Pure & Appl. Chem., Vol. 57, No. 5, pp. 741–752, 1985.
Printed in Great Britain.
© 1985 IUPAC

Synthetic advances in the carotenoid field

Erich Widmer

Central Research Units, F. Hoffmann-La Roche & Co., Ltd.,
CH-4002 Basle (Switzerland)

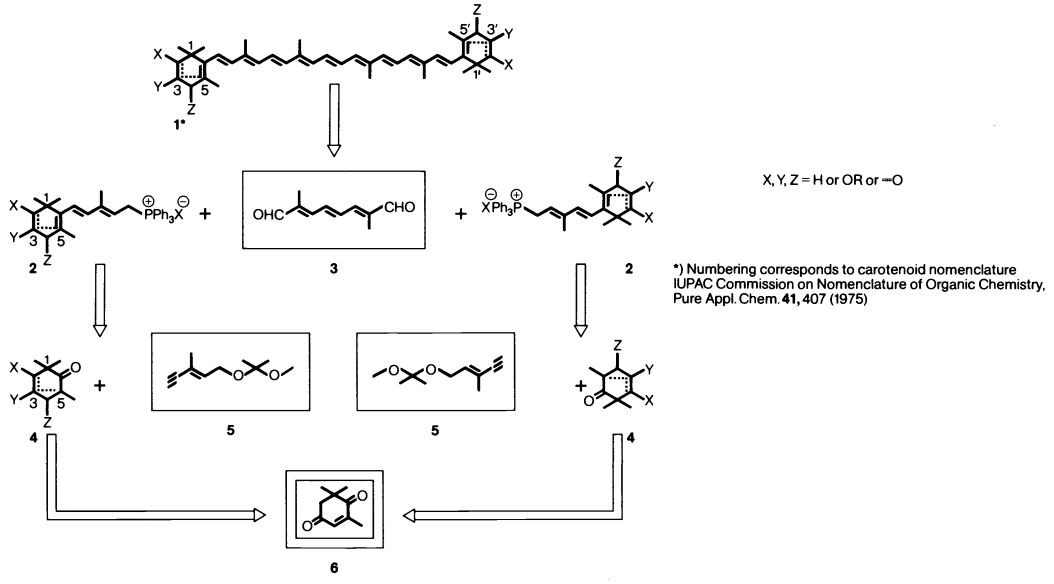
Abstract - 6-Oxo-isophorone is demonstrated to be an ideal starting material for the synthesis of numerous carotenoids possessing cyclic endgroups, including some arene- and cyclopentane-analogs. According to the generally adopted scheme ($C_9+C_6=C_{15}$; $C_{15}+C_{10}+C_{15}=C_{40}$) transformation of 6-oxo-isophorone into various cyclic ketones and their further conversion into the corresponding C_{15}-Wittig salts are discussed in detail. An acetylenic vitamin A intermediate is employed as an easily accessible C_6-building block. Double Wittig-olefination of the also readily available, symmetric C_{10}-dialdehyde finally leads in new, short and efficient syntheses to a large number of known, but also to some new carotenoids. Furthermore, some interesting reactions, such as regioselective reductions of the C(3)-keto group, oxo-transpositions, isomerization as well as reductive opening of ring epoxides, dehydrations and partial reductions of C(7)-triple bonds, are presented.

INTRODUCTION

Upon analysing the hitherto published syntheses of carotenoids with cyclic endgroups (see e.g. Refs. 1-2), a large number of different strategies are encountered. Our conclusion is that preformed intermediates of a convergent scheme should be connected to the reactive polyene only at the very end of the synthesis. Furthermore it becomes clear that functionalization of a ring already bearing an olefinic chain fragment is mostly rather detrimental or needs expensive conditions or reagents, respectively. Based on these considerations we decided to establish a generally applicable scheme requiring only minor modifications for the synthesis of most of the carotenoids possessing cyclic endgroups (Refs. 1-2).

Scheme 1:

Retrosynthetic Scheme for Carotenoids with Cyclic Endgroups



Since the C_{10}-dialdehyde 3 (Ref. 1) is readily available, the last step of this scheme must be the double Wittig condensation ($C_{15}+C_{10}+C_{15}=C_{40}$) shown in a retrosynthetic scheme (scheme 1). This approach was first used by Wittig himself for the synthesis of ß,ß-carotene (Ref. 3). What is further needed is a general concept leading to the different

C_{15}-phosphonium salts 2. So far, such compounds have been synthesized using several different synthetic schemes. Only a few authors (Refs. 4-6) - the first being Weedon - have used the readily available, unprotected bifunctional C_6-vitamin A intermediate 5 (Ref. 1) to build up C_{15}-components 2 according to the scheme $C_9+C_6=C_{15}$. This might be due to former drawbacks of this approach. The hydroxy group of this interesting C_6-building block can, however, easily be protected as an acetal using e.g. isopropenyl methyl ether as reagent (Ref. 7). The lithium salt of 5 adds almost quantitatively to the sterically hindered keto group of most of the ring components 4. Acetylenides of other metals, as well as common Grignard reagents, are less suited for this purpose. Furthermore, phosphoranes do not react in principle (Ref. 8) with sterically hindered ketones of type 4. For these cyclic precursors we have developed a set of efficient reactions leading to the specific functionalization of almost any target carotenoid. As common starting material for all these intermediates 6-oxo-isophorone 6 has been chosen. This versatile compound, possessing the essential keto group at C(6), is readily accessible by air oxidation of isophorone, a condensation product of 3 molecules of acetone, either in 1 (Ref. 9) or 2 (Refs. 10-11) steps.

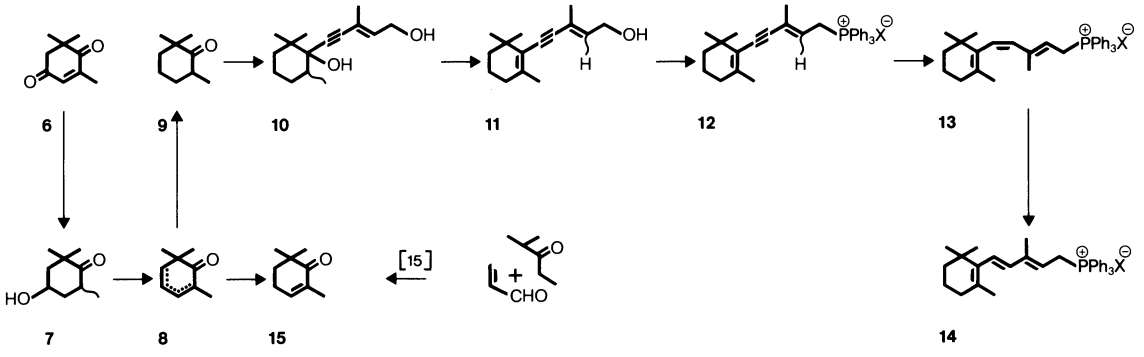
Commenting now on the conversion of 6-oxo-isophorone 6 into a representative set of carotenoids with cyclic endgroups I will first discuss the preparation of totally deoxygenated synthons and then proceed from 2-oxygenated to 4-oxygenated ring synthons. As special cases accesses to the allenic, aromatic and the nor-series will also be discussed briefly. Since the problems of converting the cyclic ketones 4 into the olefinic C_{15}-phosphonium salts 2 are closely related to the substitution pattern of the ring, the transformations leading to the C_{15}-salts will be included in these discussions. Some general remarks on the final double Wittig condensations of the C_{15}-Wittig salts 2 with the C_{10}-dialdehyde 3 will be made at the end of my contribution.

DISCUSSION

Desoxy synthons (scheme 2; Ref. 12) pose as main problem the deoxygenation of 6-oxo-isophorone 6 in 3-position. Raney-nickel hydrogenation of 6 leads almost quantitatively to the hydroxy-ketone 7 which can be dehydrated easily in the presence of a catalytic amount of acids like p-TsOH. The resulting mixture of unsaturated ketones 8 can be catalytically (e.g. Pd/C) hydrogenated to yield the trimethylcyclohexanone 9. The lithium salt of 5 in THF adds to 9 in high yields, leading to the C_{15}-intermediate 10. Under normal conditions, dehydration of the tertiary alcohol occurs only with moderate success or requires selective protection of the primary alcohol. In 1N H_2SO_4 at 70°C, however, the dehydration takes place smoothly to give the C_{15}-monoalcohol 11. En-yne systems of this type can readily undergo E→Z isomerization. For this reason compound 11 is obtained as a (9E)/(9Z)-mixture and affords the pure (9E)-phosphonium salt 12 only in a moderate yield after successive treatment with conc. HCl and triphenylphosphine in ethylene chloride. Whereas sterically hindered acetylenes such as the C_{15}-alcohols of type 11 undergo semihydrogenation unselectively, acetylenic Wittig salts like 12 can easily be hydrogenated to the (7Z)-derivatives in the presence of Raney-nickel. The (7Z)-Wittig salt 13 may be used for the preparation of (7Z)-isomers of ß,ß-carotene and vitamin A. On treatment of the (7Z)-salt 13 in boiling methanol with catalytic amounts of $Pd(OAc)_2$ 7Z→7E isomerization takes place, thus leading to the (7E)-isomer 14, which has been prepared earlier (Ref. 13) starting from ß-ionone. As an interesting extension of this series, the isomeric mixture of the unsaturated trimethylcyclohexenones 8 can be isomerized using $RuCl_3/NEt_3/PPh_3/H_2$ at 160°C or $Pd(OAc)_2/PPh_3$ at 145°C to pure 15 (see scheme 8, Ref. 41) which Baumann and Hoffmann had previously prepared starting from ethyl isopropyl ketone and acrolein (Ref. 15).

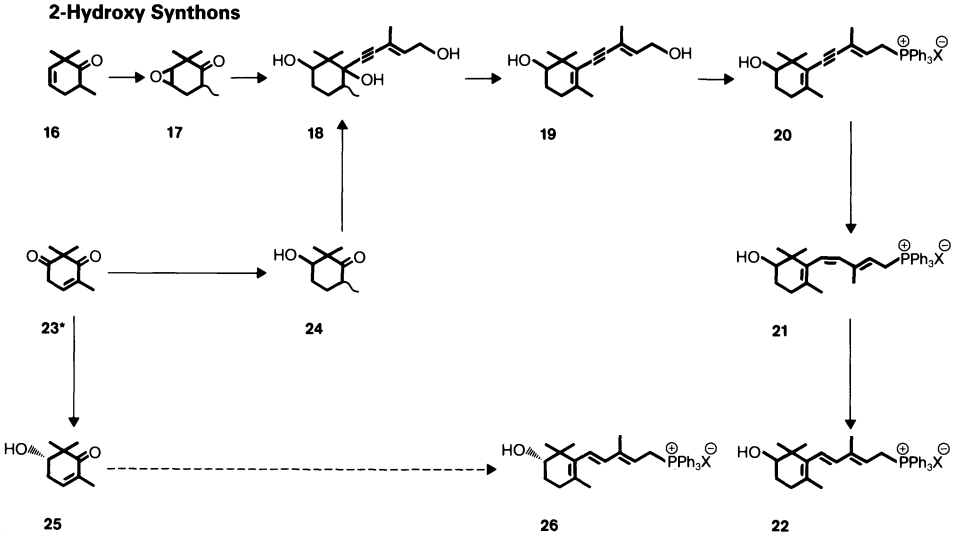
Scheme 2:

Desoxy Synthons: β, β-Carotene and E/Z-Isomers



Scheme 3:

2-Hydroxy Synthons

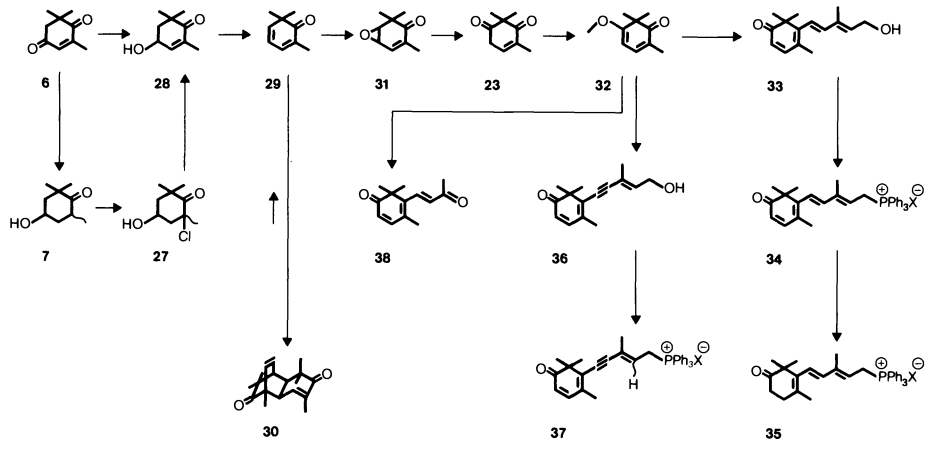


2-Hydroxy synthons (scheme 3; Ref. 16) can be prepared starting from 2,3-dehydro-1,1,5-trimethylcyclohexanone 16, which itself can easily be isolated from the above (see scheme 2) mentioned mixture of unsaturated ketones 8 by distillation. Treatment of the cyclohexenone 16 with MCPBA (m-chloroperbenzoic acid) gives almost quantitatively the epoxide 17. Then the lithium salt of the protected C_6-unit 5 is added to the epoxy ketone 17 in THF. The intermediate lithium propargylate is treated in situ with the ate-complex prepared from DIBAH and BuLi (Ref. 17) thus giving the 2-hydroxy-C_{15} compound 18 in good yield. As expected no attack at all was observed at the neopentyl position of the epoxide. In this series dehydration of the tertiary C_{15}-alcohol in aqueous H_2SO_4 leads to ring-opening products. However, the dehydration product 19 is formed in good yield by using the anhydrous system acetic anhydride/acetic acid/p-TsOH followed by saponification of the intermediate diacetate with KOH in methanol. For the conversion of the diol 19 into the acetylenic Wittig salt 20 successive treatment with $PPh_3 \cdot Cl_2$/collidine and PPh_3 in methylene chloride is required. The all-trans-Wittig salt 22 (Ref. 18) is subsequently obtained by using the procedure as described before (scheme 2).

Another approach to 2-hydroxy derivatives starts from the diketone 23, the oxo-transposition product of 6-oxo-isophorone 6 (see scheme 4). Raney-nickel hydrogenation leads in excellent yield to the saturated hydroxy-ketone 24, to which the C_6-unit 5 can directly be added in the presence of an excess of anhydrous KOH in THF. The 2-oxo compound 23 is also readily converted into the (2S)-2-hydroxy derivative 25 by microbial reduction with Geotrichum candidum (Ref. 19). Since this configuration is the unnatural one, 25 has not yet been transformed into the chiral Wittig salt 26 (Ref. 18).

Scheme 4:

2-Oxo-Synthons



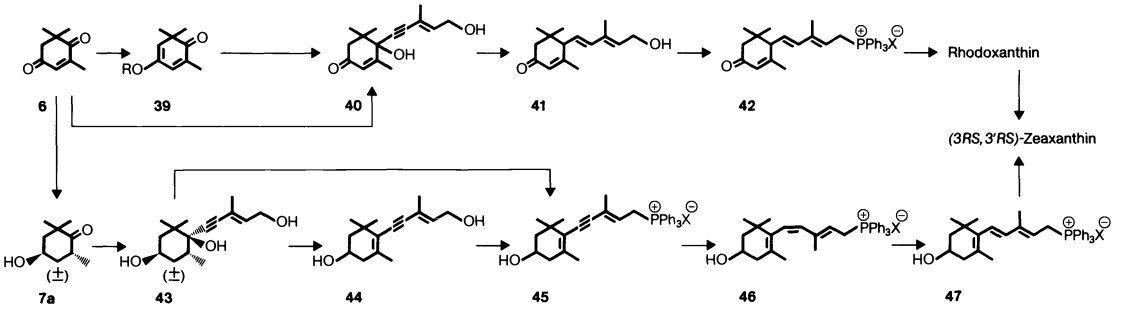
2-Oxo synthons (scheme 4; Ref. 21) are easily accessible by transposing the 3-oxo group of 6-oxo-isophorone 6 into the 2-position via 2,6,6-trimethylcyclohexadienone 29 (Ref. 22). For this purpose 6 can selectively be reduced to the unsaturated hydroxy-ketone 28 (Refs. 22-23) under Meerwein-Ponndorf conditions in moderate yields. The same intermediate is also obtained in excellent yield via the already mentioned saturated hydroxy-ketone 7 (see scheme 2) by chlorination with sulfuryl chloride and subsequent dehydrochlorination by a tert-amine. Dehydration of 28 to the spontaneously dimerising trimethylcyclohexadienone 29 (Ref. 24) is achieved by distillation under slightly reduced pressure in the presence of catalytic amounts of an acid like conc. H_2SO_4. If the reaction conditions are carefully controlled no dienone→phenol rearrangement takes place and the reaction proceeds in high yield. The dehydration can also be effected with similar success by treatment of the corresponding acetate with $Pd(OAc)_2$ and NEt_3 in boiling dioxan. The interesting dienone 29 was hitherto accessible only in low yields (Ref. 24). Treatment of 29 with MCPBA leads selectively to the epoxide 31, which then can be isomerized to the desired oxo-transposition product 23 using Pd(0) complexed with dba (dibenzylidene-acetone), PPh_3 and dpe [1,2-bis(diphenylphosphino)ethane] as catalysts. Both reactions, epoxidation and isomerization, proceed cleanly and in high yields. The 2-oxo group of the new diketone 23 can be protected as its enolether 32 using trimethylorthoformate as reagent and Amberlyst 15 as catalyst. Alkynylation with the lithium salt of 5 in ether gives, after hydrolysis, the acetylenic C_{15}-hydroxy-ketone 36 in excellent yield. If the alkynylation is carried out in hexane and the intermediate lithium propargylate is treated in situ with Redal [sodium bis(2-methoxy-ethoxy) aluminum hydride] the (7E)-olefin 33 can be isolated directly in high yield. Both C_{15}-alcohols, 33 and 36, are easily transformed into the corresponding Wittig salts 34 (Ref. 25) and 37, respectively, by successive treatment with 63 % HBr and PPh_3.

Reaction of the Wittig salt 34 with $AlCl_3$ and 2-phenylbenzothiazoline (Ref. 26) in boiling methanol for 4 hours leads in high yield to the partially hydrogenated 2,2'-dioxo-ß,ß-carotene precursor 35.

To demonstrate the versatility of the new intermediates and procedures, the enolether 32 was successively treated with the lithium salt of butynone ethylene acetal, Redal and diluted HCl in toluene, thus giving 2-oxo-3,4-dehydro-ß-ionone 38 (Ref. 18) in good yield.

Scheme 5:

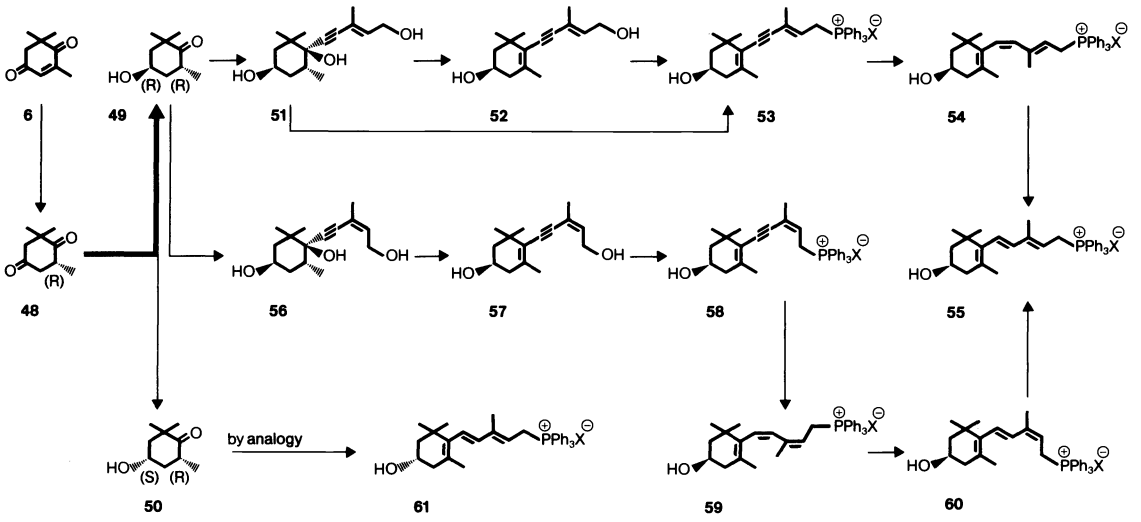
3-Oxygenated Synthons: Rhodoxanthin and *(3RS, 3'RS)*-Zeaxanthin



3-Oxygenated synthons are precursors of rhodoxanthin and (3RS,3'RS)-zeaxanthin. Our work in these series has already been published in detail (Refs. 27-28). Selective alkynylation at C(6) of 6-oxo-isophorone 6 proceeds almost quantitatively after protecting the 3-oxo group as enolether 39 or in situ as lithium enolate in liquid NH_3. In the key step of this sequence simultaneous reductive elimination of the tertiary hydroxy group and partial reduction of the triple bond, either by treatment with zinc under alkaline conditions or electrochemically, lead from the acetylenic C_{15}- intermediate 40 to the (7E)-6-desoxy derivative 41. As outlined in Helv. Chim. Acta (Ref. 28) formation of the phosphonium salt 42 followed by double Wittig condensation with the C_{10}-dialdehyde 3 gives 6,6'-dihydro-rhodoxanthin, which is easily dehydrogenated to rhodoxanthin. When rhodoxanthin is reduced with zinc/acetic acid 3,3'-dioxo-ß,ß-carotene is formed (see also Ref. 29), which on subsequent treatment with $NaBH_4$ gives (3RS, 3'RS)-zeaxanthin in excellent yield (see also Refs. 30-31). This carotenoid can also be prepared via the above mentioned hydrogenation product 7 of 6-oxo-isophorone 6. Using as starting material only the trans-isomer 7a, isolated as the major component from the cis/trans-mixture 7 by crystallization, problems in connection with the alkynylation and the subsequent dehydration to the racemic diol 44 are avoided. The sequence which is chemically identical with the corresponding part of the synthesis of the natural (3R,3'R)-zeaxanthin is discussed in more detail below in the chiral series.

Scheme 6:

3-Hydroxy Synthons: *(3R, 3'R)*- and *(3S, 3'S)*-Zeaxanthin and E/Z-Isomers



Chiral 3-hydroxy synthons (scheme 6) have already been prepared some years ago (Refs. 32+2). 6-Oxo-isophorone 6 is transformed microbiologically to the saturated (5R)-diketone 48. Hydrogenation of this chiral intermediate 48 in the presence of base-free Raney-nickel leads to a 4:1 mixture of the (3R,5R)-3-hydroxy-ketone 49 and its (3S)-enantiomer 50, which can be separated rather easily by countercurrent extraction. The naturally (3R,3'R)-configurated zeaxanthin is then synthesized (Ref. 33) starting from 49 by analogy with the above discussed synthesis of ß,ß-carotene (see scheme 2). After in situ protection of the hydroxy group as a mixed acetone acetal, the alkynylation proceeds stereoselectively and almost quantitatively to the (3R,5R,6R)-C_{15}-intermediate 51. The dehydrated phosphonium salt 53 is prepared by successive treatment of the triol 51 either with aqueous H_2SO_4, conc. HCl and PPh_3 or 63 % HBr and PPh_3, respectively, in chloroform. Under carefully controlled conditions only minor 9E→9Z isomerization occurs. Thus the following partial hydrogenation of the triple bond leads to the isomerically pure (7Z)-Wittig salt 54, which is isomerized to the all-trans-isomer 55 by $Pd(OAc)_2$.

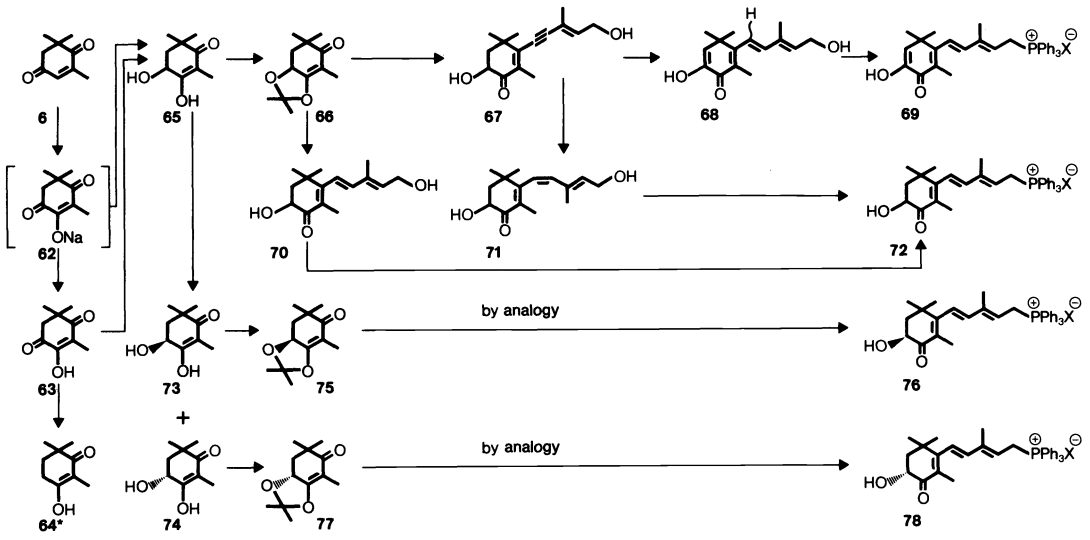
If the (3R,5R)-hydroxy-ketone 49 is alkynylated with the (Z)-isomer of the acetylenic C_6-chain fragment 5, the (9Z)-Wittig salt 60 results analogously. Selective 7Z→7E isomerization in compound 59 is achieved with $Pd(OAc)_2$, whereas 9Z→9E isomerization to the all-trans-Wittig salt 55 needs elevated temperatures. Making use of the (7Z,9E)-, (7Z,9Z)- and (7E,9Z)-Wittig salts 54, 59 and 60 the corresponding configurational isomers of (3R,3'R)-zeaxanthin can rather easily be synthesized. The acetylenic Wittig salts 53 and 58 lead to the natural manixanthin and alloxanthin, respectively (Ref. 34). Starting from the (3S,5R)-hydroxy-ketone 50 the (3S,3'S)-series is analogously accessible.

Accesses to 3,4-oxygenated synthons (scheme 7) starting from 6-oxo-isophorone 6 have already been published in detail (Refs. 35-40). Epoxidation of 6 with H_2O_2 in aqueous NaOH leads to 4-hydroxy-6-oxo-isophorone 63. The intermediate sodium salt 62 can be hydrogenated directly and almost quantitatively to the dihydroxy-ketone 65. The same compound is obtained by reducing the free hydroxy diketone 63 with zinc/acetic acid or electrochemically. The dihydroxy-ketone 65 is subsequently protected as its acetonide 66, which now can be selectively alkynylated in position 6 to give directly the C_{15}-intermediate 67 in excellent yield. Interestingly, this acetylenic dialcohol 67 is easily isomerized under slightly basic conditions to the astacene building block 68, which can be transformed almost quantitatively into the corresponding all-trans-Wittig salt 69 (Ref. 40). Acetylenic compounds such as the intermediate 67 undergo partial reduction easily due to the presence of a conjugated ketone either by treatment with zinc/acetic acid or under the specifically modified conditions of Lindlar hydrogenations. Alternatively, alkynylation of the acetonide 66 and in situ reduction of the intermediate lithium propargylate with Redal leads to the (7E)-isomer 70. Both C_{15}-dialcohols 70 and 71 are easily transformed into the all-trans-Wittig salt 72 by successive treatment with 63 % HBr and PPh_3. No catalyst is needed in this case for the isomerization of the 7,8-double bond, possibly due to the presence of a conjugated oxo function in the ring.

The enantiomeric Wittig salts 76 and 78 are accessible using exactly the same reaction path after optical resolution of the dihydroxy-ketone 65 with (+)-(R)-1-phenyl-ethylamine.

Scheme 7:

3,4-Oxygenated Synthons

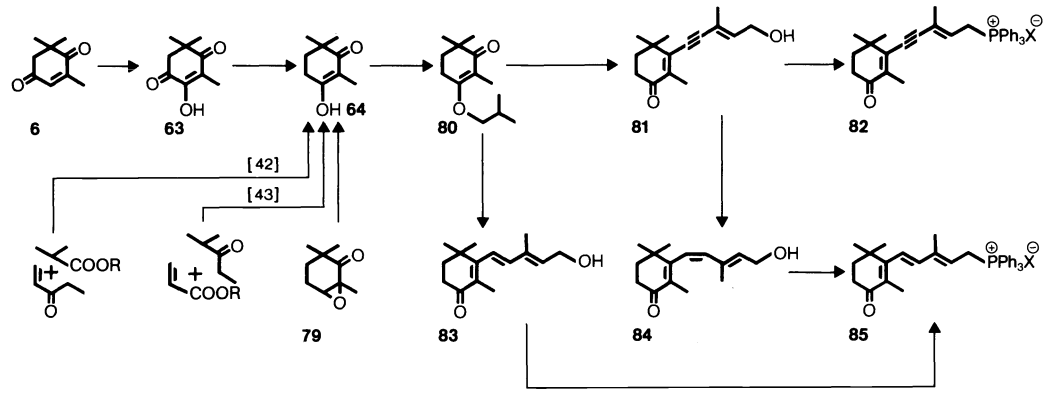


*see scheme 8

4-Oxo synthons (scheme 8), the precursors of canthaxanthin, may be synthesized exactly by analogy to the astaxanthin series (Ref. 41). Reducing the above mentioned 4-hydroxy-ketone 63 under more vigorous conditions, either with zinc/acetic acid or electrochemically, the oxygen in 3-position is removed completely to give the enolized 1,3-diketone 64 in excellent yield. This interesting building block was first prepared by Rosenberger et al. (Ref. 42) starting from ethyl vinyl ketone and methyl isobutyrate and later on by Baumann and Hoffmann (Ref. 43) by reacting isopropyl ethyl ketone with ethyl acrylate. In a most recently developed procedure (Ref. 41) the α,β-epoxy-ketone 79 is isomerized to the diketone 64 catalyzed by Pd(O) complexes. The following sequence to the isobutylether 80, the acetylenic C_{15}-hydroxy-ketone 81, its hydrogenation to the (7Z)-derivative 84 and the subsequent conversion to the Wittig bromide 85 by treatment with PBr_3 and PPh_3 was also published by Rosenberger (Ref. 42). Alternatively (Ref. 41) the triple bond can be reduced with zinc/acetic acid, or the enolether 80 can directly be transformed into the (7E)-derivative 83 by in situ reduction of the alkynylation intermediate with Redal. Successive treatment of both, the (7E)- and the (7Z)-C_{15}-alcohols, 83 and 84, with conc. HCl and PPh_3 gives directly the all-trans-Wittig chloride 85.

Scheme 8:

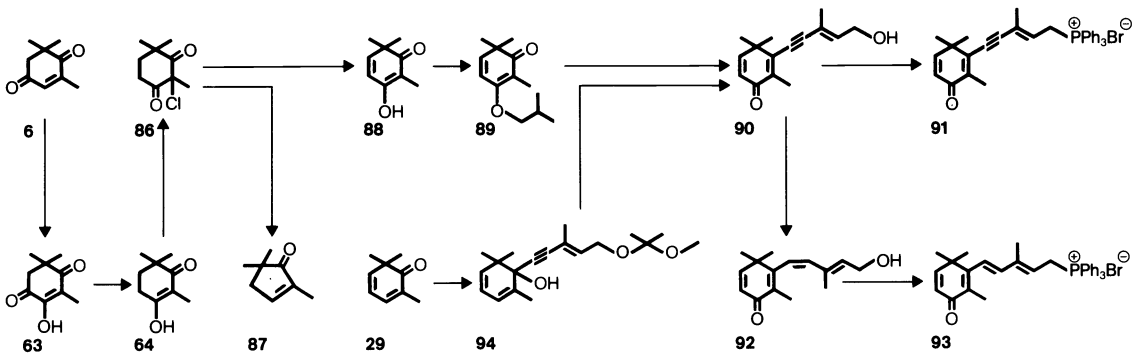
4-Oxo Synthons: Canthaxanthin-Series



2,3-Dehydro-4-oxo synthons (scheme 9; Ref. 44) are intermediates in the syntheses of 2,2',3,3'-tetradehydro-canthaxanthin and the corresponding aromatic derivatives (see scheme 11). The above discussed canthaxanthin intermediate, the enolized 1,3-diketone 64, can be chlorinated almost quantitatively with sulfuryl chloride. Treatment of the resulting chloride 86 with K_2CO_3 in boiling benzene gives the ring-contraction product 87, but in

Scheme 9:

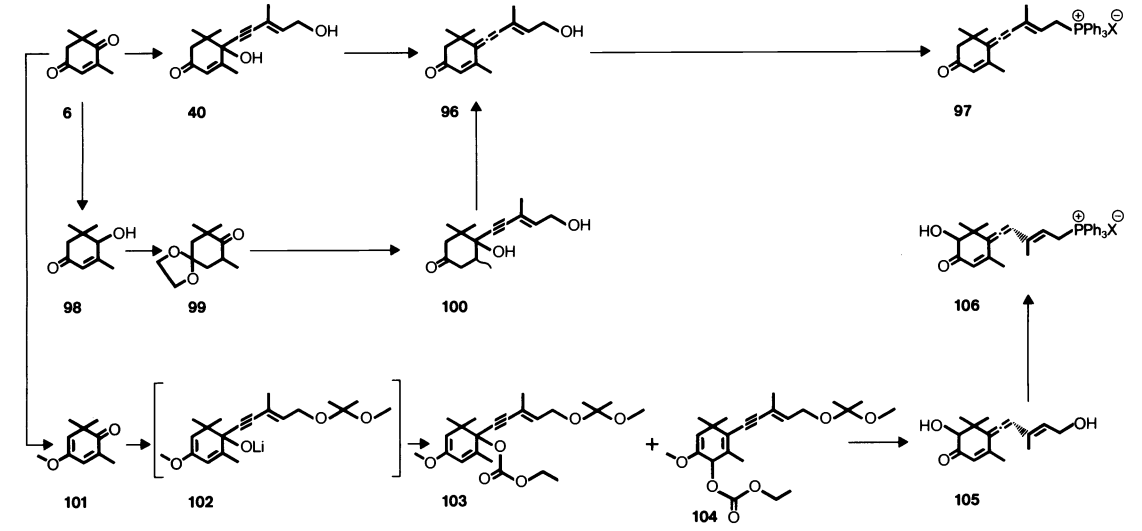
4-Oxo Synthons: 2,3-Dehydro Series



boiling pyridine the 2,3-dehydrogenated 4,6-diketone 88 is formed in high yield. Etherification with isobutanol (Ref. 45) leads to the easily dimerising dienone 89, the subsequent alkynylation of which furnishes the C_{15}-hydroxy-ketone 90. This compound can also be prepared by alkynylation of the dienone 29 followed by treatment of the tertiary alcohol 94 with MnO_2 in methylene chloride at room temperature. Conversion of the acetylenic hydroxy-ketone 90 to the corresponding Wittig salt 91 by successive treatment with 63 % HBr and PPh_3 in methylene chloride proceeds in moderate yield. Partial hydrogenation of this acetylenic phosphonium salt 91, however, is preparatively unattractive due to lack of selectivity. A better result is obtained if the acetylenic C_{15}-hydroxy-ketone 90 is reduced catalytically in the presence of 5 % Pd/C, poisoned with quinoline, or with zinc in acetic acid. Successive treatment of the (7Z)-derivative 92 with 63 % HBr and PPh_3 in methylene chloride yields smoothly the all-trans-Wittig salt 93.

Scheme 10:

Allenic Synthons (optically inactive)



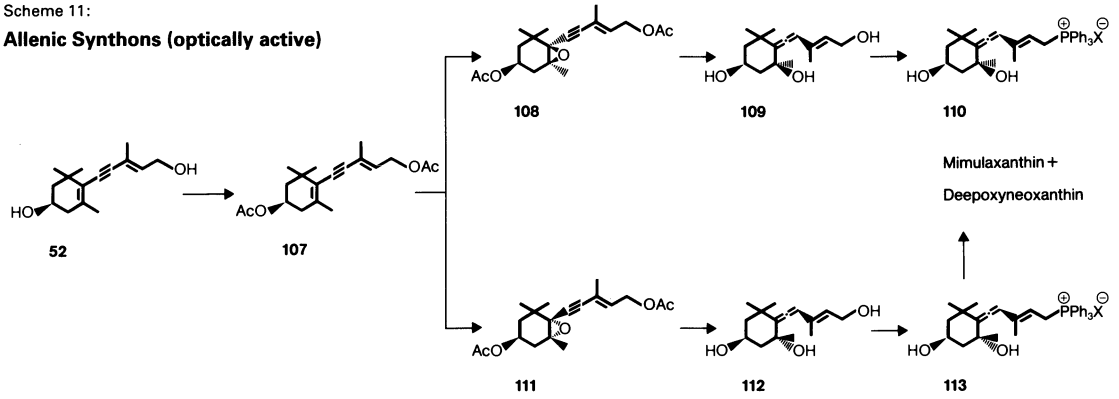
Allenic synthons (scheme 10; Ref. 46) are accessible rather easily in special cases. If for example the alkynylation product 40 of 6-oxo-isophorone 6 (see scheme 5) is reduced under carefully controlled conditions, either by zinc in the presence of NaCN in propanol/water or electrochemically, the allenic C_{15}-hydroxy-ketone 96 is obtained in good yield. An experimentally more advantageous route to the allene 96 starts with the selective hydrogenation of 6-oxo-isophorone 6 to the hydroxy-isophorone 98 in the presence of a poisoned platinum catalyst. The intermediate 98 is directly and almost quantitatively converted to the monoacetal 99 in boiling 2-ethyl-2-methyldioxolan, catalyzed by p-TsOH. Alkynylation and hydrolysis lead subsequently to the C_{15}-ketone 100. Upon treatment of this dialcohol 100 with acetic anhydride and p-TsOH in boiling acetic acid, the tertiary alcohol function is dehydrated, the unsaturated system is rearranged to the vinylogous

allenic ketone and the primary alcohol is acetylated. Saponification with KOH in methanol leads to the free alcohol 96. Its conversion to the Wittig salt 97 needs careful control of the reaction conditions due to the reactive unsaturated system present in the molecule. The intermediate allylic halide is best prepared either with $PPh_3 \cdot Br_2$ and collidine or with 48 % HBr.

The synthesis of a 2-hydroxylated analog starts from the methyl-enol ether 101 of 6-oxo-isophorone 6. Hydrolysis of the intermediate alkynylation product, the lithium propargylate 102, leads not only to the expected acetylenic derivative 40 (see also scheme 5) but also to a certain extent to the allenic side product 105. This compound can be prepared in a better, but still rather low yield via the carbonates 103 and 104. Interestingly, such a 1:1 mixture is formed almost quantitatively upon in situ treatment of the lithium alcoholate 102 in THF with ethyl-chloroformate. Rearrangement to the 2-hydroxylated C_{15}-allene 105 proceeds in wet THF, catalyzed by p-TsOH, at room temperature. Successive treatment with $PPh_3 \cdot Br_2$/collidine and PPh_3, respectively, leads to the phosphonium bromide 106.

Scheme 11:

Allenic Synthons (optically active)

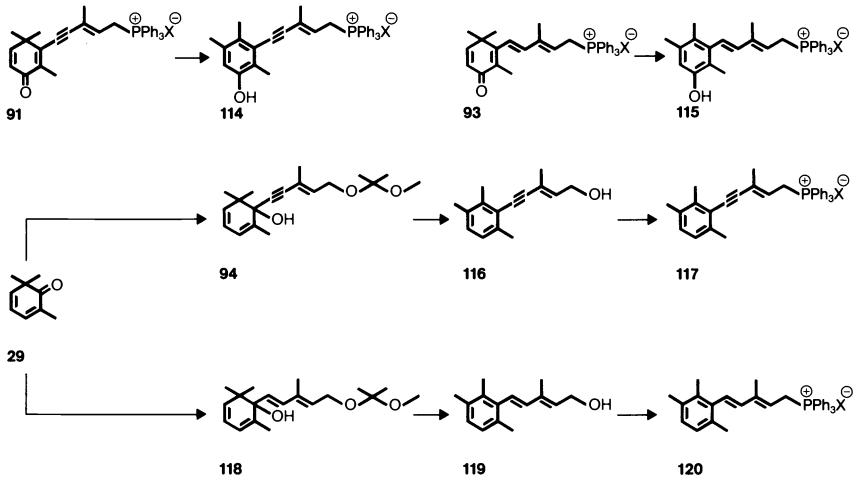


Chiral allenic synthons (scheme 11) have been synthesized by Bernhard et al. (Ref. 47), e.g. starting from the zeaxanthin intermediate 52 (see scheme 6). Acetylation with acetic anhydride/pyridine and subsequent treatment with MCPBA in methylene chloride leads to a 1:1 mixture of the diastereomeric epoxides 108 and 111. Direct reduction of the crude product with DIBAH gives a mixture of the allenic triols 109 and 112, which can be separated by column chromatography. The phosphonium bromide 113, prepared by analogy to the above discussed 2-hydroxy-allene 106 contains the endgroups of the symmetric mimulaxanthin and one endgroup of the unsymmetric deepoxyneoxanthin.

Aromatic synthons (scheme 12; Ref. 48) are readily accessible if suitable intermediates are subjected to a dienone→phenol or a dienol→benzene rearrangement. Thus, the above discussed Wittig salts 91 and 93 (see scheme 9) are converted to the corresponding trimethylphenol derivatives 114 and 115, respectively, in boiling ethylene chloride catalyzed by Amberlyst-15.

Scheme 12:

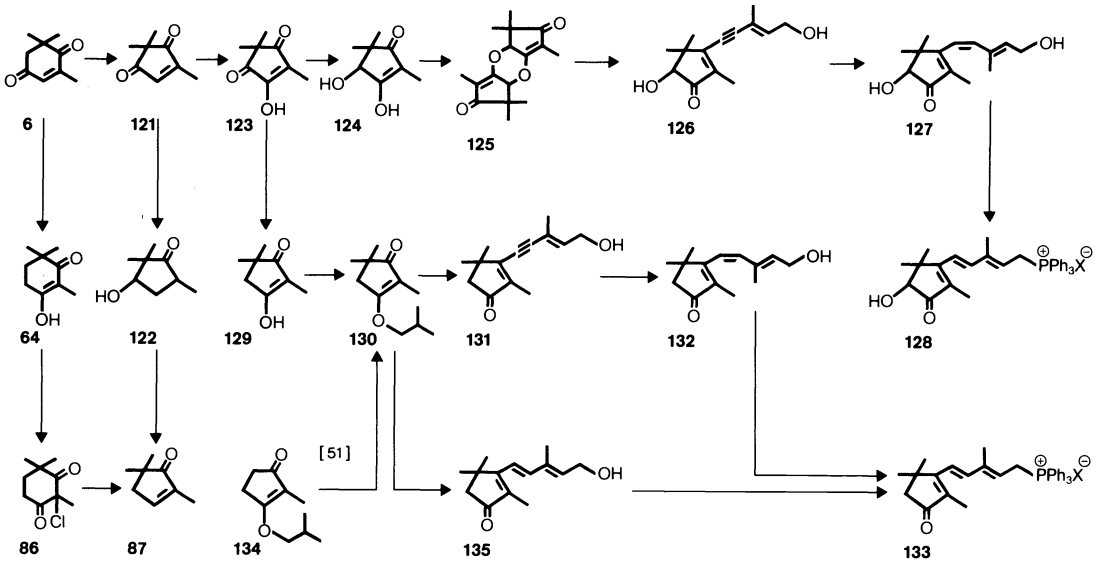
Accesses to Aromatic Synthons



The acetylenic dienol 94 (see also scheme 9) and its (7E)-olefinic analog 118, which can be prepared from the dienone 29 by combined alkynylation and reduction with Redal (see e.g. comments on scheme 4), undergo the Amberlyst-15 catalyzed dienol→benzene rearrangement in acetone/water already at room temperature. Formation of the Wittig salts 117 and 120 from the parent allylic alcohols proceeds smoothly whith 63 % HBr and PPh_3 (see e.g. comments on scheme 4).

Scheme 13:

Accesses to NOR-Synthons



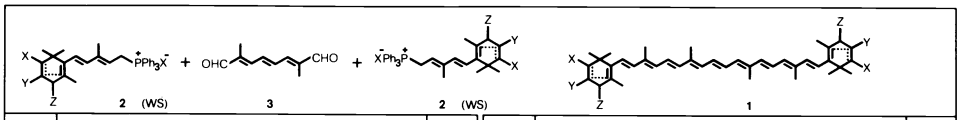
Nor-synthons (scheme 13; Ref. 49) are accessible most elegantly via the nor-oxo-isophorone 121, first prepared by Brenner (Ref. 50) by Mn(II)-catalyzed oxidation of 6-oxo-isophorone 6 with oxygen in boiling acetic acid. Raney-nickel hydrogenation of nor-oxo-isophorone 121 leads in analogy to the 6-ring series selectively to the saturated hydroxy-ketone 122. p-TsOH catalyzed dehydration of 122 under carefully controlled conditions gives trimethylcyclopentenone 87 in high yield. This interesting intermediate is also accessible by direct ring contraction from the chloro-diketone 86 as outlined in scheme 9.

In analogy to the 6-ring series (see scheme 7) nor-oxo-isophorone 121 can be oxidized with H_2O_2 in aqueous NaOH to the hydroxy-diketone 123. Hydrogenation of the corresponding sodium salt in the presence of Raney-nickel in methanol or electro-reduction gives, selectively and in high yield, the dihydroxy-ketone 124. In contrast to the 6-ring series 124 does not form a cyclic acetonide. However, protection of the dihydroxy moiety can easily be effected by dehydrative cyclodimerization to yield the dioxan 125. The subsequent alkynylation to the acetylenic C_{14}-intermediate 126 in THF, the semihydrogenation to the (Z)-olefin 127 and the formation of the C_{14}-Wittig salt 128 proceed smoothly. The purification of the so far oily phosphonium salt 128 poses some problems.

The synthesis of nor-canthaxanthin starts with the reduction of the hydroxy-diketone 123 either by zinc/acetic acid or by an electrochemical procedure. The crude 2-hydroxy derivative 124 is subsequently acetylated with acetic anhydride. The acetoxy function can now easily be eliminated again by reduction with zinc/acetic acid. The enolized 1,3-diketone 129 obtained is etherified with isobutanol (Ref. 45) to give the isobutylether 130 in almost quantitative yield. This compound was first prepared by Rosenberger (Ref. 51) by methylating the enolether 134 of 2-methyl-1,3-cyclopentadione with LDA and methyl iodide in THF. The alkynylation, semihydrogenation and formation of the Wittig salt 133 have already been published by Rosenberger (Ref. 51). Alternatively, the isobutylether 130 can be transformed directly to the all-trans-C_{14}-hydroxy-ketone 135 by *in situ* reduction of the intermediate alkynylation product, the lithium propargylate, with Redal in hexane. Final transformation to the Wittig salt 133 can be accomplished in high yield by successive treatment with 63 % HBr and PPh_3 in methylene chloride at room temperature.

Scheme 14:

Final Wittig Condensations



2 (WS) 3 2 (WS) 1

(WS)	Carotenoid	No
14		136
12		137
13		138
22		139
22		140
34		141
35		142
34		143
37		144
42		145
		146
		147
47		148
45		149
55		150
53		151
54		152
55		153
58		154
61		155
69		156
72		157
76		158
78		159
85		160
82		161
93		162
91		163
97		164
106		165
110		166
120		167
117		168
115		169
114		170
128		171
		172
133		173

The final Wittig condensations (scheme 14) according to the general strategy ($C_{15}+C_{10}+C_{15}=C_{40}$) proceed principally in high yields. The Wittig salts 2 (WS) must be added in slight excess, otherwise some mono-olefination product is formed. The reaction is best carried out in ethanol with butylene oxide as the HX acceptor. Only in special cases better results are obtained with sodium methoxide/methanol in methylene chloride. The crude product must be isomerized in a boiling solvent, from which the best crystallizing and thermodynamically preferred compound, namely the all-trans-isomer, precipitates. The yields of such Wittig reactions, however, may be decreased under certain circumstances: If e.g. triple bonds are present in the 7- and 7'-position the 9,9'-dicis-isomer is often thermodynamically more stable and tends to crystallize together with the all-trans-isomer or even as the pure compound. For this reason isolated yields and purities of acetylenic carotenoids are often somewhat lower. Poor results are obtained also if the Wittig salts 2 or the final carotenoids are unstable as is the case in the allenic series or if specific (E)/(Z)-isomers are to be synthesized. As outlined in the introduction, reactions on the final carotenoid should, whenever possible, be avoided. However, some exceptions are indicated in scheme 14. Especially rhodoxanthin 146 and violerythrin 172 are easily accessible via their polyene precursors 145 and 171, respectively.

Summary and conclusions: 6-Oxo-isophorone 6 has been demonstrated to be a well tailored substrate for the synthesis of a variety of carotenoids with different endgroups: cyclohexane derivatives functionalized in the positions 2,3 and 4, allenes, benzene derivatives and cyclopentane derivatives. Adjustment of the substitution pattern of the ring according to the target carotenoid must be carried out initially. Thus difficulties during further conversion to the corresponding C_{15}-Wittig salts ($C_9+C_6=C_{15}$) by using the bifunctional C_6-vitamin A intermediate 5 are minimized. With the ($C_{15}+C_{10}+C_{15}$) double Wittig condensation as the final step, labile intermediates and reactions with the very unsoluble and rather unstable polyene can largely be avoided.

Following these principles, very short syntheses with 5-10 steps in average for almost every carotenoid can be designed. As an example the well developed synthesis of astaxanthin 157 might be mentioned (Ref. 37), which needs 6 or 7 steps and proceeds in an overall yield of more than 50 %. Furthermore, using a semiprotected derivative of the C_{10}-dialdehyde 3 (Ref. 52) and 2 successive Wittig reactions a vast number of unsymmetric carotenoids could also be synthesized very efficiently.

ACKNOWLEDGMENTS

It is a pleasure to acknowledge the collaboration of all the collegues whose names appear in the references as well as the fruitful discussions with my collegues of the Departement of Vitamin and Nutrition Research. Special thanks are due to G. Englert and W. Arnold (NMR), W. Meister (MS), K. Noack (CD, ORD), P. Schönholzer (X-ray), A. Dirscherl (micro analysis), M. Vecchi and E. Glinz (HPLC). Many helpful discussions with Prof. H.-J. Hansen are also gratefully acknowledged.

REFERENCES

1. O. Isler (editor), Carotenoids, Birkhäuser Verlag, Basel and Stuttgart (1971); O. Straub, Key to Carotenoids: Lists of Natural Carotenoids, Birkhäuser Verlag, Basel and Stuttgart (1976).
2. H. Mayer, Pure Appl. Chem. 51, 535 (1979).
3. G. Wittig and H. Pommer, Ger. Pat. 954, 247 (1956).
4. B.C.L. Weedon, Brit. Pat. 1.173.063 (1969).
5. B.C.L. Weedon, Chem. in Britain 3, 424 (1967); B.C.L. Weedon, Pure Appl. Chem. 20, 531 (1969); B.C.L. Weedon, Rev. Pure Appl. Chem. (Australia) 20, 51 (1970).
6. F. Kienzle and H. Mayer, Helv. Chim. Acta 61, 2609 (1978).
7. E. Widmer, R. Zell, E.A. Broger, Y. Crameri, H.P. Wagner, J. Dinkel, M. Schlageter and T. Lukac, Helv. Chim. Acta 64, 2436 (1981).
8. R. Marbet and R. Zell, unpublished results.
9. M. Seuret and E. Widmer , Belg. Pat. 830.723 (1975); J.J. Becker, W. Skorianetz and P. Ulrich, Ger. Pat. 2459 148 (1974).
10. E. Widmer, Belg. Pat. 826.113 (1975); M.S. Kharasch and P.O. Tawney, J. Amer. Chem. Soc. 63, 2308 (1941); J. Meinwald and L. Hendry, J. Org. Chem. 36, 1446 (1971); J.J. Becker, K.-H. Schulte-Elte, H. Stricker and G. Ohloff, Ger. Pat. 2457157 (1973); M. Costantini, A. Dromard, M. Jouffret, US Pat. 4.092.361 (1978); iidem Fr. Dem. 75/39782 (1975); iidem Ger. Pat. 2610254 (1975); M. Costantini, A. Dromard, M. Jouffret, B. Brossard and J. Vavaguat, J. Mol. Catal. 7, 89 (1980).
11. W. Brenner, Swiss Pat. 8187/74 (1974).
12. M. Soukup, R. Zell, E. Broger, K. Steiner and E. Widmer, to be published; G.L. Olson, H.C. Cheung, K.D. Morgan, R. Borer and G. Saucy, Helv. Chim. Acta 59, 567 (1976).
13. W. Sarnecki and H. Pommer, Ger. Pat. 1060.386 (1959).
14. J. Paust, W. Hoffmann and M. Baumann; Ger. Pat. 2843 901 (1980).

15. W. Hoffmann and M. Baumann, Ger. Pat. 2504.930 (1975).
16. M. Soukup, T. Lukac and E. Widmer, to be published.
17. S. Kim and K. Han Ahn, J. Org. Chem. 49, 1717 (1984).
18. K. Tsukida, K. Saiki, M. Ito, I. Tomofuji and M. Ogawa, J. Nutr. Sci. Vitaminol. 21, 147 (1975).
19. H.G.W. Leuenberger, B. Wipf and E. Kupfer, unpublished results.
20. M. Ito, R. Masahava and K. Tsukida, Tetrahedron Lett. 32, 2767 (1977).
21. T. Lukac, M. Soukup and E. Widmer, to be published.
22. T. Lukac, M. Soukup, R. Zell and E. Widmer, to be published.
23. A. Rüttimann, unpublished results.
24. D.Y. Curtin and A.R. Stein, Org. Synth. 46, 115 (1966); M. Bertrand, P. Teisseire and G. Pelerin, Tetrahedron Lett. 21, 2055 (1980); J. M. Berge, M. Rey and A.S. Dreiding, Helv. Chim. Acta 65, 2230 (1982); F. Näf, R. Decorzant, W. Giersch and G. Ohloff, Helv. Chim. Acta 64, 1387 (1981); G. Quinkert, G. Dürner, E. Kleiner, F. Adam, E. Haupt and D. Leibfritz, Chem. Ber. 113, 2227 (1980).
25. K. Aareskjöld and S. Liaeen-Jensen, Proc. 5th Int. Symposium on Carotenoids, Madison (1978).
26. H. Chikashita, M. Miyazaki and K. Itoh, Synthesis, 308 (1984).
27. E. Widmer, M. Soukup, R. Zell, E.A. Broger, B. Lohri, R. Marbet and T. Lukac, Helv. Chim. Acta 65, 944 (1982).
28. E. Widmer, R. Zell, H.J. Grass and R. Marbet, Helv. Chim. Acta 65, 958 (1982).
29. R. Kuhn and H. Brockmann, Chem. Ber. 66, 407 (1933); iidem, ibid. 66, 1319 (1933).
30. C.D. Robeson, U.S. Pat. 667001 (T. 13) (1968).
H. Mayer and U. Schwieter, Swiss Pat. 4338/68 (1968).
31. R. Zell, E. Broger, M. Soukup and E. Widmer, to be published.
32. H.G.W. Leuenberger, W. Boguth, E. Widmer and R. Zell, Helv. Chim. Acta 59, 1832 (1976).
33. E. Widmer, R. Zell, E. Broger, M. Soukup, T. Lukac, M. Imfeld, H.P. Wagner and H. Mayer, to be published; A. Rüttimann and H. Mayer, Helv. Chim. Acta 63, 1456 (1980).
34. R. Zell and G. Englert, to be published; B.C.L. Weedon, Brit. Pat. 1 193 063 (1969); B.C.L. Weedon, Pure Appl. Chem. 20, 531 (1969); A.J. Davis, A. Khare, A.K. Mallams, R.A. Massy-Westropp, G.P. Moss and B.C.L. Weedon, J. Chem. Soc. in press; G. Saucy and G. Weber, US Pat. 890 173, 27.3.(1978).
35. F. Kienzle and H. Mayer, Helv. Chim. Acta 61, 2609 (1978).
36. E. Widmer, R. Zell, T. Lukac, M. Casadei, P. Schönholzer and E.A. Broger, Helv. Chim. Acta 64, 2405 (1981).
37. E. Widmer, R. Zell, E.A. Broger, Y. Crameri, H.-P. Wagner, J. Dinkel, M. Schlageter and T. Lukac, Helv. Chim. Acta 64, 2436 (1981).
38. R. Zell, E. Widmer, T. Lukac, H.G.W. Leuenberger, P. Schönholzer and E.A. Broger, Helv. Chim. Acta 64, 2447 (1981).
39. R. Zell and E. Widmer, Helv. Chim. Acta 64, 2463 (1981).
40. E. Widmer, T. Lukac, K. Bernhard and R. Zell, Helv. Chim. Acta 65, 671 (1982).
41. M. Soukup, T. Lukac, R. Zell, E.A. Broger, H. Stoller, H. Grass, R. Casadei and E. Widmer, to be published.
42. M. Rosenberger, P. Mc Dougal and J. Bahr, J. Org. Chem. 47, 2130 (1982).
43. M. Baumann and W. Hoffmann, Ger. Pat. 3 112 056 (1982).
44. T. Lukac, M. Soukup and E. Widmer, to be published.
45. W.F. Gannon and H.O. House, Org. Synth. 40, 41 (1960).
46. R. Zell, M. Soukup, K. Steiner, T. Lukac, A. Montavon, P. Schönholzer and E. Widmer, to be published.
47. K. Bernhard et al., to be published.
48. T. Lukac, M. Soukup and E. Widmer, to be published; H. Kjosen, S. Liaaen-Jensen and C.R. Enzell, Acta. Chim. Scand. 25, 85 (1971); R.D.G. Cooper, J.B. Davis and B.C.L. Weedon, J. Chem. Soc. 5637 (1963); M.C. Khosla and P. Karrer, Helv. Chim. Acta 43, 453 (1960); M. Yamaguchi, Bull. Chem. Soc. Japan 32, 1171 (1959) and 33, 1560 (1960); S. Akiyama, S. Nakatsuji, S. Eda, M. Kataoka and M. Nakagawa, Tetrahedron Lett. 2813 (1979).
49. E. Broger, H. Grass, T. Lukac, P. Nösberger, M. Soukup, K. Steiner, E. Widmer and R. Zell, to be published.
50. W. Brenner, Ger. Pat. 283 4557 (1978).
51. M. Rosenberger and P.J. Mc Dougal, J. Org. Chem. 47, 2134 (1982).
52. K. Bernhard, G. Englert, H. Mayer, R.K. Müller, A. Rüttimann, M. Vecchi, E. Widmer and R. Zell, Helv. Chim. Acta 64, 2469 (1981).