88. Partial Syntheses of Methyl Dehydrojasmonate and Tuberolactone[1])

by **Paul Dubs**[2]) and **Rita Stüssi**

Givaudan Ltd, Research Company, 8600 Dübendorf-Zürich

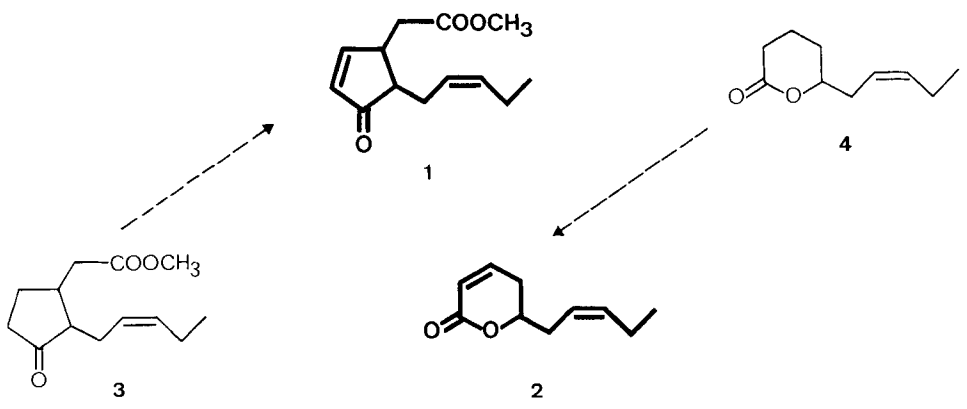
(14.XI.77)

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.

[2]) Author to whom correspondence should be addressed; new address: *Jacobs* Management & Consulting Company, Klausstrasse 4–6, CH-8034 Zürich.

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].

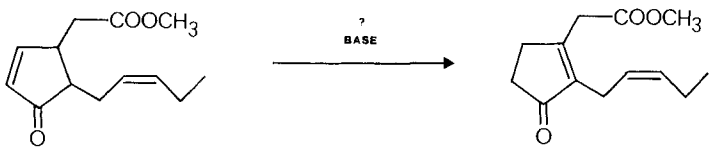
We therefore decided to synthesize compounds **1** and **2**. The obvious structural similarities of **1** and **3** as well as of **2** and **4**, very probably based on biogenetic relationships, prompted us to conceive partial syntheses **3**→**1** and **4**→**2**. Since both **3** and **4** are synthetically 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**→**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 eletrophiles 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)*.

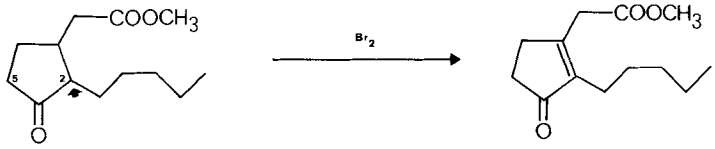
We therefore tried to activate selectively the 5-position of model **6** as well as of methyl jasmonate (**3**). The best results were obtained with the enolized formyl derivative **8**. Our initial experiments towards introduction of a phenylsulfenyl group [8] into **8** failed. Also the reaction of 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

Scheme 2



1 **5**

Scheme 3

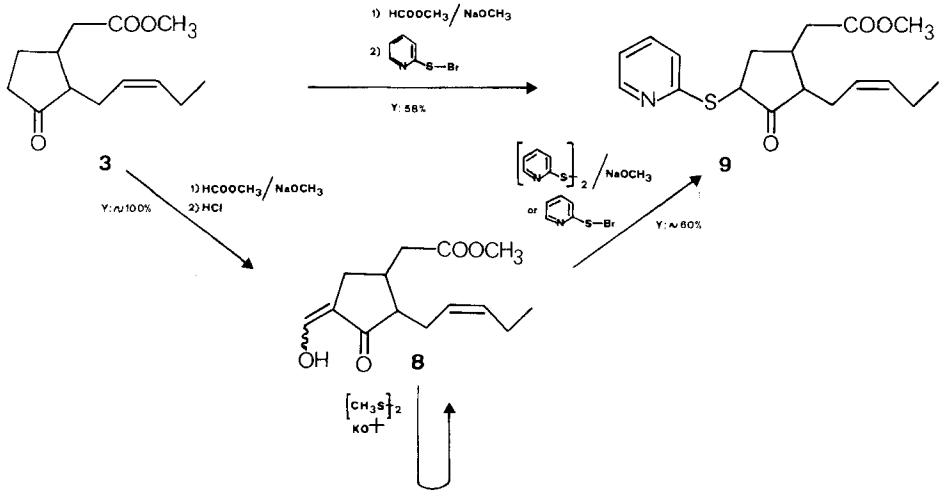


6 **7**

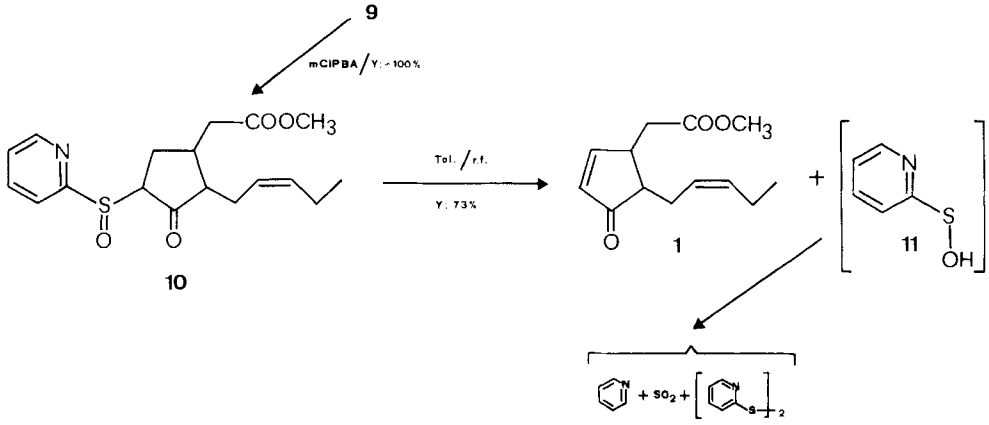
bromide, followed by a spontaneous loss of the transient activating group. Thermolysis of the pyridylthio derivative **9** did not give directly the dehydrojasmonate **1**. Therefore the thioether **9** was oxidized to sulfoxide **10** which, heated at moderate temperatures (80–120°), gave racemic **1** 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 pyridylsulfinic acid and 2-mercaptopyridine as initial step. 2-Pyridylsulfinic 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

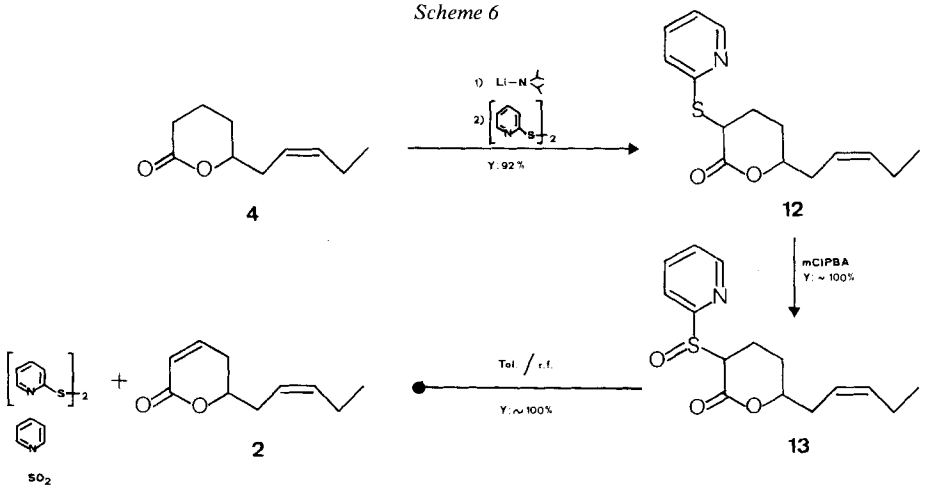


Scheme 5



Tuberolactone (2). – The sulfoxide-thermolysis technique developed for **1** was adapted to the synthesis of (±)-tuberolactone (**2**) from (±)-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 (±)-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 $NaHCO_3$-solution. The organic phase was dried (Na_2SO_4) 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. – ^{1}H-NMR.: 3.80 (*s*, 3 H, CH_3–O); 3.50 (*s*, 2 H, CH_2–COO); 2.80–1.90 (*m*, 6 H, $(CH_2)_2CO$–C–CH_2); 1.70–1.05 (br., 6 H, 3 CH_2); 0.90 (br. *t*, J=5, 3 H, CH_3). – 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 (Na_2SO_4), 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}H-NMR.: 8.70 (br. *s*, 1H, O–H); 7.20 (*s*, 1H, O–CH=C); 5.70–4.90 (*m*, 2H, HC=CH); 3.70 (*s*, 3H, CH_3–O); 3.00–1.65 (*m*, 10H); 0.95 (*t*, J=7, 3H, CH_3). – 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 Na_2CO_3-solution were added, and the whole extracted with ether (5×20 ml). The combined extracts were dried (Na_2SO_4) 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 (Na_2SO_4) 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}H-NMR.: 8.40–8.15 (*m*, 1H, CH=N); 7.60–6.75 (*m*, 3H, H–C(3), H–C(4) and H–C(5) of the pyridine ring); 5.55–5.10 (*m*, 2H, HC=CH); 3.85 (br., 1H, CH–S); 3.70 (*s*, 3H, CH_3–O); 2.90–1.60 (*m*, 10H); 0.95 (*t*, J=7, 3H, CH_3). – 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 $CHCl_3$. 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 Na_2CO_3-solution, and extracted with ether (5×20 ml). The combined extracts were dried (Na_2SO_4) 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 $CHCl_3$ 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 $CHCl_3$. After addition, stirring was continued at RT. for 30 min. The reaction mixture was extracted with saturated $NaHCO_3$-solution (3× 10 ml). The organic layer was dried (Na_2SO_4) 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}H-NMR.: 8.60 (br. *d*, J=5, 1H, CH=N); 7.95 (br. *m*, 2H, H–C(3) and H–C(5) of the pyridine ring); 7.55–7.30 (br. *m*, 1H, H–C(4) of the pyridine ring); 5.70–5.0 (*m*, 2H, HC=CH); 4.10 and 3.90 (2 br., 1H, CH–SO); 3.73 and 3.65 (2*s*, 3H, CH_3–O); 2.90–1.60 (*m*, 10H); 0.95 (br. *t*, J=7, 3H).

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 SO_2 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}H-NMR.: 7.63 (*d*× *d*, J=6 and 2, 1H, CH=C–C=O); 6,17 (*d*× *d*, J=6 and 1.5, 1H, =CH–C=O); 5.70–5.0 (*m*, 2H,

HC=CH); 3.72 (*s*, 3 H, CH_3–O); 3.30–2.82 (*m*, 1H, CH–C=); 2.75–1.80 (*m*, 7 H); 0.97 (*t*, *J* = 7, 3 H, CH_3). – 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 $NaHCO_3$-solution were added to neutralize the excess of acid. After extraction (5 × 50 ml ether), combination of the organic phases, drying (Na_2SO_4) 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; CH_2Cl_2) to remove the remainder of 2-mercatopyridine, 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. – ^{1}H-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, CH_3). – 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. – ^{1}H-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, CH_3). – 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_D^{20}: 1.4930. – IR. (liq.): 1730, 1385, 1245, 1150, 1065, 1045, 965, 840, 810. – ^{1}H-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. *qi*, *J* = 6, 1H, CH–O); 2.70–1.65 (*m*, 6 H); 0.98 (*t*, *J* = 7, 3 H, CH_3). – MS.: 166 (*M*, 1), 97 (100), 41 (43), 69 (23), 81 (22), 55 (10), 121 (3), 124 (2), 137 (2).

REFERENCES

[1] *R. Kaiser & D. Lamparsky*, Tetrahedron Letters, *1974*, 3413.

[2] *R. Kaiser & D. Lamparsky*, Tetrahedron Letters, *1976*, 1659.

[3] *E. Demole, E. Lederer & D. Mercier*, Helv. *45*, 675 (1962).

[4] *M. Winter, G. Malet, M. Pfeiffner & E. Demole*, Helv. *45*, 1250 (1962).

[5] a) *E. Demole & M. Stoll*, Helv. *45*, 692 (1962); b) *K. Sisido, S. Kurozumi & K. Utimoto*, J. org. Chemistry *34*, 2661 (1969); c) *P. Oberhänsli*, Ger. Offen. 2008878 (24.9.1970); d) *G. Büchi & B. Egger*, J. org. Chemistry *36*, 2021 (1971); e) *F. Näf*, Ger. Offen. 2163868 (22.12.1971); f) *A.I. Meyers & N. Nazarenko*, J. org. Chemistry *38*, 175 (1973); g) *P. Ducos & F. Rouessac*, Tetrahedron *29*, 3233 (1973); h) *H. Tanaka & S. Torii*, J. org. Chemistry *40*, 462 (1975); i) *S. Torii, H. Tanaka & T. Mandai*, ibid. *40*, 2221 (1975); k) *F. Johnson, P.G. Kenneth & F. Duccio*, Belg. Pat. 826150 (28.2.1975).

[6] *L.G. Heeringa, R. Fehn, J.D. Grossman & M.B. Dulal*, Ger. Offen. 1803460 (16.10.1968).

[7] *S. Bergström*, Science *157*, 382 (1967).

[8] *H.J. Reich, J.M. Renga & I.L. Reich*, J. Amer. chem. Soc. *97*, 5434 (1975).

[9] *B.M. Trost & T.N. Salzmann*, J. Amer. chem. Soc. *95*, 6840 (1973).

[10] *W. Walter & P.M. Hell*, Liebigs Ann. Chem. *727*, 35 (1969).

[11] *P. Dubs & H.-P. Schenk*, Helv., *61*, 984,1978; *P. Dubs & R. Stüssi*, Helv., *61*, 990, 1978.

[12] *P. Oberhänsli*, Swiss Pat. 509247 (30.3.1969).

[13] *E. Demole, E. Lederer & D. Mercier*, Helv. *45*, 685 (1962).