Application of the Lewis Acid-catalysed Claisen Rearrangement of 4'-(1,1-Dimethylallyloxy)coumarates to the Synthesis of Demethylsuberosin

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The synthesis of the linear coumarin demethylsuberosin (**1**) is described *via* regioselective boron trifluoride–diethyl ether-catalysed Claisen rearrangement of methyl 2'-benzyloxy-4'-(1,1-dimethylallyloxy)cinnamate (**4c**).

We have recently developed a synthesis of 6-allyl-7-hydroxycoumarin, a useful intermediate for the preparation of linear furanocoumarins, in which the key feature was the regioselective boron trichloride-catalysed Claisen rearrangement of methyl 4'-allyloxy-2'-methoxycinnamate.[1] This route constitutes an important means of preparing 6-alkylated coumarins, as electrophilic subsitution and Claisen rearrangement of 7-hydroxycoumarin derivatives result in selective functionalisation at C-8.[2]

As many natural linear coumarins are derived from 6-prenyl-7-hydroxycoumarin [demethylsuberosin (**1**)], both *in vivo*[3] and synthetically,[2] we decided to investigate the application of this sequence to the synthesis of (**1**). We were particularly concerned about the likely lability of the precursor 1,1-dimethylallyl ethers and the *ortho*-prenylated phenols under the conditions used in the sequence.[2]

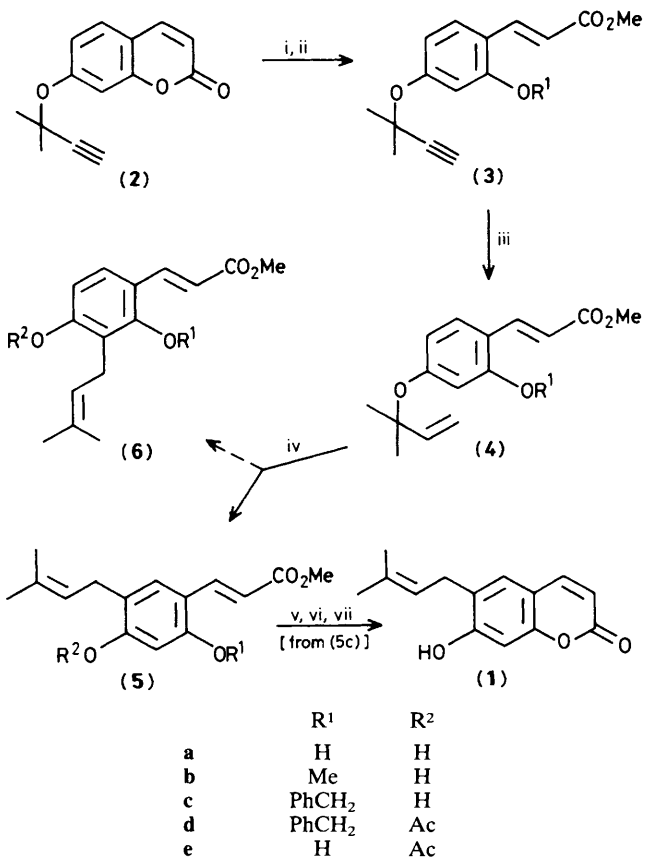
Indeed, attempted cleavage of 7-(1,1-dimethylallyloxy)coumarin,[4] using conditions which were successful with 7-allyloxycoumarin (NaOMe, MeOH, reflux),[1] resulted in Claisen rearrangement to the undesired position prior to lactone cleavage. This could be circumvented by carrying out the cleavage on the propynylic ether (**2**)† which produced the coumaric ester (**3a**) in 93% yield [n.m.r., 300 MHz, $CDCl_3$: δ 2.68 (s), ≡CH] (Scheme 1). Methylation of the phenolic hydroxy group (MeI, K_2CO_3, acetone) gave (**3b**) (90%) and reduction of the acetylene moiety (Lindlar catalyst, H_2) furnished the desired methyl coumarate (**4b**) in 90% yield [n.m.r., 300 MHz, $CDCl_3$: δ 5.17 (1H, dd, *J* 7, *J'* 1 Hz), 5.22 (1H, dd, *J* 15, *J'* 1 Hz), 6.16 (1H, dd, *J* 15, *J'* 7 Hz), 6.43 (1H, d, *J* 16 Hz), and 7.90 (1H, d, *J* 16 Hz), vinylic protons] usually accompanied by *ca.* 6% of over-reduced material.‡

Attempted rearrangement of (**4b**) under previously optimised conditions[1] (BCl_3, CH_2Cl_2, −50 °C) caused rapid cleavage of the 1,1-dimethylallylether moiety. However, after some investigation it was found that use of the milder reagent $BF_3 \cdot Et_2O$ under the same conditions resulted in the desired regioselective rearrangement to (**5b**) [60%; n.m.r., 300 MHz, $CDCl_3$: δ 6.42 (1H, s) and 7.22 (1H, s), ArH] accompanied by a small quantity of the undesired isomer (**6b**) [n.m.r., 300 MHz, $CDCl_3$: δ 6.69 (1H, d, *J* 8.5 Hz) and 7.36 (1H, d, *J* 8.5 Hz), ArH; g.c. ratio (**5b**) : (**6b**), 10 : 1]. In contrast, methyl 4'-allyloxy-2'-methoxycinnamate was shown to be totally stable to such treatment.

Unfortunately, reconstruction of the coumarin ring was thwarted as no conditions could be found to cleave the methyl

† It was necessary to avoid extended periods of reflux in the cleavage step as benzopyran formation became increasingly important with time.

‡ All new compounds isolated gave spectroscopic and analytical data in keeping with their assigned structures.



	R^1	R^2
a	H	H
b	Me	H
c	$PhCH_2$	H
d	$PhCH_2$	Ac
e	H	Ac

Scheme 1. *Reagents and conditions:* i, NaOMe, MeOH, reflux, 3 h; ii, H_3O^+ (**3a**); MeI, K_2CO_3, acetone, reflux (**3b**); $PhCH_2Br$, K_2CO_3, acetone (**3c**); iii, Lindlar cat., H_2; iv, $BF_3 \cdot Et_2O$ (2 equiv.), CH_2Cl_2, −60 °C; v, Ac_2O, C_5H_5N, room temp.; vi, BCl_3 (4 equiv.), CH_2Cl_2, −50 °C; vii, $HOCH_2CH_2OH$, reflux.

ether group of (**5b**) without also causing cyclisation of the prenyl group onto the *ortho*-hydroxy group.

We therefore examined the behaviour of other substrates (**4**) possessing various phenol protecting groups in the presence of $BF_3 \cdot Et_2O$. The milder Lewis acid conditions did not cause relactonisation of the unprotected coumarate (**4a**) to the coumarin, but cleavage of the 1,1-dimethylallyl ether occurred to the exclusion of rearrangement. However the benzyl ether (**4c**), prepared from (**3a**) by sequential benzylation ($PhCH_2Br$, K_2CO_3, acetone, reflux, 90%) and reduction with Lindlar catalyst (90%), was successfully rearranged to the desired product (**5c**) in 75% isolated yield [$BF_3 \cdot Et_2O$, CH_2Cl_2, −60 °C; n.m.r., 300 MHz, $CDCl_3$: δ 6.44 (1H, s) and 7.35 (6H, m), ArH] with none of the regioisomer (**6c**) detectable in the crude product mixture. Presumably in this instance the electronic control of the rearrangement is augmented by the greater steric bulk of the benzyl group compared with the methyl group. Unfortunately, selective hydrogenolysis of the benzyl ether in the presence of the unsaturated side chain proved impossible and Lewis acid catalysed debenzylation of (**5c**) could not be effected without cyclisation of the prenyl substituent onto the *ortho*-hydroxy group despite using milder conditions (BCl_3, CH_2Cl_2, −50 °C) than those previously required for demethylation.

However, during the course of related work[5] it had been observed that phenyl acetates were stable to the conditions which had been used to debenzylate (**5c**). Consequently, the free phenol of (**5c**) was acetylated (Ac_2O, pyridine, room temp., quantitative) and the product (**5d**) debenzylated, without loss of the acetoxy group (BCl_3, CH_2Cl_2, −50 °C) to furnish (**5e**) [95%; n.m.r., 300 MHz, $CDCl_3$: δ 2.31 (3H, s, Ac) and 6.23 (1H, br.s, removed with D_2O, ArOH)]. This represents an interesting case of selective cleavage of an aryl benzyl ether in the presence of a phenyl ester using a Lewis acid.

Recyclisation to the coumarin was effected with concomitant deacetylation (ethylene glycol, reflux, 3 h) to furnish the desired demethylsuberosin (**1**) in quantitative yield, possessing physical and spectroscopic data identical with those of an authentic sample.§

The sequence for the preparation of demethylsuberosin (**1**) herein described thus constitutes an efficient means of access to 7-oxygenated coumarins possessing side chains at C-6 derived from the prenyl unit.

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§ We thank Dr. R. D. H. Murray, Glasgow University, for a generous gift of authentic demethylsuberosin. In the n.m.r. spectrum of (**1**) the chemical shift of H-8 was found to be concentration-dependent. The following data are typical: 300 MHz, $CDCl_3$: δ 1.77 (3H, br.s), 1.80 (3H, br.s), 3.69 (2H, br. d, *J* 7 Hz), 5.33 (1H, br. t, *J* 7 Hz), 6.24 (1H, d, *J* 9.5 Hz), 6.61 (1H, br.s, removed with D_2O), 6.92 (1H, s), 7.20 (1H, s), and 7.64 (1H, d, *J* 9.5 Hz). Spectra recorded on mixtures of synthetic and authentic samples showed coincidence of all peaks at various concentrations.