Synthesis of Chiral Methyl Cucurbate and Its Analogs

Jun TAKEHARA, Takayuki ORITANI* and Kyohei YAMASHITA

Department of Agricultural Chemistry, Faculty of Agriculture,
Tohoku University, Aoba-ku, Sendai 981, Japan

Received April 30, 1991

Natural (+)-(1*R*,2*S*,3*S*)-methyl cucurbate (**1b**) and the (–)- δ -lactone of 3-epi-cucurbitic acid (**16**) were synthesized from (+)-(1*R*,6*S*,7*R*)-bicyclo[4.3.0]non-3-en-7-ol (**5**). Asymmetric hydrolysis of the acetate (**8**) of ($\pm$)-**5** with pancreatin gave optically pure the (+)-(7*R*)-alcohol (**5**) and (–)-(7*S*)-acetate (**8**). An ozonolysis product of (+)-**5** was transformed to (–)-**16** and (+)-(3*S*)-**1b** with inversion of the (7*R*)-hydroxyl group. Similarly, unnatural (–)-**1b** and (+)-**16** were prepared from optically pure (–)-**5**. The growth inhibitory activities of these synthesized chiral compounds toward lettuce seedlings were examined.

Cucurbitic acid (**1a**) has been isolated from seeds of *Cucurbita pepo* L. as a plant growth inhibitor.¹⁾ This compound has a skeleton similar to jasmonic acid (**2a**), methyl jasmonate (**2b**) and methyl epi-jasmonate (**3**), which have also been found as plant growth regulators.^{2,3)} The structure–activity relationships of **2a** and **2b** have been investigated in detail without those of **1a**.³⁾ Here, we described the first synthesis of both enantiomers of methyl cucurbate (**1b**) and their effects on the growth of lettuce seedlings.

Our synthetic plan for chiral **1b** depended on the enzymatic preparation of chiral (1*R*,6*S*,7*R*)-bicyclo-[4.3.0]-non-3-en-7-ol (**5**). Racemic **5** has often been used for the synthesis of various natural cyclopentanoids; ($\pm$)-methyl jasmonate (**2b**) and ($\pm$)-methyl epi-jasmonate (**3**) were synthesized by H. Tanaka and S. Torii in 1975⁵⁾ and the (+)-tuberolide by B. Mauer and A. Hauser in 1982.⁶⁾ In order to synthesize natural **1a** with the (3*S*)-hydroxyl

group from chiral (7*R*)-**5**, it is necessary to invert the configuration of the hydroxyl group in substrate **5**. Already, T. Kitahara *et al.* have synthesized ($\pm$)-methyl cucurbate (**1b**) based on selective hydroboration of a cyclopentene intermediate.⁷⁾ ($\pm$)-Bicyclo[4.3.0]-non-3-en-7-on (**4**)⁶⁾ (*cis*:*trans*=9:1) was reduced with NaBH₄ in the presence of CeCl₃·7H₂O in methanol to give a stereoisomeric mixture of four alcohols: 1,6-*cis*,6,7-*cis*-**5** (84%), 1,6-*cis*,6,7-*trans*-**6** (6%), and the 1,6-*trans*,6,7-*cis*- and 1,6-*trans*,6,7-*trans*-isomers (10%). Attempts to separate these isomers by silica gel chromatography failed. Thus, ($\pm$)-**5** was separated from the mixture by treating it with N-bromosuccinimide (NBS) in dry THF, which, after chromatographic separation, gave the bromoether (**7**). Reduction of **7** with Zn/NH₄Cl gave the pure alcohol (**5**), which was acetylated with acetic anhydride-pyridine to yield the ($\pm$)-acetate (**8**). Microbial hydrolysis of ($\pm$)-**8** with *Bacillus subtilis* subsp. *niger* gave the (+)-alcohol (**5**) with low optical purity. However, ($\pm$)-**8** was asymmetrically hydrolyzed with pancreatin to yield the (+)-alcohol (**5**) and (–)-acetate (**8**) with more than a 94% enantiomeric excess (*e.e.*). Deacetylation of (–)-**8** with methanolic KOH gave the (–)-alcohol (**5**). The optical purity was determined by ¹H-NMR analysis

Fig. 1

* Address correspondence to this author.

Scheme 1. a) NaBH_4 , CeCl_3 , MeOH , -70°C (95%). b) NBS , THF (83%). c) Zn , NH_4Cl , EtOH (76%). d) O_3 , $\text{MeOH}-\text{CH}_2\text{Cl}_2$, -70°C ; PPh_3 , RT (95%). e) KMnO_4 , MgSO_4 , acetone , (66%). f) CH_2N_2 (100%). g) 30% AcOH , 60°C , (77%). h) NaBH_4 , CeCl_3 , MeOH , (84%). i) Ph_3CCl , Py , DMAP , (91%). j) MsCl , Py , DMAP , RT . k) AcOK , 18-crown-6, benzene , reflux (42% from 11b). l) $p\text{-TsOH}$, MeOH , RT (71%). m) PDC , CH_2Cl_2 , RT (62%). n) $\text{Ph}_3\text{P}(\text{Pr})\text{Br}$, NaNH_2 , benzene (64%). o) 1 N NaOH , $\text{MeOH}-\text{H}_2\text{O}$, 40°C ; 10% HCl (87%). p) Ac_2O , Py , DMAP (100%).

of the (*S*)-(-)-MTPA esters of each chiral alcohol which were shifted by $\text{Eu}(\text{fod})_3$.

Enzymatic acetylation of (+)-**5** with vinyl acetate in an organic solvent gave the (+)-acetate (**8**) with high optical purity as shown in Table I.

Chiral alcohol (+)-**5** was cleaved by ozonolysis in methanol at 70°C and then reduced with triphenylphosphine to give the (+)-aldehyde (**9a**), which was then oxidized with KMnO₄, and esterified with diazomethane to yield methyl ester (+)-**9c**. Hydrolysis of (+)-**9c** with 50% acetic acid at 60°C gave the

(+)-lactol (**10**) in a 60% overall yield from (+)-**5**. Lactol **10** was reduced with NaBH₄ in the presence of 10% CeCl₃ · 7H₂O in methanol to give the (+)-diol (**11a**). The *prim*-hydroxyl group of (+)-**11a** was selectively protected with trityl chloride to give the (+)-trityl ether (**11b**), whose *sec*-hydroxyl group was then transformed to the mesylate (**11c**). This (3*R*)-**11c** was treated with AcOK and 18-crown-6 in refluxing benzene to give the (–)-(3*S*)-acetate (**12a**) with S_N2 inversion in a 47% yield⁸); the same amount of the eliminated product was observed. The reaction of **11c** with AcOK in

Table 1. ENZYMATIC RESOLUTION OF ($\pm$)-ACETATE **8** AND ($\pm$)-ALCOHOL **5**

Microorganism or enzyme		Concentration of substrate (%)	Temp. (°C)	Time (hr)	Ratio of hydrolysis (%)	Optical purity (% e.e.)
<i>Bacillus subtilis</i> subsp. <i>niger</i> IFO 3108		1.5	30	58	26	54
Pancreatin (from porcine source)		0.5	30	72–480	≤ 40	≥ 95
Enzyme	Solvent	Concentration of substrate (%)	Temp. (°C)	Time (hr)	Rate of acylation (%)	Optical purity (% e.e.)
Amano P ^a	<i>n</i> -Hexane	3.3	30	16	48	82
Amano P ^a	Benzene	3.3	30	40	36	84
Lipase MY ^b	<i>n</i> -Hexane	3.3	30	40	29	100
Pancreatin ^c	<i>n</i> -Hexane	3.3	30	42	—	—

^a Amano P was from *Pseudomonas* sp.^b Lipase MY was from *Candida cylindracea*.^c Pancreatin was from porcine pancreas.

DMF¹⁰⁾ and a Mitsunobu reaction⁸⁾ of **11c** gave only the eliminated product. The (–)-acetate (**12a**) was detritylated by treating with *p*-toluenesulfonic acid (*p*-TsOH) in methanol to give the (–)-alcohol (**12b**), which was then oxidized with pyridinium dichromate (PDC) in CH₂Cl₂ to obtain the (3*S*)-aldehyde (**12c**). A Wittig reaction of (3*S*)-**12c** with propyldienetriphenylphosphorane under salt-free conditions¹¹⁾ in benzene gave the olefine (**13**) in a 60% yield. Alkaline hydrolysis of **13** gave (+)-cucurbic acid (**1a**), whose physical data and spectral data⁷⁾ were agreed with those of the natural product. Methylation of (+)-**1a** with diazomethane gave (+)-methyl cucurbate (**1b**). As a result, natural (+)-cucurbic acid (**1a**) with the (1*R*,2*S*,3*S*)-configuration was synthesized from chiral synthon (+)-**5**. This shows that (+)-**5** had the (1*R*,6*S*,7*R*)-configuration, and enzymatic hydrolysis of substrate ($\pm$)-**5** by various lipase gave the (7*R*)-alcohol (**5**) and (7*S*)-acetate (**8**) as was expected from our previous result.⁴⁾ Furthermore, methyl 3-epi-3-O-acetoxy cucurbate (**15**) was synthesized from (+)-**11b**. Acylation of (+)-**11b**, with subsequent detritylation with *p*-TsOH in methanol, gave the (–)-alcohol (**14b**). Oxida-

Table II. INHIBITORY EFFECTS OF CHIRAL METHYL CUCURBATE AND ITS ANALOGS ON THE GROWTH OF LETTUCE SEEDLINGS (cv. *Great Lakes*)

Compound	Root length (% of the control)			
	1 ppm	10 ppm	50 ppm	100 ppm
(+)- 1b	39	33	25	25
(–)- 1b	90	87	67	70
($\pm$)- 1b	70	56	56	49
($\pm$)- 1a	52	42	38	27
(–)- 16	88	86	87	73
(+)- 16	78	91	84	59
($\pm$)- 16	88	84	96	69
($\pm$)- 2b	74	16	8	2

tion of (–)-**14b** with PDC gave the aldehyde (**14c**), which was reacted with propyldienetriphenylphosphorane to yield the acetate (**15**). Alkaline hydrolysis of **15** and subsequent acidification with dilute HCl gave 3-epi-cucurbic acid (**16**) as (–)- δ -lactone form **16**. Similarly, unnatural (–)-cucurbic acid (**1a**) and (+)- δ -lactone (**16**) were synthesized from the (–)-chiral synthon (**5**).

Finally, the growth inhibitory activities of the synthesized compounds were examined by using lettuce seedlings (cv. *Great Lakes*) (Table

II). In consequence, cucurbitic acid (**1a**) and its methyl ester (**1b**) inhibited the growth of lettuce seedlings; however, the 3-epimer (**16**) had no effect in this test. Furthermore, natural (+)-**1b** showed stronger activity than that of unnatural (–)-**1b**.

Experimental

All melting points (mp) and boiling points (bp) are uncorrected. IR spectra were recorded on a JASCO IR-810 infrared spectrometer, while ¹H-NMR spectra were recorded on a JEOL GSX-270 spectrometer at 270 MHz or JEOL JNM FX-100 spectrometer, with mass spectra being measured with a JEOL JMS-HX-105.

(±)-(1*R**,6*S**,7*R**)-Bicyclo[4.3.0]non-3-en-7-ol (**5**). To a stirred mixture of ketones **4** (*cis*:*trans* = 93:7, 29.73 g, 0.22 mol) and CeCl₃·7H₂O (8.20 g, 0.02 mol) in 400 ml of methanol was slowly added NaBH₄ (8.20 g, 0.24 mol) at –70°C. After stirring for 1 hr at the same temperature, the reaction mixture was quenched by adding dilute HCl and concentrated *in vacuo*. The residue was extracted with ether. The organic extract was washed with aq. NaHCO₃ and brine, and dried over MgSO₄. Evaporation of the extract gave alcohols consisting of four stereoisomers (28.85 g, 95% yield). To this mixture (28.85 g, 0.21 mol) in 300 ml of dry tetrahydrofuran (THF) was added *N*-bromosuccinimide (NBS; 31.77 g, 0.18 mol) at 0°C. After stirring overnight, the reaction mixture was poured into ice-cooled water and extracted with ether. The ether extract was dried over MgSO₄ and then evaporated. The residual oil was chromatographed on SiO₂ to give bromoether **7** (32.30 g, 83% yield). IR $\nu_{\max}$ cm^{–1}: 2950, 1280, 1225, 680. ¹H-NMR (CDCl₃) δ : 1.30–2.60 (10H, m), 3.70–4.50 (3H, m). A mixture of **7** (32.30 g, 0.15 mol), NH₄Cl (58.84 g, 1.10 mol) and zinc powder (58.84 g, 0.90 mol) in 300 ml of 95% ethanol was stirred under reflux for 5 hr. After filtration and concentration, the residue was extracted with ether, and the ethereal layer washed with brine and then dried. Removal of the solvent gave 15.64 g (76%) of pure (±)-**5**, bp 80°C/5 mmHg. IR $\nu_{\max}$ cm^{–1}: 3350, 3025, 1660, 1438, 1100, 1008. ¹H-NMR (CDCl₃) δ : 1.40–2.40 (11H, m), 4.20–4.40 (1H, m), 5.60–5.90 (2H, m). EI-MS (*m/z*): 138 (M⁺, 2), 120 (94), 105 (29), 91 (100).

(±)-(1*R**,6*S**,7*R**)-Bicyclo[4.3.0]non-3-en-7-yl acetate (**8**). To a solution of **5** (3.20 g, 23.2 mmol) and Ac₂O (8.29 g, 81.2 mmol) in 50 ml of dry benzene, 6.41 g of pyridine (81.2 mmol) and 100 mg of 4-dimethylaminopyridine (DMAP) were added at room temperature under nitrogen. After stirring overnight, the reaction mixture was poured into ice-cooled water and extracted with ether. The organic layer was successively washed with dilute HCl, aq. NaHCO₃ and brine, dried and then evaporated. Distillation of the residue gave (±)-acetate **8**, bp

89–92°C/7 mmHg. IR $\nu_{\max}$ (cm^{–1}): 3030, 1740, 1660, 1378, 1255, 1085. ¹H-NMR (CDCl₃) δ : 1.27–2.40 (10H, m), 2.02 (3H, s), 5.05–5.30 (1H, m), 5.55–5.75 (2H, m). EI-MS (*m/z*): 180 (M⁺, 5), 121 (58), 120 (54), 105 (28), 91 (100).

Asymmetric hydrolysis of (±)-acetate 8 with pancreatin. A mixture of (±)-**8** (0.50 g, 2.78 mmol), CaCl₂ (0.10 g) and crude pancreatin (2.00 g of powder from porcine pancreas; Nacalai Tesque Inc., Japan) in 100 ml of pH 7.0-phosphate buffer was vigorously stirred at 30°C for 3–20 days. The reaction mixture was steam-distilled, and the distillate was saturated with brine and extracted with ether. The ethereal extract was dried and concentrated. The residual oil was chromatographed on silica gel to give (–)-acetate (**8**) and optically pure (+)-**5**, mp 43–44°C, [α]_D²² +15.7° (*c* = 1.17, CHCl₃; after recrystallization from hexane). Alkaline hydrolysis of (–)-**8** and subsequent followed by crystallization from hexane, gave (–)-**5**, mp 44–45°C, [α]_D²² +14.9° (*c* = 0.68, CHCl₃).

Asymmetric acetylation of (±)-5 with lipase MY. A mixture of (±)-**5** (0.10 g, 0.72 mmol), vinyl acetate (0.06 g, 0.72 mmol) and lipase MY (0.05 g as powder from Meito Sangyo Co., Ltd.) in 5 ml of hexane was stirred at 30°C for 40 hr. After filtration and evaporation, the residual oil was chromatographed on SiO₂ to give (+)-acetate **8**. Hydrolysis of (+)-**8** with methanolic KOH gave optically pure (+)-**5** (0.03 g, 0.21 mmol, 29% yield).

(1*R*,5*S*,6*R*)-6-formylmethyl-3-methoxy-2-oxabicyclo[3.3.0]octane (**9a**). A solution of (+)-**5** (2.88 g, 20.87 mmol) in 120 ml of methanol and CH₂Cl₂ (1:1) was ozonized at –70°C. After nitrogen had been bubbled into the reaction solution to remove the excess ozone, 5.47 g of Ph₃P (20.87 mmol) was added to the solution, which was then stirred overnight at room temperature. The mixture was concentrated and chromatographed on SiO₂ to give aldehyde **9a** (3.64 g, 95% yield). IR $\nu_{\max}$ cm^{–1}: 2730, 1725, 1095, 1045, 1020, 920. ¹H-NMR (CDCl₃, 3- β form) δ : 1.40–3.00 (10H, m), 3.30 (3H, s), 4.68 (1H, m), 4.90 (1H, d, d, *J* = 5.1, 1.7 Hz), 9.80 (1H, t, *J* = 1.5 Hz).

(1*R*,5*S*,6*R*)-6-Methoxycarbonylmethyl-3-methoxy-2-oxabicyclo[3.3.0]octane (**9c**). To a solution of **9a** (0.29 g, 1.58 mmol) in 60 ml of acetone was added a solution of KMnO₄ (0.25 g, 1.58 mmol) and MgSO₄ (0.19 g, 1.58 mmol) in 6 ml of water. The mixture was stirred for 5 hr at 0°C, and 30 ml of 2-propanol was then added. After stirring for a few more hours at room temperature, the reaction mixture was filtered, and the filtrate was concentrated. The residue was acidified and extracted with CHCl₃. The extract was dried and concentrated to give an oily acid (0.21 g), which was methylated with diazomethane to give methyl ester **9c** (0.18 g, 100% yield). IR $\nu_{\max}$ cm^{–1}: 1740, 1095, 1045, 1000. ¹H-NMR (CDCl₃) δ : 1.20–3.10 (10H, m), 3.29 (3H, s), 3.67 (3H, s), 4.60 (1H, m), 4.99 (1H, d, *J* = 4.4 Hz).

(+)-(1*R*,2*S*,3*R*)-Methyl-3-hydroxy-2-(2-hydroxyethyl)-1-cyclopentaneacetate (**11a**). A mixture of methyl ester **9c** (0.18 g, 0.84 mmol) and 50 ml of 30% AcOH was stirred at 60°C for 0.5 hr. The mixture was neutralized with NaHCO₃ and extracted with CHCl₃. The extract was dried and concentrated to give (1*R*,5*S*,6*R*)-6-methoxycarbonylmethyl-3-hydroxy-2-oxabicyclo[3.3.0]octane (**10**) as an oil (0.13 g, 77% yield). IR $\nu_{\max}$ cm⁻¹: 3420, 1740, 1440, 1200, 1035, 1025. ¹H-NMR (CDCl₃) δ : 1.10–3.20 (10H, m), 3.29 (1H, br, disappeared by D₂O exchange), 3.68 (3H, s), 4.71 (1H, m), 5.54 (1H, d, *J* = 4.4 Hz). To a mixture of **10** (0.99 g, 4.95 mmol) and CeCl₃·7H₂O (0.35 g, 0.50 mmol) in 20 ml of methanol was added NaBH₄ (0.75 g, 19.8 mmol) at -10°C, the mixture being stirred for 5 hr. This mixture was acidified with acetic acid and concentrated *in vacuo*. The residue was chromatographed over SiO₂ to give (+)-**11a** (0.84 g, 84% yield), [α]_D²³ +15.9° (*c* = 1.37, CHCl₃). IR $\nu_{\max}$ cm⁻¹: 3400, 1738, 1438, 1200, 1170, 1040. ¹H-NMR (CDCl₃) δ : 1.52–2.03 (7H, m), 2.38–2.55 (3H, m), 2.50–3.00 (2H, br, disappeared by D₂O exchange), 3.69 (3H, s), 3.66–3.75 (1H, m), 3.83–3.90 (1H, m), 4.32 (1H, t, *J* = 2.7, 5.4 Hz). Anal. Found: C, 59.10; H, 9.12. Calcd. for C₁₀H₁₈O₄: C, 59.39; H, 8.97%. Similarly, (-)-**11a** was prepared from (-)-**5**, [α]_D²³ -17.6° (*c* = 1.03, CHCl₃).

(+)-(1*R*,2*S*,2*R*)-Methyl 3-hydroxy-2-(2-triphenylmethoxyethyl)-1-cyclopentaneacetate (**11b**). To a solution of (-)-**11a** (64 mg, 0.32 mmol) and trityl chloride (128 mg, 0.48 mmol) in 3 ml of dry CH₂Cl₂ was added pyridine (38 mg, 0.48 mmol) and 10 mg of DMAP under N₂. After refluxing overnight, the reaction mixture was concentrated *in vacuo* and chromatographed on SiO₂ to give (+)-**11b** (129 mg, 91% yield). [α]_D²³ +28.2° (*c* = 1.87, CHCl₃). IR $\nu_{\max}$ cm⁻¹: 3600, 1735, 1595, 1448, 1070, 705. ¹H-NMR (CDCl₃) δ : 1.30–3.40 (12H, m), 3.64 (3H, s), 4.13 (1H, m), 7.10–7.50 (15H, m). Anal. Found: C, 78.15; H, 7.46. Calcd. for C₂₉H₃₂O₄: C, 78.35; H, 7.25%.

(+)-(1*R*,2*S*,2*S*)-Methyl-3-acetoxy-2-(2-triphenylmethoxyethyl)-1-cyclopentaneacetate (**12a**). A mixture of (+)-**11b** (199 mg, 0.45 mmol), MsCl (0.21 g, 2.69 mmol), pyridine (0.21 g, 2.69 mmol) and 10 mg of DMAP in 5 ml of CH₂Cl₂ was stirred at room temperature under N₂ overnight. The reaction mixture was poured into water and extracted with CH₂Cl₂. The extract was washed with aq. CuSO₄, aq. NaHCO₃ and brine, dried over CaCl₂, and then concentrated at room temperature. This crude methanesulfonate, AcOK (0.57 g, 5.85 mmol) and 18-crown-6 (0.24 g, 0.9 mmol) was dissolved in 10 ml dry benzene. After stirring vigorously under reflux overnight, the reaction mixture was filtrated and evaporated. The residue was chromatographed on SiO₂ to give (+)-**12a** (93 mg, 42% yield from (+)-**11b**). [α]_D²³ +13.3° (*c* = 1.87, CHCl₃). IR $\nu_{\max}$ cm⁻¹: 3060, 1738, 1595, 1245, 1070, 708. ¹H-NMR (CDCl₃) δ : 1.26–2.18 (7H, m), 1.94 (3H, s), 2.15 (1H, d, *J* = 15.4, 10.0 Hz), 2.37 (1H, d, *J* = 7.8, 3.7, 3.7 Hz), 7.20–7.45 (15H, m). Anal. Found: C, 76.29; H,

7.05. Calcd. for C₃₁H₃₄O₅: C, 76.52; H, 7.04%.

(-)-(1*R*,2*S*,3*S*)-Methyl 3-acetoxy-2-(2-hydroxyethyl)-1-cyclopentaneacetate (**12b**). A mixture of (+)-**12a** (180 mg, 0.37 mmol) and 18 mg of *p*-TsOH in 15 ml of methanol was stirred at room temperature for 3 hr, and then neutralized with aq. NaHCO₃. After concentrating *in vacuo*, the residue was chromatographed on SiO₂ to give (-)-**12b** (64 mg, 71% yield). [α]_D²³ -17.6° (*c* = 1.53, CHCl₃). IR $\nu_{\max}$ cm⁻¹: 3450, 1740, 1437, 1375, 1245. ¹H-NMR (CDCl₃) δ : 1.16–2.51 (7H, m), 2.04 (3H, s), 2.27 (1H, d, *J* = 15.3, 8.9 Hz), 2.41 (1H, d, *J* = 15.4, 6.4 Hz), 2.61 (1H, m), 3.68 (3H, s), 3.63–3.83 (2H, m), 4.99 (1H, d, *J* = 7.2, 2.6, 2.5 Hz). HR-MS (*m/z*): 267.1301 (M + Na)⁺. Calcd. for C₁₂H₂₀O₅Na: 267.1208. Similarly, (+)-**12b**, [α]_D²³ +17.8° (*c* = 1.23, CHCl₃), was prepared from (-)-**5**.

(1*R*,2*S*,3*S*)-Methyl 3-acetoxy-2-formylmethyl-1-cyclopentaneacetate (**12c**). To a solution of (-)-**12b** (80 mg, 0.33 mmol) in 10 ml of CH₂Cl₂ was added pyridinium dichromate (PDC, 0.25 g, 0.66 mmol) under N₂. The mixture was stirred at room temperature overnight. After a general workup, the product was chromatographed on SiO₂ to give aldehyde **12c** (49 mg, 62% yield). IR $\nu_{\max}$ cm⁻¹: 2720, 1735, 1720, 1435, 1240, 1020. ¹H-NMR (CDCl₃) δ : 1.26–2.50 (8H, m), 2.04 (3H, s), 2.61–2.76 (23H, m), 3.68 (3H, s), 4.84 (1H, d, *J* = 7.3, 3.7, 3.7 Hz), 9.77 (1H, t, *J* = 1.8 Hz).

(1*R*,2*S*,3*S*)-Methyl 3-acetoxy-2-(2*Z*-pentenyl)-1-cyclopentaneacetate (**13**). To a stirred solution of (1*R*,2*S*,3*S*)-**12c** (67 mg, 0.28 mmol) was added a salt-free solution of propylenetriphenylphosphorane, which had been prepared from propyltriphenylphosphonium bromide (1.08 g, 2.8 mmol), in 5 ml of benzene. After stirring for 1 hr at room temperature, the reaction mixture was quenched with acetic acid, and then evaporated to a small volume. The residue was chromatographed to give 48 mg (64% yield) of acetate **13**. IR $\nu_{\max}$ cm⁻¹: 1740, 1655, 1440, 1248, 1020. ¹H-NMR (CDCl₃) δ : 0.96 (3H, t, *J* = 7.5 Hz), 1.30–2.21 (9H, m), 2.01 (3H, s), 2.24 (1H, d, *J* = 15.4, 9.3 Hz), 2.42 (1H, d, *J* = 15.3, 6.2 Hz), 2.63 (1H, d, *J* = 17.6, 9.5, 6.8 Hz), 3.67 (3H, s), 4.90 (1H, d, *J* = 6.5, 3.2, 3.2 Hz), 5.26–5.48 (2H, m).

(+)-(1*R*,2*S*,3*S*)-3-Hydroxy-2-(2*Z*-pentenyl)-1-cyclopentaneacetic acid (**1a**). To a solution of acetate **13** (36 mg, 0.13 mmol) in 1.3 ml of MeOH and 0.7 ml of water was added 1 ml of 1*N* aq. NaOH. After stirring at 40°C for several hours, the reaction solution was concentrated, acidified with dilute HCl and extracted with CHCl₃. The extract was dried over MgSO₄ and evaporated *in vacuo*. The residue was chromatographed on SiO₂ to give (+)-cucurbitic acid (**1a**, 25 mg, 87% yield). [α]_D²³ +24.0° (*c* = 0.27, CHCl₃). IR $\nu_{\max}$ cm⁻¹: 3370, 2650, 1708, 1403, 1280, 1065. ¹H-NMR (CDCl₃) δ : 0.97 (3H, t, *J* = 7.6 Hz), 1.29–2.14 (9H, m), 2.24 (1H, d, *J* = 15.4, 9.3 Hz), 2.45

(1H, d, d, $J=15.4, 6.4$ Hz), 2.68 (1H, m), 4.02 (1H, d, d, $J=5.4, 2.7, 2.7$ Hz), 5.30–5.52 (2H, m). Similarly, (–)-**1a**, $[\alpha]_D^{23} -25.0^\circ$ ($c=0.31$, CHCl_3), was prepared from (–)-**5**.

(+)-(1*R*,2*S*,3*S*)-Methyl 3-hydroxy-2-(2*Z*-pentenyl)-1-cyclopentaneacetate: methyl cucurbitate (**1b**). A solution of (+)-**1a** (17 mg, 0.08 mmol) in 1 ml of dry ether was treated with diazomethane. After evaporating, the residue was chromatographed on SiO_2 to give (+)-methyl ester **1b** (19 mg, 100% yield). $[\alpha]_D^{23} +12.0^\circ$ ($c=0.94$, CHCl_3). IR $\nu_{\text{max}} \text{ cm}^{-1}$: 3400, 3000, 1738, 1435, 1168, 1013. $^1\text{H-NMR}$ (CDCl_3) δ : 0.97 (3H, t, $J=7.5$ Hz), 1.26–2.13 (10H, m), 2.21 (1H, d, d, $J=9.3, 15.1$ Hz), 2.68 (1H, m), 3.67 (3H, s), 4.01 (1H, m), 5.31–5.51 (2H, m). HR-MS (m/z): 227.1645 ($\text{M} + \text{H}^+$). Calcd. for $\text{C}_{13}\text{H}_{23}\text{O}_3$: 227.1646. Similarly, (–)-enantiomer **1b**, $[\alpha]_D^{23} -11.0^\circ$ ($c=1.31$, CHCl_3), was prepared from (–)-**5**.

(–)-(1*R*,2*S*,3*R*)-Methyl 3-acetoxy-2-(2-triphenylmethoxyethyl)-1-cyclopentaneacetate (**14a**). A mixture of (+)-**11b** (119 mg, 0.27 mmol), Ac_2O (0.08 g, 0.80 mmol), pyridine (0.13 g, 1.60 mmol) and 10 mg of DMAP in 1 ml of dry CH_2Cl_2 was stirred at room temperature overnight. The mixture was concentrated to a small volume and chromatographed on SiO_2 to give (–)-**14a** (131 mg, 100% yield). $[\alpha]_D^{23} -9.1^\circ$ ($c=1.27$, CHCl_3). IR $\nu_{\text{max}} \text{ cm}^{-1}$: 1740, 1600, 1450, 1243, 1070, 705. $^1\text{H-NMR}$ (CDCl_3) δ : 1.47–2.52 (8H, m), 1.96 (3H, s), 2.24 (1H, d, d, $J=16.0, 11.8$ Hz), 2.42 (1H, d, d, $J=15.8, 3.8$ Hz), 3.09 (1H, m), 3.66 (3H, s), 5.01 (1H, d, d, d, $J=5.8, 5.8, 2.3$ Hz), 7.02–7.45 (15H, m). Anal. Found: C, 76.35; H, 7.23. Calcd. for $\text{C}_{31}\text{H}_{34}\text{O}_5$: C, 76.52; H, 7.04%.

(+)-(1*R*,2*S*,3*R*)-Methyl 3-acetoxy-2-(2-hydroxyethyl)-1-cyclopentaneacetate (**14b**). Detritylation of (–)-**14a** (230 mg, 0.47 mmol) by the same method as that for the case of (+)-**12a** gave (+)-**14b** (75 mg) in a 66% yield, $[\alpha]_D^{23} +7.2^\circ$ ($c=1.49$, CHCl_3). IR $\nu_{\text{max}} \text{ cm}^{-1}$: 3450, 1737, 1439, 1377, 1248, 1020. $^1\text{H-NMR}$ (CDCl_3) δ : 1.52–2.63 (9H, m), 2.05 (3H, s), 2.29 (1H, d, d, $J=15.3, 10.9$ Hz), 3.67 (2H, t, $J=6.6$ Hz), 3.69 (3H, s), 5.23 (1H, d, d, d, $J=5.4, 5.4, 2.1$ Hz). HR-MS (m/z): 245.1413 ($\text{M} + \text{H}^+$). Calcd. for $\text{C}_{12}\text{H}_{21}\text{O}_5$: 245.1388.

(1*R*,2*S*,3*R*)-Methyl 3-acetoxy-2-formylmethyl-1-cyclopentaneacetate (**14c**). Oxidation of (+)-**14b** (80 mg, 0.33 mmol) by the same method as that for the case of (–)-**12b** gave aldehyde **14c** (49 mg) in a 62% yield. IR $\nu_{\text{max}} \text{ cm}^{-1}$: 2730, 1738, 1243, 1021. $^1\text{H-NMR}$ (CDCl_3) δ : 1.46–2.75 (10H, m), 2.03 (3H, s), 3.68 (3H, s), 5.23 (1H, m), 9.77 (1H, s).

(1*R*,2*S*,3*R*)-Methyl 3-acetoxy-2-(2*Z*-pentenyl)-1-cyclopentaneacetate (**15**). A Wittig reaction with **14c** (18 mg, 0.07 mmol) by a similar method as that for the case of **12c** gave **15** (10 mg) in a 49% yield. IR $\nu_{\text{max}} \text{ cm}^{-1}$: 1738, 1655,

1438, 1375, 1240, 1020. $^1\text{H-NMR}$ (CDCl_3) δ : 0.95 (3H, t, $J=7.5$ Hz), 1.49–2.62 (11H, m), 2.04 (3H, s), 2.30 (1H, d, d, $J=15.3, 4.2$ Hz), 3.68 (3H, s), 5.15 (1H, m), 5.23–5.44 (2H, m).

(–)-(1*R*,5*R*,8*S*)-8-(2*Z*-Pentenyl)-2-oxabicyclo[3.2.1]-octan-3-one (**16**). Hydrolysis of **15** (11 mg, 0.04 mmol) in a similar manner to that for the case of **13** gave (–)-**16** (7 mg) in a 95% yield. $[\alpha]_D^{23} -71.0^\circ$ ($c=0.29$, CHCl_3). IR $\nu_{\text{max}} \text{ cm}^{-1}$: 3000, 1738, 1655, 1375, 1217, 1140, 1000. $^1\text{H-NMR}$ (CDCl_3) δ : 0.95 (3H, t, $J=7.6$ Hz), 1.61–2.40 (11H, m), 2.74 (1H, m), 4.59 (1H, m), 5.31–5.54 (2H, m). HR-MS (m/z): 217.110 ($\text{M} + \text{Na}$)⁺. Calcd. for $\text{C}_{12}\text{H}_{18}\text{O}_2\text{Na}$: 217.1204. Similarly, (+)-**16**, $[\alpha]_D^{23} +68.9^\circ$ ($c=0.52$, CHCl_3), was prepared from (–)-**14b**.

Bioassay. A group of twenty lettuce seeds each (cv. *Great Lakes*) was placed in 4 cm petri dishes, which contained a double layer of filter paper moistened with 2 ml of a test solution. Incubation was conducted at 25°C under continuous white light for 140 hr, and the root lengths was then measured.

Acknowledgment. The authors thank Zeon Japan Co., Ltd. for their provision of (±)-methyl jasmonate. We are also grateful to Meito Sangyo Co., Ltd. for their provision of Lipase MY.

References

- 1) H. Fukui, K. Koshimizu, S. Usuda and Y. Yamazaki, *Agric. Biol. Chem.*, **41**, 175 (1977).
- 2) D. C. Aldridge, S. Galt, D. Giles and W. B. Turner, *J. Chem. Soc. (C)*, **1971**, 1623; H. Fukui, K. Koshimizu, S. Usuda and Y. Yamazaki, *Agric. Biol. Chem.*, **41**, 175 (1977).
- 3) J. Ueda, J. Kato, H. Yamane and N. Takahashi, *Physiol. Plant.*, **52**, 305 (1981); H. Yamane, J. Sugawara, Y. Suzuki, E. Shimamura and N. Takahashi, *Agric. Biol. Chem.*, **44**, 2857 (1980).
- 4) T. Oritani, K. Yamashita, *J. Synth. Org. Chem. Jpn.*, **41**, 1054 (1983); K. Yamamoto, T. Nishoka and J. Oda, *Tetrahedron Lett.*, **29**, 1717 (1988).
- 5) H. Tanaka and S. Torii, *J. Org. Chem.*, **40**, 462 (1975).
- 6) B. Maurer and A. Hauser, *Helv. Chim. Acta*, **65**, 462 (1982).
- 7) T. Kitahara, K. Miura, Y. Warita, Y. Takagi and K. Mori, *Agric. Biol. Chem.*, **51**, 1129 (1987).
- 8) W. H. Kruizinga, B. Strijtveen and R. M. Kellogg, *J. Org. Chem.*, **46**, 4321 (1981).
- 9) O. Mitsunobu, *Synthesis*, **1981**, 1.
- 10) Y. Torisawa, H. Okabe and S. Ikegami, *Chem. Lett.*, **1984**, 1555.
- 11) M. Schlosser, G. Müller and K. F. Christmann, *Angew. Chem.*, **78**, 677 (1966).