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The Synthesis of Tedanin and Its Isomer, 3-Hydroxy-2,3-didehydro-β,φ-caroten-4-one[1]

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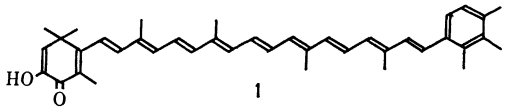
The structure, 3-hydroxy-2,3-didehydro-β,χ-caroten-4-one, assigned to tedanin, the main carotenoid pigment of the marine sponge "*Tedania digitata* (O. Schmidt)," has been confirmed by total synthesis starting with β,χ-carotene. An isomer, 3-hydroxy-2,3-didehydro-β,φ-caroten-4-one, was also synthesized from β,φ-carotene.

Tedanin was first isolated as the main carotenoid from the sea sponge "*Tedania digitata* (O. Schmidt)," and its chemical structure has been established to be 3-hydroxy-2,3-didehydro-β,χ-caroten-4-one (**1**)[3] by Okukado on the basis of chemical and spectroscopic evidence.[4] This pigment was also found in a sea sponge, "*Clathria frondifera* (Bowerbank)," by Tanaka and Katayama.[5]

In this paper, we wish to report a total synthesis of tedanin which has unambiguously confirmed the proposed structure. We also wish to report the synthesis and characterization of the isomer, 3-hydroxy-2,3-didehydro-β,φ-caroten-4-one (**2**), in which a χ-ring end group of tedanin was replaced by a φ-end group. Although its natural existence has not yet been established, the isomer can be expected to exist in nature with a high probability since a φ-end group has often been encountered in natural carotenoids.[6]



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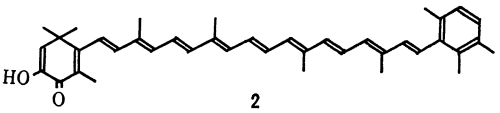

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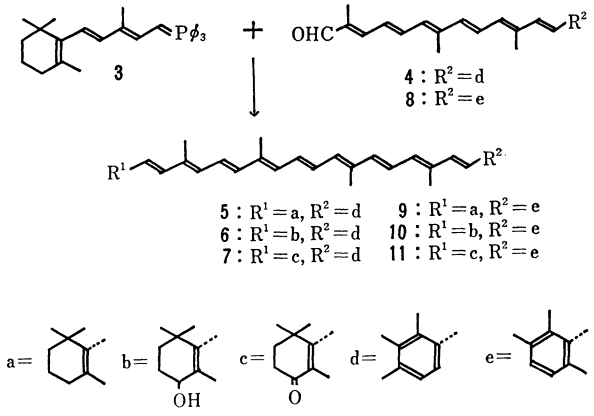
Results and Discussion

The synthesis of tedanin started with β,χ-carotene (β-isorenieratene) (**5**). The latter compound had previously been synthesized by Weedon *et al.*[7] and later reported to occur in some species of photosynthetic brown bacteria (*Phaebium*).[8] The synthesis by Weedon *et al.* was carried out according to the $C_{10}+C_{20}\rightarrow C_{30}$, $C_{30}+C_{10}\rightarrow C_{40}$ building scheme; however, a different construction principle, $C_{15}+C_{25}\rightarrow C_{40}$, was used in the present study. Thus, the Wittig reaction of 5-(2,6,6-trimethyl-1-cyclohexenyl)-3-methyl-2,4-pentadienylidenetriphenylphosphorane (**3**)[9] with 12'-apo-χ-caroten-12'-al (**4**), which we had previously used for the synthesis of 7,8-didehydrorenieratene,[10] gave β,χ-carotene (**5**) in a 51% yield after purification by column chromatography on alumina. The physical and spectroscopic properties were identical with those reported by Weedon *et al.* The treatment of **5** with *N*-bromosuccinimide and glacial acetic acid in chloroform, followed by saponification with methanolic potassium hydroxide,[11] afforded an alcohol (**6**) in a 74% yield. The alcohol has the molecular formula of $C_{40}H_{52}O$, which was determined by elemental analysis and mass spectrum; it shows ^{1}H NMR signals at δ 1.02(3H), 1.04(3H), 1.85(3H), and 4.02(1H), which can be assigned to protons of the 4-hydroxy-2,6,6-trimethyl-1-cyclohexenyl moiety.[12] The treatment of **6** with active manganese dioxide prepared by Attenburrow's method[13] gave a ketone (**7**) as purplish black crystals in a 61% yield. When γ-manganese dioxide[14] was used for this oxidation, no desired ketone (**7**) was obtained; the reaction products consisted of several components with shorter wavelength absorptions than those of the alcohol (**6**). The oxidation from **6** to **7** resulted in a bathochromic shift (8 nm), accompanied by a complete loss of fine structures in the UV spectrum.[15] Finally, the oxidation of **7** by oxygen in the presence of potassium *t*-butoxide[16] yielded tedanin (**1**) in a 71% yield after purification by chromatography on silica gel. The identity of the synthetic material with the natural specimen was established by a mixed melting-point determination and mixed chromatography as well as by a comparison of the IR, UV, NMR, and mass spectra.



The synthesis of 3-hydroxy-2,3-didehydro-β,φ-caroten-4-one (**2**) was carried out starting from β,φ-carotene (**9**) by the route adopted for the synthesis of tedanin. The chromatographic behavior of **2** was very similar to that of tedanin. The physical and spectroscopic properties will be described in the Experimental section. As expected, the isomer (**2**) showed its absorption maximum in benzene at 483 nm, shorter by 7 nm than that of tedanin (**1**), which has a χ-end group. This can be explained on the basis of the fact that the chromophore system of **2** was more distorted than that of **1** because of the steric interference between the polyene chain

and two methyl substituents at the 1- and 5-positions in the ϕ-end group compared with one substituent at the 1-position in the χ-end group.[7]

Experimental

All the melting points are uncorrected. All the reactions and operations were carried out under an atmosphere of nitrogen as far as possible. The instruments and solvents used for the measurements of the spectra were as follows: UV spectra: Hitachi, Model EPS-3T (benzene). IR spectra: Hitachi, Model R-215 (KBr). NMR spectra: Hitachi, Model R-20B ($CDCl_3$, with TMS as the internal standard). Mass spectra: Hitachi, Model RMU-6MG.

β,χ-Carotene (5). An ethereal solution of phenyllithium (1.1 mol dm^{-3}, 9 ml) was added, at room temperature, to a stirred suspension of 5-(2,6,6-trimethylcyclohexenyl)-3-methyl-2,4-pentadienyltriphenylphosphonium bromide[9] (3.015 g) in dry ether (40 ml). After 5 min, dry dichloromethane (5 ml) was added to destroy the excess phenyllithium. To this deep red solution of the ylid we then added a solution of 12′-apo-χ-caroten-12′-al[10] (**4**) (900 mg) in dichloromethane (30 ml). The mixture was stirred for 2 h at room temperature, poured into water, and extracted with benzene. The extract was dried with sodium sulfate and evaporated. The reddish residue was chromatographed on neutral alumina [Merck, deactivated by the addition of water (2%)], with a benzene–petroleum benzine mixture (3 : 7) as the developer. The main red zone was eluted with a benzene–methanol mixture (9: 1), and the eluate was concentrated under reduced pressure to give a crude product, which was then recrystallized from a dichloromethane–ethanol mixture. Red crystals (51%); mp 165 °C (lit,[7] mp 164 °C). Found: C, 89.92; H, 9.81%. Calcd for $C_{40}H_{52}$: C, 90.15; H, 9.85%. λ_{max} 506, 474 nm ($\varepsilon = 1.31 \times 10^5$); IR 3040, 2980, 2950, 1655, 970, 835 cm^{-1}; NMR δ 1.04 (6H, s, 1, 1-dimethyl), 1.75 (3H, s, 5-methyl), 2.00, and 2.09 (9H, s, and 3H, s, respectively; chain methyls), 2.23, and 2.32 (3H, s, and 6H, s, respectively; aryl methyls); MS 532 (M), 453, 440, 426, 399, 395, 374, 133, 106, 105, 92, 91.

β,χ-Caroten-4-ol (6). A cooled solution of NBS (109 mg) in a mixture of glacial acetic acid (0.49 ml) and chloroform (13 ml) was stirred into a solution of **5** (300 mg) in dry chloroform (33 ml) which had been cooled at −60 °C with Dry Ice–chloroform bath. After stirring at −60 °C for 2 h, *N*-ethylmorpholine (1.45 ml) was added; the mixture was stirred for 2 h at 0 °C and then heated under reflux for 2 h. The mixture was washed three times with aqueous hydrochloric acid (0.1 mol dm^{-3}), aqueous sodium hydrogencarbonate, and then water. After the removal of the solvent, the residue was dissolved in benzene (30 ml) and treated overnight with a 15% methanolic potassium hydroxide solution (33 ml) at room temperature. The mixture was then diluted with water, and the organic layer was washed with water, dried, and evaporated. The residue was chromatographed on alumina [deactivated by the addition of water (5%)] with benzene. The main red zone was eluted with a benzene–methanol mixture (9 : 1); the subsequent removal of the solvent gave a crude product, which was purified by recrystallization with a benzene–ethanol mixture. Purplish red needles (74%); mp 153—154 °C. Found: C, 87.22; H, 9.54%. Calcd for $C_{40}H_{52}O$: C, 87.53; H, 9.55%. λ_{max} 506, 474 ($\varepsilon = 1.28 \times 10^5$), 449 nm; IR 3460, 3040, 2950—2850, 1560, 1445, 960, 816, 804 cm^{-1}; NMR δ 1.02 and 1.04 (each 3H, s, 1,1-dimethyl), 1.85 (3H, s, 5-methyl), 1.99 and 2.07 (9H, s and 3H, s, respectively; chain methyls), 2.21 and 2.31 (3H, s and 6H, s, respectively; aryl methyls), 4.02 (1H, m, 4-methin), 6.18—7.10 (16H, m, olefinic and aromatic protons); MS 548 (M), 530, 515, 438, 424, 372, 133, 106, 105, 92, 91.

β,χ-Caroten-4-one (7). A solution of **6** (143 mg) in acetone (12 ml) and dichloromethane (24 ml) was stirred into a suspension of active manganese dioxide[13] (1.43 g) in acetone (12 ml), after which the mixture was stirred for 2.5 h at room temperature. After the filtration of the manganese dioxide and the removal of the solvent, the resulting red solid was recrystallized from a dichloromethane–ethanol mixture. Purplish black prisms (77%); mp 197—198 °C. Found: C, 87.66; H, 9.38%. Calcd for $C_{40}H_{50}O$: C, 87.86; H, 9.22%. λ_{max} 482 nm ($\varepsilon = 1.05 \times 10^5$); IR 3040, 2980—2850, 1655, 970, 835 cm^{-1}; NMR δ 1.20 (6H, s, 1,1-dimethyl), 1.89 (3H, s, 5-methyl), 2.01 and 2.08 (9H, s and 3H, s, respectively; chain methyls), 2.22 and 2.32 (3H, s and 6H, s, respectively; aryl methyls), 2.54 (2H, m, 3-methylene), 6.20—7.42 (16H, m, olefinic and aryl protons); MS 546 (M), 531, 459, 440, 388, 343, 158, 133, 106, 105, 92, 91,

Tedanin (1). A solution of potassium *t*-butoxide in *t*-butyl alcohol (*ca.* 1 mol dm^{-3}, 2.5 ml) was added to a solution of **7** (20.5 mg) in a mixture of dry benzene (12 ml) and *t*-butyl alcohol (18 ml); after stirring at room temperature for 20 min, dry oxygen gas was bubbled into the mixture for 6 h at 45 °C. The reaction mixture was then diluted with benzene, and the solution was washed successively with water, aqueous hydrochloric acid (0.1 mol dm^{-3}), aqueous sodium hydrogencarbonate, and water. After the removal of the solvent, the resulting residue was chromatographed on silica gel with a chloroform–benzene mixture (3 : 7). The elution of the main red zone and the removal of the solvent gave a crude product, which was subsequently recrystallized from a dichlomethane–ethanol mixture. Purplish black prisms (71%); mp 189—190 °C (lit,[4] mp 188—189 °C), undepressed by admixture with a natural specimen. Mixed chromatography of the synthetic and the natural pigment showed no separation on silica gel and sucrose columns. Found: C, 85.39; H, 8.67%. Calcd for $C_{40}H_{48}O_2$: C, 85.66; H, 8.63%. The spectral properties, such as the UV, IR, and NMR, were also identical with those of natural tedanin previously reported.

β,φ-Carotene (9). This was prepared by a method similar to that described above for the synthesis of β,χ-carotene (**5**), starting with **3** and 12′-apo-φ-caroten-12′-al[10] (**8**) (244.2 mg). Red plates (46%); mp 137—138 °C (lit,[7] 128 °C). Found: C, 90.02; H, 9.78%. Calcd for $C_{40}H_{52}$: C, 90.16; H, 9.84%. λ_{max} 494, 465 ($\varepsilon = 1.14 \times 10^5$), 437 nm; IR 3030, 3000—2850, 970, 955, 830, 810 cm^{-1}; NMR δ 1.04 (6H, s, 1,1-dimethyl), 1.72 (3H, s, 5-methyl), 2.00 and 2.10 (9H, s, and 3H, s, respectively; chain methyls), 2.25 and 2.28 (3H, s and 6H, s, respectively; aryl methyls), 6.15—6.90 (14H, m, olefinic protons), 6.97 (2H, s, aryl protons); MS 532 (M) 440, 426, 374, 317, 133, 105, 91.

β,φ-Caroten-4-ol (10). This was obtained from **9** (212.3 g) by a method similar to that used for β,χ-caroten-4-ol (**6**). Purplish red needles (57%); mp 136—136.5 °C. Found: C, 87.24; H, 9.29%. Calcd for $C_{40}H_{52}O$: C, 87.53; H, 9.55%. λ_{max} 492, 463 ($\varepsilon = 1.28 \times 10^5$), 436 nm; IR 3450, 3033, 2922—2858, 1560, 1445, 964, 808 cm^{-1}; NMR δ 1.03 and 1.06 (each 3H, s, 1,1-dimethyl), 1.87 (3H, s, 5-methyl), 2.00 and 2.11 (9H, s and 3H, s, respectively; chain methyls), 2.25 and 2.28 (3H, s and 6H, s, respectively; aryl methyls), 4.03 (1H, m, 4-methin), 6.05—6.85 (14H, m, olefinic protons), 6.98 (2H, s, aromatic protons); MS 548 (M), 530, 424, 372, 133, 105, 92, 91.

β,φ-Caroten-4-one (11). This was prepared from **10** (108 mg) by the same method as **7**. Purplish black needles

(62%); mp 178—179 °C. Found: C, 87.99; H, 9.22%. Calcd for $C_{40}H_{50}O$: C, 87.86; H, 9.22%. λ_{max} 469 nm ($\varepsilon=1.70\times10^5$); IR 3030, 2970—2790, 1645, 975, 830, 810 cm^{-1}; NMR δ 1.20 (6H, s, 1,1-dimethyl), 1.89 (3H, s, 5-methyl), 2.00 and 2.10 (9H, s and 3H, s, respectively; chain methyls), 2.25 and 2.28 (3H, s and 6H, s, respectively; aryl methyls), 2.49 (2H, m, 3-methylene), 6.10—6.85 (14H, m, olefinic protons), 6.98 (2H, s, aromatic protons); MS 546 (M), 454, 133, 119, 91, 84.

3-Hydroxy-2,3-didehydro-β,φ-caroten-4-one (**2**). This was obtained from **11** (38 mg) by a method similar to that used for tedanin (**1**). Purplish black needles (49%); mp 170—171 °C. Found: C, 85.63; H, 8.61%. Calcd for $C_{40}H_{48}O_2$: C, 85.67; H, 8.63%. λ_{max} 483 nm ($\varepsilon=1.87\times10^5$); IR 3425, 3030, 2990—2830, 1695, 1620, 972, 830, 808 cm^{-1}; NMR δ 1.30 (6H, s, 1,1-dimethyl), 2.02 and 2.04 (each 6H, s; chain methyls), 2.24 and 2.28 (3H, s and 6H, s, respectively; aryl methyls), 6.06—6.85 (15H, m, olefinic protons), 6.98 (2H, s, aromatic protons); MS 560(M), 544, 468, 454, 408, 204, 157, 119, 105, 91.

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2) Present adderss: Mitsui Petrochemical Industries, Ltd., Chigusakaigan, Ichihara, Chiba 299-01.

3) For the nomenclature used in this article; see the IUPAC Commission on the Nomenclature of Organic Chemistry and the IUPAC-IUB Commission on Biochemical Nomenclature, *Biochemistry*, **10**, 4827 (1971).

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