Base-Induced Decarboxylation of Polyunsaturated α-Cyano Acids Derived from Malonic Acid: Synthesis of Sesquiterpene Nitriles and Aldehydes with β-, φ-, and ψ-End Groups

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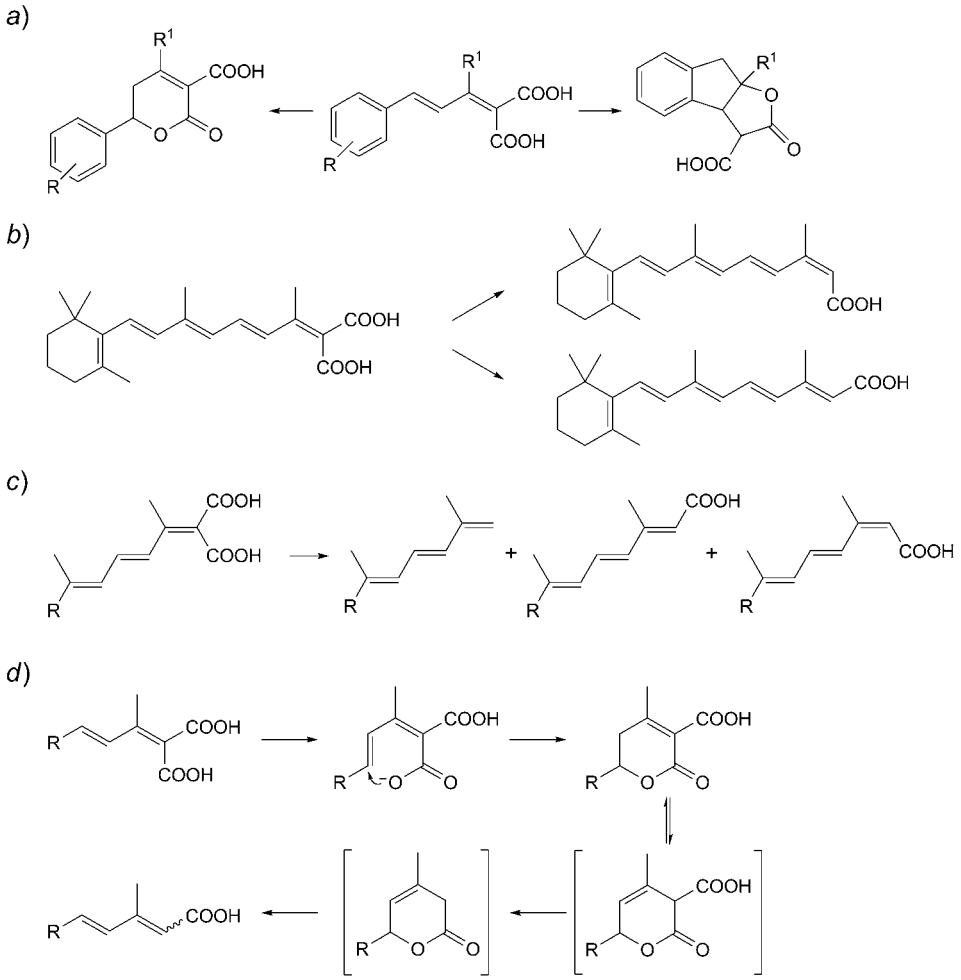
Catalytic base-induced decarboxylation of polyunsaturated α-cyano-β-methyl acids derived from malonic acid led to the corresponding nitriles **3** (*Schemes 2* and *3*), **6** (*Scheme 5*), and **9** (*Scheme 6*). This decarboxylation occurred with previous deconjugation of the α,β-alkene moiety of the α-cyano-β-methyl acid, leading to an α-cyano-β-methylene propanoic acid which was easily decarboxylated (see *Scheme 2*). β-Methylene intermediates, in some cases, could be isolated; mechanistic pathways are proposed. The nitriles **3**, **6**, and **9** were reduced to the sesquiterpene aldehydes **4** (β-end group), **7** (φ-end group), and **10** (ψ-end group), respectively.

Introduction. – Decarboxylations are important in biological systems and occur frequently in primary and secondary metabolisms: glycolysis, gluconeogenesis, glycogenolysis, and glycogenesis, degradation and synthesis of fatty acids, *Krebs* citric acid cycle (including pyruvate to acetyl-CoA, oxalosuccinate to α-ketoglutarate, α-ketoglutarate to succinyl-CoA). Other decarboxylations are important, such as formation of significant amines from amino acids, 5-HTP to serotonin, L-DOPA to dopamine.

We have worked on the base/acid-induced decarboxylation of polyunsaturated malonic acid derivatives for many years. Thus, in a strong acidic medium and depending on the substitution pattern of the side chain, we have found that γ-lactones or δ-lactones could be obtained [1] (*Scheme 1*, *a*).

In another study related to new syntheses of retinoids and carotenoids [2], we have demonstrated that stereospecific/stereoselective monodecarboxylations were possible, depending on the base used [3][4] (*Scheme 1*, *b*). In a recent work, we have revealed that bis-decarboxylation of some malonic acid derivatives could occur easily, and that this reaction is accompanied by formation of (*E*)- and (*Z*)-configured mono-acids [5] (*Scheme 1*, *c*). According to *Corey* and *Fraenkel* [6], these decarboxylations of malonic acid derivatives require a previous isomerization to an intermediary β-unsaturated δ-lactone (*Scheme 1*, *d*). In the series of corresponding cyanoacetic acid derivatives with β-, φ-, and ψ-end groups, different mechanistic pathways were proposed, which may explain the process of decarboxylation.

Scheme 1

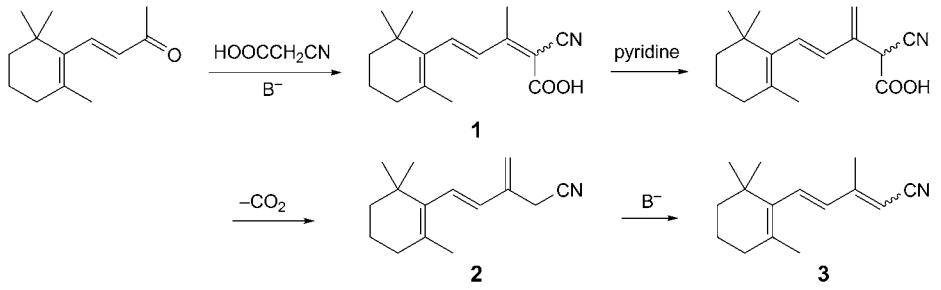


Sesquiterpenes are usually found as natural products [7] and could also be of interest in chemical synthesis. C_{15}-Sesquiterpene aldehydes are commonly used for the syntheses of diterpenes (especially related to retinoic acids, retinals, and retinols), and numerous references show them to be exceptional intermediates [8]. This paper reports on new syntheses of some β-, φ-, and ψ-sesquiterpene aldehydes as useful synthons for retinoid syntheses.

Results and Discussion. – *β-End Group. Knoevenagel* condensation of β-ionone with cyanoacetic acid led to the α-cyano-β-methyl acid **1** [9], which, after decarboxylation in pyridine furnished the β,γ-unsaturated nitrile **2** (*Scheme 2*). In a previous report, *Smit* [10] considered this step as an abnormal decarboxylation. Nitrile **2** was isomerized to the α,β-unsaturated isomers **3** ((2*E*,4*E*)/(2*Z*,4*E*) 4:1) by heating in

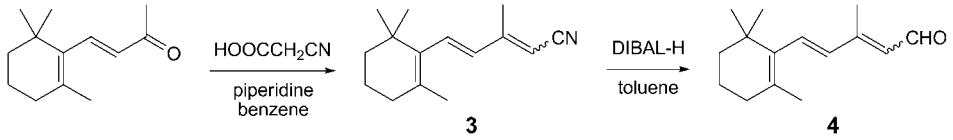
KOH/MeOH. In this case, we think that the decarboxylation occurred in a regular manner, due to the presence of the stronger electron-withdrawing effect of the nitrile group, which could induce the suggested process, *i.e.*, abstraction of a H-atom from Me–C(3) by the base prior to loss of CO_2 (*Scheme 2*).

Scheme 2



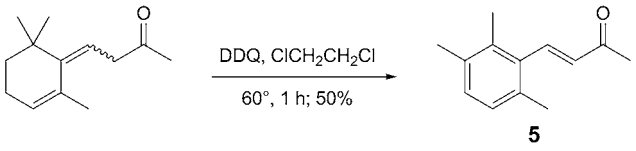
We now developed an improved process which allowed the formation of nitrile **3** in a 'one-pot' procedure, with a good regioselectivity. Thus, condensation of β-ionone with cyanoacetic acid in piperidine/benzene under reflux (*Dean–Stark*; 6.5 h) led to **3** nearly quantitatively ((2*E*,4*E*)/(2*Z*,4*E*) 95:5 to 98:2; *Scheme 3*). Piperidine (8 equiv.) and benzene (as solvent) seemed to be indispensable because other bases and solvents led to a mixture of nitriles with poor regioselectivity. Under these experimental conditions, the initially formed cyanoacetic acids were concomitantly decarboxylated in the reaction mixture. The (2*E*,4*E*)-nitrile **3** was easily purified by column chromatography (SiO_2, CH_2Cl_2). Thus, the crude C_{15}-nitrile **3** was reduced by diisobutylaluminium hydride (DIBAL-H) in toluene at 0° (30 min) to yield the sesquiterpenene aldehyde **4** ((2*E*,4*E*)/(2*Z*,4*E*) 95:5 to 98:2). The crude aldehyde was purified by column chromatography (SiO_2, CH_2Cl_2) to provide (2*E*,4*E*)-**4** as a yellow oil in 82% yield from **3** [10].

Scheme 3



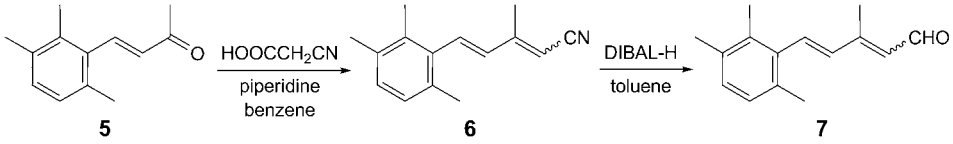
φ-End Group. We have also recently reported that oxidation of β-ionone and α-ionone having the respective β- and ε-end group of carotenoids led to the corresponding C_{13} aromatic ketone **5**. By an improved procedure, under particularly mild conditions, ketone **5** could be obtained from *retro*-ionone, an isomer of β- and α-ionones (*Scheme 4*). Hence *retro*-ionone was heated at 60° for 1 h with 3 equiv. of 4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile (DDQ) in 1,2-dichloroethane to produce the aromatic ketone **5** in 50% yield [11]. In this rapid process, extraction and purification were easier. This reaction could be integrated into a new biomimetic aromatization of a β-end group to a φ-end group, with regiospecific migration of one of the Me groups [2].

Scheme 4



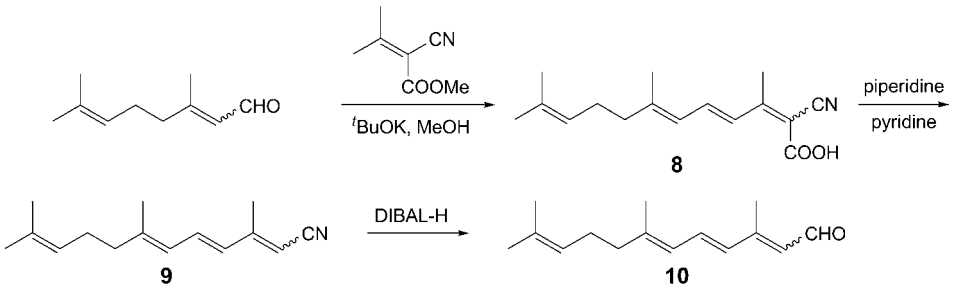
As described above (*Scheme 3*), a *Knoevenagel* condensation of aromatic ionone **5** with cyanoacetic acid in piperidine/benzene under reflux (*Dean–Stark*) led to the sesquiterpene nitrile **6** ((2*E*,4*E*)/(2*Z*,4*E*) 95:5) (*Scheme 5*). The (*E*,*E*)-nitrile was easily purified by recrystallization from pentane/Et_2O 70:30 and was further reduced by DIBAL-H in toluene at 0° (30 min) to the corresponding aldehyde **7** (85%).

Scheme 5



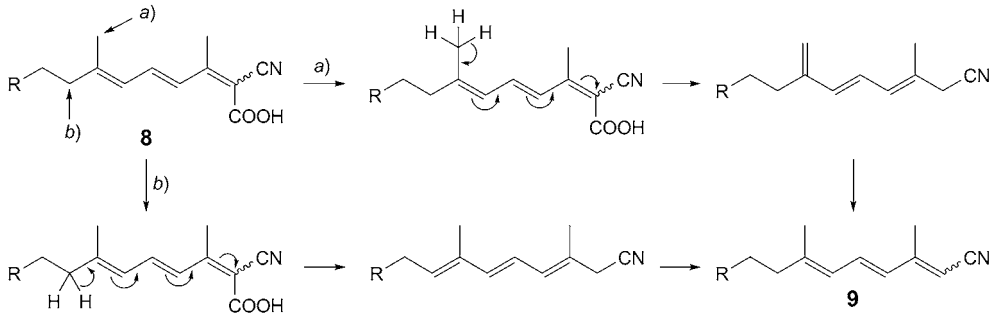
ψ-End Group. Condensation of citral with methyl cyano(isopropylidene)acetate, under *Stobbe*'s conditions (^{t}BuOK, MeOH, 0°, then 24 h r.t.) led to cyano acid **8** ((*E*)/(*Z*)-isomer *ca.* 4:1), which was further decarboxylated in pyridine/piperidine under reflux (2–3 h) to provide nitrile **9** as a 7:3 mixture of (*E*)- and (*Z*)-isomers (*Scheme 6*). After reduction with DIBAL-H at 0° (30 min), aldehyde **10** was obtained as a 7:3 mixture of (*E*)- and (*Z*)-isomers which were separated by chromatography.

Scheme 6



Taking into account the results of the above series (*Scheme 6*), two routes, *a*) and *b*), can be competing in the acyclic series as shown in *Scheme 7*, and two nitriles may be predicted as intermediates (unfortunately not detected under our experimental conditions in the decarboxylation process).

Scheme 7



Conclusion. – This work and previous ones reported elsewhere showed that decarboxylation of malonic acid derivatives or analogs can be dependent on many factors, such as base effect, steric hindrance, electron-withdrawing effect of the malonic acid derived moiety, and others.

Experimental Part

General. Starting materials and solvents were obtained from *Aldrich* (Germany) and were used without further purification. All reactions were carried out under Ar. M.p.: *Leitz-350*-microscope heating stage; not corrected. IR Spectra: *Bruker-IF-55* spectrometer; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Bruker-Avance-DPX-400* spectrometer; at 400 (^1H) and 100 MHz (^{13}C); in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, J in Hz.

*(2*E*,4*E*)- and (2*Z*,4*E*)-2-Cyano-3-methyl-5-(2,6,6-trimethylcyclohex-1-en-1-yl)penta-2,4-dienoic Acid* (**1**). Its synthesis is reported in [9][10][12]: (2*E*,4*E*)-**1** was obtained as orange crystals after recrystallization from benzene, m.p. 174°. The mother liquor (benzene) was diluted with petroleum ether to furnish (2Z,4*E*)-**1** as orange crystals, m.p. 124°.

*(4*E*)-3-Methylene-5-(2,6,6-trimethylcyclohex-1-en-1-yl)pent-4-enenitrile* (**2**). The crude α-cyano acids **1** were refluxed in pyridine for 2 h, the pyridine was distilled off under reduced pressure, and the oily mixture was acidified with 1N HCl and extracted with Et_2O. The extract was purified by filtration through SiO_2, the filtrate evaporated, and the residue distilled *in vacuo* to give **2**. Colorless oil (90%). IR (film): 2212. ^1H-NMR[1]): 6.11 (*s*, H–C(7), H–C(8)); 5.37, 5.33 (2*s*, CH_2–C(9)); 3.33 (*s*, CH_2(10)); 2.02 (*m*, CH_2(4)); 1.70 (*s*, Me–C(5)); 1.63 (*m*, CH_2(3)); 1.47 (*m*, CH_2(2)); 1.02 (*s*, 2 Me–C(1)). ^{13}C-NMR : 132.7; 129.3; 117.9; 39.8; 33.3; 29.2; 22.0; 21.6; 19.6.

*(2*E*,4*E*)- and (2*Z*,4*E*)-3-Methyl-5-(2,6,6-trimethylcyclohex-1-en-1-yl)penta-2,4-dienenitrile* (**3**). *a*) Nitrile **2** (5 g) was isomerized in 2M NaOH (100 ml) at r.t. overnight: (2*E*,4*E*)/(2Z,4*E*)-**3** 4:1. This mixture was separated by CC (SiO_2, CH_2Cl_2).

*(2*E*,4*E*)-***3***: IR (film): 2210, 1610. ^1H-NMR[1]): 6.50 (*d*, $J = 16$, H–C(7)); 6.08 (*d*, $J = 16$, H–C(8)); 5.10 (*s*, H–C(10)); 2.20 (*s*, Me–C(5)); 2.00 (*m*, CH_2(4)); 1.70 (*s*, Me–C(9)); 1.60 (*m*, CH_2(3)); 1.40 (*m*, CH_2(2)); 0.92 (*s*, 2 Me–C(1)). ^{13}C-NMR ($CDCl_3$): 156.9; 136.5; 135.3; 132.5; 132.2; 128.1; 96.2; 39.3; 34.0; 33.0; 26.7; 21.5; 16.3.

*(2*Z*,4*E*)-***3***: IR (film): 2210, 1610. ^1H-NMR[1]): 6.60 (*d*, $J = 16$, H–C(8)); 6.50 (*d*, $J = 16$, H–C(7)); 5.00 (*s*, H–C(10)); 2.00 (*s*, Me–C(5) and *m*, CH_2(4)); 1.70 (*s*, Me–C(9)); 1.60 (*m*, CH_2(3)); 1.50 (*m*, CH_2(2)); 1.02 (*s*, 2 Me–C(1)).

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[1]) Trivial atom numbering.

b) *β*-Iodone (6 g) was condensed with cyanoacetic acid (1.1 equiv.) in piperidine (20 ml) and benzene (20 ml) under reflux (*Dean-Stark* apparatus): (2*E*,4*E*)/(2*Z*,4*E*)-**3** 4:1 (nearly quant.). This mixture was separated by CC (SiO_2, CH_2Cl_2).

*(2*E*,4*E*)- and (2*Z*,4*E*)-3-Methyl-5-(2,6,6-trimethylcyclohex-1-en-1-yl)penta-2,4-dienal* (**4**). At 0°, 1,2M DIBAL-H in toluene (23.5 ml, 28.2 mmol, 1.1 equiv.) was added slowly to **3** (5.06 g) 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 washed twice with brine, dried ($MgSO_4$), and concentrated. The crude (2*E*,4*E*)/(2*Z*,4*E*)-**4** 49:1 was separated by CC (SiO_2, CH_2Cl_2): (2*E*,4*E*)-**4** (82%). Yellow oil. IR: 1668. ^{1}H-NMR[1]): 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: 135.7 (CH); 135.4 (CH); 128.7 (CH); 39.7 (CH_2); 33.4 (CH_2); 19.4 (CH_2); 28.9 (Me); 21.6 (Me); 12.9 (Me).

*(3*E*)-4-(2,3,6-Trimethylphenyl)but-3-en-2-one* (**5**). *retro-α*-Ionone (9.62 g; 50 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ; 34 g, 3 equiv.) in 1,2-dichloroethane (100 ml) were heated for 1 h at 65°. The mixture was filtered, the filtrate concentrated, and the crude product purified by CC (SiO_2, pentane/1,2-dichloroethane 1:1): **5** (50%). Yellow oil. IR (film): 1680. ^{1}H-NMR[1]): 7.72 (*d*, *J* = 16, H–C(7)); 7.05, 6.95 (2*d*, *J* = 7, H–C(3), H–C(4)); 6.25 (*d*, *J* = 16, H–C(8)); 2.40, 235, 2.30, 2.25 (4*s*, 4 Me). ^{13}C-NMR ($CDCl_3$): 188.0 (C=O); 134.6 (C); 134.5 (C); 133.5 (C); 143.1 (CH); 133.4 (CH); 129.8 (CH); 127.5 (CH); 27.4 (Me); 20.8 (Me); 16.9 (Me).

*(4*E*)-3-Methyl-5-(2,3,6-trimethylphenyl)penta-2,4-dienenitrile* (**6**). In a *Dean–Stark* apparatus, a soln. of **5** (6 g) and cyanoacetic acid (8.21 g, 3 equiv.) in benzene (30 ml) was cooled to 0°, and piperidine (25.43 ml, 8 equiv.) was slowly added. Then, the mixture was refluxed for 4 h. The benzene was evaporated, the crude product extracted with Et_2O, the org. layer washed with brine and H_2O, dried ($MgSO_4$), and concentrated, the crude product extracted with CH_2Cl_2, and this extract quickly filtered over a mixture of basic alumina and SiO_2 40:60: (2*E*,4*E*)/(2*Z*,4*E*)-**6** 95:5 (96%; ratio determined by ^{1}H-NMR). Yellow ochre crystals which were purified by recrystallization from Et_2O/pentane 30:70: major isomer (2*E*,4*E*)-**6**. M.p. 62°. IR (film): 2206. ^{1}H-NMR[1]): 7.02 (*d*, *J* = 16.3, H–C(7)); 6.98 (*d*, *J* = 7.5, H–C(3)); 6.96 (*d*, *J* = 7.5, H–C(4)); 6.28 (*d*, *J* = 16.3, H–C(8)); 5.25 (*s*, H–C(10)); 2.32 (s, Me–C(2)); 2.26 (*s*, Me–C(9)); 2.25 (*s*, Me–C(5)); 2.2 (*s*, Me–C(1)). ^{13}C-NMR (CN): 118.0; 157.1 (C); 136.0 (C); 134.9 (C); 134.7 (C); 133.8 (C); 135.9 (CH); 134.5 (CH); 129.7 (CH); 127.8 (CH); 98.3 (CH); 21.2 (Me); 20.7 (Me); 17.4 (Me); 16.9 (Me).

*(4*E*)-(2,3,6-Trimethylphenyl)penta-2,4-dienal* (**7**). At 0°, 1.2M DIBAL-H in toluene (24 ml, 1.2 equiv.) was slowly added under vigorous stirring to **6** (5 g) in toluene. The mixture was stirred for 2 h and then hydrolyzed by 2M H_2SO_4. After filtration of the aluminium salts, Et_2O (50 ml) and H_2O (50 ml) were added. The org. layer was washed with brine and H_2O, dried ($MgSO_4$), and concentrated and the crude product purified by CC (SiO_2, CH_2Cl_2): major isomer (2*E*,4*E*)-**7** (85%). Yellow oil. IR (film): 1659. ^{1}H-NMR[1]): 10.20 (*d*, *J* = 8.1, H–C(11)); 7.18 (*d*, *J* = 16.4, H–C(7)); 7.01 (2*d*, *J* = 7.6, H–C(3), H–C(4)); 6.36 (*d*, *J* = 16.4, H–C(8)); 6.14 (*d*, *J* = 8.1, H–C(10)); 2.44 (*s*, Me–C(9)); 2.26 (*s*, Me–C(1), Me–C(2)); 2.23 (*s*, Me–C(5)). ^{13}C-NMR: 191.3 (C=O); 154.1 (C); 135.9 (C); 134.5 (C); 134.4 (C); 133.5 (C); 137.2 (CH); 135.2 (CH); 129.7 (CH); 129.2 (CH); 127.5 (CH); 20.8 (Me); 20.4 (Me); 13.0 (Me); 9.7 (Me).

*(2*E*,4*E*,6*E*)- and (2*Z*,4*E*,6*E*)-2-Cyano-3,7,11-trimethydodeca-2,4,6,10-tetraenoic Acid* (**8**) *and (2*E*,4*E*,6*E*)- and (2*Z*,4*E*,6*E*)-3,7,11-Trimethydodeca-2,4,6,10-tetraenenitrile* (**9**). At 0°, a mixture of citral (1.52 g) and methyl cyano(isopropylidene)acetate (= methyl 2-cyano-3-methylbut-2-enoate; **3**; 2.325 g, 1.5 equiv.) was added to ^{t}BuOK (1.12 g, 1 equiv.) in MeOH (25 ml). The soln. was allowed to stay at r.t. for 24 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 this extract washed with H_2O, dried ($MgSO_4$), and concentrated: crude **8** as a mixture of isomers.

A soln. of crude **8** (1 g) in piperidine (50 ml) and pyridine (50 ml) was refluxed until the flow of CO_2 ceased (2–3 h). The bases were evaporated and the crude product was extracted with Et_2O. The extract was washed successively with a 1M HCl and H_2O, dried ($MgSO_4$) and concentrated: (2*E*,4*E*,6*E*)/(2*Z*,4*E*,6*E*)-**9** 7:3. This mixture was separated by CC (SiO_2, CH_2Cl_2).

*(2*E*,4*E*,6*E*)*-**9**: (85%): IR(film): 2213. ^{1}H-NMR[1]): 1.60 (*s*, Me_a–C(1)); 1.68 (*s*, Me_b–C(1)); 1.87 (*s*, Me–C(5)); 2.17 (*m*, CH_2(3), CH_2(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 : 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). (2*Z*,4*E*,6*E*)-**9**: ^{1}H-NMR[1]): 1.56 (*s*, Me_a–C(1)); 1.64 (*s*, Me_b–C(1)); 1.86 (*s*, Me–C(5)); 2.10 (*m*, CH_2(3), CH_2(4)); 2.18 (*s*, Me–C(9)); 5.11 (*m*, H–C(2), H–C(10)); 6.04 (*d*, 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: 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*)- and (2*Z*,4*E*,6*E*)-3,7-Trimethyldodeca-4,6-trienal* (**10**). As described for **7**, with **9** (0.645 g) in toluene and DIBAL-H (1.1 equiv.) in toluene. After 30 min, the reaction was quenched with 1M H_2SO_4. After filtration and usual workup, the org. layer was rapidly filtered over Al_2O_3: (2*E*,4*E*,6*E*)/(2*Z*,4*E*,6*E*)-**10** 7:3 (65%). This mixture was separated by CC (SiO_2, CH_2Cl_2).

(2*E*,4*E*,6*E*)-**10**: ^{1}H-NMR[1]): 1.60 (*s*, Me_a–C(1)); 1.70 (*s*, Me_b–C(1)); 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)); 6.24 (*m*, H–C(3), H–C(4)); 10.09 (*d*, *J* = 8.0, H–C(11)). ^{13}C-NMR: 191.6 (C=O); 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).

(2*Z*,4*E*,6*E*)-**10**: ^{1}H-NMR[1]): 1.61 (*s*, Me_a–C(1)); 1.68 (*s*, Me_b–C(1)); 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 (*m*, *J* = 15.0, H–C(8)); 7.37 (*m*, H–C(7)); 10.18 (*d*, *J* = 7.5, H–C(11)). ^{13}C-NMR: 190.4 (C=O); 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).

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