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The Synthesis of a Coumarin Analogue of Retinal

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Abstract: A new coumarin analogue of retinal was synthesised by Wittig condensation of (2-oxo-2H-chromen-3-yl)methyltriphenylphosphonium chloride and (2E,6Z) 2,6-dimethyl-8-triphenylsilyloxyocta-2,6-dien-4-yn-1-al in high yield. Subsequent triphenylsilyl group removal, MnO_2 oxidation, followed by hydrogenation over Lindlar catalyst and isomerization in the presence of traces of iodine furnished the desired polyenal. This all-trans coumarin analogue of retinal was used for study of the bacteriorhodopsin chromophore binding site. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

Retinoids are capable of mediating a wide variety of biological processes, including vision, cellular proliferation and differentiation.[1] There is undoubtedly a continuing interest in the synthesis of novel retinoids, which are used as probes for investigation of these processes.

Vitamin A can be metabolized *in vivo* to retinaldehyde, retinoic acid or to retinol derivatives, such as 14-hydroxy-retro-retinol (14-HRR) and anhydroretinol (AR).[2] The discovery of the nuclear retinoid receptors RARs (retinoic acid receptors) in 1987 and RXRs (retinoid-X receptors) in 1990 elucidated the basis of our understanding for the retinoid action. The nuclear retinoid receptors RARs and RXRs are ligand-dependent transcription factors, which are capable of binding to regulatory regions on DNA and control the transcription of specific genes, responsible for the synthesis of proteins, involved in the processes of cellular differentiation and proliferation.[3] At the current time there are intensive investigations into the synthesis of novel synthetic retinoids, which can bind to the retinoid receptors and modulate their activity,[4,5] which is related to the medicinal use of the retinoids in cancer prevention and therapy. Moreover, there are investigations into the synthesis of artificial retinoids, which can inhibit the retinoid-induced activation of HIV-1-RARE[6] as antimetabolites. In connection with the topic of this work, it is noteworthy to remark, that some coumarin-derivatives possess also anticarcinogenic[7] and anti-HIV[8] activities.

In the class of light-activated retinylidene proteins (rhodopsins and bacterial rhodopsins) one of the most studied objects is bacteriorhodopsin - a light-driven proton translocase, found in the purple membrane of the extremely halophilic bacterium *Halobacterium halobium*. Each bacteriorhodopsin molecule contains retinal as the chromophore group, bound as a protonated Schiff base to *Lys-216* from the polypeptide chain. One of the

approaches for investigations of bacteriorhodopsin is to study the functions of bacteriorhodopsin analogues, containing artificial retinal analogues in the chromophore binding site.

Important structure-function information can be given by analysis of the fluorescent properties of the retinylidene proteins. The retinyl moiety of bacteriorhodopsin does not strongly fluoresce. Fluorescent studies of bacteriorhodopsin have been carried out using retinol and retinyl moieties,[9] dimethylaminonaphthyl[10] and anthryl[11] chromophores as fluorescent probes. Polycyclic aromatic retinal analogues have been used in analyzing the red-shift characteristics of bacteriorhodopsin analogues.[12] Other fluorescent studies involving the use of energy transfer from excited tryptophans to the retinyl moiety of bacteriorhodopsin have also been made.[13] Fluorescent labeling of bacteriorhodopsin has been used in a study of the relative arrangement of the seven helical segments of the protein.[14]

Bacteriorhodopsin analogues are also intensively investigated for the purposes of molecular electronics and permanent optical storage,[15] based on the proton pumping activity of bacteriorhodopsin.

In the present work we report the synthesis of novel synthetic retinoids, containing coumarin as a fluorophore.[16]

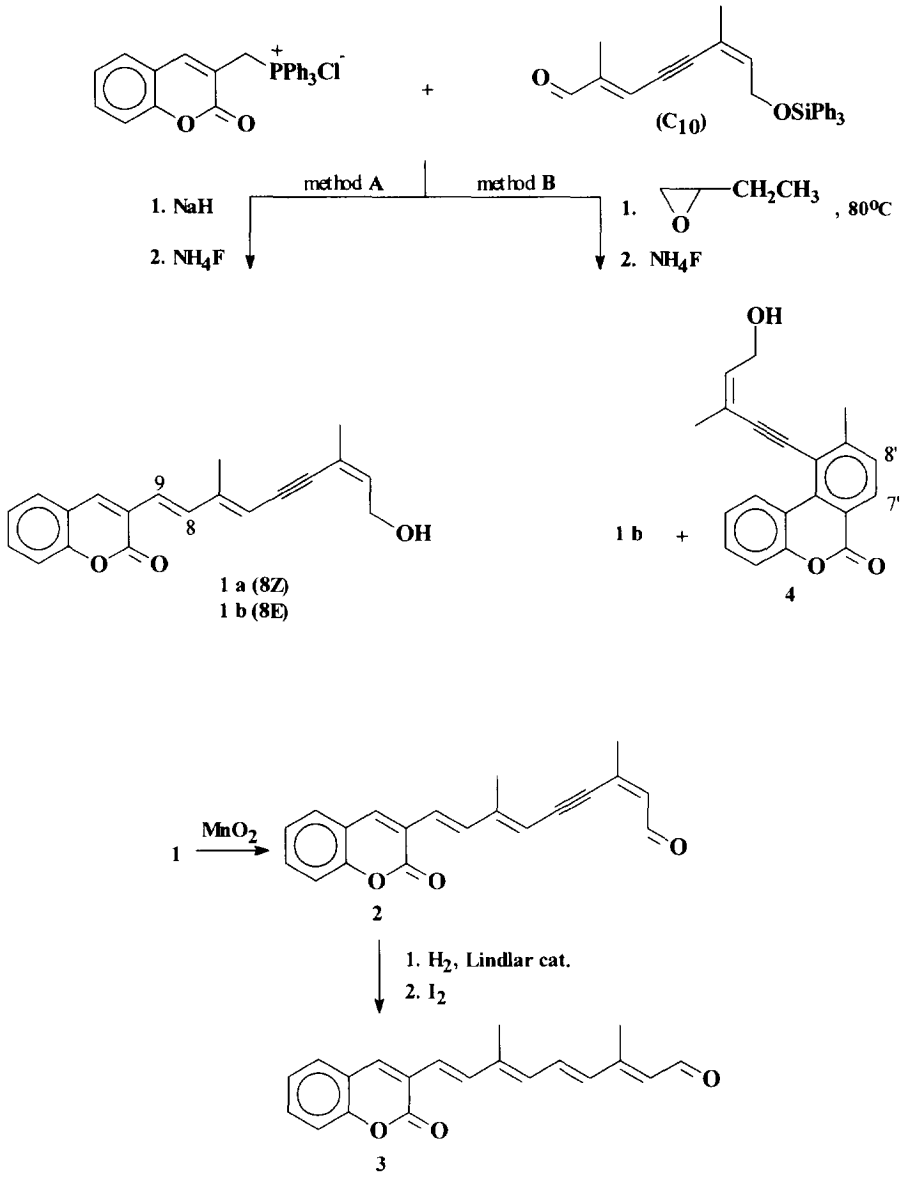
RESULTS AND DISCUSSION

The coumarin analogue of retinal **3** was synthesised by the Wittig olefination of a polyenal, using two sets of reaction conditions (Scheme 1).

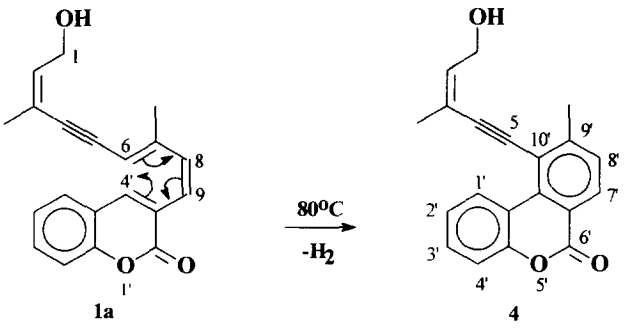
Using *method A*, the triphenylphosphonium salt of 3-chloromethylcoumarin was condensed with (2E,6Z) 2,6-dimethyl-8-triphenylsilyloxyocta-2,6-dien-4-yn-1-al (C_{10}), using sodium hydride for ylide formation. Subsequent triphenylsilyl group removal gave alcohols **1a** (2Z, 8Z) and **1b** (2Z, 8E) in 82% yield (ratio ofca. 3:1 8Z:8E). The coupling constant values of the vinyl hydrogens H-8 and H-9 in the ^{1}H-NMR spectra correspond to the proposed structure around the C_8-C_9 double bond:[17] 12.0 Hz for **1a** (2Z, 8Z) and 15.0 Hz for **1b** (2Z, 8E). The signals of the 7-Me group, H-8 and H-9 are shifted in the low field region for the 8E isomer **1b** in comparison to the 8Z isomer **1a**. Manganese dioxide oxidation of the isomeric alcohols **1a** and **1b**, followed by hydrogenation over Lindlar catalyst and isomerization in the presence of traces of iodine yielded the desired aldehyde **3**. All-trans aldehyde **3** was isolated from the isomeric mixture by high-performance liquid chromatography (HPLC).

Using *method B*, the reaction proceeded in a more complicated fashion. If 1,2-epoxybutane was used instead of sodium hydride in ylide formation at 80°C, the desired polyenic product **1b** was obtained in decreased yield (27%) and a by-product **4** was formed (in 7% yield) as the result of a thermally-induced electrocyclisation of the cisoid conformer of **1a** followed by dehydrogenation (Scheme 2). Similar electrocyclisation has been reported by Okamura and coworkers.[18]

The spectral data of the cyclic by-product **4** are in agreement with its proposed structure. Comparison of the ^{1}H-NMR spectral data of the polyenic compound **1b** and of the cyclic product **4** showed, as was expected, the absence of the signals of 6-, 8- and 9-protons of the polyenic side chain and of the 4'-proton of the heterocycle in the ^{1}H-NMR spectrum of the compound **4**. Two doublets are observed at 8.35 and 9.63 ppm, assigned to H-7' and H-8' of the cyclic by-product **4**. The UV spectrum of the compound **4** is characteristic for the benzenoid aromatic system and shows the absence of the main π-π^*-absorption band of the polyenic side


PPh3Cl
(C10)
OSiPh3
1. NaH
2. NH4F
method A
method B
1.
CH2CH3
, 80°C
2. NH4F
OH
9
8
OH
1 a (8Z)
1 b (8E)
1 b +
8'
7'
4
1
MnO2
2
1. H2, Lindlar cat.
2. I2
3

Scheme 1



Scheme 2

chain. The mass-spectrum of **4** shows a strong peak at m/z 304 (molecular ion) in contrast to the peak at m/z 306 (molecular ion) for the polyenic alcohol **1b**. These data correspond to the loss of two hydrogens and aromatisation of the ring, leading to a more stable aromatic structure. Mass fragments, due to fragmentation of the polyenic side chain at the C_8-C_9 double bond of the desired product **1b**, are not observed in the mass-spectrum of the cyclic by-product **4**.

The all-trans aldehyde **3** was used as a probe for study of the bacteriorhodopsin binding site. Incorporation of the coumarin analogue of retinal **3** into bacterioopsin resulted in formation of a pigment with absorption maximum at 475 nm. There are reported other pigments, containing reporter groups, such as anthryl.[11] spin-labeled[19] and photosensitive[20] analogues of bacteriorhodopsin, which exhibit blue-shifted absorption characteristics in comparison to the natural pigment (λ_{max} ^{bR}: 570 nm). The blue-shifted absorption properties of the coumarin analogue of bacteriorhodopsin are supposed to be due to the electronic and steric effects of the lactone on the electrostatic interactions between chromophore and apo-protein charges, located in the chromophore binding site.

EXPERIMENTAL

General methods:

^{1}H-NMR spectra were recorded on a *Bruker MSL-200* or *Bruker WM-250* spectrometer in $CDCl_3$; chemical shifts (δ) are given in *ppm*; for ^{31}P-NMR - chemical shift (δ) is given versus external 85% ortho-phosphoric acid in D_2O. UV-VIS spectra were recorded on either *Beckmann DU-6* (USA) or *Shimadzu UV-240* (Japan) spectrophotometer in absolute methanol. Mass-spectra were made on a *JEOL-JMS-D-300* mass spectrometer; for CI-MS - reactant gas: 2-methylpropane. IR-spectra were recorded on a *Shimadzu IR-435* spectrometer.

HPLC - analysis was performed on a *Kova* (Czechoslovakia) instrument with UV-VIS-detector, using a *Silasorb 600* column (8μm, 250 x 10 mm). Column chromatography was carried out on *Kieselgel 60, 230-400 mesh*; TLC was performed on *Kieselgel 60 F_{254}* (*Merck*, Germany) thin plates in the following systems: A (hexane/diethyl ether 1:2) and B (chloroform/methanol 9:1).

All purified polyenes were handled in dim red light and stored at -60°C.

Isolation of bacteriorhodopsin, bacterioopsin and regeneration of the apomembranes were carried out at the *A. N. Belozersky Institute of Physico-Chemical Biology* by the method described in the literature.[21]

Synthesis of the retinal analogues and their precursors.

3-(chloromethyl)-2H-chromen-2-one was synthesised as described in the literature.[22] The chloromethylation of coumarin proceeded much more clearly and with an increased yield (60%) if $SnCl_4$ as Lewis acid catalyst was used instead of $ZnCl_2$ at the same molar ratio. M.p. 111°C. ^{1}H-NMR δ: 4.56 (s, 2H, CH_2Cl), 7.20-7.50 (m, 4H, H_{arom}), 7.89 (s, 1H, H-4). EI-MS (70 eV): 194 ($[M]^+$). IR (nujol) ν cm^{-1}: 1710 (CO, lactone), 753 (C-Cl).

(2-oxo-2H-chromen-3-yl)methyltriphenylphosphonium chloride. To a solution of 3-(chloromethyl)-2H-chromen-2-one (1.74g, 8.9 mmol) in freshly distilled toluene was added triphenylphosphine (3.52g, 13.4 mmol). The solution was heated at reflux for 16 hours, then cooled (room temperature) and dry diethyl ether was added (ratio 1:1). The precipitate that appeared was filtered off and washed with dry diethyl ether. The solids were dissolved in dry methanol and reprecipitated with diethyl ether. Fine yellow crystals were obtained and dried *in vacuo*. Yield: 3.37g (83%). M.p. 215-217°C. R_f: 0.45 (sys. B). ^{1}H-NMR δ: 5.64 (d, $J_{P,H}$=14.6 Hz, 2H, $C\underline{H}_2P$), 7.10-8.10 (m, 19H, H_{arom}), 8.61 (s, 1H, H-4). ^{31}P-NMR (24.17 ppm). IR (nujol) ν cm^{-1}: 1700 (CO, lactone), 1440 (P-Phenyl), 743, 727 cm^{-1}. Anal. calc. for $C_{28}H_{22}ClO_2P$ (456.91): Cl 7.76, P 6.78; found: Cl 8.01, P 5.77.

(2E,6Z) 2,6-dimethyl-8-triphenylsilyloxyocta-2,6-dien-4-yn-1-al (C_{10}) was synthesised by the method of Mitsner and co-workers as described in the literature.[23]

(2Z) 3,7-dimethyl-9-(2'-oxo-2'H-chromen-3'-yl)-2,6,8-nonatrien-4-yn-1-ol 1.

Method A: To a stirred suspension of sodium hydride (0.06g, 2.50 mmol; prepared from a 80% suspension of NaH in mineral oil) in dry tetrahydrofuran, cooled to -30°C, was added (2-oxo-2H-chromen-3-yl)methyltriphenylphosphonium chloride (0.94 g, 2.06 mmol). The mixture was stirred under an argon atmosphere at room temperature for 2 hrs. Then (2E,6Z) 2,6-dimethyl-8-triphenylsilyloxyocta-2,6-dien-4-yn-1-al (C_{10}) (0.79g, 1.87 mmol) in dry THF was added dropwise at -30°C. The mixture was then allowed to stand overnight at room temperature. Then a saturated aqueous solution of NH_4Cl was added and the product was extracted with diethyl ether. The combined organic extracts were washed (water) and the solvent was removed *in vacuo*. The residue was dissolved in a mixture of acetone/water (1:1), NH_4F (1.00g) was added and the solution was allowed to stand overnight (refrigerator). After that, the product was extracted with chloroform, the combined organic layers were washed with water, dried (Na_2S0_4) and the solvent was removed *in vacuo*. The product was purified by column chromatography (heptane/diethyl ether from 0 to 100% of the diethyl ether). Fractions with R_f=0.24-0.26 (system A) were collected. Yield: 0.47g (82%) of **1** as an 8Z/8E mixture (isomeric ratio *ca.* 3:1 resp.). The 8Z isomer of this isomeric mixture can be isomerized to the 8E isomer by refluxing of the solution of 8Z and 8E isomers in acetonitrile in the presence of traces of

iodine. The isomers were separated by preparative TLC (system A). **1a** (2Z,8Z): ^{1}H-NMR δ: 1.91 (d, J=1.0 Hz, 3H, 3-CH_3), 1.96 (s, 3H, 7-CH_3), 4.32 (dd, J=6.5 Hz, J=1.0 Hz, 2H, C$\underline{H}_2$OH), 5.81 (s, 1H, H-6), 5.87 (tq, J=6.5 Hz, J=1.0 Hz, 1H, H-2), 6.36 (d, J=12.0 Hz, 1H, H-9), 6.43 (d, J=12.0 Hz, 1H, H-8), 7.20-7.52 (m, 4H, H_{arom}), 7.55 (s, 1H, H-4'$_{heterocycl}$). EI-MS : 306 ([M]$^+$), 159 ([$C_{10}H_7O_2$]$^+$), 147 ([$C_{10}H_{11}O$]$^+$). UV λ_{max} (ε.10^3) nm: 365 (19.1), 325 (15.9*i* *), 284 (14.6). M.p.: oil. R_f=0.26 (sys.A). **1b** (2Z,8E): ^{1}H-NMR δ: 2.10 (d, J=1.0 Hz, 3H, 3-CH_3), 2.17 (s, 3H, 7-CH_3), 4.36 (dd, J=6.5 Hz, J=1.0 Hz, 2H, C$\underline{H}_2$OH), 5.83 (s, 1H, H-6), 5.90 (tq, J=6.5 Hz, J=1.0 Hz, 1H, H-2), 6.70 (d, J=15.0 Hz, 1H, H-9), 7.14-7.54 (m, 5H, H_{arom} + H-8), 7.75 (s, 1H, H-4'$_{heterocycl}$). EI-MS (70 eV) = 306 ([M]$^+$), 159 ([$C_{10}H_7O_2$]$^+$), 147 ([$C_{10}H_{11}O$]$^+$). UV: λ_{max} (ε.10^3) nm: 370 (38.8), 325 (25.3*i*), 292 (20.9). M.p.: 125°C (dec.). R_f=0.24 (sys.A). IR (nujol) ν cm^{-1}: 1710 (CO, lactone), 3000-3500 (br.).

Method B: In the glass container (volume 25 ml) of an autoclave were placed (2-oxo-2H-chromen-3-yl)methyltriphenylphosphonium chloride (2.38g, 5.21 mmol), aldehyde (2E,6Z) 2,6-dimethyl-8-triphenylsilyloxyocta-2,6-dien-4-yn-1-al (C_{10}) (2.00g, 4.73 mmol) in methylene chloride and 1,2-epoxybutane (1 ml). The reaction was carried out at 80°C for 16 hrs. Then, after cooling (room temperature), the solvent was removed *in vacuo*. The residue was dissolved in diethyl ether and washed (water). After solvent evaporation the residue was dissolved in a mixture of acetone/water (1:1), NH_4F (2.50g) was added and the solution was allowed to stand overnight (refrigerator). Then the reaction mixture was worked up as it was described in method A. Yield: 0.39g (27%) of **1b** and 0.10g (7%) of the cyclic product **4**. The desired polyenic alcohol **1b** and the cyclic product **4** were separated by column chromatography (hexane/diethyl ether with gradient of the diethyl ether from 0 to 100%).

(2Z) 3-methyl-5-(9'-methyl-6'-oxo-6'H-dibenzo[b,d]pyran-10'-yl)-2-penten-4-yn-1-ol 4. ^{1}H-NMR δ: 2.13 (d, J=1.5 Hz, 3H, 3-CH_3), 2.64 (s, 3H, 9'-CH_3^{arom}), 4.50 (d, J=6.5 Hz, 2H, C$\underline{H}_2$OH), 6.10 (tq, J=6.5 Hz, J=1.5 Hz, 1H, H-2), 7.20-7.60 (m, 4H, H_{arom}), 8.35 (d, J=8.0 Hz, 1H, H-7'), 9.63 (dd, J=8.0 Hz, J=1.5 Hz, 1H, H-8'). EI-MS (70 eV): 304 ([M]$^+$). UV: λ_{max} (ε.10^3) nm : 325 (10.7), 311 (11.0), 294 (11.0), 265 (23.2). IR (nujol) ν cm^{-1}: 1719 (CO, lactone), 3000-3500 (br.). M.p.: 138-140°C. R_f=0.23 (sys.A).

(2Z) 3,7-dimethyl-9-(2'-oxo-2'H-chromen-3'-yl)-2,6,8-nonatrien-4-yn-1-al 2. To a stirred solution of the compound **1** (0.10g, 0.33mmol, as an 8Z/8E isomeric mixture) in dry benzene was added dry activated MnO_2 (0.50g). The suspension was stirred intensively at room temperature for 8 hrs. Then the solids were filtered off and washed (benzene and methanol). The solvents of the combined organic layers were evaporated *in vacuo* and the residue was purified by column chromatography (heptane/diethyl ether with gradient of the diethyl ether from 0 to 60%). Fractions with R_f=0.45-0.47 (sys.A) were collected. Yield: 0.08g (80%) of **2** as (8Z)/(8E) isomeric mixture (ratio *ca.* 3:1 resp.). The isomers were separated by preparative TLC (sys. A). **2a** (2Z,8Z): ^{1}H-NMR δ: 2.01 (d, J=1.0 Hz, 3H, 7-CH_3), 2.14 (d, J=1.2 Hz, 3H, 3-CH_3), 5.86 (s, 1H, H-6), 6.14 (dq, J=8.0 Hz, J=1.2 Hz, 1H, H-2), 6.45 (s, 2H, H-8+H-9), 7.27-7.55 (m, 4H, H_{arom}), 7.57 (s, 1H, H-4'$_{heterocycl}$), 10.02 (d, J=8.0 Hz, 1H, CHO). EI-MS (70 eV): 304 ([M]$^+$), 159 ([$C_{10}H_7O_2$]$^+$), 145 ([$C_{10}H_9O$]$^+$). UV: λ_{max} (ε.10^3) nm: 378 (33.0), 304 (22.6*i*). M.p.: oil. R_f=0.47 (sys.A). **2b** (2Z,8E): ^{1}H-NMR δ: 2.17 (d,

* the abbreviation *i* in the parentheses denotes inflection.

J=1.0 Hz, 3H, 7-CH_3), 2.19 (d, J=1.5 Hz, 3H, 3-CH_3), 5.90 (s, 1H, H-6), 6.18 (dq, J=8.0 Hz, J=1.5 Hz, 1H, H-2), 6.75 (d, J=16 Hz, 1H, H-9), 7.20-7.70 (m,5H, H_{arom}+H-8), 7.80 (s, 1H, H-4'$_{heterocycl}$), 10.10 (d, J=8.0 Hz, 1H, CHO). EI-MS (70 eV): 304 ([M]$^+$), 159 ([$C_{10}H_7O_2$]$^+$), 145 ([$C_{10}H_9O$]$^+$). UV: λ_{max} ($\varepsilon.10^3$) nm: 385 (35.8), 307 (12.1*i*). M.p. 180°C. R_f=0.45 (sys.A).

3,7-dimethyl-9-(2'-oxo-2'H-chromen-3'-yl)-2,4,6,8-nonatetraenal 3. To a stirred solution of aldehyde **2** (0.08g, 0.26 mmol. as an 8Z/8E isomeric mixture) in hexane/ethyl acetate (1:1) was added Lindlar catalyst (0.01g) and quinoline (3 μl). After that 6 ml of hydrogen were absorbed, the catalyst was filtered off, the solids were washed (methanol) and the solvents of the filtrate were evaporated *in vacuo*. The residue was purified by column chromatography (hexane/diethyl ether with gradient of the diethyl ether from 0 to 60%). Yield: 0.07g (86%). The content of the all-E isomer of **3** in this isomeric mixture was increased by refluxing in hexane/ethyl acetate (1:1) in the presence of traces of iodine.

Isomerization: (2Z) 3,7-Dimethyl-9-(2'-oxo-2'H-chromen-3'-yl)-2,4,6,8-nonatetraenal **3** (0.07g, 0.23 mmol) was dissolved in hexane/ethyl acetate (1:1) and refluxed for 4 hrs in the presence of traces of iodine. After that, the solution was cooled (room temperature) and the solvents were evaporated *in vacuo*. The isomeric mixture was purified immediately by column chromatography, fractions with R_f=0.35-0.37 (sys.A) were collected. The all-trans isomer of **3** was isolated from the isomeric mixture by High-Performance Liquid Chromatography (20% diethyl ether in benzene, 5 ml/min).

all-E 3,7-dimethyl-9-(2'-oxo-2'H-chromen-3'-yl)-2,4,6,8-nonatetraenal 3: ^{1}H-NMR δ: 2.09 (s, 3H, 7-CH_3), 2.33 (d, J=1.0 Hz, 3H, 3-CH_3), 6.00 (d, J=8.0 Hz, 1H, H-2), 6.44 (d, J=12.0 Hz, 1H, H-6), 6.45 (d, J=15.0 Hz, 1H, H-4), 6.77 (d, J=16.0 Hz, 1H, H-9), 7.13 (dd, J=15.0 Hz, J=12.0 Hz, 1H, H-5), 7.20-7.60 (m, 5H, H_{arom}+H-8), 7.76 (s, 1H, H-4'$_{heterocycl}$), 10.12 (d, J=8.0 Hz, 1H, CHO). CI-MS: 307 ([M+1]$^+$). UV: λ ($\varepsilon.10^3$) nm: 407 (42.0), 315 (14.8*i*). M.p.: 199-200°C. R_f= 0.35 (sys.A).

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