Trifluoroacetic Acid Catalysed Claisen Rearrangement of 5-Allyloxy-2-hydroxybenzoic Acid and Esters: an Efficient Synthesis of (±)-Mellein

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5-Allyloxy-2-hydroxybenzoic acid (**1a**) and the esters (**1b**—**f**) in refluxing trifluoroacetic acid are smoothly converted into 3,4-dihydro-5,8-dihydroxy-3-methylisocoumarin (**3**) and the corresponding 4-alkoxycarbonyl-2,3-dihydro-5-hydroxy-2-methylbenzofurans (**4a**—**f**) *via* regioselective Claisen rearrangement to the 6-position of the aromatic nucleus with subsequent acid catalysed cyclisation.

Regioselectivity in the Claisen rearrangement of 5-allyloxy-2-hydroxyphenyl alkyl ketones has been previously noted.[1] The equivalent benzoic acid methyl ester (**1b**) rearranges only sluggishly on heating with resultant extensive decomposition.[2] Reports[3] that trifluoroacetic acid (TFA) enhances the rate of Claisen rearrangement of simple allyl phenyl ethers by *ca.* 10^5 prompted us to apply this to (**1b**).

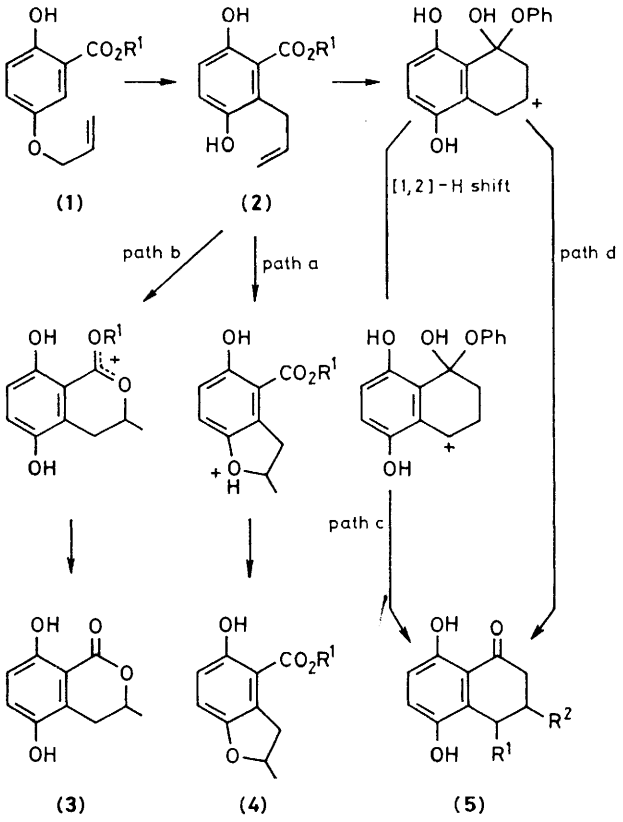
A solution of (**1b**) in TFA was completely consumed after reflux (24 h) giving rise to two major products which on isolation were shown to be the dihydroisocoumarin (**3**) [32%; ν_{max} ($CHCl_3$) 1670 cm^{-1}; δ(CD_3COCD_3, 90 MHz) 2.88 (d, *J* 9 Hz, 6-H) and 3.31 (d, *J* 9 Hz, 7-H)] and the dihydrobenzofuran (**4b**) [21%; ν_{max} (CCl_4) 1680 cm^{-1}; δ($CDCl_3$, 90 MHz) 3.23 (d, *J* 8 Hz, 7-H) and 3.38 (d, *J* 8 Hz, 6-H)].

These products presumably arise *via* the acid catalysed cyclisation of an intermediate (**2**) (Scheme 1). During such cyclisation positive charge would develop either on phenolic oxygen atoms [dihydrobenzofuran formation (path a)] or on

Table 1. TFA catalysed Claisen rearrangement of 5-allyloxy-2-hydroxybenzoates (**1a**—**f**).[a]

R^1 in (**1**)	Reaction time/h	Dihydrobenzofuran (**4**) isolated yield, %	Dihydroisocoumarin (**3**) isolated yield, %	G.c. ratio (**4**):(**3**)	Other products (isolated yield, %)
H	21	24.5	63.0	1.0:2.8	
Me	24	21.0	32.0	1.0:2.7	
Ph	19	13.5	17.5	1.0:1.9	(**5g, h**) (5)
$PhCH_2$	17	8.5[b]	31.0	1.0:3.4	2,5-dihydroxybenzoic acid (25)
Pr^i	17	10.0	43.5	1.0:4.0	
CH_2=$CHCH_2$	18	14.0	41.0	1.0:4.5	

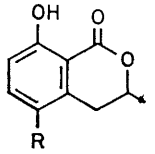
[a] Reaction conditions: TFA [2 mmol (**1**) ml^{-1}], reflux until starting material totally consumed. [b] Obtained as acid owing to lability of benzyl residue under reaction conditions. Products in this entry are therefore probably partially derived from (**1a**).



a; R^1 = H
b; R^1 = Me
c; R^1 = Ph
d; R^1 = $PhCH_2$
e; R^1 = Pr^i
f; R^1 = CH_2=$CHCH_2$
g; R^1 = OPh, R^2 = H
h; R^1 = H, R^2 = OPh

Scheme 1

the ester oxygen atoms [dihydroisocoumarin formation (path b)] and it was reasoned that an ester residue R^1, capable of stabilising an adjacent positive charge, might favour dihydroisocoumarin formation. The acid (**1a**) and esters (**1b**—**f**) were therefore submitted to TFA reflux and the product ratio (**3**):(**4**) determined by capillary g.c.–m.s. analysis of the crude product mixture.† All products constituting more than 5% of



(**6**) **a**; R = OSO_2Me
b; R = H

total peak area in the g.c. analysis were isolated and characterised.‡ The results are summarised in Table 1. The formation of the isomeric tetralones (**5g, h**) [2:5 by g.c. and n.m.r. analysis; ν_{max} ($CHCl_3$) 1630 cm^{-1}; δ(CD_3COCD_3, 220 MHz) 11.17 and 11.14 (two singlets removable with D_2O, total integration 1H), 5.05 and 4.75 (two multiplets, total integration 1H, PhOCH)] from the phenyl ester (**1c**) may be rationalised by nucleophilic attack of the double bond of intermediate (**2**) on the protonated ester group followed by partial [1,2]-hydride shift giving the more stable benzylic carbenium ion with subsequent expulsion and return of phenol (Scheme 1, paths c and d). It is noteworthy that neither products resulting from initial Claisen rearrangement to the 4-position of (**1a**—**f**) nor non-cyclised material have been observed.

Although the ratio (**3**):(**4**) is not as sensitive to R^1 as hoped, the 39.5% overall yield of (**3**) in two steps from 2,5-dihydroxybenzoic acid *via* the allyl ester (**1f**) [i, CH_2=$CHCH_2Br$(2 equiv.) –K_2CO_3–Me_2CO, 96% yield; ii, TFA, reflux] has synthetic utility owing to the ease of the operations involved. Dihydroisocoumarin (**3**) has been converted into (±)-mellein (**6b**), a product from moulds of the genus *Aspergillus*[4] which exhibits pheromonal activity in the carpenter ant.[5]

Selective methanesulphonation of the non-hydrogen bonded phenolic hydroxy-group of (**3**) gives (**6a**) [$MeSO_2Cl$–pyridine, reflux; 92% yield of colourless rhombs, m.p. 171—172 °C; ν_{max} ($CHCl_3$) 1680, 1370, and 1160 cm^{-1}; δ($CDCl_3$, 220 MHz) 11.12 (s, removable with D_2O) and 3.23 (s,-Me)] which on hydrogenolysis[6] affords (±)-mellein (**6b**) [5% Pd/C–MeOH–Et_3N–H_2 (1 atm. 60 °C); 96% yield; m.p. 38.0—38.5 °C (lit.[7] 39.0 °C)] in 35% overall yield from 2,5-dihydroxybenzoic acid.

Thus the mode of cyclisation of the acid catalysed Claisen rearrangement product (**2**) obtained from alkyl 5-allyloxy-2-hydroxybenzoates (**1a**—**f**) is dependent on the ester residue R^1 and has synthetic applications.

† Silylating system, bis(trimethylsilyl)trifluoroacetamide +1% Me_3SiCl–pyridine; column, 10% OV-1, 25 m × 0.25 mm int. diam. flexible fused quartz, splitless injection, direct coupled Perkin Elmer SIGMA 3/Kratos M.S. 25; temperature programme 100—250 °C at 5 °C min^{-1}.

‡ All new compounds described have analytical and spectral data in accord with their assigned structures. Tetralones (**5g, h**) were characterised as a mixture. Yields are of isolated material.

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