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Synthetic Selenium Carotenoids

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Lutein was reacted with benzeneselenol and $ZnCl_2$ to provide (3*R*,3′*RS*,6′*R*)-phenylseleno-β,ε-caroten-3-ol. (3*R*,3′*R*)-Zeaxanthin provided, in a Mitsunobu reaction with benzeneselenol, (3*S*)-2′,3′-didehydro-β,β-caroten-3-yl phenyl selenide, (3*R*,3′*S*)-3-phenylseleno-β,β-caroten-3-ol and (3*S*,3′*S*)-β,β-carotene-3,3′-diyl diphenyl diselenide.

Spectroscopic properties are discussed and potential applications of these new selenium carotenoids considered.

A striking coincidence is the discovery of both selenium and the carotenoid lutein (**1**) by Berzelius who in 1818 characterized selenium as a new element[1] and in 1837 extracted xanthophyll (lutein) from autumn leaves.[2] Selenium and carotenoids such as lutein (**1**) and zeaxanthin (**4**) occur together in certain plants[3–5] and algae,[6] but natural Se-containing cartenoids have not been detected. Similar properties of selenium and carotenoids, e.g., as antioxidants,[7,8] cancer preventatives[9,10] and conductors[11,12] have led to combined applications: a film of β,β-carotene and selenium has been prepared as a photoconductor layer[13] and it was found that intake of inorganic selenium and β,β-carotene has an inhibitory effect on carcinogenesis in rats.[14] Similarly, selenium retinoids showed higher cancer preventative activity than retinoids.[15] Therefore, the synthesis of selenium carotenoids became of interest. Indeed lutein phenyl selenide[16] acted as a more effective $^1O_2$ quencher than lutein.[17]

Results and discussion

Partial synthesis. Only few syntheses of selenides have been employed[18] and the reaction conditions may restrict their application to carotenoids. A mild, zinc-catalysed procedure for the substitution of hydroxy by a phenylseleno group has been developed for allylic alcohols.[18] This reaction was here successfully applied to lutein (**1**). A similar reaction was previously used for the synthesis of thiolutein.[19] Benzeneselenol was, in this work, reacted with lutein (**1**) in the presence of $ZnCl_2$ at room temperature to provide lutein phenyl selenide (**2**), Scheme 1, in 62% yield, along with three other products. Judged by the ^1H NMR data (Scheme 3) the phenyl selenide **2** was isolated as a mixture of two C′-3 epimers in a 45:55 (3′,6′-*cis*, **2a**/3′,6′-*trans*, **2b**) ratio, consistent with an allylic carbocation intermediate.

The reaction of a tertiary alcohol with benzeneselenol has also been achieved.[18] However, 1,2,1′,2′-tetrahydro-ψ,ψ-carotene-1,1′-diol (**3**) did not provide the expected selenide(s) under the described conditions, cf., Ref. 19.

The above Lewis acid catalysed reaction of allylic alcohols is not enantioselective. The synthesis of optically active selenium carotenoids was therefore based on the Mitsunobu reaction.[20] The inversion of 3β-hydroxycholestane has been performed with thiophenolate.[21] Selenophenolate is an even better nucleophile and the reaction of (3*R*,3′*R*)-zeaxanthin (**4**) with triphenylphosphine, diethyl azodicarboxylate and benzeneselenol provided the (3*R*,3′*S*)-hydroxy selenide **5**, (3*S*)-monoselenide **6** and (3*S*,3′*S*)-diselenide **7** in 23% yield, in addition to the elimination products **8** and **9**, Scheme 2.

In conclusion, the selenium carotenoid (**2**) was obtained as a C-3′ epimeric mixture in good yield by a facile synthesis from lutein (**1**) with benzeneselenol. Competing elimination reactions in the Mitsunobu reaction reduced the yield of optically active selenium carotenoids **5–7** from zeaxanthin (**4**). The new carotenoid selenides seemed to be as stable as the corresponding carotenols.

Spectroscopic properties. In the UV spectra of the selenium carotenoids **2**, **5–7** the weak transitions[22] of the phenylseleno substituent at 240 and 270 nm were not detected, and the VIS absorption spectra were, as expected, not influenced by the seleno substituent. In the IR spectrum characteristic absorptions[23] were recorded at 740 cm^{-1} ($\nu_{aryl\text{-}H}$) and 692 cm^{-1} ($\nu_{C\text{-}Se}$) for the selenides **2**, **5** and **7**.

The mass spectra of the selenium carotenoids exhibited

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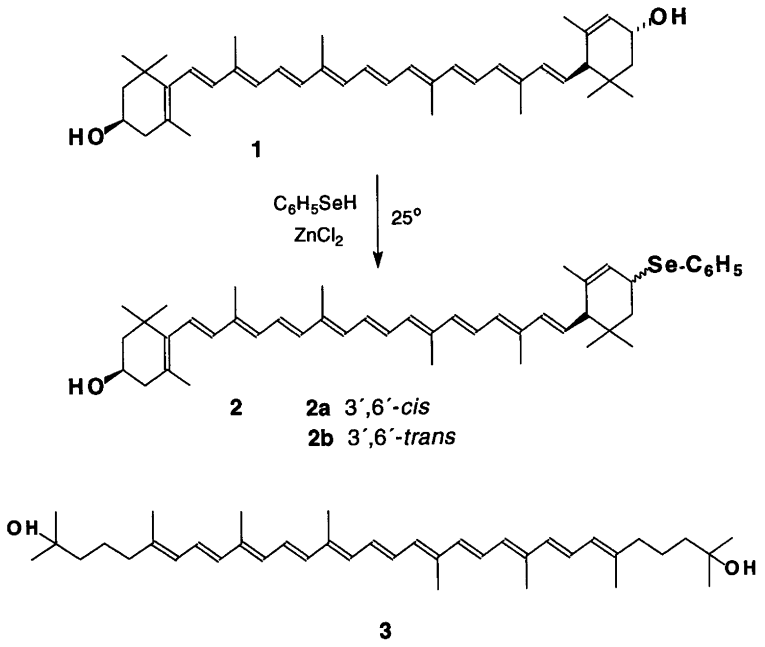
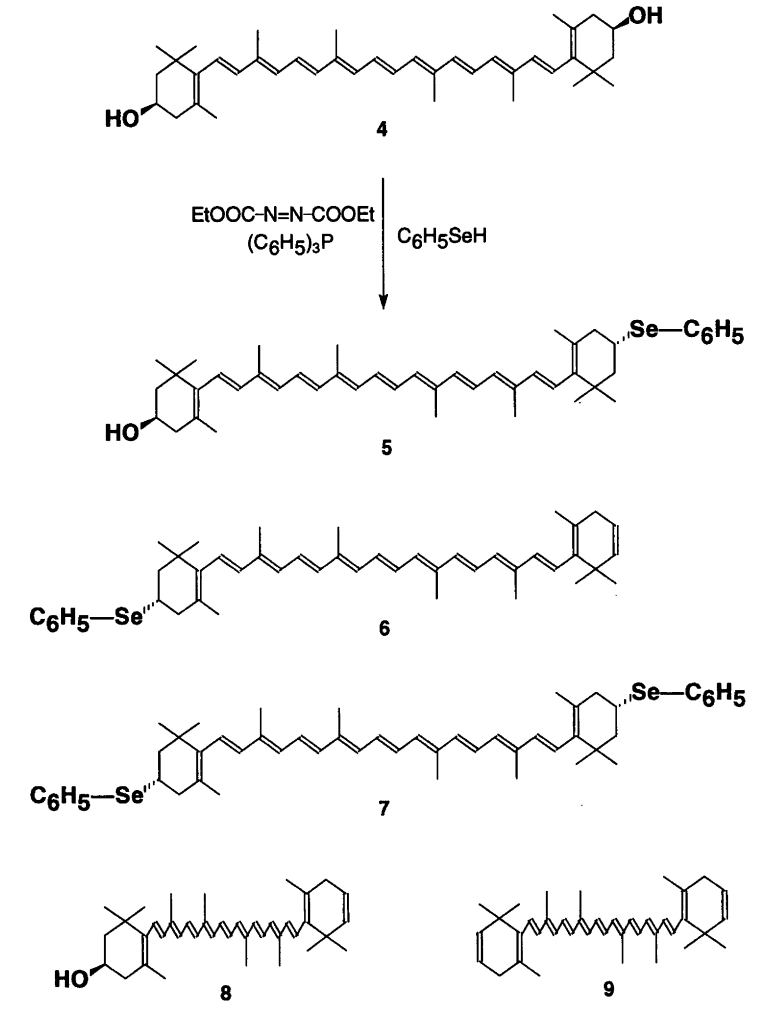


Scheme 1.



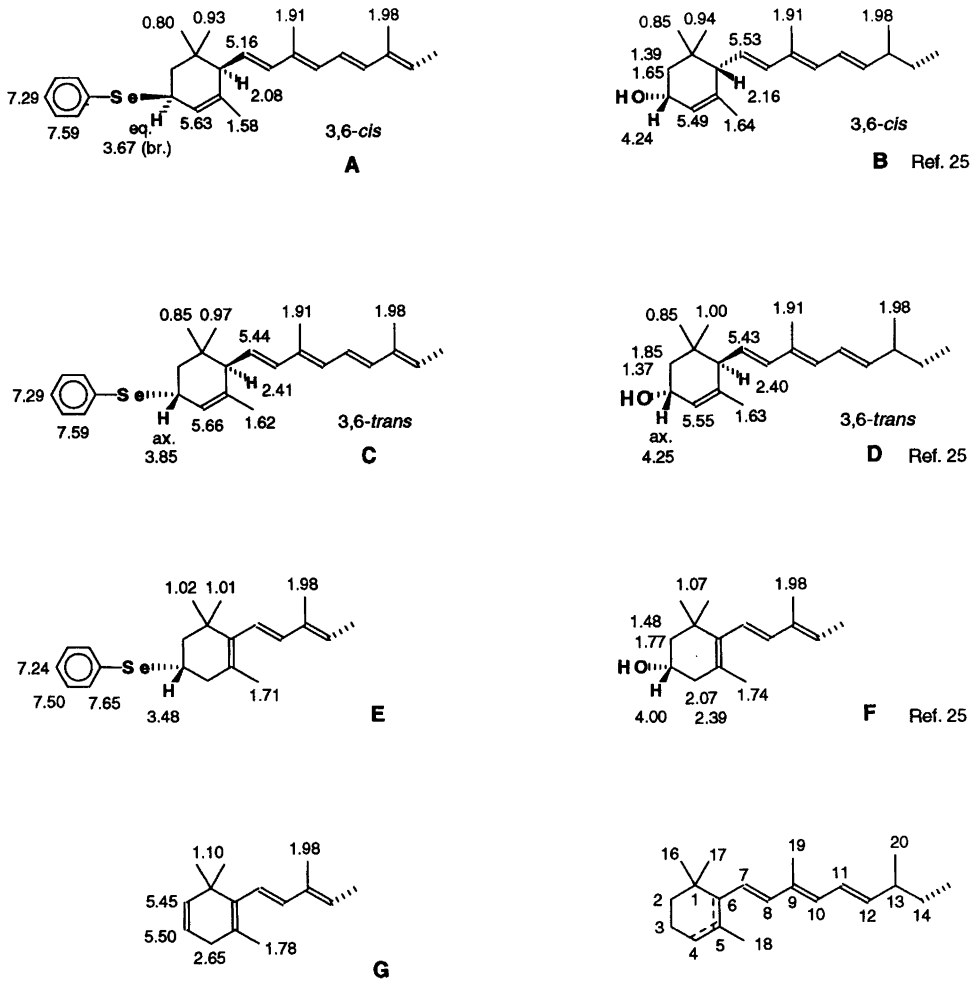
Scheme 2.

a complex pattern of the molecular ions in accordance with the calculated isotopic distribution for $C_{46}H_{60}OSe$ (**2**, **5**), $C_{46}H_{58}Se$ (**6**) and $C_{52}H_{64}Se_2$ (**7**). Common carotenoid fragmentation (M^+ – toluene, M^+ – xylene),[24] as well as $M^+ - C_6H_5Se$ were observed.

The ^1H NMR spectra were interpreted upon comparison with relevant models,[25,26] see Scheme 3. The ε-derivatives **2a** and **2b** (end groups A and C) revealed lower chemical shifts of the C-3′methine protons in A, C than in end-groups B, D, and larger influence of the C-3′ axial seleno substituents in the 3,6-*cis* (A) than for the 3,6-*trans* (B) end-group on the H-7 and CH_3-17,18 protons; for numbering of the carotenoid skeleton, see Scheme 3.

The CD-spectra confirmed the configurational inversion of the selenides **5**, **6** and **7** resulting from the Mitsunobu reaction of **4**. The Cotton effect of β,β-carotenoids originates from the twisted, inherently chiral s-*cis* diene chromophore C(5) = C(6)–C(7) = C(8), where the conformational equilibrium of the cyclohexene rings is blocked by the C-3 substituents.[27,28] In carotenoids with β,β-type chromophores each chiral end-group contributes to the CD.[27] Accordingly, the monochiral selenium (3*S*)-carotenoid **6** had a lower intensity Cotton effect than the dichiral selenium (3*S*,3′*S*)-carotenoid **7**. The Cotton effects of **6** and **7** were the opposite of those of the carotenols **8**[20] (Fig. 1) and **4**, respectively.

Unlike (3*S*,3′*R*)-3′-amino-β,β-caroten-3-ol[29] and (3*S*,3′*R*)-3′-mercapto-β,β-caroten-3-ol,[20] which can be considered as *pseudo meso* compounds owing to the absence of electronic optical activity, the dichiral hydroxy selenide **5** showed weak Cotton effects, Fig. 1. This observation indicates different conformational properties of the Se-substituted cyclohexene half chair relative to the O-substituted one. Optically active phenyl selenides have been reported to exhibit Cotton effects between 200 and 274 nm caused by $n \rightarrow \sigma^*$ (C–Se) and $\pi \rightarrow \pi^*$ (C_6H_5) transitions.[30] Such low intensity Cotton effects may be hidden in the CD spectra of **5**, **6** and **7**.



Scheme 3. ^1H NMR (500 MHz) data of diastereomeric (3*R*,3′*RS*, 6′*R*)-phenylseleno-β,ε-caroten-3-ol (**2**) A,C,F ($CDCl_3$) and (3*R*,3′*S*)-3-phenylseleno-β,β-caroten-3-ol (**5**) E,F; (3*S*)-2′,3′-didehydro-β,β-carotene-3-yl phenyl selenide (**6**) E,G and (3*S*,3′*S*)-β,β-carotene-3,3′-diyl diphenyl diselenide (**7**) E,E (CCl_4).

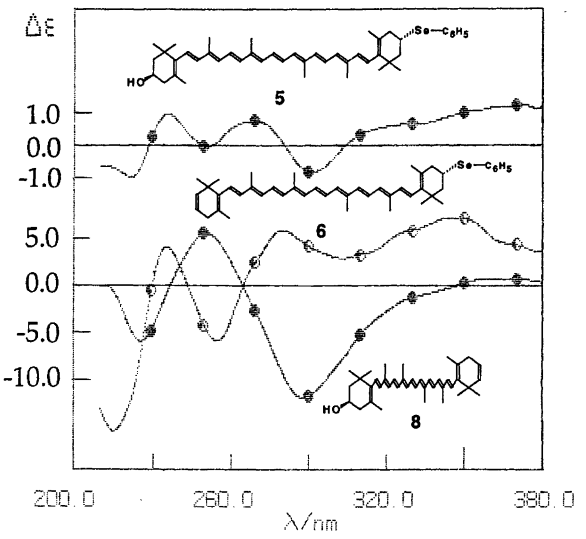


Fig. 1. CD spectra (EPA) of (3*R*,3′*S*)-3′-phenylseleno-β,β-caroten-3-ol (**5**), (3*S*)-2′,3′-didehydro-β,β-carotene-3-yl phenyl selenide (**6**) and (3*R*)-2′,3′-didehydro-β,β-caroten-3-ol (**8**).[20]

Experimental

General methods. General precautions[31] for work with carotenoids were taken. After reaction the products were adsorbed onto silica gel, dried *in vacuo* and separated by flash chromatography (silica gel 60, Merck), followed by further purification on preparative or analytical TLC plates (silica gel 60 G, Merck) with heptane–acetone mixtures. R_F-values were determined by TLC on aluminium sheets (silica gel 60, Merck) with 30% acetone–heptane (system 1) or on HPTLC plates (silica gel 60, Merck) with 20% acetone–heptane (system 2). For the IR spectra (KBr) only diagnostically useful absorptions are cited, and for the mass spectra (IP 70 eV, 210°C) only prominent or diagnostically useful peaks are reported and molecular and fragment ions refer to ^{80}Se. The CD spectra were measured in EPA (ethanol–isopentane–ether 2:5:5) at room temperature. The ^1H NMR spectra (500 MHz) and ^{13}C NMR spectra (125 MHz) were interpreted by comparison with data for related compounds.[25]

*Reaction of lutein (**1**) with benzeneselenol.* Lutein (**1**) (56.8 mg, 0.1 mmol, *ex* alfalfa, National Chlorophyll Company, lutein ent-d,[32] $R_F = 0.24$, system 1) was dissolved in CH_2Cl_2 (7 ml). Benzeneselenol (10.6 µl, 0.1 mmol) and dry $ZnCl_2$ (8.2 mg, 0.1 mmol) were added.[18] The reaction was stirred at room temperature for 3 h, after which chromatographic work-up provided four products. The main product was:

*(3R,3′RS,6′R)-Phenylseleno-β,ε-caroten-3-ol (**2**).* Yield: 43.8 mg, 62%; R_F 0.38, system 1; VIS: λ_{max} 450, 478 nm; MS: *m/z* 708 (*M*, Se-isotopic pattern), 616 (Se-isotopic pattern, *M* – toluene), 602 (Se-isotopic pattern, *M* – xylene), 550 (*M* – C_6H_5SeH), 532 (550 – H_2O), 458 (550 – toluene), 444 (550 – xylene); IR: 1073, 740, 692 cm^{-1}, cf., Ref. 23; ^1H NMR ($CHCl_3$): Scheme 3 (A,B,D); ^{13}C NMR ($CHCl_3$): δ 23.0, 23.5 (CH_3-C5), 22.9, 26.5, 29.0, 29.3 (2 CH_3-C1), 13.1 (CH_3-C9), 12.8 (CH_3-C13), 39.5, 42.8 (C2), 38.8, 39.2 (C3), 34.4, 34.7 (C1), 127.8, 129.0, 130.1, 123.5 (phenyl).

*Reaction of zeaxanthin (**4**) with benzeneselenol.* Zeaxanthin (**4**) (113.6 mg, 0.2 mmol, $R_F = 0.03$, system 2) and triphenylphosphine (115.3 mg, 0.44 mmol) were suspended in benzene (7 ml). Diethyl azodicarboxylate (69 µl, 0.44 mmol) and benzeneselenol (47 µl, 0.44 mmol) were added with a syringe. Stirring for 12 h at 35°C and subsequent chromatographic work-up separated the diphenyl diselenide and the carotenoids **5**, **6** and **7** (34.7 mg, 23%) in a ratio of 2.8:1:3.6, together with the elimination products **8** and **9**, and unchanged zeaxanthin (**4**).

*(3R,3′S)-3-Phenylseleno-β,β-caroten-3-ol (**5**).* Available: 17 mg, 49% of Se-products; R_F 0.13, system 2; HPLC (nitrile column, hexane) t_R (min): 16.7 (91%) (**8**,t_R 15.8; **4**,t_R 22.9); VIS: λ_{max} 449, 476 nm (hexane, as for **4**), 459, 480 nm (CH_2Cl_2), 447, 472 nm (EPA and EtOH); MS: *m/z* 708 (*M*, Se-isotopic pattern), 690 (Se-isotopic pattern, *M* – H_2O), 616 (Se-isotopic pattern, *M* – toluene), 602 (*M* – xylene), 550 (*M* – C_6H_5SeH), 532 (550 – H_2O), 458 (550 – toluene), 444 (550 – xylene), 392 (550 – 158); IR: 740, 690 cm^{-1}; CD: Fig. 1; ^1H NMR (CCl_4): Scheme 3, E,F.

*(3S)-2′,3′-Didehydro-β,β-carotene-3-yl phenyl selenide (**6**).* Available: 13 mg, 37% of Se products; R_F 0.70, system 2; VIS: λ_{max} 448, 472 nm (hexane), 461 (480) nm (CH_2Cl_2), 448 (470) nm (isooctane), 446, 470 nm (EPA and EtOH); MS: *m/z* 690 (*M*, Se-isotopic pattern), 598 (Se-isotopic pattern, *M* – toluene), 584 (Se-isotopic pattern, *M* – xylene), 532 (*M* – C_6H_5SeH), 440 (532 – toluene); IR: 1072, 736, 689 cm^{-1}; CD: Fig. 1; ^1H NMR (CCl_4): Scheme 3, E,G.

*(3S,3′S)-β,β-Carotene-3,3′-diyl diphenyl diselenide (**7**).* Available: 4.7 mg, 14% of Se-products; R_F 0.63, system 2; HPLC (silica column, hexane) t_R (min) 4.99 (β,β-carotene t_R 3.26); VIS: λ_{max} 456, 480 nm (CH_2Cl_2), 448 (471) nm (EtOH), 446, 471 nm (EPA); MS: *m/z* 848 (*M*, Se_2-isotopic pattern), 756 (Se_2-isotopic pattern, *M* – toluene), 742 (Se_2-isotopic pattern, *M* – xylene), 690 (Se_2-isotopic pattern, *M* – C_6H_5SeH), 598 (Se-isotopic pattern, 690 – toluene), 584 (Se-isotopic pattern, 690 – xylene), 532 (690 – C_6H_5SeH), 440 (532 – toluene); IR: 1072, 740, 692 cm^{-1}; CD nm (Δε): 235 (9.0), 254 (– 12.0), 281 (9.9), 341 (11.8); ^1H NMR (CCl_4): Scheme 3, A,A.

*(3R)-2′,3′-Didehydro-β,β-caroten-3-ol (**8**).* Available: 17 mg; R_F 0.15, system 2; VIS: λ_{max} 457, 482 nm (CH_2Cl_2); CD: Fig. 1; MS spectrum and R_F (HPTLC co-chromatography) were as described elsewhere.[29]

2,3,2′,3′-Didehydro-β,β-carotene (**9**). R_F 0.86; VIS: λ_{max} 458 (480) nm (CH_2Cl_2).

In another experiment (same quantities, reaction conditions 3 h, 40°C) chromatographic work-up provided 3.8 mg (8%) of the Se-products **5**, **6** and **7** in a ratio of 1:1:4.7, in addition to unchanged zeaxanthin (**4**) (78 mg) and the elimination products **8** (2.7 mg) and **9**.

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