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THE UNAMBIGUOUS SYNTHESIS OF LIGNANS OF THE 2,6-DIARYL-3,7-DIOXABICYCLO-[3.3.0]OCTANE SERIES. THE SYNTHESIS OF EUDESMIN AND 4,8-DIHYDROXYSESAMIN.

A. Pelter,*[1] R.S. Ward,[1] D.J. Watson;[1] P. Collins[1] and I.T. Kay[2].

1. Chemistry Department, University College, Singleton Park, Swansea SA2 8PP.
2. I.C.I. Plant Protection Division, Jealotts Hill, Bracknell, RG12 6EY.

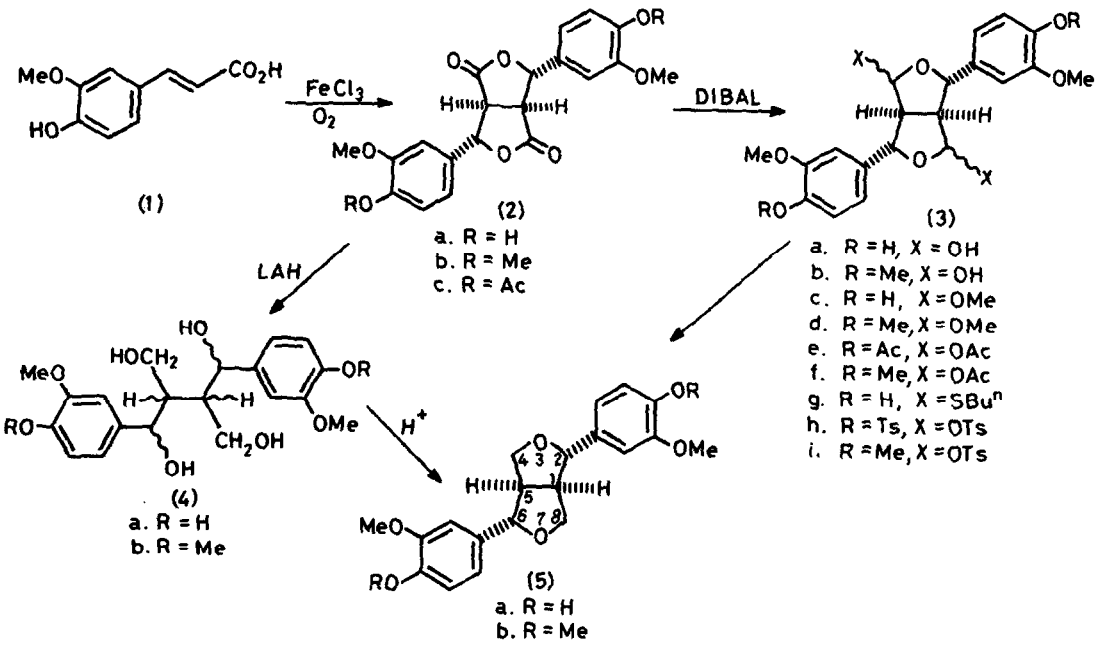
SUMMARY. The syntheses of two lignans are described. The syntheses are based on dilactones of unambiguous structure and proceed in such a way that ring opened intermediates are not involved and structures can be unequivocally assigned.

The syntheses of lignans of the 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane series have in the past been carried out using compounds which, by bond rotation, could give rise to either 2,6- or 2,4-diaryl lignans.[1] Thus, establishment of structure has had to concentrate on tedious degradation procedures, or X-ray analysis.[1] Very many structural determinations have indeed ignored the question of distinguishing between the two series or have assigned 2,6-diaryl structures by analogy with known compounds.[1]

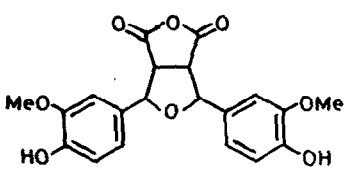
Very recently the claim[2] that a plant germination inhibitor was a lactone of the 2,4-diaryl series was questioned[3] and finally withdrawn.[4] The withdrawal of this claim involved the first unequivocal synthesis of a 2,4-diaryl lignan.[5] Various other claims for the biological production of compounds of the 2,4-series remain controversial.[6,7]

In view of the problems of distinguishing between the two series by n.m.r. or other spectroscopic means,[8] synthesis by unambiguous methods becomes a necessity and in this paper we outline an approach *via* dilactones which is one solution to the problem.

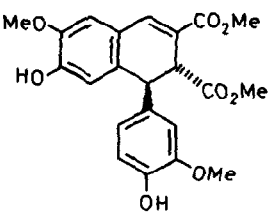
The dilactone (2a) is directly available in 20% yield by the oxidation of ferulic acid (1)[9,10] (Scheme 1). The product (2a) has a single band at 1780 cm^{-1} in the i.r. spectrum and completely lacks the bands at 1865 and 1785 cm^{-1} which would be associated with the alternative structure (6).[11] The lactone can thus be taken as a fully characterised compound. The dangers that are involved in reactions that can proceed through ring opened compounds are shown clearly in that (2a) gives the dihydronaphthalene (7) on reaction with MeOH/HCl,[10,12] whilst our attempts to methylate (2a) using MeI/KF in DMF[13] gave the diaryl-butadiene (8) in 57% yield.[14] Compound (8) could itself serve as an excellent precursor of the 2,4-diaryl series.



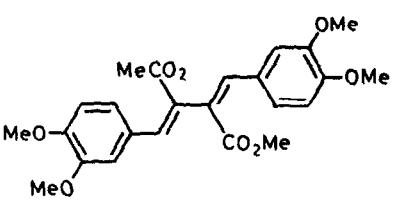
Scheme 1.



(6)



(7)



(8)

Methylation of (2a) with diazomethane gave (2b), m.p. 207-8°, whilst acetylation gave the diacetate (2c), m.p. 230-1°. Reduction of (2a) and (2b) with diisobutylaluminium hydride (DIBAL) gives the lactols (3a), m.p. 218-220°, and (3b), m.p. 219-220° in 80% and 96% yield respectively (Scheme 1). From these compounds the corresponding acetates (3e) and (3f) were readily prepared. Reaction with MeOH/HCl gave the lactol ethers (3c) and (3d) without any rearrangement to the corresponding dihydronaphthalenes.

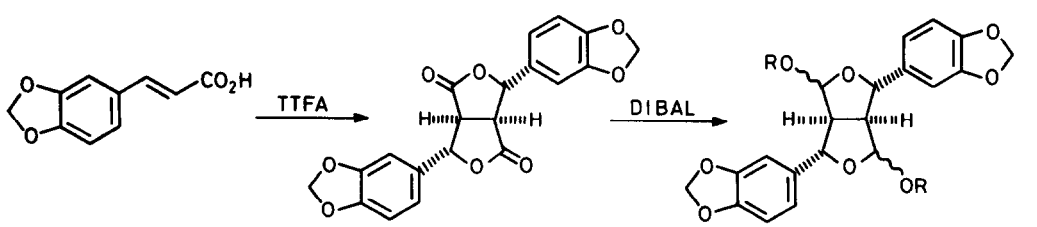
Reduction of the lactone (2c) with lithium aluminium hydride (LAH) gave mixtures of

the alcohols (4a), whilst the corresponding reduction of (2b) gave (4b). The stereochemistry of these alcohols could not be established and hence they could not be used for the unequivocal syntheses desired.

We therefore converted (3b) to (3g) using Bu^nSH/BF_3. To our surprise, despite numerous attempts under a wide variety of conditions, we did not succeed in reducing (3g) to pinoresinol (5a) using Raney nickel. We therefore converted (3a) and (3b) to their corresponding tosylates (3h) and (3i). Reduction of the latter with LAH gave eudesmin (5b). As exposure of the tetraol (4b) to LAH under similar conditions does not yield eudesmin, we conclude that the reduction of the ditosylate is a direct displacement of the tosyloxy group by hydride, as anticipated. The possibility of reduction of an oxonium ion produced by displacement of the tosyloxy group remains, but it is difficult to envisage any ring opened intermediates being involved in this reaction. Hence the sequence from cinnamic acid to the lignan, via the lactone and lactol represents the first unambiguous synthesis of a 2,6-diaryl-3,7-dioxabicyclo[3.3.0.]octane. It is also a very direct synthesis of such a lignan.

It is of interest that exposure of the mixtures of alcohols (4a) and (4b) to MeOH/HCl for 10 min. gave pinoresinol (5a), together with epipinoresinol, and eudesmin (5b) in 52% and 43% yield respectively. Therefore, in large part, the stereochemistry of the precursors (2a) and (2b) has been preserved through the LAH reduction.

The oxidation with $FeCl_3/O_2$ requires that the precursor cinnamic acid has a free para-hydroxyl group and is therefore unsuitable for the synthesis of compounds such as (11) derived from sesamin. Very recently[15] it has been shown that the oxidation of oxygenated cinnamic acids by thallium trifluoroacetate (TTFA) can yield the corresponding dilactones including lactone (10). The reaction is very vigorous and must be stopped immediately on mixing the components. It would seem unsuitable for cinnamic acids with free phenolic groups. In our hands, despite numerous modifications of the reaction conditions, the dilactone (10) was only obtained in 9% yield from (9). It was extremely similar to (2b) in its physical properties showing a single band at 1772 cm^{-1} in the i.r. spectrum. Reduction of (10) with DIBAL gave 4,8-dihydroxysesamin (11a), identical in all respects with a sample isolated from natural sources[3] (Scheme 2). Identity was confirmed by comparison of the acetates (11b).



(9) (10) (11)
a. R = H
b. R = Ac

Scheme 2.

Acknowledgement.

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