Synthesis of (±)-Methyl Epijasmonate and (±)-Methyl Dihydroepijasmonate by Diastereoselective Protonation

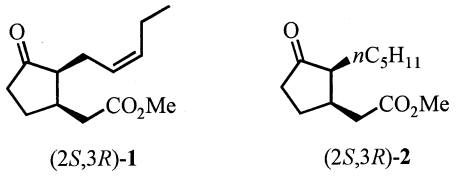
Norbert Krause*[a] and Sophia Ebert[a]

Keywords: Cuprates / Natural products / Protonation / Diastereoselectivity

The synthesis of (±)-methyl epijasmonate (**1**) was carried out by Michael addition of lithium diallylcuprate to enone **3** and diastereoselective enolate protonation with the chelating proton source 2-(methyliminomethyl)phenol (**4**; 85% *ds*), followed by ozonolysis, oxidation, esterification, and Lindlar hydrogenation. During the ozonisation, epimerization to the thermodynamically more stable *trans*-isomer takes place to some extent, so that **1** was isolated with a *cis*:*trans* ratio of 72:28. The analogous transformation of enone **7** with lithium diallylcuprate and 2-(methyliminomethyl)phenol (**4**) furnished ketone **8** with 94% *ds*; this was then transformed into (±)-methyl dihydroepijasmonate (**2**) with a *cis*:*trans* ratio of 91:9. The olfactory properties of this product are superior to those available from commercial sources

Introduction

Methyl jasmonate is a 2,3-disubstituted cyclopentanone derivative which is present in many plants; it was isolated for the first time by Demole et al.[1] from jasmine (*Jasminum grandiflorum*). It is also found in many plant extracts such as rosemary oil, lemon oil[2] or tea.[3] Although the amount of methyl jasmonate in jasmine oil does not exceed 1%, its typical jasmine-like odor dominates that of the natural extract. Methyl jamonate isolated from natural sources exists as an equilibrium mixture of the *trans*-(2*R*,3*R*)- and the *cis*-(2*S*,3*R*)-isomer **1** (methyl epijasmonate; Scheme 1) with a ratio of 95:5.[4,5]



(2*S*,3*R*)-**1** (2*S*,3*R*)-**2**

Scheme 1

cis-(2*S*,3*R*)-Methyl epijasmonate is almost exclusively responsible for the fragrance of the plant extracts;[6] it has an odor threshold concentration of only 0.012 ng/L whereas that of the epimeric *trans*-(2*R*,3*R*)-methyl jasmonate is 20 times higher.[7] All other isomers have no detectable odor. Due to these very pleasant fragrance properties, methyl jasmonate is used in many perfumes.[7] In recent years, it was also found that methyl jasmonate and jasmonic acid act as regulators of important biological functions of many plants, algae and fungi.[8] Thus, they induce the growth of potatoes (*Solanum tuberosum*),[9] control the synthesis of certain proteins (jasmonate-induced proteins, JIPs)[10] as well as the emission of ethylene, and they act as growth regulators[11] and are therefore also designated as phytohormones.[12] Furthermore, jasmonic acid takes part as a stress signal in the defense of plants against herbivores.[13] Methyl jasmonate was also identified as a component of the sexual pheromone of the male oriental fruit moth (*Grapholitha molesta*).[14] In all these cases, the stereoisomers of methyl jasmonate exhibit different activities, with *cis*-(2*S*,3*R*)-methyl epijasmonate **1** being the most active one.[15] The biosynthesis from linolenic acids also leads initially to this isomer.[16]

Methyl dihydrojasmonate, which can be prepared by catalytic hydrogenation of methyl jasmonate,[17] could until now only be detected in tea.[18] Due to its fruity flower fragrance, it is also a valuable compound for the manufacture of perfumes (trade names: Cepionate®, Hedione®).[7] Similar to methyl jasmonate, the *cis*-(2*S*,3*R*)-isomer **2** (methyl dihydroepijasmonate; Scheme 1) exhibits the strongest odor, having a threshold concentration of only 0.028 ng/L compared to a value of 1.85 ng/L for the *trans*-isomer. Several syntheses of methyl jasmonate and methyl dihydrojasmonate are known.[7] Likewise, a number of synthetic approaches to racemic, diastereomerically enriched or pure methyl epijasmonate (**1**),[19] as well as enantioselective syntheses[20] have been described, and the same holds for methyl dihydroepijasmonate (**2**).[7,20g,21] Due to their *cis*-2,3-disubstituted cycloalkanone structure, both molecules should also be accessible by diastereoselective protonation of chiral enolates with chelating proton sources.[22] This method was developed by us and has already been employed in the synthesis of the insect pheromone (2*S*,3*S*,7*RS*)-diprionyl acetate.[23]

Results and Discussion

During our investigations on the synthesis of *cis*-2,3-disubstituted cycloalkanones by the chelate-controlled diastereoselective protonation of chiral metal enolates with sali-

[a] Lehrstuhl für Organische Chemie II, Universität Dortmund, 44221 Dortmund, Germany
Fax: (internat.) +49-231/755-3884
E-mail: nkrause@pop.uni-dortmund.de

  1434–193X/01/1020–3837 $ 17.50+.50/0

cylates as the proton source,[9] it was found that five-membered enolates are the most difficult substrates to use. Thus, the 1,4-addition of lithium dimethylcuprate to 2-methyl-2-cyclopentenone and protonation with ethyl salicylate gave 2,3-dimethylcyclopentanone with a *cis*:*trans* ratio of only 89:11, whereas a value of 96:4 was achieved with the corresponding six-membered enolate.

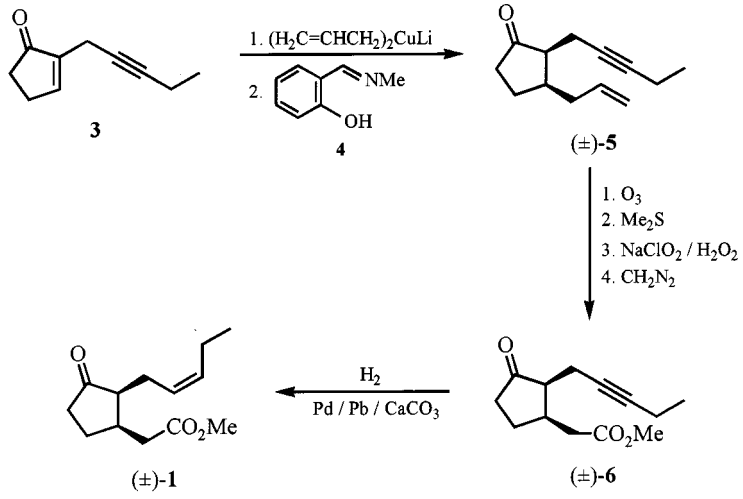
Several known syntheses of methyl jasmonate make use of the 1,4-addition of sodium dimethylmalonate to (*Z*)-2-(2-penten-1-yl)-2-cyclopentenone or 2-(2-pentyn-1-yl)-2-cyclopentenone (**3**);[24] however, only the equilibrium mixture of *cis*-**2**:*trans*-**2** = 5:95 was obtained. We intended to prepare (±)-methyl epijasmonate via the ketone **5**,[25] which should be accessible by the 1,4-addition of lithium diallylcuprate to enone **3** and subsequent diastereoselective protonation. Allyl cuprates belong to the most reactive organocopper reagents and often exhibit unsatisfactory regioselectivities in Michael additions.[26] The allyllithium required for the preparation of the cuprate can be obtained by transmetalation of allyl-tri-*n*-butylstannane with methyllithium,[27] or of tetraallyltin with 4 equiv. of phenyllithium.[28] Whereas in the first case the reaction mixture contains methyl-tri-*n*-butylstannane, the tetraphenyltin formed in the second case is removed by filtration so that a tin-free solution of the cuprate can be prepared.

In the event, the 1,4-addition of lithium diallylcuprate (from allyl-tri-*n*-butylstannane, MeLi,[27] and CuI) to enone **3**[24a] and protonation of the enolate with 2-(methyliminomethyl)phenol (**4**) furnished the desired ketone **5** with a *cis*:*trans* ratio of 85:15 (Scheme 2), whereas with the tin-free cuprate[28] a ratio of 80:20 was observed. Thus, the presence of nBu$_3$SnMe hardly affects the diastereoselectivity of the enolate protonation. Unfortunately, chromatographic purification of the 85:15 mixture caused some epimerization, to give **5** with 60% yield and a *cis*:*trans* ratio of 81:19. With other chelating proton donors, inferior stereoselectivities were obtained.[29]

Following a literature procedure for the preparation of methyl jasmonate,[24a] we then intended to transform ketone **5** into the target molecule (±)-methyl epijasmonate (**1**) by ozonolysis, oxidation, esterification and Lindlar hydrogenation of the triple bond. Initial attempts to ozonize **5** (*cis*:*trans* = 80:20), however, resulted in the complete decomposition of the starting material. Although triple bonds are attacked by ozone only under drastic conditions,[30] very few examples of the ozonization of a substrate bearing a double as well as a triple bond are known.[31] In order to avoid the presence of an excess of ozone in the reaction mixture, the reaction was carefully monitored and stopped immediately after complete consumption of **5**; reductive workup with Me_2S then gave the desired ketoaldehyde in 59% yield and with a *cis*:*trans* ratio of 72:28. Thus, under the reaction conditions epimerization of the substrate or product to the thermodynamically more stable *trans*-isomer was taking place to some extent. The ketoaldehyde was oxidized under neutral conditions with $NaClO_2/H_2O_2$,[32] and the crude epijasmonic acid thus obtained was esterified with diazomethane to provide the keto ester **6** with a diastereomeric ratio of 72:28. The final Lindlar hydrogenation to the target molecule (±)-methyl epijasmonate (**1**) did not change this ratio.

We then turned our attention to the corresponding synthesis of (±)-methyl dihydroepijasmonate (**2**). The Michael addition of lithium diallylcuprate (from allyl-tri-*n*-butylstannane, MeLi,[27] and CuI) to the commercially available enone **7** and enolate protonation with ethyl salicylate gave the ketone **8** with a *cis*:*trans* ratio of 83:17 (Scheme 3), whereas a much higher value of 94:6 resulted from the analogous reaction of **7** with the tin-free cuprate[28] and 2-(methyliminomethyl)phenol (**4**). Incidentally, this is the highest diastereoselectivity observed so far for the protonation of a chiral five-membered enolate with a chelating proton donor. Again, other chelating protonating agents displayed much lower stereoselectivities.[33]

The transformation of **8** into the target molecule (±)-methyl dihydroepijasmonate (**2**) following the route used for (±)-methyl epijasmonate (**1**) was executed without incident. Ozonolysis of **8** and reductive workup again caused a slight

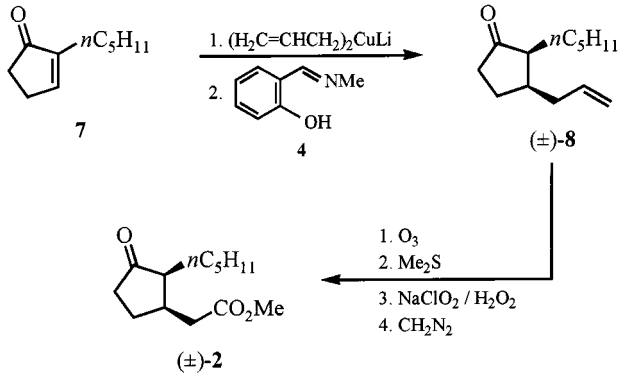


Scheme 2

Table 1. Fragrance properties of methyl dihydroepijasmonate (**2**) from different sources

Product	*cis*:*trans*	Threshold concentration (ng/L)[a]	Odor value[b]
Hedione® (Firmenich)	10:90	0.28	27 000
Cepionate® (Nippon Zeon)	30:70	0.093	82 000
Kharismal (IFF)	60:40	0.046	164 000
Super Cepionate® (Nippon Zeon)	70:30	0.040	192 000
Hedione HC® (Firmenich)	75:25	0.037	205 000
This work	91:9	0.031	249 000

[a] Olfactory detection limit. – [b] Vapor pressure (ng/L)/threshold concentration (ng/L).[7b]



Scheme 3

erosion of the diastereomeric ratio to *cis*:*trans* = 91:9, and the ketoaldehyde obtained was oxidized and esterified to give **2** with 89% yield and the same ratio of isomers. The olfactory characterization revealed that this product is superior to those available from commercial sources (see Table 1).

Conclusion

In this paper, we report diastereoselective syntheses of (±)-methyl epijasmonate (**1**) and (±)-methyl dihydroepijasmonate (**2**), making use of the diastereoselective protonation of chiral enolates with chelating proton donors. The Michael addition of lithium diallylcuprate to enone **3** and enolate protonation with 2-(methyliminomethyl)phenol (**4**) proceeded with a *cis*:*trans* selectivity of 85:15, and (±)-methyl epijasmonate (**1**) was obtained with a *cis*:*trans* ratio of 72:28 from ketone **5** by ozonolysis, oxidation, esterification and Lindlar hydrogenation. During the ozonisation, epimerization to the thermodynamically more stable *trans*-isomer takes place to some extent. The analogous transformation of enone **7** with lithium diallylcuprate and 2-(methyliminomethyl)phenol (**4**) furnished ketone **8** with 94% *ds*; this was transformed into (±)-methyl dihydroepijasmonate (**2**) with a *cis*:*trans* ratio of 91:9. The olfactory properties of this product are superior to those available from commercial sources.

Experimental Section

General Information: See preceding paper in this issue.[23] GC analyses were carried out with a Dani 86.10 gas chromatograph with hydrogen as carrier gas (0.3 bar) and an SE-30 capillary column (30 m × 0.32 mm × 0.25 μm); temperature program: 100 °C/5 min., heating rate 10 °C/min, 200 °C/30 min.

***cis*-2-(2-Pentyn-1-yl)-3-(2-propen-1-yl)cyclopentanone (5):**[25] MeLi (1.6 M solution in diethyl ether; 0.9 mL, 1.5 mmol) was added at −80 °C to a solution of allyl-tri-*n*-butylstannane (0.47 mL, 1.5 mmol) in 7 mL of THF, and the mixture was stirred for 15 min. at this temperature. In a separate flask, CuI (143 mg, 0.75 mmol) and LiCl (32 mg, 0.75 mmol) were dissolved in 3 mL of THF, and this solution was also cooled to −80 °C. The solution of allyllithium was added dropwise via a Teflon tubing to this latter mixture, and the resulting cuprate solution was warmed to −30 °C. After cooling back to −80 °C, **3**[24a] (74 mg, 0.5 mmol) in 1 mL of THF was added; the mixture was warmed to −30 °C within 1 h and then again cooled to −80 °C. It was then transferred via Teflon tubing into a solution of 2-(methyliminomethyl)phenol (**4**) (0.67 g, 5.0 mmol) in 15 mL of diethyl ether which was also kept at −80 °C. The mixture was warmed to room temperature, and 0.3 mL (5.0 mmol) of acetic acid was added. After filtration through Celite® the filtrate was washed twice with a satd. $NaHCO_3$ solution and dried with $MgSO_4$. GC analysis of the crude product obtained after removal of the solvent in vacuo revealed a ratio *cis*-**5**:*trans*-**5** of 85:15 (t_R: *cis*-**5**: 7.79 min; *trans*-**5**: 7.39 min.). Purification by column chromatography (SiO_2; petroleum ether/*tert*-butyl methyl ether, 10:1) furnished 57 mg (60%) of **5** (*cis*:*trans* = 81:19) as a colorless liquid. Alternatively, **5** was prepared with tin-free lithium diallylcuprate as follows: Allyllithium (0.86 M solution in diethyl ether; 3.5 mL, 3.0 mmol) was added at −80 °C to a solution of CuI (286 mg, 1.5 mmol) and LiCl (64 mg, 1.5 mmol) in 7 mL of THF.[28] The mixture was stirred for 5 min. at this temperature, and **3**[24a] (148 mg, 1.0 mmol) in 2 mL of THF was added. Protonation with **4** (1.35 g, 10.0 mmol) in 30 mL of diethyl ether and workup with 0.6 mL (10.0 mmol) of acetic acid were carried out as above. Yield: 114 mg (60%) of **5** (*cis*:*trans* = 80:20) as a colorless liquid. – ^{1}H NMR (C_6D_6): δ = 0.95 (t, *J* = 7.4 Hz, 3 H, 5′-H), 1.40−2.60 (m, 12 H), 4.95 (m, 2 H, 3′′-H), 5.60 (m, 1 H, 2′′-H). – ^{13}C NMR (C_6D_6): δ = 14.4 (+, C-5′), 15.5, 24.5, 32.8, 35.1, 37.6 (5−, C-4, C-5, C-1′, C-4′, C-1′′), 38.1 (+, C-3), 52.1 (+, C-2), 77.6, 82.5 (2 ×, C-2′, C-3′), 116.3 (−, C-3′′), 137.1 (+, C-2′′), 216.1 (x, C-1).

***cis*-3-(2-Oxoethyl)-2-(2-pentyn-1-yl)cyclopentanone:** Ozone was passed through a solution of **5** (*cis*:*trans*=80:20) (143 mg, 0.75 mmol) in 20 mL of dichloromethane at −80 °C. After 1, 2, and 3 min., respectively, the introduction of ozone was interrupted,

a sample of the reaction mixture was treated with a small amount of Me_2S and examined by TLC. After 3 min. reaction time, the starting material was consumed completely, and the mixture was purged with argon for 5 min. before addition of 0.1 mL (1.4 mmol) of Me_2S. After warming to room temperature, the solvent was removed in vacuo, and the residue was dissolved in diethyl ether and washed with water. The aqueous phase was washed three times with diethyl ether, and the combined organic layers were dried with $MgSO_4$. Purification of the crude product by column chromatography (SiO_2; cyclohexane/diethyl ether, 3:2) provided 72 mg (50%) of *cis*-3-(2-oxoethyl)-2-(2-pentyn-1-yl)cyclopentanone as a colorless oil which was used immediately in the next step. The diastereomeric ratio was determined by GC to be *cis*:*trans* = 72:28 (t_R: *cis*: 9.21 min; *trans*: 8.88 min.).

***cis*-3-(2-Methoxycarbonylmethyl)-2-(2-pentyn-1-yl)cyclopentanone (6):**[1b,24a,25] A solution of $NaH_2PO_4 \cdot H_2O$ (0.14 g, 1.0 mmol) and H_2O_2 (30%; 0.05 mL, 0.5 mmol) in 2 mL of water was added to a solution of *cis*-3-(2-oxoethyl)-2-(2-pentyn-1-yl)cyclopentanone (*cis*:*trans* =72:28; 70 mg, 0.36 mmol) in 5 mL of acetonitrile. A solution of $NaClO_2$ (80%; 85 mg, 0.75 mmol) in 7 mL of water was then added dropwise with slight cooling, and the mixture was stirred at room temperature for 24 h. After addition of a small amount of sodium sulfite, the mixture was washed three times with diethyl ether, and the combined organic phases were dried with $MgSO_4$. Removal of the solvent in vacuo provided 90 mg crude acid which was dissolved in 2 mL of diethyl ether; after addition of 2 drops of methanol, an ethereal diazomethane solution was added until the evolution of nitrogen had ceased and the reaction mixture remained yellow. The mixture was left at room temperature for 30 min. and then purged with argon; removal of the solvent in vacuo gave 80 mg of crude keto ester **6** as a yellow oil which was used without purification in the next step. GC analysis revealed a *cis*:*trans* ratio of 72:28 (t_R: *cis*-**6**: 11.78 min; *trans*-**6**: 11.42 min.).

(±)-Methyl Epijasmonate (1):[19,20] A solution of **6** (20 mg, 0.09 mmol) (*cis*:*trans* = 72:28) in 5 mL of hexane was treated with 2 mg of Lindlar catalyst ($Pd/Pb/CaCO_3$) and hydrogenated at ambient pressure for three days. The catalyst was filtered off and the solvent was removed in vacuo, giving 18 mg (89%) of (±)-methyl epijasmonate (*cis*-**1**:*trans*-**1** = 72:28 according to GC analysis; t_R: *cis*-**1**: 11.56 min; *trans*-**1**: 11.15 min.). – ^{1}H NMR (C_6D_6): δ = 0.92 (t, *J* = 7.3 Hz, 3 H, 5′-H), 1.60–2.85 (m, 12 H), 3.61 (s, 3 H, OMe), 5.32–5.41 (m, 2 H, 2′-H, 3′-H). – ^{13}C NMR (C_6D_6): δ = 14.1 (+, C-5′), 20.3, 22.8, 25.6 (3–, C-4, C-1′, C-4′), 33.6, 35.0 (2–, C-5, C-1′′), 35.6 (+, C-3), 51.3 (+, OMe), 52.5 (+, C-2), 125.3 (+, C-2′), 133.0 (+, C-3′), 172.7 (x, C-2′′), 218.2 (x, C-1).

***cis*-2-Pentyl-3-(2-propen-1-yl)cyclopentanone (8):** Analogous to the preparation of **5** with tin-free lithium allylcuprate, compound **7** (152 mg, 1.0 mmol) was treated with the cuprate prepared from CuI (286 mg, 1.5 mmol), LiCl (64 mg, 1.5 mmol), and allyllithium (0.86 M solution in diethyl ether; 3.5 mL, 3.0 mmol),[28] and the protonation was carried out with **4** (1.35 g, 10.0 mmol). Workup with 0.6 mL (10.0 mmol) of acetic acid and purification of the crude product by column chromatography (SiO_2; petroleum ether/*tert*-butyl methyl ether, 10:1) yielded 136 mg (70%) of **8** as a slightly yellow oil (*cis*:*trans* = 94:6 according to GC analysis; t_R: *cis*-**8**: 7.66 min; *trans*-**5**: 7.10 min.). – ^{1}H NMR (C_6D_6): δ = 0.81 (t, *J* = 7.0 Hz, 3 H, 5′-H), 1.10–2.39 (m, 16 H), 4.88 (dd, *J* = 17.0/1.5 Hz, 1 H, 3′′-H), 4.95 (dd, *J* = 9.4/1.2 Hz, 1 H, 3′′-H), 5.76 (m, 1 H, 2′′-H). – ^{13}C NMR (C_6D_6): δ = 14.3 (+, C-5′), 22.9, 24.4, 24.8, 27.7, 32.3, 32.9, 34.8 (7–, C-4, C-5, C-1′, C-2′, C-3′, C-4′, C-1′′), 38.3 (+, C-3), 53.0 (+, C-2), 116.2 (–, C-3′′),137.2 (+, C-2′′), 217.2 (x, C-1). – IR (neat): $\tilde{\nu}$ = 3050 cm^{-1} (s), 2950 (s, C–H), 1742 (s, C=O). – MS: *m*/*z* (%) = 194 (1) [M$^+$], 83 (100). – HRMS calcd. for $C_{13}H_{22}O$ 194.1670; found 194.1667.

***cis*-3-(2-Oxoethyl)-2-pentylcyclopentanone:** Similar to the preparation of *cis*-3-(2-oxoethyl)-2-(2-pentyn-1-yl)cyclopentanone, ozone was passed through a solution of **8** (*cis*:*trans* = 94:6; 291 mg, 1.5 mmol) in 20 mL of methanol at –80 °C until an intense blue color persisted (ca. 15 min.). The mixture was then purged with argon for 5 min. before addition of 0.2 mL (2.7 mmol) of Me_2S. After warming to room temperature, the solvent was removed in vacuo, and the residue was dissolved in diethyl ether and washed with water. The aqueous phase was washed three times with diethyl ether, and the combined organic layers were dried with $MgSO_4$. Purification of the crude product by column chromatography (SiO_2; cyclohexane/diethyl ether, 3:2) provided 206 mg (70%) of *cis*-3-(2-oxoethyl)-2-pentylcyclopentanone as a colorless oil. The diastereomeric ratio was determined by GC to be *cis*:*trans* = 91:9 (t_R: *cis*: 9.23 min; *trans*: 8.67 min.). – ^{1}H NMR (C_6D_6): δ = 0.89 (t, *J* = 7.1 Hz, 3 H, 5′-H), 1.10–2.35 (m, 16 H), 9.18 (s, 1 H, 2′′-H). – ^{13}C NMR (C_6D_6): δ = 14.3 (+, C-5′), 22.9, 25.2, 25.7, 27.5, 32.2, 33.0, 34.8 (7–, C-4, C-5, C-1′, C-2′, C-3′, C-4′, C-1′′),33.0 (+, C-3), 52.1 (+, C-2), 199.7 (+, C-2′′), 216.6 (x, C-1).

(±)-Methyl Dihydroepijasmonate (2):[20g,21] The oxidation of *cis*-3-(2-oxoethyl)-2-pentylcyclopentanone (*cis*:*trans* = 91:9; 147 mg, 0.75 mmol) with $NaH_2PO_4 \cdot H_2O$ (0.21 g (1.5 mmol), H_2O_2 (30%; 0.08 mL, 0.8 mmol) and $NaClO_2$ (80%; 0.12 g, 1.1 mmol), as well as the subsequent esterification of the crude acid (0.17 g) with diazomethane, were carried out according to the preparation of **6**. Purification of the crude product by column chromatography (SiO_2; cyclohexane/diethyl ether, 3:2) yielded 151 mg (89%) of **2** as a colorless liquid. According to GC analysis, the *cis*:*trans* ratio was 91:9 (t_R: *cis*-**2**: 11.87 min; *trans*-**2**: 11.42 min.). – ^{1}H NMR (C_6D_6): δ = 0.85 (t, *J* = 7.0 Hz, 3 H, 5′-H), 1.00–2.55 (m, 16 H), 3.31 (s, 3 H, OMe). – ^{13}C NMR (C_6D_6): δ = 14.3 (+, C-5′), 22.9, 25.0, 25.7, 27.5, 32.2, 33.6, 34.8 (7–, C-4, C-5, C-1′, C-2′, C-3′, C-4′, C-1′′), 35.8 (+, C-3), 51.1 (+, OMe), 52.4 (+, C-2), 172.5 (x, C-2′′), 216.9 (x, C-1).

Acknowledgments

We thank the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for financial support of this work, and Dr. P. Kraft (Givaudan Roure Research Ltd., Geneva, Switzerland) for the olfactory investigation of our sample of (±)-methyl dihydroepijasmonate and for the data given in Table 1.

[1] [1a] E. Demole, E. Lederer, D. Mercier, *Helv. Chim. Acta* **1962**, *45*, 675–685. – [1b] E. Demole, M. Stoll, *Helv. Chim. Acta.* **1962**, *45*, 692–703.
[2] R. Nishida, T. E. Acree, *J. Agric. Food. Chem.* **1984**, *32*, 1001–1003.
[3] A. Kobayashi, M. Kawamura, Y. Yamamoto, K. Shimizu, K. Kubota, T. Yamanishi, *Agric. Biol. Chem.* **1988**, *52*, 2299–2303.
[4] J. L. Ward, M. H. Beale, *J. Chem. Soc., Perkin Trans. 1* **1993**, 2379–2381.
[5] *cis* and *trans* relate to the stereogenic centers at C-2 and C-3 of the cyclopentane ring; the double bond of the pentenyl side chain always has the (*Z*)-configuration.
[6] R. Nishida, T. E. Acree, H. Fukami, *J. Agric. Food. Chem.* **1985**, *33*, 425–427.
[7] [7a] E. Demole, in *Fragrance Chemistry* (Ed.: E. T. Theimer), Academic Press, New York, **1982**, pp. 349–396. – [7b] G. Fráter, J. A. Bajgrowicz, P. Kraft, *Tetrahedron* **1998**, *54*, 7633–7703. – [7c] P. Kraft, J. A. Bajgrowicz, C. Denis, G.

Fráter, *Angew. Chem.* **2000**, *112*, 3106−3138; *Angew. Chem. Int. Ed.* **2000**, *39*, 2980−3010.
[8] O. Miersch, B. Brückner, J. Schmidt, G. Sembdner, *Phytochemistry* **1992**, *31*, 3835−3837.
[9] Y. Koda, Y, Kikuta, H. Tazaki, Y. Tsujino, S. Sakamura, T. Yoshihara, *Phytochemistry* **1991**, *30*, 1435−1438.
[10] R. A. Weidhase, H. Kramell, J. Lehmann, H. Liebisch, W. Lerbs, B. Parthier, *Plant. Sci.* **1987**, *51*, 177.
[11] H. Fukui, K. Koshimizu, Y. Yamazaki, S. Usuda, *Agric. Biol. Chem.* **1977**, *41*, 189−194.
[12] E. Falkenstein, B. Groth, A. Mithöfer, E. W. Weiler, *Planta* **1991**, *185*, 316−322.
[13] [13a] W. Boland, J. Hopke, J. Donath, J. Nüske, F. Bublitz, *Angew. Chem.* **1995**, *107*, 1715−1717; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1600−1602. − [13b] W. Boland, T. Koch, K. Bandemer, *Helv. Chim. Acta* **1997**, *80*, 838−850.
[14] T. C. Baker, R. Nishida, W. L. Roelofs, *Science* **1981**, *214*, 1359−1361.
[15] Y. Koda, Y. Kikuta, T. Kitahara, T. Nishi, K. Mori, *Phytochemistry* **1992**, *31*, 1111−1114.
[16] [16a] B. A. Vick, D. C. Zimmermann, *Plant. Physiol.* **1984**, *75*, 458−461. − [16b] L. Crombie, D. O. Morgan, *J. Chem. Soc., Chem. Commun.* **1988**, 558−560.
[17] E. Demole, E. Lederer, D. Mercier, *Helv. Chim. Acta* **1962**, *45*, 685−692.
[18] K. Bauer, D. Grabe, *Common Fragrance and Flavour Materials*, VCH, Weinheim, **1985**.
[19] [19a] H. Tanaka, S. Torii, *J. Org. Chem.* **1975**, *40*, 462−465. − [19b] T. K. Sarkar, B. Ghorai, A. Banerji, *Tetrahedron Lett.* **1994**, *35*, 6907−6908. − [19c] T. K. Sarkar, B. Ghorai, S. K. Nandy, B. Mukherjee, A. Banerji, *J. Org. Chem.* **1997**, *62*, 6006−6011.
[20] [20a] F. T. Montforts, I. Gesing-Zibulak, W. Grammenos, *Helv. Chim. Acta* **1989**, *72*, 1852−1859. − [20b] K. Weinges, U. Lernhardt, *Liebigs Ann. Chem.* **1990**, 751−754. − [20c] G. Helmchen, A. Goeke, G. Lauer, M. Urmann, J. Fries, *Angew. Chem.* **1990**, *102*, 1079−1081; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1024−1025. − [20d] T. Kitahara, T. Nishi, K. Mori, *Tetrahedron* **1991**, *47*, 6999−7006. − [20e] L. Crombie, K. M. Mistry, *J. Chem. Soc., Perkin Trans. 1* **1991**, 1981−1991. − [20f] H. Stadtmüller, P. Knochel, *Synlett* **1995**, 463−464. − [20g] G. J. Roth, S. Kirschbaum, H. J. Bestmann, *Synlett* **1997**, 618−620. − [20h] C. Fehr, J. Galindo, *Angew. Chem.* **2000**, *112*, 581−585; *Angew. Chem. Int. Ed.* **2000**, *39*, 569−573.
[21] [21a] K. Weinges, U. Lernhardt, *Liebigs. Ann. Chem.* **1990**, 751−754. − [21b] T. Ebata, K. Matsumoto, H. Matsushita, *Heterocycles* **1994**, *38*, 2231−2241. − [21c] Firmenich S. A. (Erf.: V. Rautenstrauch, J. Riedhauser), WO Patent 9,600,206; *Chem. Abstr.* **1996**, *124*, 232126c. − [21d] D. A. Dobbs, K. P. M. Vanhessche, E. Brazi, V. Rautenstrauch, J.-Y. Lenoir, J.-P. Genêt, J. Wiles, S. H. Bergens, *Angew. Chem.* **2000**, *112*, 2080−2083; *Angew. Chem. Int. Ed.* **2000**, *39*, 1992−1995.
[22] [22a] N. Krause, *Angew. Chem.* **1994**, *106*, 1845−1847; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1764−1765. − [22b] N. Krause, S. Ebert, A. Haubrich, *Liebigs Ann./Recueil* **1997**, 2409−2418. − [22c] N. Krause, M. Mackenstedt, *Tetrahedron Lett.* **1998**, *39*, 9649−9650.
[23] S. Ebert, N. Krause, preceding paper in this issue.
[24] [24a] G. Büchi, B. Egger, *J. Org. Chem.* **1971**, *36*, 2021−2023. − [24b] P. Dubs, R. Stüssi, *Helv. Chim. Acta* **1978**, *61*, 990−997. − [24c] R. Ballini, M. Petrini, *Synth. Commun.* **1989**, *19*, 575−583.
[25] A. E. Greene, P. Crabbé, *Tetrahedron Lett.* **1976**, 4867−4870.
[26] B. H. Lipshutz, S. Sengupta, *Org. React.* **1992**, *41*, 135−631
[27] B. H. Lipshutz, E. L. Ellsworth, S. H. Dimock, R. A. J. Smith, *J. Am. Chem. Soc.* **1990**, *112*, 4404−4410.
[28] G. Whitesides, H. O. House, W. F. Fischer, J. San Filippo, R. W. Basco, *J. Am. Chem. Soc.* **1969**, *91*, 4871−4882.
[29] Ratio of *cis*-**5**:*trans*-**5** for the protonation of the enolate obtained from **3** and lithium diallylcuprate: [27]2-(phenyliminomethyl)phenol: 20:80; salicylic aldehyde: 23:77; *tert*-butyl salicylate: 38:62; 2-(benzyliminomethyl)phenol: 38:62; phenyl salicylate: 41:59; ethyl salicylate: 44:56; methyl salicylate: 46:54.
[30] W. A. Prior, C. K. Govindan, D. F. Church, *J. Am. Chem. Soc.* **1982**, *104*, 7563−7570.
[31] P. M. McCurry Jr., K. Abe, *Tetrahedron Lett.* **1974**, 1387−1390.
[32] E. Dalcanale, F. Montanari, *J. Org. Chem.* **1986**, *51*, 568−569.
[33] Ratio of *cis*-**8**:*trans*-**8** for the protonation of the enolate obtained from **7** and lithium diallylcuprate: [27]2-(benzyliminomethyl)phenol: 18:82; 2-(phenyliminomethyl)phenol: 30:70; salicylic aldehyde: 33:67; phenyl salicylate: 51:49; *tert*-butyl salicylate: 55:45; methyl salicylate: 65:35.

Received March 1, 2001
[O01100]