Facile Synthesis of Aliphatic Esters, Malonates and Phenylsulfonyl Esters Using Copper-Catalyzed Addition of Methallyl Grignard Reagent to Activated Cyclopropanes

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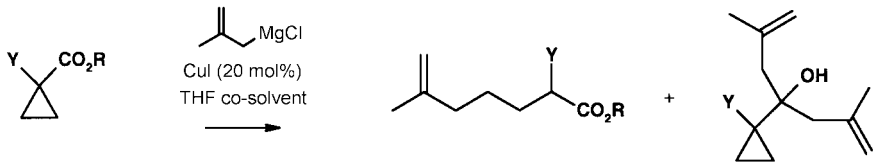
Abstract: Copper-mediated conjugate addition of allylic Grignard reagents to activated cyclopropane derivatives was studied. Unsaturated esters, malonates and phenylsulfonyl esters **2a–d** were synthesized from the respective cyclopropanes **1a–d** and methallylmagnesium chloride.

Key words: cyclopropanes, Grignard reagents, 1,5-addition, copper, esters

Nucleophilic ring opening reactions involving activated cyclopropanes and amines, mercaptans, malonate anions or related Michael donors are well known.[1] Reaction of methallyllithium cuprate, which can be generated from isobutylene with the use of BuLi·TMEDA complex,[2] with 1,1-dimethoxycarbonylcyclopropane provides the ring opened product[3] but requires a large excess of butyllithium which hampers its practical application. Addition of lithiumcuprate reagents to activated cyclopropanes have also been studied in detail in the context of certain natural product syntheses.[4,5] However, reaction of cyclopropane derivatives bearing two geminal alkoxycarbonyl or geminal alkoxycarbonyl and benzenesulfonyl groups with Grignard reagents has received little attention. Some time ago it has been shown that copper chloride-catalyzed addition of alkyl Grignard reagents to 1,1-dialkoxycarbonylcyclopropanes[6] and 1,1-diphenyl-sulfonylcyclopropane[7] occurs with opening of the cyclopropane ring. In the course of ongoing studies in one of our laboratories we were interested in applying activated cyclopropanes as a source of four or five carbon unit [$CH_2CH_2CH_2CO_2R$ or $CH_2CH_2CH(CO_2R)_2$] in the synthesis of higher aliphatic esters or malonates by a "homologous" Michael addition reaction involving Grignard reagents. For our work 1,1-dialkoxycarbonyl, 1-alkoxycarbonyl-1-phenylsulfonyl cyclopropane derivatives **1a–e** (Scheme 1) and methallyl magnesium chloride were chosen.

Treatment of di-*tert*-butyl ester **1a** with methallylmagnesium chloride (2 mol equiv) and CuI·Me_2S (0.4 mol equiv) in THF at −30 °C to −20 °C afforded smoothly the 1,5-addition product **2a** (Table). No traces of the respective 1,2-addition product **3a** could be detected (a sample of **3a** was prepared by reaction of **1a** and the Grignard reagent with no CuI added).

The reaction of the di-*iso*-propyl ester **1b** with the Grignard reagent yielded a mixture of regioisomers **2b** and **3b**. The highest proportion of the required product (94:6) was attained when HMPA (1 mol equiv) was used as a cosolvent and the reaction was carried out at −30 °C to −20 °C for 5 hours and then at room temperature for 15 hours (Table, Entry 2). Eventually, pure compound **2b** was obtained in 51% yield after chromatography. The reaction was slow at temperatures below −40 °C (Table, Entry 3). On the other hand, at higher temperatures the degree of regioselectivity was lower (Table, Entry 4). Replacement of HMPA with DMPU[8] resulted in lowering of the regioselectivity of the reaction (Table, Entry 5).



1a-e

a. Y = CO_2*tert*-Bu, R = *tert*-Bu
b. Y = CO_2*iso*-Pr, R = *iso*-Pr
c. Y = CO_2Et, R = Et
d. Y = SO_2Ph, R = *tert*-Bu

2a-d

a. Y = CO_2*tert*-Bu, R = *tert*-Bu
b. Y = CO_2*iso*-Pr, R = *iso*-Pr
c. Y = CO_2Et, R = Et
d. Y = SO_2Ph, R = *tert*-Bu
e. Y = CO_2Me, R = Me
f. Y = H, R = *tert*-Bu
g. Y = H, R = *iso*-Pr
h. Y = H, R = Et

3a-d

a. Y = CO_2*tert*-Bu
b. Y = CO_2*iso*-Pr
c. Y = CO_2Et
d. Y = SO_2Ph

Scheme 1

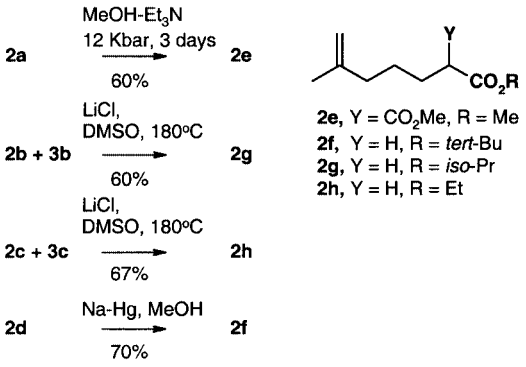
Table Cu-Catalyzed Reaction of Methallyl Grignard Reagent with Cyclopropane Derivatives

Entry	Substrate	Cosolvent	Temp. (°C)/Time	Conversion (%)	Product Ratio **2**/**3**[a]	Yield (%)	Product	Yield (%)
1	**1a**	–	−30 to −20, 5 h, then r.t.	100	100:0	85	**2a**	85
2	**1b**	HMPA	−30 to −20, 5 h, then r.t.	100	94:6	75	**2b**	51
3	**1b**	HMPA	−78 to −40, 20 h	80	87:13	–	–	–
4	**1b**	HMPA	0	100	89:11	–	–	–
5	**1b**	DMPU	−30 to −20, 5 h, then r.t.	100	61:49	–	–	–
6	**1c**	HMPA	−30 to −20, 5 h, then r.t.	100	89:11	72	**2c**	61
7	**1c**	DMPU	−30 to −20, 5 h, then r.t.	100	50:50	–	–	–
8	**1d**	HMPA	−30 to −20, 5 h, then r.t.	ca 50	–	35	**2d**	35

[a] Products ratio determined by GC.

Reactivity of diethyl ester **1c** which is one of the cheapest cyclopropane derivatives, was studied in some detail. A large scale Cu-catalyzed reaction (0.4 mol) of **1c** and methallylmagnesium chloride in the presence of HMPA provided the product in 72% yield as a mixture of **2c** and **3c** in a ratio of 89:11 (Table, Entry 6). Compound **2c** was isolated in pure form by chromatography (61% yield from **1c**). However, for synthesis of ester **2h**, the mixture of **2c** and **3c** could be conveniently used without separation (vide infra). It is noteworthy that replacement of HMPA with DMPU resulted in diminishing the regioselectivity of the addition reaction (Table, Entry 7). The copper mediated-reaction of methallylmagnesium chloride with phenylsulfonyl derivative **1d** was selective with respect to product **2d** (Table, Entry 8) but slower than the reactions of the diesters discussed above (a sample of **3d** was prepared by reaction of **1d** and the Grignard reagent with no CuI added). It is noteworthy that the reaction of organomagnesium reagent with 6,6-dimethyl-5,7-dioxaspiro[2.5]octane-4,8-dione was impractically slow. The observed relative rates of nucleophilic addition to cyclopropane derivatives **1a−c** are likely to reflect the strain of the cyclopropane ring in these compounds.

We failed in all attempts to transform the di-*tert*-butyl ester **2a** into the corresponding mono-ester or free acid under acidic conditions. On treatment of **2a** with trifluoroacetic acid under the conditions typical for *tert*-butyl ester hydrolysis[9] a complex mixture of products was formed, presumably due to participation of the ethylenic bond. On other hand, **2a** resisted alkaline hydrolysis under various conditions including those applied to very hindered esters.[10] On treatment with methanol and Et_3N under high pressure[11] (12 Kbar) **2a** gave the corresponding dimethyl ester **2e** (Scheme 2); however the reaction was too slow for preparative purposes (60% conversion after 3 days). Similarly, acid-catalyzed hydrolysis of *tert*-butyl ester **2f** (prepared as described below) failed to afford the corresponding acid.



Scheme 2

Dealkoxycarbonylation of diisopropyl esters **2b** using the Krapcho procedure[12] followed by distillation afforded the monoester **2g** in 60% yield. Reduction of sulfone **2d** with sodium amalgam afforded compound **2f** in 70% yield. In large scale preparation of the mono ester **2h**, the crude mixture of **2c** and **3c** (89:11 ratio) was subjected to the dealkoxycarbonylation reaction and the product was purified by distillation (**2h** was obtained in a 48% yield from **1c**).

In conclusion, copper-mediated 1,5-(homo)conjugate addition reaction of organomagnesium reagent to 1,1-dialkoxycarbonylcyclopopane derivatives was examined with respect to effect of the alkyl groups. Economic method for the preparation of malonates **2a−d** and esters **2e**−**g** was developed.

Melting points were determined on a Kofler hot-stage melting point apparatus. ^1H and ^{13}C NMR spectra were taken in $CDCl_3$ on a Varian Gemini 200 MHz spectrometer; chemical shifts are given as δ values (ppm); DEPT sequence was used for assignments of multiplicities in ^{13}C NMR. Mass spectra were determined at an ionizing voltage of 70 eV. GC analyses were conducted using Shimadzu apparatus, SE 30 column, initial temp. 140 °C with programmed change of temperature 15 °C/min. Commercial grade magnesium

turnings were used. Air-sensitive reactions were performed in oven- or flame-dried glassware under argon.

Preparation of a Stock Solution of Methallylmagnesium Chloride

To a stirred suspension of Mg turnings (100 g, 4.17 gram atom) in THF (1 L) under argon was added 3-chloro-2-methylpropane (98%, Fluka, 138.7g, 1.53 mol) dropwise at 0 °C. The solution was stirred at 0 °C for 3 h and then allowed to warm to r.t. After 1 h, the upper layer was transferred by a cannula into a reaction vessel or a storage flask.

Addition of Methallylmagnesium Chloride to Activated Cyclopropanes 1a−e

To a solution of methallylmagnesium chloride in THF (1.0 M, 2.0 mL) was added a solution of CuI (74.8 mg) in Me_2S (0.6 mL) at −30 °C followed by HMPA (0.36 mL, 2.0 mmol) and 1,1-diactivated cyclopropane **1** (1.0 mmol) in THF (0.5 mL). The mixture was stirred at −30 °C to −20 °C for 5 h, and then set aside at r.t. for 15 h. The reaction was quenched with aq NH_4Cl solution (5 mL), brought to pH 8 with aq 25% NH_4OH and the product was extracted with Et_2O (3 × 15 mL). The extract was dried (Na_2SO_4), the solvent evaporated and the residue was distilled. Yields and regioisomers ratios are given in the Table. The regioisomers were separated by chromatography on a silica gel column. Analytical samples were purified by distillation in a Kugelrohr apparatus.

2-(4-Methylpent-4-enyl)malonic Acid *tert*-Butyl Ester (2a)

Bp 112−114 °C/0.2 mbar.

IR (film): ν = 1746 (C=O), 1729 (C=O), 1649 (C=C) cm^{-1}.

^1H NMR: δ = 1.45 (s, 18 H), 1.69 (s, 3 H), 1.72−1.88 (m, 4 H), 2.03 (t, *J* = 7.4 Hz, 2 H), 3.13 (t, *J* = 7.5 Hz, 1H), 4.54−4.75 (m, 2 H).

^{13}C NMR: δ = 22.2, 25.1, 27.9, 28.1, 37.4, 53.8, 81.2, 110.2, 145.1, 168.9.

MS: *m*/*z* (%) = 242 (M^+, 0.5), 186 (14), 169 (22), 151 (16), 82 (66), 57 (100).

MS [LSIMS(+), NBA]: *m*/*z* = 321 (14, [M + Na^+]).

Anal. calcd for $C_{17}H_{30}O_4$ (298.4): C, 68.42; H, 10.13. Found: C, 68.19; H, 10.08.

2-(4-Methylpent-4-enyl)malonic Acid *iso*-Propyl Ester (2b)

Bp 155 °C/1.0 mbar (Kugelrohr).

IR (film): ν = 1747 (C=O), 1730 (C=O), 1650 (C=C) cm^{-1}.

^1H NMR: δ = 1.22 (d, *J* = 6.2 Hz, 12 H), 1.38−1.56 (m, 2 H), 1.69 (s, 3 H), 1.78−1.93 (m, 2 H), 2.03 (t, *J* = 7.5 Hz, 2 H), 3.25 (t, *J* = 7.5 Hz, 1 H), 4.68 (m, 2 H), 5.04 (sept, *J* = 6.2 Hz, 2 H).

^{13}C NMR: δ = 21.6, 21.7, 22.2, 25.2, 28.2, 37.3, 52.3, 68.6, 110.3, 145.0, 169.0.

MS: *m*/*z* (%) = 270 (M^+, 1), 188 (13),151 (24), 146 (10), 104 (10), 82 (100), 43 (40).

HRMS: *m*/*z* Calcd for $C_{15}H_{26}O_4$: 270.1831. Found: 270.1805.

2-(4-Methylpent-4-enyl)malonic Acid Ethyl Ester (2c)

Bp 150 °C/1.0 mbar (Kugelrohr).

IR (film): ν = 1734 (C=O), 1752 (C=O), 1649 (C=C) cm^{-1}.

^1H NMR: δ = 1.25 (t, *J* = 7.1 Hz, 6H), 1.35−1.55 (m, 2 H), 1.68 (s, 3 H), 1.80−1.93 (m, 2 H), 2.02 (t, *J* = 7.5 Hz, 2 H), 3.30 (t, *J* = 7.5 Hz, 1 H), 4.15 (q, *J* = 7.1 Hz, 4 H), 4.70 (m, 2 H).

^{13}C NMR: δ = 14.17, 22.2, 25.1, 28.2, 37.2, 51.9, 61.19, 110.3, 144.8, 169.3.

MS: *m*/*z* (%) = 242 (M^+, 1), 197 (26), 173 (43), 160 (100), 151 (65), 82 (57).

MS [LSIMS(+), NBA]: *m*/*z* = 243 (39, [M + H^+]).

Anal. calcd for $C_{13}H_{22}O_4$ (242.3): C, 64.44; H, 9.15. Found: C, 64.50; H, 9.16.

2-Benzenesulfonyl-6-methylhept-6-enoic Acid *tert*-Butyl Ester (2d)

Mp 65 °C (EtOH).

IR (film): ν = 1724 (C=O), 1648 (C=C), 1142 cm^{-1}.

^1H NMR: δ = 1.34 (s, 9 H), 1.40−1.54 (m, 2 H), 1.66 (s, 3 H), 1.80−2.60 (m, 4 H), 3.85 (dd, *J* = 10.6 Hz, 4.7, 1 H), 4.65 (m, 2 H), 7.50−7.75 (m, 3 H), 7.85−7.93 (m, 2 H).

^{13}C NMR: δ = 22.1, 24.7, 26.3, 27.6, 37.0, 71.2, 83.2, 110.7, 128.8, 129.3, 133.9, 137.4, 144.3, 164.7.

MS: *m*/*z* (%) = 282 ([M^+ − 58], 38), 265 (20), 140 (100), 123 (68), 122 (27), 95 (48), 82 (95), 57 (72), 41 (27).

MS [LSIMS(+), NBA]: *m*/*z* = 699 (14, [2 M + Na^+]), 361 (50, [M + Na^+]), 339 (2, [M + H^+]).

Anal. calcd for $C_{18}H_{26}O_4S$ (338.5): C, 63.88; H, 7.74; S, 9.47. Found: C, 63.74; H, 7.84; S, 9.60.

1-[1-Hydroxy-3-methyl-1-(2-methylallyl)but-3-enyl]cyclopropanecarboxylic Acid *tert*-Butyl Ester (3a)

A sample of **3a** was prepared in the reaction of **1a** with methallyl-Grignard reagent with no CuI added; bp 90−91 °C/0.1 mbar.

IR (film): ν = 1713 (C=O), 1642 (C=C) cm^{-1}.

^1H NMR: δ = 0.98 (4 H, m), 1.42 (s, 9 H), 1.82 (m, 6 H), 2.07 (s, 1 H), 2.45 (d, *J* = 13.3 Hz, 2 H), 2.78 (d, *J* = 13.3, 2 H), 4.71 (m, 2 H), 4.88 (m, 2 H).

^{13}C NMR: δ = 12.5, 24.8, 28.04, 30.33, 46.8, 71.2, 80.2, 115.0, 143.4, 173.0.

MS: *m*/*z* (%) = 207 (2), 170 (10), 169 (100), 152 (8), 151 (83), 123 (3), 114 (5), 113 (81), 95 (8), 83 (34), 77 (4), 69 (7), 57 (64), 55 (23), 53 (4), 43 (5), 41 (27), 39 (10).

LSIMS HRMS (electrospray technique): *m*/*z* Calcd for $C_{17}H_{28}O_3Na$: 303.1931. Found: 303.1931.

1-[1-Hydroxy-3-methyl-1-(2-methylallyl)but-3-enyl]cyclopropanecarboxylic Acid *iso*-Propyl Ester (3b)

IR (film): ν = 1713 (C=O), 1642 (C=C) cm^{-1}.

^1H NMR: δ = 1.03 (4 H, m), 1.19 (d, *J* = 6.3 Hz, 6 H), 1.81 (m, 6 H), 2.08 (s, 1 H), 2.47 (d, *J* = 13.0 Hz, 2 H), 2.77 (d, *J* = 13.0, 2 H), 4.73 (m, 2 H), 4.88 (m, 2 H), 4.98 (sept, *J* = 6.3 Hz, 1 H).

^{13}C NMR: δ = 12.5, 21.7, 24.8, 29.9, 46.8, 67.4, 71.2, 115.1, 143.4, 173.3.

MS: *m*/*z* (%) = 211 (27), 169 (60), 114 (6), 113 (100), 95 (9), 83 (34), 69 (8), 55 (23), 43 (15), 41 (14), 39 (6).

MS [LSIMS(+), NBA]: *m*/*z* = 267 ([M + H^+]).

HRMS: *m*/*z* Calcd for (M + H^+) $C_{16}H_{27}O_3$: 267.1960. Found: 267.1957.

1-[1-Hydroxy-3-methyl-1-(2-methylallyl)but-3-enyl]cyclopropanecarboxylic Acid Ethyl Ester (3c)

Bp 82−84 °C/0.1 mbar.

IR (film): ν = 1718 (C=O), 1642 (C=C) cm^{-1}.

^1H NMR: δ = 1.05 (m, 4 H), 1.21 (t, *J* = 7.1 Hz, 3 H), 1.81 (m, 6 H), 2.06 (s, 1 H), 2.47 (d, *J* = 13.3 Hz, 2 H), 2.77 (d, *J* = 13.3 Hz, 2 H), 4.07 (q, *J* = 7.1 Hz, 2 H), 4.70 (m, 2 H), 4.87 (m, 2 H).

^{13}C NMR: δ = 12.5, 14.16, 24.7, 29.8, 46.8, 60.1, 71.2, 115.1, 143.3, 173.8.

MS: *m*/*z* (%) = 207 (2), 198 (8), 197 (67), 152 (5), 151 (48), 141 (100), 123 (4), 113 (29), 95 (5), 83 (27), 69 (8), 55 (18), 53 (3), 43 (2), 41 (8), 39 (6).

LSIMS HRMS (electrospray technique): *m/z* Calcd for $(C_{15}H_{24}O_3Na)^+$: 275.1618. Found: 275.1599.

4-(1-Benzenesulfonylcyclopropyl)-2,6-dimethylhepta-1,6-dien-4-ol (3d)
Mp 86 °C.

IR (film): ν = 1140, 1285, 1640, 3480 cm^{-1}.

^1H NMR: δ = 1.30 (m, 4 H), 1.82 (s, 6 H), 2.38 (s, 1 H), 2.44 (d, *J* = 13.5 Hz, 2 H), 2.64 (d, *J* = 13.5, 2 H), 4.71 (m, 2 H), 4.94 (m, 2 H), 7.58 (m, 3 H), 7.92 (m, 2 H).

^{13}C NMR: δ = 10.5, 25.1, 29.7, 45.9, 71.5, 116.2, 128.9, 129.1, 133.4, 140.9, 142.6.

MS: *m/z* (%) = 265 (22), 210 (11), 209 (100), 141 (9), 117 (8), 105 (39), 77 (16).

MS [LSIMS(+), NBA]: *m/z* = 343 (30, $[M + Na^+]$), 321 (2, $[M + H^+]$).

HRMS: *m/z* Calcd for $(M + Na^+)$ $C_{18}H_{24}O_3NaS$: 343.1344. Found: 343.1364.

2-(4-Methylpent-4-enyl)malonic Acid Methyl Ester (2e)
A solution of **2a** (0.238 g, 0.78 mmol) in MeOH (4.0 mL) containing Et_3N (0.55 mL, 3.9 mmol) was kept under pressure 12 kbar for 3 d. The solvent was evaporated and the residue was chromatographed on silica gel (10 g, hexane/EtOAc, 20:1) to give **2e** (0.975 g, 65%); bp 150 °C/4.0 mbar (Kugelrohr).

IR (film): ν = 1737 (C=O), 1754 (C=O), 1649 (C=C) cm^{-1}.

^1H NMR: δ = 1.35−1.51 (m, 2 H), 1.68 (s, 3 H), 1.80−1.95 (m, 2 H), 2.02 (t, *J* = 7.5 Hz, 2 H), 3.36 (t, *J* = 7.8 Hz, 1 H), 3.72 (s, 6 H), 4.67 (m, 2 H).

^{13}C NMR: δ = 22.1, 25.1, 28.3, 37.2, 51.5, 52.4, 110.4, 114.8, 169.8.

MS: *m/z* (%) = 151 (68), 82 (100).

MS [LSIMS(+), NBA9: *m/z* = 215 (8, $[M + H^+]$), 214 (6).

HRMS: *m/z* Calcd for $C_{11}H_{18}O_4$: 214.1205. Found: 214.1205.

6-Methyl-6-heptenoic Acid *tert*-Butyl Ester (2f)
To a solution of sulfone **2d** (220 mg, 0.65 mmol) in MeOH (6.5 mL) were added Na_2HPO_4 (0.369 g, 2.6 mmol) and 5% sodium amalgam (0.975 g) at 0 °C. The mixture was stirred at r.t. for 1 h and then poured into H_2O. The product was extracted with Et_2O (3 × 15 mL). The extract was evaporated and the residue was chromatographed on silica gel (6 g, hexane/EtOAc, 9:1); yield: 89.0 mg (70%); bp 110 °C/5.0 mbar (Kugelrohr).

IR (film): ν = 1732 (C=O), 1650 (C=C) cm^{-1}.

^1H NMR: δ = 1.48 (s, 9 H), 1.40−1.70 (m, 4 H), 1.73 (s, 3 H), 2.05 (t, *J* = 7.4 Hz, 2 H), 2.26 (t, *J* = 7.4 Hz, 2 H), 4.67 (m, 2 H).

^{13}C NMR: δ = 22.4, 24.8, 27.0, 28.1, 35.5, 37.5, 79.9, 109.9, 145.5, 173.0.

MS: *m/z* (%) = 142 ($[M - 56]^+$, (28), 125 (32), 124 (22), 97 (13), 82 (56), 57 (100), 55 (22), 41 (22), 39 (7).

HRMS: *m/z* Calcd for $(M - 56)^+$ $C_8H_{14}O_2$: 142.0994. Found: 142.0986.

Dealkoxycarbonylation of 2b,c; General Procedure[12]
To a solution of LiCl (1.1 g, 24.9 mmol) in DMSO (14.0 mL) were added H_2O (0.15 mL, 8.3 mmol) and the respective malonate (8.3 mmol). The mixture was heated at 150−180 °C for 10 h to 12 h. Then the product and DMSO was distilled off (the fractions distilling below 180 °C were collected). The distillate was diluted with H_2O (15 mL), the organic layer separated and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with H_2O (3 × 20 mL) and the solvent was evaporated. The residue was distilled in a Kugelrohr apparatus.

6-Methyl-6-heptenoic Acid *iso*-Propyl Ester (2g)
Yield: 60%; bp 140 °C/80 mbar (Kugelrohr).

IR (film): ν = 1732 (C=O), 1650 (C=C) cm^{-1}.

^1H NMR: δ = 1.18 (d, *J* = 6.3, 6 H), 1.36−1.65 (m, 4 H), 1.66 (s, 3 H), 1.98 (t, *J* = 7.1 Hz, 2 H), 2.24 (t, *J* = 7.5 Hz, 2 H), 4.64 (m, 2 H), 4.96 (sept, *J* = 6.3 Hz, 1 H).

^{13}C NMR: δ = 21.8, 22.2, 24.6, 26.9, 34.4, 37.3, 67.2, 109.9, 145.3, 173.1.

MS: *m/z* (%) = 184 (M^+, 2), 141 (10), 125 (22), 124 (17), 97 (15), 95 (11), 87 (10), 83 (18), 82 (100), 69 (19), 67 (13), 56 (19), 55 (30), 43 (23), 41 (27), 39 (12).

HRMS: *m/z* Calcd for $C_{11}H_{20}O_2$: 184.1463. Found: 184.1467.

Ethyl 6-Methylhept-6-enoate (2h)
Yield: 67%; bp 80−82 °C/5.0 mbar.

IR (film): ν = 1737 (C=O), 1650 (C=C) cm^{-1}.

^1H NMR: δ = 1.23 (t, *J* = 7.2 Hz, 3 H), 1.36−1.65 (m, 4 H), 1.69 (s, 3 H), 2.01 (t, *J* = 7.0 Hz, 2 H), 2.29 (t, *J* = 7.2 Hz, 2 H), 4.10 (q, *J* = 7.2 Hz, 2 H), 4.67 (m, 2 H).

^{13}C NMR: δ = 14.2, 22.2, 24.5, 27.0, 34.2, 37.3, 60.12.2, 110.0, 145.4, 173.7;

MS: *m/z* (%) = 170 (M^+, 11), 124 (20), 82 (100), 55 (34), 41 (26).

HRMS: *m/z* Calcd for $C_{10}H_{18}O_2$: 170.1307. Found: 170.1288.

Ethyl 6-Methylhept-6-enoate 2h from 1c
To a solution of methallylmagnesium chloride in THF (prepared as above, 1 L) cooled to −30 °C was added a solution of CuI (30.0 g, 0.16 mol) in Me_2S (250 mL). The mixture was stirred at − 30 °C for 30 min and then HMPA (125 mL, 0.70 mol) was added followed by 1,1-diethoxycarbonylcyclopropane (**1c**; 73.0 g, 0.39 mol). The mixture was maintained at −30 °C to −20 °C for 5 h and then it was set aside at r.t. for 15 h. Sat. aq of NH_4Cl brought to pH 8 with 25% aq ammonia (500 mL) carefully added. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 300 mL). Combined organic solutions were washed with aq sat. NH_4Cl and brine, and dried. The solvent was evaporated and the residue was distilled from an oil bath collecting the fraction at 130−135 °C/1 mbar (bath temp. 170 °C). Product consisting of a mixture **2c** and **3c** (67.0 g, **2c**/**3c** = 89:11 by GC, 72% total yield) was obtained. A sample of this mixture (1 g) was chromatographed on a silica gel column (100 g, hexane/EtOAc, 9:1) to give **2c** (0.85 g, 61%). A mixture **2c** and **3c** (50.0 g, 0.21 mol), prepared as described above, was dissolved in DMSO (330 mL). LiCl (25.5 g, 0.60 mol) and H_2O (3.7 mL, 0.2 mol) were added and the mixture was heated at 175−178 °C for 6 h. After cooling, the mixture was poured into H_2O and ice (400 mL) and the product was extracted with Et_2O (3 × 250 mL). Combined organic extracts were dried and the solvent was evaporated. The residue was distilled collecting the fraction at 80 °C/5 mbar (bath temp. 115 °C); yield: 23.8 g (67%); 99.5% pure by GC.

2-Methylethyl 6-Methylhept-6-enoate (2g)
Conjugate addition reaction was carried out in an analogous manner as that described above using Mg (5 g), methallyl chloride (6.2 g, 0.68 mol), THF (45 mL), CuI (1.0 g, 5.25 mmol), Me_2S (8 mL) and **1b** (3.3 g, 0.016 mol). The product was distilled collecting the fraction at 140−145 °C/1 mbar (bath temp. 170 °C). A mixture of **2b** and **3b** was obtained (3.0 g) in 70% yield in a ratio of 93:7 as determined by GC. Compound **2b** (0.137 g, 51%) colud be separated by chromatography of a sample of the mixture (0.208 g) on a silica gel column (25 g) using hexane/EtOAc (9:1) as eluent. A mixture of **2b** and **3b** (2.4 g), LiCl (1.65 g), H_2O (0.27 g) and DMSO (15 mL) was heated at 180 °C for 12 h. The product was isolated in an analogous way as in the experiment described above. Distillation at 140 °C/80 mbar gave ester **2g** (0.92 g, 60%, 95% pure by GC).

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