Potential Isobenzofurans: their Use in the Synthesis of Naturally Occurring 1-Arylnaphthalide Lignans

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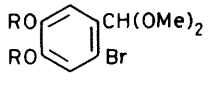
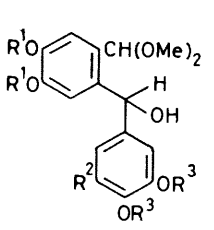
Summary A three-step synthesis of seven lignans by means of a Diels–Alder reaction followed by selective borane reduction of an aromatic ester is described.

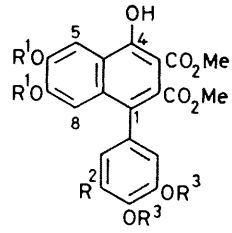
WE report an efficient, general synthesis of some 1-arylnaphthalide lignans.[1] The dimethylacetal† of 2-bromoveratraldehyde (**1a**) was treated successively with n-butyl-lithium at −78 °C and piperonal to provide the hydroxy-acetal (**2a**) as a pale yellow oil [$\delta(CDCl_3)$: 3·23 (s, 6H), 3·37 (d, 1H, J 4 Hz, disappears with D_2O), 3·85 (s, 3H), 4·18 (s, 3H), 5·35 (s, 1H), 5·87 (s, 2H), 5·97 (d, 1H, J 4 Hz, collapses to a singlet with D_2O), 6·63—6·87 (m, 3H), 6·83 (s, 1H), and 7·05 (s, 1H): ν_{OH} (neat) 3450 cm^{-1}; M^+, 362]. This compound, without further purification, was refluxed in benzene for 2 h with excess of dimethyl acetylenedicarboxylate and a trace of toluene-*p*-sulphonic acid to yield the naphthol (**3a**) [65% overall from (**1a**)] [(**3a**), m.p. 236 °C (ether–ligroin); $\delta(CDCl_3)$: 3·53 (s, 3H), 3·68 (s, 3H), 3·85 (s, 3H), 3·96 (s, 3H), 5·95 (s, 2H), 6·60—6·83 (m, 4H), 7·63 (s, 1H), and 12·00 (s, 1H); $\nu_{C=O}$ ($CHCl_3$) 1735 and 1670 cm^{-1}; M^+ 440]. The naphthols (**3b**), (**3c**), and (**3d**) were similarly obtained in comparable yields from (**1b**) through the hydroxy-acetals (**2b**), (**2c**), and (**2d**), respectively.‡ Comparison of the chemical shifts of the methoxyl protons of (**3a**), (**3b**), and (**3c**) allows the signals at δ 3·53 and 3·68 of (**3a**) to be assigned to the C-2 methoxycarbonyl and the C-7 methoxy groups respectively. The upfield locations of these signals can be attributed to the shielding effect of the aromatic ring at C-1.



(**1**)

a; R = Me
b; RR = $-CH_2-$





(**2**) (**3**)

a; R^1 = Me, R^2 = H, R^3R^3 = $-CH_2-$
b; R^1R^1 = R^3R^3 = $-CH_2-$, R^2 = H
c; R^1R^1 = $-CH_2-$, R^2 = H, R^3 = Me
d; R^1R^1 = $-CH_2-$, R^2 = OMe, R^3 = Me

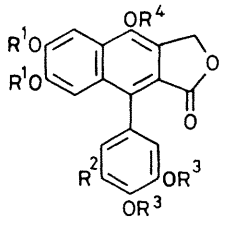
The hydroxy-acetals (**2**) may be regarded as potential isobenzofurans since the latter (**6**) are produced from (**2**) by acid treatment (Scheme) and subsequently trapped by the acetylene dicarboxylate as Diels–Alder adducts[2,3] which in turn are aromatised to the naphthols (**3**). Indeed, we have observed that a cyclic hemiacetal [of the type (**5**)] undergoes exactly the same reaction under identical conditions. Our difficulties with purifying the hydroxy-

† Prepared in 95% yield by refluxing 2-bromoveratraldehyde with trimethyl orthoformate and Dowex 50W-X2 resin in methanol.

‡ All new compounds had spectroscopic properties consistent with their assigned structures and are supported by elemental analysis and/or high resolution mass spectra.

acetals (**2**) may also be due to this same ready tendency to generate reactive isobenzofurans. Similar behaviour of a 2-(α-bromoalkyl)benzophenone has been recently reported.[3]

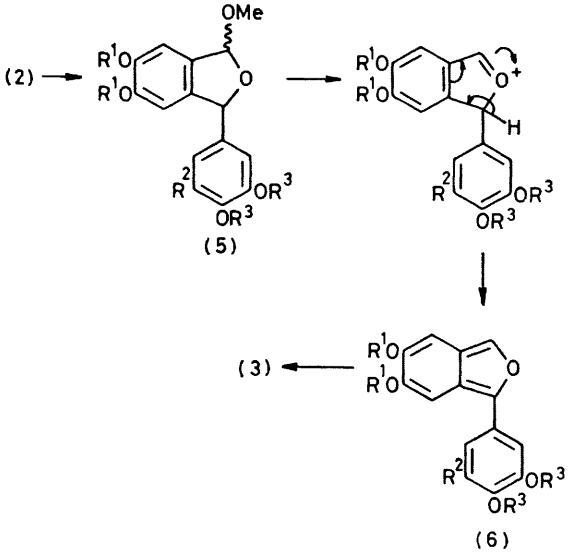
Selective reduction of the 3-methoxycarbonyl group of (**3a**) was then achieved with borane–methyl sulphide in anhydrous refluxing tetrahydrofuran (3 h). The crude product, presumably a cyclic borate, obtained by merely removing the solvent *in vacuo* showed a new singlet (2H) at δ 5·2, the loss of one methoxy group [at δ 3·85 in (**3a**)], but the retention of the high field methoxycarbonyl group at δ 3·53 in its ^{1}H n.m.r. spectrum. The i.r. spectrum of this material [$\nu_{C=O}$ ($CHCl_3$) 1720 cm^{-1}] reinforced the conclusion that reduction of only the hydrogen-bonded ester of (**3a**) had taken place. This result was confirmed when work-up of the borate gave diphyllin[4] (**4a**) which was methylated with diazomethane to justicidin A[4] (**4e**).



(**4**)

a; R^1 = Me, R^2 = R^4 = H, R^3R^3 = $-CH_2-$
b; R^1R^1 = R^3R^3 = $-CH_2-$, R^2 = R^4 = H
c; R^1R^1 = $-CH_2-$, R^2 = R^4 = H, R^3 = Me
d; R^1R^1 = $-CH_2-$, R^2 = OMe, R^3 = Me, R^4 = H
e; R^1 = R^4 = Me, R^2 = H, R^3R^3 = $-CH_2-$
f; R^1R^1 = R^3R^3 = $-CH_2-$, R^2 = H, R^3 Me
g; R^1R^1 = $-CH_2-$, R^2 = H, R^3 = R^4 = Me

The reduction with borane is noteworthy in that it appears to contradict reports[5] that aromatic esters are only very slowly reduced by this reagent; in this case prior reaction of the reagent with the adjacent hydroxy group followed by intramolecular delivery of the hydride is probably responsible. Similar results were obtained in the reduction of the naphthols (**3a**), (**3c**), and (**3d**) to taiwanin E[6] (**4b**), chinensinaphthol[7] (**4c**) and dehydropodophyllotoxin[8] (**4d**), respectively. Taiwanin E methyl ether[4] (**4f**) and chinensinaphthol methyl ether[7] (**4g**) were obtained by treatment of (**4b**) and (**4c**) respectively with diazomethane. Physical and spectroscopic properties of the synthetic samples were identical with those reported for the natural lignans except for the m.p. of synthetic taiwanin E which is much higher (340 °C) than that previously recorded[6] (263—267 °C).



SCHEME

A simple three-step process for the synthesis of these lignans in *ca.* 35% overall yield from the bromoacetals (**1**) has thus been developed. We are encouraged by the demonstrated[2,3,9] versatility of isobenzofurans in the Diels–Alder reaction to seek wider application of the strategy not only to the synthesis of podophyllotoxin but also to the elaboration of other polycyclic systems.

We thank the Natural Science and Engineering Research Council of Canada for support of this work.

(*Received*, 12*th June* 1979; *Com.* 619.)

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