

88. Partial Syntheses of Methyl Dehydrojasmonate and Tuberolactone¹⁾

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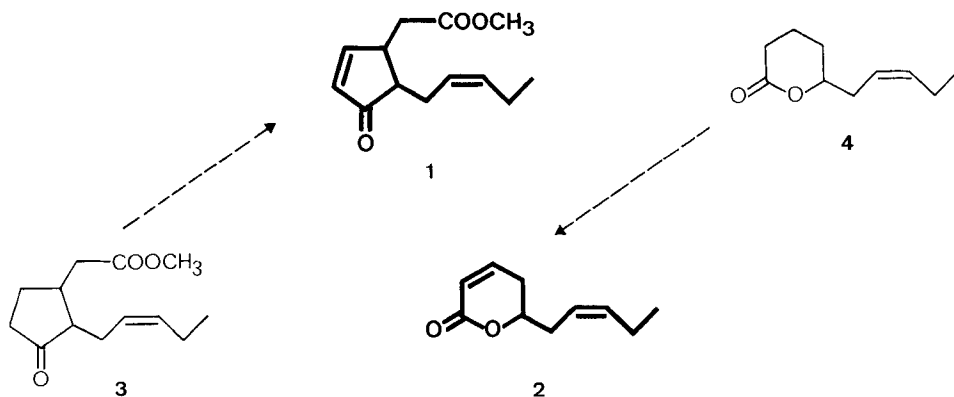
(14.XI.77)

Summary

The natural products methyl dehydrojasmonate (**1**) and tuberolactone (**2**) have been synthesized from methyl jasmonate (**3**) and jasmolactone (**4**) resp., via sulfenylation-sulfoxide pyrolysis.

Recent analytical efforts have led to the identification of the trace constituents methyl-(+) dehydrojasmonate (**1**) in the essential oil of jasmin flowers (*Jasminum grandiflorum* L.) [1], and (-)-tuberolactone (**2**) in tuberose oil [2] from the flowers of *Polyanthes tuberosa* L. Although no pertinent organoleptic data are available, these compounds were assumed to be of special olfactive importance. Moreover, they exhibit close structural relationships to the well known, olfactively interesting com-

Scheme 1



¹⁾ These results were reported by P. Dubs at the Autumn session of the Swiss Chemical Society (Oct. 8, 1977) in Berne.

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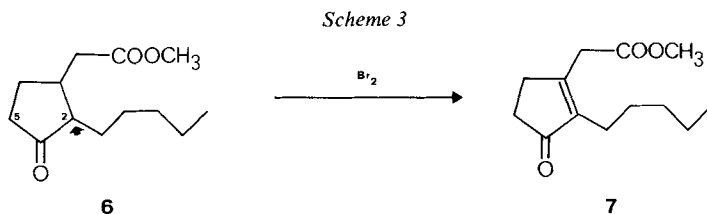
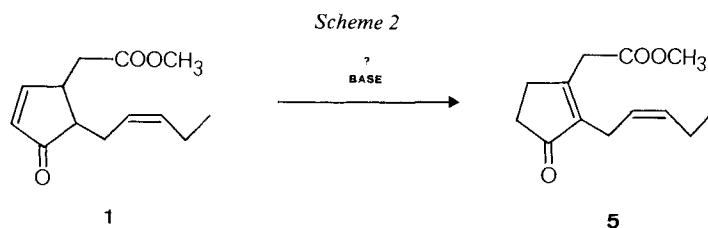
pounds **3** and **4**, found in the same oils: methyl-(–) jasmonate (**3**) in jasmin oil [3], (–)- and (+)- δ -jasmolactone (**4**) in jasmin [4] and tuberose oils [2].

We therefore decided to synthesize compounds **1** and **2**. The obvious structural similarities of **1** and **3** as well as of **2** and **4**, very probably based on biogenetic relationships, prompted us to conceive partial syntheses **3** $\rightarrow$ **1** and **4** $\rightarrow$ **2**. Since both **3** and **4** are synthetically available [5] [6], the problems were reduced to the introduction of an α,β -unsaturation into the cyclopentanone system **3** and the δ -lactone **4**, respectively.

Methyl dehydrojasmonate (1). – The construction of **1** seems to be the more demanding part than the synthesis of **2**. Earlier work had shown that in the closely related field of the prostaglandins, base-induced doublebond isomerizations (conversion of A- to B-prostaglandins) of type **1** $\rightarrow$ **5**, leading to thermodynamically more stable cyclopentenones, occur with great ease [7] (*Scheme 2*). So basic conditions had to be avoided in the final step leading to **1**.

Experiments with the model **6** convinced us that reaction with electrophiles under varied conditions (basic, neutral, acidic), would lead to functionalizations of the 2-position in **6**. Bromination of **6**, e.g. gave **7**; this result is interpreted *via* an attack in the 2-position followed by dehydrobromination (*Scheme 3*).

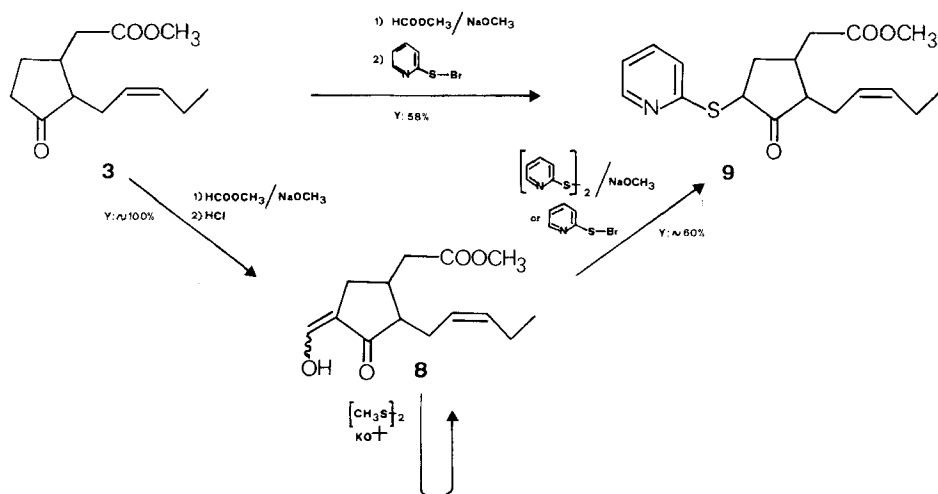
We therefore tried to activate selectively the 5-position of model **6** as well as of methyl jasmonate (**3**). The best results were obtained with the enolized formyl derivative **8**. Our initial experiments towards introduction of a phenylsulfenyl group [8] into **8** failed. Also the reaction of deprotonated **8** in *t*-butyl alcohol, with dimethyl disulfide [9], did not give a thiomethyl derivative. Methyl mercaptide might be too poor a leaving group and we therefore used the more activated 2,2'-dipyridyl disulfide as thiylating agent for **8**. To our surprise the formyl group was lost in this reaction leading directly to the thioether **9** in 60% yield. The final and best way to thioether **9** (58% overall yield) was a one-pot procedure, comprising the direct reaction of the intermediate anion of **8** in the thiylation step with 2-pyridylsulfenyl



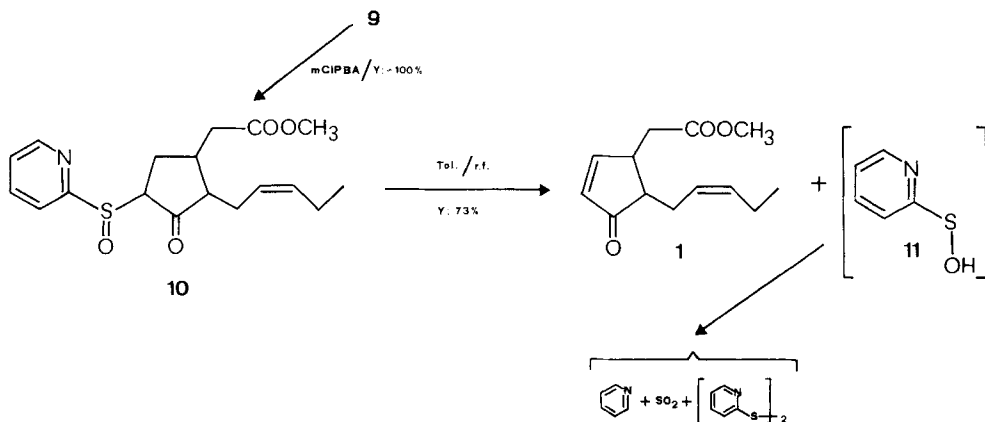
bromide, followed by a spontaneous loss of the transient activating group. Thermolysis of the pyridylthio derivative **9** did not give directly the dehydrojasmonate **1**. Therefore the thioether **9** was oxidized to sulfoxide **10** which, heated at moderate temperatures (80–120°), gave racemic **1** identical (IR., NMR. and MS.) with the natural product [**1**] and an independently synthesized sample [5 g].

The formation of pyridine, sulfur dioxide and 2,2'-dipyridyl disulfide as further reaction products may be explained by a disproportionation of the expected 2-pyridylsulfenic acid (**11**) to pyridylsulfenic acid and 2-mercaptopyridine as initial step. 2-Pyridylsulfenic acid is known to decompose to pyridine and sulfur dioxide under even milder conditions [10]. The occurrence of 2,2'-dipyridyl disulfide, one of our starting materials, could find its explanation by the reaction of 2-mercaptopyridine with 2-pyridylsulfenic acid (**11**).

Scheme 4

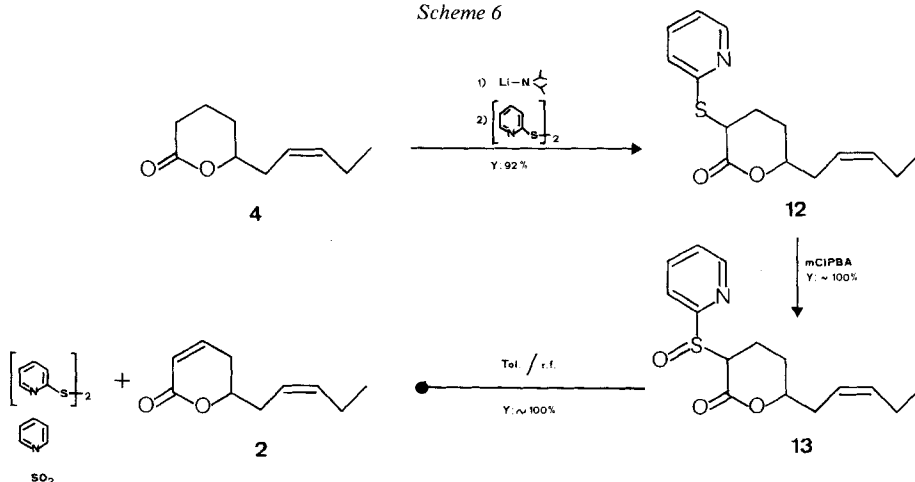


Scheme 5



Tuberolactone (2). - The sulfoxide-thermolysis technique developed for **1** was adapted to the synthesis of ($\pm$)-tuberolactone (**2**) from ($\pm$)-jasmolactone (**4**). The starting thioether **12** was prepared in a straightforward manner by reaction of deprotonated jasmolactone (**4**) with 2,2'-dipyridyl disulfide. The corresponding sulfoxide **13** was almost quantitatively transformed to ($\pm$)-tuberolactone **2** and the expected by-products. The spectral data (IR., NMR. and MS.) of the purified material **2** were identical with those of the natural product [2].

Scheme 6



We thank Dr. P. Schudel for his continuing interest in this work and for many encouraging discussions. The NMR. services of Dr. E. Billeter and Mr. J. Maerki are gratefully acknowledged.

Experimental Part

1. General. Cf [11].

2. 3-Methoxycarbonylmethyl-2-pentylcyclopent-2-en-1-one (**7**). A solution of 6.7 g (42 mmol) bromine in 10 ml acetic acid was added dropwise to a solution of 9.04 g (40 mmol) 3-methoxycarbonylmethyl-2-pentylcyclopentanone (**6**) [12] [13] in 20 ml acetic acid. The solvent was evaporated at 60°/10 Torr and the crude material diluted with ether and extracted 3 times with saturated NaHCO₃-solution. The organic phase was dried (Na₂SO₄) and concentrated at 40°/10 Torr. The product (9.44 g) consisted mainly of **7** and starting material **6** (10–20% of total) according to NMR., IR. and TLC. Prep. TLC. of a small part of the crude material (silica gel; hexane/ether 1:1) yielded pure starting material **6** (NMR., IR., TLC.) and pure dehydro compound **7**, identical (IR., NMR., TLC., GC.) with a reference sample [12]. - IR. (liq.): 1740, 1705, 1650, 1440, 1360, 1260, 1195, 1175, 1115, 1060, 1020. - ¹H-NMR.: 3.80 (s, 3 H, CH₃-O); 3.50 (s, 2 H, CH₂-COO); 2.80–1.90 (m, 6 H, (CH₂)₂CO-C-CH₂); 1.70–1.05 (br., 6 H, 3 CH₂); 0.90 (br. t, J = 5, 3 H, CH₃). - MS.: 224 (M, 2), 83 (100), 41 (60), 55 (37), 153 (26), 156 (26), 67 (24), 59 (22), 79 (18).

3. (Z)-5-Hydroxymethylidene-3-methoxycarbonylmethyl-2-(pent-2-enyl)cyclopentanone (**8**). Dry sodium methanolate (20 mmol) was suspended in 20 ml of abs. ether, cooled to 0°, and 1.2 g (20 mmol) of methyl formate was added. To this solution at 0°, 2.24 g (10 mmol) of methyl jasmonate (**3**) [5 d] were added dropwise and with good stirring. After further stirring for 2 h at 0°, 10 ml of a water/ice mixture were added, whereupon separation into two layers was observed; the very small organic layer, containing some unreacted starting material (TLC.) was discarded. The aqueous phase was acidified with 1.2 g of acetic acid (2 phases) and extracted with ether (3 × 50 ml). The organic layers were combined, dried (Na₂SO₄), and the solvent evaporated to give 2.66 g of a crude product, which was subjected to a short-path distillation at 0.06 Torr (oven temp.: 145–160°). 2.45 g (97%) of pure (TLC.) **8** were obtained. -

IR. (liq.): 3300, 1735, 1680, 1600, 1435, 1205, 1170, 1000, 955. - $^1\text{H-NMR.}$: 8.70 (br. s, 1H, O-H); 7.20 (s, 1H, O-CH=C); 5.70-4.90 (m, 2 H, HC=CH); 3.70 (s, 3 H, CH₃-O); 3.00-1.65 (m, 10 H); 0.95 (t, $J = 7$, 3 H, CH₃). - MS.: 252 (*M*, 100), 179 (88), 111 (73), 123 (47), 41 (33), 221 (30), 95 (29), 79 (19).

4. (Z)-3-Methoxycarbonylmethyl-2-(pent-2-enyl)-5-(pyridyl-2-thiyl)cyclopentanone (**9**). - a) From **8** with 2,2'-dipyridyldisulfide. Addition of 2.52 g (10 mmol) of distilled **8** to a mixture of 0.81 g (15 mmol) dry sodium methanolate and 2.2 g (10 mmol) 2,2'-dipyridyl disulfide in 10 ml abs. *t*-butyl alcohol gave a dark red solution which was kept at 80°, for 15 h, with stirring. After cooling to RT. and dilution with 70 ml water, ca. 5 ml of a saturated Na₂CO₃-solution were added, and the whole extracted with ether (5 × 20 ml). The combined extracts were dried (Na₂SO₄) and evaporated at 50°/11 Torr, yielding 2.0 g (60%) slightly impure (TLC.) **9**. The aqueous phase was acidified with conc. hydrochloric acid and extracted with ether (6 × 10 ml). These combined organic layers were dried (Na₂SO₄) and evaporated at 50°/11 Torr to give 0.9 g of a second crude product, which consisted mainly of unreacted starting material **8** (IR., NMR. and MS.; TLC.). A small part of crude **9** was purified by prep. TLC. (silica gel; hexane/ether 2:3), yielding an oily sample of **9**. - IR. (liq.): 1740, 1580, 1560, 1455, 1415, 1205, 1160, 1120, 760, 725. - $^1\text{H-NMR.}$: 8.40-8.15 (m, 1 H, CH=N); 7.60-6.75 (m, 3 H, H-C(3), H-C(4) and H-C(5) of the pyridine ring); 5.55-5.10 (m, 2 H, HC=CH); 3.85 (br., 1 H, CH-S); 3.70 (s, 3 H, CH₃-O); 2.90-1.60 (m, 10 H); 0.95 (t, $J = 7$, 3 H, CH₃). - MS.: 333 (*M*, 6), 112 (100), 78 (55), 41 (38), 67 (26), 51 (22), 55 (22), 164 (21), 136 (20).

b) From **8** with 2-pyridylsulfenylbromide. 2-Pyridylsulfenylbromide was prepared immediately before use: 0.8 g (5 mmol) bromine were added dropwise, with good stirring, to a solution of 1.1 g (5 mmol) 2,2'-dipyridyl disulfide in 6 ml CHCl₃. Stirring was continued at RT. for 30 min, then the solvent was removed by evaporation.

To a well stirred solution of 2.52 g (10 mmol) of distilled compound **8** and 0.81 g (15 mmol) dry sodium methanolate in 10 ml abs. dimethylformamide, a solution of the above 2-pyridylsulfenylbromide in 2 ml abs. dimethylformamide was added dropwise. A slightly exothermic reaction was observed. Stirring was continued at RT. for 2 h after addition. The reaction mixture was diluted with water and 5 ml of a saturated Na₂CO₃-solution, and extracted with ether (5 × 20 ml). The combined extracts were dried (Na₂SO₄) and evaporated at 60°/11 Torr to give 3.66 g of crude **9**. Extraction of the acidified aqueous phase (as in a)) gave, after work-up, a second crop consisting mainly of unreacted **8** and some dimethylformamide. The crude **9** (containing some 2,2'-dipyridyl disulfide as impurity) was purified by preparative TLC. as in a) to yield 2.04 g (61%) **9**.

c) One-pot procedure from methyl jasmonate (**3**). Formylation of methyl jasmonate (**3**) was carried out as in sect. 3. The deprotonated intermediate **8** was not worked up, but the solvent was removed and replaced by dimethylformamide (10 ml) and then the sulfenylation step was carried out as in b). The yield of pure **9** was 1.93 g (58%).

5. (Z)-3-Methoxycarbonylmethyl-2-(pent-2-enyl)-5-(pyridyl-2-sulfinyl)cyclopentanone (**10**). A solution of 0.41 g *m*-chloroperbenzoic acid (85% peracid) in 5 ml CHCl₃ was added dropwise within 15 min to a well-stirred and cooled (0°) solution of 0.67 g (2.0 mmol) thioether **9** in 10 ml CHCl₃. After addition, stirring was continued at RT. for 30 min. The reaction mixture was extracted with saturated NaHCO₃-solution (3 × 10 ml). The organic layer was dried (Na₂SO₄) and evaporated at 50°/10 Torr to give 0.7 g (100%) of a pure (TLC.) oily mixture of diastereomers. - IR. (liq.): 1740, 1580, 1560, 1450, 1420, 1200, 1150, 1080, 1050, 1035, 990, 775. - $^1\text{H-NMR.}$: 8.60 (br. d, $J = 5$, 1 H, CH=N); 7.95 (br. m, 2 H, H-C(3) and H-C(5) of the pyridine ring); 7.55-7.30 (br. m, 1 H, H-C(4) of the pyridine ring); 5.70-5.0 (m, 2 H, HC=CH); 4.10 and 3.90 (2 br., 1H, CH-SO); 3.73 and 3.65 (2s, 3 H, CH₃-O); 2.90-1.60 (m, 10 H); 0.95 (br. t, $J = 7$, 3 H).

6. (Z)-4-Methoxycarbonylmethyl-5-(pent-2-enyl)cyclopent-2-en-1-one (**1**). A solution of 0.58 g (1.66 mmol) sulfoxide **10** in 6 ml toluene was heated at reflux for 2 h (TLC. revealed that the starting material had completely reacted after 45 min). The evolution of SO₂ was detected by smelling the solution before work-up and by verification of acidic vapours above the reaction mixture. The occurrence of pyridine was detected by partially evaporating the completely reacted solution at 60°/11 Torr, smelling this concentrate, and confirming the presence of pyridine by NMR. (8.60, d, $J = 5$). The solvent was evaporated at 60°/11 Torr to yield 0.536 g of a crude material, consisting of **1** and 2,2'-dipyridyl disulfide (TLC. comparison with references samples). This was purified by preparative TLC. (silica gel; hexane/ether 2:3), yielding 60 mg pure (TLC., NMR., IR., MS.) 2,2'-dipyridyl disulfide and 270 mg (73%) pure **1**. - IR. (liq.): 1740, 1710, 1590, 1440, 1360, 1200, 1160, 1065, 1020, 990, 885. - $^1\text{H-NMR.}$: 7.63 (d × d, $J = 6$ and 2, 1 H, CH=C-C=O); 6.17 (d × d, $J = 6$ and 1.5, 1 H, =CH-C=O); 5.70-5.0 (m, 2 H,

HC=CH); 3.72 (*s*, 3 H, CH₃-O); 3.30-2.82 (*m*, 1H, CH-C=); 2.75-1.80 (*m*, 7 H); 0.97 (*t*, *J* = 7, 3 H, CH₃). - MS.: 222 (*M*, 29), 95 (100), 154 (72), 41 (53), 53 (21), 55 (18), 71 (18), 133 (18), 107 (18).

7. (Z)-6-(Pent-2-enyl)-3-(pyridyl-2-thio)tetrahydropyran-2-one (**12**). A solution of lithium *N,N*-diisopropylamide (22 mmol) was prepared under argon by dropwise addition of 2.22 g (22 mmol) *N,N*-diisopropylamine (dist. over KOH) to fresh, well stirred butyllithium (25 mmol in 7 ml ether), which was initially diluted with 20 ml abs. tetrahydrofuran and cooled to -20°. This solution was further cooled to -78°, when 3.36 g (20 mmol) of jasmolactone (**4**) [6] were added dropwise within 5 min, with good stirring. Stirring at -78° was continued for 30 min, then the cooled mixture was added with good stirring, under argon, to a solution of 4.4 g (20 mmol) 2,2'-dipyridyl disulfide in 12 ml abs. tetrahydrofuran, kept at -78°. A temperature rise to -50° was observed during addition (10 min). The reaction mixture was poured on 60 ml of 1N HCl at 0°. About 50 ml of a saturated NaHCO₃-solution were added to neutralize the excess of acid. After extraction (5 × 50 ml ether), combination of the organic phases, drying (Na₂SO₄) and evaporation of the solvent at 40°/11 Torr, 6.36 g of a crude product were obtained. To remove traces of unreacted starting material **4**, the crude material was heated in a bulb-to-bulb distillation apparatus at 100°/0.04 Torr. The residue (6.3 g) was chromatographed (silica gel; CH₂Cl₂) to remove the remainder of 2-mercaptopyridine, when 5.1 g (92%) of pure (TLC.) diastereomers **12** were obtained. - IR. (liq.): 1725, 1580, 1455, 1415, 1250, 1180, 1125, 1050, 985, 755, 720. - ¹H-NMR.: 8.55-8.30 (*br. m*, 1 H, CH=N); 7.85-6.80 (*m*, 3 H, H-C(3), H-C(4) and H-C(5) of the pyridine ring); 5.80-5.10 (*m*, 2 H, CH=CH); 5.0-3.35 (*m*, 2 H, CH-S and CH-O); 2.75-1.50 (*m*, 8 H); 1.0 (*t*, *J* = 7, 3 H, CH₃). - MS.: 277 (*M*, 0), 41 (100), 99 (93), 71 (70), 55 (53), 67 (26), 81 (22), 137 (14), 168 (8).

8. (Z)-6-(Pent-2-enyl)-3-(pyridyl-2-sulfinyl)tetrahydropyran-2-one (**13**). - Thioether **12** was converted to sulfoxide **13** under the same conditions as in sect. 5. The oily product **13**, obtained in quantitative yield, was a pure (TLC.) mixture of diastereomers. - IR. (liq.): 1725, 1575, 1560, 1450, 1420, 1240, 1180, 1050, 985, 930, 750. - ¹H-NMR.: 8.63 (*br. d*, *J* = 5, 1H, CH=N); 7.95 (*br. d*, *J* = 5, 2 H, H-C(3) and H-C(5) of the pyridine ring); 7.65-7.30 (*m*, 1H, H-C(4) of the pyridine ring); 5.75-5.00 (*m*, 2 H, HC=CH); 4.60-3.90 (*br. m*, 2 H, CH-SO and CH-O); 2.75-1.30 (*m*, 8 H); 0.95 (*t*, *J* = 7, 3 H, CH₃). - MS.: 293 (*M*, 0), 97 (100), 41 (53), 81 (27), 71 (24), 69 (23), 55 (21), 79 (18), 64 (12).

9. (Z)-6-(Pent-2-enyl)-5,6-dihydropyran-2-one (**2**). Sulfoxide **13** was thermolysed in toluene and worked up as mentioned in sect. 6 to give **2** in quantitative yield and the by-products mentioned in sect. 6. **2** was obtained pure (TLC.) by bulb-to-bulb distillation at 100°/0.03 Torr. *n*_D²⁰: 1.4930. - IR. (liq.): 1730, 1385, 1245, 1150, 1065, 1045, 965, 840, 810. - ¹H-NMR.: 6.90 (*t* × *d*, *J* = 10 and 4.5, 1H, CH=C-C=O); 6.0 (*t* × *d*, *J* = 10 and 1.5, 1H, =CH-C=O); 5.85-5.10 (*m*, 2 H, HC=CH); 4.47 (*br. q*, *J* = 6, 1H, CH-O); 2.70-1.65 (*m*, 6 H); 0.98 (*t*, *J* = 7, 3 H, CH₃). - MS.: 166 (*M*, 1), 97 (100), 41 (43), 69 (23), 81 (22), 55 (10), 121 (3), 124 (2), 137 (2).

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