Boron Halide Catalysed Regioselective *ortho*-Claisen Rearrangements of 4'-Allyloxycoumaric Acid Derivatives: Total Synthesis of Demethylsuberosin[1]

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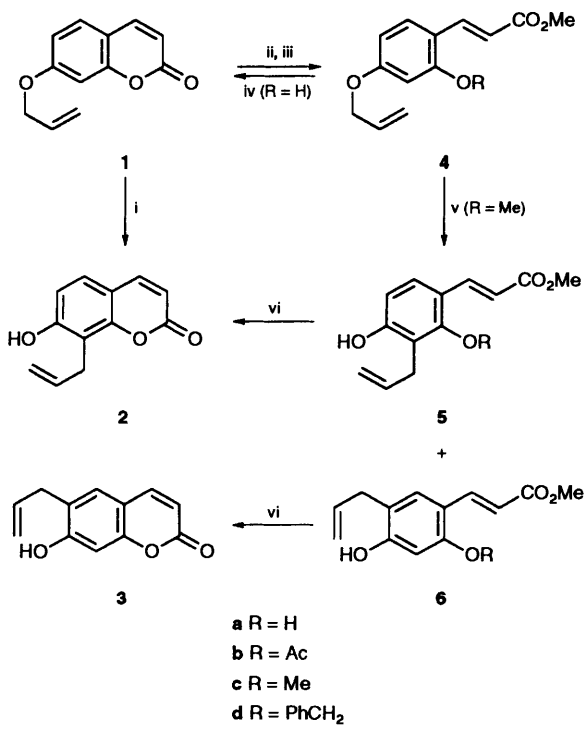
6-Allyl-7-hydroxycoumarin **3** and the naturally occurring linear coumarin, demethylsuberosin (7-hydroxy-6-prenylcoumarin) **7** have been prepared in goods yields *via* regioselective boron halide catalysed *ortho*-Claisen rearrangements. This procedure provides an efficient alternative approach to linear substituted coumarins without using a halogen to block the 8-(angular) position.

Coumarins[2] usually occur as secondary metabolites present in the seeds, roots, stems and leaves of many plant species, especially *Leguminosae*, *Orchidaceae*, *Rutaceae* and the *Umbelliferae*.[3] Their function is far from clear, though suggestions include waste products, allelopathic agents,[4] plant growth and seed dormancy regulators and fungistats and bacteriostats.[5] Coumarins have been found in small amounts in fungi and bacteria,[6] (*e.g. Streptomyces niveus* contains one of the coumarin antibiotics, novobiocin[7]) but appear to be lacking in algae, mosses and animals. Over the past 30 years interest in naturally occurring coumarins has been revived, mainly due to the wide range of physiological activity that they have been shown to possess.[8] This has led to their discovery in hundreds of plant species and many novel structures are found every year.

The vast majority of coumarins are oxygenated at C-7 and therefore 7-hydroxycoumarin (umbelliferone) is regarded as the true parent of nearly all of the naturally occurring coumarins. Coumarins offer probably the best example of a class of compounds exhibiting the greatest number of biogenetic modifications of simple isoprenoid units. Isoprenoid chains of one, two or three units are often attached to oxygen or any of the nuclear positions except 4- or 5-. Umbelliferone derivatives alkylated at C-6 are commonly referred to as linear coumarins and those alkylated at C-8 as angular coumarins. They are often key intermediates to the important linear and angular furanocoumarins and pyranocoumarins; for example 6-allyl-7-hydroxycoumarin is the key precursor to psoralen.[9]

When 7-allyloxycoumarin **1** is subjected to a thermal Claisen rearrangement at 198 °C in refluxing ethylene glycol, a mixture of two isomers, 8-allyl-7-hydroxycoumarin **2** and 6-allyl-7-hydroxycoumarin **3** results, in which **2** strongly predominates.[10] This type of regioselectivity in the substitution of aromatic substrates was first noted by Claisen in 1912 when he heated the allyl ether of 2-naphthol and obtained only 1-allyl-2-naphthol.[11] Access to angular coumarins is therefore possible *via ortho*-Claisen rearrangements of 7-allyloxycoumarins. However, preparation of the linear isomers by a similar sequence necessitates either reduction of the 3,4-double bond (linear: angular ~ 1:1)[12] or blocking of C-8 by a halogen which is normally lost on rearrangement.[13] Direct substitution of 7-hydroxycoumarins by Lewis acid catalysed reaction with tertiary allylic alcohols likewise furnishes mixtures of 6- and 8-allylated products in low yield.[14]

In earlier work, we demonstrated that the trifluoroacetic acid catalysed Claisen rearrangement[15] of methyl 4-allyloxy-2-hydroxybenzoate occurred selectively towards the 5-position.[16] We thus reasoned that disruption of the coumarin nucleus to form the vinylogous coumaric acid derivatives **4**, should permit similar selective rearrangement to products **6** and furnish the desired linear coumarin **3** on relactonisation.[17]



Scheme 1 *Reagents and conditions:* i, 220 °C; ii, NaOMe, MeOH, reflux; iii H_2O (**4a**); Ac_2O (**4b**); MeI, K_2CO_3, acetone, reflux (**4c**); $PhCH_2Br$, K_2CO_3, acetone, reflux (**4d**); iv, 180 °C; v, BCl_3 (3 equiv.), CH_2Cl_2, −50 ⟶ −20 °C; vi, BBr_3 (3 equiv.), CH_2Cl_2, room temp.

Methyl esters **4a** and **4b** were obtained efficiently by treatment of 7-allyloxycoumarin **1** with sodium methoxide in methanol at reflux with rigorous exclusion of moisture (traces of hydroxide inhibit cleavage) followed by quenching of the cooled reaction with water (**4a**, 96%) or acetic anhydride (**4b**, 76%). The esters **4c** and **4d** were obtained by alkylation of **4a** with methyl iodide or benzyl bromide, K_2CO_3 and acetone at reflux (**4c**, 96%, **4d**, 92%). Higher overall yields of **4c** and **4d** were obtained by this two-step procedure than by direct addition of halide to the reaction mixture obtained on cleavage. The olefinic protons of **4a–d** appeared as 16 Hz doublets indicating (*E*)-double bond geometry (Scheme 1).

Thermal rearrangement of methyl esters **4a** and **4b** furnished angular coumarin **2** (accompanied by some of the acetylated derivative in the case of **4b**) as the major product owing to relactonisation occurring before rearrangement. Thermal rearrangment of the methyl ether **4c** resulted in the formation of **5c** and **6c** in which the desired regioisomer was the major

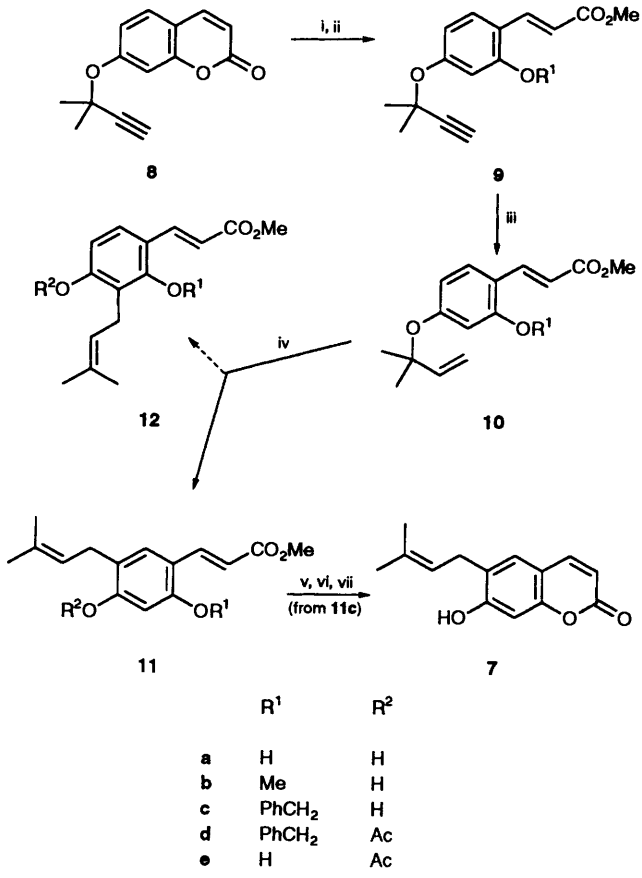
product (**5c**:**6c**, 1.0:2.5). Attempted improvement of this ratio by the use of trifluoroacetic acid catalysis caused total decomposition. In search of milder conditions, BCl_3, previously reported to catalyse Claisen rearrangements at low temperatures,[18] was investigated. Conditions could not be found to effect rearrangement without decomposition or relactonisation of **4a** and the acetate **4b** was found to be readily converted initially into **4a**. Gratifyingly, treatment of **4c** with an excess of BCl_3 (3 equiv., CH_2Cl_2, −50 °C, 1 h, −20 °C, 2 h) cleanly furnished the linear isomer **6c** contaminated with less than 10% of the angular isomer **5c** by NMR analysis. In the adopted procedure however, the mixture was not isolated, but treated directly with BBr_3 (3 equiv., room temp.) to effect demethylation and concomitant relactonisation. The mixture of **2** and **3** (GC ratio 1.0:10.5) thus obtained was separated by dry column flash chromatography[19] giving 6-allyl-7-hydroxycoumarin **3** (78% yield) together with the 8-allyl regioisomer **2** (8%). In the NMR spectrum of **3** the aromatic protons appeared as singlets at δ 7.08 and 7.22 indicating their *para*-relationship. Attempts to bias the regiocontrol further, utilising the greater steric bulk of the benzyl group of **4d**, were again thwarted by ready debenzylation of **4d** to **4a** on exposure to BCl_3.

In practice, conversion of 7-allyloxycoumarin **1** into pure 6-allyl-7-hydroxycoumarin **3**, *via* the methyl ether **4c**, can be carried out in 60% overall yield on a preparatively useful scale without separation of intermediates. A single recrystallisation is sufficient to furnish the desired product uncontaminated by its angular isomer (EtOAc–hexane, m.p. 145–148 °C, lit.,[13] 149 °C). This procedure complements the existing Claisen rearrangement approach to angular coumarin derivatives, and permits the efficient preparation of 6-allyl-7-hydroxycoumarin **3**, an important precursor to linear coumarins such as the furanocoumarin psoralen.[13]

As many natural linear coumarins are derived from 7-hydroxy-6-prenylcoumarin (demethylsuberosin **7**; prenyl = 3-methylbut-2-enyl), both *in vivo*[20] and synthetically,[2] we decided to investigate the application of this sequence to the synthesis of **7**. We were particularly concerned about the 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,[21] using conditions which were successful with 7-allyloxycoumarin **1** (NaOMe, MeOH, reflux), resulted in Claisen rearrangement to the undesired angular position prior to lactone cleavage. This could be circumvented by carrying out the cleavage on the prop-2-ynylic ether **8** which produced the coumaric ester **9a** in 93% yield [δ_H(300 MHz; $CDCl_3$) 2.68 (s), ≡CH] (Scheme 2). Methylation of the phenolic hydroxy group (MeI, K_2CO_3, acetone) gave **9b** (90%) and reduction of the acetylene moiety (Lindlar catalyst, H_2) furnished the desired methyl coumarate **10b** in 90% yield [δ_H(300 MHz; $CDCl_3$) 5.17 (1 H, dd, *J* 7, *J'* 1 Hz), 5.22 (1 H, dd, *J* 15, *J'* 1 Hz), 6.16 (1 H, dd, *J* 15, *J'* 7 Hz), 6.43 (1 H, d, *J* 16 Hz) and 7.90 (1 H, 16 Hz), vinylic protons] usually accompanied by *ca.* 6% of over-reduced material.

Attempted rearrangement of methyl coumarate **10b** under the above optimised conditions for methyl 4'-allyloxy-2'-methoxycinnamate **4c** (BCl_3, CH_2Cl_2, −50 °C) caused rapid cleavage of the 1,1-dimethylallyl ether moiety. However, after some investigation it was found that use of the milder reagent BF_3·OEt_2 under the same conditions resulted in the desired regioselective rearrangement to furnish **11b** [60%; δ_H(300 MHz; $CDCl_3$) 6.42 (1 H, s) and 7.22 (1 H, s) ArH] accompanied by a small quantity of the undesired isomer **12b** δ_H(300 MHz; $CDCl_3$: 6.69 (1 H, d, *J* 8.5 Hz) and 7.36 (1 H, d, *J* 8.5 Hz), ArH; GC ratio **11b**:**12b**, 10:1]. In contrast, methyl 4'-allyloxy(2'-methoxycinnamate **4c** 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



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

Scheme 2 *Reagents and conditions:* i, NaOMe, MeOH, reflux, 3 h; ii, H_3O^+ (**9a**); MeI, K_2CO_3, acetone, reflux (**9b**); $PhCH_2Br$, K_2CO_3, acetone (**9c**); iii, Lindlar cat., H_2; iv, BF_3·OEt_2 (2 equiv.), CH_2Cl_2, −60 °C; v, Ac_2O, pyridine, room temp.; vi, BCl_3 (4 equiv.), CH_2Cl_2, −50 °C; vii, $HOCH_2CH_2OH$, reflux

ether group of **11b** without also causing cyclisation of the prenyl group onto the *ortho*-hydroxy group. We therefore examined the behaviour of other substrates **10** possessing various phenol protecting groups in the presence of BF_3·OEt_2. The milder Lewis acid conditions did not cause relactonisation of the unprotected coumarate **10a** to the coumarin, but cleavage of the 1,1-dimethylallyl ether occurred to the exclusion of rearrangement. However, the benzyl ether **10c**, prepared from **9a** by sequential benzylation ($PhCH_2Br$, K_2CO_3, acetone reflux, 90%), and reduction with Lindlar catalyst (90%), was successfully rearranged to the desired product **11c** in 75% isolated yield [BF_3·OEt_2, CH_2Cl_2, −60 °C; δ_H(300 MHz; $CDCl_3$) 6.4 (1 H, s) and 7.35 (5 H, m), ArH] with none of the regioisomer **12c** 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 **11c** 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[22] it had been observed that phenyl acetates were stable to the conditions which had been used to debenzylate **11c**. Consequently, the free phenol of **11c** was acetylated (Ac_2O, pyridine, room temp., quantitative) and the product **11d** debenzylated, without loss of the acetoxy group (BCl_3, CH_2Cl_2, −50 °C) to furnish **11e** [95%; δ_H(300 MHz; $CDCl_3$) 2.31 (3 H, s, Ac) and 6.23 (1 H, br s, removed with D_2O, ArOH)]. This represents a very 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 **7** in quantitative yield,* possessing physical and spectroscopic data identical with those of an authentic sample.†

The sequence for the preparation of demethylsuberosin **7** herein described thus constitutes an efficient means of access to 7-oxygenated coumarins possessing side chains at C-6 derived from the prenyl unit and permits demethylsuberosin to be prepared readily in eight steps and 38% overall yield from umbelliferone.

Experimental

General Methods.—Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer 297 and 781 spectrometers. FTIR spectra were recorded on a Perkin-Elmer 1750 spectrometer. UV spectra were recorded on a Perkin-Elmer 555 spectrophotometer. 300 MHz ^{1}H NMR spectra of solutions in $CDCl_3$ or [$^2H_6$]acetone were recorded on a Bruker WH300 spectrometer. Each signal is described in terms of its chemical shift δ (downfield from tetramethylsilane), integral, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; qn, quintet; m, multiplet) and coupling constant (J given in Hz). Mass spectra were recorded on V.G. Micromass 16F and 30F spectrometers. The modes of ionisation used were electron impact (EI), in beam electron impact (IBEI), chemical ionisation (CI) and desorption chemical ionisation (DCI). Ammonia was the ionising source for the chemical ionisation. Flash column chromatography was performed using Kieselgel 60 silica (230–400 mesh, ASTA, 0.04–0.063 nm).[23] TLC was performed using Merck Kieselgel 60 F_{254} plates, which were first observed by UV (254 and 366 nm) and then stained with iodine vapour. Solvents for extractions and chromatography were distilled otherwise reagent grades were used and all starting materials and reagents were purchased from the Aldrich Chemical Company.

Methyl 4'-Allyloxy-2'-hydroxycinnamate **4a**.—7-Allyloxycoumarin **1** (4.0 g, 19.8 mmol) was added to a freshly prepared solution of sodium methoxide (1.28 g, 23.7 mmol) (made by dissolving 0.63 g of sodium in 150 cm^3 of magnesium dried methanol) and refluxed for 3 h under nitrogen. The cooled solution was then carefully neutralised with 2 mol dm^{-3} HCl and the resulting precipitate extracted into ethyl ethanoate (100 cm^3), brought to neutrality with brine and then dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure afforded methyl 4'-allyloxy-2'-hydroxycinnamate **4a**, which crystallised from ethyl ethanoate–hexane as needles, m.p. 146–148 °C (Found: C, 66.8; H, 6.1. $C_{13}H_{14}O_4$ requires C, 66.66; H, 6.02%); δ_H([$^2H_6$]acetone) 3.72 (3 H, s), 4.57 (2 H, d, J 5), 5.25 (1 H, dd, J 1.5, 10), 5.50 (1 H, dd, J 1.5, 17), 6.05 (1 H, m), 6.48 (1 H, d, J 16), 6.52 (2 H, m), 7.53 (1 H, d, J 8.5), 7.93 (1 H, d, J 16) and 9.25 (1 H, br s); ν_{max}($CHCl_3$)/cm^{-1} 3590, 1700 and 1611; λ_{max}(CCl_4)/nm 287sh, 292 and 320 ($\log_{10}\varepsilon$ 4.01, 4.06 and 4.13); m/z (IBEI) 234 (M$^+$, 50%), 202 (37), 174 (19), 162 (10), 133 (61) and 105 (13).

Methyl 2'-Acetoxy-4'-allyloxycinnamate **4b**.—Methyl 4'-allyloxy-2'-hydroxycinnamate **4a** (5.20 g, 22.2 mmol) was dissolved in a mixture of acetic anhydride (5 cm^3) and pyridine (10 cm^3) and stirred under nitrogen for 3 h. Evaporation to dryness under reduced pressure afforded methyl 2'-acetoxy-4'-allyloxycinnamate **4b** (6.04 g, 99%) which crystallised from chloroform–hexane as needles, m.p. 54–57 °C (Found: C, 65.0; H, 5.8. $C_{15}H_{16}O_5$ requires C, 65.22; H, 5.84%); δ_H($CDCl_3$) 2.38 (3 H, s), 3.80 (3 H, s), 4.56 (2 H, d, J 5), 5.32 (1 H, dd, J 1.5, 10.5), 5.42 (1 H, dd, J 1.5, 17), 6.03 (1 H, m), 6.35 (1 H, d, J 16), 6.68 (1 H, d, J 2.5), 6.83 (1 H, dd, J 2.5, 8.5), 7.57 (1 H, d, J 8.5) and 7.68 (1 H, d, J 16); ν_{max}($CHCl_3$)/cm^{-1} 1767, 1711, 1634 and 1613; λ_{max}(EtOH)/nm 206, 229 and 302 ($\log_{10}\varepsilon$ 3.91, 3.90 and 4.17); m/z (IBEI) 276 (M$^+$, 100%), 234 (69) and 203 (42).

Methyl 4'-Allyloxy-2'-methoxycinnamate **4c**.—Methyl 4'-allyloxy-2'-hydroxycinnamate **4a** (4.0 g, 17.1 mmol) was added to a stirred suspension of anhydrous potassium carbonate (3.45 g, 25 mmol) in acetone (70 cm^3) under nitrogen and then left to stand for 30 min. Methyl iodide (3.5 g, 25 mmol) was added in one portion to it and the mixture refluxed for 5 h. After filtration and evaporation of the solvent under reduced pressure the residue was dissolved in ethyl ethanoate (100 cm^3), washed with 2 mol dm^{-3} potassium carbonate (2 × 30 cm^3), then brine to neutrality and dried over anhydrous magnesium sulfate. Evaporation of the solvent under reduced pressure afforded methyl 4'-allyloxy-2'-methoxycinnamate **4c** (4.07 g, 96%) which crystallised from ethyl ethanoate–hexane as needles, m.p. 65–67 °C (Found: C, 67.9; H, 6.6. $C_{14}H_{16}O_4$ requires C, 67.73; H, 6.5%); δ_H($CDCl_3$) 3.78 (3 H, s), 3.87 (3 H, s), 4.57 (2 H, d, J 7.5), 5.32 (1 H, dd, J 1.5, 10), 5.43 (1 H, dd, J 1.5, 17), 6.05 (1 H, m), 6.43 (1 H, d, J 16), 6.50 (2 H, m), 7.42 (1 H, d, J 8.5) and 7.90 (1 H, d, J 16); ν_{max}($CHCl_3$)/cm^{-1} 1702, 1628 and 1609; ν_{max}(CCl_4)/nm 284, 293 and 324 ($\log_{10}\varepsilon$ 4.13, 4.16 and 4.23); m/z (IBEI) 248 (M$^+$, 100%), 217 (41), 208 (29), 177 (23) and 147 (36).

Thermal Claisen Rearrangement of Methyl 4'-Allyloxy-2'-methoxycinnamate **4c**.—Methyl 4'-allyloxy-2'-methoxycinnamate **4c** (0.47 g, 1.89 mmol) was dissolved in diethylaniline (20 cm^3) and the solution refluxed (217 °C) for 5 h under nitrogen when no starting material was observed by TLC (diethyl ether). After cooling, diethyl ether was added (150 cm^3) and the solution washed with 2 mol dm^{-3} hydrochloric acid (5 × 50 cm^3) then with brine to neutrality and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure followed by flash chromatography (diethyl ether–pentane, 1:2) afforded methyl 5'-allyl-4'-hydroxy-2'-methoxycinnamate **6c** (0.29 g, 61%) and methyl 3'-allyl-4'-hydroxy-2'-methoxycinnamate **5c** (0.12 g, 25%). **6c** Was crystallised from ethyl ethanoate–hexane, m.p. 111–114 °C (Found: C, 68.1; H, 6.5. $C_{14}H_{16}O_4$ requires C, 67.73; H, 6.50%); δ_H([$^2H_6$]acetone) 3.32 (2 H, d, J 5), 3.71 (3 H, s), 3.84 (3 H, s), 5.00 (1 H, dd, J 1.5, 10.5), 5.07 (1 H, dd, J 1.5, 17), 6.00 (1 H, m), 6.37 (1 H, d, J 16), 6.57 (1 H, s), 7.39 (1 H, s), 7.87 (1 H, d, J 16) and 8.92 (1 H, br s); ν_{max}(KBr disc)/cm^{-1} 3290, 1688, 1624 and 1611; λ_{max}(EtOH)/nm 202, 219, 244, 295 and 336 ($\log_{10}\varepsilon$ 4.12, 4.04, 4.03, 4.01 and 4.18); m/z (NH_3, DCI) 249 (M$^+$ + 1, 100%), 248 (M$^+$, 14) and 209 (22). **5c** Was also crystallised from ethyl ethanoate–hexane, m.p. 87–88 °C (Found: C, 68.1; H, 6.6. $C_{14}H_{16}O_4$ requires C, 67.73; H, 6.50%); δ_H([$^2H_6$]acetone) 3.42 (2 H, d, J 7.5), 3.73 (3 H, s), 3.74 (3 H, s), 4.96 (1 H, dd, J 1.5, 10.5), 5.03 (1 H, dd, J 1.5, 17), 6.02 (1 H, m), 6.39 (1 H, d, J 16), 6.75 (1 H, d, J 8.5), 7.46 (1 H, d, J 8.5), 7.86 (1 H, d, J 16) and 9.17 (1 H, s); ν_{max}($CHCl_3$)/cm^{-1} 3600, 1715, 1640 and 1610; λ_{max}(EtOH) 204, 222, 242, 252, 296sh and 328 ($\log_{10}\varepsilon$ 4.17, 4.07, 3.59, 3.49, 3.70 and 3.97); m/z (NH_3, DCI) 249 (M$^+$ + 1, 100%), 248 (M$^+$, 61), 217 (57) and 203 (32).

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

† We thank Dr. R. D. H. Murray, Glasgow University, for a generous gift of authentic demethylsuberosin **7**. In the NMR spectrum of **7** the chemical shift of 8-H was found to be concentration dependent and spectra recorded on mixtures of synthetic and authentic samples showed coincidence of all peaks at various concentrations.

BCl_3 *Catalysed Rearrangement of Methyl 4'-Allyloxy-2'-methoxycinnamate* **4c** *with Subsequent* BBr_3 *Demethylation and Relactonisation.*—Boron trichloride (1.40 g, 12 mmol, 12 cm^3 of a 1.0 mol dm^{-3} solution in dichloromethane was added dropwise to a stirred solution of methyl 4'-allyloxy-2'-methoxycinnamate **4c** (1.0 g, 4.0 mmol) in dichloromethane (100 cm^3) at −50 °C under nitrogen and then left to stand for 1 h. The mixture was then allowed to warm to −20 °C and left for a further 2 h whereupon no starting material remained by TLC analysis (Et_2O). Boron tribromide (2.5 g, 10 mmol, 10 cm^3 of a 1.0 mol dm^{-3} solution in dichloromethane) was added dropwise to the mixture at −20 °C and left for 1 h. The mixture was then allowed to warm to 20 °C and left for a further 5 h. It was then poured into ice–water, extracted with ethyl ethanoate (50 cm^3), washed with saturated sodium hydrogen carbonate (3 × 30 cm^3), brought to neutrality with brine and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure followed by flash chromatography (diethyl ether–pentane, 1:2) afforded 6-allyl-7-hydroxycoumarin **3** (0.63 g, 78%) and 8-allyl-7-hydroxycoumarin **2** (0.07 g, 8%). **3** was crystallised from ethyl ethanoate–hexane, m.p. 145–148 °C, (lit.,[13] 149 °C); $\delta_H(CDCl_3)$ 3.44 (2 H, d, *J* 7.5), 6.03 (1 H, m), 6.23 (1 H, d, *J* 9.5), 7.08 (1 H, s), 7.22 (1 H, s), 7.66 (1 H, d, *J* 9.5) and 7.78 (1 H, br s); ν_{max}(KBr disc)/cm^{-1} 3220, 1705, 1624 and 1609; λ_{max}(EtOH)/nm 206, 221, 246, 256 and 332 ($\log_{10}\varepsilon$ 4.36, 4.16, 3.58, 3.51 and 4.16); *m/z* (EI) 202 (M^+, 100%), 174 (33) and 147 (10). **2** was also crystallised from ethyl ethanoate–hexane, m.p. 164–165 °C (lit.,[24] 165 °C) $\delta_H(CDCl_3)$ 3.68 (2 H, d, *J* 7.0), 5.17 (2 H, m), 6.02 (1 H, m), 6.24 (1 H, d, *J* 9.5), 6.39 (1 H, br s), 6.82 (1 H, d, *J* 8), 7.25 (1 H, d, *J* 8) and 7.63 (1 H, d, *J* 9.5); ν_{max}(KBr disc)/cm^{-1} 3180, 1687, 1625 and 1604; λ_{max}(EtOH)/nm 206, 216sh, 243, 254 and 326 ($\log_{10}\varepsilon$ 4.23, 4.01, 3.43, 3.39 and 4.08); *m/z* (EI) 202 (M^+, 100%), 187 (50), 174 (27), 162 (63) and 134 (37).

7-O-(1,1-*Dimethylprop*-2-*ynyl*)*umbelliferone* **8**.—Prepared by the method of Murray *et al.*[21] Starting materials: umbelliferone (7-hydroxycoumarin) (2.5 g, 15.4 mmol), 3-chloromethyl-3-but-1-yne (6.12 g, 60 mmol), potassium carbonate (13.8 g, 100 mmol) acetone (150 cm^3), refluxed for 8 h (sodium iodide omitted). The product, 7-*O*-(1,1-dimethylprop-2-ynyl)umbelliferone **8** (2.67 g, 76%) crystallised from ethanol as light yellow plates, m.p. 136–139 °C (lit.,[21] 136–140 °C); $\delta_H(CDCl_3)$ 1.72 (6 H, m), 2.68 (1 H, s), 6.30 (1 H, d, *J* 9.5), 7.06 (1 H, dd, *J* 2.5, 8.5), 7.33 (1 H, d, *J* 2.5), 7.37 (1 H, d, *J* 8.5) and 7.65 (1 H, d, *J* 9.5); $\nu_{max}(CHCl_3)$/cm^{-1} 3304, 1730 and 1614; λ_{max}(EtOH)/nm 204, 213sh, 239, 250, 297sh and 319 ($\log_{10}\varepsilon$ 4.18, 3.99, 3.40, 3.36, 3.81 and 3.95); *m/z* (EI) 228 (M^+, 8%) 213 (40), 162 (100) and 134 (51).

Methyl 4'-(1,1-*Dimethylprop*-2-*ynloxy*)-2'-*hydroxycinnamate* **9a**.—Prepared by the method given above for **4a**. Starting materials: 7-*O*-(1,1-dimethylprop-2-ynyl)umbelliferone **8** (3.0 g, 13.2 mmol), sodium methoxide (3.51 g, 65 mmol), refluxed for 3 h (no longer). The product, methyl 4'-(1,1-dimethylprop-2-ynyloxy)-2'-hydroxycinnamate **9a** (3.18 g, 93%), crystallised as needles from ethyl ethanoate–hexane, m.p. 127.5–129 °C (Found: C, 69.1; H, 6.35. $C_{15}H_{16}O_4$ requires C, 69.22; H, 6.20%); $\delta_H(CDCl_3)$ 1.67 (6 H, s), 2.62 (1 H, s), 3.83 (3 H, s), 6.53 (1 H, d, *J* 6), 6.67 (1 H, br s), 6.73 (1 H, d, *J* 2.5), 6.80 (1 H, dd, *J* 2.5, 8.5), 7.37 (1 H, d, *J* 8.5) and 7.97 (1 H, d, *J* 16); $\nu_{max}(CHCl_3)$/cm^{-1} 3590, 3305, 1698 and 1608; λ_{max}(EtOH)/nm 202, 218, 236, 290 and 326 ($\log_{10}\varepsilon$ 4.12, 3.99, 3.81, 4.04 and 4.09); *m/z* (EI) 260 (M^+, 12%), 245 (28), 213 (52), 194 (35), 162 (100) and 134 (74).

Methyl 4'-(1,1-*Dimethylprop*-2-*ynyloxy*)-2'-*methoxycinnamate* **9b**.—Prepared by the method given above for methyl 4'-(1,1-dimethylprop-2-ynyloxy)-2'-hydroxycinnamate **9a** (2.15 g, 8.27 mmol), potassium carbonate (2.76 g, 20 mmol), methyl iodide (2.84 g, 20 mmol), refluxed for 3 h. The product methyl 4'-(1,1-dimethylprop-2-ynyloxy)-2'-methoxycinnamate **9b** (2.16 g, 95%), crystallised from ethyl ethanoate–hexane as needles, m.p. 133–135 °C (Found: C, 70.4; H, 6.8. $C_{16}H_{18}O_4$ requires C, 70.06; H, 6.61%); $\delta_H(CDCl_3)$ 1.69 (6 H, s), 2.68 (1 H, s), 3.79 (3 H, s), 3.86 (3 H, s), 6.45 (1 H, d, *J* 16), 6.78 (1 H, d, *J* 2.5), 6.87 (1 H, dd, *J* 2.5, 8.5), 7.40 (1 H, d, *J* 8.5) and 7.92 (1 H, d, *J* 16); $\nu_{max}(CHCl_3)$/cm^{-1} 3302, 1702, 1627 and 1604; λ_{max}(EtOH)/nm 202, 210, 235, 286sh, 289 and 325 ($\log_{10}\varepsilon$ 4.02, 4.00, 3.93, 3.98, 3.98 and 4.04); *m/z* (EI) 274 (M^+, 2%), 162 (100) and 134 (61).

Methyl 4'-(1,1-*Dimethylallyloxy*)-2'-*methoxycinnamate* **10b**.—Methyl 4'-(1,1-dimethylprop-2-ynyloxy)-2'-methoxycinnamate **9b** (0.67 g, 2.4 mmol) was dissolved in ethyl ethanoate (50 cm^3) and Lindlar catalyst (0.03 g) was added to it. The mixture was stirred under hydrogen at ambient temperature and pressure until 1 mol equiv. of hydrogen had been taken up (2 h). Filtration and evaporation of the solvent afforded methyl 4'-(1,1-dimethylallyloxy)-2'-methoxycinnamate **10b** (0.61 g, 91%) as a colourless oil (Found: C, 69.9; H, 7.35. $C_{16}H_{20}O_4$ requires C, 69.55; H, 7.30%); $\delta_H(CDCl_3)$ 1.52 (6 H, s), 3.78 (3 H, s), 3.83 (3 H, s), 5.18 (1 H, d, *J* 7), 5.22 (1 H, d, *J* 15), 6.16 (1 H, dd, *J* 7, 15), 6.43 (1 H, d, *J* 16), 6.55 (1 H, d, *J* 2.5), 6.60 (1 H, dd, *J* 2.5, 8.5), 7.33 (1 H, d, *J* 8.5) and 7.90 (1 H, d, *J* 16); $\nu_{max}(CHCl_3)$/cm^{-1} 1702, 1622 and 1601; λ_{max}(EtOH)/nm 203, 210sh, 236, 292 and 325 ($\log_{10}\varepsilon$ 4.39, 4.30, 4.24, 4.26 and 4.37); *m/z* (NH_3, CI) 277 (M^+ + 1, 100%), 231 (25), 209 (58), 208 (29), 177 (15) and 163 (10).

BF_3·OEt_2 *Catalysed Claisen Rearrangement of Methyl* 4'-(1,1(*Dimethylallyloxy*)-2'-*methoxycinnamate* **10b**.—Boron trifluoride–diethyl ether (1.42 g, 10 mmol) was added dropwise to a stirred solution of methyl 4'-(1,1-dimethylallyloxy)-2'-methoxycinnamate **10b** (1.0 g, 3.6 mmol) in dichloromethane (20 cm^3) at −50 °C under nitrogen and then left to stand for 2 h. The solution was quenched with methanol (10 cm^3) at −50 °C and then allowed to warm to room temperature. Diethyl ether (100 cm^3) was added to it and the solution washed with saturated aqueous sodium hydrogen carbonate (3 × 20 cm^3), brought to neutrality with brine and then dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure followed by flash chromatography (diethyl ether–pentane, 1:2) afforded methyl 4'-hydroxy-2'-methoxy-5'(3-methylbut-2-enyl)cinnamate **11b** (0.60 g, 60%) and methyl 4'-hydroxy-2'-methoxy-3'-(3-methylbut-2-enyl)cinnamate **12b** (0.06 g, 6%). **11b** was crystallised from diethyl ether–pentane as needles, m.p. 107–109 °C (Found: C, 69.8; H, 7.3. $C_{16}H_{20}O_4$ requires C, 69.55; H, 7.30%); $\delta_H(CDCl_3)$ 1.78 (6 H, s), 3.28 (2 H, d, *J* 7.5), 3.77 (3 H, s), 3.80 (3 H, s), 5.28 (1 H, br t, *J* 7.5), 6.05 (1 H, br s), 6.40 (1 H, d, *J* 16), 6.42 (1 H, s), 7.22 (1 H, s) and 7.88 (1 H, d, *J* 16); $\nu_{max}(CHCl_3)$/cm^{-1} 3590 (OH-π), 3430, 1699 and 1615; λ_{max}(EtOH)/nm 202, 242, 296 and 337 ($\log_{10}\varepsilon$ 4.02, 3.70, 3.63 and 3.81); *m/z* (NH_3, CI) (M^+ + 1, 100%), 276 (M^+, 11) and 221 (10). **12b** was also crystallised from diethyl ether–pentane as needles, m.p. 94–96 °C (Found: C, 69.8; H, 7.2. $C_{16}H_{20}O_4$ requires C, 69.55; H, 7.30%); $\delta_H(CDCl_3)$ 1.75 (3 H, s), 1.83 (3 H, s), 3.43 (2 H, d, *J* 7.5), 3.73 (3 H, s), 3.81 (3 H, s), 5.23 (1 H, br t, *J* 7.5), 6.07 (1 H, br s), 6.37 (1 H, d, *J* 16), 6.69 (1 H, d, *J* 8.5), 7.36 (1 H, d, *J* 8.5) and 7.90 (1 H, d, *J* 16); $\nu_{max}(CHCl_3)$/nm 3590 (OH-π), 3420, 1701, 1630 and 1595; λ_{max}(EtOH)/nm 201, 214sh, 240 and 316 ($\log_{10}\varepsilon$ 4.12, 4.00, 3.89 and 4.07); *m/z* (NH_3, CI) (M^+ + 1, 100%) and 276 (M^+, 14).

Methyl 2'-*Benzyloxy*-4'-(1,1-*dimethylprop*-2-*ynloxy*)cinnamate **9c**.—Prepared by the method given above for **9b**. Starting materials: methyl 4'-(1,1-dimethylprop-2-ynyloxy)-2'-hydroxycinnamate **9a** (2.69 g, 10.3 mmol), potassium carbonate (2.07 g, 15 mmol), benzyl bromide (2.56 g, 15 mmol), acetone

(150 cm), refluxed for 6 h. Flash chromatography (diethyl ether–pentane, 1:2) afforded methyl 2'-benzyloxy-4'-(1,1-dimethylprop-2-ynyloxy)cinnamate **9c** (3.26 g, 90%) as a yellow oil (Found: C, 75.4; H, 6.5. $C_{22}H_{22}O_4$ requires C, 75.41; H, 6.33%); $\delta_H(CDCl_3)$ 1.61 (6 H, s), 2.51 (1 H, s), 3.77 (3 H, s), 5.14 (2 H, s), 6.46 (1 H, d, *J* 16), 6.82 (2 H, m), 7.35 (6 H, m) and 7.99 (1 H, d, *J* 16); $\nu_{max}(CHCl_3)/cm^{-1}$ 3310, 1705, 1630 and 1605; λ_{max}(EtOH)/nm 212, 235, 287 and 323 ($\log_{10}\varepsilon$ 4.17, 3.91, 3.94 and 3.98); *m/z* (EI) 350 (M^+, 2.5%), 198 (5), 162 (8), 134 (6) and 91 (100).

Methyl 2'-Benzyloxy-4'-(1,1-dimethylallyloxy)cinnamate **10c**.—Prepared by the method given above for **10b**. Starting materials: methyl 2'-benzyloxy-4'-(1,1-dimethylprop-2-ynyloxy)cinnamate **9c** (1.05 g, 3.0 mmol), Lindlar catalyst (0.05 g), ethyl ethanoate (100 cm^3), stirred until 1 mol equiv. of hydrogen had been taken up (2 h). The product methyl 2'-benzyloxy-4'-(1,1-dimethylallyloxy)cinnamate **10c** (0.95 g, 90%), was obtained as a colourless oil (Found: C, 74.9; H, 6.8. $C_{22}H_{24}O_4$ requires C, 74.98; H, 6.86%); $\delta_H(CDCl_3)$ 1.42 (6 H, s), 3.78 (3 H, s), 5.12 (2 H, s), 5.15 (2 H, m), 6.10 (1 H, dd, *J* 10, 17), 6.43 (1 H, d, *J* 16), 6.58 (2 H, m), 7.37 (6 H, m) and 8.00 (1 H, d, *J* 16); $\nu_{max}(CHCl_3)/cm^{-1}$ 1701, 1625 and 1602; λ_{max}(EtOH)/nm 202, 238, 291 and 326 ($\log_{10}\varepsilon$ 4.44, 4.16, 4.20 and 4.27); *m/z* (NH_3, CI) 353 ($M^+ + 1$, 100%), 285 (54) and 91 (23).

BF_3·OEt_2 *Catalysed Claisen Rearrangement of Methyl 2'-Benzyloxy-4'-(1,1-dimethylallyloxy)cinnamate* **10c**.—Boron trifluoride–diethyl ether (0.43 g, 3.0 mmol) was added dropwise to a stirred solution of methyl 2'-benzyloxy-4'-(1,1-dimethylallyloxy)cinnamate **10c** (0.54 g, 1.5 mmol) in dichloromethane (20 cm^3) under nitrogen at −50 °C and then left to stand for 2 h. The solution was quenched with methanol (10 cm^3) at −50 °C and then allowed to warm to room temperature. Diethyl ether (50 cm^3) was added to it and the solution was washed with saturated sodium hydrogen carbonate (3 × 20 cm^3), brought to neutrality with brine and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure followed by flash chromatography (diethyl ether–pentane, 1:2) afforded methyl 2'-benzyloxy-4'-hydroxy-5'-(3-methylbut-2-enyl)cinnamate **11c** (0.41 g, 75%) which crystallised as needles, m.p. 114–117 °C (Found: C, 75.0; H, 7.0. $C_{22}H_{24}O_4$ requires C, 74.98; H, 6.86%); $\delta_H(CDCl_3)$ 1.80 (6 H, s), 3.30 (2 H, d, *J* 7.5), 3.78 (3 H, s), 5.12 (2 H, s), 5.30 (1 H, br t, *J* 7.5), 5.53 (1 H, br s), 6.43 (1 H, d, *J* 16), 6.44, (1 H, s), 7.35 (5 H, m), 7.38 (1 H, s) and 7.98 (1 H, d, *J* 16); $\nu_{max}(CHCl_3)/cm^{-1}$ 3590 (OH-π), 3420, 1700 and 1613; λ_{max}(EtOH)/nm 203, 245, 296 and 337 ($\log_{10}\varepsilon$ 4.33, 4.00, 3.88 and 4.05); *m/z* (NH_3, DCI) 353 ($M^+ + 1$, 100%), 352 (M^+, 10), 263 (26), 231 (10), 108 (13) and 91 (15).

Methyl 4'-Acetoxy-2'-benzyloxy-5'-(3-methylbut-2-enyl)cinnamate **11d**.—Methyl 2'-benzyloxy-4'-hydroxy-5'-(3-methylbut-2-enyl) cinnamate **11c** (0.15 g, 0.4 mmol) was dissolved in a mixture of acetic anhydride (0.1 g, 1.0 mmol) and pyridine (0.12 g, 1.5 mmol) in dichloromethane (10 cm^3) and stirred at 20 °C for 3 h under nitrogen. Evaporation to dryness afforded methyl 4'-acetoxy-2'-benzyloxy-5'-(3-methylbut-2-enyl)cinnamate **11d** (0.16 g, 98%) which crystallised as needles from ethyl ethanoate–hexane, m.p. 105–107 °C (Found: C, 73.3; H, 6.6. $C_{24}H_{26}O_5$ requires C, 73.08; H, 6.64%); $\delta_H(CDCl_3)$ 1.72 (3 H, s), 1.78 (3 H, s), 2.32 (3 H, s), 3.17 (2 H, d, *J* 7.5), 3.82 (3 H, s), 5.10 (2 H, s), 5.20 (1 H, br t, *J* 7.5), 6.50 (1 H, d, *J* 16), 6.68 (1 H, s), 7.35 (1 H, s), 7.40 (5 H, m) and 7.98 (1 H, d, *J* 16); $\nu_{max}(CHCl_3)/cm^{-1}$ 1761, 1705, 1631 and 1611; λ_{max}(EtOH)/nm 204, 218sh, 276 and 319 ($\log_{10}\varepsilon$ 4.63, 4.43, 4.11 and 3.98); *m/z* (NH_3, DCI) 395 ($M^+ + 1$, 100%), 305 (20) and 91 (13).

Methyl 4'-Acetoxy-2'-hydroxy-5'-(3-methylbut-2-enyl)cinnamate **11e**.—Boron trichloride (0.18 g, 1.5 mmol, 1.5 cm^3 of a 1 mol dm^{-3} solution in dichloromethane) was added dropwise over 5 min to a stirred solution of methyl 4'-acetoxy-2'-benzyloxy-5'-(3-methylbut-2-enyl)cinnamate **11d** (0.11 g, 0.3 mmol) in dichloromethane (15 cm^3) at −50 °C under nitrogen and then left to stand for 1 h. The mixture was then quenched at −50 °C with methanol (5 cm^3), poured into ice–water, extracted with ethyl ethanoate (2 × 25 cm^3), washed with saturated sodium hydrogen carbonate (3 × 15 cm^3), brought to neutrality with brine and then dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure followed by flash chromatography (diethyl ether) afforded methyl 4'-acetoxy-2'-hydroxy-5'-(3-methylbut-2-enyl)cinnamate **11e** (0.08 g, 95%) which crystallised from ethyl ethanoate–hexane as needles, m.p. 128.5–130 °C (Found: C, 67.2; H, 6.6. $C_{17}H_{20}O_5$ requires C, 67.10; H, 6.62%); $\delta_H(CDCl_3)$ 1.70 (3 H, s), 1.76 (3 H, s) 2.31 (3 H, s), 3.16 (2 H, d, *J* 7.5), 3.81 (3 H, s), 5.18 (1 H, br t, *J* 7.5 Hz), 6.23 (1 H, br s, removed with D_2O), 6.53 (1 H, d, *J* 16), 6.55 (1 H, s), 7.29 (1 H, s) and 7.87 (1 H, d, *J* 16); $\nu_{max}(CHCl_3)/cm^{-1}$ 3590, 1760, 1705, 1632 and 1613; λ_{max}(EtOH)/nm 204, 212sh, 277 and 318 ($\log_{10}\varepsilon$ 4.38, 4.27, 3.93 and 3.79); *m/z* (NH_3, CI) 305 ($M^+ + 1$, 100%), 304 (M^+, 14), 274 (17), 262 (26), 249 (14), 231 (13) and 175 (20).

Demethylsuberosin [*Hydroxy-6-(3-methylbut-2-enyl)coumarin*] **7**.—Methyl 4'-acetoxy-2'-hydroxy-5'-(3-methylbut-2-enyl)cinnamate **11e** (0.032 g, 0.11 mmol) was dissolved in ethylene glycol (5 cm^3) and refluxed for 4 h under nitrogen. Diethyl ether (25 cm^3) was added to the cooled solution which was then washed with water (5 × 10 cm^3) and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure afforded demethylsuberosin **7** (0.023 g, 95%) which crystallised from ethyl ethanoate–hexane as needles, m.p. 133–135 °C (lit.,[21] 133.5–134 °C); $\delta_H(CDCl_3)$ 1.77 (3 H, br s), 1.80 (3 H, br s), 3.69 (2 H, br d, *J* 7), 5.33 (1 H, br t, *J* 7), 6.24 (1 H, d, *J* 9.5), 6.61 (1 H, br s removed with D_2O), 6.92 (1 H, s), 7.20 (1 H, s) and 7.64 (1 H, d, *J* 9.5); $\nu_{max}(CHCl_3)/cm^{-1}$ 3580, 1722 and 1628; λ_{max}(EtOH)/nm 204, 212sh, 277 and 319 ($\log_{10}\varepsilon$ 4.23, 4.08, 3.76 and 3.62); *m/z* (NH_3, CI) 231 ($M^+ + 1$, 100%) and 175 (8).

Acknowledgements

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