Optical Resolution of Methyl Jasmonate and Methyl Epijasmonate

Ritsuo Nishida, Terry E. Acree* and Hiroshi Fukami

Pesticide Research Institute, Kyoto University,
Kyoto 606, Japan
*New York State Agricultural Experiment Station, Cornell University,
Geneva, New York 14456, U.S.A.

Received August 27, 1984

Optical isomers of methyl jasmonate were resolved from a commercial mixture via the formation of bornyl jasmonate diastereoisomers. The symmetry and magnitude of the optical rotation spectra, and the observation that only one isomer, (+)-methyl epijasmonate had the characteristic methyl jasmonate odor indicated that these preparations were optically pure.

In 1962, methyl jasmonate, (−)-methyl 2-(2-Z-pentenyl)-3-oxocyclopentyl-1-acetate (I in Fig. 1), was characterized as a fragrant component of jasmin flower oil.1 Soon afterwards, the absolute configuration of its two asymmetric centers was determined to be 1R and 2R.2 Today, this compound and its analogues are synthesized and used in many commercial fragrances.3 Recently, an isomer, methyl epijasmonate (II in Fig. 1),4 was identified in the hairpencils of the Oriental fruit moth, Grapholitha molesta (Busck), as a synergistic component of male sex pheromone.5 6 This same isomer was also isolated from lemon peels, Citrus limon Burm.,7 where it seemed to contribute odor. During these later studies, it was noticed that the characteristic odor of synthetic methyl jasmonate seemed to be caused by the presence of small amounts of methyl epijasmonate. Since most preparations of methyl jasmonate consist of an equilibrium mixture of the 2-epimers in a ratio of approximately 95:5,8 it was not clear which isomer was responsible for the various biological activities ascribed to methyl jasmonate.5 ~7<9 ~13

Before we could study the role that stereochemistry plays in determining the biological activity of methyl jasmonate, we needed to prepare the four stereoisomers. A previous attempt to do this via the formation of a ketal of (−)-2,3-butanediol9 did not account for the inevitable formation of 2-epimers. This communication describes the optical resolution of methyl jasmonate and methyl epijasmonate using the scheme shown in Fig. 1. To separate the enantiomers, the diastereoisomeric jasmonate esters of (−)-borneol were prepared and separated by liquid chromatography. Conversion to the corresponding methyl esters followed by liquid chromatography led to separation of the four stereoisomers.

Commercial methyl jasmonate containing about 2% of E-methyl jasmonate was first purified using liquid chromatography on silver nitrate-loaded silica. This was hydrolyzed to the corresponding acids, reacted with thionyl chloride and esterified with l-borneol. The resulting bornyl jasmonate diastereo-isomers, IIIa and IIIb, and not their corresponding epimers, were formed in equal quantities as shown in Fig. 2B. Both these diastereoisomers of bornyl jasmonate were purified by successive liquid chromatography, hydrolyzed and methylated. Successive liquid chromatography on silica gel was also used to separate methyl jasmonate from its 2-epimer, methyl epijasmonate, as shown in Fig. 2A. Gas chromatography (GLC) was used to monitor the purification of these two isomers.5 ~71

The individual ORD curves of the four
Fig. 1. Optical Resolution Route of Commercial Methyl Jasmonate.

Fig. 2. Liquid Chromatograms (HPLC) of Jasmonic Esters (Refractive Index Detection).

Fig. 3. ORD Curves of the Stereoisomers of Methyl Jasmonate: 1S,2S-I Is (+)-Methyl Jasmonate; 1R,2S-II Is (+)-Methyl Epijasmonate; 1S,2R-II Is (-)-Methyl Epijasmonate; and 1R,2R-I Is (-)-Methyl Jasmonate.

isomers are shown in Fig. 3. Over the entire range of wavelengths, the enantiomers showed optical rotations of equal magnitude but opposite sign. As expected, epimerization at the 2-position showed opposite Cotton effects because of its proximity to the chromophore on position 3. The curve labeled 1R, 2R is in agreement with the data reported for (-)-methyl jasmonate isolated from jasmin flower oil. This together with the spectral data justifies the assignments shown in Fig. 1.

During an informal assessment of the odor of each isomer, only (1R, 2S)-(+)-methyl epijasmonate had the characteristic jasmonate odor. This was confirmed by a more rigorous determination of their odor thresholds. It would appear that preparations of (-)-I have an odor because of the presence of (+)-II. Moreover, we suspect that the methyl epijasmonate isolated from the hairpencils of the Oriental fruit moths and from the peels of lemons also have the 1R, 2S configuration because of their characteristic jasmonate odor.

EXPERIMENTAL

Optical rotations were measured on a JASCO ORD Model J-5 spectropolarimeter. Mass spectra (MS) were measured on a Hitachi M-80 mass spectrometer. Infrared (IR) spectra were recorded as films with a Shimadzu IR-400 spectrometer. Proton magnetic resonance (PMR)
Preparation of (±)-methyl jasmonate and (±)-methyl epijasmonate. Commercial methyl jasmonate composed of methyl jasmonate (I), methyl epijasmonate (II) and their corresponding E-diastereoisomers in a ratio of 91:7:2:0.2 was chromatographed on silica gel loaded with 15% silver nitrate. Developed with hexane in ether, the E-diastereoisomer eluted first followed by the Z-diastereoisomers at about 25% of each. The purified Z-diastereoisomers containing 93% I and 7% II were separated by HPLC (Nucleosil 100-5, 300 mm x 8 mm i.d. x 2, eluted with 15% ethyl acetate in hexane, at 3 ml/min). (±)-Methyl jasmonate (I) and (±)-methyl epijasmonate (II) showed retention times of 19.6 min and 21.0 min, respectively, as shown in Fig. 2A. MS, IR, and PMR spectra of these two isomers are as follows:

(±)-Methyl jasmonate (I). MS (20 eV) m/z(%): 83 (100), 95 (31), 109 (30), 133 (20), 151 (78), 156 (39), 177 (7), 193 (21), 195 (7), 206 (4), 224 (74). IR ν cm⁻¹: 2970, 1740, 1440, 1412, 1378, 1338, 1290, 1260, 1228, 1192, 1161, 1094, 1072, 1020, 992. PMR δ: 0.97 (3H, t, J = 7.3), 1.49 (1H, m), 1.44 (1H, m), 1.90 (1H, quintet, J = 4.5), 2.06 (2H, broad quintet, J = 4.5), 2.15 ~ 2.45 (7H, m), 2.71 (1H, m), 3.70 (3H, s), 5.26 (1H, m), 5.44 (1H, m).

(±)-Methyl epijasmonate (II). MS (20 eV) m/z(%): 83 (100), 95 (58), 109 (25), 133 (20), 151 (61), 156 (25), 177 (18), 193 (11), 195 (7), 206 (33), 224 (68). IR ν cm⁻¹: 2970, 1740, 1440, 1415, 1380, 1340, 1310, 1260, 1200, 1193, 1171, 1133, 1075, 1020. PMR δ: 0.98 (3H, t, J = 7.3), 1.45 (1H, m), 1.90 (1H, quintet, J = 7.3), 2.0 ~ 2.5 (7H, m), 2.83 (1H, septet, J = 4.5), 3.70 (3H, s), 5.32 (1H, m), 5.44 (1H, m).

Preparation of l-bornyl jasmonates (IIIA and IIIB). A mixture of E-free (±)-I and (±)-II (1.7 g) was dissolved in 20 ml 5% KOH in ethanol and held at 20°C for 12 hr. After removing a portion of the solvent, the mixture was subjected to acid-base extraction using ether, 0.1 N HCl and saturated NaHCO₃. The acidic fraction was washed with saturated NaCl and dried over anhydrous Na2SO4 to yield jasmonic acid and epijasmonic acid as a yellow liquid. Methylated with diazomethane and analyzed by GLC, the jasmonic acid and epijasmonic acid as a yellow liquid. Methylated with diazomethane and analyzed by GLC, the acid mixture (1.05 g) was then dissolved in 2 ml of benzene, treated with 2.4 g of thionyl chloride and stirred for 30 min at 0°C. The excess thionyl chloride and benzene were removed under reduced pressure. A mixture of 0.77 g l-bornanol (Aldrich, recrystallized twice from hexane, [α]D^20 = -36°, c = 0.5) 0.5 ml of pyridine and 2 ml of benzene was stirred at 0°C for 5 hr. After extraction and column chromatography (Wako C-200, 50 g, eluted with 12% ethyl acetate in benzene), 0.44 g of the two diastereomers, IIIA and IIIB, was obtained as an oil.

HPLC of the mixture (three 300 mm x 8 mm i.d. silica gel columns, Nucleosil 100-5, eluting with 13% ethyl acetate in hexane at 3 ml/min) yielded two peaks of almost equal intensity as shown in Fig. 2B (IIIA, Tₚ = 22.0 min; IIIB, Tₚ = 21.6 min). Each isomer was chromatographed repeatedly until the other isomer could not be detected. Their spectral properties are as follows:

IIIA. ORD (c = 0.55, MeOH): [α]D²⁰ (nm): -28° (589), -1105° (314), +1005° (277). MS (70 eV) m/z(%): 81 (61), 95 (17), 137 (100), 209 (16), 346 (4). IR ν cm⁻¹: 1737. PMR δ: 0.83 (3H, s), 0.88 (3H, s), 0.92 (3H, s), 0.97 (3H, t, J = 7.0), 1.1 ~ 2.4 (18H, m), 2.72 (1H, m), 4.91 (1H, broad d, J = 9), 5.27 (1H, m), 5.46 (1H, m).

IIIB. ORD (c = 0.47, MeOH): [α]D²⁰ (nm): +14° (589), +945° (314), -1175° (277). MS (70 eV) m/z(%): 81 (69), 95 (17), 137 (100), 209 (13), 210 (18), 346 (3). IR ν cm⁻¹: 1737. PMR δ: 0.82 (3H, s), 0.87 (3H, s), 0.92 (3H, s), 0.96 (3H, t, J = 7.1), 1.1 ~ 2.4 (18H, m), 2.73 (1H, m), 4.91 (1H, broad d, J = 9), 5.27 (1H, m), 5.45 (1H, m).

Preparation of optically pure I and II. Seventy mg of (−)-bornyl jasmonate, IIIA, was dissolved in 1 ml of benzene, mixed with 5 ml 5% of KOH in ethanol at 0°C and held overnight at room temperature. The resulting jasmonic acid mixture (41 mg) was isolated in the same manner to that described in the previous section and methylated with diazomethane in ether. Purification with silica gel (Sep-pak cartridge, silica, Waters Associates) and elution with 10 ml of 15% ethyl acetate in hexane yielded a mixture of I and II as an oil (yield 39 mg, 85%). The diastereoisomers were separated by HPLC under the conditions described in Fig. 2A. The yield of (−)-methyl jasmonate (I) was 37 mg and (+)-methyl epijasmonate (II) was 1.8 mg. Their spectral properties are as follows:


(−)-II (1R, 2S). ORD (c = 0.2, MeOH): [α]D²⁰ (nm): +58° (589), +1540° (311), -1090° (273).

The same procedure was conducted starting with 70 mg of (−)-bornyl jasmonate (IIIB) to yield 36 mg of (+)-I and 2 mg of (−)-II with the following spectra:

(+)I (1S, 2S). ORD (c = 0.5, MeOH): [α]D²⁰ (nm): +70° (589), +2010° (313), -2010° (276).

(−)-I (1S, 2R). ORD (c = 0.14, MeOH): [α]D²⁰ (nm): -50° (589), -1610° (311), +1030° (273).

Acknowledgments. We thank Mr. T. Tsuneya and Mr. S. Uenaka of Shiono Koryo Kaisha Ltd. for (±)-methyl jasmonate. We also thank Dr. H. Fukui and Dr. K. Koshimizu of Kyoto University for the measurements of PMR and ORD spectra, respectively. This work was financially supported by The Naito Foundation Research Grant for 1982 and The Kyoto University 70th Anniversary Memorial Foundation.

Optical Resolution of Methyl Jasmonate and Epijasmonate 771
REFERENCES