

Synthesis of 11,11'-Deuterated ϵ -Carotene and Lycopene

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The synthesis of 11,11'-deuterated ϵ -carotene (7) and 11,11'-deuterated lycopene (8) by a combination of routes previously used for the unlabelled carotenes, are reported.

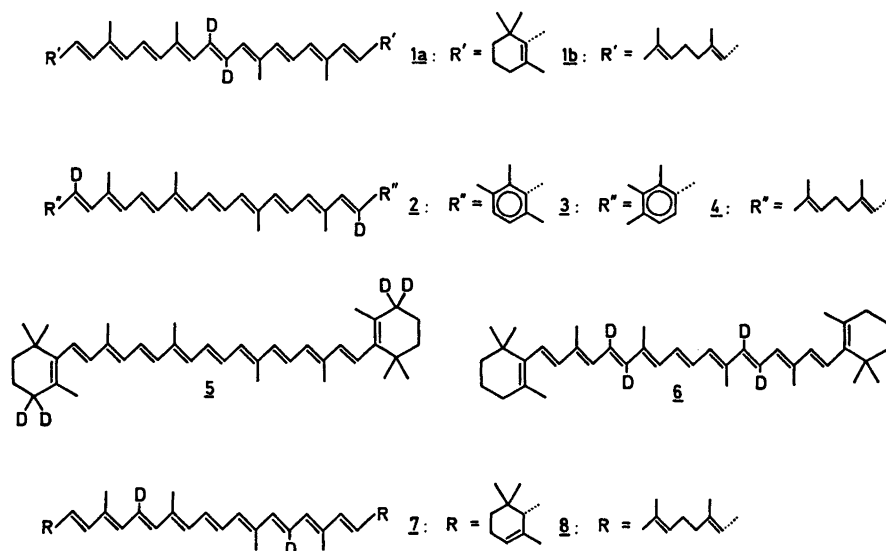
The deuterium was introduced by lithium aluminium deuteride reduction of the intermediate C_{15} -esters (10 and 15).

Specifically deuterated carotenes are of special interest for a systematic study of the electron impact induced fragmentation of carotenoids.

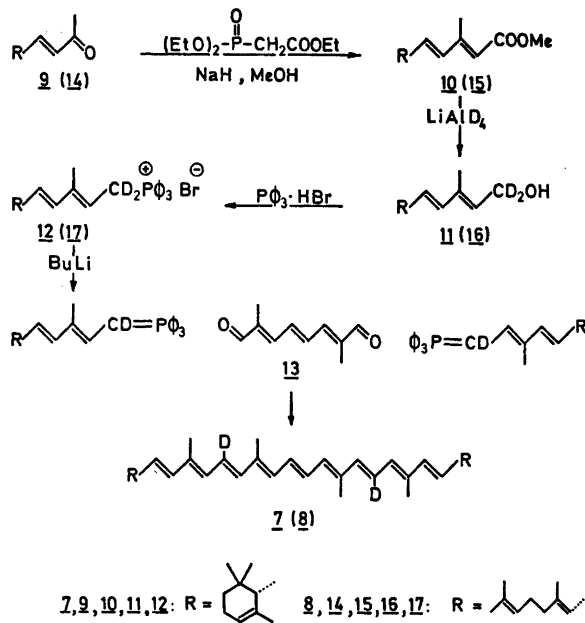
The preparation of only few specifically deuterated carotenes has been reported. Schwieter *et al.*¹ have synthesized 15,15'-dideuterio- β , β -carotene (1a, Scheme 1) and 15,15'-dideuterio-lycopene (1b) by selective deuteration of the acetylenic analogues. Some 7,7'-

deuterated carotenes (2,3,4) have been previously prepared by our group,² the deuterium atoms being introduced by lithium aluminium deuteride reduction of intermediate C_{10} -carboxylic acids. More recently the partial synthesis of 4,4'-tetra-deuterio- β -carotene (5) from canthaxanthin by reduction with lithium aluminium deuteride in the presence of aluminium chloride has been described by Brzezinka.³ The same author also prepared 11,12,11',12'-tetra-deuterio- β -carotene (6) by total synthesis; in principle by selective deuteration of an acetylenic intermediate.

We now report the synthesis of 11,11'-deuterated ϵ -carotene (7) and 11,11'-deuterated lycopene (8).



Scheme 1.



Scheme 2.

RESULTS AND DISCUSSION

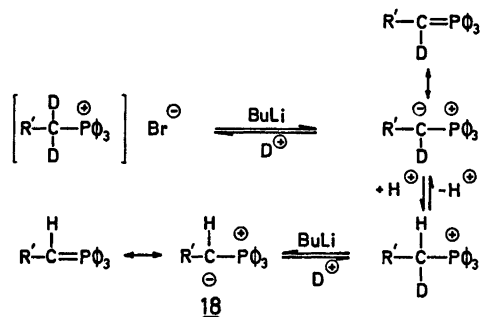
The route employed, given in Scheme 2, was based on a combination of the routes previously described by Weedon and co-workers⁴ for un-deuterated ϵ -carotene by a $C_{15} + C_{10} + C_{15} = C_{40}$ approach.

Racemic α -ionone (9) was condensed in a Horner reaction with the carbanion of ethyl diethylphosphonoacetate, obtained with sodium hydride, to the C_{15} -ester (10). The C_{15} -ester (10) was reduced with lithium aluminium deuteride to the allylic alcohol (11), which was converted to the corresponding phosphonium salt (12) with triphenylphosphine hydrobromide. In the final Wittig reaction the ylid of the phosphonium salt (12) was reacted with C_{10} -dial (13) to give 11,11'-deuterated ϵ -carotene (7).

Pseudo-ionone (14) gave 11,11'-deuterated lycopene (8) by the same route *via* 15, 16 and 17.

On first attempt the deuterium incorporation was low in ϵ -carotene. According to the PMR-spectra the allylic alcohol (11) as well as the phosphonium salt (12) had complete deuterium incorporation. The ylid formation and/or subsequent condensation consequently represented the crucial steps.

According to the accepted mechanism of ylid formation,^{5a} given in Scheme 3, deuterium-hydrogen exchange of the ylid is expected to occur in protic media, resulting in unlabelled ylid (18).



Scheme 3.

Using diethyl ether, dried over metallic sodium and distilled over lithium aluminium hydride, the following incorporation was obtained: 11,11'-deuterated ϵ -carotene (7), 87% deuterium incorporation, $D_0:D_1:D_2 = 3:23:76$ and for 11,11'-deuterated lycopene (8), 80% deuterium incorporation, $D_0:D_1:D_2 = 8:25:67$, judged by the intensity of the molecular ions observed on electron impact. Percentage deuteration

reflects average number of deuterium atoms incorporated relative to the theoretically possible incorporation. The ratio of deuterated species is calculated as in previous work,² taking into account ¹³C isotope contributions, cf. Ref. 5b.

The deuterated carotenes were characterized by means of electronic spectra, IR-spectra, and mass spectra (7 and 8) and PMR-spectrum (7), melting points and chromatographic behaviour. Undeuterated ϵ -carotene was prepared for comparison. Mixed melting points of the deuterated carotenes (7 and 8) with the corresponding undeuterated carotenes gave no depression. No chromatographic separation from undeuterated analogs was obtained. The deuterium incorporation, judged from mass spectra, was retained on chromatography and recrystallization. Extinction coefficients lower than predicted^{4,6} are ascribed to sterically inhomogeneous products (*cis* and *trans*).

The mass-spectrometric results will be discussed separately in a communication also comprising other deuterated carotenes.⁷

EXPERIMENTAL PART

Materials and methods were as generally used in this laboratory.² For column chromatography neutral alumina activity grade 2 was used. Only diagnostically useful spectroscopic properties of the intermediates are quoted.

Methyl α -ionylideneacetate (10) was prepared from α -ionone (9, 4 g) and ethyl diethylphosphonoacetate (4.5 g) by the procedure of Manchand *et al.*⁴ Column chromatography on alumina (eluent pet. ether) gave a mixture of 10 (*ca.* 80 %) and the ethyl ester (*ca.* 20 %); yield 6.2 g (70 %); τ (CDCl₃) 9.17 s and 9.08 s (*gem.* dimethyl), 8.42 s (ring methyl), 7.71 s (on-chain methyl), 6.33 s (ester methyl), 8.72 t and 5.8 q (ester ethyl) and olefinic signals; used without further purification.

Deuterated α -ionylidene-ethanol (11) was prepared by adding dropwise a suspension of LiAlD₄ (0.5 g) in anhydrous ether (25 ml) to 10 (4.0 g) in anhydrous ether at 0°C. After 1 h excess reagent was destroyed with ethyl acetate (2 ml) and the reaction mixture poured on ice and 1 N H₂SO₄. 11 was extracted with ether in the usual manner; yield 3.0 g (90 %) 11; τ (CDCl₃) 9.17 s and 9.08 s (*gem.* dimethyl), 8.42 s (ring methyl), 8.20 s (on-chain methyl), and 4.8–3.8 (olefinic protons), but no signal at τ 5.73; used without further purification.

The undeuterated analogue was similarly prepared using LiAlH₄; yield 3.1 g (90 %); τ (CDCl₃) as for 11 above and 5.73 d ($J = 7$ cps, CH₂OH).

Deuterated α -ionylidene-ethyltriphenylphosphonium bromide (12). 11 (2.0 g) and triphenylphosphonium bromide (2.3 g) in dry methanol (30 ml) was kept at room temperature for 56 h. The solvent was removed under vacuum, and the residue washed with water. The crude, colourless solid 12, yield 3.5 g (81 %); τ (CDCl₃) 9.23 s and 9.13 s (*gem.* dimethyl), 2.5–2 (aromatic protons), no signals at τ 6–5 for CH₂P; was used without further purification.

The undeuterated phosphonium salt was similarly prepared from undeuterated α -ionylidene-ethanol; yield 3.8 g (88 %); τ (CDCl₃) 9.23 s and 9.13 s (*gem.* dimethyl), 6–5 m (CH₂P), 2.5–2 (aromatic protons).

2,7-Dimethylocta-2,4,6-trienedial (13). 2,7-Dimethylocta-2,6-dien-4-ynedial (1.0 g) in ethyl acetate (50 ml) was hydrogenated in the presence of Lindlar catalyst (0.7 g) until one equivalent of hydrogen was absorbed. The catalyst was removed by filtration and the solvent evaporated. Recrystallization from methanol gave *cis* and *trans* 13 (0.5 g, 50 %); λ_{\max} (methanol) 323 nm; τ (CDCl₃) 8.05 s (6H, methyl), 3.3–2.5 m (4H, olefinic), 0.35 s (2H, aldehydic).

11,11'-Deuterated ϵ -carotene (7). To a suspension of 12 (920 mg) in anhydrous ether (75 ml, dried over Na and distilled over LiAlH₄) was added dropwise a 1 N solution of BuLi in anhydrous ether until the red phosphorane was prepared. Excess BuLi was destroyed by addition of CH₂Cl₂ (3 ml). C₁₀-dial (13, 124 mg) in CH₂Cl₂ (10 ml) was added dropwise and the reaction mixture left at room temperature over night. The solvent was removed and the residue dissolved in 90 % aqueous methanol. The pigments were transferred to pet. ether in the usual manner, chromatographed on alumina (eluent pet. ether) and 7 crystallized and recrystallized from benzene-methanol; yield 25 mg (10 %); m.p. 194–196°C, undepressed on admixture with undeuterated ϵ -carotene of m.p. 189–190°C; $R_F = 0.83$ (alumina paper, petroleum ether, no separation from undeuterated ϵ -carotene; λ_{\max} (pet. ether) 413, 437 ($E_{1\%,1\text{cm}} = 2600$) and 467 nm, % III/II⁹ = 93; ν_{\max} (KBr) 3030, 2960, 2920, and 2860 (CH), 1450 and 1435 (CH₂), 1385, 1375 and 1365 (methyl, *gem.* dimethyl) 1270, 1215, 1080, 1030, 1015, 965 (*trans* disubst. double bonds), 920 (medium, *trans*-CD=CH-, see Ref. 10), 825 (trisubst. double bonds), 800 and 730 cm⁻¹; τ (CDCl₃) 9.17 s and 9.08 s (12 H, *gem.* dimethyl), 8.42 s (6 H, 18,18'-methyl), 8.10 s (6 H, 19,19'-methyl), 8.05 s (6 H, 20,20'-methyl) and 4.6–3.0 m (olefinic protons); m/e 538 (MD₂), 537 (MD₁), 536 (MD₀), 482 (MD₂-56), 446 (MD₂-92), 445 (MD₂-93), 431 (MD₂-107), 379 (MD₂-159) with intensity ratios (MD₂-92):(MD₂-93):(MD₂-94) = 37:63:0, (MD₂-106):(MD₂-107):(MD₂-108) = 0:100:0, (MD₂-158):(MD₂-159):(MD₂-160) = 0:100:0; MD₀:MD₁:MD₂ = 3:23:74; 86 % deuterium incorporation.

Undeuterated ϵ -carotene was prepared in the

corresponding manner from the undeuterated phosphonium salt; yield 60 mg (17 %); m.p. 189–190°C; λ_{\max} (pet. ether) 413, 437 ($E_{1\%,1\text{cm}}=2400$) and 467 nm, $\% \text{ III/II}=87$, spectrum conform with that of 7; ν_{\max} (KBr) close to those of 7, but band at 920 cm^{-1} absent; τ (CDCl_3) 9.17 s and 9.08 s (12H, *gem*.dimethyl), 8.42 s (6 H, 18,18'-methyl), 8.08 s (19,19'-methyl), 8.04 s (20,20'-methyl) and 4.6–3.0 m (olefinic protons); *m/e* 536 (M), 480 (M–56), 444 (M–92), 430 (M–106), 388 (M–56–92), 378 (M–158) with intensity ratio (M–92):(M–106)=8.9.

Methyl ψ -ionylideneacetate (15) was prepared from 14 (4 g) by the same procedure as for 9; yield 6.5 g (87 %) of a mixture of the methyl ester 15 (*ca.* 75 %) and the ethyl ester (*ca.* 25 %); τ (CDCl_3) 8.39 s and 8.32 s (isopropylidene methyl), 8.19 s (end-of-chain methyl), 7.68 s (in-chain methyl), 6.34 s (ester methyl), 8.72 t and 5.85 q (ester ethyl), 5–2 m (olefinic protons); used without further purification.

Deuterated ψ -ionylidene-ethanol (16) was prepared from 14 (4 g) by the same procedure as 11 above, avoiding work-up in the presence of H_2SO_4 ; yield 2.5 g (74 %); τ (CDCl_3) 8.40 s and 8.32 s (isopropylidene methyl), 8.20 s and 8.12 s (on-chain methyl) and 5.0–2.5 (olefinic protons), but no signal at τ 5.7 for CH_2OH .

Deuterated ψ -ionylidene-ethyltriphenylphosphonium bromide (17) was prepared by the same procedure as 12 above. 16 (2.0 g) gave 17 (3.7 g) as a solid; τ (CDCl_3) 8.40 s and 8.32 s (isopropylidene methyl), 8.26 (end-of-chain methyl), 4.9 (isopropylidene H), 4.5–3.8 (olefinic protons) and 2.5–2 (aromatic protons); used without further purification.

11,11'-Deuterated lycopene (8). The same procedure as for 7 was used. 13 (40 mg) and 17 (273 mg) gave 8 (*cis+trans*, 5 mg, yield 4 %); m.p. 167–169°C, undepressed on admixture with undeuterated lycopene of m.p. 172°C; $R_F=0.50$ (alumina paper, 1 % acetone in pet.ether); λ_{\max} (pet.ether) 440, 468 and 500 nm; *m/e* 538 (MD_2), 537 (MD_1), 536 (MD_0), 469 (MD_2-69), 446 (MD_2-92), 445 (MD_2-93), 431 (MD_2-107), 379 (MD_2-159) with intensity ratios (MD_2-92):(MD_2-93):(MD_2-94)=38:62:0, (MD_2-106):(MD_2-107):(MD_2-108)=0:100:0 and (MD_2-158):(MD_2-159):(MD_2-160)=0:100:0; MD_0 : MD_1 : MD_2 =8:25:67, 80 % deuterium incorporation. Synthetic undeuterated lycopene (Roche) recorded for comparison had λ_{\max} (pet.ether) 462, 470, and 502 nm; *m/e* 536 (M), 467 (M–69), 444 (M–92), 430 (M–106), 399 (M–137), 378 (M–158).

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