perature overnight, 14 h. Benzene (20 mL) was added to the now dark brown reaction mixture containing adipoin. The latter was transferred to a Dean-Stark apparatus, and the mixture was refluxed for 15 h under a static argon atmosphere. *Note*: this reaction was monitored by gas chromatography. The volatile components were removed at reduced pressure. The residue was vacuum distilled, bp 60-67 °C (0.23 Torr), giving 1.59 g of the title compound in 68% yield. ^{1}H NMR (90 MHz, $CDCl_3$): δ 3.19-1.38 (multiplet). ^{13}C NMR (20.1 MHz, $CDCl_3$): δ 211.71 (carbonyl), 72.45 (methinyl), 51.11, 40.57, 33.35, 28.37, 23.45, 22.62. IR ($CDCl_3$): 2962 (s), 1715 cm^{-1} (s). MS: 167.1318 (d, parent ion) and 110.0995 (d, base peak).

1-(1-Pyrrolidino)-6-(1-piperidino)cyclohex-1-ene. From 11 (4.68 g, 0.026 mol) and pyrrolidine (2.10 g, 0.03 mol) in benzene (20 mL) with *p*-toluenesulfonic acid, via the procedure for **6**, there was obtained 3.91 g (64%) of the title compound, bp 97-103 °C (0.45 Torr). ^{1}H NMR (90 MHz, $CDCl_3$): δ 4.38 (tr, 1 H, 0.3 Hz, vinyl), 3.54-1.23 (mu, 25 H). ^{13}C NMR (20.1 MHz, $CDCl_3$ filtered through basic alumina): δ 143.47 (quat vinyl), 96.84 (vinyl), 59.99 (methinyl), 49.71, 47.63, 27.19, 25.22, 24.78, 23.53, 22.06, 21.28. IR ($CDCl_3$): 3043 (w), 2940 (s), 2860 (m), 2800 (m), 1625 cm^{-1} (m). MS: 234.2087 (d, parent ion) and 149.1227 (d, base peak).

1,6-Di-1-pyrrolidinocyclohex-1-ene (13). A mixture of anhydrous methanol (16 mL) bis(siloxene) **9** (15.25 g, 0.059 mol), and pyrrolidine (4.35 g, 0.061 mol) was stirred in a stoppered bottle for 20 h at room temperature under a static argon atmosphere.

Methanol and pyrrolidine were removed by rotary evaporation. To the residue were added benzene (50 mL), a few crystals of *p*-toluenesulfonic acid, and pyrrolidine (10 g, 0.14 mol). After refluxing this mixture for 63 h in a Dean-Stark apparatus, volatile components were removed under vacuum through a Vigreux column, and the residue was likewise fractionated, bp 92-100 °C (0.5 Torr), giving 8.56 g (66%) of clear **13**. The amino enamine was stored under argon in a 14/20 25-mL pear-shaped flask fitted with a glass stopcock and held in place with a spring clamp. ^{1}H NMR (90 MHz, $CDCl_3$): δ 4.39 (tr, 1 H, J = 0.4 Hz, vinyl), 3.58-0.94 (mu, 23 H). ^{13}C NMR (20.1 MHz, $CDCl_3$): δ 144.62 (quat vinyl), 96.57 (vinyl), 54.80 (methinyl), 48.84, 47.85, 25.23, 24.62, 23.91, 19.64. IR (neat) 3055 (w), 2947 (s), 1637 cm^{-1} (s). MS: 220.1937 (d, parent ion) and 149.1167 (d, base peak).

***cis*-1-(1-Piperidino)-2-(1-pyrrolidino)cyclohexane (17).** Hydrogenation of 1-(1-pyrrolidino)-6-(1-piperidino)cyclohex-1-ene (2.94 g, 0.013 mol) over 5% Pd/C (0.3 g) in ethyl acetate (50 mL), via the procedure for **7**, gave on workup 1.67 g (62%) of **17**, bp 90-95 °C (0.25 Torr). ^{1}H NMR (90 MHz, $CDCl_3$): δ 3.10-2.15 (mu, 10 H) and 2.14-1.10 (mu, 18 H). ^{13}C NMR (20.1 MHz, $CDCl_3$): δ 66.55, 63.60, 52.55, 51.84, 29.81, 26.58, 25.66, 23.14, 22.16. IR (neat) 2940 (s), 2865 (m), 2800 (m), 1453 cm^{-1} (w). MS: 236.2247 (d, parent ion) and 110.0961 (d, base peak).

This cis stereochemistry is assumed by analogy to the results with *cis*-1,2-dipiperidinocyclopentane.

***cis*-1,2-Di-1-pyrrolidinocyclohexane (18).** A mixture of adipoin (3.07 g, 0.026 mol), pyrrolidine (5.56 g, 0.078 mol), a few crystals of *p*-toluenesulfonic acid, and 40 mL of benzene was allowed to reflux for 50 h in a Dean-Stark apparatus, by which time gas chromatography indicated complete conversion of adipoin to the aminoenamine. The cooled reaction mixture was cannulated into a Parr jar and hydrogenated over 5% Pt on alumina, over a period of 10 h, via the procedure for **7**. The residue was vacuum distilled through a short-path distillation apparatus, giving 3.46 g (60%) of **18**, bp 90-98 °C (0.07 Torr). ^{1}H NMR (90 MHz, $CDCl_3$): δ 3.12-2.15 (mu, 10 H), 2.11-1.00 (mu, 16 H). ^{13}C NMR (20.1 MHz, $CDCl_3$): δ 66.30 (methinyl), 52.24, 28.90, 23.09. IR ($CDCl_3$): 2960 (s), 2883 (m), 2789 (s), 1460 cm^{-1} (m). MS: 222.2041 (d, parent ion) and 110.0976 (d, base peak).

The cis stereochemistry is assumed by analogy to the case of *cis*-1,2-dipiperidinocyclopentane.

Acknowledgment. This research was supported by the National Science Foundation, Grants CHE-8304636 and CHE-8605974. High-field NMR equipment used in this work was also financed in part by grants from the National Science Foundation. We are happy to acknowledge the technical advice from Dr. Charles Cottrell, Chemical Instrumentation Center, The Ohio State University.

Registry No. **2**, 55154-10-4; **5**, 6838-66-0; **6**, 118207-26-4; **7**, 26887-73-0; **7**·dipicrate, 118207-25-3; **9**, 6838-67-1; **11**, 118207-28-6; **12**, 118207-29-7; **13**, 118207-30-0; **14**, 26785-42-2; **15**, 89121-43-7; **16**, 26785-38-6; **17**, 118207-31-1; **18**, 26785-40-0; piperidine, 110-89-4; pyrrolidine, 123-75-1; 2-(1-pyrrolidino)cyclopentanone, 118207-27-5; adipoin dimer, 60308-50-1; 1,5-di-1-pyrrolidinocyclopent-1-ene, 118207-32-2; (*N*,*N*-dimethylamino)cyclopentanone, 79076-02-1; 1,5-di(*N*,*N*-dimethylamino)cyclopent-1-ene, 118207-33-3; dimethyl adipate, 627-93-0; 2-(1-pyrrolidino)-cyclohexanone, 118207-34-4; 1-(1-pyrrolidino)-6-(1-piperidino)-cyclohex-1-ene, 118207-35-5; adipoin, 533-60-8; dimethyl glutarate, 1119-40-0.

Supplementary Material Available: Atomic coordinates and all relevant details of X-ray crystallography of the dipicrate of **7** (11 pages). Ordering information is given on any current masthead page.

A Novel Synthesis of (±)-Abscisic Acid

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A four-step synthesis of abscisic acid (1) is described, with a yield of 32.4%. The two starting materials are known compounds but are not commercially available: compound **2** is prepared in four steps from ethyl acetoacetate and mesityl oxide, and compound **3** is prepared in two steps from 3,3-dimethylacrylic acid. The synthesis involves a Reformatsky reaction, an epoxide formation, a ketal hydrolysis, and an elimination that accompanies an epoxide rearrangement.

Abscisic acid (1), also named Abscisin II, is a plant hormone that has a role in the control of several physiological processes such as abscision of leaves and seed germination.[1] It is largely distributed in higher plants and

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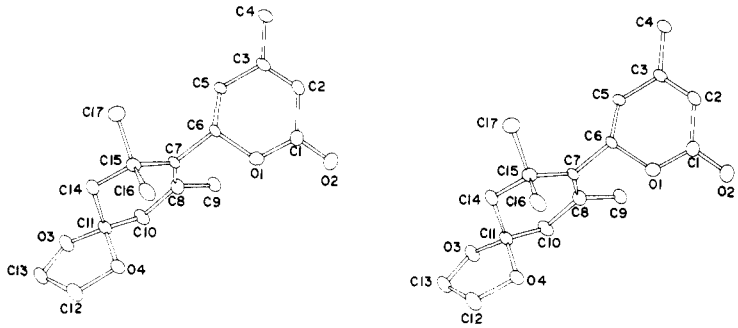


Figure 1. A stereoscopic view for compound **4**.

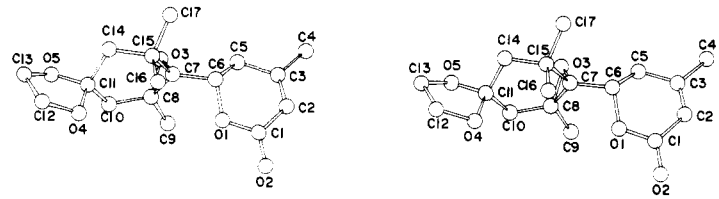
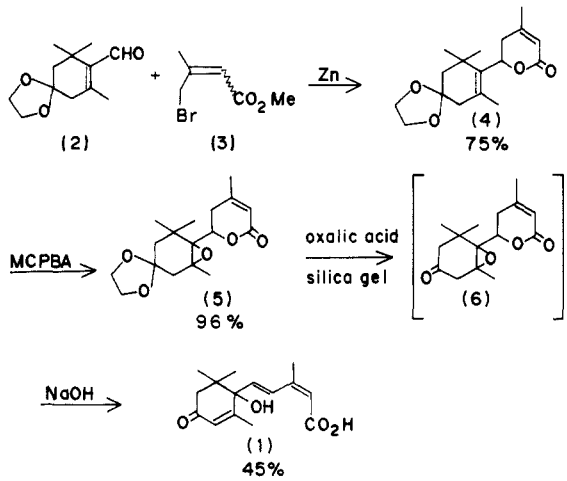
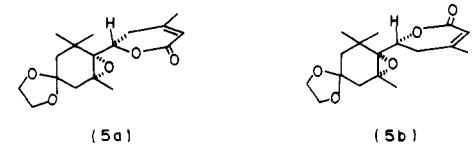


Figure 2. Stereoscopic view for compound **5a**.

Scheme I



Scheme II



its potential use as a plant growth regulator makes it particularly important.

A number of syntheses of **1** have been already described,[2] but efficiency—considered as a combination of good yields, low number of steps, and availability of starting materials—can still be improved.

In this paper we describe a four-step synthesis, which, from the known compounds **2**[3] and **3**,[4] produces abscisic acid in an yield of 32%[5] (Scheme I).

The first step is a Reformatsky reaction followed by an in situ lactonization.[6] The lactone **4** (see the X-ray structure stereoscopic projection in Figure 1, which confirms the desired structure) is produced in the same yield (75%) from either stereoisomer of **3**, indicating that an isomerization of the double bond occurs during the reaction. As a consequence, a mixture of isomers of **3** can be used, thus avoiding a tedious process of separation of *E*- and *Z*-**3**.

Oxidation of the tetrasubstituted double bond of compound **4** can be achieved in quantitative yield with *m*-chloroperoxybenzoic acid in refluxing chloroform in the presence of a phosphate buffer of pH 5.3. The buffer is essential because, with *m*-chloroperoxybenzoic acid alone in chloroform, some unidentified byproducts were formed in appreciable amounts, suggesting that hydrolysis of the ketal was probably taking place. On the other hand, in the presence of sodium bicarbonate or pH 7 buffer, the reaction was too slow. Two stereoisomers were produced in a ratio of 2.7:1 (Scheme II).

The isomers were easily separated by column chromatography, but the determination of the relative stereochemistry of the compounds could not be made by NMR analysis. A structure determination of one of them, which produced suitable single crystals for X-ray analysis, allowed us to remove the ambiguity. A stereoscopic projection of the structure of compound **5a** is shown in Figure 2.[7]

For the purpose of synthesizing racemic abscisic acid, however, this stereochemistry is not relevant, as both isomers will give the same product after two subsequent steps. In fact, either isomer of **5** was hydrolyzed with oxalic acid adsorbed on silica gel[8] to give the corresponding isomer of **6** in quantitative yield, and each one of these, without further purification, was transformed in abscisic acid (**1**) (45% yield). Both reactions were also performed with the mixture of isomers, and the same final result was obtained.

Experimental Section

Melting points were determined on a Reichert Kofler block melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 60 or 80 MHz. The ^{13}C NMR spectra were recorded at 20 MHz. Analytical

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(5) This yield is based on compound **2**, which was prepared in four steps from mesityl oxide and ethyl acetoacetate.[3] Compound **3** was prepared in two steps from 3,3-dimethylacrylic acid.[4]
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gas chromatography (GLC) separations were performed on a 6 ft × 1/8 in. stainless steel column packed with 3% OV-17 silicone on Chromosorb W operating at temperatures in the range 80–230 °C. Given yields correspond to materials with the same purity as the samples used in the following step.

5,6-Dihydro-4-methyl-6-(7′,9′,9′-trimethyl-1′,4′-dioxaspiro[4.5]dec-7′-en-8′-yl)-2*H*-pyran-2-one (4). Activated zinc[9] (133 mg, 2.04 mmol) was treated, under nitrogen atmosphere, with a crystal of iodine and about 1 mL of a solution of the bromo ester **3** (382 mg, 2.0 mmol) and the aldehyde **2** (157 mg, 0.75 mmol) in tetrahydrofuran (3.0 mL). The mixture was warmed to start the reaction, and the rest of the solution was added in small portions. The reaction mixture was then heated to reflux for 4 h, cooled to room temperature, and quenched with aqueous saturated ammonium chloride solution (2.0 mL). The mixture was diluted with water and ether, and the organic layer was separated, washed with water, and dried over anhydrous potassium carbonate. The soltuion was concentrated under vacuum, and the residue was chromatographed on silica gel, eluting with hexane–ethyl acetate–ether (2:1:1) containing 1% diisopropylamine, giving compound **4** (163 mg, 0.56 mmol, 75%). For analytical purposes a small sample was recrystallized from ethyl ether: mp 108–9 °C; IR (KBr) 1720, 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.78 (m, 1 H), 4.95 (q, J_1 = 4 Hz, J_2 = 13 Hz, 1 H), 3.87 (s, 4 H), 2.80 (q, J_1 = 19 Hz, J_2 = 13 Hz, 1 H), 2.20 (s, 2 H), 2.06 (q, J_1 = 19 Hz, J_2 = 4 Hz, 1 H), 1.90 (s, 3 H), 1.72 (d, J = 1.5 Hz, 3 H), 1.60 (s, 2 H), 1.12 (s, 3 H), 0.97 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 165.3 (s), 157.3 (s), 135.5 (s), 133.5 (s), 131.4 (s), 116.1 (d), 107.0 (s), 74.8 (d), 63.8 (t), 45.5 (t), 43.2 (t), 37.1 (s), 35.1 (t), 28.6 (q), 28.3 (q), 22.6 (q), 21.0 (q). Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.56; H, 8.43.

5,6-Dihydro-4-methyl-6-[2″,6″,6″-trimethylspiro[1′,3′-dioxolane-2′,4″-[7]oxabicyclo[4.1.0]hept-1″-yl]]-2*H*-pyran-2-one (5). *m*-Chloroperoxybenzoic acid[10] (126 mg, 0.73 mmol) was added in small portions to a magnetically stirred mixture of compound **4** (102 mg, 0.35 mmol) dissolved in chloroform (2.0 mL) and phosphate buffer pH 5.3 (2.0 mL). The reaction mixture was refluxed for 4 h and cooled to room temperature, 10% sodium bisulfite solution was added, and stirring was continued for 10 min. The mixture was diluted with water and chloroform, the organic layer was separated, washed successively with a 5% sodium hydrogen carbonate solution and saturated sodium chloride solution, and dried over anhydrous potassium carbonate. The solution was concentrated under vacuum, and the crude epoxide **5** (107 mg, 0.35 mmol, 100%) was obtained as a mixture of isomers with a very small amount of impurities.

Separation of Diastereoisomers 5a and 5b. The diastereoisomeric mixture **5** (107 mg) was chromatographed on silica gel, eluting with hexane–ethyl acetate–chloroform (1:1:2), containing 1% diisopropylamine.

(i) **5a** (75.2 mg, 70%): for analytical purposes a small sample was recrystallized from ethyl ether; mp 163–4 °C; IR (KBr) 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.65 (m, 1 H), 5.07 (q, J_1 = 5 Hz, J_2 = 13 Hz, 1 H), 3.92 (s, 4 H), 3.50–1.50 (m, 4 H), 2.17 (s, 2 H), 2.03 (s, 3 H), 1.42 (s, 3 H), 1.33 (s, 3 H), 1.00 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 164.1 (s), 157.0 (s), 116.3 (d), 106.4 (s), 76.3 (d), 68.7 (s), 64.3 (t), 64.1 (t), 63.5 (t), 42.3 (t), 35.4 (s), 32.4 (t), 26.2 (q), 24.0 (q), 22.9 (q), 22.8 (q). Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 66.26; H, 7.95.

(ii) **5b** (28.5 mg, 26%): for analytical purposes a sample was recrystallized from ethyl ether–hexane; mp 96–8 °C; IR (KBr) 1751 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.73 (m, 1 H), 4.47 (q, J_1 = 4 Hz, J_2 = 13 Hz, 1 H), 3.80 (s, 4 H), 2.79 (q, J_1 = 18 Hz, J_2 = 13 Hz, 1 H), 2.28 (q, J_1 = 18 Hz, J_2 = 4 Hz, 1 H), 2.17 and 2.02 (q AB, J = 16 Hz, 2 H), 1.93 (d, J = 1.5 Hz, 3 H), 1.61 and 1.24 (q AB, J = 13 Hz, 2 H), 1.37 (s, 3 H), 1.27 (s, 3 H), 1.12 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 164.0 (s), 157.7 (s), 116.3 (d), 106.5 (s), 77.0 (d), 66.2 (t), 63.9 (t), 63.8 (t), 45.4 (t), 41.8 (t), 35.4 (s), 32.6 (t), 27.3 (q), 26.1 (q), 22.8 (q), 21.4 (q). Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 65.81; H, 7.90.

5,6-Dihydro-4-methyl-6-(2′,6′,6′-trimethyl-4′-oxo[7]oxabicyclo[4.1.0]hept-1′-yl)-2*H*-pyran-2-one (6). a. (1*S*,1′*R*,2′*R*)-6a and Its Enantiomer (as a racemic mixture). An aqueous solution of 15% oxalic acid (50 μL) was added to a stirred suspension of silica gel (500 mg) in dichloromethane (2.0 mL).[8] Compound **5a** (55.6 mg, 0.18 mmol) was added, and stirring was continued at room temperature for 7 h. The solid phase was separated by filtration, and the organic phase was diluted, washed with water, and dried over anhydrous magnesium sulfate. The solution was concentrated under vacuum, giving **6a** as a white crystalline solid (47.5 mg, 0.18 mmol, 100%). This product was impure, as demonstrated by TLC and NMR; however, the amount of impurities was small, and this permitted good interpretation of spectral data. In view of the sensitivity of this compound to acids and bases, it was not purified and was used directly and successfully in the next step: IR (KBr) 1710, 1245 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.75 (m, 1 H), 5.05 (q, J_1 = 5 Hz, J_2 = 13 Hz, 1 H), 2.67 and 2.53 (qAB, J = 22 Hz, 2 H), 2.58 (q, J_1 = 19 Hz, J_2 = 13 Hz, 1 H), 1.99 (q, J_1 = 19 Hz, J_2 = 5 Hz, 1 H), 2.40 and 1.83 (q AB, J = 16 Hz, 2 H), 1.93 (d, J = 1.5 Hz, 3 H), 1.55 (s, 3 H), 1.23 (s, 3 H), 1.02 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 206.2 (s), 163.6 (s), 157.0 (s), 116.2 (d), 75.5 (d), 68.4 (s), 50.5 (t), 44.4 (t), 36.7 (s), 31.9 (t), 25.0 (q), 23.6 (q), 22.9 (q), 21.8 (q).

b. (1*R*,1′*R*,2′*R*)-6b and Its Enantiomer (as a racemic mixture). Isomer **6b** was prepared analogously and in similar yield. The solid product obtained was also not purified: IR (KBr) 1720, 1245 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.90 (s, 1 H), 4.72 (q, J_1 = 4 Hz, J_2 = 13 Hz, 1 H), 2.77 (s, 2 H), 2.60–1.60 (m, 4 H), 2.05 (s, 3 H), 1.43 (s, 3 H), 1.35 (s, 6 H).

c. The same reaction was carried out also with a mixture of compounds **5a** and **5b**, and a mixture of **6a** and **6b** was obtained with the same yield.

(±)-Abscisic Acid (1). A solution of compound **6a** (50.4 mg, 0.19 mmol) in pyridine (1.0 mL) was added to a 10% solution of sodium hydroxide in 1:1 ethanol and pyridine (4.0 mL). After 1.5 h of magnetic stirring at room temperature, the reaction mixture was diluted with ether and acidified with 10% hydrochloric acid. The organic layer was separated, washed with water, and dried over anhydrous magnesium sulfate. The solution was concentrated under vacuum, and the residue was chromatographed on silica gel, eluting with benzene–acetone–acetic acid (45:5:2), giving **1** (22.8 mg, 0.086 mmol, 45%) as a white crystalline solid, pure by TLC and identical with an authentic sample[2] by TLC, IR, and ^1H NMR: mp 185–6 °C (lit.[11] mp 188–190 °C); ^1H NMR ($CDCl_3/CD_3OD$)[12] δ 7.74 (d, J = 16 Hz, 1 H), 6.15 (d, J = 16 Hz, 1 H), 5.92 (s, 1 H), 5.77 (s, 1 H), 2.48 and 2.27 (q AB, J = 17 Hz, 2 H), 2.02 (d, J = 1.5 Hz, 3 H), 1.93 (d, J = 1.5 Hz, 3 H), 1.10 (s, 3 H), 1.02 (s, 3 H). An authentic sample[2] measured in the same solvent gave the same peaks within 0.01 ppm. Deviations from the previously reported data[2] are due to differences in the $CDCl_3/CD_3OD$ ratio.

The same reaction was carried out also with the isomer **6b** and with the crude mixture of isomers, with similar yields (45 and 39%, respectively).

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Registry No. (±)-**1**, 14375-45-2; **2**, 23069-08-1; (*E*)-**3**, 19041-17-9; (*Z*)-**3**, 27652-13-7; (±)-**4**, 117940-42-8; (±)-**5a**, 118015-60-4; (±)-**5b**, 117940-44-0; (±)-**6a**, 117940-43-9; (±)-**6b**, 118014-54-3; $CH_3COCH_2CO_2Et$, 141-97-9; $(CH_3)_2C{=}CHCO_2H$, 541-47-9; mesityl oxide, 141-79-7.

(9) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1967; Vol. 1, p 1285.

(10) A *m*-chloroperoxybenzoic acid solution in 80% benzene–20% ether was washed with a phosphate buffer solution (prepared by dissolving 297 mg of sodium monohydrogen phosphate and 8.85 g of potassium dihydrogen phosphate in 1 L of water) to remove all the benzoic acid.

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(12) A 9:1 (v/v) $CDCl_3/CD_3OD$ solvent was used; the solution was prepared by dissolving abscisic acid (3.6 mg) in the solvent (0.3 mL).