

239. An Efficient Synthesis of Methyl ($\pm$)-Jasmonate and (*Z*)-Jasmone

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In memory of Professor *Emil Hardegger*

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Summary

An efficient synthesis of methyl ($\pm$)-jasmonate and (*Z*)-jasmone is described. The key step is a phase-transfer reaction between cyclopentanone (**9**) and 1,4-dibromo-2-pentene (**6a/b**) to give the spiro[2.4]hepten-4-ones **4a** and **4b**.

Since the structure elucidation and first synthesis of (*Z*)-jasmone (**1**) [1] [2] and methyl jasmonate (**2**) [3] over one hundred syntheses of jasmine-type odorants have been published¹⁾. However, because of the high price, methyl jasmonate has not yet become common commercially, and is therefore precluded from broad utilization in perfumery. Despite the success of structurally simpler and cheaper substitutes, e.g. methyl dihydrojasmonate (HEDIONE®²⁾), methyl jasmonate is still considered to have finer odour qualities [33]. (*Z*)-jasmone on the other hand, is commercially available, but on account of its elevated price only used in fine perfumery.

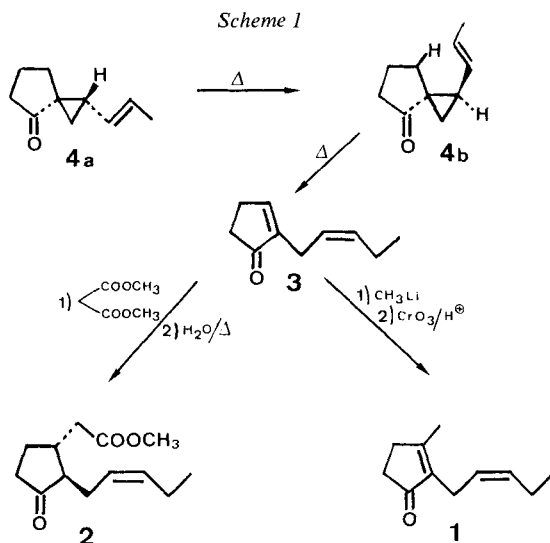
We now report an efficient procedure for manufacturing both methyl ($\pm$)-jasmonate (**2**) and (*Z*)-jasmone (**1**) using the intermediates **4a** and **4b** [34] for which we have developed a new, two-step synthesis from piperylene (**5**) and cyclopentanone (**9**).

Descotes et al. [34] reported that the spiro compound **4a** undergoes thermal rearrangement to 2-(*Z*-pentenyl)-2-cyclopenten-1-one (**3**), a well known, convenient intermediate for methyl jasmonate [8] [35] and (*Z*)-jasmone [34] [36]. A plausible mechanism, already proposed by these authors, involves an epimerization of **4a** into **4b** (not detected), followed by a rapid homo[1,5]hydrogen shift³⁾ (*Scheme 1*). The remarkable feature of these rearrangements consists in the product- and stereo-selective formation of the (*Z*)-pentenylcyclopentenone **3** without the intermediacy of an acetylenic precursor or the use of the *Wittig* reaction. The big drawback of a jasmone synthesis using these rearrangements, however, was the inaccessibility of the

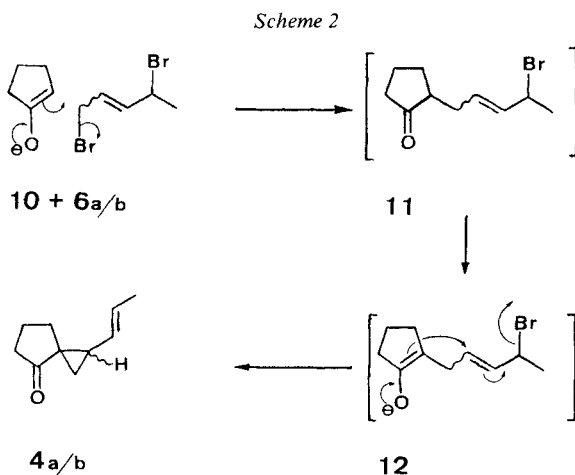
¹⁾ For reviews see [4–7], and for the more recent syntheses of (*Z*)-jasmone and methyl jasmonate, see [8–32].

²⁾ Registered trade name of *Firmenich SA*, Geneva.

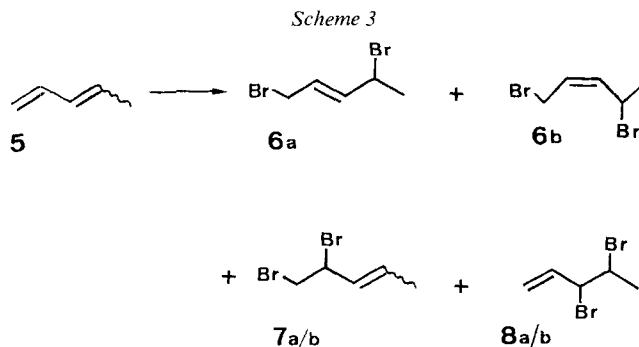
³⁾ The first example of such a shift was reported in 1960 by *Ohloff* [37]; for subsequent leading references, see [38].



critical spiro intermediate **4a** (or **4b**). Descotes *et al.* prepared **4a** by a seven-step low yield route from cyclopentanone (**9**) (~7.5% overall yield from **9**). We have now found that a 1:4 mixture of **4a** and **4b** can easily be made from cyclopentanone (**9**) and 1,4-dibromo-2-pentene (**6a/b**) [39] using phase-transfer conditions (aqueous KOH, Aliquat 336, 2 h at 60–65°; 40–55% yield). The reaction may be rationalized as a double displacement at the 1,4-dibromo moiety **6a/b**: direct displacement of the primary bromide by cyclopentanone enolate **10** to give the intermediate **11** followed by generation of enolate **12** and subsequent intramolecular displacement of the secondary bromide. The spiro compounds **4a** and **4b** were also obtained by using NaH or NaNH₂ (2 h at 65° in THF; 41–48% yield). Apart from the desired products some α -cyclopentylidenecyclopentanone and polymers were always formed.

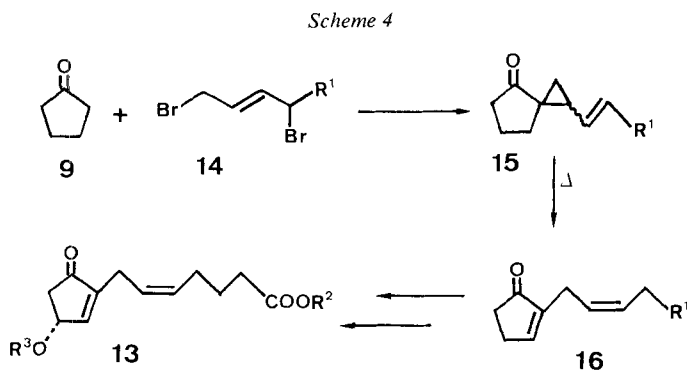


The 1,4-dibromo-2-pentenenes **6a/b** were obtained as main products on brominating piperylene (**5**) (*Z/E* ratio 1:2) as described [39].



The crude bromination mixture, containing about 60% of **6a**, 5% of **6b**, 30% of **7a/b** (diastereomers), and 5% of **8a/b** (diastereomers), could be used directly with or without solvent in the phase-transfer step. Thermolysis of the mixture **4a/b** (1:4 ratio) in the gas phase at 330–350° gave 2-(2*Z*-pentenyl)-2-cyclopenten-1-one (**3**, 89% yield). At lower temperatures, however, *e.g.* by injection of the same mixture into the gas chromatograph (injector temp. 220°, column temp. 200°), **4b** rearranged to **3** much faster than did **4a**, thus providing good chemical evidence for the configurational assignment of the epimeric spiro compounds. (*Z*)-Pentenylcyclopentenone **3** was then transformed into methyl ($\pm$)-jasmonate by the known two-step sequence of methyl malonate addition and decarboxylative saponification [8] [35]. Alternatively, (*Z*)-jasmonone (**1**) was made from **3** by reaction of methyllithium and subsequent oxidation of the alcoholic intermediate [34] [36] (Scheme 1).

We are at present exploring an analogous principle for the construction of the known prostaglandin intermediate **13** [40–44] along the lines depicted in Scheme 4.



We are indebted to Dr. H. Rodé for an excellent bibliography on the synthesis of jasmine-type compounds.

Experimental Part

General. The 90-MHz- ^1H -NMR. spectra were run on a *Bruker* HFX-90/15", and the 360-MHz- ^1H -NMR. spectra on a *Bruker* WH-360 instrument using CDCl_3 as solvent and TMS ($\delta = 0.00$ ppm) as internal standard; abbreviations: *d*=doublet, *t*=triplet, *qa*=quadruplet, *m*=multiplet, *J*=spin-spin couplings (Hz). Mass spectra (MS.) were measured on an *Atlas* CH₄ spectrometer, inlet temp. ca. 150°, electron energy ca. 70 eV; the molecular ions (M^+) and fragment ions are given as *m/e* with relative peak intensities in % of the most abundant peak. The infrared (IR.) spectra were taken on a *Perkin-Elmer* 125 instrument; characteristic maxima in cm^{-1} . The ultraviolet (UV.) spectra were recorded on a *Unicam* SP 700 A apparatus. Gas chromatography (GC.) was performed on a *Carlo Erba* Fractovap Series 2350 instrument; carrier gas: He (40 ml/min); glass columns: 4 mm $\times$ 2 m, column carrier: Chromosorb W/60–80 mesh, acid washed. A *Büchi* Rotavapor was used as rotary evaporator (RV.). For bulb-to-bulb distillation a *Büchi* apparatus with external temperature reading was used.

1. Bromination of piperylene. Piperylene (*Z/E* ratio 1:2; 930 g, 80% pure, 11 mol) in light petroleum (b.p. 50–70°) (500 ml) was brominated with a solution of bromine (510 ml=1.6 kg, 10 mol) in light petroleum (b.p. 50–70°) (500 ml) with stirring and external cooling (dry ice/isopropanol) at 0° ($\pm 2^\circ$) for 2 h. The resulting mixture was stirred for 30 min without cooling and then directly used for the next step. After *Vigreux* distillation, b.p. 40–45°/0.05 Torr, the same reaction on a one-molar scale gave 192 g of distillate which showed four major peaks (GC., 10% silicon gum, at 100°): peak 1 (~5%) **8a/b**, peak 2 (~30%) **7a/b**, peak 3 (~5%) **6b**, and peak 4 (~60%) **6a**. The NMR. and IR. spectra of all substances were identical with those published [38]. Yield of **6a/b** ca. 55%.

2a. Spiro compounds 4a and 4b by alkylation using NaNH_2 . Sodium amide was freshly prepared in liquid ammonia (100 ml) from 5.75 g (0.25 mol) of sodium. The ammonia was allowed to evaporate and anhyd. THF (200 ml) and 1,4-dibromo-2-pentene (**6a/b**, 22.8 g of 65% purity, 0.065 mol) were added. Anhydrous cyclopentanone (8.4 g, 0.1 mol) in anhyd. THF (20 ml) was then added dropwise to the stirred mixture at ~65° (reflux) during ~30 min. Stirring at 65° was continued for 2 h, when the mixture was poured on ice and extracted twice with ether. The ethereal phase was washed (2*N* HCl, NaHCO_3 , water), dried (MgSO_4) and concentrated to give ~13 g of crude product. Bulb distillation at 100–150°/10 Torr gave 7.35 g of an oil containing 6% of unknown volatiles, 43% of **4a**, 21% of **4b** and 22% of *a*-cyclopentylidenecyclopentanone by GC.⁴⁾ Yield of **4a/b**: ~48%.

4a. IR. (neat): 1720, 970 cm^{-1} . – ^1H -NMR. (360 MHz): 1.26 (*d* $\times$ *d*, $J_1 = 8$ Hz, $J_2 = 4$ Hz, 1H, cyclopropyl-H); 1.37 (*d* $\times$ *d*, $J_1 = 11$ Hz, $J_2 = 4$ Hz, 1H, cyclopropyl-H); 1.67 (*d* $\times$ *d*, $J_1 = 6$ Hz, $J_2 = 1$ Hz, 3 H, =C–CH₃); 2.3 (*m*, 2 H, CH₂–C=O); 5.5 (*d* $\times$ *d*, $J_1 = 15$ Hz, $J_2 = 9$ Hz, 1H, =CH); 5.59 (*d* $\times$ *qa*, $J_1 = 15$ Hz, $J_2 = 6$ Hz). – MS.: 150 (65, M^+), 135 (21), 121 (80), 107 (21), 94 (51), 79 (100), 67 (27), 55 (36), 41 (33), 39 (36), 27 (28).

4b. IR. (neat): 1720, 960 cm^{-1} . – ^1H -NMR. (90 MHz): 0.95 (*d* $\times$ *d*, $J_1 = 4$ Hz, $J_2 = 6.5$ Hz, 1H, cyclopropyl-H₉); 1.48 (*d* $\times$ *d*, $J_1 = 9$ Hz, $J_2 = 4$ Hz, 1H, cyclopropyl-H₆); 1.71 (*d* $\times$ *d*, $J_1 \cong 6.2$, $J_2 \cong 0.8$, 3 H, =C–CH₃); ~2 (*m*, 1H, cyclopropyl-H-allyl); ~2.28 (*m*, 2 H, CH₂–C=O); 5.07 (*d* $\times$ *d* with fine splitting, $J_1 = 16$ Hz, $J_2 = 8$ Hz, 1H, =CH); 5.64 (*d* $\times$ *qa*, $J_1 = 16$ Hz, $J_2 \cong 6.2$ Hz, 1H, =CH). Irrad. at ~2 $\rightarrow$ *d* $\times$ *d* at 5.07 becomes *d* ($J = 16$ Hz). – MS.: 150 (65, M^+), 135 (20), 121 (79), 107 (20), 94 (50), 79 (100), 67 (27), 55 (32), 41 (28), 39 (35), 27 (26).

2b. Spiro compounds 4a and 4b by alkylation using NaH . Sodium hydride (7.5 g of 80%, 0.25 mol) was degreased with pentane and stirred one night at RT. in anhyd. THF (200 ml). The suspension was then heated to 65° (reflux) and treated dropwise during 30 min with a solution of 1,4-dibromo-2-pentene (**6a/b**, 35 g of 65% purity, 0.1 mol), anhyd. cyclopentanone (33.6 g, 0.4 mol) and anhyd. THF (100 ml). After the addition stirring was continued for 2 h at 65°. The cold reaction mixture was poured on ice and extracted twice with ether. The ethereal phase was washed (2*N* HCl, dil. NaHCO_3 , water), dried (MgSO_4) and concentrated to give ~31.5 g of crude product. Distillation (*Vigreux*) at 82–94°/0.05 Torr gave 15.2 g of a product which, after column chromatography on 150 g silica gel (*Merck*, 0.05–0.2 mm) with hexane/ether 95:5, furnished 7.1 g of **4a/b** (87% pure, 3:2 ratio, 41% yield).

⁴⁾ Order of retention time on 10% Carbowax at 200°: **4a** < **4b** < *a*-cyclopentylidenecyclopentanone.

2c. *Spiro compounds 4a and 4b by phase-transfer alkylation.* A 6.5 l round-bottomed reactor fitted with a mechanical stirrer (~ 800 rev/min), a dropping funnel and a thermometer, was charged with KOH (1.65 kg of 84% content, 25 mol), water (1 l). Aliquat 336 (100 g), and light petroleum (b.p. 50–70°, 200 ml). The stirrer was started and the mixture heated to reflux ($\sim 60^\circ$). A mixture of the crude bromide solution (~ 5.5 mol of **6a/b**) and cyclopentanone (**9**) (840 g, 10 mol) was added dropwise. An exothermic reaction with formation of solid KBr resulted, and the reflux rate was kept under control by the speed of the addition. After ~ 2 h the addition was finished, and stirring at reflux was continued for 2 h. The mixture was cooled to RT. and the liquid decanted. The crystalline residue was washed with light petroleum (2×100 ml) and the combined liquid phases were separated. The aqueous phase was discarded and the organic phase concentrated in a RV. (bath temp. 70° , pressure 30 Torr). The crude product (1.17 kg) obtained was distilled in a *Leybold-Heraeus* KDL 1 falling film still (evaporator temp. 100° , pressure: 10 Torr, speed 1–2 ml/min) giving ca. 500 g of distillate and 620 g of residue. The residue was redistilled on the same apparatus ($100^\circ/0.001$ Torr) yielding 121 g of volatile material and ~ 480 g of residue. The two distillates were combined and fractionated over small pieces of marble (~ 10 g) (*Vigreux* column, 20×2 cm). Fraction 1 (b.p. up to $67^\circ/0.2$ Torr) contained 96 g of decomposition products of the piperylene dibromides, fraction 2 (b.p. $67\text{--}72^\circ/0.05$ Torr) 345 g of **4a/b** (1:4 ratio, 93% pure by GC. by using 10% Carbowax at 200°), and higher boiling material and residue made up ~ 185 g. Fraction 2 was directly used for the next step. Yield of **4a/b** ($\sim 1:4$ ratio) $\sim 40\%$ based on **6a/b**. On a one-molar scale the yield was $\sim 55\%$.

3. *2-(2Z-Pentenyl)-2-cyclopenten-1-one (3) by thermolysis of 4a/b.* A horizontal quartz tube (18 mm $\times$ 1 m), surrounded by an electrical heating jacket, filled with small quartz tubes ($\sim 5 \times 5$ mm) and having three thermocouples at regular intervals, was connected with a reflux condenser (length 15 cm) above which was placed a dropping funnel. At the bottom a round-bottomed flask cooled with dry ice/2-propanol served as recipient. The apparatus was heated to $300\text{--}350^\circ$ and a continuous slow stream of argon was allowed to pass. A solution of **4a/b** (ratio 1:4, 816 g = 5.44 mol) in hexane (3.3 l) was allowed to pass the pyrolysis tube at a rate of ~ 2 drops/s. The reaction product was concentrated and fractionated using a *Vigreux* column (20×2 cm). At $78\text{--}83^\circ/10$ Torr, 732 g of pure **3** (89% yield) was obtained. The spectral data were identical with those published [8] [34] [36]: UV. (EtOH): λ_{max} 227 nm (ϵ 10,000). – IR. (neat): 1700, 1630, 735 cm^{-1} . – $^1\text{H-NMR}$. (60 MHz): 0.95 (t, $J = 7.5$ Hz, 3 H, CH_3); 2.04 (d $\times$ qa, $J_1 = 7$ Hz, $J_2 = 7.5$ Hz, 2 H, $\text{CH}_2\text{--C=}$); 2.9 (m, 2 H, $=\text{C--CH}_2\text{--C=}$); ~ 5.47 (m, 2 H, CH=CH); ~ 7.3 (m, 1H, CH=C--C=O). – MS.: 150 (95, M^+), 135 (40), 121 (79), 107 (27), 91 (49), 79 (100), 67 (35), 55 (77), 41 (47), 27 (31).

4. *Methyl ($\pm$)-jasmonate (2) and (Z)-jasnone (1).* Both these compounds were obtained from **3** by known methods; for experimental details, see references in the theoretical part.

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