Improvement on the synthesis of (*E*)-alk-3-enoic acids

Nikitas Ragoussis [a] **and Valentine Ragoussis** *[b]

[a] *VIORYL S.A. Research Department, Kato Kifissia, 145-64, Greece*
[b] *Department of Chemistry, Laboratory of Organic Chemistry, University of Athens, Panepistimiopolis Zographou, 157 71 Athens, Greece*

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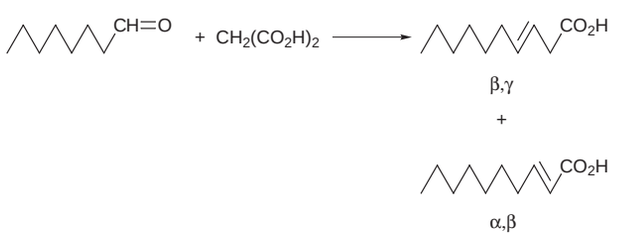
(*E*)-Alk-3-enoic acids have been prepared in high yield (85–90%) and excellent stereoselectivity (98–99%) by a modified Knoevenagel condensation of a straight carbon chain aldehyde with malonic acid, in dimethyl sulfoxide (DMSO) or dimethylformamide (DMF) at 100 °C, in the presence of piperidinium acetate as catalyst. Condensation of the aldehyde with a monoester of malonic acid, under the above conditions, gave the corresponding ester of (*E*)-alk-3-enoic acid in high yield (76–82%) and good stereoselectivity (90–92%). Condensation of the aldehyde with cyanoacetic acid gave the β,γ-unsaturated nitrile in moderate yield (35–40%) without stereoselectivity.

Simple linear β,γ-unsaturated acids and esters are natural products, identified among the volatile constituents isolated from various fruits and food.[1] For example non-3-enoic acid is found in grapes,[2] methyl hex-3-enoate in nectarines[3] and pineapples,[4] ethyl hex-3-enoate and ethyl oct-3-enoate in pineapples,[4] passion fruit[4] and mango[5] *etc.* Several β,γ-unsaturated acids and derivatives have also been reported as pheromones. Thus ethyl oct-3-enoate is identified as one of the main components of the male-produced sex pheromone of the Mediterranean fruit fly *Ceratitis capitata*,[5,6] dec-3-enoic acid is the pheromone of the furniture carpet beetle *Anthrenus flavipes*[7] and dodec-3-enyl acetate is the pheromone of the sugar beet moth *Scrobipalpa ocellatella*.[8] Furthermore the above acids and esters are versatile intermediates that can be easily transformed by simple reactions into lactones,[9] homoallylic alcohols[10] and unsaturated macrolides.[11] Hence, the preparation of alk-3-enoic acids is attractive and interesting in organic synthesis. A variety of methods have been reported for preparing the 3-unsaturated acid or ester moiety. Some characteristic examples are: the partial reduction of the corresponding 2,4-dienoic acids,[12] the deconjugation of α,β-unsaturated esters either by photochemical isomerisation[13] or by deprotonation with a strong base and reprotonation,[14] the Pd(0) catalyzed alkoxycarbonylation of allylic phosphates or acetates,[15] the addition of organocopper reagents to β-vinyl-β-propiolactone[16] and the base promoted alkylation with 1-alkenyl-9-BBN derivatives of ethyl bromoacetate[17] or ethyl dimethylsulfuranylideneacetate.[18] Although the above mentioned methods give the 3-unsaturated acids or esters in good yield, they offer only a partial solution to the problem of synthesizing these compounds, because of the specific reagents and catalysts used, the severe reaction conditions or the low selectivity. None of them is as simple as the classical Knoevenagel condensation[19] (Linstead modification), which however suffers from very low yields.

Several years ago we reported a modification of the Knoevenagel condensation of an aldehyde with malonic acid, which was accomplished in refluxing xylene and afforded exclusively the (*E*)-alk-3-enoic acids in very good yield.[20] As an extension of this work, a study of similar condensations in polar aprotic solvents was undertaken, in order to ameliorate the yield and eventually to simplify the experimental procedure. We describe in this paper a very simple and more efficient procedure for the preparation of (*E*)-alk-3-enoic acids and esters by the condensation of a straight carbon chain aldehyde with malonic acid, in dimethyl sulfoxide (DMSO) or dimethylformamide (DMF) at 100 °C, in the presence of piperidinium acetate as catalyst.

Table 1 Condensation of *n*-octanal with malonic acid [a]



Entry	Solvent	*t*/h	*T*/°C	Yield [b] (%)	Ratio [c] β,γ : α,β
1	DMSO	5.0	30	—	—
2	DMSO	4.5	100	88	98 : 2
3	DMF [d]	4.5	100	86	98 : 2
4	MeCN	5.0	100	18	95 : 5
5	Diglyme	5.0	100	22	96 : 4
6	Triethanolamine	5.0	100	22	92 : 8
7	Neat	5.0	100	20	95 : 5

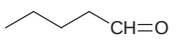
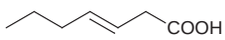
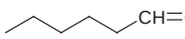
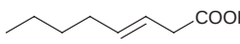
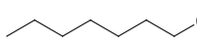
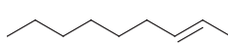
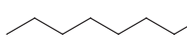
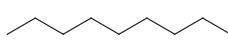
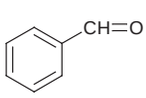
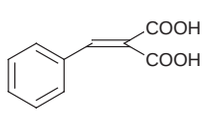
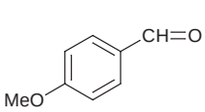
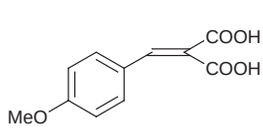
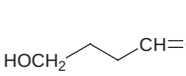
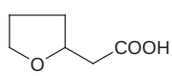
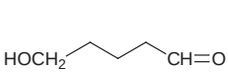
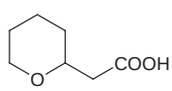
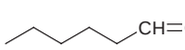
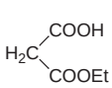
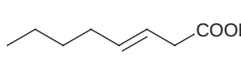
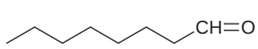
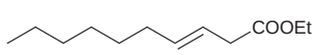
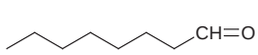
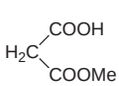
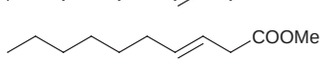
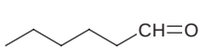
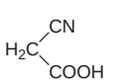
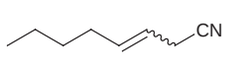
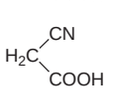
[a] Malonic acid : aldehyde : piperidinium acetate 2 : 1 : 0.02. [b] Distilled product (based on the aldehyde). [c] Ratio determined by GC. [d] DMF must be recently purified. Commercial solvent without purification gave equal yield but reduced selectivity (ratio β,γ : α,β 90 : 10).

Results and discussion

The condensation of *n*-octanal with malonic acid for the preparation of dec-3-enoic acid was studied as a model, screening a variety of common polar aprotic solvents. The results are listed in Table 1.

As shown in Table 1, at room temperature there is no reaction and decarboxylation was not observed. When the reaction mixture was heated on a steam bath, rapid evolution of carbon dioxide occurred and the reaction was accomplished in four to five hours. A two molar excess of malonic acid was needed to consume all the aldehyde. DMSO and DMF were the solvents giving the best results. (*E*)-Dec-3-enoic acid was obtained in 88% yield and excellent selectivity. The intense infrared absorption of the carbonyl (1710 cm^{-1}) and the *trans* olefin absorption (970 cm^{-1}) strongly suggested the (*E*)-alk-3-enoic acid structure.[21] Additionally in a high resolution ^1H NMR the expanded alkene region analyzes as two doublets of triplets with a coupling constant 15.6 Hz, which unequivocally establishes the *trans* stereochemistry of the double bond.[22] Less than 2% of the (*E*)-dec-2-enoic acid and 0.1% of (*Z*)-dec-3-enoic were present in the distilled reaction product. The purity of the products and

Table 2 Condensation of aldehydes with malonic acid and malonic acid derivatives

Entry	Aldehyde	Reagent	Product	Yield (%)	Ratio β,γ : α,β
a		$CH_2(COOH)_2$		86	98 : 2
b		"		88	98 : 2
c		"		86	98 : 2
d		"		90	98 : 2
e		"		34	
f		"		42	
g		"		64[a]	
h		"		71[a]	
i				80	92 : 8
j		"		82	92 : 8
k				76	90 : 10
l				40	92 : 8[b]
m				35	94 : 6[b]

[a] Results from ref. 23. [b] The alk-3-enenitriles are a mixture of *cis* and *trans* isomers in the ratio 1 : 1 as determined in the ^1H NMR spectra.

the β,γ : α,β ratio of isomers were determined by gas chromatography. The condensation in acetonitrile, mono- and di-glyme gave only 20% of (*E*)-dec-3-enoic acid. This yield is nearly the same as for the condensation in triethanolamine (Linstead modification,[19] entry 6) as well as for the condensation in the absence of solvent (entry 7). Piperidinium acetate has been proved the best catalyst at a level of 1–4 mol% relative to the aldehyde.

The condensation of a variety of aldehydes with malonic acid was then studied under the optimum conditions and the results are summarized in Table 2.

As apparent from Table 2, straight carbon chain aldehydes afforded the corresponding (*E*)-alk-3-enoic acids in very good yield and excellent selectivity (entries a–d).

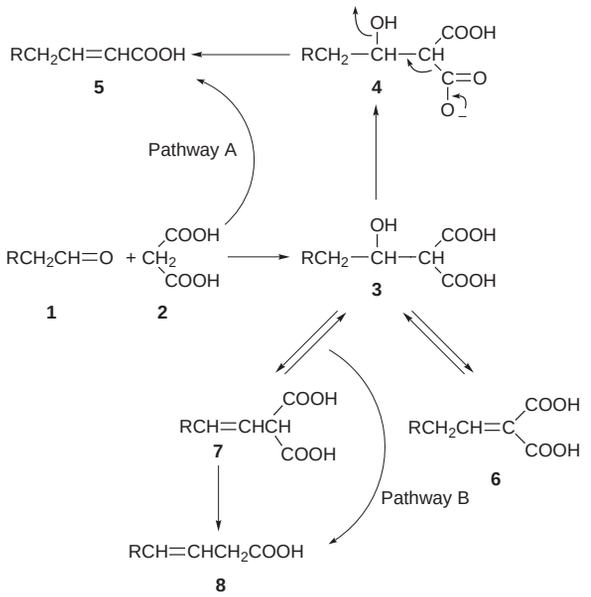
Aromatic aldehydes gave the corresponding phenylmethylenemalonic acid (entries e–f), leaving a substantial amount of the starting material intact. No decarboxylation of the condensation product leading to cinnamic acid was observed under the conditions described herein, as normally happens during condensation in pyridine solution.[19]

Suitably substituted hydroxy aldehydes (entries g–h) gave in high yield (64–71%) the corresponding tetrahydrofuranyl or tetrahydropyranylacetic acids,[23] while in pyridine solution only 9% of the above oxacyclic acetic acids were formed beside the 7-hydroxyhept-2-enoic acid, which was the main reaction product (43%).[24]

It is noteworthy that the 2-alkyl substituted aldehydes, such as 2-methyloctanal or 2-ethylhexanal, did not react in the above conditions and were recovered intact, even if the reaction temperature was raised to 140 °C and a five molar excess of malonic acid was added. Also simple linear ketones, such as the octan-2-one and hexan-3-one or cyclic ketones, such as cyclohexanone and cyclopentanone, are also recovered intact from the reaction mixture.

Although no specific mechanistic studies were performed during the present or the previously reported work,[20] a plausible mechanism for the formation of (*E*)-alk-3-enoic acids as well as for the products produced with a notable differentiation of the Knoevenagel condensation caused by the change of the reaction solvent, is illustrated in Scheme 1.

The generally accepted mechanism for the classical Knoevenagel condensation, proposed by E. J. Corey[25] in 1952, is outlined in Scheme 1 by pathway A. The main feature of this condensation, leading to an (*E*)-alk-2-enoic acid **5**, is the concurrent decarboxylative elimination of water from the hydroxymalonic acid **3**, *via* the anionic intermediate **4**, which is



Scheme 1

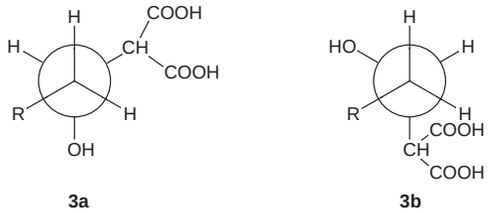


Fig. 1

easily formed in the basic medium (pyridine as solvent) of the reaction. In DMSO or DMF as well as in refluxing xylene, the absence of any basic component avoids the formation of the anionic intermediate **4** and the decarboxylative elimination of water does not occur. On the other hand the presence of piperidinium acetate, a well known dehydration catalyst,[26] catalyzes the dehydration of the intermediate hydroxymalonic acid **3** and leads to the unsaturated malonic acids **6** or **7**. Since the alkylidenemalonic acid **6** is an α,β-unsaturated dicarboxylic acid, it is known that its decarboxylation does not occur under the normal reaction conditions. Thus, if **6** is formed, it isomerises by a reversible hydration–dehydration process to the β,γ-unsaturated dicarboxylic acid **7**, which then decarboxylates to give the alk-3-enoic acid **8**. Indeed, E. J. Corey has synthesized α,β-unsaturated malonic acids by mild hydrolysis of the corresponding diethyl esters and has proved[25] that these acids undergo isomerisation to the β,γ-unsaturated malonic acids and then smoothly decarboxylate to the β,γ-unsaturated acids in high yield.

A conformational analysis of the Newman's projections of the hydroxymalonic acid **3** shows clearly, that between the two possible conformations **3a** and **3b** in the dehydration step (Fig. 1) the conformation **3a**, leading to a *trans* double bond, is by far the more stable.

In the case of the aromatic aldehydes (entries e–f), where there are no protons adjacent to the carbonyl, the dehydration of the intermediate **3** leads only to the corresponding phenylmethylenemalonic acids, which are not decarboxylated and are isolated as the sole reaction products.

Finally, in the case of hydroxy aldehydes (entries g,h) dehydration of the intermediate dihydroxymalonic acid does not take place, because of the presence of a hydroxy group in a suitable position which facilitates the cyclisation to the furano or pyrano derivative, giving after decarboxylation, the corresponding oxacyclic acetic acid.

According to the proposed mechanism, it seems reasonable to assume that the main factor affecting the course of a Knoevenagel condensation is the ease of formation of the anionic intermediate **4** (Scheme 1). Therefore the pyridine as solvent favors the formation of the anionic intermediate **4** and consequently the (*E*)-alk-2-enoic acids are obtained, through pathway A. Under the present reaction conditions (non basic polar aprotic solvents) or xylene as solvent[20] as well as when triethanolamine or other hindered amines[27] are used as solvents, the anionic intermediate **4** is not formed and the reaction follows pathway B, which heavily favors the formation of (*E*)-alk-3-enoic acids. It should be pointed out that, when the reaction follows pathway B, the presence of a dehydration catalyst (piperidinium acetate) is essential for a high yield reaction.

Further attempts were made to obtain derivatives of (*E*)-alk-3-enoic acids, by direct condensation of a straight carbon chain aldehyde with a monoester of malonic acid or cyanoacetic acid. Thus condensation of *n*-octanal with monomethyl or monoethyl malonate gave methyl or ethyl (*E*)-dec-3-enoate in very good yield (76–82%) and good selectivity. In the distilled product 8–10% of the corresponding methyl or ethyl (*E*)-alk-2-enoate was present (entries i–k). Finally the condensation of hexanal and undecanal (entries l–m) with cyanoacetic acid gave the corresponding β,γ-unsaturated nitriles in a yield not exceeding 40%, without stereoselectivity. The ^{1}H NMR analysis of the distilled reaction product showed the presence of the (*E*)-alk-3-enenitrile and the (*Z*)-alk-3-enenitrile in a ratio 1:1. The presence of the alk-2-enenitrile is also evident from the ^{1}H NMR spectrum and it was estimated by gas chromatography to be 6–8%.

In conclusion a very simple, efficient and selective synthesis of (*E*)-alk-3-enoic acids is described by a modified Knoevenagel condensation of a straight carbon chain aldehyde with malonic acid, either in DMSO or DMF solution at 100 °C or in refluxing xylene.[20] The solvent of choice is DMSO because (a) it can be used without a previous tedious purification as is necessary for DMF; (b) the reaction is carried out in a homogeneous medium and at a lower temperature than the reaction effected in refluxing xylene and (c) half of the amount of malonic acid used in refluxing xylene is sufficient for the completion of the reaction.

Finally for the synthesis of (*E*)-alk-3-enoic acid esters, it is preferable to esterify the corresponding acid rather than to effect a direct condensation with a malonic acid half-ester, since in the latter the selectivity of the reaction is lower.

Experimental

DMSO was of commercial normal reagent grade, from freshly opened containers. DMF was carefully purified before use by treatment with 3 Å molecular sieves, shaking with Na_2CO_3 for 24 hours, distillation under nitrogen and storage over 3 Å molecular sieves.[28] All aldehydes were purified before use by distillation and showed minimum purity 98% by GC. Monoethyl and monomethyl malonates were prepared according to the literature.[29] Piperidinium acetate was prepared *in situ* by mixing equivalent quantities of piperidine and acetic acid in 5 ml of the reaction solvent. IR spectra were obtained on a Perkin-Elmer 7200 spectrophotometer in 5% CCl_4 solutions. ^{1}H NMR and ^{13}C spectra were recorded on a Varian Mercury 200 MHz spectrometer using $CDCl_3$ as solvent and TMS as internal standard. Mass spectra were measured on a GC-MS Hewlett-Packard 5890-5970 system. GC analyses were performed on a carbowax 20M 50 m or a SE30 50 m fused silica capillary columns.

(*E*)-Dec-3-enoic acid (typical procedure)

In a one litre round bottomed flask, equipped with a condenser and a bubbler connected to the exit of the condenser, filled with the reaction solvent, a solution of malonic acid (104.0 g, 1.0 mol), piperidinium acetate (from 0.85 g piperidine and 0.6 g

acetic acid, 0.01 mol) and *n*-octanal (64.0 g, 0.5 mol) in DMSO or DMF (500 cm^3), was stirred under nitrogen at room temperature for 20 min. Then the nitrogen was removed and the solution was heated on a steam bath under stirring. A rapid evolution of CO_2 was observed. Heating was maintained until the evolution of CO_2 ceased (4 hours). The solution was cooled at room temperature, poured into 1 l of cold water and extracted with diethyl ether. The combined extracts were washed with water, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by distillation under vacuum using a simple, 30 cm high Vigreux column to give (*E*)-dec-3-enoic acid (73.1 g, 86%); bp 110–112 °C/1 mmHg; ν_{max}/cm^{-1} 1712, 968; δ_H 0.88 (3H, t, J = 6.9), 1.28–1.39 (8H, br s), 1.99–2.08 (2H, m), 3.07 (2H, d, J = 5.4), 5.38 (1H, dt, J_1 = 15.6, J_2 = 5.4), 5.44 (1H, dt, J_1 = 15.6, J_2 = 5.6); δ_C 14.04, 22.06, 28.78, 29.04, 31.67, 32.45, 37.84, 120.60, 135.54, 178.96; *m*/*z* 152 (M − 18, 20%), 110 (35), 96 (20), 69 (69), 55 (92), 43 (100), 41 (89).

(*E*)-Hept-3-enoic acid. The title compound was obtained by the typical procedure from *n*-valeraldehyde (43.0 g, 0.5 mol) as a clear liquid (55.0 g, 86%); bp 80–82 °C/1 mmHg; ν_{max}/cm^{-1} 1712, 968; δ_H 0.88 (3H, t, J = 7.2), 1.27–1.48 (4H, m), 1.98–2.08 (2H, m), 3.06 (2H, d, J = 5.5), 5.45 (1H, dt, J_1 = 15.6, J_2 = 5.4), 5.56 (1H, dt, J_1 = 15.6, J_2 = 5.6); δ_C 13.53, 22.18, 34.46, 37.80, 120.86, 135.21, 178.61; *m*/*z* 110 (M − 18, 38%), 82 (18), 69 (72), 68 (100), 55 (81), 41 (93).

(*E*)-Oct-3-enoic acid. The title compound was obtained by the typical procedure from *n*-hexanal (50.0 g, 0.15 mol) as a yellowish liquid (62.5 g, 88%); bp 90–92 °C/1 mmHg (lit.,[30] 92 °C/1.4 mmHg); ν_{max}/cm^{-1} 1712, 968; δ_H 0.90 (3H, t, J = 6.9), 1.20–1.44 (4H, m), 1.99–2.09 (2H, m), 3.07 (2H, d, J = 5.1), 5.48 (1H, dt, J_1 = 15.7, J_2 = 5.3), 5.56 (1H, dt, J_1 = 15.7, J_2 = 5.1); δ_C 13.85, 22.14, 31.20, 32.10, 37.83, 120.58, 135.47, 179.00; *m*/*z* 124 (M − 18, 28%), 96 (23), 82 (79), 55 (100), 43 (86), 41 (97).

(*E*)-Dodec-3-enoic acid. The title compound was obtained by the typical procedure from *n*-decanal (78.0 g, 0.5 mol) as a yellowish liquid (85.1g, 86%); bp 123–125 °C/1 mmHg; ν_{max}/cm^{-1} 1716, 970; δ_H 0.88 (3H, t, J = 6.9), 1.26–1.39 (12H, br s), 1.98–2.08 (2H, m), 3.05 (2H, d, J = 5.5), 5.37 (1H, dt, J_1 = 15.6, J_2 = 5.4), 5.43 (1H, dt, J_1 = 15.6, J_2 = 5.6); δ_C 14.07, 22.65, 29.08, 29.13, 29.25, 29.42, 31.85, 32.46, 37.84, 120.58, 135.56, 178.94; *m*/*z* 180 (M − 18, 8%), 138 (11), 110 (13), 96 (24), 83 (30), 69 (42), 55 (80), 43 (98), 41 (100).

Benzylidenemalonic acid. The reaction was run according to the typical procedure from benzaldehyde (10.6 g, 0.1 mol). The crude product was treated with hot toluene (50 ml) until dissolution and then cooled at 4 °C for two hours. The white crystals formed were separated by filtration, washed with cold toluene and dried under vacuum at 50 °C to give pure benzylidenemalonic acid as white flakes (6.5 g, 34%); mp 193–195 °C (lit.,[31] 195–196 °C).

***p*-Methoxybenzylidenemalonic acid.** The title compound was prepared as above from *p*-anisaldehyde (13.6 g, 0.1 mol) as white crystals (9.4 g, 42%); mp 184–186 °C (lit.,[32] 186–187 °C).

Ethyl (*E*)-oct-3-enoate. The title compound was prepared by the typical procedure from *n*-hexanal (50.0 g, 0.5 mol) and monoethyl malonate (132.0 g, 1.0 mol) as a clear liquid (136 g, 80%); bp 123–125 °C/1 mmHg (lit.,[17] 93–95 °C/10 mmHg); ν_{max}/cm^{-1} 1739, 1252, 970; δ_H 0.85 (3H, t, J = 6.9), 1.22 (3H, t, J = 6.9), 1.22–1.35 (4H, m), 2.97 (2H, d, J = 5.5), 4.10 (2H, q, J = 6.9), 5.51 (1H, dt, J_1 = 15.4, J_2 = 5.5), 5.56 (1H, dt, J_1 = 15.4, J_2 = 5.4); δ_C 13.82, 14.10, 22.08, 31.23, 32.08, 38.09, 60.44, 121.47, 134.70, 172.22; *m*/*z* 170 (M^+, 4%), 124 (27), 96 (29), 88 (30), 82 (30), 55 (100), 43 (29), 41 (32).

Methyl (*E*)-non-3-enoate. The title compound was prepared by the typical procedure from *n*-heptanal (57.0 g, 0.5 mol) and monomethyl malonate (118.0 g, 1.0 mol) as a clear liquid (129.2 g, 76%); bp 69–71 °C/0.5 mmHg; ν_{max}/cm^{-1} 1745, 1250, 970; δ_H 0.88 (3H, t, J = 7.0), 1.25–1.34 (6H, m), 1.95–2.03 (2H, m), 3.0 (2H, d, J = 5.5), 3.85 (3H, s), 5.45 (2H, m); δ_C 13.80, 14.00, 22.08, 31.20, 31.28, 32.08, 38.09, 122.42, 134.60, 178.15; *m*/*z* 170 (M^+, 3%), 138 (46), 96 (98), 74 (100), 69 (54), 59 (76), 55 (83), 41 (60).

Ethyl (*E*)-dec-3-enoate. The title compound was prepared by the typical procedure from *n*-octanal (64.0 g, 0.5 mol) and monoethyl malonate (132.0 g, 1.0 mol) as a clear liquid (162.3 g, 82%); bp 80–82 °C/0.5 mmHg (lit.,[17] 78–80 °C/0.6 mmHg); ν_{max}/cm^{-1} 1740, 1250, 970; δ_H 0.88 (3H, t, J = 6.9), 1.25 (3H, t, 6.9), 1.28–1.45 (8H, m), 2.0–2.15 (2H, m), 3.02 (2H, d, J = 5.3), 4.15 (2H, q, J = 6.9), 5.50 (1H, dt, J_1 = 15.4, J_2 = 5.3), 5.57 (1H, dt, J_1 = 15.4, J_2 = 5.2); δ_C 13.80, 13.99, 22.45, 28.60, 29.62, 31.70, 32.38, 38.00, 60.10, 121.70, 134.41, 171.64; *m*/*z* 198 (M^+, 2%), 152 (28), 110 (85), 96 (38), 88 (91), 69 (100), 55 (85).

Oct-3-enenitrile. The title compound was prepared by the typical procedure from *n*-hexanal (50.0 g, 0.5 mol) and cyanoacetic acid (51.0 g, 0.6 mol), as a clear liquid (49.2 g, 40%); bp 58–60 °C/1.5 mmHg; ν_{max}/cm^{-1} 2250, 968; δ_H 0.87 (3H, t, J = 6.9), 1.18–1.40 (4H, br s), 2.01–2.14 (2H, m), 5.02–5.41 (1H, *cis* isomer, m), 5.58–5.85 (1H, *trans* isomer, m); *m*/*z* 123 (M^+, 2%), 108 (2), 94 (6), 66 (8), 57 (45), 43 (100), 41 (96).

Tridec-3-enenitrile. The title compound was prepared by the typical procedure from undecanal (85.0 g, 0.5 mol) and cyanoacetic acid (51.0 g, 0.6 mol) as a clear liquid (67.0 g, 35%); bp 105–107 °C/0.5 mmHg; ν_{max}/cm^{-1} 2254, 969; δ_H 0.87 (3H, t, J = 6.8), 1.15–1.30 (14H, m), 2.00–2.15 (2H, m), 3.05–3.15 (2H, m), 5.22–5.41 (1H, *cis* isomer, m), 5.60–5.93 (1H, *trans* isomer, m); *m*/*z* 193 (M^+, 2%), 178 (4), 164 (20), 136 (25), 122 (23), 108 (30), 57 (25), 43 (90), 41 (100).

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