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DEUTERIUM LABELLING BY CLEMMENSEN REDUCTION

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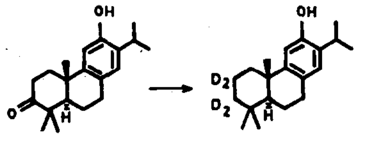
The study of deuterium labelled compounds has become an important requisite in the interpretation of mass spectrometric fragmentation processes. Several methods exist for the preparation of such derivatives and these have recently been surveyed[1]. The methods used for replacement of a carbonyl oxygen by deuterium suffers however from certain disadvantages. Desulphurisation of mercaptals with Raney nickel in a deuterium atmosphere frequently leads to considerable isotopic scrambling often accompanied by formation of olefins[1,2]. Reduction of tosylhydrazones of hindered ketones, such as 4,4-dimethyl-3-oxosteroids, gives rise to substantial amounts of unsaturated products which are often difficult to separate from the desired saturated compounds[3]. Conversion to alcohols by complex metal deuterides followed by tosylation and deuteriolysis is also sensitive to steric hindrance and may be unsuccesful or lead to dehydration, while catalytic reduction of the olefin that may be obtained in certain cases by dehydration of the alcohol, often leads to extensive isotopic scrambling[1,4,5].

In connection with a mass spectrometric study of aromatic diterpenes[6,7] the possibility of utilising the Clemmensen reduction as a convenient and cheap method of introducing deuterium was investigated[5]. It was found that keto and aldehyde groups were reduced with replacement of the carbonyl oxygen by deuterium on refluxing the compounds with amalgamated zinc and a mixture of deuteriochloric and deuterioacetic acids[x] until the reaction was complete, as shown by thin layer chromatography. Not unexpectedly, the hydrogens on the α-carbons and in the aromatic ring were exchanged simultaneously and back-exchange of the aromatic deuterons was therefore undertaken by repeating the procedure on the first products using conventional reagents. The method was applied to several *podocarpa*-8,11,13-triene derivatives and some pertinent examples are shown below; the isotopic purities, determined by mass spectrometry, are given in table 1.



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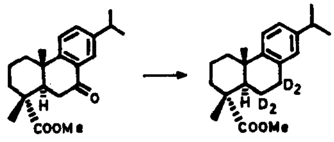

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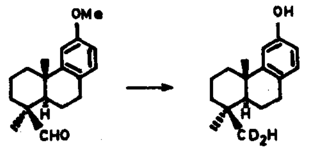

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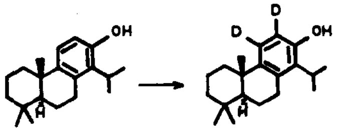

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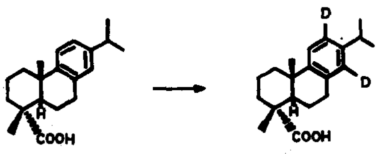

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[x] Readily obtained from acetyl chloride and deuterium oxide (2:1 ratio).

TABLE 1

Compound	Isotopic purity (%)	Isotopic impurities (%)
2,2,3,3-d_4-Ferruginol (2)	83	d_3(17)
6,6,7,7-d_4-Dehydroabietic acid methyl ester (3)	89	d_3(11)
17,17-d_2-Podocarpa-8,11,13-triene-12-ol (4)	92	d_1(8)
11,12-d_2-Totarol (5)	71	d_1(29)
12,14-d_2-Dehydroabietic acid (6)	81	d_3(9), d_1(6), d_0(4)

It has recently been shown that base-catalysed exchange of enolisable hydrogens in ketones are in many cases far from compcomplete and that back-exchange may occur in the mass spectrometer [4,8-10]. *) Hence, when the method is used for determining the number of hydrogens on the carbons α to the oxo group it may lead to erroneous conclusions and, therefore the present procedure, apparently offers a more reliable alternative for such determinations.

The exchange of aromatic protons during the Clemmensen reduction, which seems to be of more general applicability and will be investigated further, was taken advantage of for the preparation of 11,12-d_2-totarol (5) and 12,14-d_2-dehydroabietic acid (6). The isotopic purity of the former was 71 per cent (29 % d_1-derivative) after a twelve hour treatment at reflux temperature and of the latter, 81 per cent after treatment under the same conditions for six hours. The quite specific introduction of only two deuterons in the aromatic part of dehydroabietic acid can be assigned to steric factors. The position of the remaining aromatic proton followed from a comparison of the

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*) Also observed for ketone 1[5]

infrared and nmr spectra of deuterated and non-deuterated material. Finally it is worth noting that no exchange of aromatic deuterons in a dehydroabietane derivative took place under conditions analogous to those previously used for platinum catalysed hydrogen-deuterium exchange in tetralin[11].

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