Access to Phenolic Fungal Metabolites *via* the Acid-catalysed Claisen Rearrangement. The Total Synthesis of (±)-Mellein, Aurocitrin, and 5',6'-Dihydroaurocitrin

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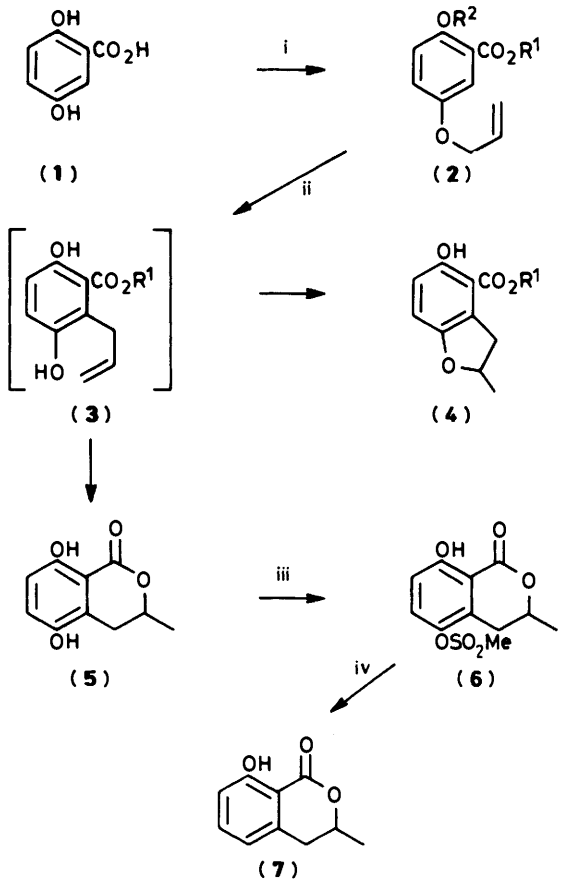
Regioselective trifluoroacetic acid catalysed rearrangement of allyl 5-allyloxy-2-hydroxybenzoate (2b) with concomitant cyclisation of the initial product permits the simple preparation of 3,4-dihydro-5,8-dihydroxy-3-methylisocoumarin (**5**). Hydrogenolysis of the non-hydrogen bonded hydroxy group yields (±)-mellein (**7**) whereas elaboration of the lactone moiety of compound (**5**) provides access to aurocitrin (**8b**) and its side chain analogues.

Our previous studies[1,2] on the mechanism and regioselectivity of the trifluoroacetic acid catalysed Claisen rearrangement[3] of esters of 5-allyloxy-2-hydroxybenzoic acid (**2a**) have shown that in all cases the initial rearrangement of this system occurs with complete regiospecificity to the more sterically congested position *ortho* to the ester substituent. Under the reaction conditions the initially formed products (**3**) suffered concomitant acid catalysed cyclisation involving either the ester group, to form the dihydroisocoumarin (**5**), or the newly formed phenolic hydroxy group, to form the dihydrobenzofurans (**4**)[1] (Scheme 1).

The ready accessibility of dihydroisocoumarin (**5**) from 2,5-dihydroxybenzoic acid suggested it as a key precursor in the synthesis of several naturally occurring phenolic compounds. The dihydroisocoumarin (**5**) has itself been identified in extracts of Brazilian wood infected by fungi;[4] the structurally similar mellein (**7**) which, as its (*R*)-antipode, is a metabolite of *Aspergillus melleus*[5] and *Septoria nodorum*[6] and has been proposed as the active agent in promoting stomatal resistance of rice,[6,7] occurs more widely. (*R*)-Mellein is also a constituent of the mandibular secretion of carpenter ants (*Camponotus*)[8] and may have pheromonal properties, at least in *C. pennsylvanicus*.[9] Prior to our work racemic mellein had been synthesised several times, but *via* lengthy[10] sequences or from complex reagents and starting materials.[11] [Since the initial communication reporting our work,[1] an asymmetric synthesis of the methyl ether of (*R*)-mellein with an enantiomeric excess of 53% has been reported.[12]]

Aurocitrin (**8b**) is produced by the fungus *Hypocrea citrina* and inhibits *Staphylococcus aureus* at concentrations of less than 1 p.p.m.[13] At the commencement of our work the proposed structure (**8b**) was based on spectroscopic data,[13] but was later confirmed by total synthesis[14] following a different approach from our own. It was envisaged that the isocoumarin (**5**), possessing the required substitution pattern, would constitute a valid synthetic precursor to aurocitrin and its side chain analogues.

The dihydroisocoumarin (**5**) was readily prepared in two steps from 2,5-dihydroxybenzoic acid (**1**) *via* the allyl 5-allyloxy-2-hydroxybenzoate (**2b**). The ester (**2b**) was obtained in near quantitative yield by refluxing compound (**1**) with allyl bromide (2 equiv.) in acetone in the presence of an excess of anhydrous potassium carbonate under nitrogen (Scheme 1). The acid catalysed rearrangement of the ester (**2b**) in refluxing trifluoroacetic acid gave the required dihydroisocoumarin (**5**) in 41% recrystallised yield accompanied by the dihydrobenzofuran (**4b**) (14%). The overall yield of compound (**5**) from 2,5-dihydroxybenzoic acid was 35—40%. The conversion of compound (**5**) into mellein took advantage of the large difference in acidity between the 5-hydroxy and the hydrogen bonded 8-hydroxy groups. It was possible to prepare the 5-methanesulphonate (**6**) in quantitative yield by treatment of compound (**5**) with methanesulphonyl chloride in pyridine at 60 °C. The i.r. spectrum of the crude product showed only one carbonyl absorption at 1 680 cm^{-1}, corresponding to the



a; $R^1 = R^2 = H$
b; $R^1 = CH_2CH{=}CH_2$, $R^2 = H$
c; $R^1 = R^2 = CH_2CH{=}CH_2$

Scheme 1. *Reagents:* i, $CH_2{=}CHCH_2Br$ (2 equiv.), K_2CO_3, acetone, reflux; ii, CF_3CO_2H, reflux; iii, CH_3SO_2Cl, pyridine, 60 °C; iv, H_2 (1 atm), Pd–C, Et_3N, MeOH, reflux

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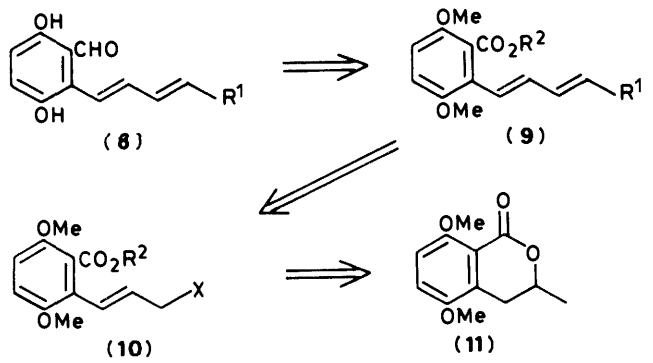


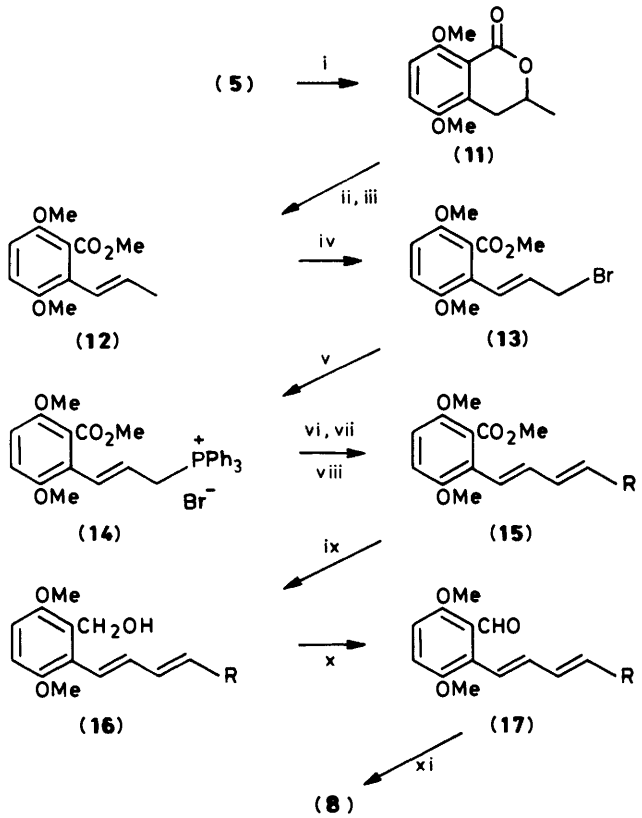
a; $R^1 = (CH_2)_6CH_3$
b; $R^1 = CH{=}^tCH(CH_2)_4CH_3$

Scheme 2.

hydrogen bonded lactone. This material was then quantitatively converted into (±)-mellein (**7**) by hydrogenation over 5% palladium-on-carbon in refluxing methanol containing triethylamine.[15] The overall yield of (±)-mellein from 2,5-dihydroxybenzoic acid was thus 35%.

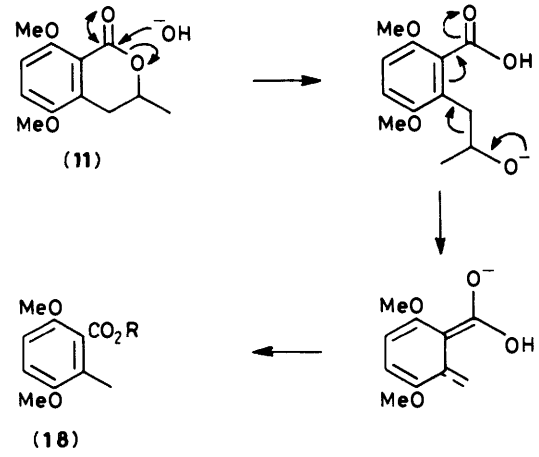
We next turned our attention to the synthesis of aurocitrin (**8b**) following the retrosynthetic rationale outlined in Scheme 2. It was proposed that aurocitrin would be available from a protected triene ester (**9b**) which in turn could be constructed by a Wittig condensation between (**10**; X = PPh_3) and octenal, the stabilised ylide favouring *E*-geometry of the newly formed double bond.[16] The system (**10**; X = Br) was to be prepared from the *O*-protected dihydroisocoumarin (**11**) *via* base-induced eliminative cleavage of the lactone, a reaction with direct precedent from degradation studies on mellein.[17]

Dimethylation of dihydroisocoumarin (**5**) with dimethyl sulphate–potassium carbonate required long reaction times (8 days) and the use of butan-2-one as solvent instead of acetone to permit elevated reaction temperatures. Under these conditions the protected material (**11**) could be obtained in moderate yield (Scheme 3). The attempted cleavage of compound (**11**) using powdered potassium hydroxide at 140 °C, followed by methylation of the crude acid mixture with diazomethane, gave low and variable yields of the required ester (**12**) accompanied by significant quantities of a second ester. Spectroscopic evidence permitted the assignment of structure (**18**) to this product (Scheme 4), the presence of a three-proton singlet at δ 2.13 in the n.m.r. spectrum and a molecular ion at 210 proving conclusive. The formation of compound (**18**) can be rationalised (Scheme 4) by nucleophilic ring opening of the lactone by hydroxide followed by loss of acetaldehyde to give an *o*-quinodimethanide which on aromisation would lead to the observed product. Use of potassium t-butoxide in refluxing toluene as a non-nucleophilic base completely inhibited the formation of compound (**18**), enabling the ester (**12**), possessing the required *E*-propenyl substituent, to be obtained in 84% yield. Allylic bromination of this material with *N*-bromosuccinimide in the presence of benzoyl peroxide gave, in 82% yield, a single product (**13**) by capillary g.l.c. examination. The *E*-geometry of the double bond was assigned on the basis of a coupling constant of 16 Hz between the two vinylic protons in the n.m.r. spectrum. The attempted formation of the phosphonium bromide (**14**) by the reaction of compound (**13**) with triphenylphosphine in refluxing toluene led to extensive decomposition of the allylic bromide. However, the reaction went cleanly in acetonitrile at room temperature during 48 h to give the required phosphonium bromide in 82% yield after recrystallisation.



a; R = $(CH_2)_6CH_3$
b; R = $CH{=}^tCH(CH_2)_4CH_3$

Scheme 3. *Reagents:* i, Me_2SO_4 (excess), K_2CO_3, butan-2-one, reflux, 8 days; ii, $KOBu^t$, toluene, reflux; iii, CH_2N_2; iv, NBS, benzoyl peroxide, CCl_4, reflux; v, Ph_3P, CH_3CN, 20 °C; vi, Bu^nLi, THF, −20 °C; vii, RCHO; viii, I_2 (cat.), CCl_4, reflux; ix, $LiAlH_4$, Et_2O; x, Me_2SO–$(COCl)_2$, CH_2Cl_2, −20 °C; xi, BI_3, CH_2Cl_2, −20 °C



Scheme 4.

With quantities of this important intermediate readily available it was decided first to the explore the validity of the remainder of the route using the diene ester (**15a**), prepared by condensing the ylide, derived from (**14**), with octanal. After some experimentation it was found that the best material yield from this reaction was obtained by generating the ylide with n-butyl-lithium in tetrahydrofuran at −20 °C and treating it

with the aldehyde at this temperature. Under these conditions the initial reaction product was found to be an almost equal mixture of two products by h.p.l.c. examination. However, brief treatment of the mixture with a small crystal of iodine in refluxing carbon tetrachloride caused this ratio to change to 88:12 in favour of the more polar constituent. The major product was obtained pure by chromatography in 61% yield. In the 300 MHz n.m.r. spectrum each vinylic proton showed a coupling constant of 15 Hz indicating the *E,E*-geometry of the side chain unsaturation. Direct reduction of the ester (**15a**) to the aldehyde (**17a**) with di-isobutylaluminium hydride proved not to be possible and therefore an oxidation–reduction sequence was undertaken. The unstable alcohol (**16a**) was obtained by lithium aluminium hydride reduction of (**15a**) in 92% yield, but only small yields of the desired aldehyde (**17a**) were obtained using activated manganese dioxide, pyridinium chlorochromate, or pyridinium dichromate. Fortunately, Swern oxidation[18] with dimethyl sulphoxide activated by oxalyl chloride gave compound (**17a**) cleanly in 65% purified yield [60% overall from ester (**15a**)]. The lability of the aldehyde precluded the successful use of a wide range of demethylating agents. For example, boron tribromide,[19] ceric ammonium nitrate,[20] silver dipicolinate,[21] and trimethylsilyl iodide[22] all caused decomposition of the starting material. Eventually the demethylation was accomplished using a solution of boron triiodide[23] in dichloromethane saturated at −20 °C, with ethylene as an acid scavenger. Carrying out the reaction at −20 °C until the initial dark blue colour became magenta, and quenching by filtration of the reaction mixture through a pad of silica, gave 5′,6′-dihydroaurocitrin (**8a**) in 24% purified yield.

With the synthetic sequence complete in the diene series, we turned our attention to the synthesis of aurocitrin itself. Wittig condensation of the ylide derived from compound (**14**) with (*E*)-oct-2-enal[24] following the procedure described above gave a material which was indicated to be a mixture of two products by h.p.l.c. analysis. Treatment with iodine once again gave one major product which was purified by chromatography giving the ester (**15b**) in 56% yield.

The undecatrienyl side chain was established by 300 MHz n.m.r. spectroscopy to have the desired *E,E,E*-geometry, each vinylic proton displaying a coupling constant of 15 Hz. The ester (**15b**) was reduced to the alcohol (**16b**) (94%) and then subjected to Swern oxidation to give the aldehyde (**17b**) (59%), following the previous procedures. However, the acid sensitivity of these intermediates was aggravated by the introduction of additional unsaturation into the side chain. This manifested itself in the low yield of the demethylation step, when aurocitrin (**8b**) could be isolated in only 5% yield after purification. The product thus obtained had chemical and physical properties which corresponded to those of an authentic sample of aurocitrin.†

The syntheses herein described underline the synthetic utility of the acid catalysed Claisen rearrangement of the 5-allyloxy-2-hydroxybenzoate system and work is continuing on further applications.

Experimental

M.p.s were determined on a Kofler hot stage and are uncorrected. Capillary g.c. analyses were performed on a Carlo Erba Fractovap HRGC, series 4130 (employing a 10% OV-1, 25 mm × 0.25 mm internal diameter flexible fused quartz column). H.p.l.c. analyses were carried out with a Waters Associates 600A pump and a spherisorb 5μ silica stationary phase, eluting with 1:1 dichloromethane–hexane at 1 ml min^{-1}. N.m.r. spectra were recorded at 90 MHz on a Perkin-Elmer R32B, 220 MHz on a Perkin-Elmer R34, and 300 MHz on a Varian S.C. 300 instrument. The phrase 'usual work-up' refers to washing the organic phase with 5% aqueous hydrochloric acid, saturated aqueous sodium hydrogen carbonate, drying over anhydrous magnesium sulphate, filtering and removal of the solvent under reduced pressure with gentle warming. Ether refers to diethyl ether.

Allyl 5-Allyloxy-2-hydroxybenzoate (**2b**).—2,5-Dihydroxybenzoic acid (15.4 g, 100 mmol) and allyl bromide (25.3 g, 210 mmol) in acetone (100 ml) were heated to reflux with anhydrous potassium carbonate (25.0 g) under nitrogen for 16 h. The solvent was removed under reduced pressure and the residue triturated with ether (3 × 100 ml). The combined ethereal extracts were washed with saturated aqueous sodium hydrogen carbonate and dried. Filtration and removal of solvent gave a brown oil (22.4 g). The crude *allyl 5-allyloxy-2-hydroxybenzoate* (**2b**) was contaminated with *ca.* 5% *allyl 2,5-bis(allyloxy)benzoate* (**2c**) (n.m.r.) but was used as such for following work.

A pure sample of (**2b**) was obtained as colourless *needles* by low temperature crystallisation from pentane, m.p. 43.5—44.5 °C (Found: C, 66.7; H, 6.05. $C_{13}H_{14}O_4$ requires C, 66.66; H, 6.03%); $\nu_{max.}(CCl_4)$ 3 500—3 100, 3 075, and 1 670 cm^{-1}; δ (220 MHz; $CDCl_3$) 4.47 (2 H, dt, *J* 6, *J′* 1.5 Hz), 4.83 (2 H, dt, *J* 6, *J′* 1.5 Hz), 5.20—5.50 (4 H, m), 5.90—6.15 (4 H, m), 6.90 (1 H, d, *J* 9 Hz), 7.10 (1 H, dd, *J* 9, *J′* 4 Hz), 7.35 (1 H, d, *J* 4 Hz), and 10.30 (1 H, s, removable with D_2O); *m/z* 234 (M^+, 45%), 193 (90), and 135 (100).

Chromatography on silica eluting with pentane–ether followed by short-path distillation gave a pure sample of (**2c**), b.p. 100 °C/0.03 mmHg (Found: C, 69.9; H, 6.8. $C_{16}H_{18}O_4$ requires C, 70.06; H, 6.61%); $\nu_{max.}$(film) 1 720 cm^{-1}; δ (220 MHz; $CDCl_3$) 4.40—4.70 (4 H, m), 4.78 (2 H, dt, *J* 6, *J′* 1.5 Hz), 5.10—5.40 (4 H, m), 5.43—5.58 (2 H, m), 5.70—6.40 (3 H, m), 6.85 (1 H, d, *J* 9 Hz), 7.01 (1 H, dd, *J* 9, *J′* 4 Hz), and 7.36 (1 H, d, *J* 4 Hz); *m/z* 274 (M^+, 10%), 135 (40), and 41 (100, $CH_2{=}CHCH_2^+$).

Acid-catalysed Rearrangement of the Ester (**2b**).—A solution of the ester (**2b**) (4.68 g, 20 mmol) was heated to reflux in trifluoroacetic acid (20 ml) under nitrogen for 18 h. The solvent was removed under reduced pressure, the black gummy residue was dissolved in ethyl acetate, and the solution was washed with saturated aqueous sodium hydrogen carbonate (2 × 50 ml). Extraction of the organic phase with 10% aqueous sodium hydroxide (3 × 100 ml) was followed by acidification of the aqueous phase to give, after re-extraction (ethyl acetate, 2 × 50 ml), drying, and removal of solvent, 3,4-dihydro-5,8-dihydroxy-3-methylisocoumarin (**5**) as a brown solid (2.67 g). Recrystallisation from toluene gave a grey powder (1.58 g, 41%), m.p. 194 °C (lit.,[4] 198—200 °C) (Found: C, 61.9; H, 5.2. Calc. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19%); $\nu_{max.}(CHCl_3)$ 3 600—2 800, 1 670, and 1 600 cm^{-1}; δ (90 MHz; CD_3COCD_3) 1.51 (3 H, d, *J* 7 Hz), 2.65 (1 H, dd, *J* 17, *J′* 11 Hz), 6.78 (1 H, dd, *J* 17, *J′* 4 Hz), 4.55—4.95 (1 H, m), 6.69 (1 H, d, *J* 9 Hz), 7.12 (1 H, d, *J* 9 Hz), 8.16—8.25 (1 H, m, removable with D_2O), and 10.56 (1 H, s, removable with D_2O); *m/z* 194 (M^+), 176, 165, and 150. *Allyl 2,3-dihydro-5-hydroxy-2-methylbenzofuran-4-carboxylate* (**4b**) was obtained from the original base-extracted ethyl acetate solution by usual work-up followed by chromatography on silica (ether–pentane) (0.65 g, 14%), m.p. 76.5—77.5 °C (from pentane) (Found: C, 66.5; H, 6.0. $C_{13}H_{14}O_4$ requires C, 66.66; H, 6.03%); $\nu_{max.}(CCl_4)$ 3 320—3 000, 1 665, 1 605, and 1 190 cm^{-1}; δ (220 MHz; $CDCl_3$) 1.43 (3 H, d, *J* 7 Hz), 3.03 (1 H, dd, *J* 18, *J′* 8 Hz), 3.58 (1 H, dd, *J* 18, *J′* 9 Hz), 4.80—4.95 (3 H, m),

† The author thanks Dr. M. S. Nair for the generous gift of an authentic sample of aurocitrin.

5.29—5.46 (2 H, m), 5.93—6.14 (1 H, m), 6.78 (1 H, d, *J* 9 Hz), 6.90 (1 H, d, *J* 9 Hz), and 10.38 (1 H, s, removable with D_2O); *m/z* 234 (M^+, 38%), and 176 (100).

3,4-*Dihydro*-8-*hydroxy*-3-*methyl*-5-*methylsulphonyloxyisocoumarin* (**6**).—A solution of dihydroisocoumarin (**5**) (970 mg, 5 mmol) and methanesulphonyl chloride (680 mg, 6 mmol) dissolved in anhydrous pyridine (20 ml) was heated to 60 °C for 60 h under nitrogen. Removal of pyridine at reduced pressure gave a fawn residue which was triturated with tetrahydrofuran (3 × 20 ml), the only common solvent in which the product was readily soluble. The solution was decolourised with charcoal and washed with brine containing *ca.* 5% hydrochloric acid (20 ml) and saturated aqueous sodium hydrogen carbonate (20 ml). Drying, filtering, and removal of solvent gave pale cream crystals of pure *compound* (**6**) (1 405 mg, quantitative yield), m.p. 171—172 °C (1 254 mg, 92%, colourless rhombs from tetrahydrofuran–pentane) (Found: C, 48.6; H, 4.4; S, 11.7. $C_{11}H_{12}O_6S$ requires C, 48.53; H, 4.44; S, 11.78%); $\nu_{max.}$($CHCl_3$) 3 480—3 000, 1 680, 1 370, and 1 160 cm^{-1}; δ (220 MHz; $CDCl_3$) 1.45 (3 H, d, *J* 7 Hz), 2.86 (1 H, dd, *J* 17, *J'* 12 Hz), 3.23 (4 H, m, composed of a 3 H s centred on a dd *J* 17, *J'* 3 Hz), 4.60—4.87 (1 H, m), 6.95 (1 H, d, *J* 9 Hz), 7.42 (1 H, d, *J* 9 Hz), and 11.12 (1 H, s, removable with D_2O); *m/z* 272 (M^+, 20%), 193 (100), and 175 (95).

Hydrogenolysis of the Methanesulphonate (**6**).—A solution of the methanesulphonate (**6**) (1 088 mg, 4 mmol) and triethylamine (440 mg) in methanol (10 ml) was heated to reflux with stirring under hydrogen (1 atm) in the presence of 5% palladium-on-charcoal (100 mg). During 21 h 2.2 equivalents of hydrogen was absorbed. Filtration of the reaction mixture through a short pad of silica gave pure (±)-mellein (3,4-dihydro-8-hydroxy-3-methylisocoumarin) (**7**) (683 mg, 96%) as a colourless oil which solidified on standing, m.p. 34—36 °C. Recrystallisation from aqueous ethanol gave colourless needles, m.p. 38.0—38.5 °C (lit.,[11] 39 °C). All spectroscopic data were in accord with those published for (±)-mellein.[12]

3,4-*Dihydro*-5,8-*dimethoxy*-3-*methylisocoumarin* (**11**).—A solution of 3,4-dihydro-5,8-dihydroxy-3-methylisocoumarin (5) (10.20 g) and dimethyl sulphate (30 g) in methyl ethyl ketone (300 ml) was heated to reflux with stirring over anhydrous potassium carbonate (30 g) for 8 days. Removal of the solvent and extraction of the residue with ethyl acetate (3 × 50 ml) gave, after the usual work-up, crude compound (**11**) as a brown oil (8.76 g). Chromatography on silica gave pure 3,4-*dihydro*-5,8-*dimethoxy*-3-*methylisocoumarin* (**11**) (6.83 g, 58.5%) as colourless rhombs, m.p. 69—70 °C (Found: C, 64.7; H. 6.5. $C_{12}H_{14}O_4$ requires C, 64.85; H, 6.35%); $\nu_{max.}$(CCl_4) 1 725 cm^{-1}; δ (220 MHz; $CDCl_3$) 1.48 (3 H, d, *J* 8 Hz), 2.56 (1 H, dd, *J* 17, *J'* 13 Hz), 3.16 (1 H, dd, *J* 17, *J'* 4 Hz), 3.83 (3 H, s), 3.90 (3 H, s), 4.5 (1 H, m), 6.88 (1 H, d, *J* 9 Hz), and 7.07 (1 H, d, *J* 9 Hz); *m/z* 222 (M^+, 87%), 189 (35), 176 (54), 163 (95), and 161 (100).

Methyl 3,6-*Dimethoxy*-2-[(E)-*prop*-1-*enyl*]*benzoate* (**12**).—A solution of 3,4-dihydro-5,8-dimethoxy-3-methylisocoumarin (**11**) (5.41 g) in dry toluene (200 ml) was heated to reflux under nitrogen with potassium t-butoxide (6.10 g) for 3 h. The fawn coloured heterogeneous mixture was allowed to cool and was then poured into water (200 ml). The aqueous phase was separated, washing the toluene with further water (30 ml). The aqueous phase was extracted with ether (30 ml), acidified to pH 1 with 5% aqueous hydrochloric acid, and extracted with ethyl acetate (3 × 50 ml). Drying, filtering, and removal of solvent yielded the crude acid (5.51 g) as a brown solid which was methylated with excess of ethereal diazomethane (**CAUTION**). Removal of ether under reduced pressure gave crude *methyl* 3,6-*dimethoxy*-2-[(E)-*prop*-1-*enyl*]*benzoate* (**12**) as an orange oil which crystallised on standing (5.69 g). Chromatography on silica (ether–pentane) gave the pure ester as a colourless solid (4.85 g, 84%), m.p. 47—50 °C (from ether, pentane) (Found: C, 65.9; H, 7.0. $C_{13}H_{16}O_4$ requires C, 66.09; H, 6.83%); $\nu_{max.}$(CCl_4) 1 720 and 1 650 cm^{-1}; δ (220 MHz; $CDCl_3$) 1.86 (3 H, dd, *J* 7, *J'* 2 Hz), 3.78, 3.76 (6 H, 2 superimposed s), 3.88 (3 H, s), 6.17 (1 H, dq, *J* 16, *J'* 7 Hz), 6.42 (1 H, dq, *J* 16, *J'* 2 Hz), 6.75 (1 H, d, *J* 9 Hz), and 6.84 (1 H, d, *J* 9 Hz); *m/z* 236 (M^+, 97%), 221 (15), 205 (40), 193 (25), 189 (28), 81 (40), and 69 (100).

Allylic Bromination of the Ester (**12**).—To a solution of the ester (**12**) (4.85 g, 20.5 mmol) in carbon tetrachloride (300 ml) was added recrystallised *N*-bromosuccinimide (4.39 g, 24.7 mmol, 1.2 equiv.) and benzoyl peroxide (500 mg). The mixture was refluxed under nitrogen for 5 h when t.l.c. indicated the disappearance of the starting material. After being cooled the mixture was filtered and the crude material obtained on removal of solvent at reduced pressure was chromatographed on silica (pentane–ether) to give *methyl* 2-[3-*bromo*-(E)-*prop*-1-*enyl*]-3,6-*dimethoxybenzoate* (**13**) (5.43 g, 82%). Capillary g.l.c. of this material (10% OV-1) showed only one peak under all temperature programme conditions, m.p. 74.5—75.5 °C (from ether–pentane) (Found: C, 49.6; H, 4.8; Br, 25.2. $C_{13}H_{15}BrO_4$ requires C, 49.54; H, 4.80; Br, 25.35%); $\nu_{max.}$(CCl_4) 1 730 cm^{-1}; δ (220 MHz; $CDCl_3$) 3.80, 3.81 (6 H, 2 superimposed s), 3.92 (3 H, s), 4.18 (2 H, d, *J* 7 Hz), 6.49 (1 H, dt, *J* 16, *J'* 7 Hz), 6.67 (1 H, d, *J* 16 Hz), 6.82 (1 H, d, *J* 8 Hz), and 6.87 (1 H, d, *J* 8 Hz); *m/z* 314, 316 (M^+, 3%), and 235 (100).

Preparation of the Phosphonium Bromide (**14**).—The bromide (**13**) (5.43 g) and triphenylphosphine (4.52 g, 1 equiv.) were dissolved in acetonitrile (50 ml) and the solution allowed to stand for 48 h at room temperature. Removal of the solvent at reduced pressure and trituration of the residue with ether yielded the pure phosphonium bromide (**14**) as a pale yellow powder (8.13 g, 82%), m.p. 202—204 °C (colourless rhombs from acetonitrile–ether) (Found: C, 64.3; H, 5.3; Br, 13.9; P, 5.5. $C_{31}H_{30}BrO_4P$ requires C, 64.48; H, 5.24; Br, 13.84; P, 5.36%); $\nu_{max.}$($CHCl_3$) 1 720 cm^{-1}; δ (220 MHz; $CDCl_3$) 3.60 (3 H, s), 3.66 (3 H, s), 3.74 (3 H, s), 4.84 (2 H, dd, *J* 16, *J'* 7 Hz), 6.14 (1 H, ddt, *J* 16, *J'* 7, *J''* 5 Hz), 6.69 (1 H, dd, *J* 16, *J'* 5 Hz), and 7.60—7.95 (17 H, m); *m/z* 277 ($CH_3PPh_3^+$, 100%) and 262 (75).

Preparation of the (E,E)-*Diene Ester* (**15a**).—n-Butyl-lithium (1.55M solution in hexane; 1.55 ml, 2.40 mmol) was added to a stirred suspension of the phosphonium bromide (**14**) (1 226 mg, 2.13 mmol) in anhydrous tetrahydrofuran (THF) (30 ml) at −20 °C under nitrogen. The mixture was stirred for 1 h during which time it developed a deep red colour. Octanal (400 mg, 3.13 mmol, 1.5. equiv.) in THF (2 ml) was added and the mixture was allowed to warm to room temperature, resulting in a brown solution. Usual work-up followed by chromatography on silica (pentane–ether, gradient elution) gave a material (599 mg, 81%) which was shown by analytical h.p.l.c. (5μ Spherisorb, dichloromethane–hexane, 1:1, 1 ml min^{-1}, 254 nm observation wavelength) to consist of two products in the ratio 54:46. Treatment of this material with a crystal of iodine in refluxing carbon tetrachloride (30 min) gave, after removal of the solvent and a second purification by chromatography, a single product (h.p.l.c.) (450 mg, 61%), m.p. 42—44 °C (from pentane–ether). This material was identified as the required *methyl* 3,6-*dimethoxy*-2-[(1E,3E)-*undeca*-1,3-*dienyl*]*benzoate* (**15a**) by its spectroscopic properties (Found: C, 72.7; H, 8.5. $C_{21}H_{30}O_4$ requires C, 72.80; H, 8.73%); $\nu_{max.}$(CCl_4) 1 720 cm^{-1}; δ (300 MHz; $CDCl_3$) 0.91 (3 H, br t, *J* 6 Hz), 1.20—1.53 (10 H, m), 2.15 (2 H, q, *J* 7 Hz), 3.81 (3 H, s), 3.83 (3 H, s), 3.92 (3 H, s), 5.86 (1 H, dt, *J* 15, *J'* 7 Hz), 6.21 (1 H, dd, *J* 15, *J'* 10 Hz), 6.47 (1 H, d, *J* 15

Hz), 6.78 (1 H, d, *J* 8 Hz), 6.83 (1 H, dd, *J* 15, *J'* 10 Hz), and 6.87 (1 H, d, *J* 8 Hz) (3 H, m); *m/z* 346 (M^+, 50%), 287 (45), 229 (90), 189 (40), 145 (80), and 127 (100).

Preparation of the (E,E,E)-*Triene Ester* (**15d**).—By an analogous procedure to that described for (**15a**), the ylide derived from (**14**) (2 830 mg, 5 mmol) was treated with (2*E*)-oct-2-enal[24] (1 260 mg, 10 mmol) to give, after isomerisation with iodine and chromatography, *methyl* 3,6-*dimethoxy*-2-[(1E,3E,5E)-*undeca*-1,3,5-*trienyl*]*benzoate* (**15b**) (970 mg, 56%), m.p. 63—66 °C (pale yellow powder from pentane–ether); $\nu_{max.}$(CCl_4) 1 730 cm^{-1}; δ (300 MHz; $CDCl_3$) 0.88 (3 H, br, t, *J* 7 Hz), 1.15—1.50 (6 H, m), 2.09 (2 H, q, *J* 7 Hz), 3.76 (3 H, s), 3.78 (3 H, s), 3.87 (3 H, s), 5.77 (1 H, dt, *J* 15, *J'* 7 Hz), 6.10 (1 H, dd, *J* 15, *J'* 10 Hz), 6.21 (1 H, dd, *J* 15, *J'* 10 Hz), 6.29 (1 H, dd, *J'* 15, *J'* 10 Hz), 6.48 (1 H, d, *J* 15 Hz), 6.73 (1 H, d, *J* 9 Hz), 6.83 (1 H, d, *J* 9 Hz), and 6.86 (1 H, dd, *J* 15, *J'* 10 Hz); *m/z* 344 (M^+, 20%), 262 (80), and 203 (100) (Found: M^+, 344.1985. $C_{21}H_{28}O_4$ requires 344.1987).

Reduction of the Diene Ester (**15a**) *to Alcohol* (**16a**).—Lithium aluminium hydride (100 mg, excess) was added to a solution of the diene ester (**15c**) (347 mg, 1 mmol) in anhydrous ether (40 ml) and the mixture was stirred at room temperature for 3 h. The usual work-up gave 3,6-*dimethoxy*-2-[(1E,3E)-*undeca*-1,3-*dienyl*]*benzyl alcohol* (**16a**) (294 mg, 92%) as a colourless oil, $\nu_{max.}$(CCl_4) 3 650—3 100 cm^{-1}; δ (300 MHz; $CDCl_3$) 0.90 (3 H, br t, *J* 6 Hz), 1.20—1.56 (10 H, m), 2.13 (2 H, q, *J* 7 Hz), 2.34—2.46 (1 H, m, removable with D_2O), 3.80 (3 H, s), 3.86 (3 H, s), 4.81 (2 H, br s), 5.86 (1 H, dt, *J* 15, *J'* 7 Hz), 6.29 (1 H, dd, *J* 15, *J'* 9 Hz), 6.62 (1 H, d, *J* 15 Hz), 6.70 (1 H, dd, *J* 15, *J'* 9 Hz), 6.70 (1 H, d, *J* 9 Hz), and 6.83 (1 H, d, *J* 9 Hz); *m/z* 318 (M^+, 55%), 287 (20), 219 (20), 205 (60), 191 (60), 189 (40), and 179 (100) (Found: *M*, 318.2178. $C_{20}H_{30}O_3$ requires 31.2195). p-*Nitrobenzoate*, m.p. 93.0—95.0 °C (cream needles from pentane–ether) (Found: C, 69.2; H, 7.1; N, 3.0. $C_{27}H_{33}NO_6$ requires C, 69.35; H, 7.16; N, 3.01%).

Reduction of the Triene Ester (**15b**) *to Alcohol* (**16b**).—By the same method as in the preparation of compound (**16a**), the triene ester (1 080 mg, 3.14 mmol) was reduced with lithium aluminium hydride (100 mg) in anhydrous ether (60 ml) for 12 h to give 3,6-*dimethoxy*-2-[(1E,3E,5E)-*undeca*-1,3,5-*trienyl*]-*benzyl alcohol* (**16b**) (930 mg, 94%) as an unstable colourless oil; $\nu_{max.}$(CCl_4) 3 600, 1 600, 1 250, 1 120, and 910 cm^{-1}; δ (300 MHz; $CDCl_3$) 0.90 (3 H, br t, *J* 7 Hz), 1.10—1.70 (7 H, m, 1 H removable with D_2O), 2.11 (2 H, q, *J* 7 Hz), 3.78 (3 H, s), 3.83 (3 H, s), 4.78 (2 H, s), 5.76 (1 H, dt, *J* 15, *J'* 7 Hz), 6.15 (1 H, dd, *J* 15, *J'* 11 Hz), 6.28—6.42 (2 H, m), 6.69 (1 H, d, *J* 15 Hz), and 6.70—6.85 (3 H, m); *m/z* 316 (M^+, 25%), 298 (15), and 179 (100). p-*Nitrobenzoate*, m.p. 125—127 °C (from pentane–ether) (Found: C, 69.65; H, 6.7; N, 3.3. $C_{27}H_{31}NO_6$ requires C, 69.66; H, 6.71; N, 3.01%).

Swern Oxidation[18] *of the Alcohol* (**16a**) *to Diene Aldehyde* (**17a**).—Oxalyl chloride (165 μl, 233 mg, 1.83 mmol) was added dropwise to a stirred solution of dimethyl sulphoxide (400 μl, 440 mg, 5.65 mmol) in dichloromethane at −20 °C under nitrogen. After 15 min the alcohol (**16c**) (184 mg, 0.58 mmol) in dichloromethane (2 ml) was added and the reaction mixture stirred for a further 45 min. Triethylamine (1 ml) was added and the mixture allowed to warm to room temperature giving a pale yellow solution. The usual work-up followed by chromatography on silica (pentane–dichloromethane) gave pure 3,6-*dimethoxy*-2-[(1E,3E)-*undeca*-1,3-*dienyl*]*benzaldehyde* (**17a**) (119 mg, 65%) m.p. 63.5—65.5 °C (cream powder from pentane) (Found: C, 76.1; H, 9.1. $C_{20}H_{28}O_3$ requires C, 75.91; H, 8.92%); $\nu_{max.}$(CCl_4) 1 680 and 1 455 cm^{-1}; δ (300 MHz; $CDCl_3$) 0.92 (3 H, br t, *J* 6 Hz), 1.20—1.60 (10 H, m), 2.18 (2 H, q, *J* 7 Hz), 3.86 (3 H, s), 3.89 (3 H, s), 5.91 (1 H, dt, *J* 15, *J'* 7 Hz), 6.33 (1 H, dd, *J* 15, *J'* 10 Hz), 6.65 (1 H, dd, *J* 15, *J'* 10 Hz), 6.88 (1 H, d, *J* 9 Hz), 6.97 (1 H, d, *J* 15 Hz), 7.09 (1 H, d, *J* 9 Hz), and 10.34 (1 H, s); *m/z* 316 (M^+, 10%), 231 (25), and 191 (100).

Preparation of the Triene Aldehyde (**17b**).—Following the procedure described for the preparation of (**17a**), the alcohol (**16b**) (96 mg, 0.30 mmol) was oxidised to 3,6-*dimethoxy*-2-[(1E,3E,5E)-*undeca*-1,3,5-*trienyl*]*benzaldehyde* (**17b**) (56 mg, 59%), m.p. 68—70 °C (yellow powder from pentane) (Found: C, 76.2; H, 8.6. $C_{20}H_{26}O_3$ requires C, 76.40; H, 8.34%); $\nu_{max.}$(CCl_4) 1 680, 1 455, and 1 250 cm^{-1}; δ (300 MHz; $CDCl_3$) 0.92 (3 H, br t, *J* 6 Hz), 1.20—1.40 (6 H, m), 1.16 (2 H, q, *J* 6 Hz), 3.86 (3 H, s), 3.90 (3 H, s), 5.84 (1 H, dt, *J* 14, *J'* 6 Hz), 6.2 (1 H, dd, *J* 14, *J'* 9 Hz), 6.34—6.46 (2 H, m), 6.80 (1 H, dd, *J* 14, *J'* 9 Hz), 6.89 (1 H, d, *J* 8 Hz), 7.10 (1 H, d, *J* 8 Hz), 7.11 (1 H, d, *J* 14 Hz), and 10.38 (1 H, s); *m/z* 314 (M^+, 45%), 257 (30), 191 (60), and 43 (100).

Preparation of 5',6'-*Dihydroaurocitrin* {3,6-*Dihydroxy*-2-[(1E,3E)-*undeca*-1,3-*dienyl*]*benzaldehyde*} (**8a**).—A solution of the aldehyde (**17a**) (9 mg) in dichloromethane (5 ml) was cooled to −20 °C and saturated with ethylene. Boron tri-iodide (*ca.* 20 mg) was added in one portion and the mixture stirred at −20 °C for 30 min during which time the initially formed deep blue colour became magenta. The mixture was rapidly filtered through a 2-cm pad of silica, washing with ether. The solvents were removed under reduced pressure and the orange residue was purified by preparative thin layer chromatography, eluting with dichloromethane, to give 5',6'-*dihydroaurocitrin* (**8a**) (2 mg, 24%); $\nu_{max.}$(CCl_4) 3 600, 3 550, 1 650, 1 460, and 1 285 cm^{-1}; δ (300 MHz; $CDCl_3$) 0.93 (3 H, br t, *J* 7 Hz), 1.23—1.65 (10 H, m), 2.13 (2 H, q, *J* 6 Hz), 5.04 (1 H, s, removable with D_2O), 6.01 (1 H, dt, *J* 13, *J'* 6 Hz), 6.38 (1 H, dd, *J* 13, *J'* 8 Hz), 6.58 (1 H, dd, *J* 13, *J'* 8 Hz), 6.66 (1 H, d, *J* 13 Hz), 6.90 (1 H, d, *J* 9 Hz), 7.21 (1 H, d, *J* 9 Hz), 10.16 (1 H, s), and 11.49 (1 H, s, removable with D_2O); *m/z* 288 (M^+, 70%), 203 (30), 189 (30), 177 (45), 175 (45), and 163 (100) (Found: M^+, 288.1727. $C_{18}H_{24}O_3$ requires *M*, 288.1725).

Preparation of Aurocitrin (**8b**).—In a similar manner to the preparation of (**8a**) the triene aldehyde (**17d**) (10 mg) was bisdemethylated to give *aurocitrin* (**8b**) (0.5 mg, 5%) which had physical and spectroscopic properties corresponding to those of an authentic sample.[13]

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