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Short Research Article

Synthesis of stable deuterium labelled lignan derivatives and studies of H/D exchange at the aromatic sites†

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Introduction

The lignans are a large group of compounds found in the plant kingdom from where they end up as mammalian metabolic products. They vary widely in structure, but most of the lignans appear as polyphenols.

The growing interest in these compounds is based on their possible health effects.[1] Quantitation and qualification of lignans require good resolution and sensitivity because lignan concentrations are quite low in biological samples. Thus, the analytical techniques used for lignans are based on HPLC-MS and ID-GC-MS.[2] In these methods stable isotope polylabelled compounds are needed as internal standards.

Materials and methods

Deuterium labels, available from the relatively inexpensive D_2 and D_2O, have been commonly used for butyrolactone-type lignans. Deuterium atoms have been attached either to the aliphatic region of the lignan skeleton or to the aromatic region. Dibenzylbutyrolactone-type lignans are readily accessed by a tandem Michael addition–alkylation reaction followed by desulfurization and debenzylation with Raney nickel.[3] Wanting to avoid synthetic labelling schemes relying on laborious and expensive total synthesis using prelabelled starting materials, we have studied H/D exchange reactions within the lignan molecule framework.

All our aromatic region lignan labelling methods are based on H/D exchange reactions under acidic conditions. In our earlier work, enterolactone was refluxed with a mixture of PBr_3/D_2O to give [2,4,6,2′,4′,6′-D_6]-enterolactone.[4] In this method, as in other former methods, aromatic hydrogens *ortho* and *para* to the phenolic hydroxy group are exchanged to deuteriums while the less active *meta* sites remain intact.

Results and discussion

In our recent work the deuterium labelling is carried out under strongly acidic conditions by deuterated phosphoric acid–boron trifluoride complex, prepared *in situ*.[5,6] The method is found to be expedient for various butyrolactone-type lignans. In this method all aromatic protons are exchanged to deuteriums, even from the inactivated positions, but no exchange occurs at the benzylic or α-carbonyl sites (Scheme 1).

However, at very highly activated positions the deuterium labels may undergo back exchange. Hence, we have established de-deuteration conditions to remove the less stable D labels so as to obtain stable, isotopically homogenously labelled derivatives (Figure 1). These polylabelled compounds can be used safely as internal standards in isotope dilution methods.

We have also studied the order of H/D exchange at the aromatic sites. This was done by comparing the empirical exchange observations with electron density calculations to estimate the relative reactivities of the aromatic protons (Figure 1). The effect of aromatic ring substituents on the stability of the deuterium labels is also examined.

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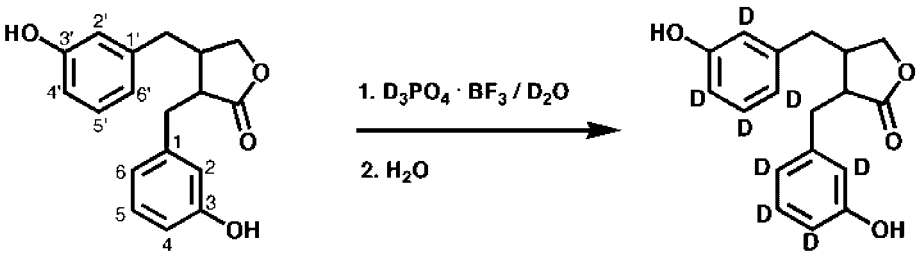

Scheme 1 Even the inactivated 5- and 5′-protons are exchanged to deuteriums giving [D_8]-ENL in isotopic purity as high as 99%.[5]

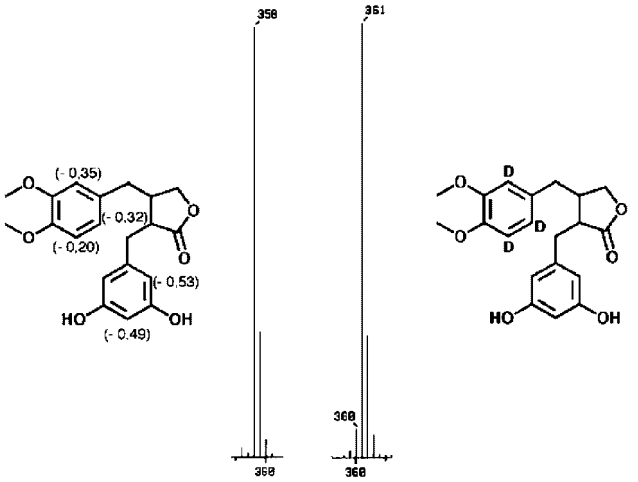

Figure 1 M+ of unlabelled and deuterated 3,5-dihydroxy-3′,4′-dimethoxylignano-9,9′-lactone. The isotopic purity of D_3-product is over 95% according to MS. Electrostatic potential values (in parenthesis) were calculated to estimate the relative reactivities of the aromatic protons.

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REFERENCES

1. Raffaelli B, Hoikkala A, Leppälä E, Wähälä K. *J Chromatogr B* 2002; **777**: 29.
2. Hoikkala A, Schiavoni E, Wähälä K. *Br J Nutr* 2003; **89**(Suppl. 1): 5.
3. Raffaelli B, Leppälä E, Chappuis C, Wähälä K. *Environ Chem Lett* 2006; **4**: 1.
4. Wähälä K, Mäkelä T, Bäckström R, Brunow G, Hase T. *J Chem Soc Perkin Trans I* 1986; 95.
5. Leppälä E, Wähälä K. *J Label Compd Radiopharm* 2004; **47**: 25.
6. Wähälä K, Rasku S. *Tetrahedron Lett* 1997; **38**: 7287.

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