New Syntheses of Retinal and Its Acyclic Analog γ-Retinal by an Extended Aldol Reaction with a C_6 Building Block That Incorporates a C_5 Unit after Decarboxylation. A Formal Route to Lycopene and β-Carotene

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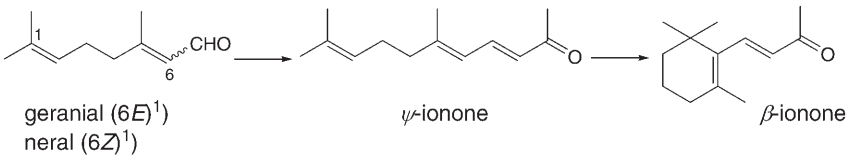
Since the C_{15} β-end-group aldehyde **10** ((β-ionylidene)acetaldehyde), an excellent intermediate in the syntheses of retinoids, can be synthesized in many ways from β-ionone, and since the corresponding acyclic C_{15} ψ-end-group aldehyde **5** can easily be synthesized from citral (**1**) (*Scheme 3*), we applied the $C_{15}+C_5$ route to the syntheses of γ-retinal ((*all-E*)-**8**) (*Scheme 3*) and retinal ((*all-E*)-**13**) (*Scheme 4*), and therefore, by coupling ($2\times C_{20}\rightarrow C_{40}$), to the preparation of lycopene (**14**) and β-carotene (**15**) (*Scheme 5*). Our new syntheses of retinal ((*all-E*)-**13**) and γ-retinal ((*all-E*)-**8** use an extended aldol reaction with a C_6 building block that incorporates a C_5 unit after decarboxylation.

Introduction. – Fruits and vegetables of the human diet contain a lot of the over 600 carotenoid pigments described to occur in Nature. Among these, two major carotenoids are β-carotene ($=\beta,\beta$-carotene) and lycopene ($=\psi,\psi$-carotene). β-Carotene is a very potent antioxidant which protects the cell against singlet oxygen, and lycopene acts also as an effective singlet-oxygen quencher in human plasma and exhibits a quenching rate constant with singlet oxygen almost twice as high as that of β-carotene. The remarkable role of β-carotene as an 'unusual antioxidant' in reactions under various oxygen pressures becomes clearer. The so-called 'pro-oxidant effects' concern primarily the antioxidant itself and its degradation, since no or very little damage to the substrate occurs in this type of experience. The role of lycopene has been of particular interest recently as regards its role in treatment of prostate cancer. β-Carotene is a provitamin-A carotenoid, and this is a fundamental role because vitamin A and other natural retinoids are present in all living organisms and are known as fundamental mediators for many biological processes, *e.g.*, vision, cellular growth, differentiation of epithelial tissue, reproduction, *etc.* Retinal occupies an intermediate position in this respect, with the ability to convert to both retinol and retinoic acid. Considering the interplay between the configuration of retinoids and carotenoids and their biological activities, any synthetic approach to these compounds must meet the requirement of stereochemical control, in order to obtain the desired isomer in a highly regioselective manner. Despite the recent achievements in the preparation of conjugated (E/Z)-

dienes and trienes by a variety of synthetic procedures, there is still a need for versatile and efficient approaches to synthesize higher unsaturated (*E*/*Z*)-polyolefins with convenient configuration. The emphasis for the past twenty years has been the stereoselective/regioselective syntheses of economically important retinoids and carotenoids, such as retinol, retinal, retinoic acid, β-carotene, and lycopene.

Citral (= 3,7-dimethylocta-2,6-dienal) is the main constituent of lemon-grass oil [1], as a mixture of two geometric isomers (*i.e.*, geranial (6*E*)[1]) and neral (6*Z*)[1])). It is also present in various natural products such as citrus fruits [2] and flowers and trees [3]. Citral has been extensively produced by synthesis for a long time [4], and we have recently reported alternative syntheses of this terpene aldehyde [5]. It is commonly used for the preparation of ψ-ionone [6], which is an important compound for the production of β-ionone, a key-step intermediate in retinoid and carotenoid chemistry [7] (*Scheme 1*).

Scheme 1



A lot of natural (and synthetic) terpenes exhibit important properties such as cytotoxicity [8], antitumor [9], antiviral [10], anti-inflammatory [11], or immunosuppressive [12] activities.

Syntheses of γ-retinal (=(2*E*,4*E*,6*E*,8*E*,10*E*)-3,7,11,15-tetramethylhexadeca-2,4,6,8,10,14-hexaenal; (*all-E*)-**8**) have been poorly documented [13], comparatively to its isomer retinal ((*all-E*)-**13**) (for recent ref., see [14]).

The latter is a chromophore in the visual system of the retina which binds with a lysine residue of opsin through a *Schiff* base [15]. The obtained rhodopsin is moved on to an excited state by photons, which induces a bleaching process by an enzymatic cascade, and signals are transferred to the brain through synapses [16].

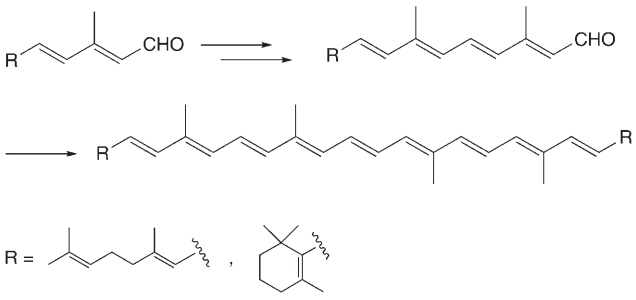
Retinal has been found to be active in the regulation and differentiation of epithelium, and, therefore, been tested to fight skin diseases [17]. The decrease in vascular endothelial growth factor (VEGF) expression by keratinocytes on contact with retinal has been recently published, and the conclusions showed that the decrease in VEGF expression may prevent skin neoangiogenesis in certain skin diseases [18]. We recently reported on the syntheses of 9-methylene- and 13-methyleneretinals[1]) [19].

Since 1990, more than forty references have reported (β-ionylidene)acetaldehyde (= 3-methyl-5-(2,6,6-trimethylcyclohex-1-en-1-yl)penta-2,4-dienal; **10**) as an exceptional intermediate in the syntheses of retinoids [20]. This could be attributed to the fact that C_{15} aldehyde **10** can be synthesized in many ways from β-ionone, a relatively inexpensive C_{13} product. Thus, we have selected the $C_{15} + C_5$ route for the syntheses of

[1]) Carotenoid numbering.

γ-retinal and retinal, and therefore, by coupling ($2 \times C_{20} \rightarrow C_{40}$), for the preparation of lycopene and β-carotene, as illustrated in *Scheme 2*.

Scheme 2

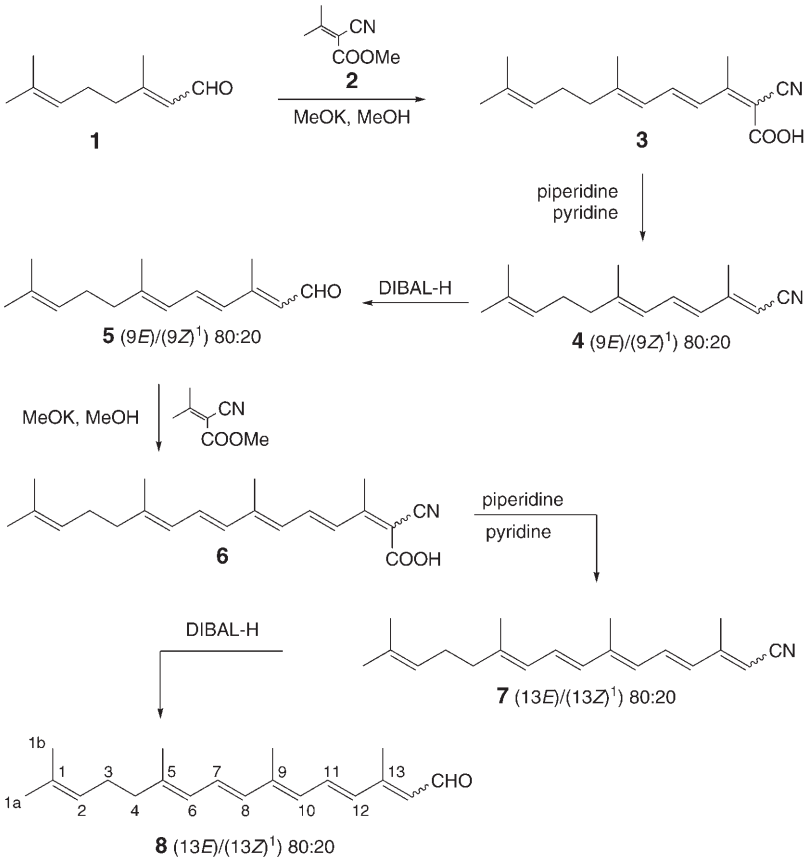


Results. – To synthesize γ-retinal ((*all-E*)-**8**), the required C_{15} aldehyde **5** was synthesized by condensation of citral (**1**) with methyl 2-cyano-3-methylbut-2-enoate (**2**) under *Stobbe*'s conditions (MeOK, MeOH, 0°, then 48 h at room temp.). Under these experimental conditions, isomerization of the C=C bond of the starting citral takes place, and the obtained α-cyano acid **3** (as a $(9E)/(9Z)^1$) mixture of 80:20) was further decarboxylated in pyridine/piperidine (reflux, 2–4 h) to provide nitrile **4** ((9*E*)/(9*Z*) 80:20). After reduction with diisobutylaluminium hydride (DIBAL-H; 0°, 30 min), aldehyde **5** ((9*E*)/(9*Z*) 80:20) was condensed in an iterative way with methyl cyanobutenoate **2** to provide a mixture **6** of α-cyano acids. Further decarboxylation in piperidine/pyridine led to the γ-retinonitrile **7** ((13*E*)/(13*Z*) 80:20) which was reduced with DIBAL-H into γ-retinal **8** ((13*E*)/(13*Z*) 80:20) (*Scheme 3*).

Analogously, retinal ((*all-E*)-**13**) was synthesized *via* the C_{15} (β-ionylidene)acetaldehyde **10** which has been prepared previously (for recent ref., see [21]). We now report a new improved synthesis which allowed to produce aldehyde **10** in only two steps, with excellent yield (82%) and good regioselectivity. Thus, a *Knoevenagel* condensation of β-ionone with cyanoacetic acid in piperidine/benzene (*Dean–Stark*, reflux) led to nitrile **9** in nearly quantitative yield ($(9E)/(9Z)^1$) 95:5–98:2; *Scheme 4*). Piperidine (8 equiv.) and benzene (as solvent) seemed to be indispensable because other bases and solvents led to a mixture of nitriles. Under the chosen experimental conditions, the α-cyano acids initially formed ($(9E)/(9Z)^1$) 95:5–98:2) were concomitantly decarboxylated in the reaction mixture. The C_{15} nitrile **9** was then reduced by DIBAL-H in toluene (0°, 30 min) into (β-ionylidene)acetaldehyde **10** (82%; (9*E*)/(9*Z*) 95:5–98:2), and the latter condensed with methyl cyanobutenoate **2** to give the C_{20} α-cyano acid **11** ((13*E*)/(13*Z*) 70:30) in 75% yield. Subsequent decarboxylation in piperidine/pyridine (reflux, 2–4 h) gave the retinonitrile **12** ((13*E*)/(13*Z*) 70:30; 90%) which was reduced with DIBAL-H (0°, 30 min) to retinal (**13**; (13*E*)/(13*Z*) 70:30) in 75% yield.

McMurry coupling (low-valent titanium coupling) of γ-retinal ((*all-E*)-**8**) and retinal ((*all-E*)-**13**) led to lycopene (**14**) and β-carotene (**15**; *Scheme 5*). The synthesis of β-carotene (**15**) by this process has been previously reported [22].

Scheme 3



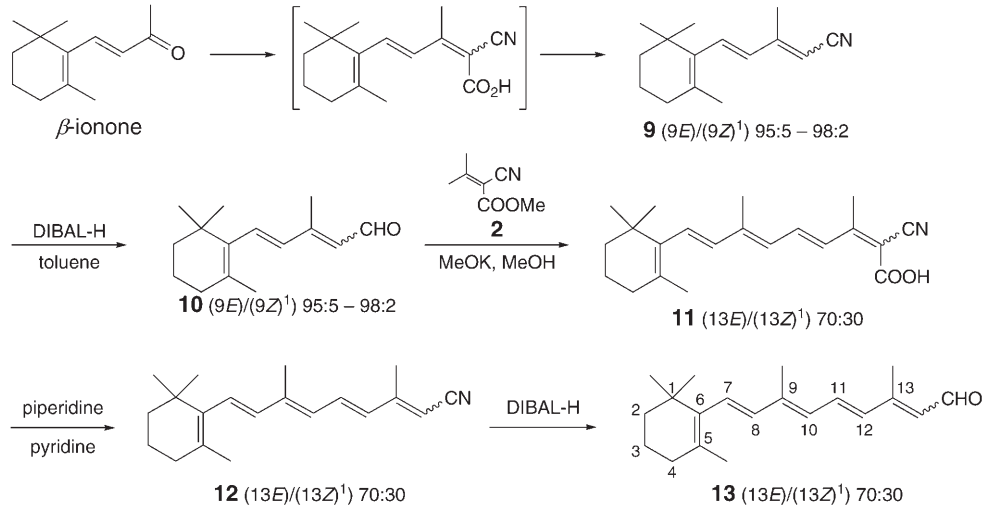
Experimental Part

Methyl 2-Cyano-3-methylbutanoate (**2**). In a flask equipped with a *Soxhlet* extractor containing $CaCl_2$, methyl cyanoacetate (177 ml, 1.986 mol), β-alanine (0.88 g, 9.9 mmol, 0.005 equiv.), acetone (294 ml, 3.972 mol, 2 equiv.), and AcOH (37.5 ml, 655.4 mmol, 0.33 equiv.) were refluxed for 19 h. After cooling to r.t., the crude mixture was neutralized with sat. $NaHCO_3$ soln. The solvent was removed under reduced pressure, and the crude product was rectified at 88–90°/2 Torr: 133 g (49%) of **2**. Colorless oil. IR: 2259, 1734. ^{1}H-NMR ($CDCl_3$, 400 MHz): 3.82 (*s*, CO_2Me); 2.41 (*s*, Me); 2.32 (*s*, Me).

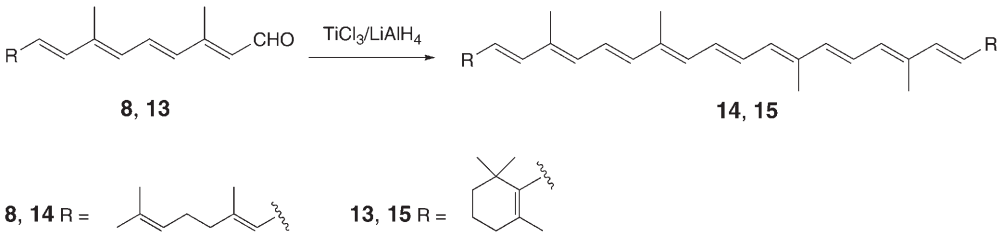
*(2*E*,4*E*,6*E*,)/(2*Z*,4*E*,6*E*)-2-Cyano-3,7,11-trimethyldodeca-2,4,6,10-tetraenoic Acid* (**3**). At 0°, a mixture of citral (**1**; 1.52 g, 10^{-2} mol) and **2** (2.325 g, $1.5 \cdot 10^{-2}$ mol) was added to ^{t}BuOK (1.12 g, 10^{-2} mol) in MeOH (25 ml). The soln. was then stirred at r.t. for 48 h. The MeOH was evaporated and ice (100 g) was added. The mixture was extracted with Et_2O, the aq. layer acidified and extracted with Et_2O, and the extract washed with H_2O, dried ($MgSO_4$), and concentrated: **3**.

*(2*E*,4*E*,6*E*)/(2*Z*,4*E*,6*E*)-3,7,11-Trimethyldodeca-2,4,6,10-tetraenenitrile* (**4**). A soln. of crude **3** (1.06 g, $0.4 \cdot 10^{-2}$ mol) in piperidine/pyridine 1:1 (100 ml) was refluxed until the release of CO_2 was completed (2–3 h). The bases were evaporated and the crude product was extracted with Et_2O and the extract washed successively with 1M HCl and H_2O, dried ($MgSO_4$), and concentrated: **4** (85%), (*E*)/(*Z*) 80:20. The isomers were separated by column chromatography (CC; silica gel, CH_2Cl_2).

Scheme 4



Scheme 5



*Data of (*all-E*)-***4***[1]*): IR: 2213 (CN). ^{1}H-NMR ($CDCl_3$): 1.60 (*s*, Me(1a)); 1.68 (*s*, Me(1b)); 1.87 (*s*, Me–C(5)); 2.17 (*m*, CH_2(3), CH_2C(4)); 2.21 (*s*, Me–C(9)); 5.17 (*m*, H–C(2)); 5.29 (*s*, H–C(10)); 5.93 (*d*, *J* = 11.0, H–C(6)); 6.19 (*d*, *J* = 15.2, H–C(8)); 6.76 (*dd*, *J* = 15.2, 11.0, H–C(7)). ^{13}C-NMR ($CDCl_3$, 75 MHz): 133.0 (CH); 130.2 (CH); 127.6 (CH); 123.8 (CH); 96.4 (CH) 40.7 (CH_2); 26.8; (CH_2); 26.1 (Me); 18.1 (Me); 17.0 (Me).

*Data of (9Z)-***4***[1]*): ^{1}H-NMR ($CDCl_3$): 1.56 (*s*, Me(1a)); 1.64 (*s*, Me(1b)), 3 H); 1.86 (*s*, Me–C(5)); 2.10 (*m*, CH_2(3), CH_2(4)); 2.18 (*s*, Me–(9)); 5.11 (*m*, H–C(2), H–C(10)); 6.04 (*d*, *J* = 11.0, H–C(6)); 6.70 (*d*, *J* = 15.0, H–C(8)); 6.76 (*dd*, *J* = 15.0, 11.0, H–C(7)). ^{13}C-NMR ($CDCl_3$, 75 MHz): 133.5 (CH); 129.9 (CH); 125.7 (CH); 124.8 (CH); 95.0 (CH); 33.3 (CH_2); 27.2 (CH_2); 24.8 (Me); 19.8 (Me); 18.1 (Me).

*(2*E*,4*E*,6*E*)/(2*Z*,4*E*,6*E*)-3,7,11-Trimethyldodeca-2,4,6,10-tetraenal* (**5**). Nitrile **4** (0.645 g, $0.3 \cdot 10^{-2}$ mol) in toluene was reduced at 0° by DIBAL-H (1.1 equiv.) in toluene. After 30 min, the reaction was quenched with 1M H_2SO_4. After filtration of the salts and usual workup, the org. layer was rapidly filtered over Al_2O_3: **5** (65%), (9*E*)/(9*Z*)[1]) 80:20. The isomers were separated by CC (silica gel, CH_2Cl_2).

*Data of (*all-E*)-***5***[1]*): IR: 1661 (CO). ^{1}H-NMR ($CDCl_3$): 1.60 (*s*, Me(1a)); 1.70 (*s*, Me(1b)); 1.89 (*s*, Me–C(5)); 2.05 (*m*, CH_2(3), CH_2(4)); 2.36 (*s*, Me–C(9)); 5.11 (*m*, H–C(2)); 5.96 (*d*, *J* = 8.1, H–C(10)); 6.03 (*m*, H–C(8)); 6.24 (*m*, H–C(6), H–C(7)); 10.09 (*d*, *J* = 8.0, H–C(11)). ^{13}C-NMR ($CDCl_3$, 75 MHz): 191.6 (CO); 133.1 (CH); 129.1 (CH); 126.3 (CH); 125.3 (CH); 123.8 (CH); 40.7 (CH_2); 26.8 (CH_2); 26.1 (Me); 17.7 (Me); 13.5 (Me).

*Data of (9Z)-***5**[1]): ^{1}H-NMR ($CDCl_3$): 1.61 (*s*, Me(1a)); 1.68 (*s*, Me(1b)); 1.87 (*s*, Me–C(5)); 2.15 (*m*, CH_2(3), CH_2(4)); 2.3 (*s*, Me–C(9)); 5.08 (*m*, H–C(2)); 5.85 (*d*, *J* = 8.0, H–C(10)); 5.95 (*d*, *J* = 15.0, H–C(6)); 6.98 (*d*, *J* = 15.0, H–C(8)); 7.37 (*m*, H–C(7)); 10.18 (*d*, *J* = 7.5, H–C(11)). ^{13}C-NMR ($CDCl_3$, 75 MHz): 190.4 (CO); 134.0 (CH); 133.3 (CH); 127.9 (CH); 125.4 (CH); 125.1 (CH); 33.4 (CH_2); 27.2 (CH_2); 24.9 (Me); 21.6 (Me); 18.1 (Me).

(2E,4E,6E,8E,10E)/(2Z,4E,6E,10E)-2-Cyano-3,7,11,15-tetramethylhexadeca-2,4,6,8,10,14-hexadienoic Acid (**6**). As described for **3**: **6** (80%) as a mixture of isomers.

(2E,4E,6E,8E,10E)/(2Z,4E,6E,10E)-3,7,11,15-Tetramethylhexadeca-2,4,6,8,10,14-hexadienenitrile (**7**). As described for **4**: **7** (90%), (*all-E*)/(13*Z*)[1]) 80 : 20. The isomers were separated by CC (silica gel, CH_2Cl_2).

*Data of (*all-E*)-***7**[1]): IR: 2215 (CN). ^{1}H-NMR ($CDCl_3$): 1.62 (*s*, Me(1a)); 1.69 (*s*, Me(1b)); 1.84 (*s*, Me–C(5)); 2.02 (*s*, Me–C(9)); 2.17 (*m*, CH_2(3), CH_2(4)); 2.22 (*s*, Me–C(13)); 5.1 (*m*, H–C(2)); 5.17 (*s*, H–C(14)); 5.97 (*m*, H–C(6)); 6.15 (*m*, H–C(10)); 6.28 (*m*, H–C(8)); 6.61 (*m*, H–C(12)); 6.65 (*m*, H–C(7)); 6.92 (*m*, H–C(11)).

*Data of (13Z)-***7**[1]): ^{1}H-NMR ($CDCl_3$): 1.62 (*s*, Me(1a)); 1.69 (*s*, Me(1b)); 1.84 (*s*, Me–C(5)); 2.02 (*s*, Me–C(9)); 2.13 (*s*, Me–C(13)); 2.17 (*m*, CH_2(3), CH_2(4)); 5.07 (*s*, H–C(14)); 5.1 (*m*, H–C(2)); 5.97 (*m*, H–C(6)); 6.15 (*m*, H–C(10)); 6.28 (*m*, H–C(8)); 6.65 (*m*, H–C(7)); 6.82 (*m*, H–C(12)); 6.92 (*m*, H–C(11)).

(2E,4E,6E,8E,10E)/(2Z,4E,6E,8E,10E)-3,7,11,15-Tetramethylhexadeca-2,4,6,8,10,14-hexadienal (**8**). As described for **5**: **8** (55%), (*all-E*)/(13*Z*)[1]) 80 : 20. The isomers were separated by CC (silica gel, CH_2Cl_2).

*Data of γ-Retinal (*all-E*)-***8**[1])[2]): IR: 1659 (CO). ^{1}H-NMR ($CDCl_3$): 1.56 (*s*, Me(1a)); 1.62 (*s*, Me(1b)); 1.72 (*s*, Me–C(5)); 1.87 (*s*, Me–C(9)); 2.07 (*m*, CH_2(3), CH_2(4)); 2.14 (*s*, Me–C(13)); 5.14 (*m*, H–C(2)); 5.97–6.32 (*m*, H–C(6), H–C(8), H–C(10), H–C(14)); 6.77 (*m*, H–C(12)); 7.05 (*m*, H–C(7)); 7.5 (*m*, H–C(11)); 9.60 (*d*, *J* = 8.05, H–C(15)).

*Data of (13Z)-***8**[1]): ^{1}H-NMR ($CDCl_3$): 1.56 (*s*, Me(1a)); 1.62 (*s*, Me(1b)); 1.69 (*s*, Me–C(5)); 1.87 (*s*, Me–C(9)); 2.02 (*s*, Me–C(13)); 2.29–2.32 (2*m*, CH_2(3), CH_2(4)); 5.12 (*m*, H–C(2)); 5.97–6.39 (*m*, H–C(6), H–C(7), H–C(8), H–C(10), H–C(14)); 6.63 (*m*, H–C(11)); 7.10 (*m*, H–C(12)); 10.10 (*d*, *J* = 8.3, H–C(15)).

(2E,4E)/(2Z,4E)-3-Methyl-5-(2,6,6-trimethylcyclohex-1-en-1-yl)penta-2,4-dienenitrile (**9**). In a *Dean–Stark* apparatus, at 0°, piperidine (60 ml, 2 equiv.) was slowly added to β-ionone (58.27 g) and cyanoacetic acid (51.85 g, 2 equiv.) in benzene (100 ml). The heterogeneous mixture was refluxed for 6.30 h (removal of formed H_2O). After cooling, the mixture was washed twice with H_2O (50 ml) the org. layer dried ($MgSO_4$), the benzene evaporated and the oily product dissolved in CH_2Cl_2 (150 ml). This soln. was rapidly filtered over basic alumina (20 g): **9** (*ca.* 100%) (9*E*)/(9*Z*)[1]) 95 : 5–98 : 2. A pure sample of the (*all-E*)-**9** was obtained by CC (SiO_2, CH_2Cl_2). IR: 2206. ^{1}H-NMR[1]) ($CDCl_3$, 400 MHz): 6.55 (*d*, *J* = 16.1, H–C(7)); 6.13 (*d*, *J* = 16.1, H–C(8)); 5.15 (*s*, H–C(10)); 2.44 (*s*, Me–C(9)); 2.02 (*t*, CH_2(4)); 1.74 (*s*, Me–C(5)); 1.61 (*m*, CH_2(3)); 1.46 (*m*, CH_2(2)); 1.01 (*s*, 2 Me–C(1)). ^{13}C-NMR ($CDCl_3$, 75 MHz): 132.5 (CH); 128.1 (CH); 39.3 (CH_2); 33.0 (CH_2); 26.7 (Me); 21.5 (Me); 16.9 (CH_2); 16.3 (Me).

(2E4E)/(2Z,4E)-3-Methyl-5-(2,6,6-trimethylcyclohexa-1-en-1-yl)penta-2,4-dienal (**10**). Under Ar, at 0°, 1.2M DIBAL-H in toluene (23.5 ml, 28.2 mmol, 1.1 equiv.) was added slowly to **9** (5.06 g, 23.5 mmol) in toluene (20 ml). After 30 min, the reaction was quenched with 1M H_2SO_4. The salts were filtered off, and Et_2O (40 ml) and H_2O (20 ml) were added. The org. layer was decanted, washed twice with brine, dried ($MgSO_4$), and concentrated. The crude **10** ((9*E*)/(9*Z*) 95 : 5–98 : 2) was purified by CC (SiO_2, CH_2Cl_2): 4.21 g (82%) of **10**, (*all-E*). Yellow oil. IR: 1668. ^{1}H-NMR[1]) ($CDCl_3$, 400 MHz): 10.11 (*d*, *J* = 8.16, H–C(11)); 6.73 (*d*, *J* = 16.2, H–C(7)); 6.20 (*d*, *J* = 16.2, H–C(8)); 5.92 (*d*, *J* = 8.16, H–C(10)); 2.3 (*s*, Me–C(9)); 2.03 (*m*, CH_2(4)); 1.71 (*s*, Me–C(5)); 1.6 (*m*, CH_2(3)); 1.47 (*m*, CH_2(2)); 1.03 (*s*, 2 Me–C(1)). ^{13}C-NMR ($CDCl_3$, 75 MHz): 135.7 (CH); 135.4 (CH); 128.7 (CH); 39.7 (CH_2); 33.4 (CH_2); 28.9 (Me); 21.6 (Me); 19.4 (CH_2); 12.9 (Me).

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[2]) The NMR data are identical to these described in [13][23].

*(2*E*,4*E*,6*E*,8*E*)/(2*Z*,4*E*,6*E*,8*E*)-2-Cyano-3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-en-1-yl)nona-2,4,6,8-tetraenoic Acid* (**11**). As described for **3**, from the (*all-E*) aldehyde **10**: **11** (75%), mixture of isomers.

*(2*E*,4*E*,6*E*,8*E*)/(2*Z*,4*E*,6*E*,8*E*)-3,7-Dimethyl-9-(2,6,6-trimethylcyclohex-1-en-1-yl)nona-2,4,6,8-tetraenenitrile* (**12**). As described for **4**: **12** (90%), (*all-E*)/(13*Z*)[1]) 70 : 30. The isomers were separated by CC (silica gel, CH_2Cl_2).

*Data of (*all-E*)-***12***[1]*): IR: 2213 (CN). ^{1}H-NMR ($CDCl_3$): 1.00 (*s*, 2 Me−C(1)); 1.40 (*m*, CH_2(2)); 1.60 (*m*, CH_2(3)); 1.70 (*s*, Me−C(5)); 2.00 (*m*, CH_2(4)); 2.00 (*s*, Me−C(9)); 2.20 (*s*, Me−C(13)); 5.20 (*s*, H−C(14)); 6.10 (*d*, *J* = 16.0, H−C(7)); 6.10 (*d*, *J* = 11.0, H−C(10)); 6.30 (*d*, *J* = 16.0, H−C(8)); 6.30 (*d*, *J* = 15.0, H−C(12)); 6.90 (*dd*, *J* = 15.0, 11.0, H−C(11)). ^{13}C-NMR ($CDCl_3$, 75 MHz): 137.6 (CH); 132.5 (CH); 131.2 (CH); 130.4 (CH); 129.6 (CH); 39.5 (CH_2); 33.1 (CH_2); 28.9 (Me); 21.7 (Me); 19.1 (CH_2); 16.5 (Me); 12.9 (Me).

*Data of (13*Z*)-***12***[1]*): IR: 2209 (CN). ^{1}H-NMR ($CDCl_3$): 1.05 (*s*, 2 Me−C(1)); 1.49 (*m*, CH_2(2)); 1.63 (*m*, CH_2(3)); 1.74 (*s*, Me−C(5)); 1.97 (*s*, Me−C(9)); 2.06 (*m*, CH_2(4)); 2.09 (*s*, Me−C(13)); 5.10 (*s*, H−C(14)); 6.18 (*d*, *J* = 16.0, H−C(8)); 6.10 (*d*, *J* = 11.0, H−C(10)); 6.30 (*d*, *J* = 16.0, H−C(7)); 6.30 (*d*, *J* = 15.0, H−C(11)); 6.90 (*dd*, *J* = 15.0, 11.0, H−C(12)). ^{13}C-NMR ($CDCl_3$, 75 MHz): 136.9 (CH); 132.9 (CH); 129.6 (CH); 128.9 (CH); 128.5 (CH); 39.5 (CH_2); 33.0 (CH_2); 28.9 (Me); 21.7 (Me); 19.3 (Me); 19.1 (CH_2); 12.9 (Me).

*(2*E*,4*E*,6*E*,8*E*)/(2*Z*,4*E*,6*E8*E*)-3,7-Dimethyl-9-(2,6,6-trimethylcyclohex-1-en-1-yl)nona2,4,6,8-tetraenal* (**13**). As described for **5**: **13** (75%), (*all-E*)/(13*Z*)[1]) 70 : 30. The isomers were separated by CC (silica gel, CH_2Cl_2).

*Data of Retinal (all-E-***13***)*[1]): IR: 1671 (CO). ^{1}H-NMR ($CDCl_3$): 1.03 (*s*, 2 Me−C(1)); 1.47 (*m*, CH_2(2)); 1.61 (*m*, CH_2(3)); 1.72 (*s*, Me−C(5)); 2.03 (*s*, Me−C(9)); 2.04 (*m*, CH_2(4)); 2.32 (*s*, Me−C(13)); 5.97 (*d*, *J* = 8.2, H−C(14)); 6.16 (*d*, *J* = 16.0, H−C(8)); 6.18 (*d*, *J* = 11.7, H−C(10)); 6.33 (*d*, *J* = 16.0, H−C(7)); 6.35 (*d*, *J* = 16.0, H−C(12)); 7.14 (*dd*, *J* = 16.0, 11.7, H−C(11)); 10.10 (*d*, *J* = 8.2, H−C(15)). ^{13}C-NMR: ($CDCl_3$, 75 MHz): 139.0 (CH); 137.1 (CH); 134.4 (CH); 132.7 (CH); 129.6 (CH); 129.4 (CH); 129.2 (CH); 39.2 (CH_2); 33.0 (CH_2); 28.9 (Me); 22.0 (Me); 21.2 (Me); 19.0 (CH_2); 13.1 (Me).

*Data of (13*Z*)-***13***[1]*): IR: 1668 (CO). ^{1}H-NMR ($CDCl_3$): 1.01 (*s*, 2 Me−C(1)); 1.44 (*m*, CH_2(2)); 1.59 (*m*, CH_2(3)); 1.71 (*s*, Me−C(5)); 2.02 (*s*, Me−C(9)); 2.00 (*m*, CH_2(4)); 2.15 (*s*, Me−C(13)); 5.83 (*d*, *J* = 8.3, H−C(13)); 6.16 (*d*, *J* = 16.0, H−C(8)); 6.22 (*d*, *J* = 11.6, H−C(10)); 6.32 (*d*, *J* = 16.0, H−C(7)); 7.04 (*dd*, *J* = 16.0, 11.6, H−C(11)); 10.22 (*d*, *J* = 8.3, H−C(15)). ^{13}C-NMR ($CDCl_3$, 75 MHz): 134.4 (CH); 133.5 (CH); 129.6 (CH); 129.4 (CH); 129.3 (CH); 127.6 (CH); 125.8 (CH); 39.2 (CH_2); 33.0 (CH_2); 28.9 (Me); 21.9 (Me); 21.4 (Me); 19.0 (CH_2); 13.1 (Me).

Lycopene (**14**) *and β-Carotene* (**15**): *General Procedure* (the *McMurry* reaction has not been used previously for the synthesis of lycopene from γ-retinal): Under Ar, $LiAlH_4$ (1.1 equiv.) was slowly added to a stirred soln. of of $TiCl_3$ (2.2 equiv.) in anh. THF (10 ml). The soln. was stirred at r.t. for 2 h. Then, a soln. of 500 mg (1 equiv.) of γ-retinal ((*all-E*)-**8**) or of retinal ((*all-E*)-**13**) in anh. THF (5 ml) was slowly added, and the mixture was left overnight at r.t. The mixture was cooled at 0° and hydrolyzed by 2M HCl (30 ml). The crude mixture was extracted with Et_2O, the org. layer washed with H_2O, dried ($MgSO_4$), and concentrated: crude **14** (75%) or crude **15** (84%), resp. ^{1}H- and ^{13}C-NMR: identical to those reported in [22][24] for the (*all-E*) compounds.

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