Partial Syntheses of Diastereomeric Carotenols

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The application of the Mitsunobu reaction was successfully tested on (3*R*,3′*R*)-zeaxanthin, giving the (3*S*,3′*S*)-enantiomer and the *meso* form. Applied to natural (3*R*,3′*R*,6′*R*)-lutein, this inversion reaction allowed the preparation of the three other 6′*R* diastereomers. (3*S*,3′*S*,6′*R*)-lutein with 3′,6′-*cis*-configuration of the ε-ring has not been synthesized before.

The observed Cotton effects of the eight lutein diastereomers are rationalized by application of the additivity hypothesis.

New trivial names are suggested for the eight lutein isomers on the basis of structural relationships.

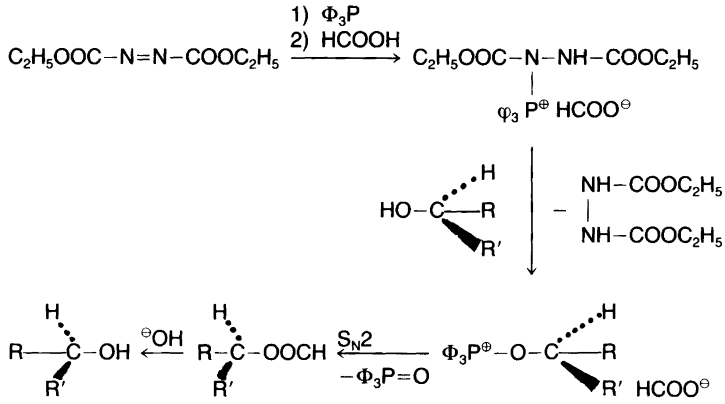
The enantioselective synthesis of carotenols with 3,6-*cis*-configurated ε-rings seems to be difficult. So far, four of the eight diastereomers of lutein have been prepared by total syntheses.[1] The so-called 3′-epilutein has been obtained by partial synthesis.[2]

We describe here a reaction which, in principle, allows the preparation of the eight all-*trans* optically active isomers of lutein, namely (3*S*,3′*R*,6′*S*)-, (3*R*,3′*R*,6′*S*)-, (3*R*,3′*S*,6′*S*)- and (3*S*,3′*S*,6′*S*)-lutein and their enantiomers, starting with any (6′*S*)- or (6′*R*)-lutein.

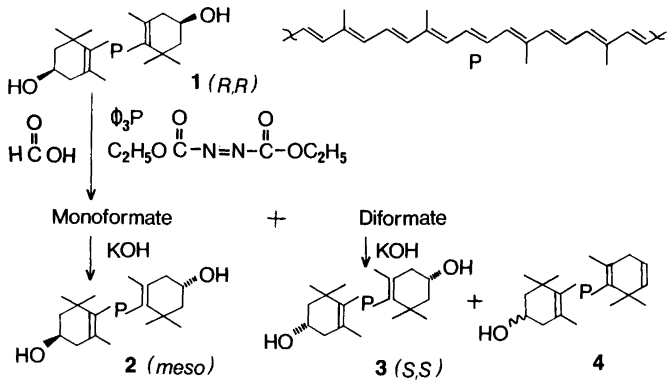
Results and discussion

In the total synthesis of carotenoids, inversion of *sec*-allylic alcohols has been achieved via the corresponding mesylates or acetates.[3] However, the inversion has been restricted to small synthons.

In steroid chemistry the configuration of the hydroxy groups of sterols has been inverted via benzoates or formates by the Mitsunobu reaction[4] (Scheme 1). Plausible mechanisms for this inversion reaction have been discussed.[5,6] Diethyl azodicarboxylate, triphenylphosphine and an appropriate carboxylic acid form a quaternary



Scheme 1.

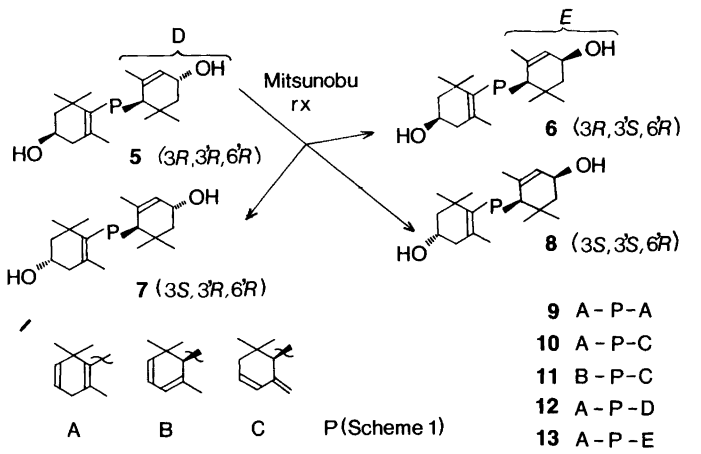


Scheme 2. Inversion of (3R,3′*R*)-zeaxanthin (**1**).

phosphonium salt. Subsequent reaction with a chiral *sec*-alcohol provides an alkoxyphosphonium salt. S_N2-type displacement with inversion gives, via the ester, the inverted *sec*-alcohol.

The present work reports the application of the Mitsunobu reaction to carotenols. Since *sec*-carotenols form benzoates, readily identified by ^1H NMR spectroscopy, inversion of (3*R*,3′*R*)-zeaxanthin (β,β-carotene-3,3′-diol, **1**) was first attempted via the benzoate, but without success. However, when benzoic acid was replaced by formic acid, the desired zeaxanthin diformate was obtained. Hydrolysis of the diester in methanolic KOH afforded optically pure (3*S*,3′*S*)-zeaxanthin (**3**), besides dehydrated products formed by competing elimination reactions (cf. Ref. 7). With the stoichiometrically required reactants for formation of zeaxanthin monoformate, *meso*-zeaxanthin (**2**) was obtained (see Scheme 2). The optical purity of the zeaxanthin products was checked by conversion to the dicarbamates followed by HPLC analysis.[8] The carbamates of both the completely and partly inverted zeaxanthin showed the characteristic retention times of the authentic carbamates of (3*R*,3′*S*,*meso*)-(**2**) and (3*S*,3′*S*)-zeaxanthin (**3**), respectively. 2′,3′-Didehydro-β,β-caroten-3-ol (**4**) was characterized as a by-product.

The two zeaxanthin enantiomers (**1**,**3**) and the *meso* form (**2**) have each been synthesized before in ca. 11 % yield in 9 steps.[9] The inversion reaction described here is simpler compared with the total syntheses. However, because of the low yield, not yet optimized [1 % for (*S*,*S*)-(**3**) and



Scheme 3. Inversion of (3*R*,3′*R*,6′*R*)-lutein (**5**).

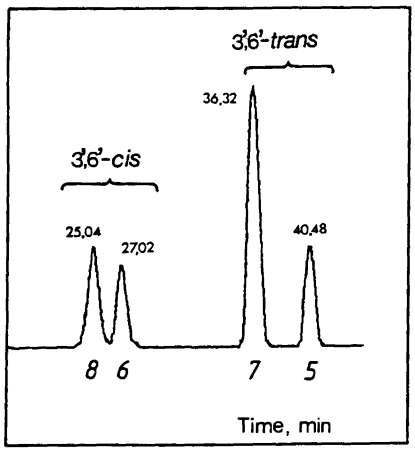


Fig. 1. Separation of the carbamates of (3*S*,3'*S*,6'*R*)-lutein (**8**), (3*R*,3'*S*,6'*R*)-lutein (**6**), (3*S*,3'*R*,6'*R*)-lutein (**7**) and (3*R*,3'*R*,6'*R*)-lutein (**5**) by HPLC (2×25 cm SiO_2 columns; hexane:isopropyl acetate 88:12).

0.1 % for (*R*,*S*)-(**2**)], the reaction does not seem to be of preparative interest.

Applied to lutein (β,ε-carotene-3,3'-diol), the Mitsunobu reaction offers advantages over total synthesis for the preparation of various lutein diastereomers.

(3*R*,3'*R*,6'*R*)-Lutein (**5**) gave, under the recommended conditions,[5] lutein mono- and diformates, which after alkaline hydrolysis provided (in 5 % total yield) the lutein diastereomers inverted at C-3' (**6**), at C-3 (**7**) and at C-3,3' (**8**, major) (Scheme 3). Mono- and didehydro products were also formed (cf. Ref. 7). When (3*R*,3'*R*,6'*R*)-lutein (**5**) was treated with the stoichiometric amount of reactants, inversion at C-3', bearing the allylic hydroxy group, was favoured over inversion at C-3, bearing the non-allylic hydroxy group.

The lutein diastereomers were characterized as the corresponding carbamates by HPLC.[8] The carbamates of luteins **6**[2,10] and **7**[1] showed the same retention times as authentic samples. Furthermore, the carbamates of the four lutein diastereomers of the 6'*R* series (**5**,**6**,**7** and **8**) were well separated by HPLC (Fig. 1). The HPLC peaks of underivatized luteins **6** and **8**, both possessing 3',6'-*cis* ε-rings, coincided. However, separation of 3',6'-*cis* and 3',6'-*trans* isomers was obtained by HPLC (Fig. 2) as well as by TLC.

The dehydrocarotenes **9**,**10** and **11** were obtained as di-elimination products. Upon hydrolysis, monoformates afforded also the mono-elimination products **12** and **13**.

With reference to Scheme 4, the method described allowed the preparation of all the (6'*R*)-luteins (**5**,**6**,**7** and **8**) in amounts sufficient for reference purposes. With access to a (6'*S*)-lutein, the four enantiomers **14**,**15**,**16** and **17** may also be prepared.

The 3',6'-*trans* luteins **5** and **7** (6'*R*) and **16** and **17** (6'*S*) have been prepared by total syntheses,[1] and 3'-epilutein (**6**) by partial synthesis.[2] Besides the most common naturally occurring (3*R*,3'*R*,6'*R*)-lutein (**5**)[11] and 3'-epilutein (**6**), both of which have been known for a long time,[12] (3*S*,3'*R*,6'*S*)-lutein (**14**), (3*R*,3'*R*,6'*S*)-lutein (**15**) and (3*R*,3'*S*,6'*S*)-lutein (**16**) have recently been detected in fish.[13] (3*S*,3'*S*,6'*R*)-Lutein (**8**), not previously characterized, represents the last of the theoretically eight optical isomers of lutein.

Particularly for oral communication, trivial names for the eight isomers would be convenient. We propose the assignment of trivial names in a systematic manner according to the structures (Scheme 4) as lutein *a* (three α-substituents), lutein ent-*a* (3'-epilutein), luteins *b*, ent-*b* and *c*, ent-*c* and *d* (all-*S*), and ent-*d* (all-*R*, the most common lutein). The *a* and *b* enantiomeric pairs have 3',6'-*cis* ε-rings and the *c* and *d* pairs possess

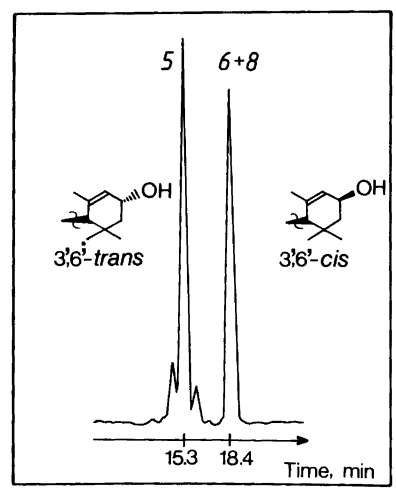
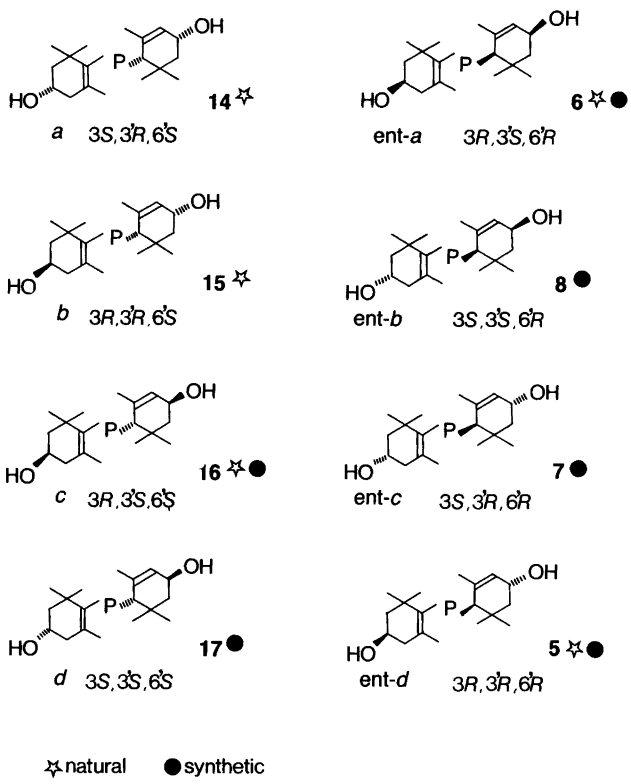


Fig. 2. HPLC (2×25 cm SiO_2 columns, hexane:isopropyl acetate:acetone 76:17:7) of (3*R*,3'*R*,6'*R*)-lutein (**5**), (3*R*,3'*R*,6'*R*)-lutein (**6**) and (3*S*,3'*S*,6'*R*)-lutein (**8**).



Scheme 4. Suggested semi-rational designations for the lutein isomers.

3',6'-*trans* ε-rings. A similar nomenclature system has been developed for the ten chiral isomers of ε,ε-carotene-3,3'-diol. The non-systematic A–H designations for the eight lutein diastereomers[10] and the A–J tunaxanthin designations for the ten ε,ε-carotene-3,3'-diol diastereomers[13] are not recommended.

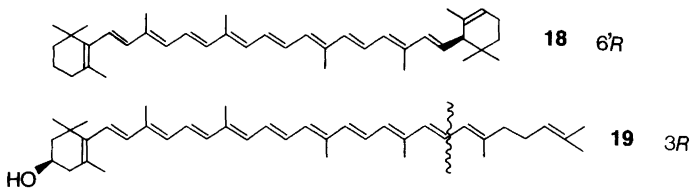
Cotton effects. The eight diastereomeric luteins (Scheme 4) should, in principle, be represented by four different CD spectra for luteins *a,b,c* and *d* and the corresponding mirror image spectra for ent-*a*, ent-*b*, ent-*c* and ent-*d*.

Quantitative CD spectra are available for ent-*a*-lutein (**6**),[2] for totally synthetic *c*- (**16**) and ent-*c*-lutein (**7**),[1] and for totally synthetic *d*- (**17**) and ent-*d*-lutein (**5**).[1] The CD spectra reported for *b*-lutein (**15**)[14] and our spectrum for ent-*b* (**8**) are in fair agreement; the Cotton effect for *b*-lutein is entirely negative and for ent-*b* entirely positive, with peaks at 245 and 265 nm.

It is therefore possible on the basis of CD spectra alone to identify each of the eight lutein isomers, although the CD spectra of the *a* and *d* series are so similar that ^{1}H NMR data in the case of 3',6'-*cis* versus 3',6'-*trans* substitution[15] or carbamate derivatization[8] are desirable as supplementary evidence.

A chiral centre at C-3 in an ε-ring of a carotenoid has been considered to have no particular influence on the Cotton effect caused by that end group, which is mainly determined by the C-6 centre[16,17] [cf. the quantitative CD spectra reported for ent-*d*- (**5**) and end-*a*-lutein (**6**)[2]]. With this approximation the Cotton effect of the eight lutein isomers should mainly be influenced by the chiralities at C-3 and C-6'.

According to the additivity hypothesis[18] for carotenoids with identical chromophores, the observed Cotton effect represents the sum of the CD contributions from the two chiral end groups. For construction of the CD spectra of the various



$\Delta\varepsilon$ **5** (3*R*,6'*R*) or $\Delta\varepsilon$ **6** (3*R*,6'*R*) $\approx$ $\Delta\varepsilon$ **18** (6'*R*) + $\Delta\varepsilon$ **19** (3*R*) corr.

Scheme 5. Application of the additivity hypothesis for estimation of the Cotton effect of lutein isomers.

lutein isomers the components (6'*R*)-β,ε-carotene (**18**) (Scheme 5), with available quantitative CD,[19] and a monocyclic 3-hydroxy-β-decaene, at present best approximated by the monocyclic 3-hydroxy-β-undecaene (3*R*)-rubixanthin (**19**) with reported quantitative CD,[20] are required. In order to compensate for chromophoric differences at the achiral end, a 12 nm hypsochromic shift is corrected for in the CD spectrum of **19**.

The constructed spectra of ent-*a*-lutein (**5**) and ent-*d*-lutein (**6**), both with 3*R*,6'*R*-configuration (Fig. 3), are in good qualitative and reasonable quantitative agreement with the measured spectra. The fit is best for the 3',6'-*cis* isomer **6**.[2]

The estimated spectra for the (3*S*,6'*R*)-luteins (Fig. 3) and (3*R*,6'*S*)-luteins exhibit non-conservative,[21] completely positive and negative Cotton effects, respectively, with one strong maximum around 278 nm. This is in reasonable agreement with the reported spectra[1] for 3',6'-*trans* synthetic *c*- (**16**, $\Delta\varepsilon$ = −12.5, 278 nm) and ent-*c*-lutein (**7**, $\Delta\varepsilon$ = +11.3, 278 nm). For the 3',6'-*cis* pair *b* (**15**)[14] and ent-*b* (**8**) the fit is least satisfactory, although the signs of the Cotton effects are as predicted.

Experimental

General methods. The general methods and instrumentation were those normally employed in our laboratory.[22]

All inversion reactions were carried out by previously described procedures.[4,5]

*(3*R,3'S*)-Zeaxanthin* (**2**, *meso*). Synthetic (3*R*,3'*R*)-zeaxanthin[9] (**1**, 56.8 mg), triphenylphosphine (52.5 mg), formic acid (7.6 μl) and di-

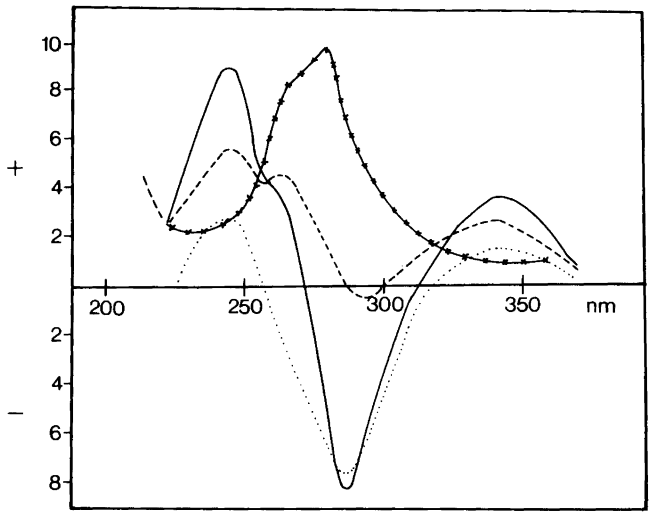


Fig. 3. CD Spectra of – – – – (6*R*)-β,ε-carotene (**18**) in dioxane[20] and ····· (3*R*)-rubixanthin (**19**) in EPA,[21] bathochromically displaced 12 nm. ---- Sum of $\Delta\varepsilon$ **18** + $\Delta\varepsilon$ **19** corr.; CD estimated for ent-*a*-lutein (**5**) and ent-*d*-lutein (**6**). −×−×− Sum of $\Delta\varepsilon$ **18** + + (−$\Delta\varepsilon$ **19** corr.); CD estimated for ent-*b*-lutein (**8**) and ent-*c*- lutein (**7**).

ethyl azodicarboxylate (31.5 μl, Fluka) in dry benzene (10 ml) were stirred for 6 days at room temperature. Extraction with ether followed by chromatography (TLC, SiO_2, 40 % acetone-hexane) gave, besides other products, zeaxanthin monoformate (R_f = 0.47, 30 % acetone-hexane). The monoformate was hydrolysed with 10 % methanolic KOH and gave, after extractive work-up and TLC purification, *meso*-zeaxanthin (**2**), yield 0.05 mg (0.1 %); R_f = 0.23 (SiO_2, 30 % acetone-hexane), same as for authentic **3**[9] and **1**; VIS λ_{max} (CH_3OH): (425), 450, 476 nm, same as for authentic **1**, % III/II[23] = 38.

(3S,3'S)-Zeaxanthin (**3**). Synthetic (3*R*,3'*R*)-zeaxanthin (**1**, 5.7 mg), triphenylphosphine (21 mg), formic acid (3 μl) and diethyl azodicarboxylate (12.7 μl) in dry benzene (1 ml) were stirred for 65 h at room temperature. Extraction and chromatography (TLC, SiO_2) provided, besides other products, the diformate [R_f = 0.57 (SiO_2, 40 % acetone-hexane)]. Hydrolysis with methanolic KOH, extraction with ether, and TLC gave **3**, yield 0.04 mg (1 %); R_f = 0.38 (SiO_2, 40 % acetone-hexane), identical with that of an authentic[9] sample. The by-products were not characterized.

Carbamate of (3R,3'S)- (**2**) *and (3S,3'S)-zeaxanthin* (**3**). (*S*)-(+)-α-(1-naphthyl)ethyl isocyanate was purchased from JPS-Chimie, Bevaix, Switzerland. The prepared carbamates were examined by HPLC[8] in order to compare with the authentic carbamates of synthetic[9] **1**, **2** and **3**. The retention times of the carbamates of partially synthetic **2** and **3**, 35.4 min and 33.3 min, respectively, were identical with those of the authentic samples.

2',3'-Didehydro-β,β-caroten-3-ol (**4**) was obtained as a by-product during the preparation of *meso*-zeaxanthin (**2**), yield 0,2 mg (0.4 %); R_f = 0.83 (SiO_2, 30 % acetone-hexane); VIS λ_{max} (CH_3OH): (425), 446, 471 nm; ^1H NMR ($CDCl_3$): δ 1.08 (s, 6H, CH_3-16, 17), 1.11 (s, 6H, CH_3-16', 17'), 1.74 (s, 3H, CH_3-5), 1.78 (s, 3H, CH_3-5'), 2.67 (m, 2H, H-4), ca. 4.0 (m, 1H, H-3), 5.5 (m, 2H, H-2', 3'), 6.1–6.7 (m, conj. olefinic H), cf. Ref. 24; MS [200 °C; *m/z* (% rel. int.)]: 550 (76, M) 52 (5, M-18), 458 (8, M-92), 149 (100).

Inversion reactions with (3R,3'R,6'R)-lutein (**5**). **5** (*ex* alfalfa, National Chlorophyll and Chemical Company), R_f = 0.50 (SiO_2, 35 % ethyl acetate-benzene), VIS λ_{max} (CH_3OH): 419, 444, 472 nm, % III/II[23] = 56 %, was used in all experiments.
(a) **5** (56.8 mg), triphenylphosphine (104.9 mg) and formic acid (15.1 μl) were suspended in dry benzene (5 ml). The addition of diethyl azodicarboxylate (62.7 μl) produced a clear solution, which was stirred for 18 h.
(b) To **5** (52.5 mg), triphenylphosphine (52.5 mg) and formic acid (7.6 μl) suspended in dry benzene (5 ml) was added diethyl azodicarboxylate (31.4 μl) at 5 °C. The mixture was stirred (3.5 h at 7 °C, 14 h at 20 °C, 2 h at 40 °C).

Extractive work-up followed by column chromatography (SiO_2) with hexane and hexane-acetone mixtures and TLC (SiO_2) afforded the carotenoids described below.

(3R,3'S,6'R)-Lutein (**6**, 3'-epilutein). **6** was obtained from preparation (a), last column fraction V [R_f = 0.15 (SiO_2, 20 % acetone-hexane)] after hydrolysis with 10 % KOH in methanol. Yield after TLC (SiO_2, 35 % ethyl acetate-benzene) 0.01 mg (0.3 %). Preparation (b) afforded, after a final TLC on special plates,[25] as the major product all-*trans* **6** (0.08 mg) and a geometrical *cis* isomer (0.03 mg); total yield 0.11 mg (0.2 %). All-*trans* **6** had R_f = 0.52 (SiO_2, 35 % ethyl acetate-benzene), the same as for **8**, and the HPLC R_T (18.4 min) was identical with that of an authentic sample[10] (see Fig. 2); VIS λ_{max} as for **5**.

The carbamate was prepared[8] as for **2** and **3** (for HPLC, see Fig. 1).

(3S,3'R,6'R)-Lutein (**7**) was also obtained upon alkaline hydrolysis of column fraction (a) V; yield 0.05 mg, R_f = 0.50 (SiO_2, 35 % ethyl acetate-benzene), the same as for **5**, and the HPLC R_T (Fig. 2) and VIS λ_{max} were also as for **5**.

The carbamate was prepared[8] as for **6** (for HPLC see Fig. 1). No separation was obtained by HPLC from the carbamate of an authentic, synthetic sample of **7**.

(3S,3'S,6'R)-Lutein (**8**) was obtained from column fraction (a) III, R_f = 0.39 (SiO_2, 20 % acetone-hexane), after alkaline hydrolysis; yield after TLC (SiO_2, 35 % ethyl acetate-benzene) 3.0 mg (5 %); R_f = 0.52 (SiO_2, 35 % ethyl acetate-benzene), the same as for **6**; R_T (Fig. 2); VIS λ_{max} the same as for **5**; after precipitation ^1H NMR

(400 MHz, $CDCl_3$): 0.85 and 0.94 (each s, each 3H, CH_3-16′, 17′; 3′, 6′-*cis*[15]), 1.07 (s, 6H, CH_3-16, 17), 1.39 (dd, 1H, J_1 = 9.5 Hz, J_2 = 12 Hz, H-2′α), 1.48 (dd, 1H, J_1 = J_2 = 12 Hz, H-2β), ca. 1.65 (m, 1H, H-2′β), 1.64 (s, 3H, CH_3-18′), 1.73 (s, 3H, CH_3-18), 1.78 (m, 1H, H-2α), 1.91 (s, 3H, CH_3-19′), 1.97 (s, 9H, CH_3-19, 20, 20′), 2.05 (dd, 1H, J_1 = 6 Hz, J_2 = 17 Hz, H-4β), 2.16 (d, 1H, J = 9.5 Hz, H-6′), 2.39 (dd, 1H, J_1 = 17 Hz, J_2 = 10 Hz, H-4α), 4.03 (m, 1H, H-3), 4.23 (m, 1H, H-3′), 5.48 (m, 1H, H-4′), 5.56 (dd, 1H, J_1 = 9.5 Hz, J_2 = 15.5 Hz, H-7′), 6.11–6.70 (m, 12H, conj. olefinic), cf. Ref. 15; CD (EPA) nm (Δε) 210 (+7.0), 220 (+5.0), 245 (+8.1), 255 (+3.8), 265 (+3.9), 270 (+2.0), 295 (+2.1), 305 (+1.0), 350 (+0.5).

The carbamate was prepared[8] for HPLC comparison (see Fig. 1).

Elimination products. The first column fraction (a) I, 0.3 mg, R_f = 0.64 (SiO_2, 20% acetone-hexane), contained, according to HPLC, VIS and NMR, a mixture of 2,3,2′,3′-tetradehydro-β,ε-carotene (**9**, 60% of total), 2,3,3′,4′-tetradehydro-β,γ-carotene (**10**, 30% of total) and 2,3-didehydrolutein (**11**) formate (10% of total).

^{1}H NMR (400 MHz, $CDCl_3$), 2,3-didehydro-β-ring: δ 1.11 (s, CH_3-16, 17), 1.78 (s, CH_3-18), 2.67 (br.s, H-4), 5.50 (m, H-2), 5.59 (m, H-3), cf. Ref. 24; 2′,3′-didehydro-γ-ring: δ 0.88 and 0.89 (both s, CH_3-16′, 17′), 4.81 and 4.88 (both s, = CH_2), ca. 5.5 (m, H-3′, 4′), cf. Ref. 7; 3-methanoloxy-ε-ring: δ 0.88 and 0.98 (both s, CH_3-16, 17), 1.64 (s, CH_3-18), 5.29 (m, H-3), 5.47 (m, H-4), 8.04 (s, HCO-).

(3′R,6′R)2,3-Didehydro-β,ε-caroten-3′-ol (**12**). Column fraction (a) IV [R_f = 0.23 (SiO_2, 20% acetone-hexane), 1.2 mg, VIS λ_{max} the same as for **5**, purified on special plates][25] gave after alkaline hydrolysis and TLC (SiO_2, 35% ethyl acetate-benzene, R_f = 0.50) **12**, yield 0.46 mg; VIS λ_{max} the same as for **5**; ^{1}H NMR (100 MHz, $CDCl_3$): δ 0.85 and 1.00 (each s, each 3H, CH_3-16′, 17′; 3′, 6′-*trans*[15]), 1.11 (s, 6H, CH_3-16, 17), 1.62 (s, 3H, CH_3-5′), 1.78 (s, 3H, CH_3-18), 1.91 (s, 3H, CH_3-19), 1.96 (s, 9H, CH_3-19, 20, 20′), 2.45 (m, 1H, H-6′), 2.67 (m, 2H, H-4), 4.25 (m, 1H, H-3′), 5.52 and 5.55 (both m, 3H, H-2, 3, 4′), 5.45 (m, 1H, H-7′), 6.0–6.7 (m, conj. olefinic H).

(3′S,6′R)-2,3-Didehydro-β,ε-caroten-3′-ol (**13**), obtained as for **12**, R_f = 0.56 (SiO_2, 35% ethyl acetate-benzene), yield 0.13 m,g; VIS λ_{max} the same as for **5**; ^{1}H NMR (100 MHz, $CDCl_3$): δ 0.85 and 0.94 (each s, each 3H, CH_3-16′, 17′; 3′, 6′-*cis*[15]), 1.11 (s, 6H, CH_3-16, 17), 1.64 (s, 3H, CH_3-18′), 1.78 (s, 3H, CH_3-18), 1.91 (s, 3H, CH_3-19), 1.96 (s, 9H, CH_3-19, 20, 20′), 2.67 (m, 2H, H-4), 4.25 (m, 1H, H-3′), 5.49 (m, 1H, H-4′), 5.52 (m, 1H, H-2), 5.55 (m, 1H, H-3), 6.0–6.7 (m, olefinic H).

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