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Selective Oxidation of Lignan Compounds by Dimethyldioxirane. Diastereoselective Opening of Asarinin Furo-furan Skeleton.

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Abstract: Asarinin, a furo-furan lignan compound with two benzyl-ethereal carbons of opposite stereochemistry, was monooxidised at a selected centre by DMD to a chiral substituted tetrahydrofuran. Use of a dilute solution of DMD was crucial for the success of the process. The stereochemistry of the product was confirmed by a similar oxidation of sesamin, the C-7' isomer of asarinin.

The investigation of the potential of dimethyldioxirane (DMD) in selective transformations of natural targets for synthetic purposes is a useful exercise.

Recently we reported several examples in which DMD was shown to be a very effective and selective oxidant for molecules bearing two functional groups with similar reactivity.[1] We also reported our observations about the efficiency of the oxidative process when the target of the reaction is an activated ethereal carbon.[2]

These observations, together with the increasing interest in recent years in the chemistry of lignans,[3] prompted us to assess the possibilities of a selective transformation of model furo-furan lignans into the corresponding furan lignans, a class of compound with a wide range of biological activity. To our knowledge, efficient syntheses for these compounds are rare.[4]

Asarinin[5] and sesamin,[6] furo-furan lignans bearing two aromatic substituents in ethereal positions, were selected as material for preliminary experiments. For asarinin, the *cis* junction between the condensed tetrahydrofuran cycles and the different stereochemistry of the benzyl-ethereal centres could make possible a selective attack by DMD. However, we predicted that the known high reactivity of tertiary benzyl-ethereal

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carbon atoms with this reagent[7] would make it difficult to control.

The first reactions that we performed were frustrating since in all conditions we obtained a complex mixture of products, most of which appeared to be polyhydroxylated compounds, probably due to radical hydroxylations of the aromatic rings. A dark-red colour of the mixture, revealing uncontrolled reactions,[8] appeared a few minutes after the addition of DMD (0.09M solution in acetone).[9] The same reaction, carried out at temperatures less then –20°, did not proceed at all.

Finally we performed the reaction at –20° using a 0.03-0.04M solution of DMD (1 eq for 2 days) and we obtained in good yield (80%) a product which was characterised as an acetate. This compound, by NMR analysis was shown to derive from the oxidative opening of just one ring, revealing the high selectivity of the attack. Moreover the product appeared to be diastereoisomerically pure, indicating that DMD was able to approach a carbon centre with a specific stereochemistry in a highly diastereoselective process.

Physical data were in agreement with a monoxidised compound and H-NMR signals were quite different from that reported for the related compound **5** (Fig. 1),[10] suggesting an attack from the endo face of the molecule to give a compound with the C-8 *S* configuration.

To better investigate the stereochemistry of **2**, we carried out the same reaction on sesamin **3**, the C-7' isomer of asarinin, extracted from the bark of *fagara macrophylla*.[6] The aim was to monooxidise this material and compare the product with that obtained from asarinin. In this case, the selection of any of the two benzylethereal carbons would have produced the same compound.

The reaction proceeded as expected and gave in 75% yield a product identical to that obtained from the oxidation of asarinin. This means the centre C-7 with the *R* configuration in asarinin was chosen by DMD.

On the basis of molecular modelling this behaviour may be explained from reaction of a less hindered proton, *exo* to the framework of the molecule. Moreover this reaction confirms the necessity of DMD to approach the reaction site with rigid stereoelectronic controls.[11]

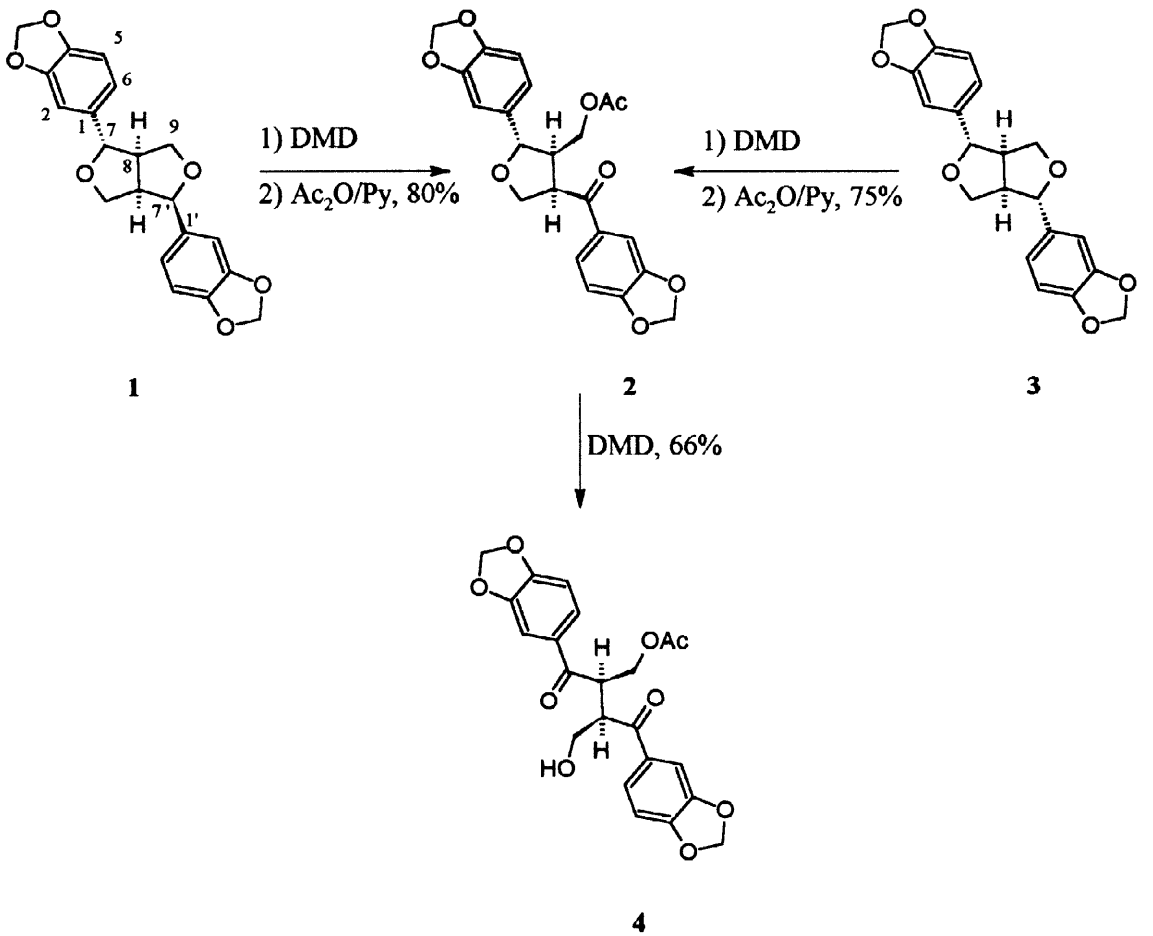
Evidently in this case, the approach from the *endo* face doesn't satisfy the stereoelectronic demands and the attack from the *exo* face is favoured. To confirm this observation, comparative experiments showed that asarinin reacts three times faster than sesamin.

Under the same reaction conditions, a second mole of diluted DMD leads to attack on the ethereal aliphatic ring to give **4** in good yield (66%) from **2**.

Both compounds have defined chiral centres and are highly functionalised. The process may be seen as a diastereoselective transformation of furo-furan lignans to furan compounds and 1,4-butanediol derivatives, useful for synthetic purposes. Furan lignans are common in nature and are often extracted from plants used in traditional medicine[10,12] as well as 1,4-butandiol type compounds, such as **4**.[12]

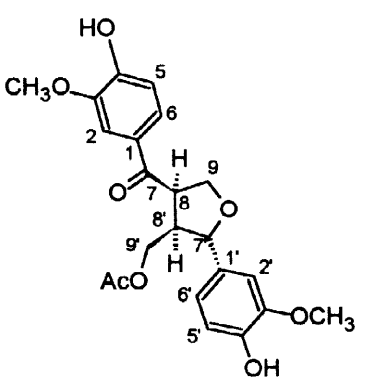
Our major interest in continuation of this research is to investigate practical applications of this method to prepare new bioactive products starting from readily available lignans.

Scheme 1. Selective oxidation of Asarinin by DMD



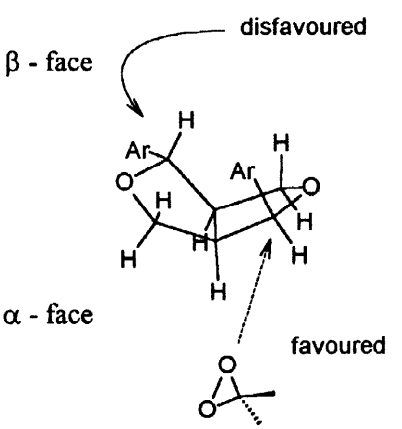
1 2 3 4

Fig.1



5

Fig. 2



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