Revision of the Absolute Stereochemistry of (+)-Abscisic Acid

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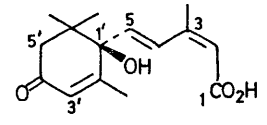
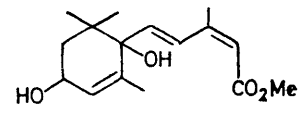
Summary By a chemical correlation with malic acid, the absolute configuration of natural (+)-abscisic acid has been established as *S* according to the 1966 Cahn–Ingold–Prelog convention.

AN absolute configuration (I) for natural (+)-abscisic acid was deduced in this laboratory in 1966[1] by applying Mills' rule[2] to the derivatives (IIa) and (IIb), epimeric at C-4'. As a result of discussions with Dr. G. Snatzke we came to view this as an insecure assignment. In a homoconjugated system such as (II), any change in conformation accompanying the epimerisation, and hence in overlap of the π-orbitals of the ring and side-chain double bonds, could lead to large rotational differences at the D line (as in the Cotton effect region[1]), which could swamp those to which Mills' rule applies. Further doubt on the configuration (I) was cast by the conversion[3] of violaxanthin, to which the stereochemistry shown in the partial formula (III) had been assigned,[4] into (+)-abscisic acid, suggesting that the latter should be revised to (IV). The configuration at C-6 in (III), which had not been rigorously established, has recently been related to the certain configuration at C-3 by a complicated sequence of biological conversions, providing very strong evidence that the formulae (III) and (IV) are correct.[5] The partly stereospecific synthesis of ethyl (−)-abscisate from (−)-α-ionone can also be best explained if (+)-abscisic acid is (IV).[6] To provide additional and unambiguous proof of the stereochemistry, a chemical correlation with malic acid was undertaken.

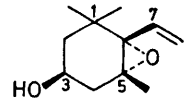
Methyl (*S*)-2-acetoxy-3-carboxypropionate (V) derived from (*S*)-malic acid,[7] and an excess of methyl dimethyl-



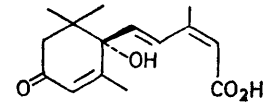
(I)



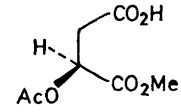
(II) a; *cis*-diol
b; *trans*-diol



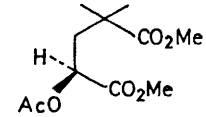
(III)



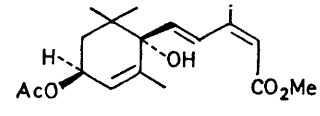
(IV)



(V)



(VI)



(VII)

malonate were electrolysed in methanol containing sodium methoxide[7] to give the laevorotatory acetoxy-diester (VI) as a liquid, δ ($CDCl_3$) 1·19 and 1·23 (6H), 2·08 (3H), 1·9—2·4 (*ca.* 2H, m), 3·69 and 3·74 (6H), and 5·11 (1H, q, *J* 4 and 9 Hz) p.p.m.; *m/e* 215 (10%) ($M^+ - 31$), 204 (20), 187 (50), 173 (40), 145 (95), 127 (45), 113 (100), 102 (25), 95 (20), 85 (55), and 43 (> 500); $[\Phi]_D - 65°$, $[\Phi]_{333} - 170°$, $[\Phi]_{273}$ 0°, $[\Phi]_{229} + 3600°$ peak, and $[\Phi]_{217}$ 0° (MeOH).

Acetylation of the racemic *trans*-diol ester[1] (IIb) afforded the racemic monoacetate (VII), m.p. 126°, λ_{max} 266 nm (EtOH). This was degraded in *ca.* 24% yield to racemic (VI) by ozonolysis in EtOAc–EtCl at −70°, oxidation[8] with performic acid at 20°, methylation with diazomethane, and preparative t.l.c. Identical treatment of the (+)-*trans*-diol ester (4·4 mg) derived from (+)-abscisic acid isolated from avocado fruit yielded *laevorotatory* (VI) (0·8 mg), $[\Phi]_D - 66°$, $[\Phi]_{333} - 150°$, $[\Phi]_{267}$ 0°, $[\Phi]_{229} + 2800°$ peak, and $[\Phi]_{217}$ 0° (MeOH), with a correct mass spectrum. This defines the absolute stereochemistry of the intermediate *trans*-diol acetate as (VII), and of natural (+)-abscisic acid as (IV).

In the earlier paper[1] the configuration (I) was specified as (*S*) according to the then officially approved system of Cahn, Ingold, and Prelog,[9] and the new stereochemistry (IV) would have been designated as (*R*). However, in 1966 a modified way of dealing with double bonds when applying the sequence rules was proposed,[10] which at C-1′ in abscisic acid and related compounds has the effect of changing the designation of a given configuration from (*S*) to (*R*), or from (*R*) to (*S*). The proposal appears to have been generally adopted, and (IV) is now (*S*)-(+)-abscisic acid.[11] Fortunately, therefore, no correction of (*S*) to (*R*) in the earlier literature will be required,† though of course the projection diagrams need to be replaced by their mirror-image forms. For complete clarity natural abscisic acid should be specified as (+), and the unnatural enantiomer as (−), whether or not the configurational symbols are also used.

I am indebted to Dr. J. A. Schofield for the methyl (*S*)-2-acetoxy-3-carboxypropionate, to Dr. B. V. Milborrow for several milligrams of natural abscisic acid, and to Miss P. R. Barham for technical assistance.

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† Except where the sequence rules have been incorrectly applied.[6,12]

[1] J. W. Cornforth, W. Draber, B. V. Milborrow, and G. Ryback, *Chem. Comm.*, 1967, 114.
[2] J. A. Mills, *J. Chem. Soc.*, 1952, 4976.
[3] R. S. Burden and H. F. Taylor, *Tetrahedron Letters*, 1970, 4071; H. F. Taylor and R. S. Burden, *Proc. Roy. Soc.*, 1972, *B*, **180**, 317.
[4] T. E. DeVille, M. B. Hursthouse, S. W. Russell, and B. C. L. Weedon, *Chem. Comm.*, 1969, 1311.
[5] B. V. Milborrow, R. S. Burden, and H. F. Taylor, in preparation.
[6] T. Oritani and K. Yamashita, *Tetrahedron Letters*, 1972, 2521.
[7] *Cf.* D. H. S. Horn and Y. Y. Pretorius, *J. Chem. Soc.*, 1954, 1460.
[8] J. W. Cornforth, R. H. Cornforth, G. Popják, and L. Yengoyan, *J. Biol. Chem.*, 1966, **241**, 3970.
[9] R. S. Cahn, C. K. Ingold, and V. Prelog, *Experentia*, 1956, **12**, 81.
[10] R. S. Cahn, C. K. Ingold, and V. Prelog, *Angew. Chem. Internat. Edn.*, 1966, **5**, 385.
[11] *Cf.* B. C. L. Weedon, in 'Carotenoids,' ed. by O. Isler, p. 318, Birkhauser Verlag, 1971.
[12] G. P. Moss, in 'Terpenoids and Steroids' (Chem. Soc. Specialist Periodical Report), vol. 1, 1971, 214.