

Advances in the synthesis of optically active carotenoids

Hanspeter Pfander

Institute of Organic Chemistry, University of Berne, Freiestr. 3,
CH-3012 Bern, Switzerland

Abstract - The synthesis of the following optically active carotenoids are reported: (S)-1,2-epoxy-1,2-dihydro-lycopene, (S)-1',2'-epoxy-1',2'-dihydro- γ -carotene, (S)-1,2-epoxy-1,2-dihydro- ζ -carotene, (R)- β,β -carotene-2-ol, (S)-plectanixanthin, (2S,2'S)-bisanhydro-bacterioruberin, (S)-2-isopentenyl-3,4-dehydrorhodopin, (S)-tris-anhydrobacterioruberin and (2R,2'R)-2,2'-bis(4-hydroxy-3-methyl-2-butenyl)- β,β -carotene (C.p. 450).

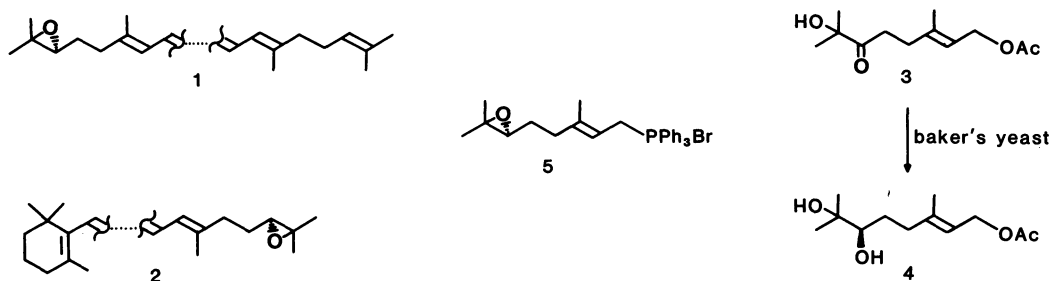
INTRODUCTION

In the past few years major efforts have been made toward the synthesis of optically active carotenoids. A complete and excellent review on this topic was given at the 5th International Symposium on Carotenoids (Ref. 1). It was shown that at that time twenty different optically active end groups and carotenoids had been synthesised, as e.g. (3S,3'S)- and (3R,3'R)-astaxanthin and (3S,3'S)- and (3R,3'R)-zeaxanthin. In the meantime various other optically active end groups and carotenoids were synthesised, as e.g. carotenoids with the optically active hydroxylated ϵ -end group (lutein group, fritschiellaxanthin monoacetate, tunaxanthin group) (Ref. 2&3) and the red pepper carotenoids ((3S,5R,3'S,5'R)-capsorubin, (3R,3'S,5'R)-capsanthin, (3S,5R)-cryptocapsin) (Ref. 4). Major advances were also made in the synthesis of 3,4-oxygenated xanthophylls (Ref. 5).

In the following review some recent advances in the synthesis of optically active carotenoids originating from our laboratories are presented.

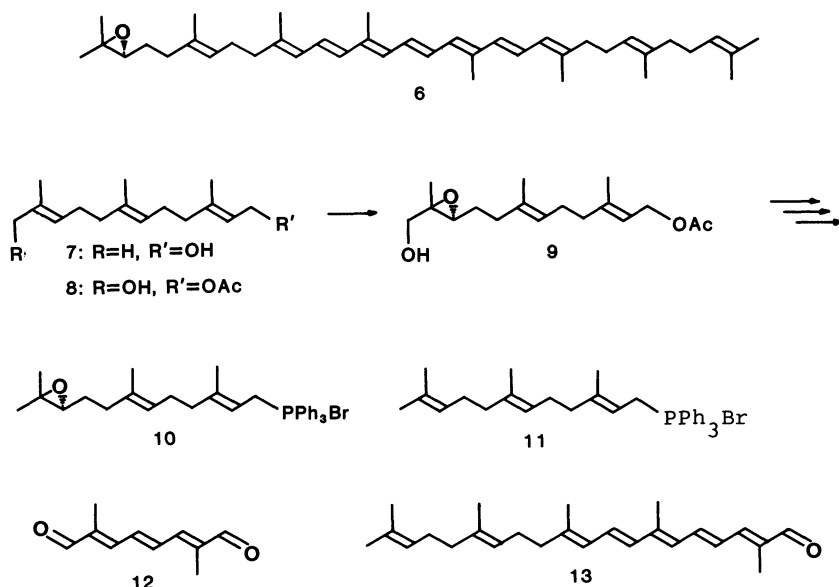
SYNTHESIS OF OPTICALLY ACTIVE 1,2-EPOXYCAROTENOIDS

Carotenoids with an epoxy function in the acyclic ψ -end group were isolated some time ago from tomatoes (Ref. 6). After having completed the synthesis of racemic 1,2-epoxy-1,2-dihydro-lycopene, 1',2'-epoxy-1',2'-dihydro- γ -carotene and 1',2'-epoxy-1',2'-dihydro- δ -carotene (Ref. 7) we have recently synthesised (S)-1,2-epoxy-1,2-dihydro-lycopene (1) and (S)-1',2'-epoxy-1',2'-dihydro- γ -carotene (2) (Ref. 8). The key step for the synthesis was the reduction of the α -hydroxy-ketone 3 to the corresponding (-)-(R)-diol 4 with baker's yeast. It was also shown by transformation of (-)-4 and of (+)-4 to the camphanic acid esters and separation by HPLC that this reduction proceeds with an enan-



tiomeric excess of 81%. The Wittig salt (S)-5 was obtained from (R)-4 through standard procedures and the reaction with 8'-apo- ψ -carotene-8'-al and 8'-apo- β -carotene-8'-al respectively gave 1 (60% of the all-(E)-, 25% of the (7Z)- and 15% of the (7'Z)-isomer) and 2 (60% of the all-(E)- and 30% of the (7'Z)-isomer). These isomers were separated by HPLC (Ref. 9) and subjected to extensive $^1\text{H-NMR}$ - and CD-studies. It was also shown by comparison of the CD-data of the synthetic and of the natural products (Ref. 10) that the natural 1 and 2 have the (S)-configuration.

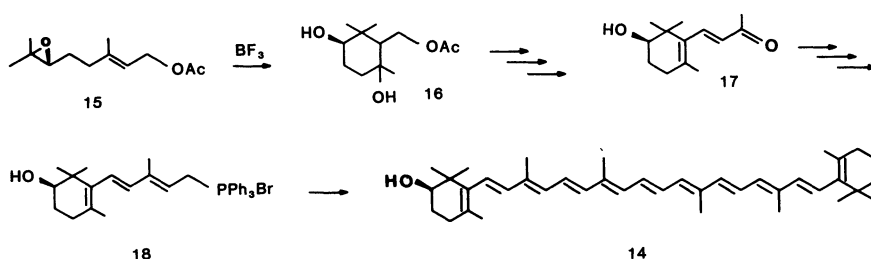
Recently we have also synthesised (S)-1,2-epoxy-1,2-dihydro- ζ -carotene (6) (Ref. 11). (E,E)-Farnesol (7) was converted to the allylic alcohol 8 and epoxidation according to Sharpless (Ref. 12) gave 9. This compound was afterwards transformed (tosylation, conversion to the iodide, reduction, saponification, bromination and reaction with Ph_3P) to the desired (S)-epoxyfarnesyl-



Wittig salt (10). The other end group 11 was synthesised starting also from (E,E)-farnesol. The Wittig reaction ($\text{NaOH}/\text{CH}_2\text{Cl}_2$) of 11 with the C_{10} -dialdehyde 12 gave the C_{25} -aldehyde 13 in good yield. The final step of the synthesis, the reaction of 13 with the optically active Wittig salt 10 ($\text{NaOH}/\text{CH}_2\text{Cl}_2$) gave with low yield the desired 1,2-epoxy-1,2-dihydro- ζ -carotene (6). The CD-data of the synthetic product may now be used for the comparison with the natural product to determine its configuration.

SYNTHESIS OF (R)- β , β -CAROTENE-2-OL

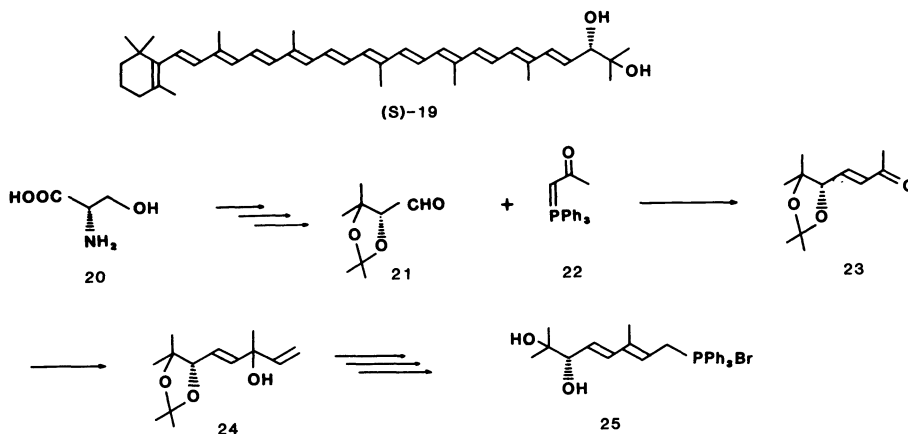
Carotenoids with the (R)-2-hydroxy- β -end group such as β , β -carotene-2-ol, β , ϵ -carotene-2-ol and β , β -carotene-2,2'-diol were isolated for the first time from the green algae *Trentepohlia iolithus* (Ref. 13). Later these carotenoids were also isolated from stick insects (Ref. 14). The (R)-configuration at the asymmetric carbon atom was determined by chemical degradation and application of the modified Horeau method (Ref. 15). Later the synthesis of the unnatural (S)- β , β -carotene-2-ol was reported (Ref. 16). 2-Oxo- β -ionone was reduced with baker's yeast to (S)-2-hydroxy- β -ionone and transformed following known procedures to (S)- β , β -carotene-2-ol. Recently we have synthesised the natural (R)- β , β -carotene-2-ol (14) (Ref. 17); the acid catalyzed cyclization of acetylated (R)-geraniol epoxide 15 to compound 16 was the important step. The acetylated (R)-geraniol epoxide 15 was prepared according to known procedures using again the epoxidation according to Sharpless (Ref. 12). The cyclization was as expected the crucial step of the synthesis and after trying out different conditions compound 16 was obtained by reaction of 15 with $\text{BF}_3/\text{CH}_2\text{Cl}_2$ at



-70°C in 16% yield. The cyclic compound 16 was afterwards converted to (R)-2-hydroxy- β -ionone (17) by protecting first the two hydroxy groups of 16, afterwards saponification, oxidation, aldol condensation with acetone and at the same time elimination of the hydroxy group at C(5) and deprotection of the hydroxy group at C(2). The Wittig salt 18 was obtained by the reaction of 17 with vinylmagnesium bromide, followed by the reaction with triphenylphosphonium bromide. According to the scheme $C_{15} + C_{25} = C_{40}$ the Wittig salt 18 was reacted with 12'-apo- β -carotene-12'-al to (R)- β , β -carotene-2-ol (14). Comparison of the CD-spectra of the synthetic product with the CD-spectra of the natural product (Ref. 13) proves the postulated (R)-configuration of the natural product. The optical purity of the synthesised product was determined by transformation of 16 to the corresponding diastereomeric camphanic acid esters. The separation by HPLC showed that the enantiomeric excess is >95%.

SYNTHESIS OF (S)-PLECTANIAXANTHIN

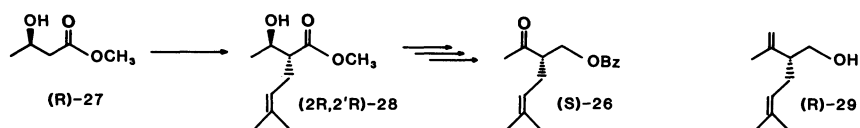
Plectaniaxanthin (19), a carotenoid with the chiral 1,2-dihydroxy-3,4-didehydro- ψ -end group was isolated for the first time from the fungus Plectania coccinea (Ref. 18). Later this carotenoid was isolated from other fungi (Ref. 19). By comparison of the CD-spectra of synthetic (S)-16',17'-dinorplectaniaxanthin-acetonide (ex D-mannitol) and of the acetonide of the natural compound the (R)-configuration was proposed for the latter (Ref. 20). In view of the synthesis of optically active plectaniaxanthin we have recently shown (Ref. 21) that starting from L-serine (20) compound 21 can be obtained in high chemical and optical yield. Starting from 21 we have now accomplished the synthesis of (S)-plectaniaxanthin (S-19) (Ref. 22). The Wittig reaction of the aldehyde 21 gave in a good yield the ketone 23 which gave with vinylmagnesium bromide the tertiary alcohol 24. Bromination with PBr_3 and reaction with PPh_3 gave afterwards the corresponding Wittig salt. The protecting group was afterwards removed by boiling in 10% acetic acid to give 25. For the determination of the optical purity of our building block the ketone 23 was deprotected and the resulting diol esterified with camphanic acid chloride and compared with the camphanic acid esters prepared from the racemic dihydroxy-ketone. It was shown that the enantiomeric excess of 23 was >96%. In the final step of the synthesis the Wittig salt 25 gave with 8'-apo- β -carotene-8'-al in epoxybutane the desired (S)-plectaniaxanthin in low yield. Comparison of the CD-data of our synthesised product with the data of the isolated compound are consistent with the (R)-configuration of the natural compound.



SYNTHESIS OF OPTICALLY ACTIVE ACYCLIC AND CYCLIC C₄₅- AND C₅₀-CAROTENOIDS

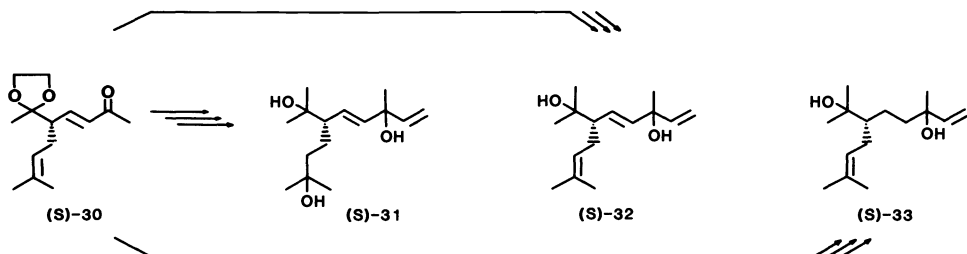
In previous communications (Ref. 23-25) we reported on our work directed toward the synthesis of optically active acyclic C₄₅- and C₅₀-carotenoids.

According to Straub (Ref. 26) eight compounds of this group were isolated from halophilic bacteria (Ref. 27). The key intermediates (R)-26 and (S)-26 which appeared to be suitable for the synthesis of the three chiral end groups of acyclic C₄₅- and C₅₀-carotenoids were prepared starting from methyl(3R)-3-

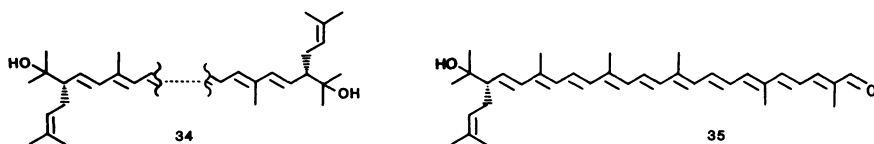


hydroxy-butanoate ((R)-27) and ethyl(3S)-3-hydroxy-butanoate ((S)-27) according to Frater (Ref. 28). It was shown that α -alkylation of the dilithium derivatives of optically active esters of β -hydroxy-carboxylic acids give with a selectivity of >90% the erythro isomer. The resulting compounds (2R,1'R)-28 and (2S,1'S)-28 were afterwards converted in three steps with good chemical yields to the compounds (R)- and (S)-26. The synthesis of (R)- and (S)-lavan-dulol ((R)- and (S)-29) and the comparison of the data with isolated (R)-lavan-dulol (Ref. 29) prove the excellent optical purity of the synthons. In a four step synthesis (acetalisation, hydrolysis, oxidation and Wittig reaction) the key intermediate (S)-26 was converted to compound (S)-30 (e.e. >92%;

¹H-NMR, Eu(tfc)₃). From this compound the end group (S)-31 of (2S,2'S)-bacterioruberin was synthesised in seven steps in 21% yield. The compound (S)-32 - the end group for the preparation of (2S,2'S)-bisanhdrobacterioruberin, (S)-isopentenyl-3,4-dehydrorhodopin and (S)-trisanhydrobacterioruberin - was prepared in 47% yield (five steps) and the third end group (S)-33 which is characteristic of bisanhydrotetrahydrobacterioruberin was formed in 56% yield (four steps). Recently we have accomplished the first synthesis of optically active C₄₅- and C₅₀-carotenoids (Ref. 30).

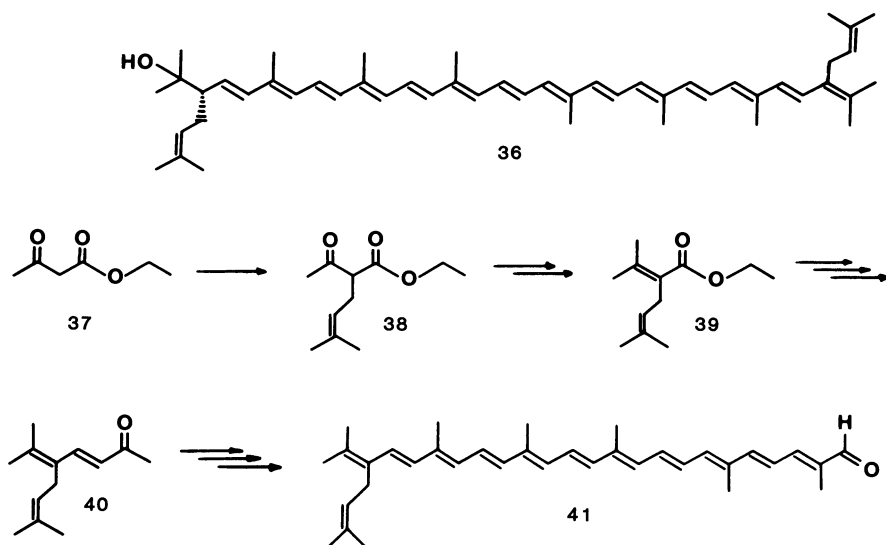


The compound (S)-32 was converted to the corresponding Wittig salt in 65% yield and the reaction with crocetinindialdehyde gave after chromatography and crystallisation (all-E,2S,2'S)-bisanhdrobacterioruberin ((all-E,2S,2'S)-34) in 37% yield and the C₃₅-aldehyde (S)-35 as by-product. The latter compound was



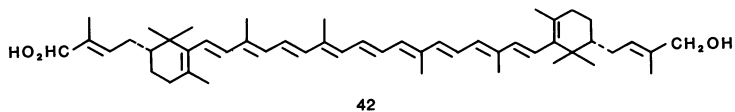
subjected to extended NMR-studies (Ref. 30). The C₄₅-carotenoid (S)-2-isopentenyl-3,4-dehydrorhodopin was synthesised by reaction of the Wittig salt with 8'-apo- ψ -carotene-8'-al.

For the synthesis of (S)-trisanhydrobacterioruberin (36) a new achiral end group was synthesised (Ref. 31). The β -keto-ester 37 was alkylated to give 38.

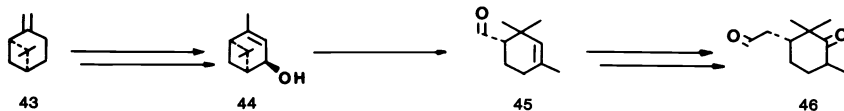


By reaction with diethylchlorophosphate and coupling with lithiumdimethylcuprate this compound gave the ester 39. Reduction, followed by oxidation and a Wittig reaction gave the desired compound 40 in good yield. Reaction of 40 with vinylmagnesium bromide gave the corresponding C_{15} -compound which was afterwards converted to the Wittig salt. Reaction of this Wittig salt with crocetininaldehyde in $CH_2Cl_2/NaOH$ gave the C_{35} -aldehyde 41. The reaction of this compound with the optically active end group of (2*S*,2'*S*)-bisanhydrobacterioruberin gave (S)-trisanhydrobacterioruberin.

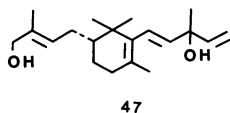
Beside the acyclic C_{45} - and C_{50} -carotenoids thirteen naturally occurring cyclic compounds have been reported (Ref. 26). The structure of these carotenoids partially seem uncertain due to the missing high field NMR-spectra. Recently the structure of C.p. 450 which was isolated from *Corynebacterium poinsettiae* was revised to (2*R*,2'*R*)-2,2'-bis(4-hydroxy-3-methyl-2-butenyl)- β,β -carotene (42) (Ref. 32). This symmetrical structure has two identically substituted β -



end groups each with one primary allylic hydroxy group in the (E)-position. In our laboratories we have recently synthesised optically active C.p. 450 (Ref. 33). (-)- β -Pinene (43) was transformed following known procedures to (-)-verbenol (44) which on pyrolysis (Ref. 34) gave the optically active alde-



hyde 45 with an e.e. >90% (determined by reduction, esterification with camphanic acid chloride and GC analysis). This compound was afterwards transformed to the keto-aldehyde 46. For the synthesis of the side chain of 47 a



Horner reaction was used whereas for the elongation of the polyene chain Grignard reactions were used. For the synthesis of C.p. 450 the primary hydroxy group of 47 was converted to the acetate and afterwards the corresponding Wittig salt was prepared. Condensation of the Wittig salt with the C_{10} -dialdehyde (12) gave, after chromatography and crystallisation (all-E)-42 in moderate yield.

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