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AN APPROACH TO THE BIOMIMETIC SYNTHESIS OF ARYLTETRALIN LIGNANS

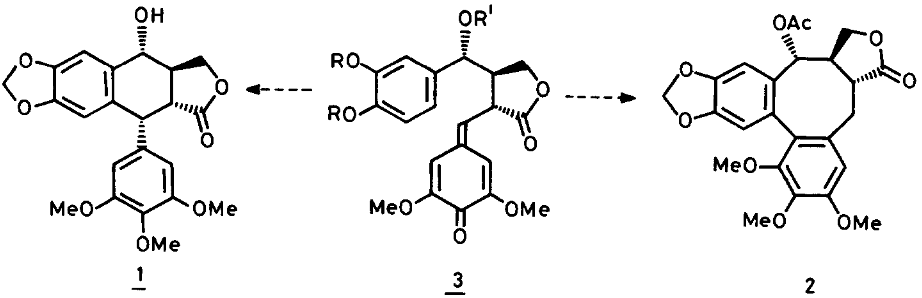
BY Andrew Pelter, Robert S. Ward and Ramohan R. Rao.

Chemistry Department, University College of Swansea, Singleton Park,
Swansea SA2 8PP

Summary The BF_3 catalysed cyclisation of 3-arylpropyl substituted quinone-methide ketals affords a biomimetic route to aryltetralins which proceeds under mild conditions.

Lignan lactones of the aryltetralin (1) and dibenzocyclooctadiene (2) series are known to exhibit important biological properties including anti-tumour activity.[1,2] In an attempt to find an efficient route to such compounds compatible with the diverse functionality present we chose to investigate mild cyclisation reactions which resemble key steps involved in their biosynthesis. (Scheme 1).[3]

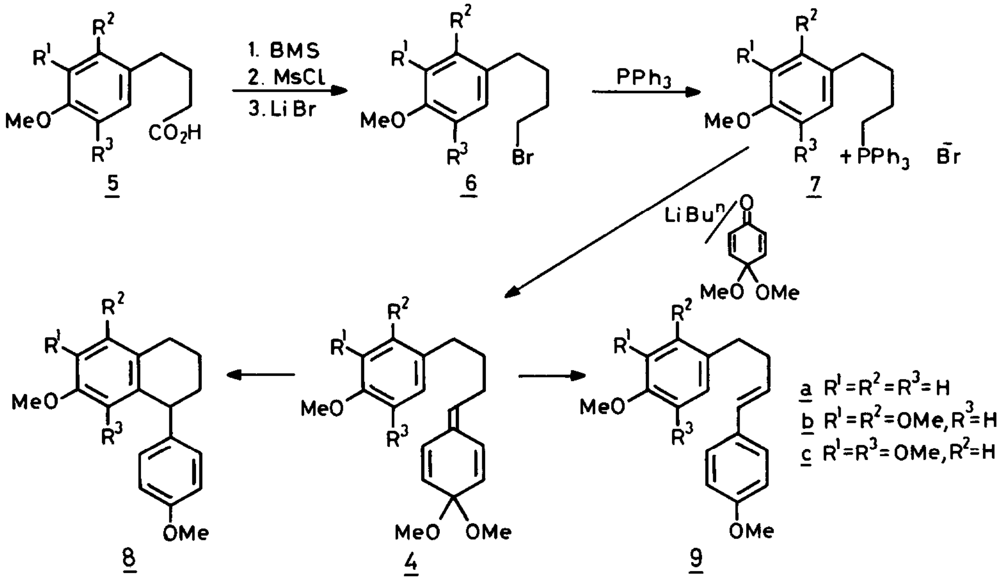
In order to study the feasibility of such biomimetic reactions we have prepared a series of model quinone-methide ketals (4) and studied their cyclisation with Lewis acid catalysts.



Scheme 1

The quinone-methide ketals (4) were prepared starting from the corresponding 4-arylbutanoic acids (5)[4-6] as shown in Scheme 2. The acids were reduced using borane-dimethyl sulphide (BMS) to give the corresponding alcohols in almost quantitative yields. Mesylation using methanesulphonyl chloride and triethylamine followed by treatment with lithium bromide in acetone gave the 4-arylbutyl bromides (6) in 84-90% yield. Quaternisation with triphenylphosphine in refluxing benzene gave 80-90% yields of the phosphonium salts (7) which were subjected to Wittig reaction with 4,4-dimethoxy-cyclohexa-2,5-dienone.[7,8] This gave the required quinone-methide ketals (4) which were used without purification as indicated below.

Treatment of 4a with trifluoroacetic anhydride gave only the corresponding alkene, (9). However treatment with BF_3 etherate[6,7] gave a new compound which was identified on the basis of its ^1H and ^{13}C n.m.r. and mass spectra as the aryltetralin 8a. The structure of the product was subsequently confirmed by carrying out an independent synthesis of 8a



Scheme 2

starting from the corresponding tetralone.[9] Similarly treatment of 4b and 4c with BF_3 etherate gave the corresponding aryltetralins 8b and 8c whose structures were also confirmed by independent synthesis. The yields of the aryltetralins obtained were 40-44% based on the corresponding phosphonium salts 7a-c.

Work is now in hand to synthesise lignan lactones using this approach and also to extend it to include dibenzocyclooctadiene lignans.

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4. For preparation of 5a see D.G. Thomas and A.H. Nathan, J.Amer.Chem.Soc., 1948, **70**, 331.
5. Compound 5b was prepared by Friedel Crafts acylation of 1,2,3-trimethoxybenzene, followed by Clemmensen reduction.
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9. Authentic samples of aryltetralins were prepared by treating the 4-tetralone with p-methoxyphenyl magnesium bromide, followed by hydrogenolysis.

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