Methyl Homologues of Methyl Jasmonate and Methyl Dihydrojasmonate (*Hedione*®) from Sorbyl Alcohol

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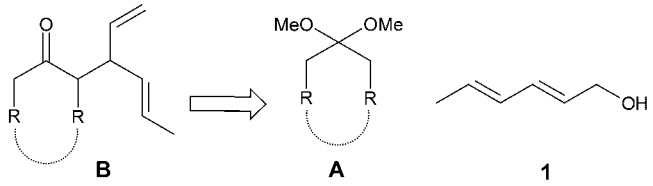
Dedicated to *Günther Ohloff* on the occasion of his 80th birthday

Treatment of cycloalkanone dimethyl acetals **3**–**6** with sorbyl alcohol (=(2*E*,4*E*)-hexa-2,4-dien-1-ol; **1**) in the presence of acids afforded the novel cycloalkenones **8**, **9**, **11**, and **13** *via* a domino reaction (*Claisen* rearrangement with intramolecular ene reaction and *retro*-ene reaction). Cyclopentenone **8** was readily transformed into **14** and **15**, methyl homologues of racemic methyl jasmonate (**16**) and methyl dihydrojasmonate (= *Hedione*®; **17**), respectively. The organoleptic properties of **14** and **15** are also discussed.

1. Introduction. – As part of a screening program comprising the synthesis of new odorant compounds, we decided to study the acid-catalyzed reaction of sorbyl alcohol[1]) (**1**) with dimethyl acetals of general structure **A**, thus offering potential access to dienones **B** *via Claisen* rearrangement[2]) (*Scheme 1*).

Scheme 1

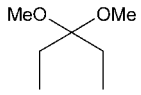
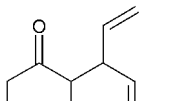
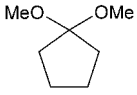
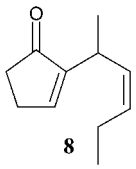
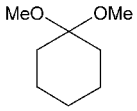
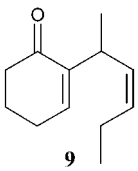
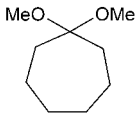
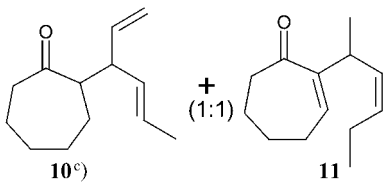
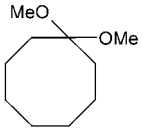
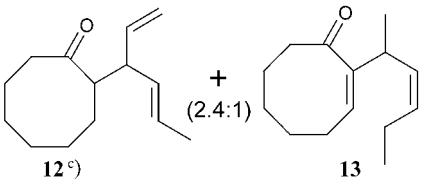


2. Results and Discussion. – 2.1. *Acid-Catalyzed Reaction of* **1** *with* **2**–**6**. Dimethyl acetals **2**–**6** (3 mol-equiv.), readily available from corresponding ketones by a standard acetalization procedure [1], were heated individually with **1** (1 mol-equiv.) in the presence of a catalytic amount of malonic acid (0.01 mol-equiv.)[3]) in an *Inox* autoclave at 200° during 48 h. Cooling of resulting product mixtures to room temperature was followed by bulb-to-bulb distillation *in vacuo*, whereby the compounds **7**–**13** (see

[1]) Sorbyl alcohol is the trivial name for (2*E*,4*E*)-hexa-2,4-dien-1-ol.
[2]) For the same strategy applied to prop-2-en-1-ol, see [1].
[3]) Other *Brønsted* acids such as, *e.g.*, citric acid, TsOH, and H_2SO_4 could also be employed as catalyst.

Table) were isolated and spectroscopically characterized[4]). For *Entries 4* and *5*, preparative GC was necessary to separate the mixtures **10**/**11** and **12**/**13**.

Table. *Acid-Catalyzed Reaction of Sorbyl Alcohol* (**1**) *with Dimethyl Acetals* **2**–**6**[a])

Entry	Substrate	Product(s)	Yield [%][b])
1	 **2**	 **7**[c])	47
2	 **3**	 **8**	73
3	 **4**	 **9**	68
4	 **5**	 **10**[c]) **11**	83
5	 **6**	 **12**[c]) **13**	68

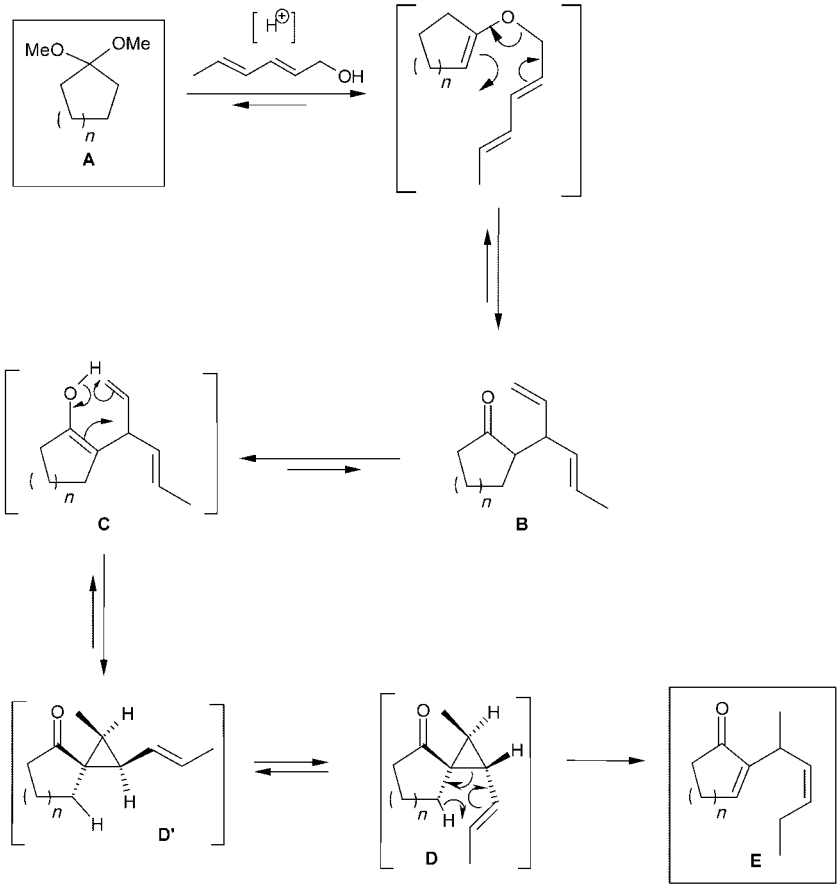
[a]) Reaction conditions: substrate (3 mol-equiv.), **1** (1 mol-equiv.), malonic acid (0.01 mol-equiv.), 200°, 48 h.
[b]) Isolated yield based on **1**. [c]) 2:1 Diastereoisomer mixture.

As can be seen from the *Table*, the acyclic substrate **2** gave only the expected *Claisen* rearrangement product **7**, as a 2:1 diastereoisomer mixture in 47% yield (*Entry 1*)[5]). In contrast, the cyclic substrates **3**–**6** afforded cycloalkenone **E**, either

[4]) All chiral compounds reported in this work are racemic and were fully characterized, see *Exper. Part*.
[5]) Despite this only moderate yield, no other compound (>5%) was detected by GC in the crude product mixture.

exclusively or as one of the principal products. Thus, **3** and **4** afforded **8** and **9** in 73% and 68% yield, respectively (*Entries 2* and *3*), whereas **5** and **6** afforded mixtures of the dienone **B** and the corresponding cycloalkenone **E**, *i.e.*, **10**/**11** 1:1 and **12**/**13** 2.4:1 in 83% and 68% yield, respectively (*Entries 4* and *5*). As shown in *Scheme 2*, the formation of the (*Z*)-configured **E** can be rationalized by invoking a domino reaction [2] in which the enol tautomer **C** of the initially formed *Claisen*-rearrangement product **B** undergoes an intramolecular ene reaction followed by a 1,5-H transfer (*retro*-ene reaction) of the intermediate cyclopropyl ketone **D**[6]). It is important to note that the stereoselectivity of the conversion of **C** to **D** and/or **D′** has no influence on the formation of **E**, due to the known epimerization (**D** ⇌ **D′**) of these systems [4]. The difference in behavior between **2** and **3**–**6** is almost certainly due to the (*Z*)-configuration of **C**, which favors the transition state of the subsequent ene reaction. However, in contrast to *Entries 2* and *3*, the requisite transition-state geometry in

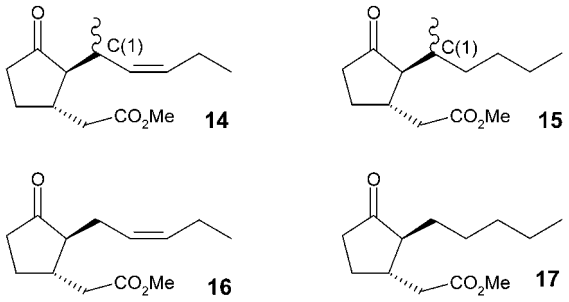
Scheme 2. *Mechanistic Proposal for the Formation of* **E** *from* **A** (*via* **B**)



[6]) For a literature precedent of an analogous domino reaction, see [3].

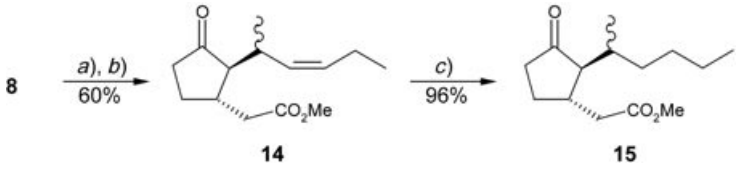
Entries 4 and *5* is progressively harder to attain, due to the higher conformational strain of the seven- and eight-membered rings.

2.2. *Synthesis of* **14** *and* **15** *from* **8**. With **8** in hand, we now had ready access to **14** and **15**, methyl homologues of (±)-methyl jasmonate (**16**)[7]) and (±)-methyl dihydrojasmonate (= *Hedione*[8]); **17**) both well-known jasmine-type odorants [7].



Accordingly, treatment of **8** with dimethyl malonate under basic conditions followed by decarboxylative saponification [8] and subsequent esterification afforded **14** (diastereoisomer mixture at C(1)) in 60% overall yield. Catalytic hydrogenation then furnished **15** (diastereoisomer mixture at C(1)) in 96% yield, in a straightforward manner (*Scheme 3*).

Scheme 3. *Synthesis of* **14** *and* **15** *from* **8**. Compounds **14** and **15** contained *ca.* 5–10% of the corresponding *cis* diastereoisomer.



a) NaOMe, dimethyl malonate, −5°, 5 d. *b*) NaOH, MeOH, then H_2SO_4, MeOH, reflux. *c*) 10% Pd/C, MeOH, H_2.

2.3. *Organoleptic Evaluation of* **14** *and* **15**. The odor of **14** has a floral, jasminic note, is more indolic than *Hedione*®, and has a fruity-raspberry undertone. Compound **15** smells floral, *Hedione*®-like, but with a citrus connotation. It is finer, not as powerful, but more long-lasting than *Hedione*®.

We thank Dr. *Pierre-Alain Blanc* for the organoleptic evaluation, Dr. *Roger L. Snowden* for help in the preparation of the manuscript and *Walter Thommen* for the discussion of the NMR spectra.

Experimental Part

General. Flash chromatography (FC): Silica gel *60*, 35–70 μm. Anal. GC: *Varian STAR 3400*; He as carrier gas; fused-silica capillary columns *SPB-1* and *Supelcowax*®, each 30 m × 0.25 mm i.d. with 0.25-μm film. Prep. GC: *JAS-2000* system, column *HP-Wax*, 10 m × 0.1 μm, 50–250°, 30°/min. ^{1}H- and ^{13}C-NMR Spectra: *Bruker-*

[7]) For the isolation of (−)-methyl jasmonate from jasmine oil, see [5]; for synthetic work, see [6].

[8]) Registered trade name of *Firmenich SA*.

DPX-400 or *AV-500* spectrometers; δ in ppm downfield from $SiMe_4$, J in Hz. GC-MS: *Hewlett-Packard-5890* or *-6890* system equipped with a capillary column (30 m × 0.25 μm i.d.), coupled with a *Hewlett-Packard MSD-5972* or *-5973* quadrupole mass spectrometer; electron energy *ca.* 70 eV; in *m/z* (rel. int. in % of the base peak).

1. *Dimethyl Acetals* **2**–**6**: *General Procedure.* To a stirred soln. of the ketone (2 mol), trimethyl orthoformate (5 mol), and MeOH (700 ml), TsOH (500 mg) was added at r.t. After 4 days, the mixture was poured onto ice, worked up with Et_2O, and washed with sat. $NaHCO_3$ soln. and brine, then distilled.

3,3-Dimethoxypentane (**2**) [9]: 115 g (63%). B.p. 120–124°. ^{1}H-NMR: 0.82 (*t*, *J* = 7.3, 6 H); 1.60 (*q*, *J* = 7.3, 4 H); 3.15 (*s*, 6 H). MS: 144 (< 0.5, M^+), 103 (100), 101 (60), 69 (11), 57 (43), 45 (28).

1,1-Dimethoxycyclopentane (**3**) [10]: 172 g (66%). B.p. 138–140°. ^{1}H-NMR: 1.6–1.8 (*m*, 8 H); 3.2 (*s*, 6 H). MS: 130 (1, M^+), 101 (100), 99 (48), 67 (42), 57 (22), 41 (10).

1,1-Dimethoxycyclohexane (**4**) [11]: 199 g (69.4%). B.p. 75–78°/40 mbar. ^{1}H-NMR: 1.35–1.7 (*m*, 10 H); 3.2 (*s*, 6 H). MS: 144 (5, M^+), 113 (45), 101 (100), 81 (31), 55 (13), 43 (11).

1,1-Dimethoxycycloheptane (**5**) [12]: 255 g (74%). B.p. 85–89°/36 mbar. ^{1}H-NMR: 1.55 (br. *s*, 8 H); 1.78 (*m*, 4 H); 3.16 (*s*, 6 H). ^{13}C-NMR: 21.7 (*t*); 29.2 (*t*); 36.1 (*t*); 47.8 (*q*); 104.4 (*s*). MS: 158 (8, M^+), 127 (46), 115 (12), 101 (100), 95 (20), 55 (19).

1,1-Dimethoxycyclooctane (**6**) [13]: 254 g (74%). B.p. 85–89°/36 mbar. ^{1}H-NMR: 1.55 (*s*, 10 H); 1.76 (br. *s*, 4 H); 3.14 (*s*, 6 H). ^{13}C-NMR: 21.3 (*t*); 24.6 (*t*); 28.2 (*t*); 30.3 (*t*); 47.7 (*q*); 103.8 (*s*). MS: 172 (6, M^+), 141 (48), 101 (100), 88 (44), 67 (26), 55 (25), 41 (22).

2. *Acid-Catalyzed Reaction of Sorbyl Alcohol* (**1**) *with the Dimethyl Acetals* **2**–**6**: *General Procedure.* A mixture of **1** (1 mol-equiv.), acetal (3 mol-equiv.), and malonic acid (100 mg) was heated with stirring in an autoclave (*Bergauf*; 100 ml, 100 mbar) to 200° during 48 h. The mixture was then bulb-to-bulb distilled under vacuum.

*(±)-(6*E*)-5-Ethenyl-4-methyloct-6-en-3-one* (**7**): 4 g (47%). B.p. 120°/14 mbar. ^{1}H-NMR: 0.98–1.04 (*m*, 6 H); 1.58–1.69 (*m*, 3 H); 2.33–2.47 (*m*, 2 H); 2.55 (*quint.*, *J* = 8.2, 1 H); 2.9 (*quint.*, *J* = 8.2, 1 H); 4.94–5.07 (*m*, 2 H); 5.22–5.78 (*m*, 3 H). ^{13}C-NMR: 7.49, 7.90 (2*q*); 14.49, 14.54 (2*q*); 18.00 (*q*); 35.59, 35.72 (2*t*); 49.95, 50.21 (2*d*); 50.30 (*d*); 115.07, 115.08 (2*t*); 126.49, 127.30 (2*d*); 130.82, 131.24 (2*d*); 138.58, 139.17 (2*d*); 214.40 (*s*). MS: 166 (2, M^+), 151 (9), 137 (30), 109 (11), 81 (100), 67 (18), 57 (43), 41 (27), 29 (23).

*(±)-2-[(2*Z*)-1-Methylpent-2-enyl]cyclopent-2-en-1-one* (**8**): 6 g (73%). B.p. 98°/16 mbar. ^{1}H-NMR: 0.95 (*t*, *J* = 7.5, 3 H); 1.14 (*d*, *J* = 7.1, 3 H); 1.66–2.659 (*m*, 6 H); 3.5 (*quint.*, *J* = 7.1, 1 H); 5.31 (*dd*, *J* = 10, 10, 1 H); 5.37 (*dt*, *J* = 10, 7, 1 H); 7.3 (*m*, 1 H). ^{13}C-NMR: 14.3 (*q*); 20.4 (*q*); 20.7 (*t*); 26.4 (*t*); 28.3 (*d*); 34.9 (*t*); 131.6 (*d*); 131.8 (*d*); 150.4 (*s*); 156.2 (*d*); 209.0 (*s*).

*(±)-2-[(2*Z*)-1-Methylpent-2-enyl]cyclohex-2-en-1-one* (**9**): 8.5 g (68%). B.p. 108°/13 mbar. ^{1}H-NMR: 0.94 (*t*, *J* = 7.5, 3 H); 1.07 (*d*, *J* = 6.8, 3 H); 1.90–2.45 (*m*, 8 H); 3.7 (*quint.*, *J* = 7.5, 1 H); 5.25 (*dd*, *J* = 10, 10, 1 H); 5.32 (*dt*, *J* = 6.8, 10, 1 H); 6.73 (*m*, 1 H). ^{13}C-NMR: 14.3 (*q*); 20.8 (*t*); 21.1 (*q*); 22.9 (*t*); 26.1 (*t*); 30.3 (*d*); 131.1 (*d*); 133.0 (*d*); 143.5 (*d*); 144.2 (*s*); 198.6 (*s*). MS: 178 (16, M^+), 163 (11), 149 (100), 135 (9), 121 (12), 107 (10), 93 (28), 79 (22), 67 (12), 55 (37), 41 (20).

*(±)-2-[(2*E*)-1-Ethenylbut-2-enyl]cycloheptanone* (**10**) *and (±)-2-[(2*Z*)-1-Methylpent-2-enyl]cyclohept-2-en-1-one* (**11**): 1.60 g (83%). B.p. 130/13 mbar. Separation of the isomers was effected by prep. GC.

Data of **10**[9]): ^{1}H-NMR: 4.95–5.05 (*m*, 2 H); 5.30–5.52 (*m*, 2 H); 5.65–5.80 (1 H). ^{13}C-NMR: major isomer: 18.0 (*q*); 24.8 (*t*); 28.3 (*t*); 28.4 (*t*); 29.5 (*t*); 43.5 (*t*); 49.3 (*d*); 56.8 (*d*); 114.8 (*t*); 127.4 (*d*); 130.2 (*d*); 139.8 (*d*); 215.7 (*s*); minor isomer: 18.0 (*q*); 24.8 (*t*); 28.3 (*t*); 28.4 (*t*); 29.5 (*t*); 43.5 (*t*); 49.5 (*d*); 56.8 (*d*); 115.8 (*t*); 126.3 (*d*); 131.5 (*d*); 138.7 (*d*); 215.5 (*s*). MS: major isomer: 192 (8, M^+); 177 (5), 163 (9), 149 (63), 81 (100), 55 (24), 41 (36); minor isomer: 192 (8, M^+), 177 (5), 193 (9), 149 (62), 81 (100), 55 (22), 41 (33).

Data of **11**: ^{1}H-NMR: 0.93 (*t*, *J* = 7.3, 3 H); 1.06 (*d*, *J* = 7.0, 3 H); 1.65–1.78 (*m*, 4 H); 2.05 (*m*, 2 H); 2.35 (*m*, 2 H); 2.54 (*m*, 2 H); 3.7 (*m*, 1 H); 5.2 (*dd*, *J* = 9.5, 10.5, 1 H); 5.32 (*dt*, *J* = 7.5, 10.5, 1 H); 6.36 (*t*, *J* = 6.4, 1 H). ^{13}C-NMR: 14.3 (*q*); 20.7 (*t*); 21.0 (*q*); 21.6 (*t*); 24.9 (*t*); 27.3 (*t*); 33.3 (*d*); 42.9 (*t*); 131.4 (*d*); 133.1 (*d*); 137.6 (*d*); 206.0 (*s*). MS: 192 (< 0.5, M^+), 178 (1), 177 (5), 163 (100), 135 (19), 121 (15), 107 (19), 93 (35), 79 (37), 67 (25), 55 (32), 41 (35).

*(±)-2-[(2*E*)-1-Ehenylbut-2-enyl]cyclooctanone* (**12**) *and (±)-2-[(2*Z*)-1-Methylpent-2-enyl]cyclooct-2-en-1-one* (**13**): 1.40 g (68%). B.p. 145°/13 mbar. Separation of the isomers was effected by prep. GC.

Data of **12**[9]): Major isomer: ^{1}H-NMR: 5.00–5.07 (*m*, 2 H); 5.23–5.30 (*m*, 1 H); 5.32–5.42 (*m*, 1 H); 5.6–5.68 (*m*, 1 H). ^{13}C-NMR: 18.1 (*q*); 24.8 (*t*); 25.0 (*t*); 25.8 (*t*); 27.8 (*t*); 31.3 (*t*); 43.8 (*t*); 50.5 (*d*); 54.2 (*d*); 115.8 (*t*); 126.4 (*d*); 131.2 (*d*); 139.2 (*d*); 219.5 (*s*). MS: 206 (5, M^+), 191 (2), 177 (5), 163 (10), 149 (29), 135 (5), 121 (5),

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[9]) 3:1-Mixture of diastereoisomers.

107 (10), 93 (11), 81 (100), 67 (11), 55 (23), 41 (30). Minor isomer: ^{1}H-NMR: 4.91–4.97 (*m*, 2 H); 5.22–5.30 (*m*, 1 H); 5.43–5.52 (*m*, 1 H); 5.60–5.68 (*m*, 1 H). ^{13}C-NMR: 18.0 (*q*); 24.8 (*t*); 25.0 (*t*); 25.9 (*t*); 27.8 (*t*); 31.3 (*t*); 43.8 (*t*); 50.5 (*d*); 54.5 (*d*); 114.9 (*t*); 127.3 (*d*); 131 (*d*); 139.4 (*d*); 219.6 (*s*). MS: 206 (7, M^+), 191 (2), 177 (4), 163 (12), 149 (33), 135 (5), 121 (4), 107 (11), 98 (11), 81 (100), 55 (6), 41 (33).

Data of **13**: ^{1}H-NMR: 0.93 (*t*, *J* = 7, 3 H); 1.09 (*d*, *J* = 7, 3 H); 5.12 (br. *dd*, *J* = 11, 11, 1 H); 5.36 (*dt*, *J* = 7, 11, 1 H); 5.75 (*dt*, *J* = 1.3, 7.4, 1 H). ^{13}C-NMR: 14.3 (*q*); 20.0 (*q*); 20.4 (*t*); 22.1 (*t*); 22.8 (*t*); 28.9 (*t*); 29.4 (*t*); 36.3 (*d*); 43.7 (*t*); 129.0 (*d*); 131.8 (*d*); 132.0 (*d*); 142.6 (*s*); 213.6 (*s*). MS: 206 (7, M^+), 191 (8), 177 (100), 163 (28), 149 (20), 135 (19), 121 (22), 107 (32), 93 (53), 81 (58), 67 (42), 55 (71), 41 (67).

(±)-Methyl 2-[(2Z)-1-Methylpent-2-enyl]-3-oxocyclopentaneacetate (**14**). To a cooled (−15°) mixture of dimethyl malonate (50 g, 0.4 mol) and Na (0.17 g, 7 mmol) was added a soln. of **8** (10 g, 61 mmol), dimethyl malonate (7 g), and MeOH (13 ml) with stirring under N_2. After complete addition, the mixture was stirred at −5° for 5 days, then neutralized with AcOH (4 g, 20 mmol), diluted with Et_2O, washed with H_2O, and distilled at 110–120°/0.4 mbar. The distillate (17.8 g, 98%) was then refluxed in H_2O (200 ml) in the presence of KOH (8 g, 143 mmol) for 5 h. After cooling, the mixture was washed with pentane (2 × 100 ml), the aq. soln. acidified with ice/H_2SO_4 and extracted with Et_2O, the Et_2O phase evaporated, and the residue esterified with MeOH (150 ml) and conc. H_2SO_4 soln. (5 ml) at r.t. during 5 days. Then the MeOH was distilled off, the remaining mixture diluted with Et_2O, and the Et_2O soln. washed with brine and distilled: **14** (8.6 g, 60%) as a diastereoisomer mixture. B.p. 170°/0.6 mbar. MS: 238 (25, M^+), 220 (32), 165 (54), 149 (23), 147 (33), 135 (24), 123 (26), 109 (47), 107 (26), 95 (28), 93 (33), 83 (100), 82 (41), 67 (29), 55 (80), 41 (31); the MS of the isomers are identical.

(±)-Methyl 2-(1-Methylpentyl)-3-oxocyclopentaneacetate (**15**). A mixture of **14** (3 g, 12 mmol), 10% Pd/C (50 mg), and MeOH (50 ml) was hydrogenated at r.t. and 1 atm and then filtered. The filtrate was evaporated and the residue purified by FC (heptane/AcOEt 95:5): **15** (1.4 g, 46%) as an isomer mixture. B.p. 150°/0.6 mbar. ^{13}C-NMR: isomer A: 14.1 (*q*); 16.6 (*q*); 22.8 (*t*); 27.4 (*t*); 30.1 (*t*); 32.7 (*d*); 34.2 (*t*); 36.2 (*d*); 39.0 (*t*); 39.5 (*t*); 51.6 (*q*); 58.5 (*d*); 172.6 (*s*); 220.0 (*s*); isomer B: 14.1 (*q*); 16.9 (*q*); 22.8 (*t*); 27.4 (*t*); 30.1 (*t*); 32.9 (*d*); 34.2 (*t*); 34.8 (*d*); 38.6 (*t*); 39.9 (*t*); 51.6 (*q*); 58.5 (*d*); 172.7 (*s*); 219.3 (*s*). MS: 240 (2, M^+), 209 (3), 183 (6), 167 (10), 156 (42), 109 (7), 96 (7), 83 (100), 55 (19), 41 (20); the MS of both isomers are identical.

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