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Synthesis of abscisic acid

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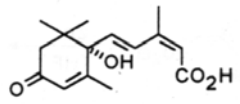
(+) - Abscisic acid (1) is a natural product, a plant hormone that has a role in the control of several physiological processes such as abscission of leaves, seed germination, dormancy, growth, etc. According to its activity in plants, (1) is also named dormin and abscisin; the recent Chemical Abstracts indexes use the name [S-(Z,E)]-5-(1-hydroxy-2,6,6-trimethyl-4-oxo-2-cyclohexen-1-yl)-3-methyl-2,4-pentadienoic acid.

The importance of (1) in biological studies can be estimated by the high number of publications on the subject in the last years.



(1)

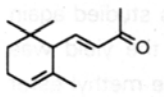
The object of this work is not to make an extensive review about abscisic acid, a matter that has been already reviewed several times, but only to discuss critically the syntheses and methods used to prepare this important product.

The early syntheses of (1), as well as most of more recent work, refer to racemic materials, so this point will not be stressed in this text; only when optically active products are obtained this subject will be mentioned.

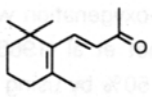
Some of the structure features of (1) which should be considered while planning or selecting a synthesis are the following:

- It is a highly functionalized molecule, i. e., it contains a high number of reactive functions in relation to the number of carbon atoms;
- The cyclic moiety has a structure commonly found in many carotenoids;
- The tertiary -OH group is allylic either in relation to the side chain or to the cyclic residue;
- All double bonds are conjugated to some other unsaturation; this possibly eliminates the problem of regiochemistry in the synthesis of the double bonds; however, the stereochemistry of the double bonds in the side chain is a major problem;
- There is only one chiral center in the molecule.

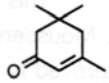
The abscisic acid structure resembles the structure of some more simple and easily available compounds such as α- and β-ionone (2) and (3), or isophorone (4); this structural relationship naturally leads authors to think in these compounds as starting materials for the synthesis of abscisic acid.



(2) α-ionone



(3) β-ionone

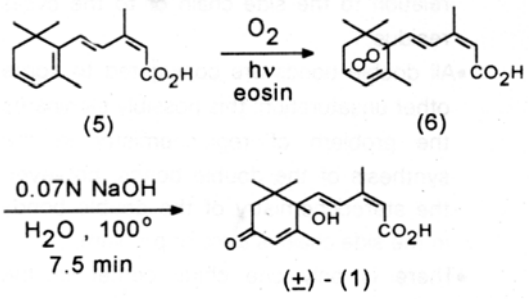


(4) isophorone

However, the experimental results obtained by several authors demonstrate that, despite the structural similarity, the chemical transformations that are necessary to convert these compounds into abscisic acid can hardly be regarded as simple modifications.

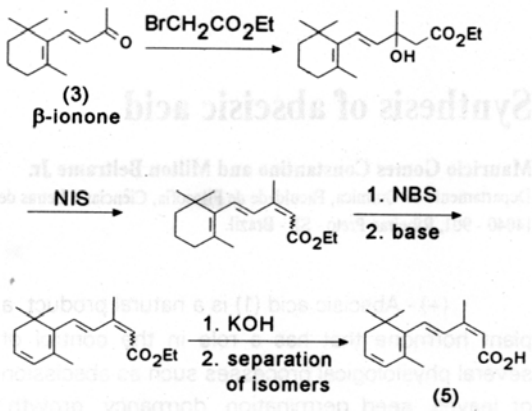
The cyclic moiety of the ionones must be oxidized in a very specific way, while the side chain must be extended with simultaneous formation of a Z-trisubstituted double bond. α-Ionone was used by Roberts et al (1968) and, in its optically active form, by Oritani and Yamashita (1972); β-ionone was used by Cornforth et al (1965), Mousseron-Canet et al (1966) and Findlay and MacKay (1971).

The first synthesis was made by Cornforth et al (1965), and the short paper describes only the last two steps: starting with the acid (5), a photo-oxygenation produced the peroxide (6), which was rearranged by base to abscisic acid (1):

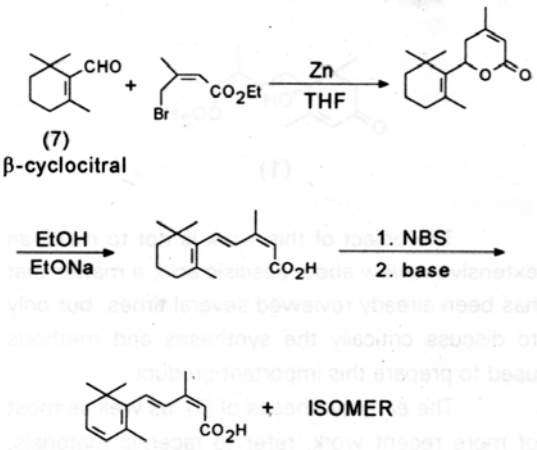


Besides the fact that this is the first reported synthesis, one can see here an elegant way for oxidizing the ring to the particular structure of abscisic acid. However, the efficiency is low: the yield of these two steps is 7% and compound (5) cannot be considered an accessible starting material.

This photo-oxygenation was studied again by Mousseron-Canet et al (1966); the yield was improved to about 50% by using the methyl ester of (5) and rearranging the peroxide with Al_2O_3. On the other hand, the synthesis of (5) as proposed in this paper has a low yield: from 57.6g of β-ionone, only 4.2g of (5) can be obtained.

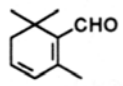


It is interesting to notice that these authors have described in this paper a very efficient way for the stereoselective synthesis of the side chain of abscisic acid, later used by several authors (see ahead), consisting of a Reformatsky reaction with formation of a lactone:



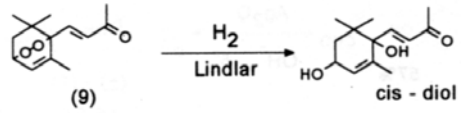
The main problem in this synthesis is the isomerization produced by the NBS in the last

step. Apparently the authors did not consider the possibility of solving this problem by using safranal (8) as starting material instead of β-cyclocitral (7).

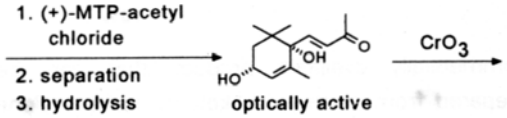


(8)
safranal

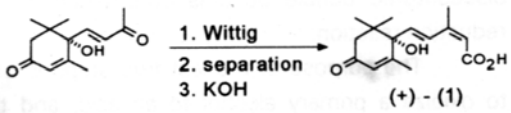
Koreeda et al (1973) have also used a peroxide (9) (better prepared from α-ionone) to oxidize the ring, in a synthesis realized with the objective of establishing the absolute configuration of natural abscisic acid.



(9) cis - diol



optically active

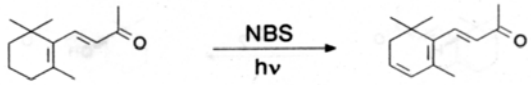


(+) - (1)

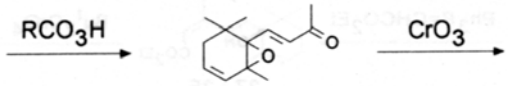
Findlay and MacKay (1971) have described an alternative method for the oxidation of the ring of β-ionone:

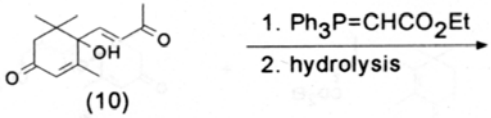
The intermediate (10) is obtained in 43% yield from β-ionone (3), but the Wittig reaction to produce the trisubstituted double bond cannot be considered the ideal solution.

Starting with α-ionone (2), Roberts et al (1968) have made a synthesis in three steps of abscisic acid with an overall yield of 11%. The

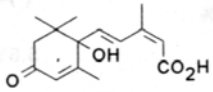


(3)
β-ionone



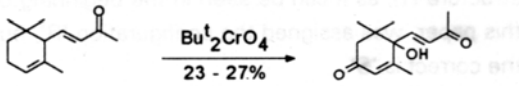


(10)

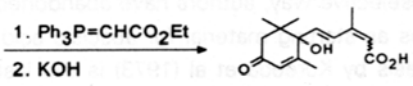


(±) - (1)

oxidation of the ring was accomplished with t-butyl chromate, in moderate yield, and the side chain was extended by the Wittig reaction, which has produced a 1:1 mixture of stereoisomers.



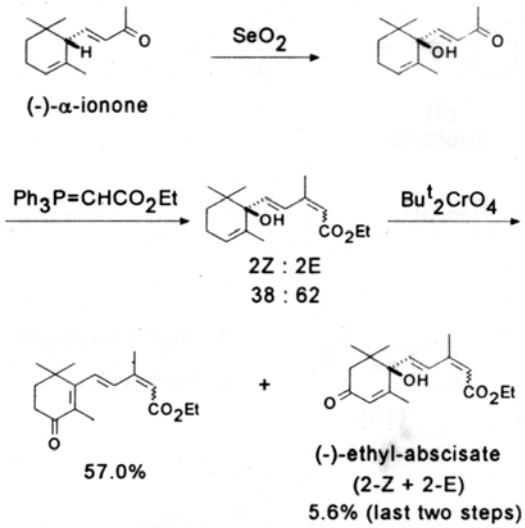
(2)
α-ionone

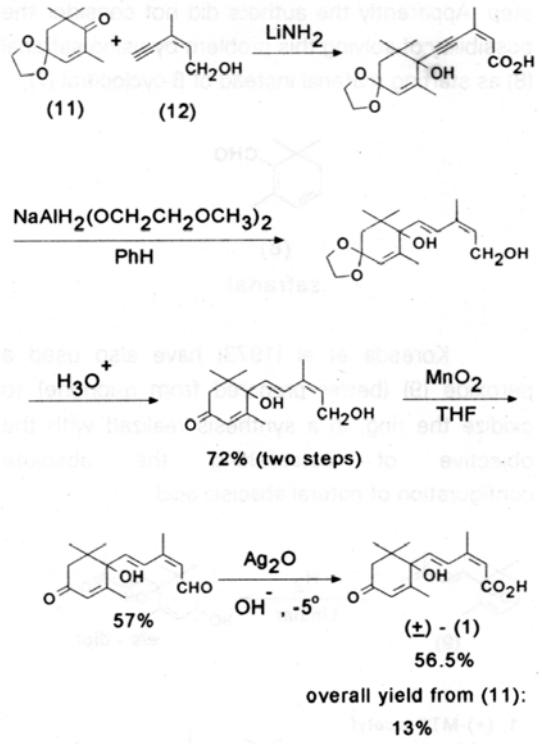


1 : 1 E/Z
(±) - (1)

Oritani and Yamashita (1972) have used optically active (-)-α-ionone as starting material; the oxidation with selenium dioxide occurs with retention of optical activity, thus producing optically active abscisic acid ester at the end of the synthesis.

This is an interesting synthesis to help in the confirmation of the absolute stereochemistry





of abscisic acid; unfortunately, it has little preparative value because of the low yields. Note that the compound obtained is the ester of the enantiomer of natural abscisic acid. It should be mentioned that there is a mistake in the publication by Oritani and Yamashita: to the structure (1), as it can be seen in the beginning of this paper, was assigned the configuration "R", but the correct is "S".

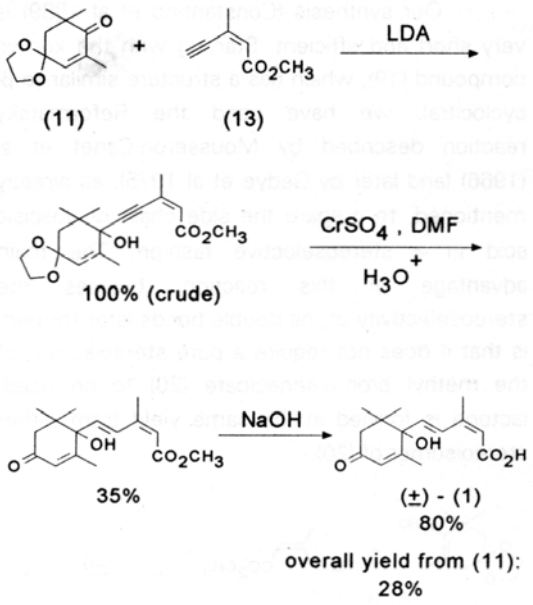
Presumably because of the difficulties in oxidizing the ring and in extending the side chain in a stereoselective way, authors have abandoned the ionones as starting material for abscisic acid. The synthesis by Koreeda et al (1973) is the last work in which these compounds are used.

Mayer et al (1976) were the first to use isophorone (4). The actual starting material in this synthesis is described by Mayer et al as being compound (11), which can be prepared from isophorone in five steps according to Marx and Sondheimer (1966), in three steps (Constantino et al 1986) or two steps (Widmer and Seuret 1975).

In this synthesis, the configuration of the trisubstituted double bond of the side chain is already established in the starting material (12), a commercially available product that can be prepared from methyl-vinyl-ketone and acetylene (addition followed by rearrangement and separation of isomers). The configuration of the disubstituted double bond is determined in the reduction reaction.

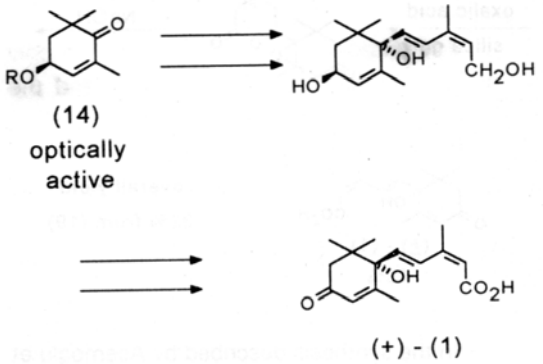
The purpose of the last two steps is only to oxidize a primary alcohol to an acid, and the yield of this transformation is 32%.

In an attempt to overcome this difficulty we have proposed a synthesis (Constantino et al 1986) in which the starting material (12) was already oxidized to (13). The overall yield was really improved, but the reduction of the triple bond to an E-double bond cannot be considered an efficient reaction; in fact, it has about the same yield as the Mayer's oxidation, despite the fact that a crude product was used as starting material in our reduction, and a ketal hydrolysis is also

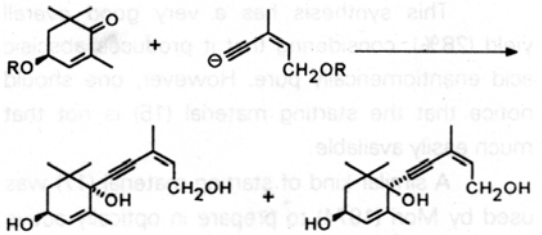


occurring in the same reaction.

In another synthesis, following very closely the steps of Mayer's synthesis (Mayer et al 1976), Kienzle et al (1978) have used an optically active starting material (14), also available from isophorone (Leuenberger et al 1976), to prepare optically active abscisic acid.

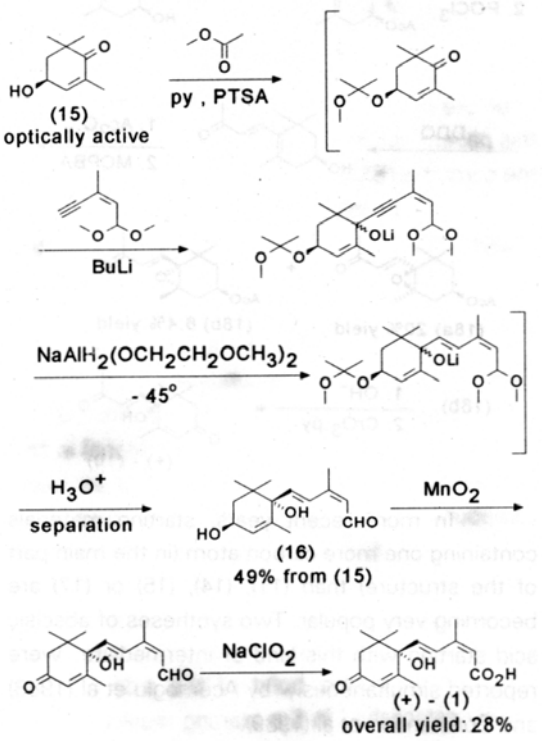


The stereochemistry of the first reaction is as follows:



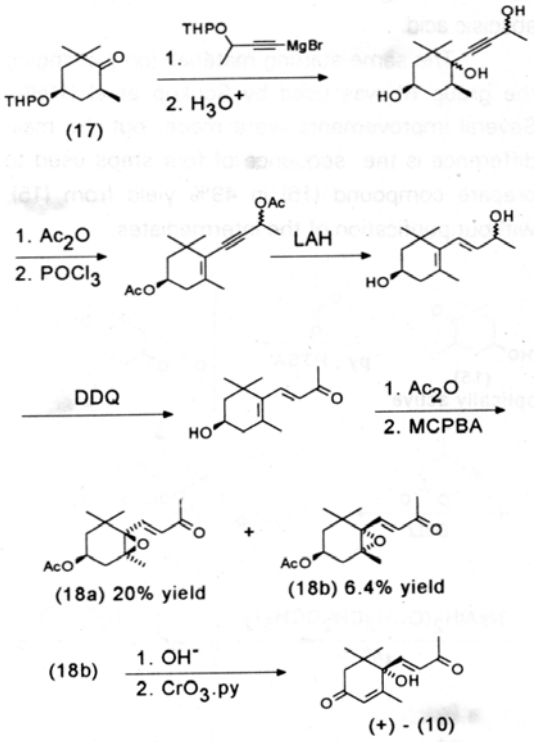
Thus the original chiral center induces the correct configuration on the chiral carbon of abscisic acid.

The same starting material (only changing the group R) was used by Soukup et al (1989). Several improvements were made, but the main difference is the sequence of four steps used to prepare compound (16) in 49% yield from (15), without purification of the intermediates.



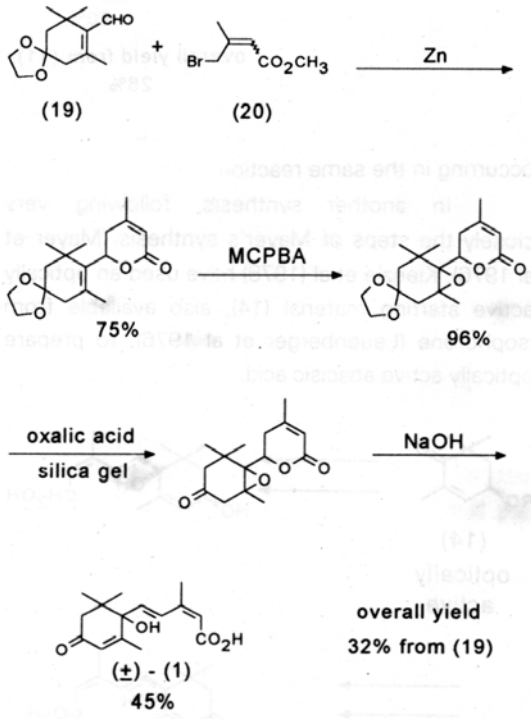
This synthesis has a very good overall yield (28%), considering that it produces abscisic acid enantiomerically pure. However, one should notice that the starting material (15) is not that much easily available.

A similar kind of starting material (17) was used by Mori (1974) to prepare in optically active form the hydroxy dione (10), previously prepared in racemic form by Roberts et al (1968) and Findlay and MacKay (1971) as an intermediate in the synthesis of abscisic acid.



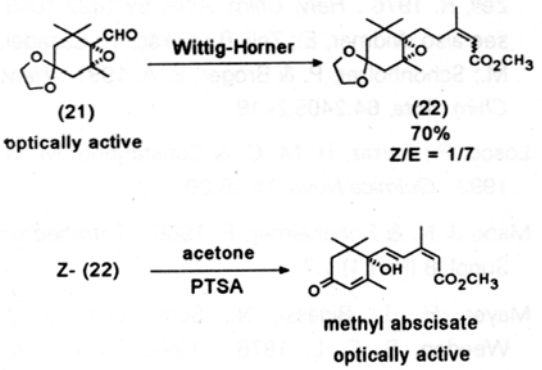
In more recent years, starting materials containing one more carbon atom (in the main part of the structure) than (11), (14), (15) or (17) are becoming very popular. Two syntheses of abscisic acid starting with this kind of intermediate were reported simultaneously by Acemoglu et al (1988) and Constantino et al (1989).

Our synthesis (Constantino et al 1989) is very short and efficient. Starting with the known compound (19), which has a structure similar to β-cyclocitral, we have used the Reformatsky reaction described by Mousseron-Canet et al (1966) (and later by Gedye et al 1975), as already mentioned, to prepare the side chain of abscisic acid in a stereoselective fashion. The main advantage of this reaction, besides the stereoselectivity of the double bonds later formed, is that it does not require a pure stereoisomer of the methyl bromo-senecioate (20) to be used; lactone is formed in the same yield from either stereoisomer of (20).

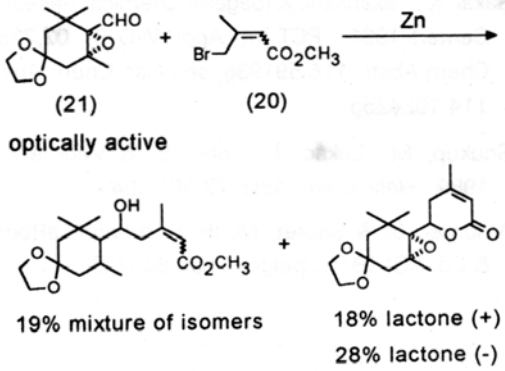


In the synthesis described by Acemoglu et al (1988), optically active methyl abscisate is produced. A similar kind of starting material (note, however, that (21) is optically active) is used, but

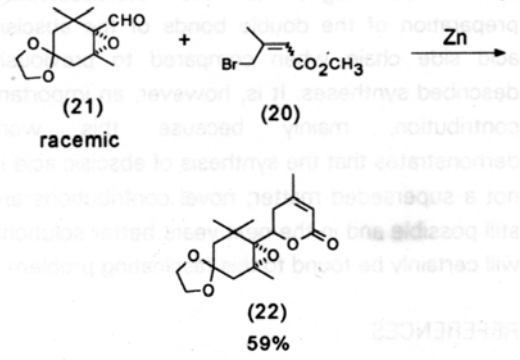
Acemoglu used a Wittig-Horner reaction to introduce the side chain, producing a mixture in which the desired product was the minor isomer.



A combination of these two syntheses, to take advantage of the positive points of each one, could be the best way to prepare abscisic acid nowadays. The first suggestion of a synthesis that could be understood as such combination was made by Sakay and Takahashi (1991), who have realized the Reformatsky reaction between aldehyde (21) (optically active) with methyl bromo-senecioate (20):

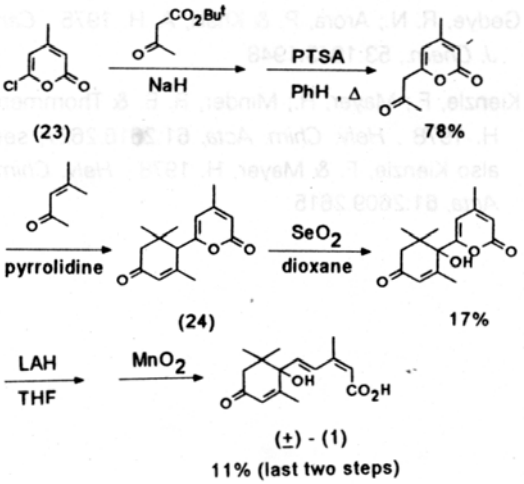


They have, however, obtained a complex mixture of products, contrasting with the results obtained by Losco et al (1992). These authors have used a racemic starting material, but the Reformatsky reaction produced only the diastereoisomeric mixture of the lactones (22) in 59% yield.



The diastereoisomers of (22) are identical to the previously described (Constantino et al 1989), so this mixture can be converted into racemic abscisic acid in the same way (45% yield). As the relevant chiral center of (21) is not modified in these reactions, an optically active starting material (21) can be used to produce optically active abscisic acid by this method.

Recently a very different approach to the synthesis of abscisic acid has been described by Cornforth et al (1992). A pyranone ring is used as a precursor of the side chain, and the ring of the abscisic acid structure is formed in three steps.



This is a nicely conceived synthesis but, contrary to the claims of the authors, it brings no special advantages to the stereoselective preparation of the double bonds of the abscisic acid side chain when compared to previously described syntheses. It is, however, an important contribution, mainly because this work demonstrates that the synthesis of abscisic acid is not a superseded matter; novel contributions are still possible and in the next years better solutions will certainly be found to this fascinating problem.

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