SOME RECENT ADVANCES IN THE SYNTHESIS OF CAROTENOIDS

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ABSTRACT

A route to unsymmetrical polyene dialdehydes is described. The utility of these intermediates is illustrated by a synthesis of okenone.

The stereochemistry assigned to methyl natural bixin has been confirmed by preparation of the *cis*-4 isomer. Support has been obtained for the *cis*-6 formulation of natural *cis*-crocetin.

Oxidation of astacene with manganese dioxide yields violaxanthin.

The synthesis of stereoisomers of alloxanthin and crocoxanthin has confirmed the structures of these acetylenic carotenoids, and identified the principal *cis* isomers formed on stereomutation.

The synthesis has been achieved of racemic forms of the allenic ketone from grasshoppers, and of an allenic degradation product from fucoxanthin.

INTRODUCTION

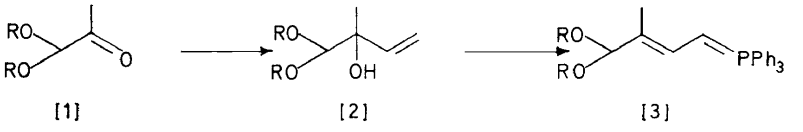
In this paper I propose to review some recent developments in the use of synthesis for studying the structures of carotenoids. I shall cover partial, as well as total synthesis, and, at times, the not unrelated technique of partial degradation. I shall also have to outline briefly the scope of some of the newer classes of carotenoids so as to indicate the relevance of the synthetic studies themselves.

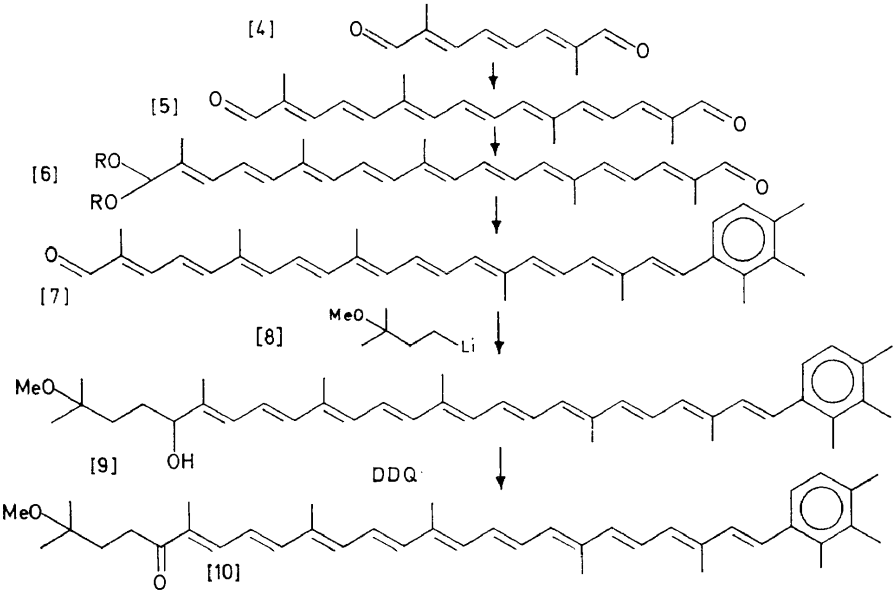
POLYENE DIALDEHYDES

The value of symmetrical polyene dialdehydes, in particular of the C_{10}- and C_{20}-dials [4] and [5] and their central acetylene analogues, as intermediates for the synthesis of carotenoids, is well known. The carbon skeleton of many symmetrical carotenoids can be built up quite simply by reacting one of these dialdehydes with an excess of the appropriate Wittig reagent. Fortunately, as was predicted on electronic grounds, the nucleophilic attack of the first aldehyde group by the Wittig reagent is appreciably faster than that of the second. It is therefore possible to carry out a selective reaction at one end of the dialdehyde with a Wittig reagent, and then react the remaining aldehyde group with a different reagent. In this way many unsymmetrical carotenoids have also been prepared[1].

The most convenient Wittig reagents for the introduction of the two end groups of some unsymmetrical carotenoids may, however, be of different size. We have therefore explored the possibility of preparing and using the unsymmetrical polyene dialdehydes. The Wittig reagent [3] was first made by Makin[2] from 1-ethoxy-2-methylbuta-1,3-diene, but can be obtained

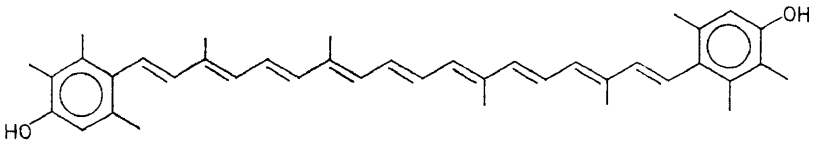
more conveniently by reacting the acetal [1][3] with vinylmagnesium bromide and then converting the alcohol [2] into [3] in the usual way. This 'C_5-reagent' can be reacted at both ends of a symmetrical dialdehyde to give, after hydrolysis of the bis-acetal formed initially, the 'bis-isoprenologue'. In this manner the C_{10}-dials (e.g. [4]) may be converted into the C_{20}-dials (e.g. [5]) and the latter into the C_{30}-dials. Alternatively, selective reaction may be carried out at one end of the molecule leading, after hydrolysis, to the unsymmetrical C_{15}-, and C_{25}-dials. The intermediate acetals (e.g. [6]) can readily be isolated, and therefore one carotenoid end group can be introduced by a suitable Wittig reaction before the other aldehyde group is liberated for reaction with a second Wittig or other





reagent of different size. These possibilities have been deomonstrated by a synthesis of okenone [10][3]. Reaction of the aldehyde [6] with the appropriate benzylic Wittig reagent, followed by hydrolysis of the protecting group, gave the C_{35}-aldehyde [7]. Treatment of the latter with the lithium alkyl [8] yielded okenol which on allylic oxidation with dichlorodicyanobenzoquinone (DDQ) furnished okenone [10]. Another synthesis of this compound has been reported by Aasen and Jensen[4]. These authors prepared the 4-desoxy compound from the C_{20}-dial [5] by the normal two step Wittig reaction, and then found that NBS attacks the 4-position preferentially leading to a mixture of the 3,4-dehydro-derivative and okenol [9]. Oxidation of the latter again gave okenone.

Wittig reactions with the C_{20}-dial have also been used recently by Arcamone *et al.*[5a] to confirm the novel phenolic structures [11] and [12] which they proposed for two new carotenoids from *Streptomyces mediolani*.



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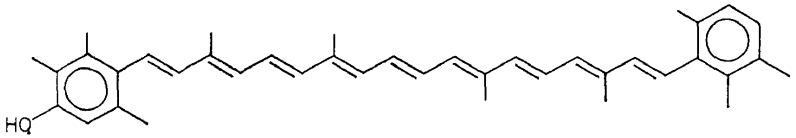
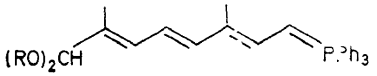


[12]

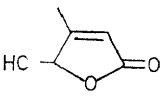
Attention must also be drawn to the elegant syntheses by Schwieter and co-workers[5] of polyene dialdehydes from the 'C_{10}-reagent' [13] and related compounds.



[13]

BIXIN AND CROCETIN

The controlled synthesis of *cis*-isomers of polyenes by reactions of the Wittig type has received attention in the last few years. Full details have been published of the preparation of *cis* and di-*cis* isomers of vitamin A acid and related compounds from the lactols [14] and [15; R = H or Me][6,7]. It is noteworthy that the di-*cis* compounds which predominate



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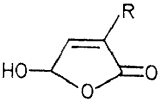
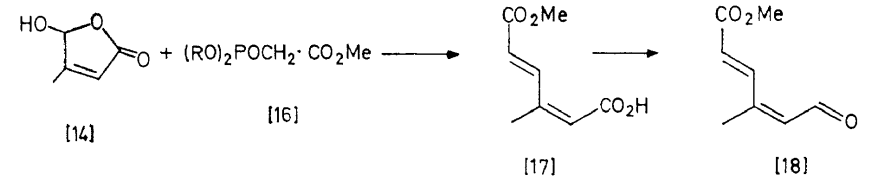
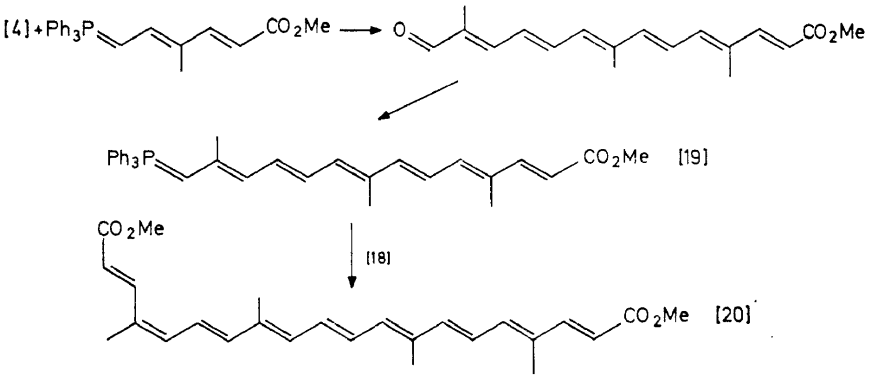


[15]

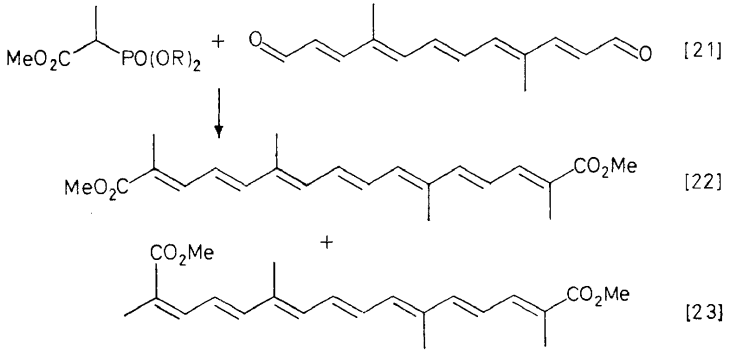
from the condensation of the lactols [14] and [15, R = Me] with many Wittig reagents possess a sterically hindered double bond.

Condensation of the lactol [14] with the phosphonate [16] gave the *cis*, *trans* half ester [17]. Reduction of its acid chloride with lithium tri-*t*-butoxyaluminohydride led to the corresponding aldehyde [18] with complete retention of stereochemistry. Reaction of the aldehyde [18] with the Wittig reagent [19], which was prepared from the C_{10}-dial [4], then yielded the *cis*-4 isomer of methylbixin [20] which proved to be identical in all respects with the methyl ester of natural bixin[8]. This synthesis confirms the stereochemistry assigned to methyl natural bixin on n.m.r. evidence[9].

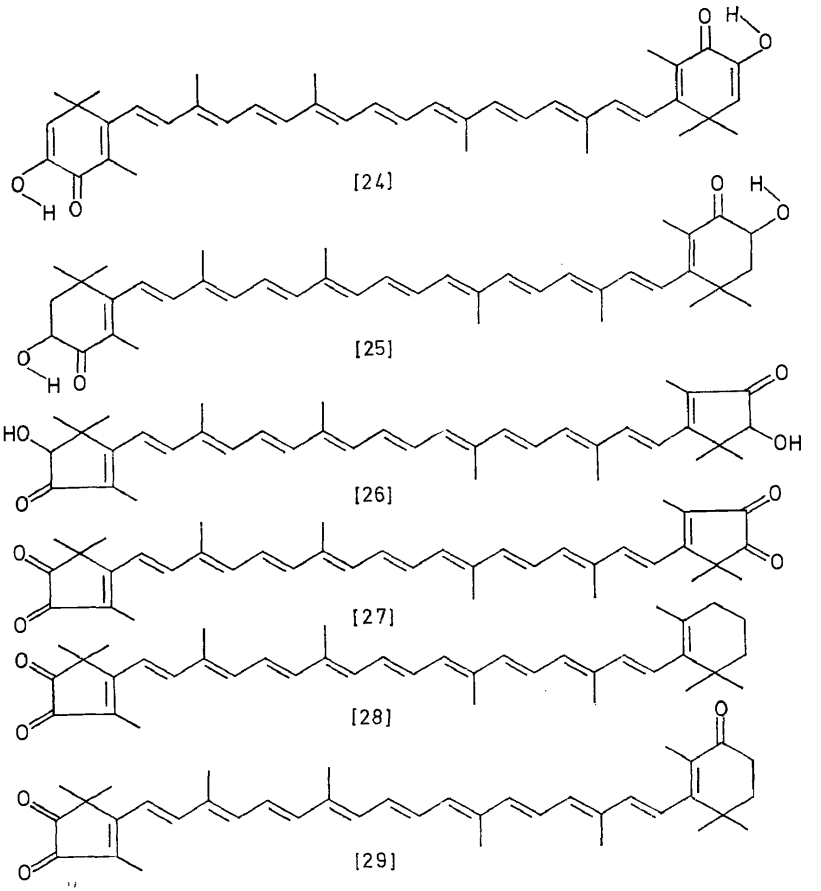




Zechmeister[10] has suggested that the unstable *cis*-isomer of crocetin, isolated as the dimethyl ester by Kuhn and Winterstein[11], has the corresponding *cis*-2 structure [23]. We found [12] that reaction of the pentaenedial [21][13] with the phosphonate derived from α-bromopropionate gave a mixture of all-*trans*- and *cis*-2 methyl crocetin [22] and [23]. The *cis*-isomer was isolated by chromatography and shown to have light absorption and i.r. properties significantly different from those reported for the natural



isomer. It also proved to be comparatively stable. From spectral evidence, natural *cis* crocetin appears to be an isomer with one, sterically unhindered, *cis* bond. Of the three conceivable structures of this type, the central-*cis*[14] and *cis*-2 have now been excluded by synthesis. It therefore seems probable that natural *cis*-crocetin has the *cis*-6 formulation favoured by Kuhn *et al.*[14]



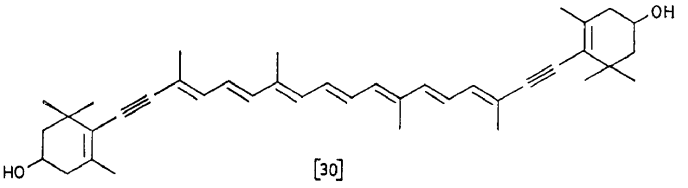
CYCLOPENTENEDIONES

At Trondheim I reported on the preparation of astacene [24] and related carotenoids. I also described how these diosphenols can be converted into compounds of the astaxanthin [25] type by reduction with lithium aluminium hydride, and careful selective oxidation of the allylic hydroxyls in the resulting products.[1] In attempting to carry out these selective oxidations with manganese dioxide or nickel dioxide we observed the formation of highly coloured by-products. These have now been identified[15] as the cyclopentenediones resulting from over-oxidation of the diosphenols by a reaction of a type that has been noted previously in the steroid field[16]. Recently Hertzberg and Liaaen-Jensen[17] concluded that actinioerythrin is a diester of the glycol [26] and that violerythrin, the blue pigment formed from it on treatment with alkali, is the corresponding tetraketone [27]. Direct comparison of authentic violerythrin with the synthetic C_{38}-tetraketone [27] isolated in *ca.* 10 per cent yield from the oxidation of astacene [24] with manganese dioxide, confirms these conclusions. We have also synthesised the C_{39}-di- and tri-ketones [28] and [29], which may well prove to be related to other natural pigments, and the 15,15′-dehydro-analogues of [27], [28], [29][18].

The substitution of a triple bond for the central double bond in this series results in an unusually large shift of λ_{max} to shorter wavelengths (*ca.* 40 mμ).

ACETYLENES

Acetylenic analogues of zeaxanthin and related pigments constitute another important group of natural carotenoids recognised since the Trondheim meeting. This new class was discovered as the result of studies on



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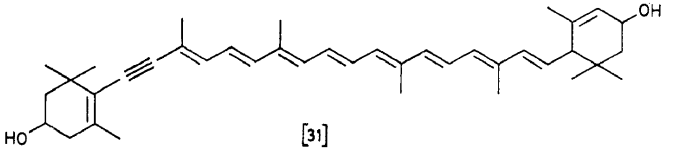

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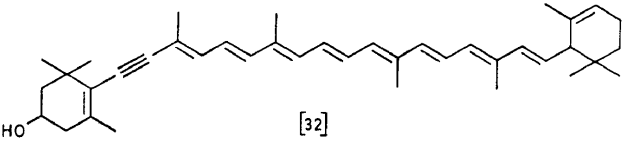

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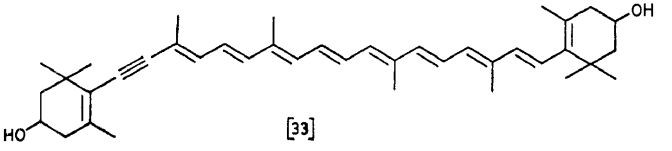

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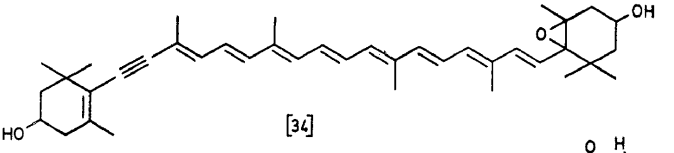

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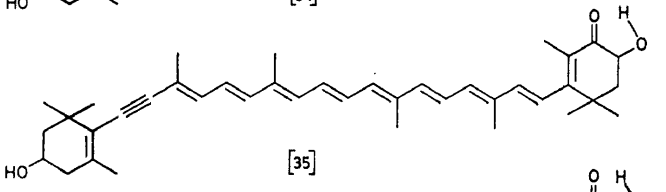

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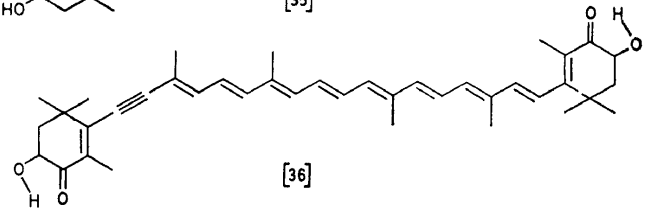
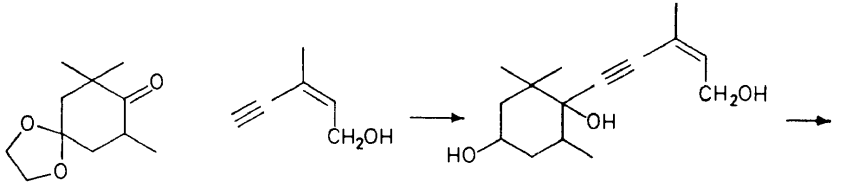


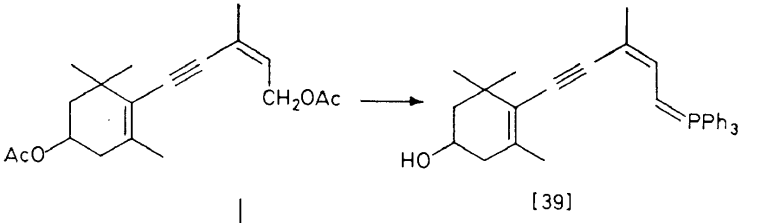
[36]

pigments from flagellates of the Cryptophyceae algae[19]. The principal carotenoid, alloxanthin, had light absorption properties and chromatographic properties very similar to those of zeaxanthin. However, the two pigments had very different n.m.r. properties; although alloxanthin was clearly a symmetrical compound, the deshielding of the methyls in the end groups seemed quite novel. Furthermore mass spectrometry revealed that the alloxanthin molecule contains four fewer hydrogen atoms than that of zeaxanthin. Careful examination of the i.r. spectrum of alloxanthin revealed weak absorption attributable to disubstituted acetylenes, and alloxanthin was therefore formulated as [30]. Subsequently it was shown[20] that two previously reported[21] natural pigments, pectenoxanthin from the giant scallop *Pecten maximus*, and cynthiaxanthin from the tunicate *Halocynthia papillosa*, are identical with alloxanthin. The latter was also isolated from the common mussel, *Mytilus edulis*[20].

Monadoxanthin and crocoxanthin, two further pigments from Crypto-



[37] [38]



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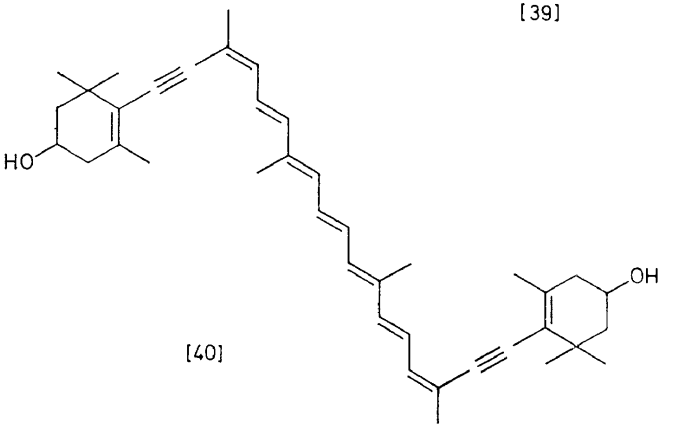


[40]

phyceae algae were identified as [31] and [32] respectively.[19] Diatoxanthin, a common pigment in diatoms and Chrysophyceae, was shown to be [33][19]. Later Strain *et al.*[22] found that diadinoxanthin, an epoxide related to diato-

xanthin which can be isomerised into the corresponding furanoid oxide, has the structure [34].

In addition to alloxanthin, the gonads of the giant scallop also contain astaxanthin [25] and a new acetylenic pigment, pectenolone [35], which has one end group identical with those in alloxanthin, and the other with those in astaxanthin[20]. A further example of an acetylenic keto-carotenoid was provided by a recent re-examination of asterinic acid from the starfish, *Asterias rubens*. This pigment, formerly regarded as identical with astaxanthin, is now known to be a mono- or di-acetylenic analogue [36 or its 7′,8′-dehydro-derivative], or possibly a mixture of the two[23].

Alloxanthin and crocoxanthin very readily undergo stereomutation. At equilibrium very little all-*trans* carotenoid remains and the principal products were formulated as *cis*-9,*cis*-9′-alloxanthin [40] and *cis*-9-crocoxanthin respectively. These assignments, and hence the structures of the natural acetylenes themselves, have been confirmed by synthesis of the optically inactive forms of the geometrical isomers. The Wittig reagent [39] was prepared from the ketone [37] and 3-methylpent-*cis*-2-en-4-ynol [38] by the method outlined in the accompanying formulae. Reaction at both ends of the C_{10}-dial [4] then gave *cis*-9,*cis*-9′-alloxanthin identical (apart from optical activity) with the stereomutation product of natural alloxanthin. Condensation of the Wittig reagent with the (C_{25}-) apo-12′-α-carotenal gave the *cis*-9 isomer of crocoxanthin which was identified with the stereomutation product of natural crocoxanthin. Various modifications of these synthetic schemes have also been examined[24].

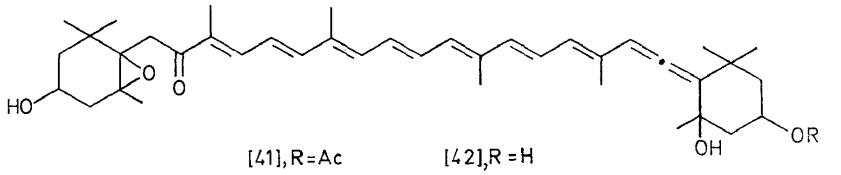
ALLENES

Finally I should like to refer to the allenic carotenoids. These complex substances present problems in synthesis which have not as yet been overcome.

The first allenic carotenoid to be discovered was fucoxanthin. This occurs in many common seaweeds, where it probably functions as an accessory pigment in photosynthesis, and is regarded as the most abundant carotenoid in nature. We were able to establish structure [41] for this compound by chemical and spectroscopic studies on fucoxanthin itself, and on a number of its derivatives[25–27]. Independent studies by A. Jensen supported this conclusion[28].

Fucoxanthin is unique among natural carotenoids in possessing an acetoxy group. Attempts to prepare the parent C_{40}- compound, fucoxanthinol [42], by alkaline or acid hydrolysis were abortive. On treatment with alkali under suitable conditions fucoxanthin is smoothly converted into isofucoxanthin [43][27,28] presumably by base attack at the C-7 methylene which is activated by the adjacent keto-group (Scheme A). Under more vigorous conditions isofucoxanthinol [44] is also produced. It is interesting to note that eggs from chickens fed on seaweed meal contain a yellow pigment in the yolks which is believed to be identical with isofucoxanthin[28,29]. The difficulties involved in the preparation of fucoxanthinol [42] were overcome by reducing fucoxanthin with lithium aluminium hydride, and selective oxidation of the allylic hydroxyl group in the resulting fucoxanthols[26,27].

Similarities between the properties of isofucoxanthinol [44] and those



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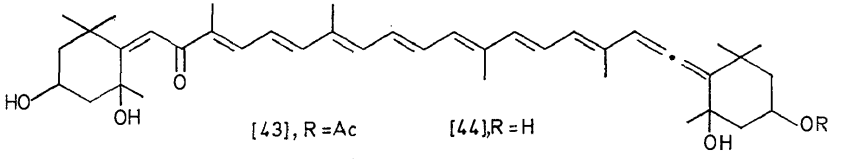

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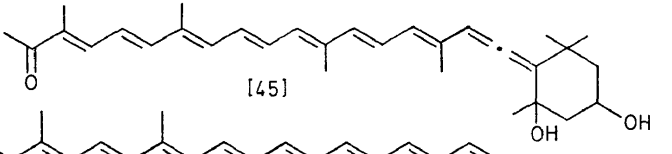

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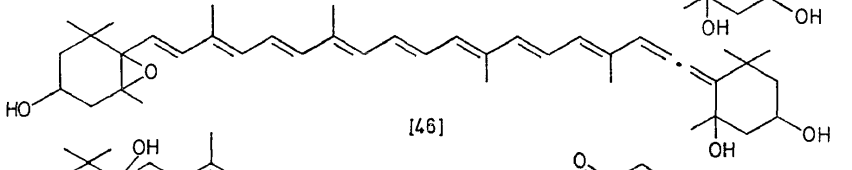

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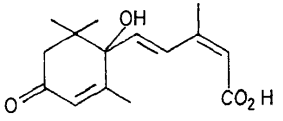

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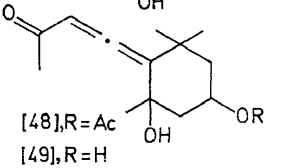
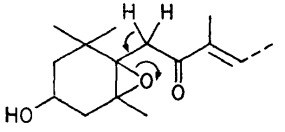


[48], R=Ac
[49], R=H



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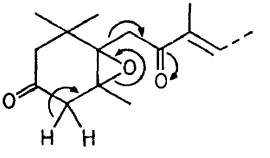

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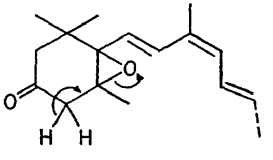


(C)

reported in 1935 by Lederer[21] for pentaxanthin prompted a reinvestigation[30] of the pigments in the sea urchin, *Paracentrotus lividus*. Three allenic pigments were obtained from the coelomic epithelium. One, present in very small amounts, was identified as fucoxanthin. The major pigment proved to be identical with our semi-synthetic fucoxanthinol [42]. The natural pigment is presumably formed in the sea urchin by absorption of fucoxanthin from the diet, and subsequent enzymatic hydrolysis of the acetate group. The third allenic pigment, paracentrone, was characterised as a novel C_{31}-carotenoid and assigned structure [45].

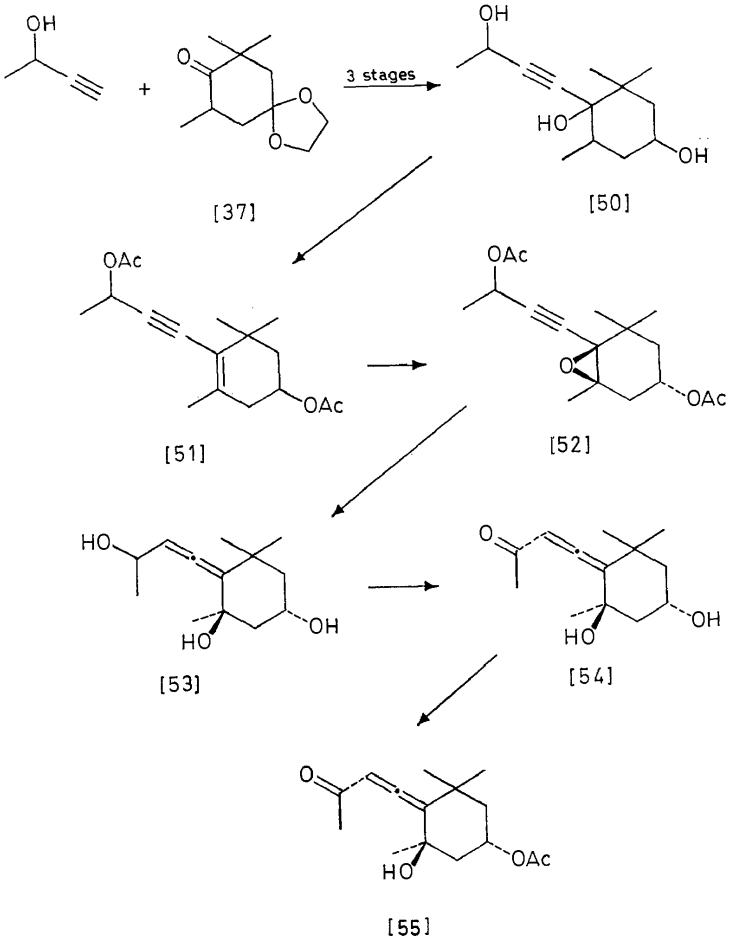
It seems likely that paracentrone is also a metabolic product of fucoxanthin in the sea urchin. It occurred to us that this transformation might involve an initial oxidation at C-3, followed by a fission of the type shown in Scheme B. We have therefore attempted to simulate this process in the laboratory. On oxidation of fucoxanthin with cyclohexanone and aluminium *tert.*-butoxide, paracentrone acetate was formed directly in *ca.* 10 per cent yield, and on subsequent hydrolysis gave paracentrone[31].

Another important example of an allenic carotenoid is provided by neoxanthin. This pigment was first isolated by Strain in 1938, and is now regarded as a constituent of all green leaves[32]. Spectroscopic and chemical studies established its structure as [46] in which one end group is identical with the allenic end of fucoxanthinol [42], and the other with the end groups of violaxanthin[33–36]. The all-*trans* form of neoxanthin occurs in nature but readily undergoes stereomutation during isolation to give the *cis*-9 isomer[34].

Recently it has been shown that neoxanthin and violaxanthin, both of which are widely distributed in plants, are converted into a plant growth inhibitor on exposure to light[37,38]. These findings may explain some of the responses of plants to blue light; they suggest, for example, a mechanism for phototropism. If the inhibitor is related to the natural growth regulator, abscisic acid [47], the conversion can be rationalised as involving the oxidation of the 3-hydroxy group in the *cis*-9 isomer of neoxanthin or violaxanthin and opening of the epoxide ring by an elimination (Scheme C) analogous to that proposed for the conversion of fucoxanthin into paracentrone, and oxidative fission of the polyene chain.

During studies on the structure of fucoxanthin, the allenic ketone [48] was obtained by permanganate oxidation of the natural carotenoid[26,27], and by ozonolysis of its benzoate.[39] Later Meinwald *et al*[41] suggested structure [49] for a crystalline ketone which they isolated from an ant repellant secretion of the large flightless grasshopper, *Romalea microptera*. It is conceivable that this ketone is formed from neoxanthin, present in the leaf diet of these insects, by an oxidative degradation *in vivo* formally analogous to that carried out *in vitro* with fucoxanthin.

The grasshopper ketone [49] is the simplest allenic terpene yet discovered. It embodies many of the unique structural features present in the allenic carotenoids, and therefore provides the obvious target for initial attempts at devising synthetic methods for introducing the allenic group and, at the same time, the correct (relative) configuration at three asymmetric centres (C-3, C-5 and the allenic group itself). Our approach to this problem is outlined below.



A Grignard reaction between but-3-yn-2-ol and the ketone [37], liberation of the protected keto-group in the product, and reduction with sodium borohydride, gave the acetylenic triol [50]. Selective acetylation of the secondary hydroxyl groups, and dehydration of the product with phosphorus oxychloride in pyridine, yielded the enyne diacetate [51]. Oxidation with monoperphthalic acid then furnished a mixture of epoxides which was separated by chromatography on silica gel. Reaction of the minor, more strongly adsorbed product, regarded as the *trans* isomer [52], with lithum aluminium hydride led to the allenic triol [53]. Selective oxidation of the latter with manganese dioxide yielded a (racemic) ketone [54] with light absorption and n.m.r. properties in good agreement with those of the natural grasshopper ketone. The major product of epoxidation was similarly converted into an epimer of [54] which exhibited different n.m.r. properties. Furthermore partial acetylation of the former product gave an acetate with chromatographic behaviour (in four solvent systems) and n.m.r. properties (in deuterochloroform and D_6-acetone) which were identical within experi-

mental error with those of the fucoxanthin degradation product [48][41]. It is therefore concluded that the synthetic compounds [54] and [55] from the minor epoxide are the racemic forms of the grasshopper ketone [49] and the fucoxanthin degradation product [48] respectively. As reported at this meeting by Dr M. B. Hursthouse, an X-ray crystallographic analysis of the *p*-bromobenzoate of the racemate [54] shows that the tertiary hydroxyl group is *trans* with respect to both other oxygen functions[42].

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