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A Stereospecific Synthesis of (±)-Abscisic Acid*

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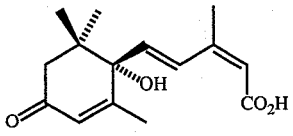
Abstract

A convenient separation of (*E*)- and (*Z*)-3-methylpent-2-enedioic acids was devised, and it was shown that with acetyl chloride or thionyl chloride the (*Z*)-acid yields the cyclic anhydride while the (*E*)-acid forms 6-chloro-4-methylpyran-2-one. The chloropyranone by conventional chemistry gave 4-methyl-6-(2′-oxopropyl)pyran-2-one which condensed with 4-methylpent-3-en-2-one in the presence of pyrrolidine, yielding 4-methyl-6-(2′,6′,6′-trimethyl-4′-oxocyclohex-2′-enyl)pyran-2-one. Oxidation with selenium dioxide or t-butyl chromate then gave 6-(1′-hydroxy-2′,6′,6′-trimethyl-4′-oxocyclohex-2′-enyl)-4-methylpyran-2-one, which on reduction by lithium aluminium hydride and reoxidation afforded (±)-abscisic acid stereospecifically.

Since the original synthesis[1] of the plant hormone abscisic acid (1), a number of syntheses have been reported,[2–8] though it cannot yet be said that a convenient large-scale synthesis has been found. Hitherto, all syntheses have used the commercially available α- or β-ionone, or 4-oxoisophorone, as starting material. The work reported here uses an entirely novel approach based on



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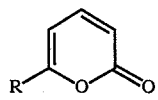

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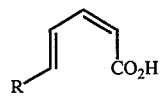

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* Dedicated to Arthur Birch, *primus inter alia.*

[1] Cornforth, J. W., Milborrow, B. V., and Ryback, G., *Nature (London)*, 1965, **206**, 715.
[2] Roberts, D. L., Heckman, R. A., Hege, B. P., and Bellin, S. A., *J. Org. Chem.*, 1968, **33**, 356.
[3] Cornforth, J. W., Mallaby, R., and Ryback, G., *J. Chem. Soc. C*, 1968, 1565.
[4] Tamura, S., and Nagao, M., *Agric. Biol. Chem.*, 1969, **33**, 1357.
[5] Oritani, T., and Yamashita, K., *Agric. Biol. Chem.*, 1973, **37**, 1115.
[6] Mayer, H. J., Rigassi, N., Schwieter, U., and Weedon, B. C. L., *Helv. Chim. Acta*, 1976, **59**, 1424.
[7] Kienzle, F., Mayer, H., Minder, R. E., and Thomann, H., *Helv. Chim. Acta*, 1978, **61**, 2616.
[8] Soukup, M., Lukáč, T., Lohri, B., and Widmer, E., *Helv. Chim. Acta*, 1989, **72**, 361.

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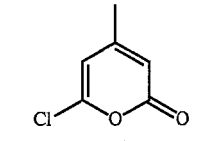
pyranone chemistry, and its starting point was the observation[9,10] that reduction of pyran-2-ones (2) by complex metal hydrides can yield, stereospecifically, (2*Z*,4*E*)-pentadienoic acids (3) with geometry corresponding to that of the side chain in (1). For construction of the necessary attachment to this potential side chain, we required a convenient synthesis of 6-chloro-4-methylpyran-2-one (4).



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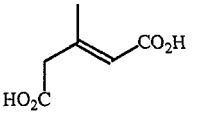

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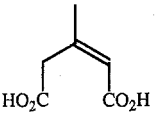

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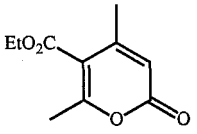

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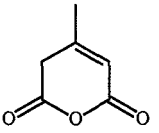

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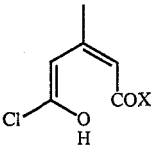


(9) X = Cl or OAc

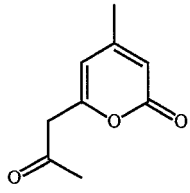
This substance was first made[11] by the action of acetyl chloride on a preparation of 3-methylglutaconic acid now known[12] to have been a mixture of the (*E*)- and (*Z*)-isomers (5) and (6). The mixture of acids has generally been made by alkaline cleavage of 'isodehydracetic acid' or its ester, prepared by acid-catalysed self-condensation of ethyl acetoacetate. We improved a preparation[13] of ethyl isodehydracetate (ethyl 4,6-dimethyl-2-oxopyran-5-carboxylate) (7) and its hydrolysis, to obtain a 6 : 4 mixture of (5) and (6) in 52% overall yield. When the mixture was stirred with 0·5 equiv. of acetic anhydride in warm benzene, all the (*Z*)-acid and some of the (*E*)-acid went into solution as the anhydride (8), leaving pure (*E*)-acid. Cold hydrolysis of the benzene-soluble fraction with a limited amount of alkali then gave pure (*Z*)-acid, or hot alkaline isomerization gave the 6 : 4 mixture of acids from which further (*E*)-acid could be separated as before. This separation of the geometrical isomers, a procedure which can be used to prepare either isomer at the expense of the other, is much more convenient than the original method[12] for separating pure (*E*)-acid (ultraviolet irradiation followed by a tedious solvent treatment). For reasons which will become clear, we maximized the recovery of (*E*)-acid.

Separate treatment of the isomeric acids with acetyl chloride revealed that only the (*E*)-acid (5) afforded 6-chloro-4-methylpyran-2-one, the (*Z*)-acid yielding anhydride (8) exclusively. Thionyl chloride was another reagent for preparation of the chloropyranone from the (*E*)-acid. The mixed acids with acetyl chloride produced a mixture of chloropyranone and anhydride, separable by distillation.

[9] Yamada, K., Naito, T., Okuhara, K., Nakata, H., and Hirata, Y., *Bull. Chem. Soc. Jpn*, 1960, **33**, 1303.
[10] Vogel, G., *Chem. Ind. (London)*, 1962, 268.
[11] Bland, N., and Thorpe, J. F., *J. Chem. Soc.*, 1912, **101**, 856.
[12] Jackman, L. M., and Wiley, R. H., *J. Chem. Soc.*, 1960, 2886, and earlier references quoted therein.
[13] Goss, F. R., Ingold, C. K., and Thorpe, J. F., *J. Chem. Soc.*, 1923, **123**, 327.

The anhydride (8) could not be converted into the chloropyranone by acetyl chloride, by thionyl chloride, or by phosphorus pentachloride in chloroform (though a conversion in unspecified yield and purity by prolonged heating with phosphorus pentachloride in phosphoryl chloride has been reported).[14] It seems that in these acidic conditions the essential (*E*) → (*Z*) isomerization, probably a prototropic process entailing ionization of a methylene hydrogen, is slow unless both carboxy groups in (5) are activated, and that a transient tautomer such as (9) is the immediate source of the chloropyranone. With the (*Z*)-acid, where isomerization is not needed, irreversible formation of the anhydride presumably occurs rapidly after activation of only one carboxy group.

The reactions of 6-chloropyran-2-ones have been little studied; yet as acid chloride vinylogues they have obvious potential for construction of new C–C bonds at the 6-position. In fact, reaction of the chloropyranone (4) with a cold suspension of sodio t-butyl acetoacetate, followed by acid-catalysed fission of the ester group, gave a good yield of 4-methyl-6-(2′-oxopropyl)pyran-2-one (10). The spectra of this substance showed only the ketonic form, but it was quite acidic and its sparingly soluble sodium salt crystallized from aqueous solution.



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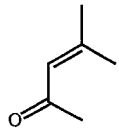

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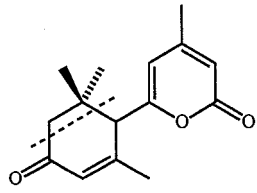

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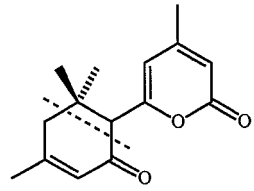


(13)

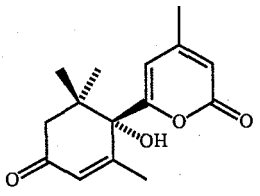
A trimethylcyclohexenone (11) was constructed with somewhat unexpected ease from the pyranone (10) and mesityl oxide (12) with pyrrolidine as catalyst. With potassium t-butoxide instead of pyrrolidine, the isomer (13) was the sole product isolated. There is precedent[15] for this difference, depending on the reagent, in the direction of ring closure. Assignment of structures to the two isomers was initially on the basis of mass spectra, which showed prominent fragment ions arising from the cleavages shown by the broken lines. The assignments are of course confirmed by the conversion of one isomer (11) into abscisic acid.

Introduction of a hydroxy group into the cyclohexenone (11) at the point of attachment of the pyranone ring was the most difficult and least satisfactory step of the synthesis. Many reagents were tried without success. Two, selenium dioxide and t-butyl chromate, gave poor yields of the tertiary alcohol (14); for convenience of isolation, the chromate was somewhat preferable. It seems that steric hindrance was operating against an otherwise favourable activation.

It had been proposed to effect the reductive opening of the pyranone ring in the intermediate (11), whereafter a final oxidative introduction of the tertiary hydroxy group might well have been easier. However, lithium

[14] Pirkle, W. H., and Turner, W. V., *J. Org. Chem.*, 1975, **40**, 1617.
[15] Begbie, A. L., and Golding, B. T., *J. Chem. Soc., Perkin Trans. 1*, 1972, 602.

borohydride affected only the α,β-unsaturated ketone function, the strong pyranone absorption at 300 nm remaining unchanged; and lithium aluminium hydride, though it reduced the pyranone function, did not yield any dienoic acid. A possible complicating factor here was the acidity of the tertiary hydrogen in (11): a strong orange colour produced by both reagents could be attributed to a degenerate enolate anion such as (15), which could not be assumed to behave like a pyranone on reduction.



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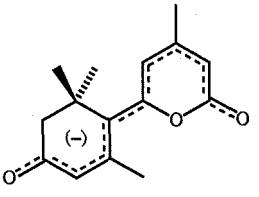

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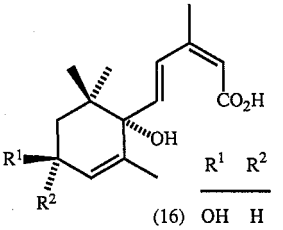

	R^1	R^2
(16)	OH	H
(17)	H	OH

This enolization cannot occur with the hydroxylated derivative (14), and there is also the possibility that formation of a hydridoaluminate on the tertiary hydroxy group can favour intramolecular hydride attack on the adjacent 6-position of the pyranone ring, thus overcoming steric hindrance. In fact, reduction of this derivative with lithium aluminium hydride in tetrahydrofuran gave a mixture in which the two diols (16) and (17) obtainable by borohydride reduction of abscisic acid[16] were identified by t.l.c. and confirmed by oxidation of the mixture with manganese dioxide or with Jones reagent, whereupon these components disappeared and crystalline abscisic acid (1), not previously present, was isolated by chromatography and identified with authentic material. This completed the synthesis and vindicated the strategy. The ring opening was not optimized and its yield might well be bettered, but unless the hydroxylation step can be decisively improved or circumvented the objective (which the earlier steps fully meet) of a convenient large-scale synthesis will not be reached by this route.

Experimental

Mass spectra were obtained by electron impact in an AEI MS9 spectrometer. Infrared spectra were obtained from compressed KCl disks, ultraviolet spectra were run in methanol, and n.m.r. spectra were run in $CDCl_3$, except when otherwise stated. Melting points were determined in an Electrothermal heating block. 'Ether' means diethyl ether; 'petrol' means light petroleum with b.p. 60–80°C. The proportions of solvent mixtures are by volume.

3-Methylpent-2-enedioic Acids (E/Z Mixture)

(A) Ethyl triphenylphosphoranylideneacetate (495 g; m.p. 122–125°C), prepared[17] from ethyl bromoacetate and triphenylphosphine, was stirred under nitrogen with ethyl acetoacetate (314 g), and heated slowly to 120°C. After 46 h at 115–120°C the mixture was cooled to 50°C, treated with petrol (1000 ml), stirred until cold, and filtered. Distillation of the filtrate and

[16] Cornforth, J. W., Draber, W., Milborrow, B. V., and Ryback, G., *J. Chem. Soc., Chem. Commun.*, 1967, 114.

[17] Gerecke, M., Ryser, G., and Zeller, P., (to Hofmann–La Roche Inc.) U.S. Pat. No. 2,912,467 (1959).

washings (4×250 ml petrol, then 500 ml 1:1 ether/petrol) gave diethyl 3-methylpent-2-enedioate (154 g, 54·2% on ylide), b.p. 66–74°C/0·3 mmHg. This was boiled under reflux for 7 h with sodium hydroxide (82 g) in water (700 ml), then cooled, and acidified to pH 1 with hydrochloric acid. The precipitated 3-methylglutaconic acids were isolated as below.

(B) Ethyl acetoacetate (1190 g), freshly distilled and protected from moisture, was stirred and cooled while dry hydrogen chloride was passed in for 1 h at a rate that did not raise the temperature above 5°C (around 200 g absorbed). The mixture was left at *c.* 20°C for 7 days, then cooled in ice and treated with water (1500 ml). The lower oily layer was removed; the aqueous layer was neutralized with calcium hydroxide (about 200 g), and extracted with ether (3×100 ml). The combined organic layers were dried ($CaCl_2$) and distilled. Pure ethyl 4,6-dimethyl-2-oxopyran-5-carboxylate (502 g, 56·3%) distilled at 114°C/0·25 mmHg (Found: C, 61·3; H, 6·4. Calc. for $C_{10}H_{12}O_4$: C, 61·2; H, 6·2%). N.m.r. δ 1·37, t, J 6·5 Hz, ester CH_3; 2·21, s, 4-CH_3; 2·40, s, 6-CH_3; 4·35, q, J 6·5 Hz, ester CH_2; 5·97, s, H3. This ester (397 g) in water (3500 ml) containing sodium hydroxide (320 g) was stirred at 70°C for 3 h, then cooled in ice, and treated with hydrochloric acid (695·3 ml of 11·5 M). Water was removed at low pressure until sodium chloride began to separate; then the mixture was extracted with ether (3×150 ml), which was dried ($MgSO_4$), and evaporated at low pressure to constant weight leaving the crystalline mixed acids (268 g, 93%), m.p. 115–116°C.

Separation of (E)*-Acid (5) and* (Z)*-Acid (6)*

The mixed acids (144 g, 1 mol), suspended in dry benzene (500 ml), were stirred with acetic anhydride (50 g, 0·49 mol) at 45–50°C for 12 h. The residual solid when collected, washed with benzene, and vacuum-dried was pure (*E*)-3-methylpent-2-enedioic acid (5) (56 g), m.p. 140–142°C (lit.[12] 139–140°C). N.m.r. [$(CD_3)_2SO$] δ 2·13, 3H; 3·12, 2H; 5·74, 1H. Evaporation of the filtrate left a red oil which was boiled under reflux with sodium hydroxide (80 g) in water (750 ml) for 4 h. After addition of hydrochloric acid (174 ml of 11·5 M) the mixed acids (84·4 g) were recovered as above and recycled to yield more of the (*E*)-acid (5).

Alternatively, the red oil was stirred with 1 equiv. of 10% aqueous sodium hydroxide at room temperature for 1 h. The solution after being washed with ether was acidified, concentrated and extracted as before, yielding the pure (*Z*)-acid (6), m.p. 149–150°C (lit.[18] 149–150°C). N.m.r. [$(CD_3)_2SO$] δ 1·90, 3H; 3·55, 2H; 5·74, 1H.

6-Chloro-4-methylpyran-2-one

(A) (*E*)-3-Methylpent-2-enedioic acid (10 g) was boiled under reflux with thionyl chloride (50 ml) for 2 h. The solution was evaporated and the residue was distilled; the fraction boiling at 80°C/0·4 mmHg was recrystallized from ether/petrol to yield the pure chloropyranone (4) (7 g, 70%), m.p. 51–52°C (lit.[11] 43°C) (Found: C, 49·8; H, 3·5; Cl, 24·6. Calc. for $C_6H_5ClO_2$: C, 49·8; H, 3·5; Cl, 24·7%).

(B) The total mixed acids from hydrolysis of diethyl 3-methylglutaconate (154 g; see above) were boiled under reflux with acetyl chloride (695 ml) for 12 h. The filtered solution was evaporated and the residue was distilled, yielding the chloropyranone (4), b.p. 90°C/0·5 mmHg (59·3 g, 53·5%).

The corresponding (*Z*)-acid (see above) on treatment with acetyl chloride, thionyl chloride or phosphorus pentachloride yielded only 3-methylglutaconic anhydride and no chloropyranone.

4-Methyl-6-(2′-oxopropyl)pyran-2-one

Sodium hydride (9·6 g of 50% in oil, 0·2 mol) was washed with petrol, and then stirred in ether (125 ml) during addition over 1 h of t-butyl acetoacetate (31·6 g, 0·2 mol). The white paste was stirred for a further 45 min, and then the chloropyranone (4) (14·4 g; 0·1 mol) was added over 40 min and followed 2·5 h later by acetic acid (6·2 g) in ether. After 1 h the mixture was filtered; the solid was taken up in water (100 ml) which was then

[18] Adams, R., and van Duuren, B. L., *J. Am. Chem. Soc.*, 1953, **75**, 2377.

acidified to pH 5 and extracted with ether. The united ether solutions were dried ($MgSO_4$) and evaporated. On distillation at low pressure t-butyl acetoacetate (13·6 g) was recovered. The residue (21·6 g) was boiled under reflux for 12 h with dry benzene (50 mL) containing toluene-4-sulfonic acid (0·3 g). Sodium acetate (0·13 g) was added and the mixture was distilled at low pressure. The fraction of b.p. 116–132°C/0·1–0·3 mmHg crystallized from ether, yielding the pure *pyranone* (10), m.p. 64°C (12·9 g, 78%) (Found: C, 65·2; H, 6·2. $C_9H_{10}O_3$ requires C, 65·1; H, 6·1%). λ_{max} 295 nm (ϵ 7030). ν_{max} ($CHCl_3$) 1710vs, 1640s cm^{-1}. N.m.r. δ 2·17, 4-CH_3; 2·26, H_3CCO; 3·61, H_2C; 6·08, m, H3, H5. The pyranone dissolved in dilute aqueous sodium hydroxide to a yellow solution from which a sparingly soluble sodium salt crystallized. In 0·1 M NaOH, λ_{max} was at 412 nm (ϵ 26140, sinking to 12000 overnight).

4-Methyl-6-(4′,6′,6′-trimethyl-2′-oxocyclohex-3′-enyl)pyran-2-one

Mesityl oxide (4-methylpent-3-en-2-one) (1·01 g) and the pyranone (10) (1·66 g) were added to a solution of potassium (0·05 g) in t-butyl alcohol (1 ml). The mixture was heated for 12 h at reflux, cooled, acidified with hydrochloric acid, and extracted with ether. From the ether solution on concentration, the *pyranone* (13) (1·0 g) crystallized, m.p. 123–124°C (Found: C, 73·4; H, 7·5. $C_{15}H_{18}O_3$ requires C, 73·2; H, 7·4%). λ_{max} 297 (ϵ 7700), 247 nm (11500). In 0·1 M NaOH, λ_{max} was at 480 nm. Mass spectrum: main peaks at 246 (M), 164 (M−82).

4-Methyl-6-(2′,6′,6′-trimethyl-4′-oxocyclohex-2′-enyl)pyran-2-one

Mesityl oxide (4-methylpent-3-en-2-one) (11 g, 115 mmol) was stirred with the pyranone (10) (9·28 g, 56 mmol), and pyrrolidine (0·8 g, 11·6 mmol) was added after 20 min. After a futher 5 min the temperature was raised to 70°C and maintained for 7 h. The orange mixture was poured on ice (20 g), and acidified to pH 2 with hydrochloric acid before extraction with ether. The dried ($MgSO_4$) extract on concentration deposited the crystalline pyranone (11) (5·33 g); a further 0·56 g was recovered from the mother liquor by chromatography on neutral alumina (elution with benzene/ethyl acetate, 11:1). The *pyranone* (11) had m.p. 104·5–105°C (Found: C, 73·5; H, 7·6. $C_{15}H_{18}O_3$ requires C, 73·2; H, 7·4%). λ_{max} 296 (ϵ 7700), 232 nm (12900). ν_{max} (KBr) 1625–1725br, 1555s cm^{-1}. N.m.r. δ 1·21 and 1·32, s, 6′,6′-$(CH_3)_2$; 2·12, 2′-CH_3; 2·38, 4-CH_3; 2·22, d, and 2·80, d, J 16 Hz, (H5′)$_2$; 3·15, H1′; 6·13, m, H3, H5, H3′. Mass spectrum: major peaks at *m/z* 246, 190, 134, 109, 53.

6-(1′-Hydroxy-2′,6′,6′-trimethyl-4′-oxocyclohex-2′-enyl)-4-methylpyran-2-one

(A) A solution of chromium trioxide (5·8 g, 60 mmol) and acetic anhydride (5·5 ml, 60 mmol) in t-butyl alcohol (20 ml) was added to a solution of the pyranone (11) (2·46 g, 10 mmol) in t-butyl alcohol (10 ml), and the mixture was heated under reflux for 21 h. The cooled mixture was stirred for 30 min with water (20 ml) and methanolic oxalic acid (20 ml; saturated), and extracted with chloroform (3×20 ml) which was then washed ($NaHCO_3$), dried ($MgSO_4$) and evaporated. The residue in ether deposited unidentified red crystals; the supernatant liquid was subject to preparative thin-layer chromatography on silica with toluene/ethyl acetate/acetic acid (50:30:3). The required *pyranone* (14) (0·29 g, 12%) was recrystallized from chloroform/petrol, m.p. 154–154·5°C (Found: C, 68·4; H, 7·0. $C_{15}H_{18}O_4$ requires C, 68·7; H, 6·9%). λ_{max} 296 (ϵ 6700), 228 nm (11300). ν_{max} (KBr) 3350s 1715vs, 1670vs, 1550s cm^{-1}. N.m.r. δ 0·95 and 1·15, s, 6′,6′-$(CH_3)_2$; 1·9, s, 2′-CH_3; 2·18, s, 4-CH_3; 2·23, d, and 2·73, d, J 16 Hz, (H5′)$_2$; 3·1, s, 1′-OH; 6·05, m, H3, H3′; 6·3, d, H5.

(B) Selenium dioxide (0·551 g, 5 mmol) was added to a solution of the pyranone (11) (0·247 g, 1 mmol) in dioxan (20 ml), and the whole heated at reflux for 40 min. Selenium was removed as far as possible by centrifuging, evaporation at low pressure, boiling the residue with acetone, and centrifuging again. The product (0·045 g, 17%) was isolated as in (A). A considerable amount of starting material remained unoxidized but was difficult to quantify.

(±)-*Abscisic Acid*

The pyranone (14) (26·4 mg, 0·1 mmol) in dry tetrahydrofuran (4 ml) was treated at room temperature with a solution of lithium aluminium hydride (0·15 mmol) in tetrahydrofuran. After 15 min the yellow suspension was stirred at 45°C for a further 90 min. Acidification and ether extraction then gave a product which was oxidized in dry chloroform (2 ml) with active manganese dioxide (120 mg) for 60 h at room temperature [or, alternatively, with Jones reagent (0·1 ml) in acetone for 5 min]. From the product, abscisic acid (3 mg) was isolated by chromatography on silica (Kieselgel F_{254}; toluene/ethyl acetate/acetic acid, 50:30:3), m.p. 188–190°C, identified with authentic material[1] by infrared and ultraviolet spectroscopy.