Acta Chemica Scandinavica B 38 (1984) 43–47

# Total Synthesis of 3,4,3′,4′-Tetradehydro-β,β-carotene-2,2′-dione

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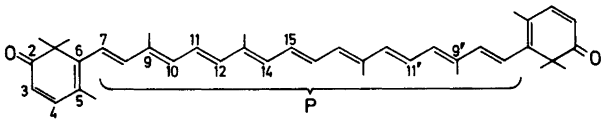
The first total synthesis of 3,4,3′,4′-tetradehydro-β,β-carotene-2,2′-dione is reported, confirming the structure previously assigned to a carotenoid isolated from stick insects (Phasmida).

Conversion of the corresponding bisallylic diol to the aromatic isorenieratene failed.

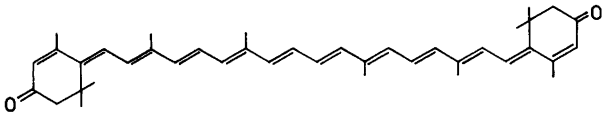
The plausible ω,ω′-diketone structure *1* was assigned by Kayser[1] to a carotenoid isolated from an insect, *Carausius morosus*; subsequently also obtained from other stick insects.[2] Structure *1* represents the most unsaturated polyene ω,ω′-dione in the dicyclic carotenoid series. Rhodoxanthin (*2*) and canthaxanthin (*3*) have long been known,[3] Scheme 1. We now report the first total synthesis of 3,4,3′,4′-tetradehydro-β,β-carotene-2,2′-dione (*1*), thereby confirming the structural assignment.

## RESULTS AND DISCUSSION

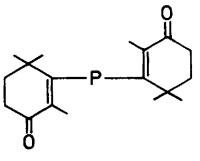
The synthesis was effected from β-ionone (*4*) as outlined in Scheme 2. The carbon skeleton was elongated in a Horner reaction to provide β-ionylidene acetate (*5*)[4] by standard procedure. A conjugated double bond was introduced by reaction with *N*-bromosuccinimide and subsequent base treatment of the intermediary allylic bromide. The resulting didehydro ester *6*[4] was reduced to the primary alcohol *7*,[4] which was converted to its acetate *8*. Introduction of an oxygen function at C-2 (carotenoid nomenclature, Scheme 1) represented a key step. Whereas introduction of an allylic acetoxy function with *N*-bromosuccinimide–acetic acid[5] failed,[6] selenium dioxide oxidation in dioxane[7] provided the conjugated ketone *9* in low yield. The latter was




*1*

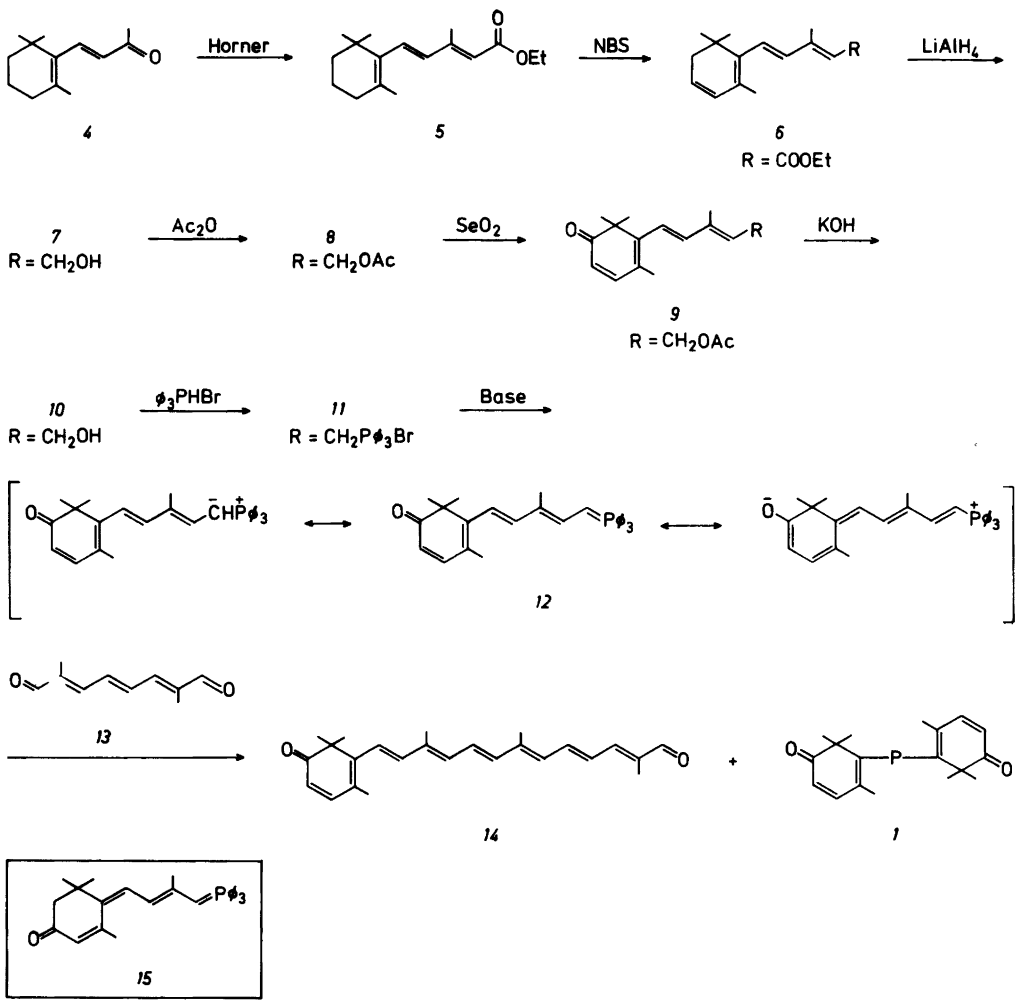



*2*




*3*

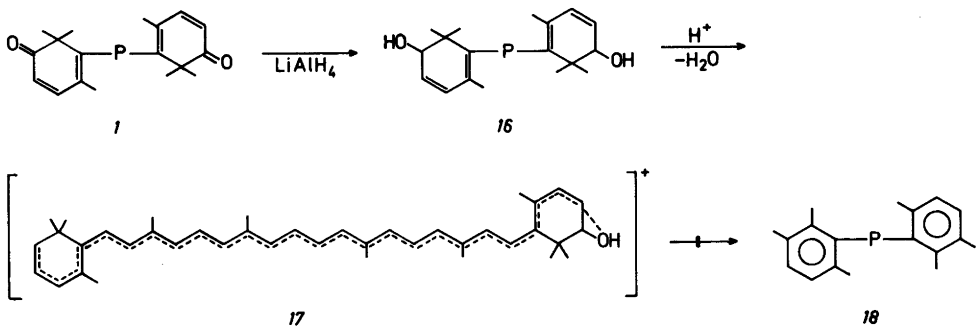
0302-4369/84 $2.50




converted *via* the allylic alcohol *10* to the phosphonium bromide *11*, which upon treatment with base afforded a dark blue ylid *12*. The colour is rationalized by electron delocalization to the oxygen function. A deep blue-red colour has previously been reported for the related ylid *15*, representing an intermediate in the total synthesis of rhodoxanthin (*2*, Scheme 1).[8] Wittig condensation of the ylid *12* with $C_{10}$-dial (*13*) gave the apocarotenal *14* and the target compound *1*. *cis-trans* Isomers of the intermediates *5*–*11* were not separated and the $C_{40}$-dione *1* was obtained as a mixture of all-*trans* (major) and *cis*-isomers (*Δ*9,11,9′,11′ *cis* bonds are predicted from the route empoloyed), the all-*trans* isomer being obtained by crystallization.

The synthetic dione *1* was characterized by *vis.*, IR, $^1$H NMR and mass spectra and could not be differentiated from natural *1 ex Carausius morosus*[1] on HPLC and by visible and mass spectra.

The title compound (*1*) was reduced with lithium aluminium hydride to the bisallylic diol *16*, Scheme 3. Attempted conversion of *16* to the aromatic isorenieratene *18* by acid treatment failed. The required carbocation intermediate *17* is strongly resonance stabilized and presumably had no tendency to undergo methyl shift and rearrangement to a tertiary carbocation. Other *in vitro* aromatization reactions of carotenoids have recently been reviewed.[9]




## EXPERIMENTAL

*General methods and instruments.* These were as commonly employed in our laboratory.[10]

*Ethyl 3-methyl-5-(2,6,6-trimethylcyclohexenyl)-2,4-pentadienoate; ethyl β-ionylidene acetate (5).* To a stirred solution of β-ionone (*4*, 192 g) and ethyl diethylphosphonoacetate (224 g) in benzene (700 ml) was added a solution of NaOEt in EtOH (26 g Na in 650 ml dry EtOH) during 9 h. After 30 h at room temperature the reaction mixture was treated in the usual manner.[7,11] Vacuum distillation provided *5* (222 g, 85 %) of b.p. 130 °C/-0.3 mm Hg with $\lambda_{max}$ (MeOH), $\nu_{max}$ (liq.), $^1$H NMR $\delta$ ($CCl_4$) and *m/e* (M=262.1931 corresponding to $C_{18}H_{26}O_2$) values[12] consistent with previously reported data.[4,11,13]

*Ethyl 3-methyl-5-(2,6,6-trimethyl-1,3-cyclohexadien-1-yl)-2,4-pentadienoate; ethyl 3,4-didehydro-β-ionylidene acetate (6).* To β-ionylidene acetate (*5*, 105 g) in $CH_2Cl_2$ (200 ml) was added NBS (71.3 g), CaO (17.9 g) and $NaHCO_3$ (60.5 g) at 7–8 °C upon stirring. The reaction was monitored by TLC and quinoline (50 ml) was added after 12 h. The products were isolated[12] by the procedure earlier described.[4,13,14] Column chromatography on $SiO_2$ (hexane) and distillation provided *6* (70 g, 70 %) of b.p. 105–110 °C/0.3 mmHg with $\lambda_{max}$ (hexane), $\nu_{max}$ (liq.), $^1$H NMR $\delta$ ($CCl_4$) and *m/e* values[12] as previously reported.[4,13,14] $^1$H NMR (for the C–1 and C–5 methyl groups) revealed a 7:3 ratio of the all-*trans* and 9-*cis* esters.

*3-Methyl-5-(2,6,6-trimethylcyclohexa-1,3-dien-1-yl)-2,4-pentadien-1-ol;3,4-didehydro-β-ionylidene-ethanol (7).* A solution of 3,4-didehydro-β-ionylidene acetate (*6*, 26 g) in dry ether (100 ml) was reacted with $LiAlH_4$ (5 g) in dry ether (200 ml, dropwise addition) at 0 °C for 1 h. The reaction was monitored by TLC and the products isolated[11] as previously described.[4,15,16] Chromatography provided *7* with $\lambda_{max}$ (MeOH) and $\nu_{max}$ (liq.)[12] as previously reported;[4,15,16] $^1$H NMR $\delta$ ($CDCl_3$) 1.0s (6H, *gem.* dimethyl), 1.8s (3H, $CH_3$-5), 1.9s (3H, $CH_3$-9), 2.05d (2H, $CH_2$-2), 2.2 (1H, OH), 4.18d (2H, $CH_2$-11, $J$=7 Hz) and 5.3–6.4 (5H, olefinic); *m/e* 218 (M), 203 (M–15), 200 (M–18), 192, 189 (M–29), 187, 174, 133, 105.

*1-Acetoxy-3-methyl-5-(2,6,6-trimethylcyclohexa-1,3-dien-1-yl)penta-2,4-diene; 3,4-didehydro-β-ionylidene acetate (8).* 3,4-Didehydro-β-ionylidene-ethanol (19.5 g) in dry pyridine (100 ml) was reacted with $Ac_2O$ (15.3 g) for 4 h at room temp. The reaction was monitored by TLC. Isolation by the common procedure provided *8* (20.3 g crude, 87 %), purified by chromatography ($SiO_2$, 20 % acetone in hexane); $\lambda_{max}$ (MeOH) 240 ($\varepsilon$=9700) and 314 ($\varepsilon$=10 400) nm; $\nu_{max}$ (liq.) 3040–2800 (CH), 1740 (ester C=O), 1615 (C=C), 1230 (C–O) and 970 (CH=CH, *trans*) cm$^{-1}$; $^1$H NMR $\delta$ ($CCl_4$) 1.02s (6H, *gem.* dimethyl), 1.86s (3H, $CH_3$-5 by carotenoid numbering, *cf.* Scheme 1), 1.90s (3H, $CH_3$-9), 2.0s (3H, $CH_3C$=O), 4.63d (2H, $CH_2$-11, $J$=7 Hz), 5.3–6.5 (5H, olefinic); *m/e* 260 (M, 31 %), 202 (10 %), 185 (52 %), 157 (27 %), 146 (22 %).

*5-(5-Acetoxy-3-methylpenta-1,3-dienyl)-4,6,6-trimethylcyclohexa-2,4-dienone; 2-oxo-3,4-didehydro-β-ionylideneethyl acetate (9).* To a solution of 3,4-didehydro-β-ionylideneethyl acetate *8* (10.5 g) in dioxane (100 ml) was added freshly sublimed $SeO_2$[17,18] (4.44 g). After 2.5 h at 57 °C, the solvent was evaporated, and chromatography ($SiO_2$, 20–30 % $CHCl_3$ in $CCl_4$) provided a yellow fraction (3 g) containing *9*. Repetitive chromatography (TLC, $SiO_2$, 25 % acetone in hexane) provided *9* (510 mg, 5 %); $\lambda_{max}$ (MeOH) 255 ($\varepsilon$=12 700 and 357 ($\varepsilon$=16 230) nm; $\nu_{max}$ (liq.) 3040–2860 (CH), 1740 (ester C=O), 1660 (conj. C=O), 1230 (C–O), 1030 (C–O) and 970 (CH=CH, *trans*); $^1$H NMR $\delta$ ($CDCl_3$) 1.26s (6H, *gem.* dimethyl), 1.92s (3H, $CH_3$–9, carotenoid numbering *cf.* Scheme 1), 2.05s (3H, $CH_3$-5), 2.07s (3H, $CH_3C$=O), 4.75d (2H, $CH_2$-11, $J$=7 Hz), 5.66t (1H, H-10, $J$=7 Hz), 5.96d (1H, H-3,

$J$=9.8 Hz), 6.27 and 6.30 (2H, H-7 and H-8), 6.96d (H, H-4, $J$=9.8 Hz; *m/e* 274 (M, 5 %), 259 (M−15, 3 %), 246 (1 %), 231 (M−43, 2 %), 214 (M−60, 6 %), 201 (16 %), 171 (19 %), 145 (11 %), 133 (15 %).

*5-(5-Hydroxy-3-methyl-1,3-pentadienyl)-4,6,6-trimethylcyclohexa-2,4-dienone; 2-oxo-3,4-didehydro-β-ionylideneethanol (10).* 2-Oxo-3,4-didehydro-β-ionylidene ethyl acetate (*9*, 450 mg) in ether (10 ml) was hydrolyzed with 10 % KOH in MeOH (10 ml) for 30 min. Standard work-up and preparative TLC ($SiO_2$) provided *10* (250 mg, 65 %) with $\lambda_{max}$ (MeOH) 259 and 360 nm; $\nu_{max}$ (liq.) 3200−2800, chelated OH, CH), 1660 (conj. C=O), 1630 (C=C), 1010 ($CH_2OH$) and 970 (CH=CH, *trans*); $^1$H NMR $\delta$ ($CDCl_3$) 1.27s (6H, *gem.* dimethyl), 1.87 (3H, $CH_3$-9, carotenoid numbering), 2.04s (3H, $CH_3$-5), 2.56 (OH), 4.32d (2H, $CH_2$-11, $J$=7 Hz), 5.74 t (1H, H-10, $J$=7 Hz), 5.99d (1H, H-3, $J$=9.8 Hz), 6.20 and 6.27 (H-7 and H-8), 5.99 (1H, H-4, $J$=9.8 Hz), assignments of the H-3,4 protons were confirmed by double resonance; *m/e* 232 (M), 217 (M−15), 214 (M−18), 201, 188, 133, 129.

*3-Methyl-5-(5-oxo-2,6,6-trimethyl-1,3-cyclohexadienyl)-2,4-pentadienyltriphenylphosphonium bromide; 2-oxo-3,4-didehydro-β-ionylidene ethyltriphenylphosphonium bromide (11).* A solution of 2-oxo-3,4-didehydro-β-ionylidene-ethanol (150 mg) and triphenylphosphine hydrobromide (500 mg) in $CH_2Cl_2$ (7 ml) was stirred at room temp. for 24 h. Column chromatography ($SiO_2$, 0−20 % acetone in $CHCl_3$) provided *11* (330 mg, 90 %). Treatment of *11* with a drop of sodium methylate−MeOH gave a strong blue colour.

*Wittig condensation of 2-oxo-3,4-didehydro-β-ionylideneethyl triphenylphosphonium bromide (11) and $C_{10}$-dial (13).* A solution of the above phosphonium salt (*11*, 185 mg) and $C_{10}$-dial (*13*, 6.5 mg) in $CH_2Cl_2$ (5 ml) was stirred under nitrogen. NaH (50 mg) was added and the mixture stirred for 8 h. Standard work-up including extraction with $CH_2Cl_2$ and chromatography (TLC, $SiO_2$, 20 % acetone) provided *14+1* in mixture ($R_F$=0.27, 11 mg).

*12'-Apo-2-oxo-3,4-didehydro-β-carotene-12'-al (14).* The mixture of *14* and *1* could be separated only on $CaCO_3$-MgO-$SiO_2$ TLC plates [19] and had $R_F$=0.5 (20 % acetone in hexane), $\lambda_{max}$ (ether) 445 nm (round-shaped); *m/e* 362 (M, 100 %), 105 (3 %) 91 (3 %).

*3,4,3',4'-Tetradehydro-β,β-carotene-2,2'-dione (1),* $R_F$=0.37 in the above system, was crystallized from acetone−hexane, m.p. 185−186 °C, yield *ca.* 2 mg, $\lambda_{max}$ (acetone) 490 ($E^{1\%}_{1cm}$=2400) nm (round-shaped); $\nu_{max}$ (KBr) 3020 (=CH), 3000−2870 (CH), 1660 (conj. C=O), 1550−1500 (C=C), 1450, 1380 ($CH_3$) and 970 (CH=CH, *trans*) cm$^{-1}$; $^1$H NMR $\delta$ ($CDCl_3$) 1.30 s (12H, *gem.* dimethyl), 2.00s (12H, $CH_3$-9,13,9',13'), 2.09s (6H, $CH_3$-5,5'), 5.99d (2H, H-3,3', $J$=9.8 Hz), 6.2−6.7 (14H, olefinic) 6.97d (2H, H-4,4', $J$=9.8 Hz), assignments of C-3,4 and C-3',4' protons were confirmed by spin decoupling; *m/e* 560 (M, 100 %), 468 (M–92, 1 %), 454 (M–106, 1 %), 280 ($M^{2+}$, 1 %), 209 (4 %), 187 (4 %), 173 (4 %), 159 (5 %), 157 (5 %), 145 (6 %), 133 (6 %), 119 (6 %) and 91 (9 %).

A solution of synthetic *1* (stored in solution) and natural *1 ex Carausius morosus* showed separately and in mixture the same retention time by HPLC analyses (Spherisorb 5 μm, hexane+acetone 1 %/min., 300 psi, 1.4 ml/min.): major peak (16.5 min, $\lambda_{max}$=489 nm, all-*trans*, *ca.* 70 %) and minor peak (16.7 min, $\lambda_{max}$ 484 nm, unspecified *cis*, *ca.* 30 %).

*3,4,3',4'-Tetradehydro-β,β-carotene-2,2'-diol (16).* To the above synthetic dione (*1*, 0.8 mg) in dry ether (25 ml) was added a filtered, saturated solution of $LiAlH_4$ at 0 °C. The diol *16*, isolated by chromatography (TLC, $SiO_2$, 20 % acetone in hexane) had $R_F$=0.10; $\lambda_{max}$ (ether) 465 nm; *m/e* 564 (M, 1 %), 546 (M–18, 5 %), 528 (M–18–18, 33 %), 436 (M–18–18–92, 2 %), 422 (M–18–18–106, (1 %), 133 (100 %), 520 (M-44, 5 %).

*Acid treatment of 3,4,3',4'-tetradehydro-β,β-carotene-2,2'-diol (16).* To a solution of *16* (0.1 mg) in $CHCl_3$ (2 ml) was added a 0.05 N solution of HCl in $CHCl_3$ (5 ml). The mixture turned green. Aqueous 5 % $NaHCO_3$ was added after 10 min. TLC ($SiO_2$, 15 % acetone in hexane) revealed several green and yellow products. No isorenieratene (*18*) could be detected.

*Acknowledgements.* We thank Dr. H. Kayser, *Abteilung für Biologie I, Universität Ulm,* for a reference sample of the natural dione and Hoffmann-La Roche, Basel, for gifts of $C_{10}$-dial.

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Received March 28, 1983.