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Selective Hydrogenation of Carotenones II.† Reduction of Rhodoxanthin to Lutein and Zeaxanthin, and of Canthaxanthin to a Dihydro-*retro*-carotenediol by Tellurium Hydride

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Racemic lutein and racemic zeaxanthin have been prepared from rhodoxanthin by reduction with tellurium hydride. Similarly, canthaxanthin was transformed into a *retro*-carotenediol.

Carotenoids with different degrees of saturation are found in crude oil, perhydrocarotenoids being the ultimate degradation product of geohistorical carotenoids.[2] Hydrocarotenoids also occur in living species.[3,4] Catalytic hydrogenation of carotenoids has previously been used for determining the total number of carbon–carbon double bonds in carotenoids.[5] Selective hydrogenation of carotenoids has been less studied.[6,7] We report here the syntheses of hydrocarotenoids by selective hydrogenation of carotenones with tellurium hydride.[8,9]

Reaction with rhodoxanthin. Rhodoxanthin (**3**) reacted with NaTeH–$NaBH_4$ (Ref. 8) to give yellow, more polar products, compatible with a shortening of the polyene chain and the formation of hydroxy groups. The mass spectrum of the main product revealed the addition of six hydrogen atoms. HPLC showed two peaks inseparable by co-chromatography from 3′,6′-*trans*- and 3′,6′-*cis*-β,ε-carotene-3,3′-diol (lutein) (**1**)[10] and a third peak with the same t_R-value as for authentic zeaxanthin (**2**). The VIS spectra, recorded during HPLC, corresponded to reference spectra of lutein (**1**) and zeaxanthin (**2**), respectively. The ^1H and ^{13}C NMR spectra indicated the presence of β-rings (**1**, **2**) and of 3′,6′-*trans*- and 3′,6′-*cis*-3-hydroxy ε-rings (**1**), in agreement with published data.[10,11] The tellurium hydride reduction of double bonds conjugated with a carbonyl group may follow a hydride transfer reaction,[12] involving dissociation of TeH^- into Te and H^-, Scheme 1. The hydride could then attack the C-4 atom in a Michael-type addition, leading to an isomerisation of the *retro*-polyene chain[13] with C-3′ enol formation. Tautomerisation of the intermediate enol in protic solvents to β,ε-carotene-3,3′-dione (**4**) or alternatively to the diketone **5** would be expected.[14] The reduction of ketones to alcohols by TeH^- is not known, and the formation of the diols **1** and **2** is ascribed to the excess of $NaBH_4$ employed for the preparation of the sodium hydrogen telluride reagent.[8] By the present synthesis racemic lutein (**1**) and racemic zeaxanthin (**2**) were obtained in a ratio of about 4:1 with a total yield of 6%, similar to the yields of partial and multistep total syntheses.[10,13,15–17]

Lutein (**1**) is an abundant naturally occurring carotenoid which often co-occurs with zeaxanthin (**2**) in plants and animals.[18,19] All eight optically active isomers of lutein (**1**) have now been detected in Nature[20] or have been synthesised.[10] However, investigations with lutein are still based mainly on one single diastereoisomer.[21] Rhodoxanthin (**3**) has been employed in a two-step synthesis of racemic zeaxanthin (**2**).[22] However, a similar straightforward synthesis of racemic lutein (**1**) has not been available. The reaction with tellurium hydride presents a simple, albeit low-yield synthesis of lutein (**1**) and zeaxanthin (**2**) from rhodoxanthin (**3**).

Reaction with canthaxanthin. Canthaxanthin (**6**) reacted with NaTeH[8] to give yellow, more polar products. The VIS spectrum (λ_{max} and fine structure) of the main product was compatible with an aliphatic octaene chromophore. The mass spectrum indicated the addition of four hydrogen atoms. The presence of one hydroxy group was assumed after co-chromatography (TLC) with 4′-hydroxyechinenone. ^1H and ^{13}C NMR spectra were partly in agreement with the available reference data for **7**.[11] Two doublets at 3.11 and 3.16 ppm, not

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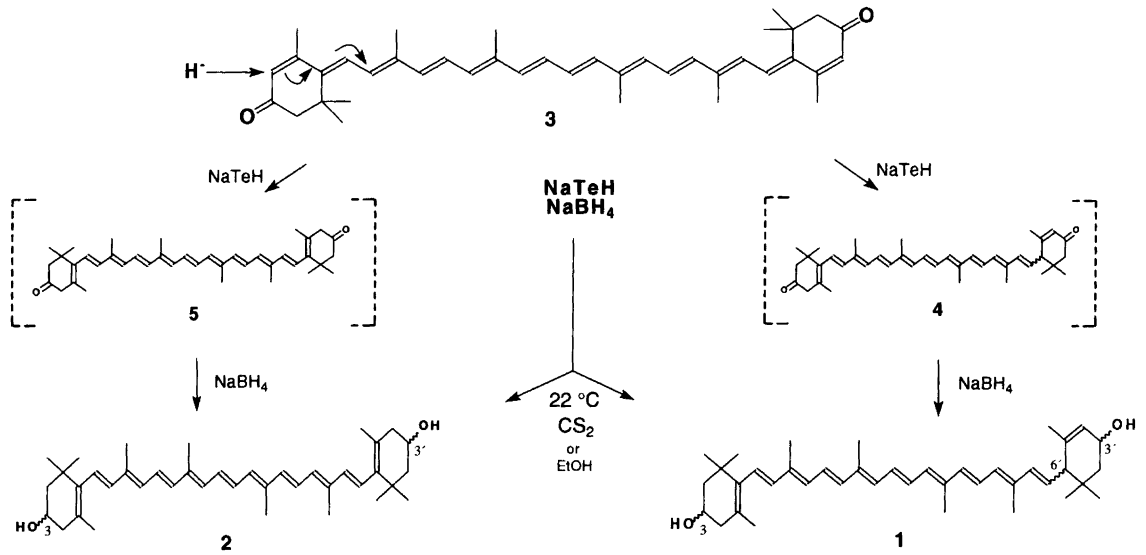
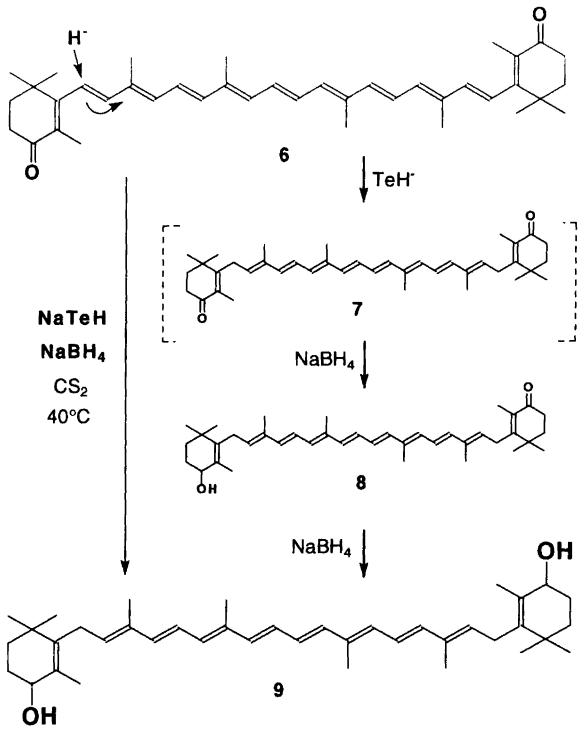
† Part 1: Ref. 1.



Scheme 1.

present in the spectrum of **6**, indicated bisallylic protons at C-7 and C-7′, respectively. Peaks at 72.5 and 199.8 ppm in the ^{13}C NMR spectrum were consistent with the presence of a hydroxy group at C-4′ and a keto group at C-4. From these data the product was identified as the hydroxy ketone **8**. When **8** was subsequently treated with $NaBH_4$, 7,7′-dihydro-8,8′-*retro*-β,β-carotene-4,4′-diol **9** was obtained in 5% yield, similar to the yield of the reaction with rhodoxanthin (**3**). The tellurium hydride reduction of canthaxanthin (**6**) may follow a similar hydride-transfer reaction as suggested for rhodoxanthin. However, because of steric hindrance, the hydride addition at C-7 was favoured, Scheme 2. A synthesis of the *retro*-carotenone **7** from **6** with dithionine has been mentioned without experimental details.[23] Related hydrocarotenoids have been obtained by the reaction of β,β-carotene with Na and Li.[24]



Scheme 2.

Experimental

Rhodoxanthin reaction. Tellurium powder (64 mg, 0.5 mmol) and $NaBH_4$ (45.6 mg, 1.2 mmol) were refluxed in abs. ethanol (3 ml) under N_2 for 15 min. After cooling to 40 °C rhodoxanthin (**1**) (11.2 mg, 0.02 mmol, 93% all-*trans*, ^1H NMR evidence[25]) suspended in abs. ethanol or preferably dissolved in CS_2 (5 ml) was added with a syringe to the NaTeH solution.[8] After 20 min most of **1** had reacted. The solvent was removed, the residue dissolved in CH_2Cl_2, washed until neutral with water and dried over anhydrous Na_2SO_4. Flash chromatography of the products on silica and further purification by prep. TLC (silica) with heptane–acetone mixtures and HPLC [analytical silica gel column, 5 μm, 25 cm, eluent: hexane (90.9%)–CH_2Cl_2 (6.5%)–2-propanol (2.5%)–*N*-ethyldiisopropylamine (0.1% v/v)[26]] of the main fraction showed the presence of lutein (**1**) by the two peaks of the 3′6′-*cis*, 3′6′-*trans* lutein diastereoisomers and the presence of zeaxanthin (**2**) by a third peak: (3*R*,3′*R*,6′*R*)-lutein (**1** *ent*-d)[10] 44%, t_R = 21.8 min; zeaxanthin (**2**) (24%), t_R = 24.8 min; and 3*R*,3′*S*,6′*R*-lutein (**1** *ent-a*) 31%, t_R = 25.2 min. Zeaxanthin (**2**) and the 3′,6′-*cis* isomer **1** *ent-a* were not baseline separated. The products were found to have the same t_R-values by co-chromatography with reference authentic samples. The HPLC reference of epimeric (3*R*,3′*RS*,6′*R*)-lutein (**1** *ent*-a, **1** *ent*-b) was prepared from (3*R*,6′*R*)-3-hydroxy-β,ε-caroten-3′-one[27] by reduction with $NaBH_4$.

The VIS and MS spectra were in agreement with spectra of authentic lutein (**1** *ent*-d). In the ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra signals from both the 3′,6′-*cis* and the 3′,6′-*trans* ε-isomers were detected,[10,11] besides the signals from the β-rings of **1** and **2**. The diols **1** and **2** (0.7 mg, 6%) were formed in a ratio of about 4:1.

Canthaxantin reaction. Tellurium powder (132 mg, 1.03 mmol) and $NaBH_4$ (98 mg, 2.58 mmol) were refluxed in abs. EtOH (4 ml) under N_2 for 15 min.[8] After cooling to 40 °C, canthaxanthin (**6**) (56.4 mg, 0.1 mmol), dissolved in CS_2, was added with a syringe. After 30 min the solvent was removed and the residue was dissolved in CH_2Cl_2, washed until neutral with water and dried over anhydrous Na_2SO_4. Flash-chromatography with heptane–acetone mixtures and TLC of the main fraction gave the hydroxy ketone **8** (3 mg, 5%) $R_F = 0.46$, (**6** = 0.54, 4′-hydroxyechinenone = 0.46, 40% v/v acetone/heptane); VIS (CH_2Cl_2): 430, 457 nm, (cf. isozeaxanthin: 458, 486 nm); MS *m/z*): 568 (*M*), 550 ($M-H_2O$), 476 *M*−toluene), 462 (*M*−xylene); IR (KBr, film): 1717, 1655 cm^{-1}; ^1H NMR 400 MHz ($CDCl_3$): δ 1.14, 1.19 (2 CH_3, C-1), 1.35, 1.54 (2 H, C-2), 1.68, 1.87 (2 H, C-3), 3.72 (H, C-4), 1.73 (CH_3, C-5), 3.33 (2 H, C-7), 5.30 (H, C-8) 1.95 (CH_3, C-9). ^{13}C NMR 100 MHz ($CDCl_3$): δ 26.2, 27.7 (2 CH_3, C-1, 36.3, 38.8 (C-2, C-3), 72.5 (C-4), 14.2 (CH_3, C-5), 30.8 (C-7), 13.0 (CH_3, C-9). The data for the keto β-ring were in agreement with published references.[11] The hydroxy ketone **8** was dissolved in EtOH and stirred for 30 min at 40 °C with $NaBH_4$. Chromatographic work-up gave the diol **9**. $R_F = 0.33$, 30% v/v acetone–heptane); MS (*m/z*): 570 (*M*), 552 ($M-H_2O$), 534 ($552-H_2O$), 460 (552−toluene), 446 (552−xylene).

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