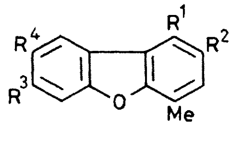
Synthesis of Ruscodibenzofuran (8-acetyl-7-hydroxy-1,4-dimethyldibenzofuran)

By Ralph T. Scannell and Robert Stevenson*
(*Department of Chemistry, Brandeis University, Waltham, Massachusetts* 02254)

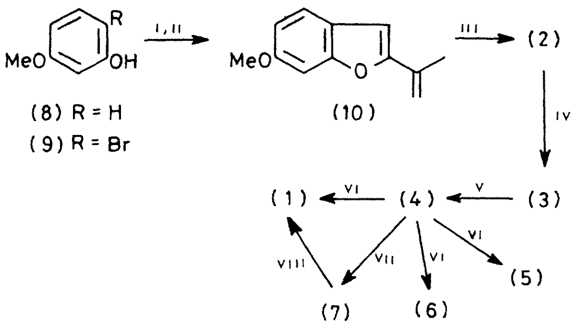
Summary A short synthesis of ruscodibenzofuran (**1**), a dibenzofuran extractive of *Ruscus aculeatus*, is described, the two significant steps of which exemplify a general route for the conversion of phenols into dibenzofurans.

Extracts of *Ruscus aculeatus* (Liliaceae) have been used for their diuretic and anti-inflammatory activity and, among the constituents, ruscodibenzofuran (8-acetyl-7-hydroxy-1,4-dimethyldibenzofuran) (**1**) has been isolated.[1] The structure was convincingly demonstrated from spectroscopic data and *X*-ray diffraction analysis[2] and recently confirmed by synthesis.[3] We report here an alternative, short pathway to this product, apparently the first dibenzofuran obtained from a higher plant.



(**1**) R^1 = Me, R^2 = H, R^3 = OH, R^4 = Ac
(**2**) R^1 = CO_2Me, R^2 = R^4 = H, R^3 = MeO
(**3**) R^1 = CH_2OH, R^2 = R^4 = H, R^3 = MeO
(**4**) R^1 = Me, R^2 = R^4 = H, R^3 = MeO
(**5**) R^1 = Me, R^2 = R^4 = Ac, R^3 = OH
(**6**) R^1 = Me, R^2 = Ac, R^3 = MeO, R^4 = H
(**7**) R^1 = Me, R^2 = H, R^3 = MeO, R^4 = Ac

2-Bromo-5-methoxyphenol (**9**) [b.p. 87 °C at 0·9 mm Hg, ^{1}H n.m.r. δ 3·76 (s, OMe), 6·43 (dd, *J* 9 and 2 Hz, H-4), 6·63 (d, *J* 2 Hz, H-6), and 7·33 (d, *J* 9 Hz, H-3)], obtained from 3-methoxyphenol (**8**) by treatment with dioxan dibromide in diethyl ether, gave 2-isopropenyl-6-methoxybenzofuran (**10**) in 24% yield [oil, ^{1}H n.m.r. δ (CCl_4) 2·06 br (s, Me), 3·77 (s, OMe), 5·03 (m, vinyl H), 5·66 br (s, vinyl H), 6·45 br (s,



SCHEME *Reagents* i, dioxan dibromide, Et$_2$O ii, copper(I) isopropenylacetylide iii reflux, MePh, HC≡CCO$_2$Me iv, LiAlH$_4$ v, Pd–C, AcOEt vi, AcCl AlCl$_3$, CH$_2$Cl$_2$ vii, AcCl, TiCl$_4$ viii, BBr$_3$, C$_6$H$_6$

H-3), 6·72 (dd, *J* 9 and 2 Hz, H-5), 6 89 (d, *J* 2 Hz, H-7), and 7·26 (d, *J* 9 Hz, H-4) by reaction with copper(I) isopropenylacetylide[4] in pyridine On heating (**10**) under reflux in toluene with methyl propiolate, the desired product of regioselective addition and dehydrogenation was obtained in 20% yield, *i e* the methyl dibenzofuranylcarboxylate (**2**) [m p 101—102 °C, ^{1}H n m r δ 2·11 (s, Me), 3 91 (s, OMe), 4·02 (s, CO$_2$Me), 6·97 (dd, *J* 9 and 3 Hz, H-8), 7·10 (d, *J* 3 Hz, H-6), 7·21 (d, *J* 9 Hz, H-9), 7 91 (d, *J* 9 Hz H-3), and 8·64 (d, *J* 9 Hz, H-2)] Reduction of (**2**) with lithium aluminium hydride yielded the benzylic alcohol (**3**) in 81% yield {m p 126—127 °C, ^{1}H n m r δ 2·56 (s, Me), 3·90 (s, OMe), 5·08 (s, ArC*H*$_2$O), 6·94 (dd, *J* 8·5 and 2·5 Hz, H-8), 7·12 (d, *J* 2·5 Hz, H-6), 7·16 br [s, H-2 and -3, doublets (*J* 8 Hz) at δ 7·22 and 7·29 in (CD$_3$)$_2$CO], and 7·94 (d, *J* 8·5 Hz, H-9)} which, on hydrogenolysis with palladium–carbon in ethyl acetate gave the known 7-methoxy-1,4-dimethyldibenzofuran (**4**) in 87% yield, m p 69·5—70·5 °C (lit [3] m p 69—70 °C) This formally completes a synthesis of ruscodibenzofuran (**1**) since (**4**) has been converted into (**1**) in 67% yield by treatment with acetyl chloride and aluminium chloride in dichloromethane [3]†

Since in our hands, treatment of (**4**) with these reagents yielded instead 2,8-diacetyl-7-hydroxy-1,4-dimethyldibenzofuran (**5**), in 16% yield, m p 223—224·5 °C and 2-acetyl-7-methoxy-1,4-dimethyldibenzofuran (**6**) in 38% yield, m p 112—112 5 °C as the major products,† we sought an alternative conversion of (**4**) into (**1**) This was achieved in a two-step procedure consisting of acetylation of (**4**) with acetyl chloride and titanium tetrachloride to give the known ruscodibenzofuran methyl ether (**7**), m p 155—156 °C, followed by demethylation with boron tribromide in benzene to yield ruscodibenzofuran, m p 173—174·5 °C Both steps proceeded in an essentially quantitative yield

This scheme, consisting of the reaction of an *o*-halogenophenol with the cuprous salt of a conjugated enyne to yield a 2-vinylbenzofuran[4,5,6] reactive towards dienophiles,[7–9] exemplifies a convenient route from phenols to polyfunctional dibenzofurans

Satisfactory elemental analyses were obtained for all new crystalline compounds and ^{1}H n m r spectra were determined in [^{2}H]chloroform (unless otherwise stated)

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† We are particularly grateful to Dr Hans-Erik Hogberg for providing details of this experiment, authentic product samples, and n m r spectra We are unaware of the subtle differences in conditions which account for this divergent result, but consider that reactivity differences of the aluminium chloride may be responsible Dr Hogberg has informed us that he also has isolated compound (**6**) in one experiment

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