The stereochemically restricted bicyclic analogue of 7-epi-jasmonic acid was synthesized from a known bicyclo[3.3.0]octane derivative. The enol triflate derived from the bicyclic compound was subjected to palladium-catalyzed coupling with allyltributyltin to give the desired carbon skeleton. Selective catalytic hydrogenation and subsequent acidic hydrolysis gave a new bicyclic analogue of 7-epi-jasmonic acid. The ACC conjugate of the bicyclic analogue was also synthesized. This ACC conjugate exhibited only slightly weaker potato cell expansion-inducing activity than that of the JA standard.

Key words: 7-epi-jasmonic acid; phytohormone; jasmonic acid analogue; bicyclo[3.3.0]octane

Jasmonoids have recently been postulated as a class of phytohormones. The cis-isomer, 7-epi-jasmonic acid (7-epi-JA, I), is first biosynthesized and readily isomerizes to the thermodynamically stable trans-isomer, jasmonic acid (JA, 2). Therefore, I is considered to be an essential endogenous plant regulator. In fact, it has been reported that the methyl ester of I, when exogenously supplied, exhibited higher biological activity than that of 2.5 We have previously reported that a natural product, coronafacic acid (5), can be regarded as a stereochemically cis-restricted bicyclic analogue of 1.3 Furthermore, some analogues have been synthesized to restrict the cis-configuration and conformation of two side chains on the cyclopentanone ring of 1 and 2.43) In order to increase the acidity at the C7 position, 5-oxa-JA analogues have been synthesized.8) However, most of these analogues exhibited no or weak activity in jasmonate bioassays. Thus, new stereochemically cis-restricted bicyclic analogues (3 and 4) were designed to confirm the biological activity of 1. The exo-olefin analogue (3) can be designed by C=C bond formation between the C2 and C3 positions in 1. The endo-olefin analogue (4) can be designed by migration of the olefin in 1 or by C=C bond formation between the C5 and C7 positions in 5. The stereochemistry of the jun-
a-Linolenic acid \[\xrightarrow{\text{Biosynthesis}}\] 7-epi-JA (1) \[\xrightarrow{\text{Epimerization}}\] JA (2)

**Fig.** Design of the Stereochemically Restricted Bicyclic Analogue of 7-epi-JA.

**Scheme.** (a) NaH, Tf,NPh/THF; (b) Pd(PPh$_3$)$_2$, LiCl, allylttributyltin/THF (60%, 2 steps); (c) H$_2$, 10% Pd-C/EtOAc (100%); (d) 2 N HCl (50%); (e) ACC methyl ester hydrochloride, Et$_3$N = C = N(CH$_3$)$_2$NMe$_2$: HCl, Et$_3$N, DMAP/CH$_2$Cl$_2$; (f) 3 N KOH/MeOH (25%, 2 steps).

alkaline hydrolysis gave 10 in a 25% yield (2 steps).

In conclusion, 4, a hitherto unknown and stereochemically restricted bicyclic analogue of 1, was synthesized in 4 steps from a known bicyclo[3.3.0]octane derivative. Furthermore, ACC conjugate 10 was also synthesized. The synthesis of another exo-olefin analogue (3) is in progress by a different route. As the preliminary result of a potato cell expansion-inducing assay,$^{11}$ 4 exhibited no activity in the concentration range from $10^{-6}$ to $10^{-4}$ M, but 10 exhibited slightly weaker activity than that of the JA standard.$^{12}$ It seems that the closeness of the carboxyl group to the alkyl part in 4 might have decreased this biological activity. Both 4 and 10 would provide significant information in their application to other jasmonate bioassays.
Experimental

General methods. ¹H- and ¹³C-NMR spectra were recorded with a JEOL JNM-EX-270 spectrometer (¹H at 270 MHz; ¹³C at 67.5 MHz). In the ¹H-NMR spectra, chemical shifts are reported as δ (ppm) values relative to the residual proton (δ 7.26 ppm) of CDCl₃. In the ¹³C-NMR spectra, chemical shifts are reported as δ (ppm) values relative to the carbon signal (δ 77.0 ppm) of CDCl₃. IR spectra were measured with a Perkin Elmer System 2000 FT-IR spectrometer, and mass spectra were recorded with a JEOL JMS-AX500 or JEOL JMS-SX102A spectrometer. Column chromatography was carried out with silica gel 60 (spherical, 70–140 mesh ASTM; Kanto Chemical Co., Japan).

Ethyl (1S*, 5S*)-6,6-(1,2-dimethylhenylenedioxy)-3-oxobicyclo[3.3.0]octane-2-carboxylate (6). To a stirred solution of 6 (496 mg, 1.76 mmol) in dry THF (6.0 ml) at 4°C in an argon atmosphere was added sodium hydride (77.0 mg, 1.93 mmol, 60% in oil), and the mixture was stirred for 10 min at the same temperature. To the resulting solution at 4°C was added N-phenyltriflimide (760 mg, 2.13 mmol), and the mixture was stirred for 8 h at room temperature. The reaction mixture was quenched by adding sat. aq. NH₄Cl (20 ml) and then extracted with Et₂O (30 ml × 3). The combined extracts were washed with brine (30 ml), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:Et₂O = 5:1) to give 8 (324 mg, 60%) as a colorless oil. IR νmax (film) (cm⁻¹): 2875, 2975, 2936, 2920, 2875, 1714, 1343, 1443, 1373, 1302, 1257, 1206, 1108, 1042, 994, 955, 915; ¹H-NMR (270 MHz, CDCl₃) δ: 1.15–1.30 (9H, m, Me×3), 1.55–1.70 (3H, m), 1.95 (1H, m), 2.35–2.75 (3H, m), 3.29 (2H, d, J = 6.9 Hz, CH₂CH = CH₂), 3.52–3.64 (3H, m), 4.16 (2H, m, CO₂CH₂Me), 5.02 (1H, br. d, J = 10.2 Hz, CH₂CH = CHH), 5.10 (1H, br. d, J = 17.2 Hz, CH₂CH = CHH), 5.78 (1H, ddt, J = 10.2, 17.2, 6.6 Hz, CH₃CH = CHCH₃); EI-MS m/z: 306 (5.6, M⁺), 261 (8.7, M⁺–C₂H₅O), 235 (9.3), 127 (100); HR-MS m/z (M⁺): calcd. for C₁₅H₂₀O₃, 306.1831; found, 306.1822.

Ethyl (1S*, 5S*)-6,6-(1,2-dimethylhenylenedioxy)-3-propylbicyclo[3.3.0]oct-2-ene-2-carboxylate (9). A solution of 8 (76.0 mg, 248 μmol) in ethyl acetate (3.0 ml) was hydrogenated in the presence of 10% palladium on carbon (2.0 mg) at room temperature under ordinary pressure. The catalyst was filtered off, and the combined filtrate and washings were concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:Et₂O = 5:1) to give 9 (77.0 mg, 100%) as a colorless oil. IR νmax (film) (cm⁻¹): 2969, 2920, 2873, 1709, 1641, 1456, 1374, 1304, 1256, 1205, 1107, 1034, 954; ¹H-NMR (270 MHz, CDCl₃) δ: 0.92 (3H, t, J = 7.3 Hz, CH₃CH₂Me), 1.15–1.30 (9H, m, Me×3), 1.40–1.70 (5H, m), 1.95 (1H, m), 2.35–2.75 (5H, m), 3.52–3.64 (3H, m), 4.16 (2H, m, CO₂CH₂Me); EI-MS m/z: 308 (4.2, M⁺), 263 (8.0, M⁺–C₂H₅O), 237 (5.5, 127 (100); HR-MS m/z (M⁺): calcd. for C₁₅H₂₀O₃, 308.1988; found, 308.2002.

(1S*, 5S*)-6-oxo-3-propylbicyclo[3.3.0]oct-2-ene-2-carboxylic acid (4). A solution of 9 (98.0 mg, 317 μmol) in 2 N HCl (40 ml) was refluxed for 4 h. The reaction mixture was extracted with Et₂O (40 ml × 3). The combined extracts were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CHCl₃:EtOAc:AcOH = 60:40:1) to give 4 (33.0 mg, 50%) as a colorless oil. IR νmax (film) (cm⁻¹): 2962, 2934, 2876, 1739, 1682, 1634, 1434, 1278, 1302, 1208, 1132, 931, 755; ¹H-NMR (270 MHz, CDCl₃) δ: 0.90 (3H, t, J = 7.3 Hz, CH₃CH₂Me), 1.48 (2H, m, CH₂CH₂Me), 2.08–2.35 (4H, m, C₆H₅H and C₆H₅Me), 2.47–2.83 (5H, m, C₆H₅H, C₆H₅H, and C₆H₅Me), 3.83 (1H, br. s, CH₃), the apparent proton signal of carboxylic acid (COOH) could not be detected due to broadening; ¹³C-NMR (67.5 MHz, CDCl₃) δ: 14.0, 21.2, 25.5, 32.0, 36.5, 41.0, 47.4, 48.5, 128.5, 163.2, 170.7, 222.7; EI-MS m/z: 208 (100, M⁺), 190 (14, M⁺–H₂O), 211 (16.6, M⁺+H), 194 (7.0, M⁺–H₂O), 167 (1.69, M⁺–CO₂H),
153 (4.39), 144 (34.6), 126 (34.8), 85 (100); HR-MS m/z (M⁺): calcd. for C₁₂H₁₆O₃, 208.1099; found, 208.1085.

(1S*, 5S*)-2-[(1-carboxycyclopropyl)-carbamoyl]-6-oxo-3-propylbicyclo[3.3.0]oct-2-ene (10). A mixture of 4 (260.0 mg, 125 μl), triethylamine (120 μl, 860 μmol), 4-dimethylaminopyridine (30.0 mg, 250 μmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (30.0 mg, 260 μmol), and ACC methyl ester hydrochloride (58.0 mg, 380 μmol) in dichloromethane (2.0 ml) was stirred at room temperature for 20 h. After adding 2 N HCl (5.0 ml), the reaction mixture was extracted with EtOAc (10 ml × 3). The combined extracts were washed with sat. aq. NaHCO₃ and brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. To a solution of the crude amide in MeOH (2.0 ml) was added 3 N KOH (2.0 ml) at 4°C, and the mixture was stirred for 20 h at room temperature. After acidification with 2 N HCl (10 ml), the reaction mixture was extracted with EtOAc (10 ml × 3). The combined extracts were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CHCl₃:MeOH = 5:1) to give 10 (9.0 mg, 25%, 2 steps) as a colorless oil. IR νmax (film) cm⁻¹: 3400–2500 (CHC=O), 3400–2500 (CHC=O), 1533, 1535, 1263, 1142, 1048, 935, 753; ¹H-NMR (270 MHz, CDCl₃) δ: 0.87 (3H, t, J=7.3 Hz, CH₃CH₂Me), 1.18–1.25 (2H, m, cyclopropane-C-H₂), 1.44 (2H, sext., J=7.3 Hz, CH₂CH₂Me), 1.61–1.65 (2H, m, cyclopropane-C-H₂), 2.08–2.21 (4H, m, C₆H₅ and C₆H₅), 2.47–2.83 (5H, m, C₆H₅, C₆H₅, and C₆H₅), and 3.83 (1H, br. s, CH₂), 6.70 (1H, s, CONH), the apparent proton signal of carboxylic acid (COOH) could not be detected due to broadening; ¹³C-NMR (67.5 MHz, CDCl₃) δ: 14.0, 18.3, 21.1, 24.5, 29.7, 31.5, 33.3, 36.3, 39.9, 48.1, 49.0, 132.7, 151.9, 168.0, 177.4, 222.9; EI-MS m/z: 291 (18.0, M⁺), 191 (100); HR-MS m/z (M⁺): calcd. for C₁₂H₁₆O₃, 291.1470; found, 291.1477.

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References

8) Compound 6 was obtained as an inseparable mixture of diastereomers because racemic 2,3-butanediol containing ca. 5% of the meso form was used for acetalization.
10) Compounds 8 and 9 were also obtained as an inseparable mixture of diastereomers.
12) A mixture of minor (±)-1 (5%) and major (±)-2 (95%), which had been prepared from commercially available methyl (±)-jasmonate, was used as the JA standard for the bioassay.