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Bacterial Carotenoids. XLIII.* C_{50}-Carotenoids. 13.** Synthesis of (2*R*,2′*R*)-2,2′-Dimethyl-β,β-carotene and Absolute Configuration of (2*R*,2′*R*)-2-(4-Hydroxy-3-hydroxymethyl-2-butenyl)-2′-(3-methyl-2-butenyl)-β,β-carotene

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This first assignment of absolute stereochemistry to a C_{50}-carotenoid, *C.p.* 450 = (2*R*,2′*R*)-2-(4-hydroxy-3-hydroxymethyl-2-butenyl)-2′-(3-methyl-2-butenyl)-β,β-carotene (*5*), followed from CD-correlation with natural (2*R*,2′*R*)-β,β-carotene-2,2′-diol (*4*) and (2*R*, 2′*R*)-2,2′-dimethyl-β,β-carotene (*12*) synthesized here.

All fourteen [1–4] known naturally occurring C_{45}- and C_{50}-carotenoids are distinguished by having additional C_5-isopentenyl units formally added to the 2- or 2,2′-positions on a C_{40}-skeleton; exemplified by bacterioruberin (*1*), bisanhydrobacterioruberin (*2*), and decaprenoxanthin (*3*), Scheme 1. Provided enzymatic control, this addition induces optical activity at C-2 (2′), indicated by asterisks in Scheme 1. From CD correlation bacterioruberin (*1*) and bisanhydrobacterioruberin (*2*) are known to possess the same absolute configurations.[5] Chiroptical properties of decaprenoxanthin (*3*) have also been reported.[5,6] However, despite rapid advances in the stereochemistry of C_{40}-carotenoids, no absolute configurations of C_{45}- or C_{50}-carotenoids have hitherto been reported.

Recent reports on the absolute stereochemistry of (+)-(*R*)-β-irone (*7*, Scheme 2) [7] and tentative stereochemical assignment to (2*R*,2′*R*)-β,β-carotene-2,2′-diol (*4*) [8] prompted us to investigate the stereochemistry of some C_{50}-carotenoids; in particular that of 2-(4-hydroxy-3-hydroxymethyl-2-butenyl)-2′-(3-methyl-2-butenyl)-β,β-carotene (*5*; *C.p.* 450 [3]), Scheme 1.

(2*R*,2′*R*)-β,β-Carotene-2,2′-diol (*4*) and *C.p.* 450 (*5*, stereochemistry hitherto unknown) have common chromophores and differ only in the nature of the 2-substituent. Each have termini which may be regarded as 4-substituted cyclohexenes (see structure *6*, Scheme 1). From Mills' rule,[9,10] the optical rotation of cyclohexene systems with an asymmetric carbon at position 4 is caused by a preferred conformation of the cyclohexene ring itself and the nature of the substituent is not relevant. Application of Mills' rule may lead to erroneous results,[11] although its validity in the carotenoid series for the stereochemical correlation of (2*R*,2′*R*)-β,β-carotene-2,2′-diol (*4*) and zeaxanthin (3*R*,3′*R*)-β,β-carotene-3,3′-diol) has recently been confirmed.[12a] As a further model for CD-correlation (2*R*,2′*R*)-2,2′-dimethyl-β,β-carotene (12) was synthesized from (+)-(*R*)-β-irone (*7*). Optically inactive *12* has previously been synthesized by Eugster *et al.*[12b] by a different route.

RESULTS AND DISCUSSION

(+)-(6*R*)-β-Irone (*7*) was isolated by preparative GLC from a base-isomerized mixture of natural irones.[7] The synthesis of (2*R*,2′*R*)-2,2′-dimethyl-β,β-carotene (*12*) followed the route

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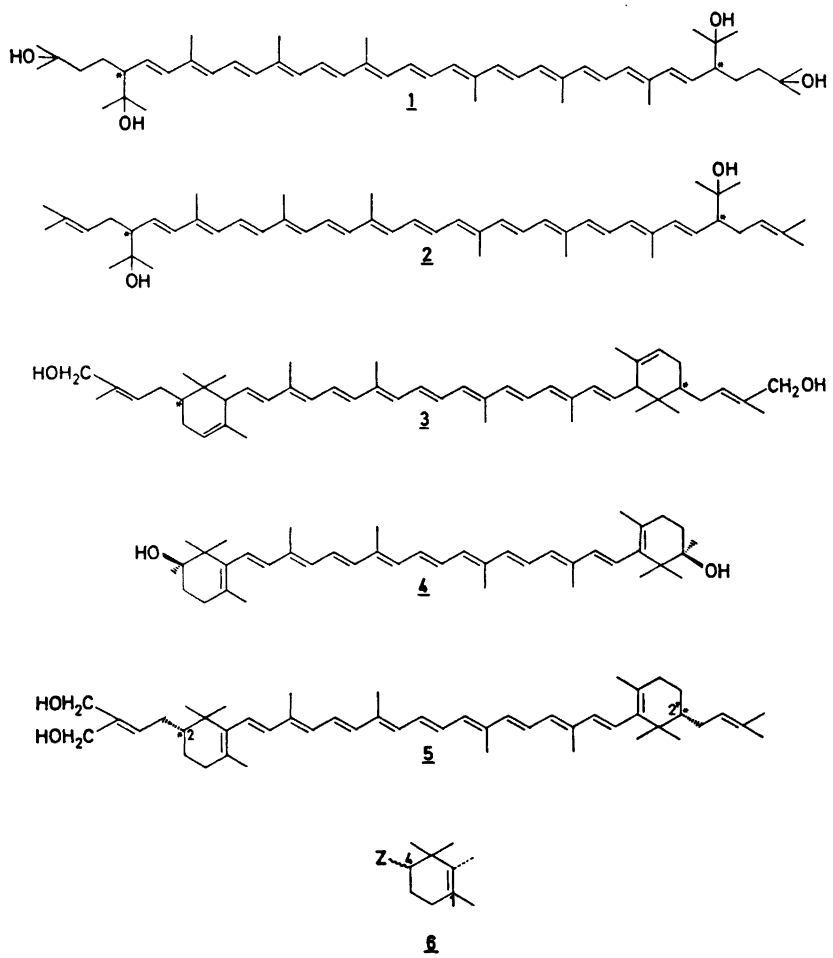


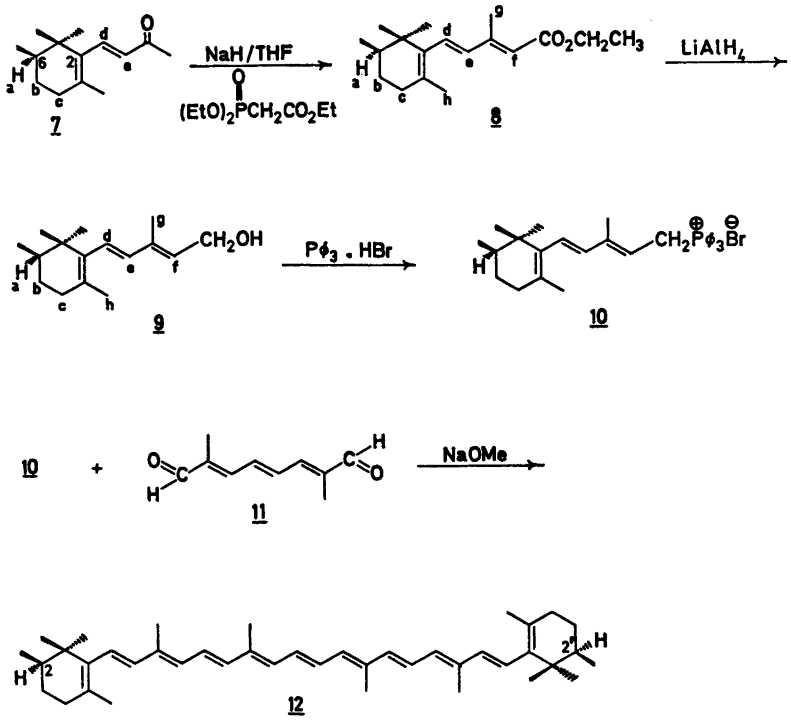
Scheme 1.

shown in Scheme 2. Treatment of *7* with ethyl diethylphosphonoacetate gave (*R*)-β-ironylidene acetate (*8*). Reduction with $LiAlH_4$ provided the allylic alcohol *9* which was converted to the corresponding phosphonium bromide *10*. Condensation of *10* with the trienedial *11* gave (2*R*,2′*R*)-2,2′-dimethyl-β,β-carotene (*12*).

The electronic absorption spectrum of *12* corresponded to that of β-carotene. The ^1H NMR spectrum, including signal assignments, is reproduced in Fig. 1. The upper mass region of the mass spectrum is shown in Fig. 2.

The CD spectra of *trans* (2*R*,2′*R*)-2,2′-dimethyl-β,β-carotene (*12*), (2*R*,2′*R*)-β,β-carotene-2,2′-diol (*4*) and *C.p.* 450 (*5*, available from a previous investigation [3]) are shown in Fig. 3. Immediately apparent is the similarity between the curves of *4* and *12*, possessing the same absolute stereochemistry, and differing only in the nature of the 2-substituent, hydroxyl *versus* methyl. This compatibility further confirms that the principle of Mills' rule is applicable to these carotenoid systems.

The CD spectrum of *C.p.* 450 (*5*) is virtually exactly opposite to those of *4* and *12*, revealing opposite absolute configuration in 2,2′-positions. *C.p.* 450 has therefore configuration *5*. Formally, *C.p.* 450 is (2*R*,2′*R*)-2-(4-hydroxy-3-hydroxymethyl-2-butenyl)-2′-(3-methyl-2-butenyl)-β,β-carotene.[13]



Scheme 2.

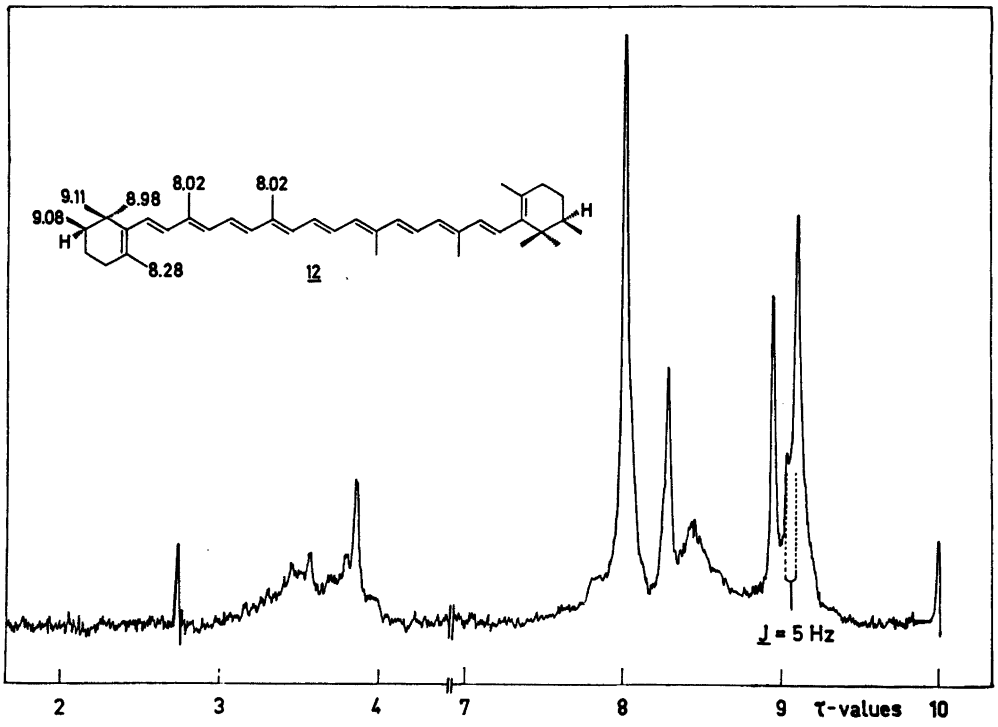


Fig. 1. ^{1}H NMR spectrum of (2*R*,2′*R*)-2,2′-dimethyl-β,β-carotene (*12*).

Fig. 2. Mass spectrum of (2*R*,2′*R*)-2,2′-dimethyl-β,β-carotene (*12*).

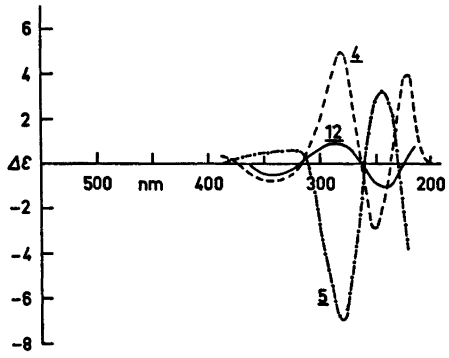


Fig. 3. CD-spectra of (2*R*,2′*R*)-2,2′-dimethyl-β,β-carotene (*12*, ———), (2*R*,2′*R*)-β,β-carotene-2,2′-diol (4, – – –) and *C.p.* 450 (*5*, - · - ·) in EPA.

Further studies on the absolute configurations of other C_{50}-carotenoids are in progress.

EXPERIMENTAL

Material and methods. All solvents were of analytical grade or distilled before use. Comparative TLC of carotenoid intermediates was on silica gel HF_{254} plates developed with petroleum ether-acetone solutions. Separation and purification of synthetic carotenoids were accomplished with alumina plates (1 mm) developed with petroleum ether-ethyl ether (97:3). Comparative chromatography of carotenoids was on Merck alumina HF_{254} Type E pre-coated plates (0.2 mm).

Instruments used were as specified elsewhere.[14] Specific rotations of carotenoid intermediates were obtained on a Perkin-Elmer 141 polarimeter and CD spectra recorded in EPA (ether-isopentane-ethanol, 5:5:2) on a Roussel-Jouane Dicrographe.

(+)-(*R*)-β-Irone (*7*) was isolated with an Aerograph Autoprep A-700 chromatograph using a 4.5 m × 12 mm metal column packed with Carbowax 20M (15 %) on Chromosorb W (60 – 80 mesh) at 190°C and 190 ml/min (helium). Carotenoid intermediates (*7*, *8*, *9* were examined for purity with a Perkin-Elmer F-11 gas chromatograph fitted with a 1.8 m glass column packed with OV-17 (5 %) on Chromosorb W;

temperature programmed from 110 °C at 2°/min.

C.p. 450 (5). 5 was available from an earlier reported study.[3] The CD spectrum is given in Fig. 3.

Composition of natural Iris oil. GLC analysis of natural Iris oil (Absolute Iris Essence) showed the following irone composition: (−)-(2*R*,6*R*)-*trans*-α-irone (numbering and nomenclature of irones follow that used by Rautenstrauch and Ohloff,[7] *cf.* *7*, Scheme 2), 20.7 % (of total irones); (+)-(2*S*,6*R*)-*cis*-α-irone (*cis* refers to the 2,6-substituents), 41.8 %; (+)-(2*S*,6*R*)-*cis*-γ-irone, 37.4 %.

Alkali-catalyzed isomerization of Iris oil. Iris oil (3 g) in a MeOH-H_2O (20 ml, 85:15) solution containing 10 % KOH was heated at 40 °C under N_2 for 24 h.[7] The ether extractable fraction was concentrated under vacuum and distilled at 0.3 Torr. A yellow oil (2 g) which distilled at 110 − 130 °C was collected and (+)-(6*R*)-β-irone (*7*, 0.85 g) isolated by preparative GLC. Irone composition of oil after isomerization: (+)-(6*R*)-β-irone (*7*), 61.6 %; (+)-(2*S*,6*R*)-*cis*-α-irone, 8.2 %; (−)-(2*R*,6*R*)-*trans*-α-irone, 30.2 %. Analytical GLC showed the β-irone (*7*) collected exceeded 98 % purity. The following physical properties for *7* were recorded: $[\alpha]^{20}$ (EtOH) 589 nm = 16°, 578 nm = 17°, 546 nm = 20° and 436 nm = 36°; λ_{max} 296 nm in MeOH; IR (liq.) 2980, 2920, 2860 (s, C−H), 1690, 1670 (s, C=O), 1605 (s, C=C), 1360 (s), 1250 (s, C=O), 980 cm^{-1} (m, *trans* −HC=CH−); τ($CDCl_3$; signal assignments with reference to *7*, Scheme 2) 9.083 d(3 H, *J* = 5 Hz, CH−CH_3), 9.080, 8.95 (6 H, *gem.* dimethyl), 8.8 − 8.4 (3 H, H-*a*,*b*), 8.27 (3 H, =C-CH_3), 8.1 − 7.8 (2 H, H-*c*), 7.75 (3 H, O=C−CH_3), 3.94 d(1 H, *J* = 16 Hz, H-*e*), 2.77 d(1 H, *J* = 16 Hz, H-*d*); *m/e* 206 (M), 191 (M − 15), 149 (M − 57), 135 (M − 71) and 122 (M − 84).

Ethyl (+)-(6R)-β-ironylideneacetate (8). Ethyl diethylphosphonoacetate [15a] (1.7 g) was added to a suspension of NaH (200 mg) in tetrahydrofuran (THF, 6 ml) and stirred at 20 °C for 1 h. The mixture was cooled to 0 °C and *7* (0.85 g) in THF (1 ml) added. The reaction was stirred for 3 h at 0 − 5 °C, then at 20 °C for an additional 15 h. Water was added and the mixture extracted with ether. The organic layer was dried with Na_2SO_4, concentrated under vacuum and chromatographed on a kieselgel column developed with benzene from which *8* was isolated (1.016 g, 89 %). GLC and ^1H NMR analysis showed *8* to consist of 85 % *trans*- and 15 % *cis*-isomers (around the new double bond). The product *8* had: $[\alpha]^{20}$ (EPA) 589 nm = 33°, 578 nm = 35°, 546 nm = 41°, and 436 nm = 81°; λ_{max} (MeOH) 260, 295 nm; ν_{max} (liq.) 2960, 2920, 2840 (s, C−H), 1715 (s, C=O), 1610 (s, C=C), 1450 (m), 1235 (s, C−O), 1153 (s, C−O), 1050 (s), 970 cm^{-1} (m, *trans* −CH=CH−); τ($CDCl_3$; signal assignments with reference to *8*, Scheme 2) 9.12, 8.97 (6 *H*, *gem.* dimethyl), 9.06 d(3 H, *J* = 2.5 Hz, −CH−CH_3), 8.72 t(3 H, *J* = 7 Hz, CH_2−CH_3), 8.7 − 8.3 (3 H, H-*a*,*b*), 8.32 (3 H, H-*h*) 8.1 − 7.8 (2 H, CH_3-*c*), 7.66 (3 H, CH_3-*g*), 5.77 q (2 H, *J* = 7 Hz, C$H_2$$CH_3$), 4.35 (1 H, *cis*-H-*f*, *cf.* Ref. 15b), 4.25 (1 H, *trans*-H-*f*), 3.97 d(1 H, *J* = 16 Hz, H-*e*), 3.40 d(1 H, *J* = 16 Hz, H-*d*); *m/e* 276 (M) 263 (M − 15), 231 (M − 45) and 203 (M − 73).

(+)-(6R)-β-Ironylidene-ethanol (9). *8*, (0.94 g) in THF (10 ml) was added to a stirred solution of $LiAlH_4$ (0.2 g) in THF (20 ml) at 0 °C during 30 min. Stirring was continued for 1 h and the reaction monitored by TLC (disappearance of starting material). The complex was decomposed by cautious addition of MeOH followed by a saturated solution of NH_4Cl. After ether extraction *9* (0.84 g, quantitative yield) was isolated; $[\alpha]^{20}$ (EPA) 589 nm = 30°, 578 nm = 31°, 546 nm = 37°, 436 nm = 68° and 365 nm = 327°; λ_{max} (MeOH) 237, 265 nm; ν_{max} (liq.) 3320 (s, OH), 2960, 2920, 2860 (s, C−H), 1000 (m, OH), 920 cm^{-1} (s, *trans* −CH=CH− τ($CDCl_3$; signal assignments with reference to *9*, Scheme 2) 9.13, 8.99 (6 H, *gem.* dimethyl), 9.09 d(3 H, *J* = *ca.* 5 Hz, −CH−CH_3), 8.7 − 8.3 (3 H, H-*a*,*b*), 8.32 (3 H, CH_3-*h*), 8.14 (3 H, CH_3-*g*), 8.25 − 7.85 (2 H, H-*c*), 5.17 d(2 H, *J* = 7 Hz, CH_2−OH), 4.38 broad t(1 H, *J* = 6.5 Hz, H-*f*), 3.95 (2 H, H-*d*,*e*; *m/e* 234 (M) and 219 (M − 15).

(6R)-β-Ironylidene-ethyltriphenylphosphonium bromide (10). A solution of *9* (0.8 g) and triphenylphosphonium bromide (1.5 g) in $CHCl_3$ (5 ml) was stirred at 20 °C for 48 h under N_2. The solvent was removed under vacuum and the oily residue dissolved in a minimum amount of acetone (5 ml) and chromatographed on a kieselgel column. Elution with acetone removed unreacted *9* and triphenylphosphine. *10* was eluted with MeOH and obtained as an amorphous powder after removal of solvent. Yield of *10* was 1.74 g (84 %).

(2R,2'R)-2,2'-Dimethyl-β,β-carotene (12). NaOMe (0.6 M) was slowly added to a stirred solution of *10* (200 mg) in dry MeOH (5 ml) until the phosphonium salt was completely converted to the deep red phosphorane. A solution of 2,7-dimethylocta-2,4,6-trienedial (*11*, 200 mg, prepared from the acetylenic analogue [16]) in CH_2Cl_2 (0.5 ml) was added and the mixture stirred. Progress of the reaction was monitored by TLC and additional phosphorane, generated externally, was added until *11* was completely converted to *12*. Water was added, the crude product extracted into ether, concentrated under vacuum and chromatographed on a kieselgel column developed with benzene. Yield of *12* (*cis-trans* mixture) was 42 mg (34 % based on dial *11*). *12* was purified on alumina plates from which the all *trans*-isomer was collected. Crystallized from MeOH-acetone solution *12* melted at 179 °C. Comparative TLC on precoated alumina plates developed with petroleum ether-ethyl ether (97:3) showed *12* to have R_F = 0.42; β,β-carotene in this system had R_F = 0.38. On Schleicher & Schüll paper No. 288 (Al_2O_3) developed with petroleum ether + ethyl ether (99 + 1) *12* had R_F = 0.33; β,β-carotene in the

same system had $R_F = 0.20$. *12* had λ_{max} (hexane) 265, (423), 449 [E (1 %, 1 cm) = 2428; $\varepsilon = 137\,000$ compared with $\varepsilon = 134\,000$ for β,β-carotene [17]], 476 nm [E(1 %, 1 cm) = 2072; $\varepsilon = 117\,000$], (acetone) (427), 451, 479 nm; $\tau(CDCl_3)$ see Fig. 1 with signal assignments; CD (EPA), see Fig. 3; *m/e* 564 (M), 549 (M − 15), 472 (M − 92), 458 (M − 106), 415 (M − 149), 406 (M − 158), 420 (M − 162), 373 (M − 191), 360 (M − 204), 347 (M − 217) and 282, see Fig. *2*.

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REFERENCES

1. Liaaen-Jensen, S. *Acta Chem. Scand. 21* (1967) 1972.
2. Kelly, M., Norgård, S. and Liaaen-Jensen, S. *Acta Chem. Scand. 24* (1970) 2169.
3. Norgård, S., Aasen, A. J. and Liaaen-Jensen, S. *Acta Chem. Scand. 24* (1970) 2183.
4. Weeks, O. B. and Andrewes, A. G. In Chichester, C. O., Ed., *The Chemistry of Plant Pigments*, Academic, New York 1972, Chapter 3.
5. Borch, G., Norgård, S. and Liaaen-Jensen, S. *Acta Chem. Scand. 26* (1972) 402.
6. Bartlett, L., Klyne, W., Mose, W. P., Scopes, P. M., Galasko, G., Mallams, A. K., Weedon, B. C. L., Szabolcs, J. and Toth, G. *J. Chem. Soc. C* (1969) 2527.
7. Rautenstrauch, V. and Ohloff, G. *Helv. Chim. Acta 54* (1971) 1776.
8. Kjøsen, H., Arpin, N. and Liaaen-Jensen, S. *Acta Chem. Scand. 26* (1972) 3053.
9. Mills, J. A. *J. Chem. Soc.* (1952) 4976.
10. Eliel, E. L. *Stereochemistry of Carbon Compounds*, McGraw, New York 1962.
11. Ryback, G. *Chem. Commun.* (1972) 1190.
12. a. Buchecker, R., Eugster, C. H., Kjøsen, H. and Liaaen-Jensen, S. *Acta Chem. Scand. B 28* (1974) 449; b. Eugster, C. H., Trivedi, A. H. and Karrer, P. *Helv. Chim. Acta 38* (1955) 1360.
13. *IUPAC Commission on the Nomenclature of Organic Chemistry and IUPAC-IUB Commission on Biochemical Nomenclature, Biochemistry 10* (1971) 4827.
14. Kjøsen, H. and Liaaen-Jensen, S. *Acta Chem. Scand. 26* (1972) 4121.
15. a. Wadsworth, W. S. and Emmons, W. D. *J. Amer. Chem. Soc. 83* (1961) 1733; b. Vetter, W., Englert, G., Rigassi, N. and Schwieter, U. In Isler, O., Ed., *Carotenoids*, Birkhäuser, Basel 1971, Chapter IV.
16. Surmatis, J. D. and Ofner, A. *J. Org. Chem. 28* (1963) 2735.
17. Davies, B. H. In Goodwin, T. W., Ed., *Chemistry and Biochemistry of Plant Pigments*, Academic, New York 1965, Chapter 18.

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