The Preparation of Lignans *via* Intermolecular Cycloadditions with Quinodimethanes

John Mann* and Susan E. Piper

Department of Chemistry, Reading University, Whiteknights, Reading RG6 2AD, U.K.

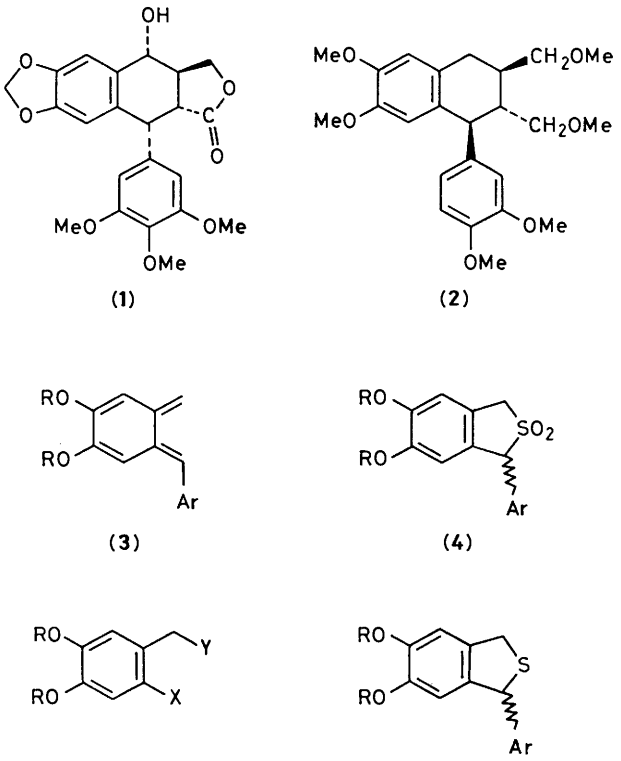
Certain lignans can be prepared using, as the key step, a thermal reaction between 1-(aryl)-1,3-dihydro-5,6-dialkoxy-benzo[*c*]thiophen 2,2-dioxides and dienophiles.

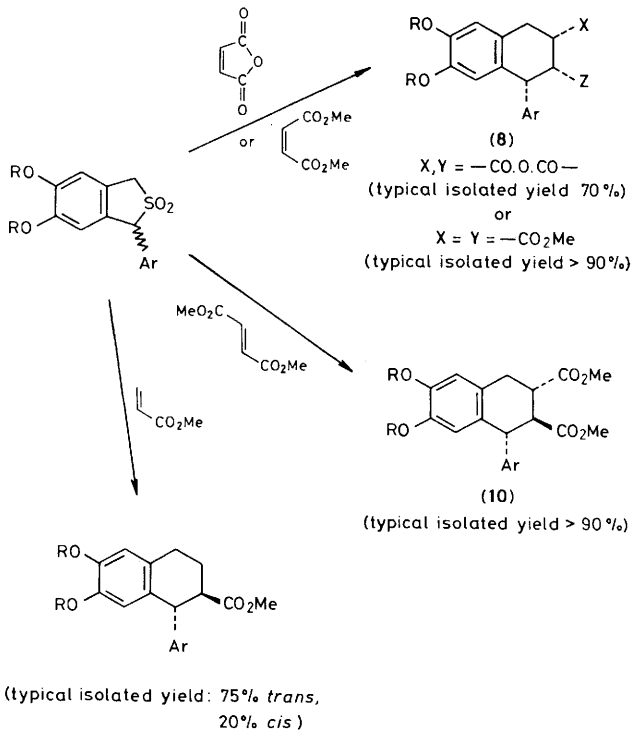
Many naturally occurring lignans have interesting biological activities, for example (−)-podophyllotoxin (**1**) from *Podophyllum peltatum* (this has cytotoxic activity, and two semi-synthetic derivatives are in clinical use as agents of cancer chemotherapy),[1] and (+)-phyltetralin (**2**) from *Phyllanthus niruri* (this plant is used in folk medicine for the treatment of asthma and bronchial infections[2]). We report herein a short and flexible synthesis of the basic ring systems of such lignans.

The key step is the intermolecular cycloaddition between *o*-quinodimethanes (**3**) and dienophiles. Of the possible precursors of these reactive intermediates, we chose to utilise 1-(aryl)-1,3-dihydro-5,6-dialkoxy-benzo[*c*]thiophen 2,2-dioxides (**4**). The chelotropic reactions of such sulphones to yield *o*-quinodimethanes, and their subsequent cycloadditions with dienophiles, were first studied by Cava,[3] but although *intra*molecular cycloadditions that employ substituted sulphones have been used in the synthesis of, for example estrogens,[4] most of the syntheses *via inter*molecular cycloaddition processes have employed photo-enolisation as the key step.[5] They thus employ photo-enols (hydroxy-*o*-quinodimethanes) rather than *o*-quinodimethanes as reactive intermediates.

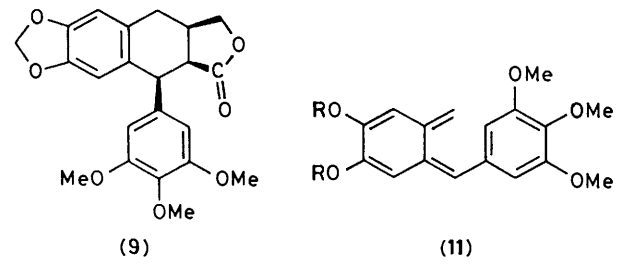
The sulphones (**4**) were prepared in four steps from the bromo-alcohols (**5**, Y=OH). Reaction of (**5**; Y=OH) with n-butyl-lithium (2 equiv., tetrahydrofuran, −78 °C) and then with the required aromatic aldehyde gave the diols (**6**, Y=OH) (70—80% yields). These diols were converted into thiophthalans (**7**) by activation of the hydroxy-groups ($MeSO_2Cl$, 2 equiv.; Et_3N, 2.2 equiv.; CH_2Cl_2; 0 °C),† subsequent reaction with sodium sulphide in dimethyl sulphoxide (stirring at room temp. for 4 h), and finally acidification (conc. HCl) [*ca.* 55 % overall yield of (**7**) after flash chromatography]. Alternatively, the bromo-thiols (**5**, Y=SH) were produced from the

† It is interesting that the dichloride is formed in this sequence, and we have shown that the chloride is also the sole product when attempting to prepare methanesulphonates of piperonyl alcohol or benzhydrol by this method.





Scheme 1. Two series of compounds: (a) R,R=$-CH_2-$, Ar=3,4,5-trimethoxyphenyl; (b) R=Me, Ar=3,4-dimethoxyphenyl.



bromo-alcohols (**5**, Y=OH) by bromination (48 % aq. HBr) followed by treatment with thiourea in dimethyl sulphoxide then aqueous sodium hydroxide solution. These were treated with sodium hydride in tetrahydrofuran (1 equiv. at room temp.), then with n-butyl-lithium (1 equiv. at −78 °C), and finally with the required aromatic aldehydes. Treatment with acid (conc. HCl) then gave the thiophthalans (**7**) (*ca.* 40 % overall from the bromothiols). The thiophthalans (**7**) produced *via* either route were oxidised to the sulphones (**4**) in essentially quantitative yields using 40 % peracetic acid.

Cycloadditions were carried out in di-n-butyl phthalate under an atmosphere of argon with a three-fold molar excess of dienophile at temperatures ranging from 170 to 210 °C, and reaction times of 2—3 h. They proceeded in high yield and with good to excellent stereoselectivity as shown in Scheme 1. Structure assignment was accomplished by conversion into known compounds for chromatographic and spectroscopic comparison. Thus, for example, the diester (**8**) was reduced (lithium triethylborohydride, 2 equiv.) to give isodeoxypicrophyllotoxin (**9**) (together with the alternative all-*cis* lactone). Similarly, the diester (**10b**) was reduced ($LiAlH_4$ in tetrahydrofuran) to the corresponding diol, and converted into (±)-phyltetralin (**2**) (MeI, dimethyl sulphoxide, NaH, 80 °C).

The stereochemical outcome of these reactions deserves some comment. Two consecutive processes are involved: a chelotropic reaction of a sulphone at elevated temperature to produce an *o*-quinodimethane, and a subsequent Diels–Alder reaction between this diene and a dienophile. There is ample literature precedent,[6] from the reactions of 1,4-diphenylbutadienes with dienophiles, to indicate that the stereochemical outcome in our cycloadditions is best explained if an *E*-diene [like (**3**)] is participating. Indeed, if a *Z*-diene was involved there is precedent for intramolecular cycloaddition *via* a species like (**11**). We have never obtained cycloadducts derived from compounds of this type. Other reports[7] on the Diels–Alder reactions between 1-*E*-phenylbutadienes and dienophiles also record stereochemical results in accord with our own. Finally, although the regioselectivity of the cycloaddition with methyl acrylate is expected (it should be frontier orbital-controlled),[8] the stereochemistry is surprising. The expected product is the 1,2-*cis*-cycloadduct, and this represents 20–25 % of the isolated product mixture after 3 h at 200 °C, though the major product is the 1,2-*trans*-cycloadduct. Repetition of this reaction (which must be carried out in a sealed tube) using shorter reaction times, led to greater quantities of the 1,2-*cis*-cycloadduct (as much as 35 % of the total after 20 min at 200 °C). We suggest that the Diels–Alder reaction is reversible, such that the thermodynamic product is preferred.

In summary, we believe that our initial experiments have demonstrated that these cycloadditions proceed with a high degree of stereoselectivity and regioselectivity, and offer a novel and flexible approach to the preparation of 1-aryl lignans.

We thank Dr David Ayres, Professor Robert Stevenson, and Professor Walter Gensler for authentic lignans, and the

S.E.R.C. and the Imperial Cancer Research Campaign for a C.A.S.E. award to S.E.P.

Received, 16th November 1981; Com. 1341

References

1 I. Jardine, in 'Anti-cancer Agents based on Natural Product Models,' eds. J. M. Cassady and J. D. Douros, Academic Press, New York, 1980, ch. 9.
2 P. A. Ganeshpure, G. E. Schneiders, and R. Stevenson, *Tetrahedron Lett.*, 1981, 393.
3 M. P. Cava and A. A. Deana, *J. Am. Chem. Soc.*, 1959, **81**, 4266.
4 K. C. Nicolaou and W. E. Barnette, *J. Chem. Soc., Chem. Commun.*, 1979, 1119; W. Oppolzer and D. A. Roberts, *Helv. Chim. Acta*, 1980, **63**, 1703.
5 B. J. Arnold, S. M. Mellows, and P. G. Sammes, *J. Chem. Soc., Perkin Trans.* 1, 1973, 1266.
6 R. Huisgen and H. Seidel, *Tetrahedron Lett.*, 1964, 3381.
7 K. Alder, H. Vagt, and W. Vogt, *Liebigs Ann. Chem.*, 1949, **565**, 135; K. Alder, J. Haydn, K. Heimbach, K. Neufang, G. Hansen, and W. Gerhard, *ibid.*, 1954, **586**, 110.
8 I. Fleming, 'Frontier Orbitals and Organic Chemical Reactions,' Wiley, New York, 1976.