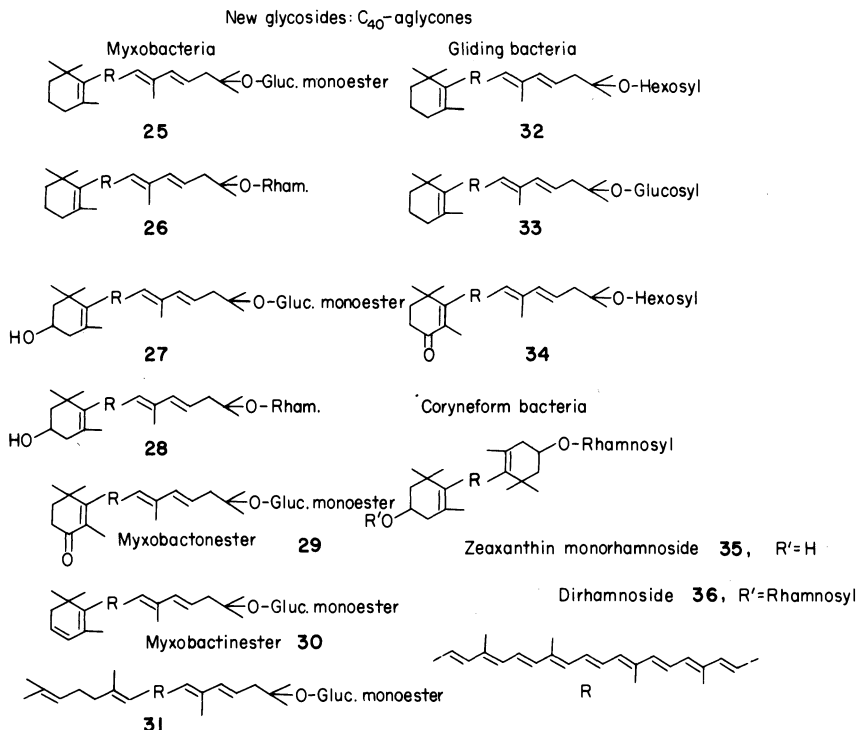
From micro scale chemical transformations loniceraxanthin has been assigned structure 51, and structure 52 for webbiaxanthin has been discussed.¹⁰⁶ The structure of trikentrionrhodin (53)¹¹ was elucidated by analogy with the enolized β -diketone mytiloxanthin (11).⁷⁶ Also isolated from a marine source is tedanin, reported to have one aryl and one diosphenol end group (53b).^{101b} Additional evidence in favour of the structure of siphonaxanthin and siphonein has been discussed.^{109,110}

Additional alcohols, Scheme 8. Several new alcohols containing none of the functionalities so far discussed have been reported. These include the new series of xanthophylls with 2-hydroxylated β -ring. Since the first isolation of the monools 54 and 55 and the diol 56 from *Trentepohlia iolithus*,⁷⁹ two additional epoxides 57 and 58 have been isolated from the same green algae.⁹⁶ Subsequently the

occurrence of 2-hydroxyplectanixanthin (59) in red yeast¹¹⁴ and of β,β -carotene-2,3,3'-triol (60) in a blue-green alga¹¹⁵ have been reported. Observations on the chemical behaviour of carotenoids containing 2-hydroxy- β -rings have been published.⁹⁷

2-Hydroxylated aliphatic end-groups as in 2'-OH-flexixanthin (61)² represents no new structural feature, but aleurixanthin (62)^{14,80} has a unique end-group.

Pyrenoxanthin is shown to be identical with loroxanthin.⁹³ Identity of trollein with loroxanthin has also been discussed.⁹³ For trollixanthin, recently shown to be identical with neoxanthin^{48,37} of known structure, evidence in favour of the tetrol structure 63 has been presented.⁵⁴ The different biological sources should be kept in mind and the pigment *ex oranges* should be designated otherwise. 3-Hydroxy- β -zeacarotene (64)⁴⁷ has been isolated from a *Flavobacterium* sp., and from DPA-inhibited cultures of *Rhodospirillum rubrum* 1,2,7',8',11',12'-hexahydrolycopene-1-ol (65)⁴⁷ has been isolated. Authentic taraxanthin is eventually proved to be a mixture of lutein epoxide



and minor carotenoids of known structure.^{37b} Finally calthaxanthin⁴⁴ is claimed to be the C-3' epimer of lutein.

C₄₅- and C₅₀-carotenoids

Additional C₄₅- and C₅₀-carotenoids, Scheme 9, all conforming to the C-2(2') isopentenylolation pattern of C₄₀-skeletons have been isolated. The monocyclic A.g. 470 from *Arthrobacter glacialis* has been assigned structure 66.¹⁶ Decaprenoxanthin monoglucoside (67) and diglucoside (68) obtained from another *Arthrobacter* sp.¹² and bacterioruberin monoglucoside (69) and diglucoside (70) from a halophilic bacterium,¹⁵ represent new glycosides of known aglucones. The structural elucidation of higher carotenoids from *Sarcina lutea*^{18,95,62,59} has offered a surprise, the supernumerary C₅-unit being attached to a γ end group^{62,59} and not an ϵ -ring as previously assumed.^{18,95}

Sarcinaxanthin is now assigned structure 71 with a twofold axis of symmetry, the mono- β -D-glucoside⁹⁵ structure 72 and a recently observed dihexoside structure 73.^{62,59} In view of recent findings^{62,59} one of the previously isolated minor C₅₀-carotenoids probably is 74 and one minor C₄₅-carotenoid presumably 75, where the partial structures of additional minor C₄₅- and C₅₀-carotenoids need further studies.

Nor-carotenoids

An additional nor-carotenoid (Scheme 10) occurs in sea anemones. Roseerythrin, isolated after careful alkali treatment, has been assigned structure 78⁵⁰ and the parent nor-carotenoid structure 79.⁵⁰ Details on the structural elucidation of peridinin are in press.^{117,81} Peridinin related nor-carotenoids have been obtained from Dinophyceae, including peridinol (80),⁷⁵ pyrroxanthin (81)⁷⁵ and pyrroxanthinol (82).⁷⁸

Apo-carotenoids

Citranaxanthin and reticulaxanthin are shown to be artefacts formed during the isolation,¹¹⁶ and these methyl ketones consequently do not represent naturally occurring carotenoids. Related C₄₃-artefacts have been observed for cross-conjugated carotenals of the rhodopinal series.¹¹¹ However, by analogy with the presumed biosynthesis of paracetrone⁶⁷ a new minor methyl ketone 77 (Scheme 11) from *Coccolithus huxleyi*¹⁹ is not likely to be an artefact. 3-Hydroxy-5,8-epoxy-5,8-dihydro-8'-apo- β -caroten-8'-al (84) is reported from orange juice.⁵⁴ Simpler apo-carotenals are found in a photosynthetic bacterium (85 and 86)¹¹ and a *Flavobacterium* sp. (87).⁸⁶

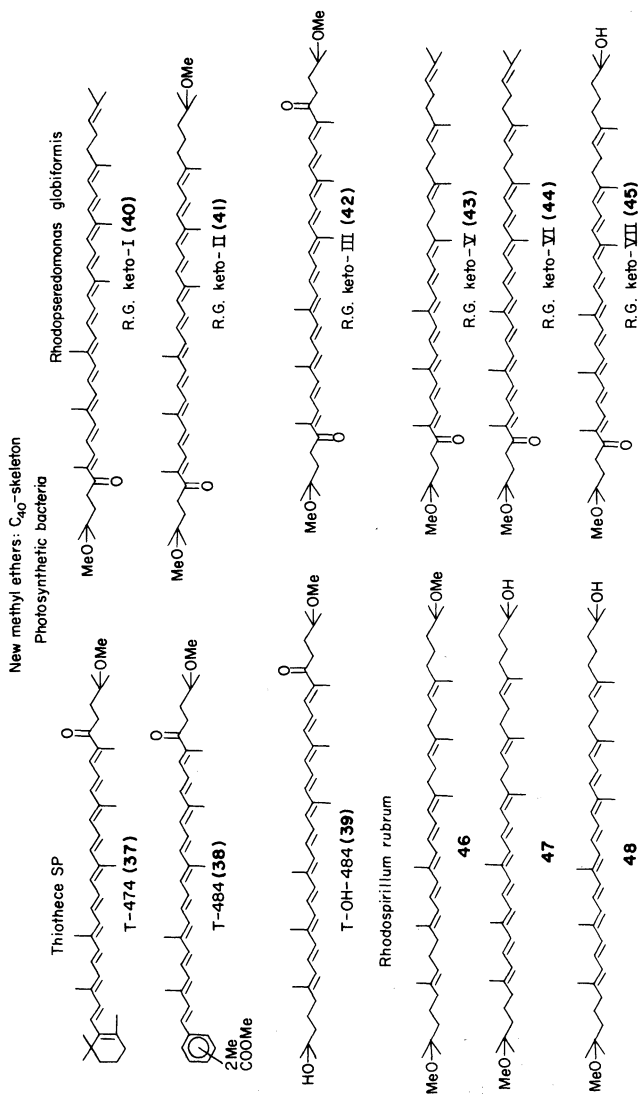
CHEMICAL BEHAVIOUR

The reader is referred to various reactions reported since the appearance of Isler's⁷⁰ book, which may prove useful for structural studies.

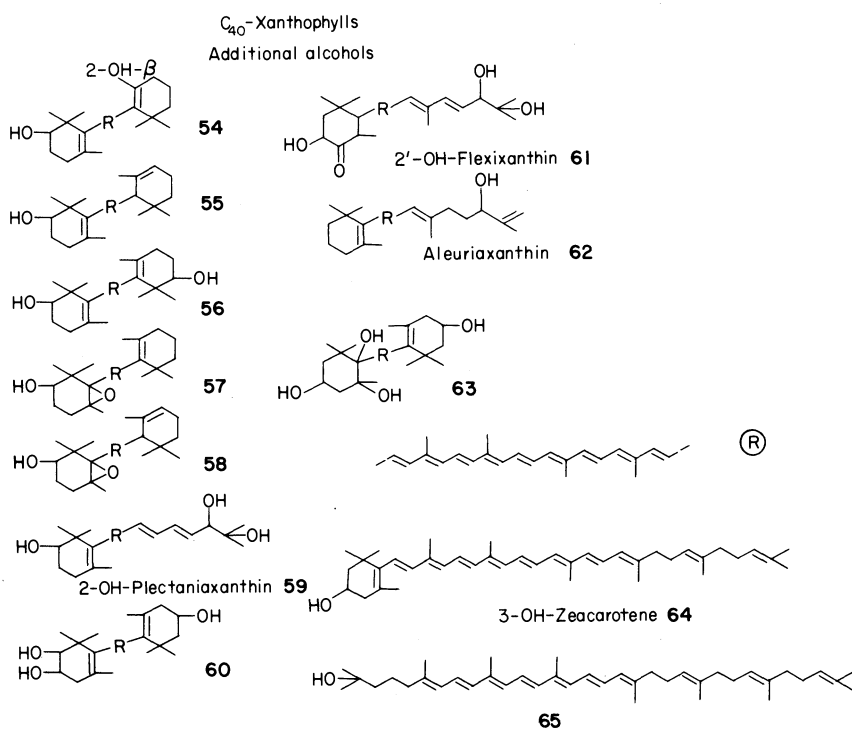
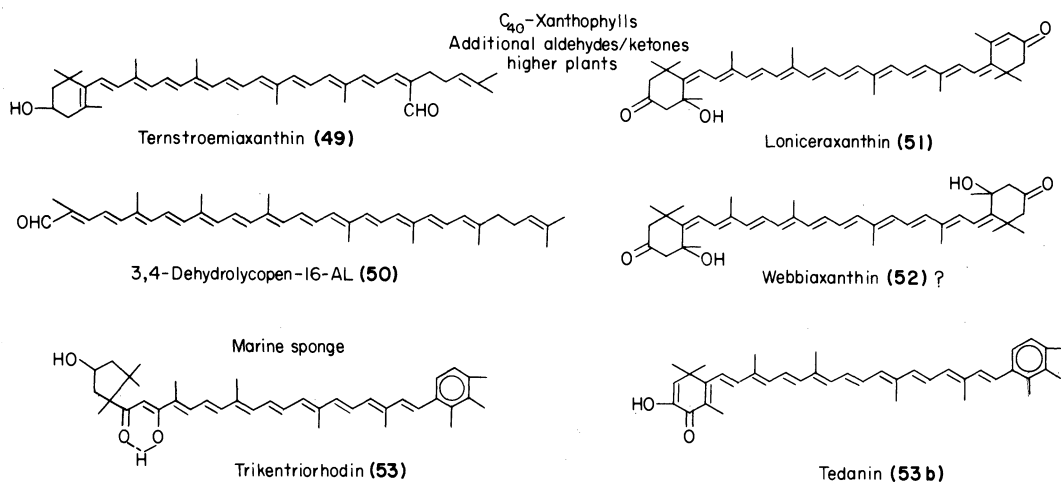
These include photooxidation of carotenoids,⁷¹ chromic acid degradation,¹¹³ oxidation of 3,4-dihydroxy- β -rings with CrO₃/graphite,⁶⁶ reactions with peracids,^{100,119} acid reactions of allenes to give halogenated carotenoids,^{72,33} conversion of allenes to acetylenes with acid,^{91,94,72,33} furanoid formation of 5,6-glycols,^{99,54,36} opening of epoxides to 5,6-glycols in aqueous acid,³⁴ acid/alkaline reactions of peridinin,⁸¹ aldol condensation of carotenals,^{111,116} isomerization of ϵ - to β -rings,⁴ alkaline cleavage of C₅₀-carotenoids,¹⁶ alkaline hydrolysis of glycosides,^{83,113} partial synthesis of glycosides,¹¹³ improved O-methylation,⁹⁸ reactions of carotenoids with 2-hydroxy- β -rings,⁹⁷ silylation in configurational studies³⁴ and the improbable, but claimed conversion of heteroxanthin (133, Scheme 22) to diadinoxanthin (134) by LiAlH₄.⁹⁰

STEREOCHEMICAL PROGRESS

Recent work on the absolute configuration of



Scheme 6.



carotenoids has been carried out by Eugster's school, Weedon's school and ourselves. Contributions from these three laboratories, including some work on geometrical isomerism, will now be discussed. The main approaches used for studies on absolute configuration are:

A. X-ray crystallography of (a) intact carotenoids, (b) oxidative degradation products.

B. Total and partial synthesis of chiral model carotenoids for ORD or CD comparison.

C. Correlations based on (a) ORD, (b) CD, (c) ¹H NMR, of suitable derivatives (i) with intact C-skeleton, (ii) degradation products.

D. Horeau analysis of secondary alcohols

Successful X-ray analysis of any chiral, intact carotenoid has not been reported. However, the crystal structure of capsanthin bis (*p*-bromobenzoate) has been

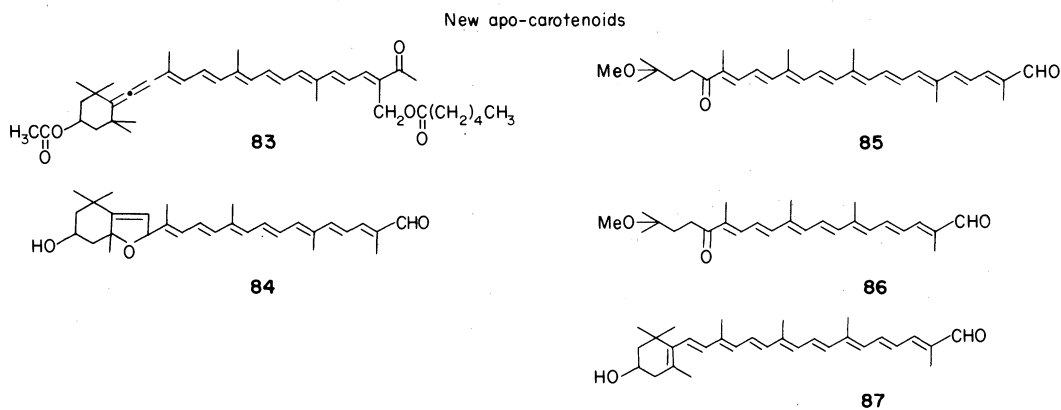
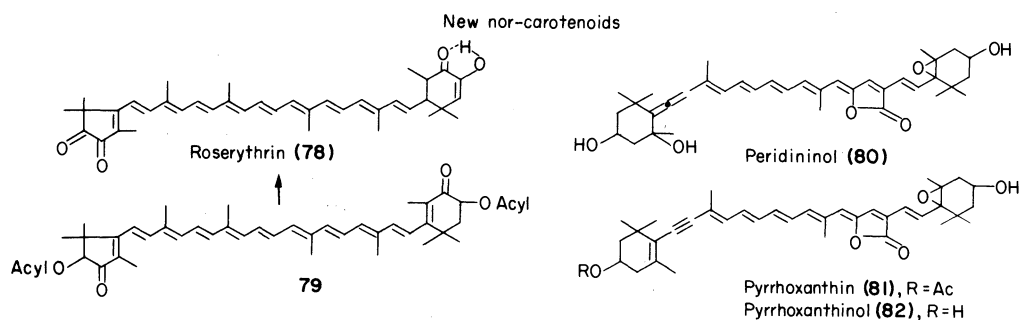
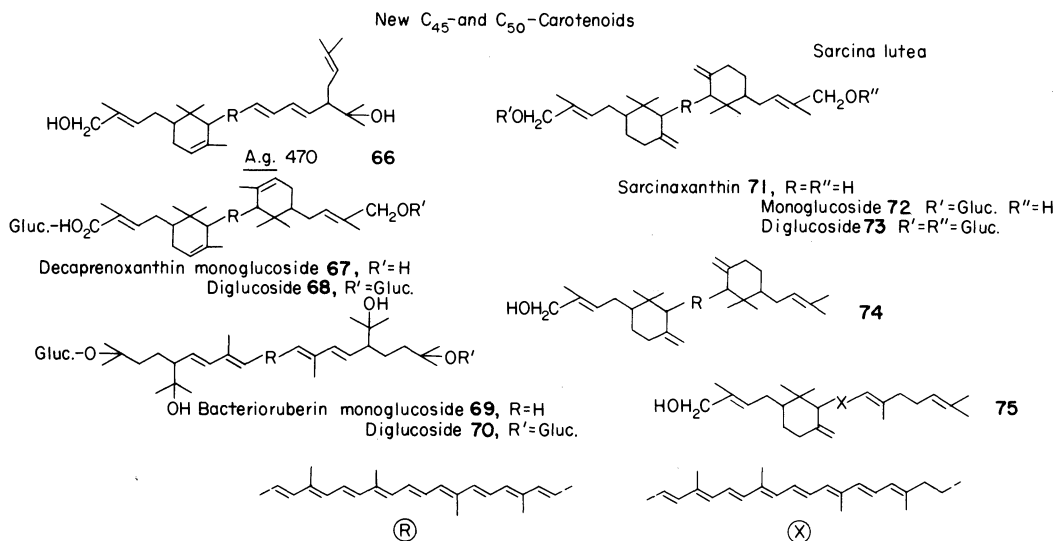
published recently^{121b} in support of the previous configurational assignment. The X-ray structure of the achiral crocetinindiol has also been reported in this period.⁶⁴

Work by Eugster's group (see Scheme 12) has mainly been based on approach Cbi,ii.

Details of the previously reported configurational assignment of α -carotene and ϵ -carotene have now been published.²⁶

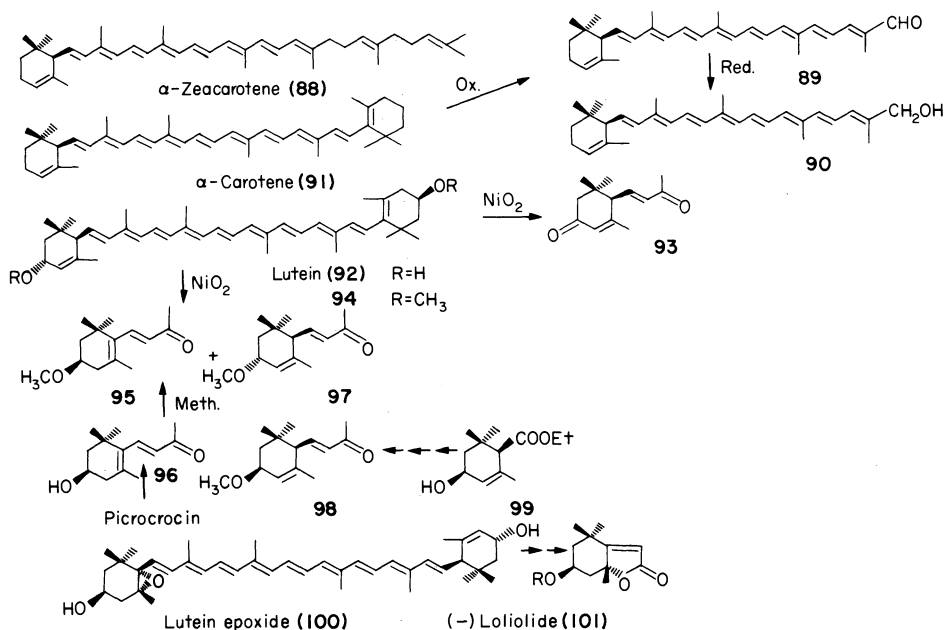
The 6*R*-chirality of α -zeacarotene (88) followed from identical CD-properties with apo-8- α -carotenol (90) with the same chromophore, prepared by Meerwein-Ponndorf reduction of natural apo-8- α -carotenol (89). Since apo-8- α -carotenol (89) had previously been prepared by oxidative degradation of α -carotene (91), the same chirality was concluded for these four compounds.²⁸

The revision of the configurational assignment of lutein⁵³



was based on a major project.^{30,31,32} The configuration of lutein (**92**) at C-6 followed from NiO₂-oxidation to (6-*R*)-3-oxo- α -ionone (**93**) and CD-comparison with the enantiomeric (6-*S*)-3-oxo- α -ionone, prepared by *t*-butylchromate oxidation of (6-*S*)- α -ionone. Photooxidation or NiO₂-oxidation of lutein dimethyl ether (**94**) provided (3-*R*)-3-methoxy- β -ionone (**95**), also obtained by partial synthesis from picrocrocin of known chirality²⁷ via **96**. (3*S*)-3-methoxy- α -ionone (**97**) was also obtained by NiO₂-oxidation of the dimethyl ether **93**. Configurational assignment followed from CD-comparison with its C-3

epimer **98**, prepared by multistep synthesis from the 3,5-*cis* hydroxy ester **99**, and use of Mill's⁸⁹ rule. ¹H NMR analysis of the diastereomeric methyl ethers **97** and **98** provided additional support. Independent evidence for structure **92** for lutein was obtained in Trondheim by base-isomerization⁴ to optically inactive meso zeaxanthin.⁶ In this context the evidence by others⁴⁴ in favour of calthaxanthin being the C-3' epimer of lutein (**92**) is interesting, but insufficient. Isomerization to 3*R*,3'*R*-zeaxanthin (**107**) is required. It is pointed out that the C-3' center of lutein (**92**) does not contribute to the CD since lutein (**92**) in acidic



methanol gives a monomethyl ether with unchanged CD, although configurational changes at C-3' must have occurred.⁶⁰

Natural lutein epoxide (**100**) after conversion to the two diastereomeric C-8 furanoxides and protection of the hydroxy groups by acetylation, gave by NiO_2 -oxidation (-)-loliolide (**101**) of known configuration, thus proving the *trans* stereochemistry of the hydroxy and epoxy functions in lutein epoxide (**100**).⁴¹

The same 3-hydroxy-epoxy end group is encountered in a series of other carotenoids.²¹ The configuration at C-3 rested on direct correlation whereas that at C-5,6 was based on the preferred *cis*-epoxidation of cyclohex-3-enols and their acetates. However, additional evidence has now been presented by Weedon's school based on ^1H NMR data of the furanoxides.⁵²

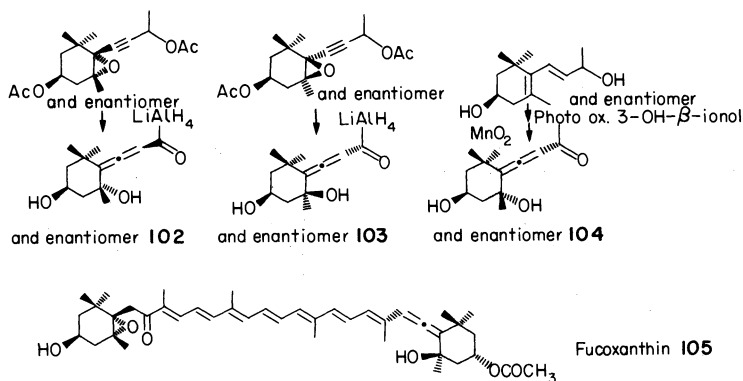
By reactions that preserve the stereochemistry at C-3 and C-5, Weedon and co-workers⁶⁵ have synthesized the racemic, allenic ketones **102**, **103** and **104**, Scheme 13. The two former were prepared by LiAlH_4 -treatment of the corresponding, racemic acetylenic *trans* and *cis* epoxides, whereas **104** was obtained via photosensitized oxidation of racemic 3-hydroxy- β -ionol. ^1H NMR features serving to

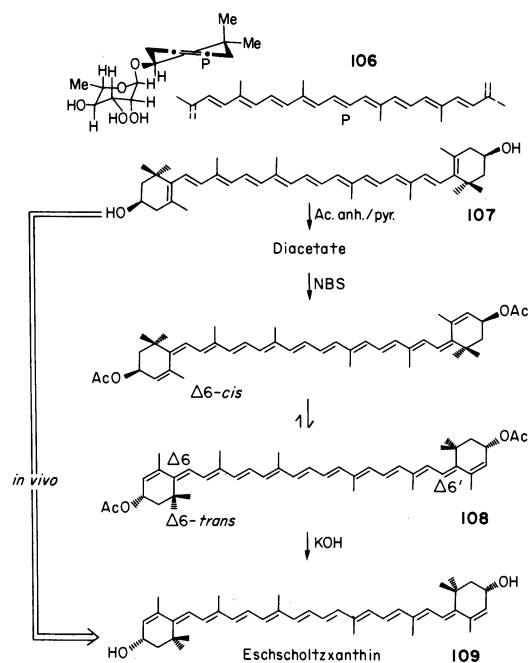
distinguish the three racemates **102**, **103** and **104** were presented, and **102** was found identical (except chiroptical properties) with the allenic ketone *ex* fucoxanthin (**105**). This work confirms previous configurational assignments of fucoxanthin (**105**), neoxanthin and zeaxanthin.

Two other contributions from Weedon's laboratory deal with geometrical isomerism. A short communication⁷⁷ describes the synthesis by stereochemically controlled routes of triene models relevant to the stereochemistry of phytoene. From ^1H NMR data it is concluded that phytoene from *Flavobacterium dehydrogenus* is all-*trans*. Another communication²³ characterizes *cis* isomers of fucoxanthin (**105**), claiming rotation of the allenic bond on iodine catalyzed stereomutation.

In the following will be discussed some work carried out in Trondheim on the absolute configuration of carotenoids using approach B, Cbi and D, avoiding sample requiring degradation to smaller molecules.

Starting with zeaxanthin-related carotenoids, a recently isolated zeaxanthin dirhamnoside of bacterial origin⁹⁹ was shown (as hexaacetate) to have the same CD-spectrum as zeaxanthin,²⁴ establishing 3*R*,3'*R*-configuration also for the rhamnoside. α -L-assignment and 1C conformation





Scheme 14.

(106, Scheme 14) is based on ¹H NMR data^{61,62} by direct comparison with spectra of the α -L and β -L triacetyl methylrhamsosides.⁵⁸

Natural zeaxanthin (107), after protection of the hydroxy groups by acetylation, gave on NBS-dehydrogenation eschscholtzξανthin diacetate (108), subsequently hydrolyzed to eschscholtzξανthin (109). Natural (*ex* Californian poppies) and semisynthetic eschscholtzξανthin exhibited characteristic and identical CD spectra, proving the same chirality for zeaxanthin (107) and eschscholtzξανthin (109),⁵ consistent with the presumed biosynthesis of eschscholtzξανthin from zeaxanthin.¹²⁵ Eschscholtzξανthin (109) is $\Delta 6$ -*trans*⁵ judged by ¹H NMR analysis and model studies of related $\Delta 6$ -*trans* and $\Delta 6$ -*cis* apo-carotenals studied by Englert using nuclear Overhauser experiments.⁴⁹

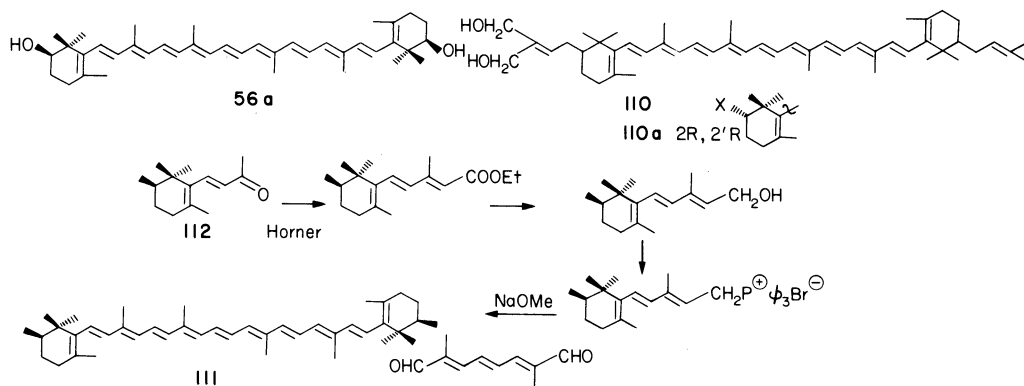
From the green algae *Trentepohlia iolithus* we had isolated the first carotenoids with 2-hydroxylated β -ring, 54, 55 and 56, Scheme 8.^{79,97} 2*R*,(2'*R*)-configuration was suggested from CD considerations,³ discussed in the previous carotenoid symposium.⁹⁸ This assignment was subsequently proved in collaboration with Buchecker and

Eugster,²⁹ using the modified Horeau method.²⁵ The 6-*R* assignment of β , ϵ -caroten-2-ol (55) was also confirmed by oxidative degradation to (+)-(6-*R*)- α -ionone.²⁹

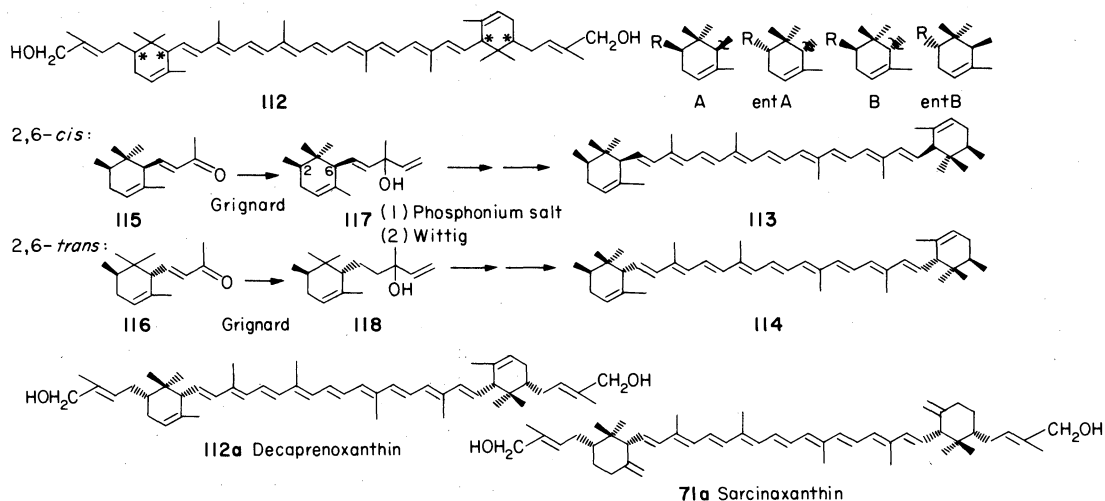
It should be mentioned that the 5,6-epoxides of 54 and 55 occur as minor carotenoids (57 and 58, Scheme 4),⁹⁶ and evidence for these carotenoids being *cis* epoxides (relative to the 2-hydroxy group) has been presented by partial synthesis from 54 and 55 of known configuration. Their chiroptical properties are not yet known.

The CD spectrum of the bacterial C₅₀-carotenoid *C.p.* 450 (110, Scheme 15) is very similar in shape, but opposite in sign to that of the 2,2'-diol 56a with the same chromophore. Since the nature of the substituent in a 4-substituted cyclohexene according to Mills' rule⁸⁹ should be irrelevant, the chiroptical properties support opposite stereochemistry in 2-position for these carotenoids, Scheme 15. This inference was checked by total synthesis of (2*R*,2'*R*)-2,2'-dimethyl- β , β -carotene (111) from *R*- β -irone (112) by the route outlined in Scheme 15.¹³ The CD-spectrum of 111 proved to be very similar to that of (2*R*,2'*R*)- β , β -carotene-2,2'-diol (56a), proving the applicability of Mill's rule to these carotenoid systems. Since the CD-spectrum of *C.p.* 450 is virtually opposite to that of the two model compounds 111 and 56a, the opposite configuration (110a) for *C.p.* 450 was concluded.¹³

Decaprenoxanthin (112, Scheme 16) with ϵ -rings and two chiral centres in each ring, is representative of another series of C₅₀-carotenoids. Since decaprenoxanthin is optically active²⁴ it is not a meso compound. From biosynthetic and ¹H NMR considerations the chirality of each end group is likely to be the same. Four alternatives = two enantiomeric pairs for this end group exist. In principle CD spectra of two model carotenoids with end groups A and B should therefore allow a differentiation between these four possibilities. Two irone-type carotenoid models of type A,A (113) and B,B (114) have been synthesized from the respective α -irones 115 and 116 via 2,6-*cis*-vinyl- α -ironol (117) and 2,6-*trans*-vinyl- α -ironol (118),^{6b} Scheme 16. Carotenoid numbering is used here also for the irone derivatives. The appropriate irones were obtained by base-catalyzed isomerization of natural irones.¹⁰⁷ The similarity of the CD-spectra of the 2,6-*trans* model 114 and that of decaprenoxanthin (112) is striking and could be taken to support the same (2*S*,6*R*) configuration for decaprenoxanthin. However, the ¹H NMR signals of the *gem.* dimethyl groups of these synthetic models clearly demonstrated a larger shielding of one of the *gem.* dimethyl groups in the 2,6-*cis* than the 2,6-*trans* derivatives. The difference in chemical shift between the two *gem.* dimethyl signals is *ca.* 0.16 ppm in the 2,6-*cis* series (115, 113, 117) vs



Scheme 15.



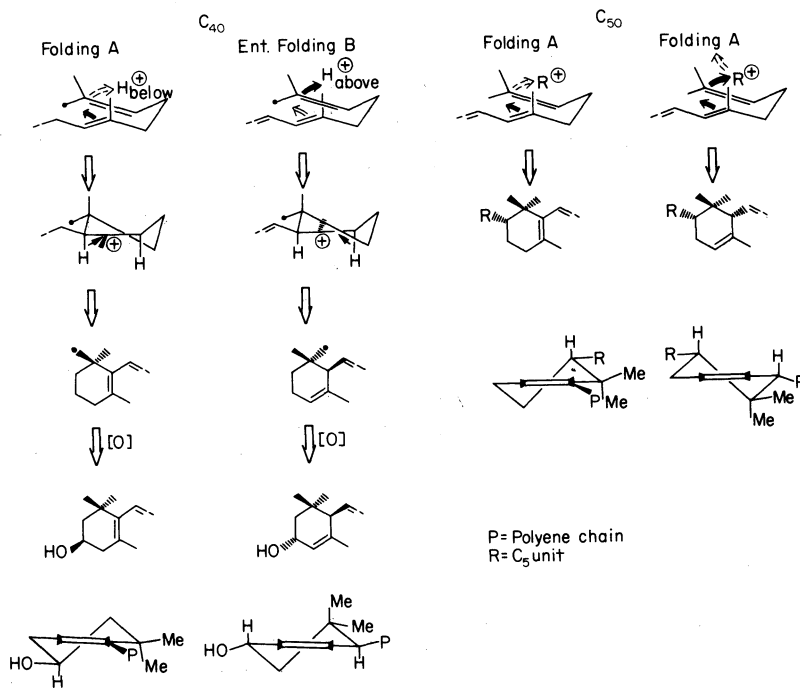
Scheme 16.

ca. 0.04 ppm in the 2,6-*trans* series (116, 114, 118). The situation for decaprenoxanthin clearly favours 2,6-*cis*. Since it has previously been observed for α -ionone/ α -irones that the CD is dictated nearly exclusively by the C-6 center¹⁰⁷ we conclude that decaprenoxanthin has configuration 112a (2*R*,6*R*,2'*R*,6'*R*),^{13b} the CD spectrum defining the chirality at C-6,6' and the ¹H NMR spectrum the relative configuration 2,6(2',6')*cis*. Direct proof of the chirality at C-2,2' was sought by base-catalyzed isomerization^{4,6} to the β -analogue without success.^{13b}

The chirality of decaprenoxanthin (112a) is biosynthetically interesting, since all C₄₀-carotenoids with ϵ -rings have the opposite configuration at C-6. According to work by Bu'lock *et al.*⁴⁰ on trisporic acid, enantiomeric foldings result in cyclization to β - and ϵ -end groups. Subsequent equatorial hydroxylation is consistent with the

stereochemistry of the zeaxanthin and lutein end groups, Scheme 17. In the C₅₀-series isopentenylation could precede or initiate cyclization (no cyclic C₄₀-carotenoids are yet found in organisms producing C₅₀-carotenoids). Folding A would give the observed stereochemistry for the C.*p.* 450 end group and the same folding is required to give the decaprenoxanthin end group. In the ϵ -series (lutein (92) and decaprenoxanthin (112a)) Nature appears to have chosen configurations stabilized by equatorial hydroxyl or alkyl substitution. However, Ohloff *et al.*¹⁰¹ have assumed that in order to account for the high $\Delta\epsilon$ values of ϵ -rings in ionone/irone systems the polyene chain occupies the quasixial position, thus making these hydroxyl and alkyl substituents axial.

The CD spectrum of sarcinoxanthin (71) with γ -rings is remarkably similar to that of decaprenoxanthin (112a)²⁴



Scheme 17.

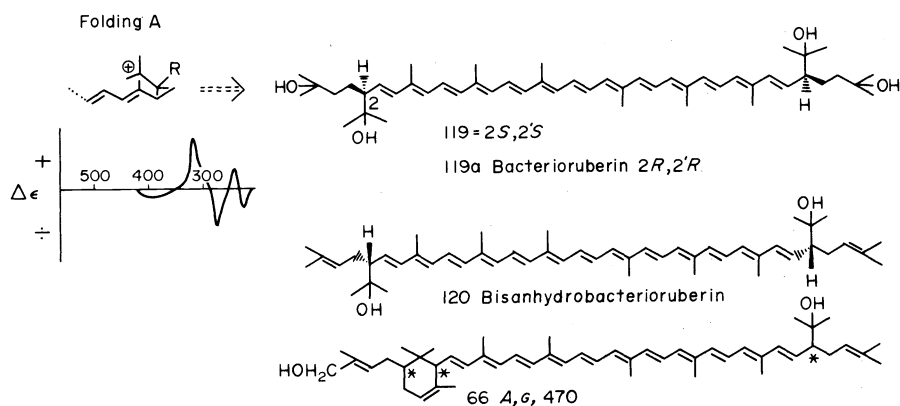
and opposite to that of a C_{42} γ -irone type carotenoid model¹² with opposite configuration at C-6 (6').¹² From biosynthetic and CD-considerations sarcinaxanthin (71a) and its glucosides are 6*R*,6'*R* and on biogenetic grounds and from ¹H NMR data of γ -irone type carotenoid models¹² 2,6 *cis* configuration as in decaprenoxanthin (112a) is favoured.⁶² Scheme 16.

Provided isopentenylolation preceded cyclization aliphatic C_{50} -carotenoids like bacterioruberin would be expected to have 2*S*,2'*S*-configuration (119, Scheme 18). However, recent total synthesis of the C_{50} -hydrocarbon tridecaene desoxybacterioruberin of the same configuration as 119, has revealed that bacterioruberin has the opposite 2*R*,2'*R*-configuration (119a).^{†73} Biogenetically the results suggest that isopentenylolation/cyclization and isopentenylolation/hydroxylation are concerted processes.

Bisanhydrobacterioruberin (120) is known from its chiroptical properties to have the same configuration as bacterioruberin (119a). The monocyclic representative 66 occurring together with decaprenoxanthin (112a) and bac-

conformation like zeaxanthin (107). The tetrol mixture and zeaxanthin (107) exhibited nearly identical CD. Assuming that the sign of the CD was determined solely by the helicity of the preferred half-chair conformation, this was taken to prove the same chirality at C-3 for the tetrol (and hence astaxanthin) and zeaxanthin (107). Astaxanthin *ex* spider mite, where astaxanthin is formed from β -carotene,¹²² has the same configuration judged by CD spectra.¹²³

By the same line of reasoning we have subsequently examined the chirality of monoacetylenic and diacetylenic asterinic acid. Biosynthetically *in vivo* formation from astaxanthin (121, Scheme 20) is predicted and supported by the present results.¹⁰⁶ Monoacetylenic asterinic acid (122) was converted to the corresponding tetrol (123) with CD corresponding closely to that of diatoxanthin (124) of known configuration.²¹ Similar transformation of the diacetylenic analogue (125) to the tetrol 126 and CD correlation with alloxanthin (127)²¹ support 3*S*,3'*S*-configuration for 125.



Scheme 18.

terioruberin (119), would be expected to be half 112a + half 119. In this case, however, the additivity of the CD increments from each end group is not convincing.¹⁶ In general we have observed that the additivity hypothesis is not valid if the chromophore between two chiral end groups is changed.

Leaving the C_{50} -carotenoids at this point we shall turn to the chirality of astaxanthin (121), Scheme 19, now solved.⁷ The result throws doubt on the postulated biosynthesis⁶⁸ of astaxanthin (121) from lutein (92), since an epimerization at C-3' would be required and was not implied in the route suggested.⁶⁸ Moreover, the bisdianion structure⁸⁵ for the protein complex (121b) of astaxanthin from lobster eggs cannot be correct, since mere extraction with solvent should not create chirality.

The chirality of astaxanthin was established by a conformational analysis of the tetrol obtained by $LiAlH_4$ -reduction. Assuming 3*S*,3'*S*-configuration for astaxanthin (121) the tetrol presumably represented a mixture of diastereomers with *cis* diol and *trans* diol end groups, Scheme 18. Both were found to prefer the M-helical⁷⁴

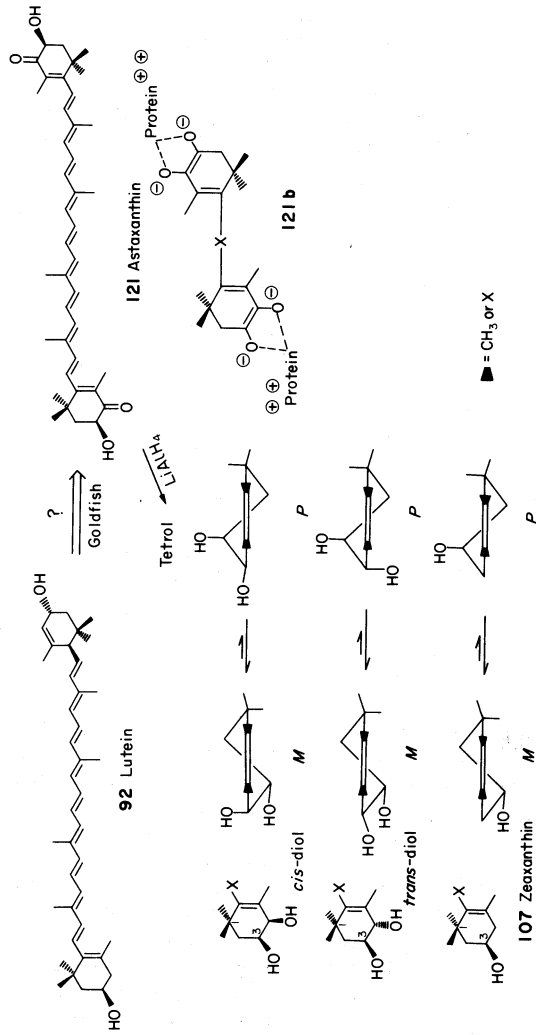
Turning now to a consideration of chiral aliphatic end groups in the C_{40} -series the absolute configuration of aleurixanthin (128, Scheme 21) has been established by the modified Horeau method.²⁵ α -Glycol end groups at present in plectanixanthin (129), 2'-hydroxy-plectanixanthin (130)¹¹⁴ and 2'-hydroxy-flexixanthin (131)² exhibit very small Cotton effects.^{35,38,103} Judged from Horeau analysis plectanixanthin (129) appears to be largely racemic.³⁵ However, 129 exhibits a weak CD, stronger in the natural diester. Interesting enough the CD is exactly opposite to that of phlei-xanthophyll (132) in which the tertiary hydroxy group is glucosidically bound.³⁵ Whatever the final results turn out to be Nature may offer some stereochemical variation in this type of end group.

Regarding trihydroxycyclohexyl end groups with three chiral centres evidence is obtained for the absolute configuration of heteroxanthin (133), and for diadinoxanthin (134) by the correlations indicated in Scheme 22.³⁴ Again the CD-contribution of this type of end groups is very small.

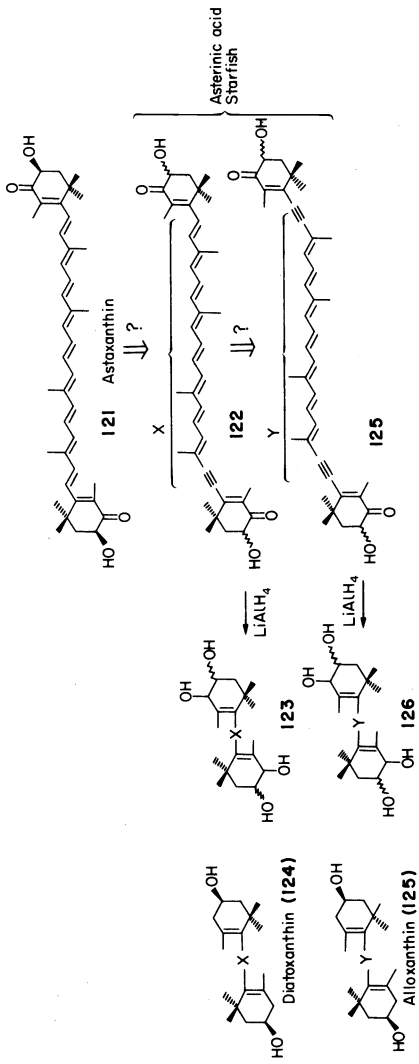
Finally I would like to report the influence of some modifications in the polyene chain on carotenoid CD spectra. According to reports from Weedon's school 9-*cis* neoxanthin and various *cis* isomers of fucoxanthin have CD spectra of opposite sign relative to their *trans* isom-

[†]See more recent proof of 2*S*,2'*S*-configuration.⁷⁴

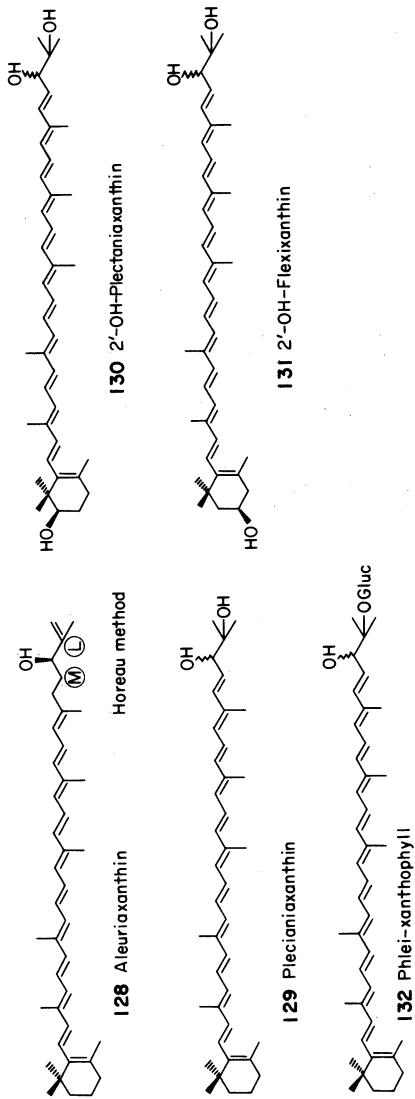
[‡]It is pointed out that different definitions of helicity are in use.^{7,79,30}



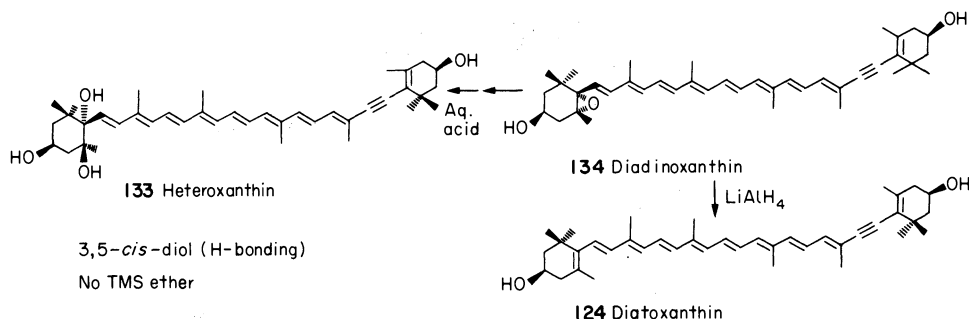
Scheme 19.



Scheme 20.



Scheme 21.



Scheme 22.

ers.^{21,23} We have prepared monoisomers of zeaxanthin (107), lutein (92) and diatoxanthin (124).⁶⁰ Two conclusions may be drawn

(a) For lutein the sign of the Cotton effect is reversed in the two monoisomers for all bands except the 220 nm one at lowest wavelength. For the two monoisomers of zeaxanthin and one monoisomer of diatoxanthin all bands are reversed relative to the *trans* isomer.


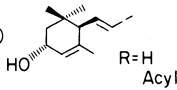
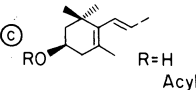
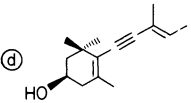
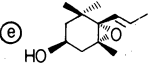
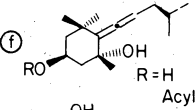
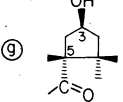
(b) The CD band in the *cis*-peak region is enhanced in the mono-*cis* isomers; most for the *cis* isomers with near-central *cis* double bonds.

Caution must therefore be shown in interpretation of CD spectra of carotenoids that readily undergo *cis*-isomerization such as acetylenic carotenoids^{124,69,42} and in-chain substituted carotenoids.¹ Our work suggesting

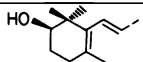
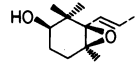
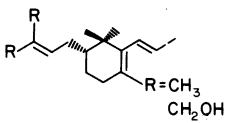
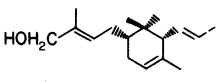
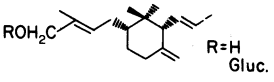
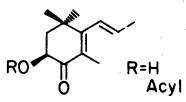
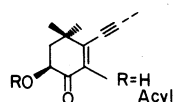
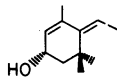
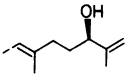
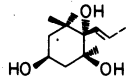
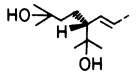
that cross-conjugated carotenals of the rhodopinal type have the double bond adjacent to the aldehyde group in *cis*-configuration¹ has recently been confirmed by SCF MOCI analysis of the low-temperature spectrum, supporting 13-*cis*, 12 *s-trans* assignment with the double bond twisted by a dihedral angle of *ca.* 20°. Corresponding allylic alcohols also show a preference for *cis*-configuration.¹ Loroaxanthin (125) according to ¹H NMR data is in solution also a not readily separable *cis-trans* mixture, not permitting CD comparison with lutein (92).⁸ Attempts to convert loroaxanthin (125) to lutein (92) have failed⁸ and oxidative degradation is desired.

Fucoaxanthin and 19'-hexanoyloxy-fucoaxanthin (17) exhibit very weak CD spectra, and oxidative degradation of 17⁶³ and of peridinin⁷⁴ is being pursued for configura-

Chiral carotenoids (38) listed in Islers monograph (1971)
Work by Karrer's school and Weedon's school

End group	Established presence in No. carotenoids	Key information
(a) 	6	Total synt. from (+)- α -ionone
(b) 	4	As revised by Eugster's school (discussed in this paper)
(c) 	11	Conversion of fucoxanthin (e,f) zeaxanthin (c,c)
(d) 	3	Hydrogenation to perhydro c
(e) 	6	(1) LiAlH ₄ -red. to c (C-3) (2) Partial synt. from c (C-5,6)
(f) 	4	ZnMnO ₄ ox. \rightarrow allenic ketone (X-ray)
(g) 	4	(1) Ozonolysis to camphoronic acid (C-5) (2) IR H-bonding C ₄₀ -derivatives (C-3,5) (3) Synthesis of model carotenoids ¹ H NMR

Scheme 23.

New chiral carotenoid end-groups (1970-75)			
	End group	Established presence No. carotenoids	Key information
(h)		4	(1) Mills rule: CD (2) Horeau analysis
(i)		2	Partial synt. from <i>h</i>
(j)		1	Total synt. C ₄₂ -model CD, ¹ H NMR
(k)		1	Total synt. C ₄₂ -models CD, ¹ H NMR
(l)		3	Total synt. C ₄₂ model CD, ¹ H NMR
(m)		4	CD corresponding diol
(n)		4	CD corresponding diol
(o)		1	Partial synt. from Zeax. (<i>c, c</i>) ¹ H NMR
(p)		1	Horeau analysis
(q)		1	Hydrogen bonding, silylation CD Partial synt. from <i>e</i>
(r)		2	Synthesis of C ₅₀ -model CD

Scheme 24.

tional assignments. So far ozonolysis of 17 has provided the corresponding allenic ketone, readily obtained from fucoxanthin, *cfr.* 112, with CD properties (together with ¹H NMR data of 17) demonstrating the same chirality for the allenic end group. From ¹H NMR data the epoxy end group has the same relative configuration as in fucoxanthin.

In Scheme 24 is summarized the eleven (*h-r*) chiral carotenoid end groups established since 1970, the number of carotenoids in which these are shown to be present and the key information on which the conclusions are based. These end groups represent an extension of the seven

(*a-g*) chiral end groups previously known (Scheme 22, including the revised lutein end group *b*).

Chiral carotenoid end groups not yet solved comprise the γ -end groups of C₄₀-carotenoids (biosynthetic considerations would predict 6-*R*-chirality as in α -carotene and opposite to that of sarcinaxanthin (71)), the cyclopentenol end group of actinioerythrin, aliphatic 1,2-glycols and the azafrin end group.†

In conclusion, after an explosion of new carotenoid structures after introduction of ¹H NMR and particularly mass spectrometry in the sixties, the absolute configuration is being extensively studied in the seventies. Because of the scarcity of most carotenoids the necessity of finding sample-saving methods is obvious with X-ray studies

†See recent configurational assignment by Eschenmoser and Eugster. *Proc. 4th Carot. Symp.*

confined to some key derivatives. We are in a period where particularly the scope and limitation of chiroptical methods in the carotenoid field is being investigated. Carotenoid ORD and CD spectra are not yet well understood,^{21,7} but factors governing these spectra may become more evident as more data are compiled. Knowledge of the absolute configuration of carotenoids will no doubt be very useful for biosynthetic considerations.

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