Syntheses and Odor Descriptions of Cyclopropanated Compounds

Part 5[1])

Analogs of Methyl Jasmonate to Fix the Relative Configuration of the Two Side Chains

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Analogs of methyl jasmonate (= methyl (1*R**,2*R**)-3-oxo-2-[(*Z*)-pent-2-enyl]cyclopentaneacetate; MJA) bearing a cyclopropane ring, double bond, or a F-substituent were synthesized, and their odor characteristics were examined. Most of the analogs with the same stereochemical properties as methyl epijasmonate showed odor properties superior to MJA. Interestingly, the enol acetate of MJA had a diffusive orchid-like note.

1. Introduction. – Methyl jasmonate (= methyl (1*R**,2*R**)-3-oxo-2-[(*Z*)-pent-2-enyl]cyclopentaneacetate; MJA; **1**), supplied by industrial production [2], is greatly appreciated in perfumery [3] as an important source for jasmine note since its discovery [4]. *Nishida et al*. found that only (+)-methyl epijasmonate (**2**), which is thermodynamically unstable, has the key jasmine note [5]. We have investigated the odor alteration of natural odorants by introducing cyclopropane rings [1][6]. Previous studies revealed that cyclopropanation on the C=C bond of the side chain intensified the original odor, while that on the cyclopentanone ring of jasmone and methyl dihydrojasmonate gave poor results [6a,b]. Based on these results, we intended to introduce a C=C bond [7], a F-substituent [8], or a cyclopropane ring on the cyclopentanone ring of MJA (**1**) to produce analogs (*e.g.*, **3**, **4**, and **5**; *Fig.*) with the same configuration as that of methyl epijasmonate. Namely, the two side chains of each analog were fixed in a *cis*-orientation. In addition to the compounds shown above, the 12,12,12-trifluoro analog **7** was prepared for odor description [9]. We expected that modification at the end of the side chain might alter the original odor quality, because 11,12-didehydrojasmonate **8**, isolated from the orchid *Cymbidium goeringii*, contributed to its unique lily-like scent [10]. Here, we describe the syntheses and odor evaluations of analogs with fixed structures and related compounds.

2. Results and Discussion. – 2.1. *Synthesis of the Analogs.* Introduction of a C=C bond between C(3) and C(7)[2]) as in compound **3** could fix the geometry of the two side chains. Synthesis of **3** from (±)-MJA (**1**) was reported previously by us and other

[1]) For Part 4, see [1].
[2]) Trivial C-atom numbering.

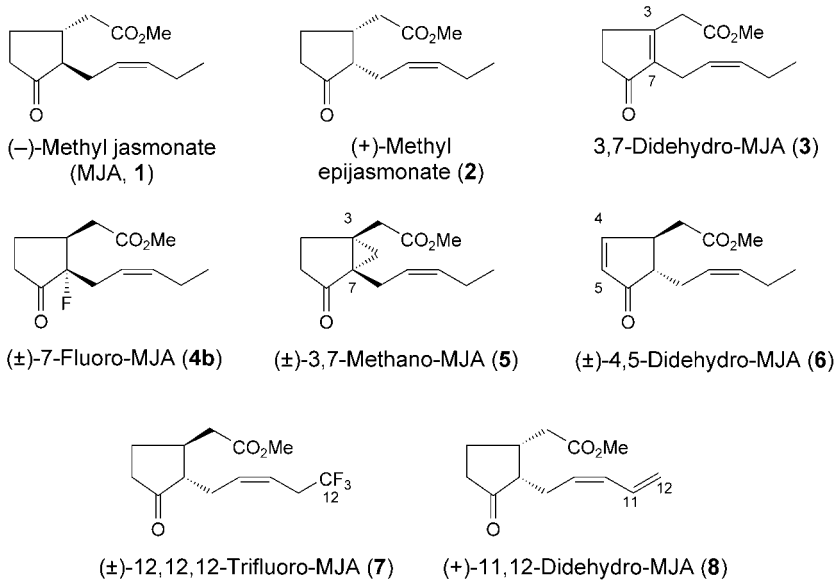


Figure. *Structures of methyl jasmonate* (**1**) *and related compounds*

groups [7]. Methyl 4,5-didehydrojasmonate (**6**), isolated from jasmine absolute [11a], was prepared as a synthetic intermediate and was subjected to odor evaluation. This compound contained $<3\%$ of epijasmonate-type diastereoisomers. Several syntheses of **6** were also reported [11b–d].

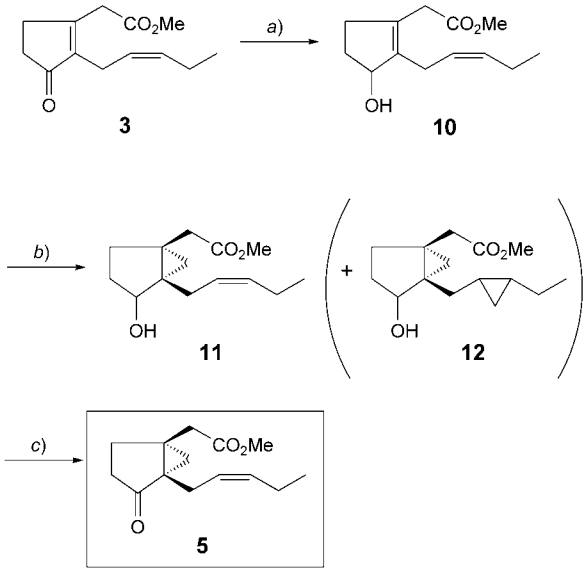
The 7-fluorojasmonates **4a** and **4b** were synthesized according to the method of *Taapken et al.* [8]. We tentatively determined the relative configuration of each compound from the odor evaluation. The intermediate enol acetate **9** was also tested for odor evaluation.

Synthesis of 3,7-methanojasmonate (**5**) was performed by a similar method previously reported by us [6b]. The keto group of methyl 3,7-didehydrojasmonate (**3**) was selectively reduced with $NaBH_4$ in the presence of $CeCl_3$ to give cucurbate derivative **10** (*Scheme*). Selective cyclopropanation [12] of the C=C bond in the cyclopentene ring, which is located closer to the OH group, was achieved with a smaller amount of reagents, because mono- and dicyclopropanated compounds **11** and **12** were hardly separable on TLC. Thus, the yield was low, and most of the starting material **10** was recovered. Finally, the OH group was oxidized with *Dess–Martin* periodinane [13] to give the desired compound **5**.

The methyl 12,12,12-trifluorojasmonate (**7**) was prepared by our method reported previously [9]. The ^{1}H- and ^{13}C-NMR-spectral signals were re-assigned by DEPT, ^{1}H-^{1}H COSY, HMBC, and HSQC methods. It contained *ca.* 91% of **7** and 4% of 7-*epi*-**7**.

2.2. *Odor Evaluation*. The results of the odor evaluation for the synthetic compounds are summarized in the *Table*. The compounds **3**, **4a**, **4b**, **5**, **6**, and **7** showed floral jasmine note with slight modification. Especially, odor quality and volume of **3**, **4b**, and **5**, designed as epijasmonate analogs, were superior to those of MJA. The *cis*-

Scheme. *Synthesis of Cyclopropanated Analogs*



a) $NaBH_4$, $CeCl_3 \cdot 7\,H_2O$, MeOH (78%). *b*) CH_2I_2, Et_2Zn, THF. *c*) *Dess–Martin* periodinane, CH_2Cl_2 (27% over two steps).

configuration of **4b** was presumed by these results. Consequently, we concluded that the key jasmine note of methyl epijasmonate (**2**) was mainly due to the orientation of the two side chains. In contrast to the plant physiological activities, effects of electrostatic properties around C(3) and/or C(7) in the cyclopentanone ring was not relevant for the odor. It was surprising that the analog **4a** (MJA-type relative configuration) had some jasmine note, as *Nishida et al.* had reported that pure MJA had not shown jasmine note [5]. We thought that the F-substituent slightly affected the odor property.

Modification of the cyclopentanone ring as in **6** altered the original odor to more green-like. For compounds **6** and **7**, the corresponding epijasmonate-type compounds (3–4%) would be more responsible for odor quality.

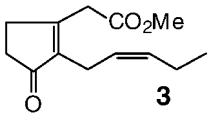
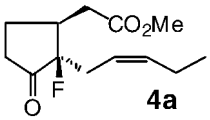
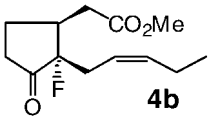
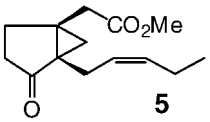
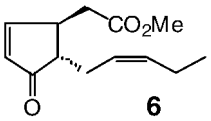
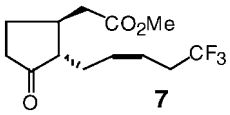
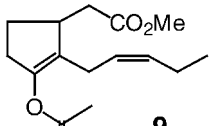
The result that the 12,12,12-trifluoro analog **7** preserved jasmine note, indicating that the electrostatic property and/or bulkiness at the end of the side chain influenced the odor property. In addition, further modification around these positions would be useful to develop new odors as in the derivative **8**.

Interestingly, MJA-enol acetate **9** did not have the jasmine note, but a powerful and diffusive orchid note.

Experimental Part

General. Methyl jasmonate (*JASMONEIGE*®): *Nippon Zeon Co., Ltd.* Column chromatography (CC): *Merck* silica gel *60* (70–230 mesh) and *Kanto* silica gel *60 N* (70–140 mesh). GLC: *Hewlett-Packard HP 6890*; column, *HP-1* (30 m × 0.25 mm, *Hewlett-Packard*); column temp., 150° to 180° at 5°/min (*A*), 50° to 200° at 5°/

Table. *Results of Odor Evaluations of the Synthetic Compounds*

Compounds	Odor description
MJA (**1**)	Fresh-sweet-floral note
 **3**	More powerful fresh-green-floral note with slightly woody nuances
 **4a**	Delicate jasmine note (but monotone and less order than MJA)
 **4b**	Full bodied, sweet floral, deep jasmine note (superior to MJA)
 **5**	Powerful floral jasmine note (similar to MJA)
 **6**	Green-floral note, having weak and less volume than MJA and **3** (contained $<3\%$ *epi*-form)
 **7**	Jasmine note inferior to MJA (contained 4% *epi*-form)
 **9**	Powerful diffusive *orchid* note

min (*B*); injection temp., 250°; detector temp., 250°. IR: *Jeol JIR DIAMOND20 FT-IR*. ^{1}H- and ^{13}C-NMR: *Varian Unity 600* (600 MHz for ^{1}H and 150 MHz for ^{13}C) and *Varian Unity Inova-500* (500 MHz for ^{1}H) in $CDCl_3$. Mass spectra: *Jeol JMS-700*.

Methyl 3,7- and 4,5-Didehydrojasmonates[1]) (**3** and **6**, resp.). These compounds were prepared according to our procedure [7]. **3**: GLC (*B*): t_R 26.3 min (82%); **6**: GLC (*B*): t_R 24.8 min (91%) and 25.7 min (2.3%, epijasmonate form).

Methyl 7-Fluorojasmonates (**4a** and **4b**). These compounds were prepared according to the method of *Taapken et al.* [8] *via* MJA-enol acetate **9**. ^{1}H- and ^{13}C-NMR spectral data were reassigned.

Data of **4a** (less polar): GLC (*A*): t_R 9.5 min (93.2%). ^{1}H-NMR (500 MHz)[1]): 0.97 (*t*, *J* = 7.7, Me(12)); 1.75 (*m*, 1 H–C(4)); 2.07 (*dq*, *J* = 1.4, 7.4, CH_2(11)); 2.19 (*m*, 1 H–C(5)); 2.21 (*m*, 1 H–C(4)); 2.39 (*dd*, *J* = 15.9, 9.6,

1 H–C(2)); 2.47 (*m*, 1 H–C(5)); 2.48 (*m*, H–C(3)); 2.49 (*m*, 1 H–C(8)); 2.63 (*m*, 1 H–C(8)); 2.72 (*dd*, *J* = 15.9, 4.1, 1 H–C(2)); 3.71 (*s*, MeO); 5.19 (*dtt*, *J* = 7.7, 9.3, 1.7, H–C(10)); 5.71 (*m*, H–C(9)). ^{13}C-NMR (75 MHz): 13.7 (C(12)); 20.5 (C(11)); 24.2 (C(4)); 29.2 (*d*, ^{2}J(C,F) = 24.6, C(8)); 32.8 (*d*, ^{3}J(C,F) = 7.4, C(2)); 34.9 (C(5)); 39.2 (*d*, ^{2}J(C,F) = 18.9, C(3)); 51.7 (MeO); 97.1 (*d*, ^{1}J(C,F) = 186, C(7)); 119.8 (*d*, ^{3}J(C,F) = 9.7, C(9)); 136.8 (C(10)); 172.6 (C(1)); 211.6 (*d*, ^{2}J(C,F) = 16.0, C(6)).

Data of **4b** (more polar): GLC (*A*): t_R 11.4 min (84%). ^{1}H-NMR (300 MHz): 0.96 (*t*, *J* = 7.6, Me(12)); 1.59 (*m*, 1 H–C(4)); 2.02 (*m*, CH_2(11)); 2.33 (*m*, 1 H–C(4)); 2.36 (*m*, 1 H–C(2)); 2.50 (*m*, CH_2(8)); 2.71 (*dd*, *J* = 15.1, 8.9, 1 H–C(2)); 2.77 (*m*, H–C(3)); 3.72 (*s*, MeO); 5.34 (*m*, H–C(9)); 5.57 (*m*, H–C(10)). ^{13}C-NMR (75 MHz): 13.9 (C(12)); 20.6 (C(11)); 22.8 (*d*, ^{3}J(C,F) = 8.4, C(4)); 27.8 (*d*, ^{2}J(C,F) = 25.4, C(8)); 33.4 (C(5)); 33.6 (C(2)); 41.3 (*d*, ^{2}J(C,F) = 21.1, C(3)); 52.0 (MeO); 98.6 (*d*, ^{1}J(C,F) = 193, C(7)); 119.1 (*d*, ^{3}J(C,F) = 6.3, C(9)); 136.2 (C(10)); 171.9 (C(1)); 211.9 (C(6)).

9: GLC (*A*): t_R 17.4 min (82%).

*Methyl 3-Hydroxy-2-[(*Z*)-pent-2-enyl]cyclopent-1-eneacetate* (**10**). To a soln. of **3** (1.01 g, 4.54 mmol) and $CeCl_3 \cdot 7\ H_2O$ (1.82 g, 4.89 mmol) in MeOH (20 ml) $NaBH_4$ (169 mg, 4.46 mmol) was added, and the mixture was stirred at r.t. for 5 min. The mixture was poured into a sat aq. NH_4Cl soln. and extracted with AcOEt. The org. layer was washed with a sat. aq. $NaHCO_3$ soln. and brine, dried ($MgSO_4$), and concentrated *in vacuo.* The residue was chromatographed on neutral silica gel (hexane/AcOEt 20 : 1) to give **10** (883 mg, 3.94 mmol, 87%). Pale yellow oil. IR (film): 3400*m* (O–H), 3010*m* (C=C), 2960*s*, 2940*s*, 280*m*, 1740*s* (C=O), 1430*m*, 1270*m*, 1190*m*, 1170*m*, 1040*m*. ^{1}H-NMR (500 MHz): 0.99 (*t*, *J* = 7.6, *Me*CH_2); 1.64–1.69 (*m*, CH_2(4)); 2.12–2.18 (*m*, MeCH_2); 2.24–2.32 (*m*, CH_2(5)); 2.50 (*t*, *J* = 10.7, H–C(3)); 2.86–2.98 (*m*, 2 H); 3.11–3.20 (*m*, CH_2CO_2Me); 3.68 (*s*, MeO); 4.71 (*s*, OH); 5.32 (*m*, C(2)CH_2C*H*=); 5.45 (*m*, C(2)CH_2CH=C*H*). EI-MS: 224, 206, 191, 177, 175, 147, 132, 117, 105, 91, 84, 79, 77, 41. HR-EI-MS: 224.1412 (M^+, $C_{13}H_{20}O_3^+$; calc. 224.1412).

Methyl 3,7-Methanojasmonate (**5**). To a soln. of **10** (883 mg, 3.94 mmol) in THF (20 ml) was added Et_2Zn (1M in hexane, 4 ml, 4 mmol), followed by CH_2I_2 (960 mg, 3.6 mmol) at 0° for 30 min under N_2, and the mixture was heated under reflux for 2 d. The mixture was poured into a sat. aq. NH_4Cl soln. and extracted with AcOEt. The org. layer was washed with a sat. aq. $NaHCO_3$ soln. and brine, dried ($MgSO_4$), and concentrated *in vacuo* to give a crude cyclopropanated compound (**11**, 984 mg) as pale yellow oil. IR (film): 3400*s* (O–H), 3050*w*, 1735*s* (C=O). This alcohol was used in the next step without further purification. The crude oil and *Dess–Martin* periodinane (1.70 g, 4.00 mmol) in CH_2Cl_2 (10 ml) was stirred at r.t. for 1 h. The mixture was diluted with AcOEt, the reaction was quenched with a sat. aq. $Na_2S_2O_3$ soln., the mixture was washed with a sat. aq. $NaHCO_3$ soln. and brine, dried ($MgSO_4$), and concentrated *in vacuo.* The residue was purified by neutral silica-gel chromatography (hexane/AcOEt 10 : 1–5 : 1) to give **5** (229 mg, 0.966 mmol, 25% from **3**). Pale yellow oil. GLC: t_R 15.1 min (75%). IR (film): 3064*w*, 2962*m*, 2937*m*, 2875*m*, 1730*s* (C=O), 1436*m*, 1218*m*, 1070*m*, 771*s*. ^{1}H-NMR (600 MHz): 0.97 (*t*, *J* = 7.4, Me(12)); 1.03 (*d*, *J* = 4.9, 1 H, methano); 1.19 (*d*, *J* = 4.9, 1 H, methano); 1.97 (*m*, 1 H–C(4)); 2.05 (*dq*, *J* = 7.4, 7.4, CH_2(11)); 2.12 (*m*, CH_2(5)); 2.14 (*m*, 1 H–C(4)); 2.27 (*dd*, *J* = 15.7, 6.6, 1 H–C(8)); 2.44 (*dd*, *J* = 15.7, 7.2, 1 H–C(8)); 2.47 (*d*, *J* = 16.2, 1 H–C(2)); 2.64 (*d*, *J* = 16.2, 1 H–C(2)); 3.72 (*s*, MeO); 5.28 (*m*, H–C(9)); 5.40 (*m*, H–C(10)). ^{13}C-NMR (125 MHz): 14.0 (C(12)); 20.6 (C(11)); 23.6 (methano); 23.7 (C(8)); 27.0 (C(4)); 32.5 (C(5)); 34.0 (C(7)); 38.2 (C(2)); 40.9 (C(3)); 51.8 (MeO); 123.4 (C(9)); 133.0 (C(10)); 171.8 (C(1)); 214.5 (C(6)). EI-MS: 236, 221, 207, 205, 177, 163, 147, 133, 121, 105, 91, 79, 77, 59, 41. HR-EI-MS: 236.1412 (M^+, $C_{14}H_{20}O_3^+$; calc. 236.1412).

Methyl 12,12,12-Trifluorojasmonate (**7**). This compound was prepared according to our procedure [9]. GLC (*A*): t_R 8.7 min (91%), 9.3 min (4.2% of 7-*epi*-**7**). ^{1}H-NMR (600 MHz): 1.52 (*pseudo-dt*, *J* = 19.5, 10.5, 1 H–C(4)); 1.95 (*pseudo-dt*, *J* = 10.3, 5.3, H–C(7)); 2.12 (*ddd*, *J* = 20.3, 11.5, 8.8, 1 H–C(5)); 2.26 (*m*, H–C(3)); 2.28 (*m*, 1 H–C(4)); 2.35 (*m*, H–C(2)); 2.37 (*m*, 1 H–C(8)); 2.39 (*m*, 1 H–C(5)); 2.66 (*dd*, *J* = 15.4, 4.4, 1 H–C(2)); 2.8–3.0 (*m*, CH_2(11)); 3.70 (*s*, MeO); 5.49 (*pseudo-dt*, *J* = 9.5, 7.3, H–C(10)); 5.71 (*dt*, *J* = 9.5, 8.0, H–C(9)). ^{13}C-NMR (150 MHz): 25.4 (C(8)); 27.2 (C(4)); 32.2 (*q*, ^{2}J(C,F) = 29.5, C(11)); 37.5 (C(5)); 37.7 (C(3)); 38.5 (C(2)); 51.6 (MeO), 53.7 (C(7)); 119.3 (*q*, ^{3}J(C,F) = 3.3, C(10)); 126.0 (*q*, ^{1}J(C,F) = 276, C(12)); 132.4 (C(9)); 172.3 (C(1)); 218.3 (C(6)).

Tests of Odor Evaluations. A test of odor evaluation was performed by an experienced panelist on an EtOH solution (10% (*v*/*v*)) of each sample on a blotter paper. The odor characteristics and intensity of each sample were compared with those of *(±)-methyl jasmonate* (**1**).

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