151. Synthesis of Abscisic Acid

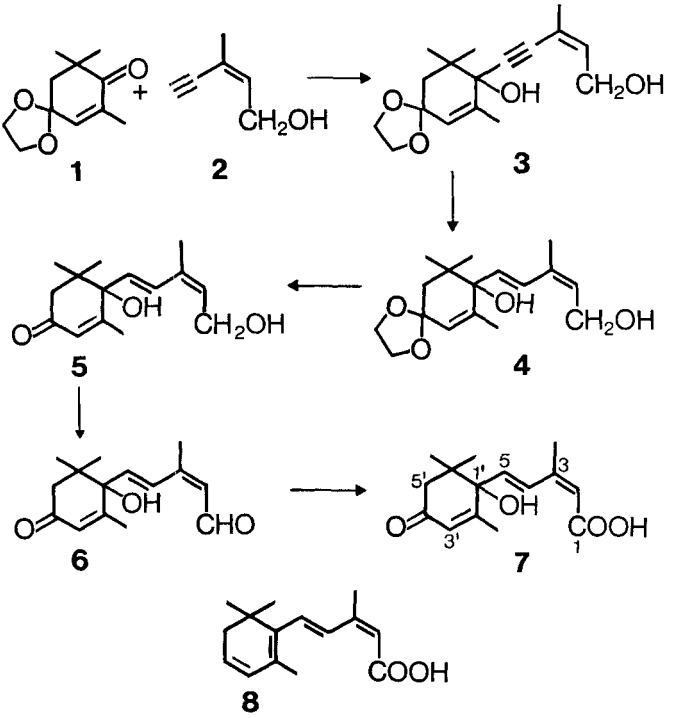
by **Hans J. Mayer, Norbert Rigassi** and **Ulrich Schwieter**
F. Hoffmann-La Roche & Co. AG., Basel
and **Basil C. L. Weedon**
Queen Mary College, Mile End Road, London E1 4NS

(28. IV. 76)

Summary. A stereoselective synthesis of (±)-abscisic acid (**7**) is described in which 2-*cis* 3-methylpent-2-en-4-yn-1-ol (**2**) is used to introduce the 2-*cis*, 4-*trans* geometry.

Abscisic acid, a widely distributed natural plant-growth regulator [1] [2] is the dextrotatory (1'*S*)-enantiomer of the 2-*cis*,4-*trans* acid **7** [3]. Its 2-*trans*,4-*trans* isomer is stated to have little or no biological activity, though both geometrical isomers are readily converted into an equilibrium mixture (*ca.* 1:1) of the two forms on irradiation [1] [2].

The racemate of abscisic acid, and that of its 2-*trans*,4-*trans* isomer, were first synthesised by *Cornforth et al.* [4]. Their starting materials were the 2-*cis* (**8**) and 2-*trans* forms respectively of dehydro-β-ionylidene-acetic acid, which can be separated by fractional crystallisation [5]. Others have described the preparations of mixtures of the two racemates [6] [7], which may be separated by chromatography [8], or by fractional crystallization [6]. The natural (+)-enantiomer of abscisic acid has been



obtained by resolution of synthetic racemates [9], and a product enriched in the (–)-enantiomer has been synthesized from (–)-α-ionone [10].

We now describe an alternative, stereoselective, route to racemic abscisic acid [11].

Anionotropic rearrangement of 3-methylpent-1-en-4-yn-3-ol, formed by condensation of methyl vinyl ketone with acetylene, forms a mixture of 3-methylpent-2-en-4-yn-1-ols [12]. The predominant *cis* isomer **2** may be separated by fractional distillation [13], and provides a convenient starting material for introducing the required configuration.

Reaction of the lithium derivative of the *cis* isomer **2** with the ketone **1** derived from isophorone [14] gave the expected *2-cis* compound **3**. This on reduction with sodium bis-(2-methoxyethoxy-)-aluminium hydride [15] then furnished the *2-cis-*, 4-*trans*-diene-diol **4** which, without purification, was treated with acid to give the dihydroxy-ketone **5**. Allylic oxidation of the primary hydroxyl group with manganese dioxide gave the aldehyde **6** which, on further oxidation with silver oxide, yielded (±)-abscisic acid.

With the exception of the intermediate **4**, all products were isolated as crystalline solids. Their NMR. spectra confirmed the given stereochemical course of the reactions. The C(4) and C(5) protons in the conjugated dienes **5**, **6** and **7** gave rise to *AB*-quartets, and the coupling constants (J = 16 Hz) established the *trans* configuration of the 4,5-double bonds. The deshielding observed with the β-methyl bands in the aldehyde **6**, the acid **7** and its methyl ester was characteristic of *2-cis* structures [16].

Experimental Part

Reactions were carried out in an inert atmosphere, and solvents were evaporated under reduced pressure. UV. spectra were run in ethanol, and NMR. spectra at 60 MHz in deuteriochloroform, unless the contrary is indicated. Selected MS. lines only are quoted.

2-cis-3-Methyl-5-(4'-ethylenedioxy-1'-hydroxy-2', 6', 6'-trimethylcyclohex-2'-en-1'-yl)-pent-2-en-4-yn-1-ol (**3**). Lithium (16.4 g) was added in small portions (of *ca.* 1 g) to a solution of ferric nitrate (0.5 g) in liquid ammonia (2 l). After the disappearance of the blue colour, indicating the completion of the conversion of lithium into lithamide, *cis*-3-methylpent-2-en-4-yn-1-ol (**2**) (99 g) in ether (100 ml) was added slowly. The ammonia was allowed to evaporate and replaced by ether (1 l). A solution of 4-ethylenedioxy-2,6,6-trimethylcyclohex-2-en-1-one (**1**) [14] (184 g) in ether (300 ml) was then added dropwise. The mixture was stirred at RT. for 16 h, and then poured into ice cold 10% aqueous ammonium chloride. The product was extracted with ether and the combined ethereal extracts were washed (4×) with water, dried (Na_2SO_4), and evaporated. The residual oil (275 g; λ_{max} 230 nm, $E^{1\%}_{1\,cm}$ 506) was dissolved in ether (400 ml). Addition of light petroleum (b.p. 40–60°) yielded **3** (146 g), m.p. 109–111°. – UV.: λ_{max} 230 nm ($E^{1\%}_{1\,cm}$ 520, ε 15,200). – NMR.: 1.11 (3H, H_3C—C(6')); 1.14 (3H, H_3C—C(6')); 1.88 (3H, *d*, J = 1, H_3C at C(2') or C(3)); 1.92 (3H, *d*, J = 1, H_3C at C(3) or C(2')); 3.91 (4H, OCH_2CH_2O); 4.25 (2H, *d*, J = 7, 2H—C(1)); 5.32 (1H, H—C(3')); 5.85 (1H, *t*, J = 7, H—C(2)). – MS.: *m/e* 292 (M^+, $C_{17}H_{24}O_4$ requires 292), 277 ($M-15$), 274 ($M-18$).

2-cis,4-trans-3-Methyl-5-(1'-hydroxy-4'-oxo-2', 6', 6'-trimethylcyclohex-2'-en-1'-yl)-penta-2,4-dien-1-ol (**5**). A 70% solution (474 g) of sodium bis-(2-methoxyethoxy)-aluminium hydride in benzene was diluted with tetrahydrofuran (780 ml) and then added dropwise at *ca.* 0° to a solution of the glycol **3** (120 g) in tetrahydrofuran (2.4 l). The mixture was stirred at RT. for 5 h, and then the excess of hydride was destroyed by the cautious addition of water/ethanol 1:1, followed by water (600 ml). The product was extracted with ether, and the ethereal extracts were combined, washed with water, dried and evaporated. The resulting crude diene-diol **4** (120 g, λ_{max} 238 nm, $E^{1\%}_{1\,cm}$ 746) was dissolved in acetone (780 ml), and 1N sulfuric acid (132 ml) was added. The mixture was

stirred at RT. for 1 h and then poured onto ice and sodium hydrogen carbonate. The product was extracted with ether, and the ethereal extracts were combined, washed with water, dried (Na_2SO_4), and evaporated. Crystallization of the crude product (102 g) from hexane/ethyl acetate gave the *glycol* **5** (78 g), m.p. 126–128°. – UV.: λ_{max} 233 nm ($E^{1\%}_{1\,cm}$ 1010, ε 29,700). – NMR.: 1.01 (3H, H_3C–C(6')); 1.10 (3H, H_3C–C(6')); 1.91 (3H, *d*, J = 1, H_3C–C(2')); 1.88 (3H, *d*, J = 1, H_3C–C(3)); 2.20 (1H, *d*, J = 17, H–C(5')); 2.54 (1H, *d*, J = 17, H–C(5')); 4.29 (2H, *d*, J = 7, 2H–C(1)); 5.64 (1H, *t*, J = 7, 2H–C(2)); 5.80 (1H, *d*, J = 16, H–C(5)); 6.78 (1H, *d*, J = 16, H–C(4)). – MS.: *m/e* (M^+), 232 ($M-18$).

$C_{15}H_{22}O_3$ (250.33) Calc. C 71.97 H 8.86% Found C 71.84 H 8.88%

2-cis,4-trans-3-Methyl-5-(1'-hydroxy-4'-oxo-2',6',6'-trimethylcyclohex-2'-en-1'-yl)-penta-2,4-dien-1-al (**6**). Manganese dioxide (650 g) was added to a solution of the glycol **5** (97 g) in tetrahydrofuran (800 ml), and the mixture was shaken at RT. for 18 h and then filtered. The solid was washed with ether, and the filtrate and washings were combined and evaporated. Crystallization of the residue from ether/light petroleum (b.p. 40–60°) gave the *aldehyde* **6** (55 g), m.p. 113–115°. – UV.: λ_{max} 230 and 281 nm ($E^{1\%}_{1\,cm}$ 485 and 1030, ε 12,000 and 25,500). – NMR.: 1.08 (3H, H_3C–C(1')); 1.13 (3H, H_3C–C(1')); 1.93 (3H, *d*, J = 1, H_3C–C(2')); 2.11 (3H, *d*, J = 1, H_3C–C(3)); 2.41 (2H, 2H–C(5')); ~5.90 (1H, H–C(2)); 6.21 (1H, *d*, J = 16, H–C(5)); 7.52 (1H, *d*, J = 16, H–C(4)); 10.2 (1H, *d*, J = 8, H–C(1)). – MS.: *m/e* 248 (M^+), 233 ($M-15$), 230 ($M-18$).

$C_{15}H_{20}O_3$ (248.31) Calc. C 72.55 H 8.12% Found C 72.44 H 8.21%

2-cis, 4-trans-3-Methyl-5-(1'-hydroxy-4'-oxo-2',6',6'-trimethylcyclohex-2'-en-1'-yl)-penta-2,4-dienoic acid (**7**). Sodium hydroxide (42 g) in water (50 ml) was added rapidly to silver nitrate (42 g) in water (135 ml). To the resulting suspension of silver oxide, the aldehyde **6** (30 g) in methanol (150 ml) was added at – 5°. The mixture was stirred at – 5° for 30 min, and then filtered rapidly through a filter aid. The solid was washed with methanol/water 1:1, and the washings and filtrate were combined, diluted with water, and extracted with ether. The aqueous solution was acidified with ice cold 1N sulfuric acid, and the product was extracted with methylene chloride. The extract was washed with water, dried (Na_2SO_4) and evaporated. Crystallization of the residue from ethyl acetate gave (±)-abscisic acid (**7**) (18 g), m.p. 188–190°; *Cornforth et al.* [4] gave m.p. 188–190°. – UV.: λ_{max} 260 nm ($E^{1\%}_{1\,cm}$ 805, ε 21,300). – NMR. (100 MHz): 1.04 (3H, H_3C–C(1')); 1.14 (3H, H_3C–C(1')); 1.93 (3H, *d*, J = 1, H_3C–C(2')); 2.05 (3H, *d*, J = 1, H_3C–C(3)); 2.26 (1H, *d*, J = 17, H–C(5')); 2.51 (3H, *d*, J = 17, H–C(5')); 5.75 (1H, H–C(2)); 5.95 (1H, H–C(3')); 6.16 (1H, *d*, J = 16, H–C(5)); 7.80 (1H, *d*, J = 16, H–C(4)). – NMR. (natural isomer) [19]: 1.10 (3H); 1.17 (3H); 1.99 (3H); 2.10 (3H); 2.41; 2.47; 5.79 (1H); 5.98 (1H); 6.17 (1H. *d*, J = 16); 7.81 (1H, *d*, J = 16). – NMR. (100 MHz; 85% $CDCl_3$, 15% $(CH_3)_2SO$): 1.01 (3H); 1.12 (3H); 1.91 (3H, *d*, J = 1); 2.00 (3H, *d*, J = 1); 2.17 (1H, *d*, J = 17); 2.45 (1H, *d*, J = 17); 5.69 (1H); 5.86 (1H); 6.12 (1H, *d*, J = 16); 7.78 (1H, *d*, J = 16); irradiation at 5.69 sharpened the band at 2.00: irradiation at 5.86 sharpened that at 1.91. – NMR. ($(CD_3)_2CO$): 1.01 (3H); 1.08 (3H); 1.92 (3H, *d*, J = 1); 2.07 (3H); *ca.* 2.17 (1H, *d*); 2.53 (1H, *d*, J = 17); 5.73 (1H); 5.81 (1H); 6.33 (1H, *d*, J = 16); 7.90 (1H, *d*, J = 16). – MS.: *m/e* 264 (M^+; $C_{15}H_{20}O_4$ requires 264), 249 ($M-15$), 246 ($M-18$). Chromatography of the mother liquors on silica gel, using 20% ethyl acetate in methylene chloride as eluent, gave the *2-trans,4-trans*-isomer (0.2 g), m.p. 159–161°.

Treatment of a sample of (±)-abscisic acid in ether with diazomethane gave the methyl ester. – IR. (nujol): $\tilde{\nu}_{max}$ 1710, 1645, 1620, 1600, 980, 720 cm^{-1}. – NMR. (100 MHz): 1.06 (3H, H_3C–C(1')); 1.14 (3H, H_3C–C(1')); 1.96 (2H, *d*, J = 1); 2.04 (3H, *d*, J = 1); 2.28 (1H, *d*, J = 17, H–C(5')); 2.47 (1H, *d*, J = 17, H–C(5')); 3.65 (3H, OCH_3); 5.72 (1H, 2H–C(2)); 5.94 (1H, H–C(3')); 6.20 (1H, *d*, J = 16, H–C(5)); 7.80 (1H, *d*, J = 16, H–C(4)).

The authors thank Dr. *A. Khare* and Mr. *P. Ellis* for some of the spectral data.

REFERENCES

[1] *B. V. Milborrow*, Ann. Rev. Plant Physiol. *25*, 259 (1974).
[2] *R. S. Burden & H. F. Taylor*, Pure appl. Chemistry in the press.
[3] *G. Ryback*, Chem. Commun. *1972*, 1190.

[4] *J. W. Cornforth, B. W. Milborrow & G. Ryback*, Nature *206*, 715 (1965).
[5] *U. Schwieter, C. v. Planta, R. Rüegg & O. Isler*, Helv. *45*, 528 (1965).
[6] *D. L. Roberts, R. A. Heckman, B. P. Hege & S. A. Bellin*, J. org. Chemistry *33*, 3568 (1968).
[7] *J. A. Findley & W. D. Mackay*, Canad. J. Chemistry *49*, 2369 (1971).
[8] *J. W. Cornforth, R. Mallaby & G. Ryback*, J. chem Soc. *1968*, 1565.
[9] *J. W. Cornforth, W. Draber, B. V. Milborrow & G. Ryback*, Chem. Commun. *1967*, 114; *E. Sondheimer, E. C. Galson, Y. P. Chang & D. C. Walton*, Science *174*, 829 (1971); *J. C. Bonnafous, J. C. Mani, J. L. Olive & M. Mousseron-Canet*, Tetrahedron Letters *1973*, 1119.
[10] *T. Oritani & K. Yamashita*, Tetrahedron Letters *1972*, 1190.
[11] cf. *B. C. L. Weedon, H. J. Mayer & U. Schwieter*, Brit. Patent 1,199,012 (1970).
[12] *J. Cymerman, I. M. Heilbron & E. R. H. Jones*, J. chem. Soc. *1945*, 90.
[13] *C. von Planta, U. Schwieter, L. Chopard-dit-Jean, R. Rüegg, M. Kofler & O. Isler*, Helv. *45*, 548 (1962).
[14] *H. Mayer, M. Montavon, R. Rüegg & O. Isler*, Helv. *50*, 1606 (1967).
[15] *V. Bazant, M. Čapka, M. Černý, V. Chvalovský, K. Kochloefl, M. Kraus & J. Malek*, Tetrahedron Letters *1968*, 3303.
[16] *B. C. L. Weedon*, Chap. V in 'Carotenoids', ed. O. Isler, Birkhäuser Verlag, Basel 1971.
[17] *K. Ohkuma, F. T. Addicott, O. E. Smith & W. E. Thiessen*, Tetrahedron Letters, *1965*, 2529.

152. Dediazoniation of Arenediazonium Ions in Homogeneous Solution. Part VIII[1]). Reaction Kinetics and Products in Dimethyl Sulfoxide

by **Yoji Hirose, George H. Wahl, jr.**[2]) and **Heinrich Zollinger**
Technisch-Chemisches Laboratorium, Eidgenössische Technische Hochschule Zürich

(27. III. 76)

Summary. *p*-Nitrobenzenediazonium tetrafluoroborate dissolved in dimethylsulfoxide (DMSO) at 50° forms *p*-nitrophenol in 88–90% yield. The phenolic oxygen atom originates exclusively from the oxygen atom of DMSO as demonstrated by the use of ^{18}O-labelled DMSO. The first-order rate of dediazoniation is the same under N_2 as it is in the presence of air. The rate is little influenced by the addition of benzene or iodobenzene. However, the products formed in the presence of these additives are significantly different. UV. spectra and the reactivity of diazonium salt solutions in DMSO when mixed with reagents in aqueous solution demonstrate that a relatively stable charge-transfer complex is formed between the diazonium ion and DMSO. The product analyses and the kinetic and spectral results of dediazoniation in DMSO with and without additives are consistent with a mechanism in which the rate-limiting step is the formation of a *p*-nitrophenyl radical from the charge-transfer complex. *p*-Nitrophenol and the products with benzene and iodobenzene are formed in subsequent fast competition steps. In the presence of small amounts of pyridine the dediazoniation is much faster and follows a different kinetic law. Pyridine effectively competes with DMSO in the reaction with diazonium ions.

1. Introduction. – Some years ago we investigated arylations of benzene and nitrobenzene with arenediazonium salts in dimethyl sulfoxide (DMSO) as solvent [2]. Products and other experimental evidence indicated a heterolytic arylation if benzenediazonium ion was used as arylating reagent, but a homolytic mechanism with *p*-nitrobenzenediazonium ion. We [3] as well as other research groups, *e.g. Ritchie et al.* [4] are interested in interactions of solvents with diazonium ions on a more general basis. Since reaction products of *p*-nitrobenzenediazonium tetrafluoroborate

[1]) Part VII: See [1].
[2]) On leave from the Department of Chemistry, North Carolina State University, Raleigh, N.C. 27607, U.S.A.