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Recent advances in the synthesis of achiral carotenoids

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Abstract - The syntheses of ß-carotene, lycopene, (3R,3'R)-zeaxanthin, canthaxanthin, (3RS,3'RS)-astaxanthin, 8'-apo-ß-caroten-8'-al and crocetindialdehyde by an aldehyde-sulfone route are discussed. The preparation of gram amounts of (9Z)-, (13Z)-, (9Z,9'Z)-, (9Z,15Z)- and (13Z,15Z)-ß-carotene and of 3-hydroxy-4-oxoretinal, 12'-apoastaxanthinal, 8'-apoastaxanthinal and gelliodesxanthin by Wittig olefination is then described.

INTRODUCTION

The search for new and better possibilities for forming carbon-carbon double bonds remains an attractive challenge in carotenoid synthesis. During recent years, the Wittig olefination has been established as the most important reaction for preparing polyenes. A major drawback of this olefination reaction, however, is the formation of triphenylphosphineoxide which, on an industrial production scale, has to be recycled by reduction to triphenylphosphine. Any type of synthesis which circumvents problems of that kind is of potential value in large scale synthesis of polyenes.

Recently, (Z)-isomers of carotenoids have received increasing attention. In view of the fact that various natural sources, e.g. carrots (ref. 1), algae (ref. 2), contain not only (all-E)-ß-carotene, but also relatively high amounts of its geometrical isomers, our aim is to make available larger amounts of these isomers by total synthesis and to investigate their physicochemical and biological properties (e.g. provitamin A activity) and metabolism.

At the Boston Carotenoid Symposium, we traced the fascinating story of astaxanthin from research to commercialization (ref. 3). The growing importance of this product in aquaculture has led us to synthesize apoastaxanthinals, to help obtain a better insight into biological and analytical aspects.

SYNTHESIS BY AN ALDEHYDE-SULFONE ROUTE

In 1973, Julia and co-workers reported a new olefination reaction that used sulfones. These were either condensed with halides followed by desulfonation with tertiary butylate (ref. 4) or condensed with carbonyl compounds and subsequently reduced with sodium amalgam (refs. 5, 6). The potential of the first procedure was demonstrated by Julia and Arnould in the synthesis of vitamin A acid ethyl ester (ethyl retinoate) (ref. 7), by reaction either of C_{15}-sulfone with C_5-bromide or of C_{15}-bromide with C_5-sulfone.

Whereas this halide-sulfone version was frequently pursued further in polyene synthesis by other groups (refs. 8-12), the carbonyl-sulfone combination was virtually abandoned, probably due to lack of stereoselectivity and unsuitability of the sodium amalgam reduction of the intermediate vinyl sulfones for technical syntheses.

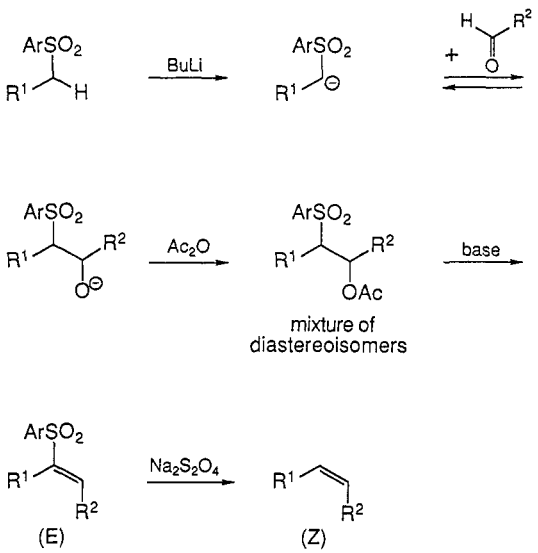
According to Julia and co-workers, alkyl α-tosyloxysulfones, under basic conditions, stereoselectively form (E)-vinylic sulfones from the erythro-isomer, whereas (Z)-vinylsulfones are formed from the threo-isomer. α-Acetoxysulfones, however, only furnish (E)-vinyl sulfones from the erythro- and threo-isomers (ref. 13). The vinyl sulfones can be reduced stereoselectively to the corresponding olefins by sodium dithionite (refs. 14, 15). It seemed attractive to apply these results from the olefin field to the synthesis of carotenoids.

In scheme 1, a general overview of our procedure is presented. The sulfones used as building blocks were prepared, whenever possible, directly from the corresponding alcohols or from halides (ref. 7). The polyene sulfones usually crystallize well and are stable over long periods under inert gas in the refrigerator.

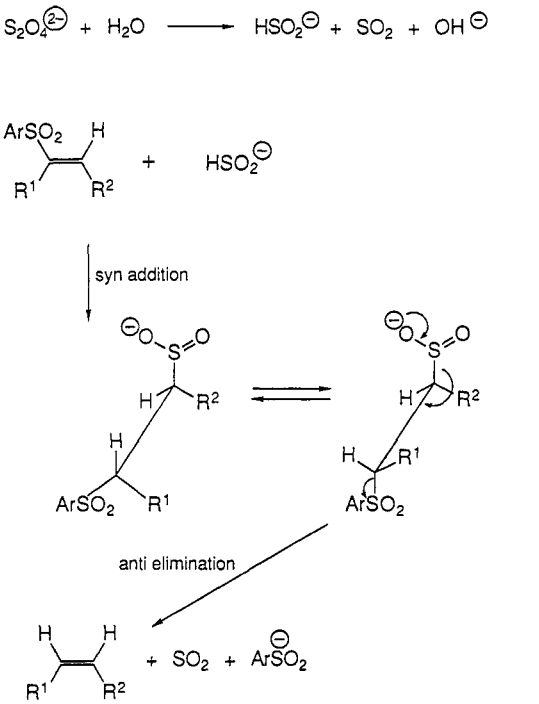
After α-deprotonation by butyllithium at -60 °C, the polyene aldehyde was added. Because our attempts to isolate the intermediate α-hydroxysulfones that were formed first failed, the equilibrium reaction was quenched with acetic anhydride to obtain a diastereoisomeric mixture of α-acetoxysulfones. Subsequent treatment with aqueous base furnished the polyene sulfones whose (all-E)-configuration could be confirmed first by X-ray crystallography and then by NMR spectroscopy. These new compounds were obtained in pure form by crystallization in yields up to 85%. These first four stages could be performed in a single reaction vessel.

The reduction with dithionites according to the literature procedure for monoolefins (ref. 14), i.e. aqueous dimethylformamide / hydrogencarbonate, aqueous ethanol / carbonate, or cyclohexane / water with phase transfer catalyst / hydrogencarbonate, furnished carotenoids in very low yield only. However, by running the reactions in aqueous tetrahydrofuran or 1,2-dimethoxyethane with 25% ammonia or organic bases, such as diethylamine, the (Z)-carotenoids were formed in yields up to 90% (ref. 16).

Scheme 1



Scheme 2

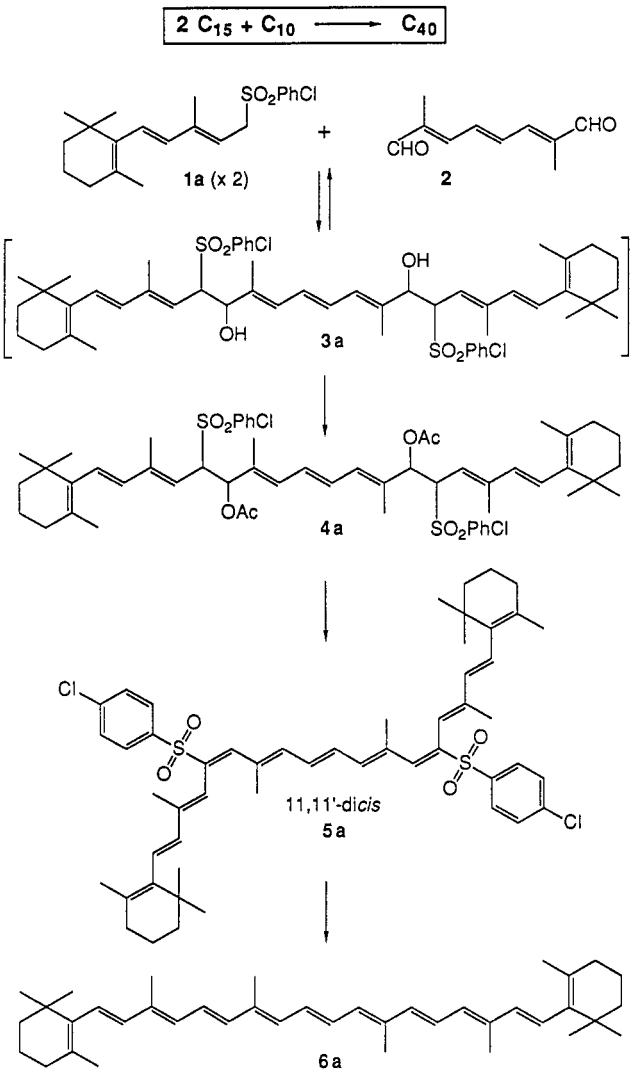


Scheme 2 depicts the mechanism of the dithionite reduction according to Julia and co-workers (ref. 15). Most probably, in a first step, a hydrogensulfinate adds in syn-orientation to the double bond. Then, an anti-elimination leads to the (Z)-olefin, thus retaining the configuration overall. Additional products are sulfur dioxide and the aryl sulfinate which may be recycled.

We have applied four different routes:

1.	2 C_{15}-sulfone + C_{10}-dialdehyde:	ß-carotene, (3R,3'R)-zeaxanthin, canthaxanthin, (3RS,3'RS)-astaxanthin
2.	C_{20}-sulfone + C_{20}-aldehyde:	ß-carotene
3.	2 C_{10}-sulfone + C_{20}-dialdehyde:	lycopene
4.	C_5-sulfone + C_{25}-aldehyde:	8'-apo-ß-caroten-8'-al
	2 C_5-sulfone + C_{10}-dialdehyde:	crocetindialdehyde

Scheme 3



The first experiments of the C_{15} + C_{10} route (scheme 3) were directed to the synthesis of ß-carotene 6a. Deprotonation of 1a by butyllithium and addition of 2 at -60 °C gave, after in situ acetylation of 3a to 4a, treatment with aqueous sodium hydroxide and crystallization, the orange (all-E)-11,11'-bis [(p-chloro-phenyl)-sulfonyl]-ß,ß-carotene (5a) in 85% yield, (m.p. 174-5 °C). An X-ray analysis of a single crystal of 5a obtained from acetonitrile/water revealed the propeller-like molecular structure and consequently the (all-E)- or 11,11'-dicis configuration (Fig. 1). This ORTEP graph gives 40% probability for the thermal ellipsoids.

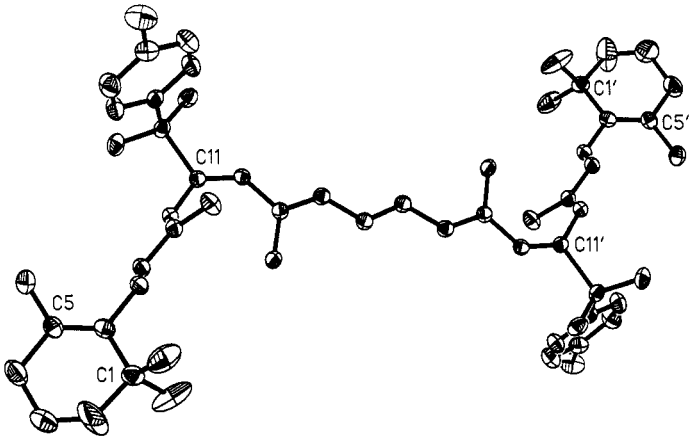
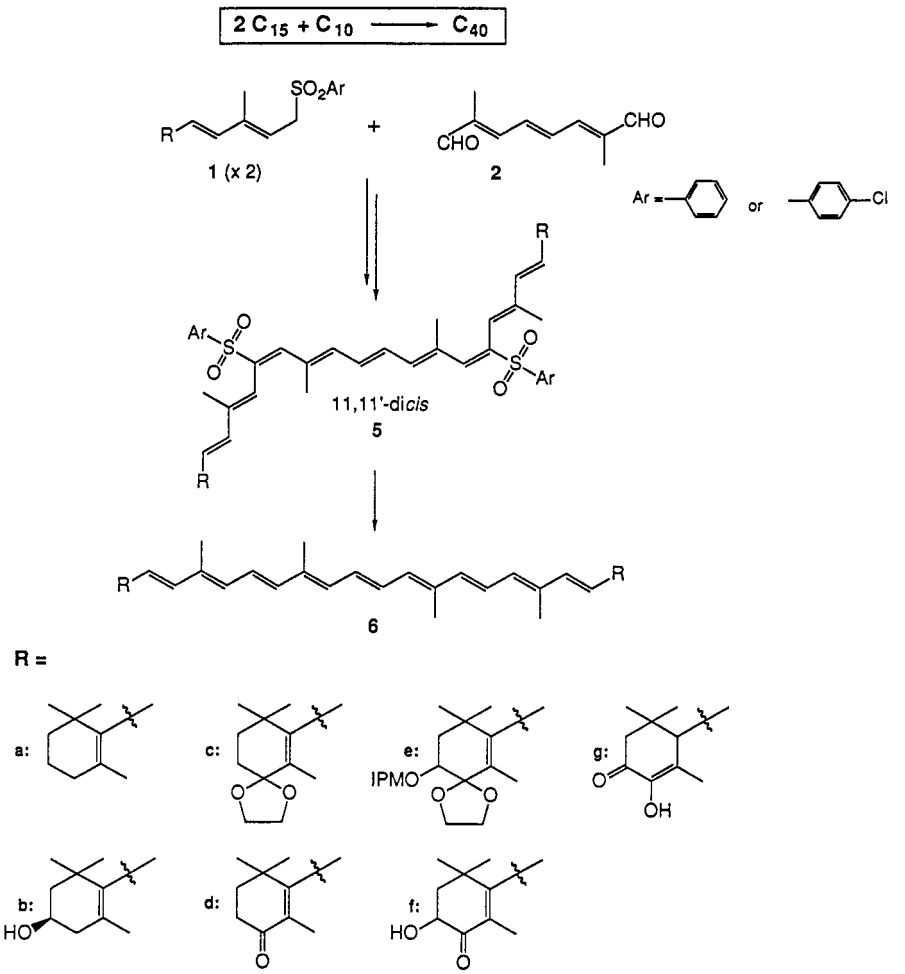


Fig.1.
X-Ray graph of 5a (Oak Ridge Thermal Ellipsoid Plot)

Scheme 4



Extensive NMR spectroscopy investigations on disulfone 5a (scheme 3) proved very helpful for stereochemical elucidation of the polyene sulfones prepared later. Thus, in the ^{1}H NMR, the chemical shift in chloroform of the protons in positions 10 and 12 were 6.012 ppm and 7.387 ppm, respectively, for the 11-cis configuration in 5a. Typical ^{13}C NMR signals were those for C(20) at 14.68 ppm and for C(10) at 118.90 ppm in chloroform.

If the reaction was performed at higher temperatures, the yield of 5a and the relative proportion of the (all-E) product decreased considerably.

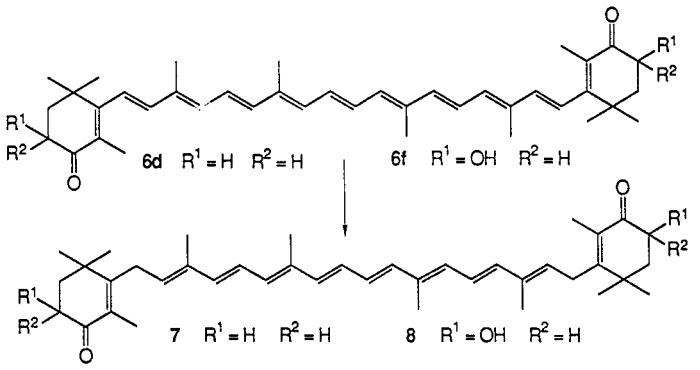
Compound 5a could be reduced by an excess of sodium dithionite / 25% ammonia in 1,2-dimethoxyethane. After isomerization and crystallization, red-violet ß-carotene 6a was obtained in ca. 90% yield [HPLC: 90% by weight (all-E), 3% (9Z); m.p. 176-7 °C].

If the one-pot procedure was interrupted at the level of 4a, a single isomer crystallized spontaneously from the colourless oily mixture of diastereoisomers; the structure of the crystalline product (m.p. 178-9°C) was confirmed spectroscopically. In an analogous way, (3R,3'R)-zeaxanthin 6b could be prepared from sulfone 1b which contains a free hydroxy-group (scheme 4).

Dithionites are known to reduce aldehydes and ketones (ref. 17). Recently, it was shown that α,ß-unsaturated aldehydes and ketones are reduced selectively to the corresponding saturated aldehydes and ketones (ref. 18).

If canthaxanthin 6d and astaxanthin 6f (scheme 5) were treated with dithionite/diethylamine under the conditions used in the previous synthesis of ß-carotene 6a, the (E/Z)-mixtures of yellow products were formed. Spectroscopic investigation of the orange crystals obtained from the reduction of canthaxanthin 6d revealed (all-E)-7,8-dihydro-8,7'-retro-ß,ß-carotene-4,4'-dione (7) (m.p. 206-9 °C) with typical retro fine structure in UV/VIS spectra. In an analogous way, astaxanthin 6f was converted into the retro carotenoid 8.

Scheme 5



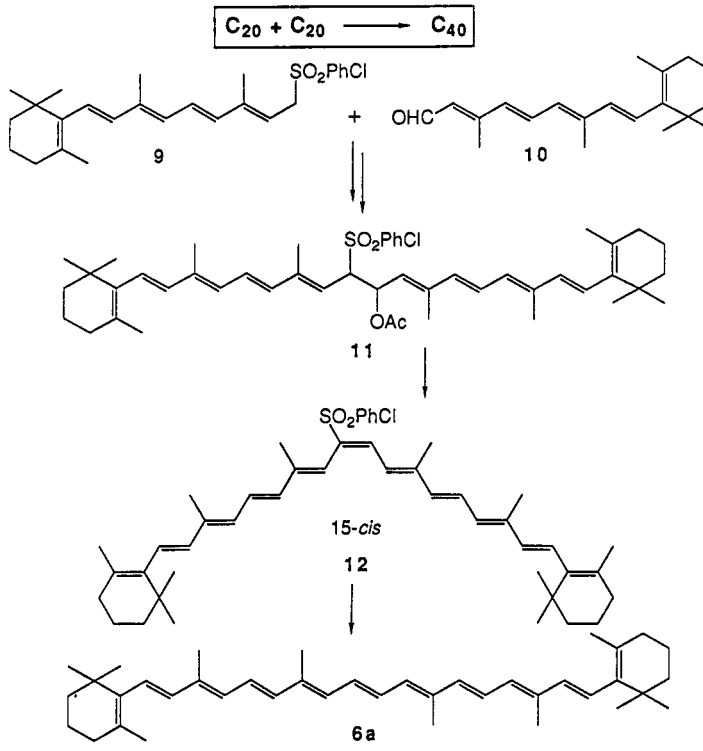
Thus for the synthesis of canthaxanthin, ketal sulfone 1c or for astaxanthin, ketal sulfone 1e (scheme 4), were reacted with C_{10}-dialdehyde 2 to give the corresponding disulfones 5c and 5e, respectively. In their ^{1}H NMR spectra, the chemical shifts for (H10,10') and (H12,12') were 6.018 ppm and 7.392 ppm, respectively, i.e. very close to those of 11,11'-di*cis*-ß-carotene disulfones 5a, thus confirming the 11,11'-di*cis* configuration for 5c, melting at 209-10 °C (with Ar = p-ClPh) and for 5e (m.p. 147-8 °C with Ar = p-ClPh), both of which were obtained in ca. 70% yield as crystalline, orange powders.

To obtain crystalline astaxanthin (6f), disulfone 5e was subjected to reduction with sodium dithionite, as described for ß-carotene disulfone, followed by acid hydrolysis and isomerization (scheme 4). If 5e was first hydrolysed and then reduced, isoastaxanthin (6g) resulted.

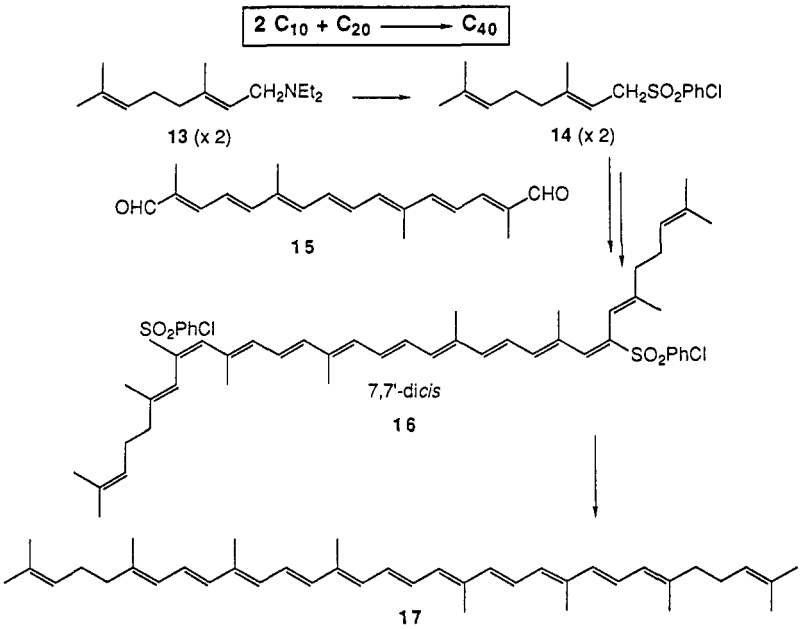
Crystalline canthaxanthin (6d) (scheme 4) was obtained from 6c by dithionite reduction, subsequent deprotection and isomerization.

The C_{20} + C_{20} route was applied in the synthesis of ß-carotene (6a) (scheme 6). Sulfone 9 was prepared from vitamin A acetate. Under the same conditions described for the previous syntheses, retinal (10) was coupled with the crude, yellow, powdery compound 9. The intermediate 11 was not isolated, but directly converted into the C_{40}-sulfone 12. ^{1}H NMR spectroscopy of the crystallized orange compound (m.p. 99-100 °C) revealed the expected (all-E) or 15-*cis* configuration; chemical shifts of (H14) and (H15') were at 6.034 ppm and a doublet at 7.677 ppm and 7.707 ppm, respectively. The UV/VIS spectrum was completely different from that of (15Z)-ß-carotene: the fine

Scheme 6



Scheme 7



structure was reduced to two absorption maxima at 339 nm and 410 nm in hexane. The reduction of sulfone 12 to ß-carotene (6a) by dithionite as described before took much longer than that of the disulfone 5a described earlier. The yield of crude ß-carotene obtained was in the range of 80%.

The C_{10} + C_{20} + C_{10} route was investigated for the synthesis of lycopene 17 (scheme 7). Geranyl-diethylamine (13) was converted into geranylsulfone 14, a crystalline compound melting at 54 °C, via the corresponding chloride (ref. 19). Coupling with C_{20}-dialdehyde 15 and further reaction according to our standard conditions provided the expected C_{40}-disulfone, whose 7,7'-di*cis* configuration 16 was confirmed by ^{1}H and ^{13}C NMR spectroscopy; the orange polyenoic disulfone melted at 179-80 °C. A comparison of its UV/VIS spectrum with that of (7Z,7'Z)-lycopene revealed an enhanced fine structure and a bathochromic shift of ca. 5 nm for disulfone 16. If disulfone 16 was treated with dithionite/diethylamine, lycopene 17 with an (all-E)-content greater than 90% was obtained after isomerization and crystallization.

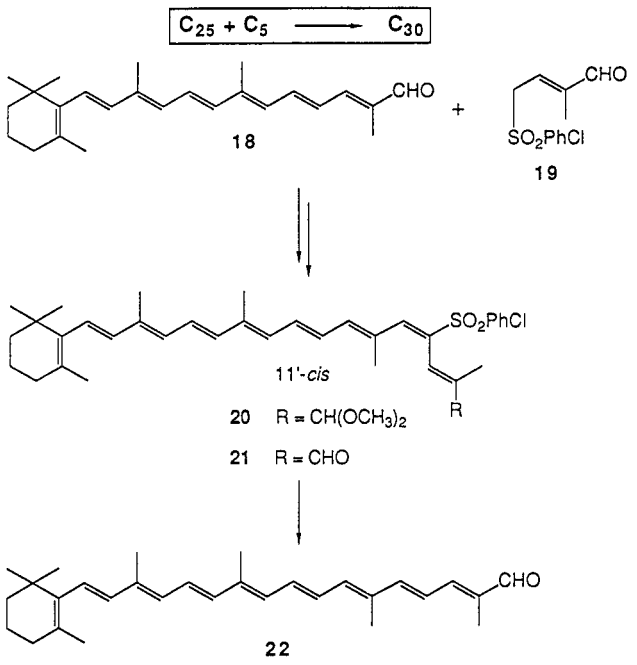
For the preparation of 8'-apo-ß-caroten-8'-al (22) (scheme 8), C_5-sulfone 19 was synthesized (m.p. 97-8 °C). After acetalization of its aldehyde function, sulfone 19 was reacted with 12'-apo-ß-caroten-12'-al (18). A sample of the crude oily product, acetal 20, was hydrolyzed to the corresponding orange crystalline aldehyde 21 (m.p. 162-3 °C). Again, ^{1}H NMR proved the (all-E) or 11'-*cis* configuration, indicated by chemical shifts for (H12') at 7.505 ppm and (H10') at 7.080 ppm. If sulfone 20 was reduced, hydrolyzed and isomerized, pure (all-E)-8'-apo-ß-caroten-8'-al (22) could be obtained in good yield (m.p. 126-8 °C).

The same C_5-sulfone 19 was finally applied in the synthesis of crocetindialdehyde (15) by a C_5 + C_{10} + C_5 scheme (scheme 9). After acetalization *in situ*, compound 19 reacted with C_{10}-dialdehyde 2 to give the crude oily C_{20}-diacetal-disulfone 23. A sample which was hydrolyzed to dialdehyde 24 crystallized as yellow needles, melting at 182-4 °C. The chemical shifts of (H12,12') and of (H10,10') were 7.491 ppm and 7.055 ppm, indicating the 11,11'-di*cis* configuration. Sulfone 23 could be reduced to crocetindialdehyde (15) with dithionite under standard conditions.

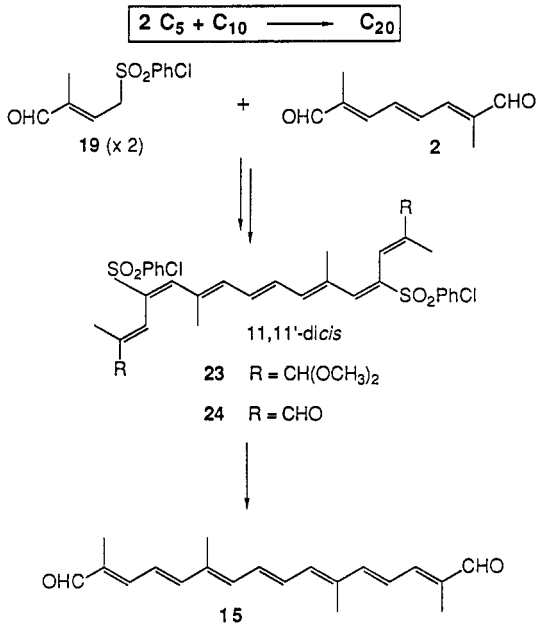
GEOMETRICAL ISOMERS OF β-CAROTENE

According to Pauling (ref. 20), two categories of double bonds exist in the acyclic polyene chain of carotenoids: those for which the adoption of a (Z)-configuration involves very little steric hindrance between two hydrogen atoms [(9Z), (13Z), (15Z) in ß-carotene], and those for which a (Z)-configuration results in a strong steric hindrance between two methyl groups or a methyl group and a hydrogen atom, respectively [(7Z), (11Z) in ß-carotene].

Scheme 8

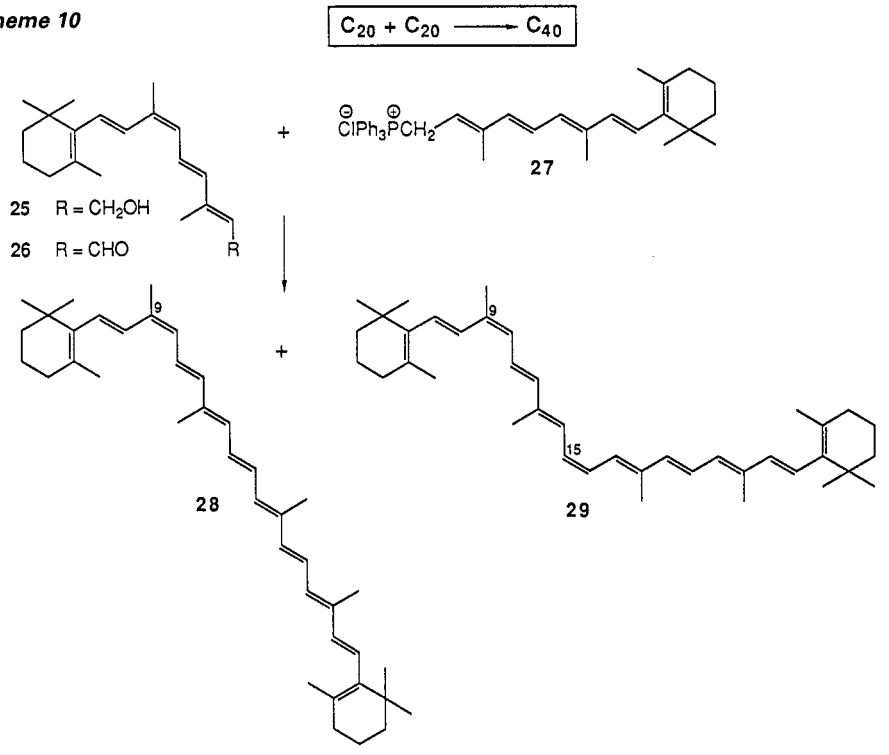


Scheme 9

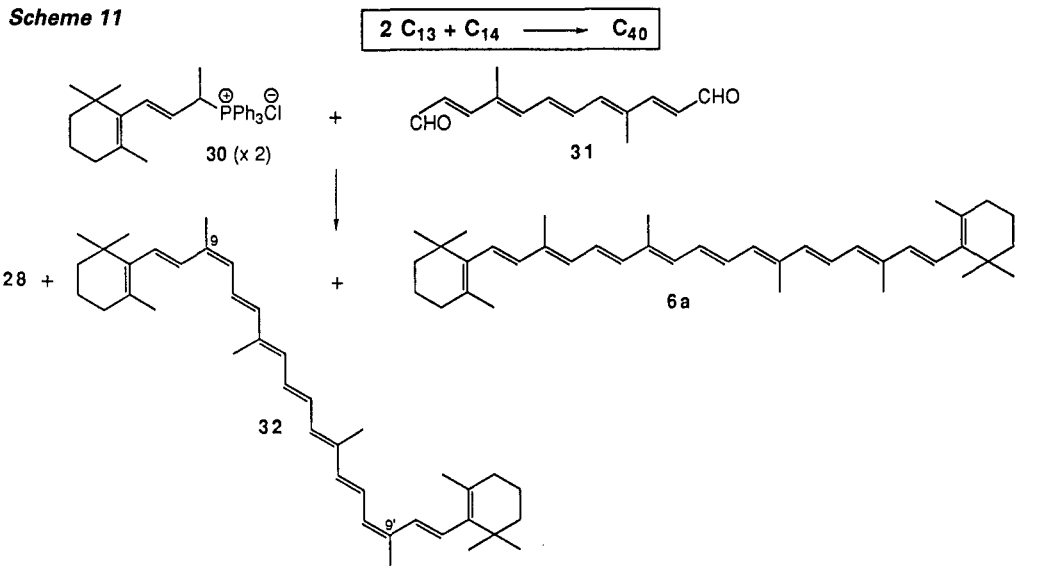


Supported by sophisticated analytical methods, we were able to synthesize highly pure (9Z)-, (9Z,15Z)-, (9Z,9'Z)-, (13Z)- and (13Z,15Z)-ß-carotene on a gram scale. These and other (E/Z)-isomers have recently been isolated on an analytical scale by HPLC and identified by NMR (refs. 1, 21). The preparation of (9Z)-ß-carotene was carried out according to $C_{20} + C_{20} \rightarrow C_{40}$ (scheme 10). The key compound was (9Z)-retinal (26) which was prepared by isomerization of (all-E)-retinol or its acetate via (9Z)-retinol (25) followed by allylic oxidation (ref. 22). Wittig reaction of aldehyde 26 with the retinyl phosphonium salt 27 gave a mixture of (9Z)-ß-carotene (28) and (9Z,15Z)-ß-carotene (29) which could be separated into the pure isomers by column chromatography and crystallization. Interestingly, the crystalline (9Z)-compound is readily soluble in hexane, contrary to the (all-E)-isomer.

Scheme 10



Scheme 11

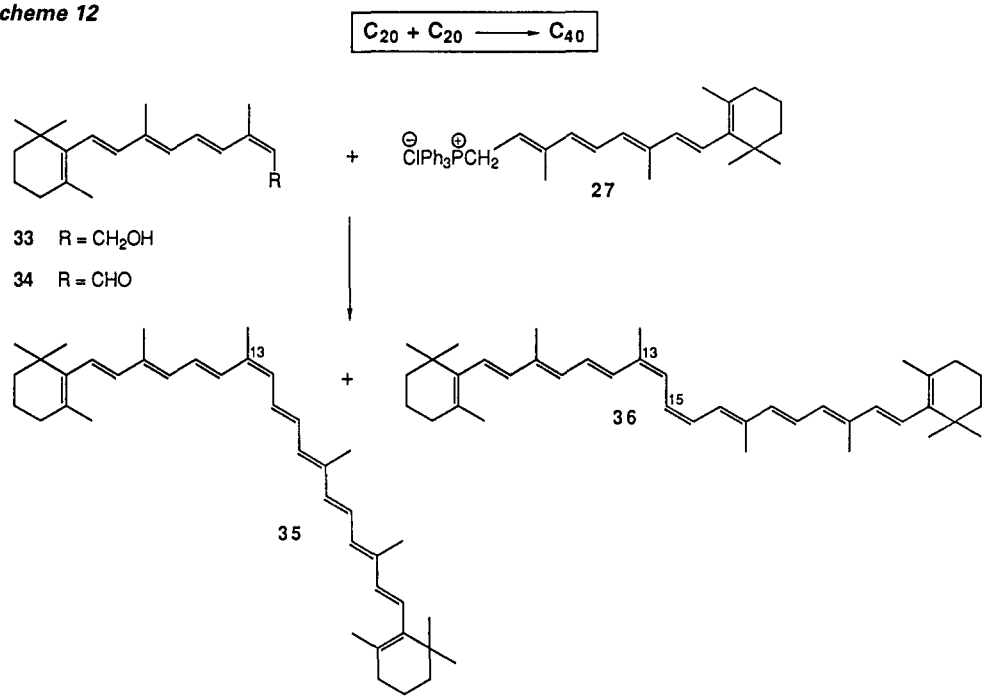


The synthesis of (9Z,9'Z)-ß-carotene (32) proved to be much more difficult. In this case, we chose the $C_{13} + C_{14} + C_{13} \rightarrow C_{40}$ approach (scheme 11), hoping that the (9Z,9'Z)-isomer would be formed direct. In fact, the reaction of the readily available C_{13}-Wittig salt 30 with the C_{14}-dialdehyde 31 gave a mixture of (9Z,9'Z)-ß-carotene (32), some (9Z)-ß-carotene (28) and (all-E)-ß-carotene (6a) from which the pure (9Z,9'Z)-isomer was isolated by chromatography and crystallization.

The $C_{20} + C_{20} \rightarrow C_{40}$ scheme was applied for the preparation of (13Z)-ß-carotene (35) (scheme 12), first obtained in small amounts by chemists of ROCHE Nutley in 1966 (ref. 23). Thus, Wittig reaction of (13Z)-retinal (34), readily available from (13Z)-retinol (33) (ref. 22), with the retinyl phosphonium salt 27 gave a mixture of (13Z)-ß-carotene (35) and (13Z,15Z)-ß-carotene (36) which was separated into the pure isomers by chromatography and crystallization. (13Z)-ß-Carotene (35) shows an increased solubility in hexane compared to (all-E)-ß-carotene.

The synthesis of additional geometrical isomers, such as (13Z,13'Z)- and (9Z,13Z)-ß-carotene is under active investigation.

Scheme 12

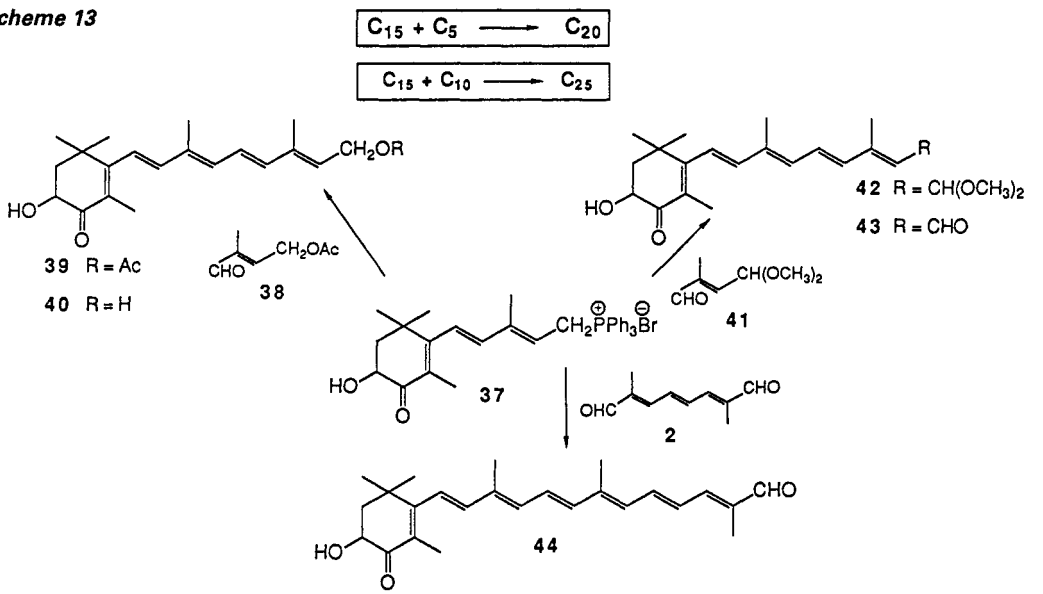


3-HYDROXY-4-OXORETINOL, 3-HYDROXY-4-OXORETINAL AND APOASTAXANTHINALS

A program for the synthesis of a series of racemic C_{25}-, C_{30}- and C_{37}-apoastaxanthinals has been initiated. Our first goal was 3-hydroxy-4-oxoretinol (40) which was prepared by condensation of the readily available C_{15}-Wittig salt 37 with the C_5-aldehyde 38 to give first the acetate 39 which was then hydrolyzed into compound 40 (m.p. 123-5 °C) (scheme 13). Analogously, reaction of phosphonium salt 37 with the aldehyde 41 gave the acetal 42 which, on hydrolysis, afforded the corresponding C_{20}-aldehyde 43 (m.p. 108 °C).

The C_{25}-analog 44 (m.p. 157-160 °C) was synthesized by a Wittig reaction of one mole of compound 37 with C_{10}-dialdehyde 2 as shown in scheme 13.

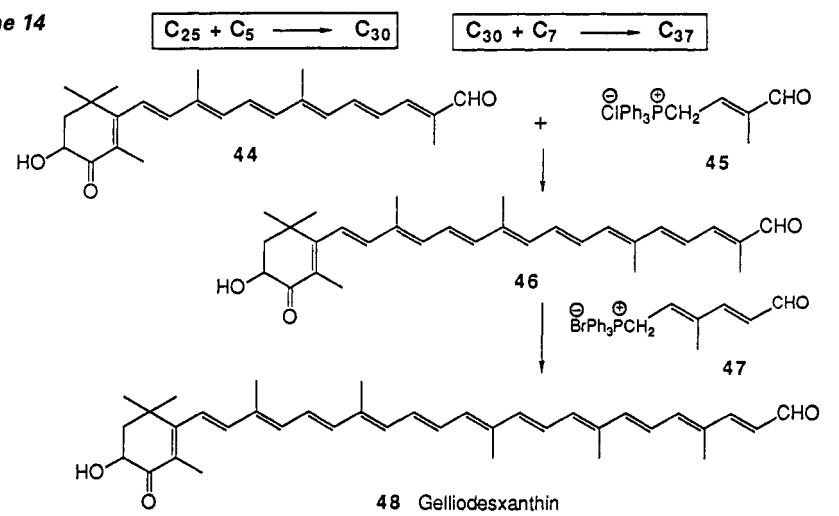
Scheme 13



Chain lengthening of the latter compound with the C_5-phosphonium salt 45, after *in situ* acetalization, afforded the C_{30}-apoaldehyde 46 (m.p. 160-2 °C) (scheme 14). To our knowledge, this compound has not yet been detected in nature.

Apoaldehyde 46 served as intermediate for gelliodesxanthin (48) (scheme 14), a new C_{37}-apocarotenal that was recently isolated from the sea sponge *Gelliodes callista* (ref. 24: m.p. 161-165 °C, UV/VIS (petrolether): 467, 495, 527 nm). Chain lengthening with the C_7-phosphonium salt 47, after *in situ* acetalization, smoothly led to the desired compound 48 which was isolated as dark red crystals (m.p. 193-4 °C; UV/VIS (hexane): 472, 497, 529 nm). The ^1H NMR was in good agreement with gelliodesxanthin in ref. 24.

Scheme 14



Acknowledgements

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