Synthesis based on Cyclohexadienes: Part 4.[1] Novel Synthesis of the 6-Aryl-2,4-dimethoxybenzoates. Alternariol and Methyl Trimethylaltenusin

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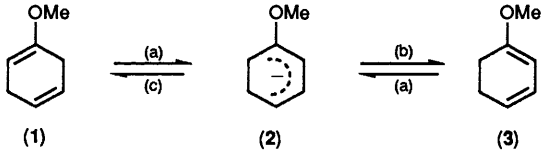
A novel method for the preparation of 6-aryl-2,4-dimethoxybenzoic acids involving the Alder–Rickert reaction of 1,5-dimethoxycyclohexa-1,4-dienes and arylpropiolic esters is described. This strategy has been extended to the synthesis of the mould metabolite alternariol and methyl trimethylaltenusin.

Biphenic acids are important precursors in the synthesis of several naturally occurring biphenyls,[2] benzocoumarins,[3] and fluorenones.[4] Alternariol (**20a**) and altenusin (**21b**) have been isolated[5–7] from the fungus *Alternaria tenuis* (*syn: A. alternata*) and shown to be derivatives of biphenic acid. Some benzocoumarins derived from 6-aryl-2-hydroxybenzoic acids have been identified[7] as fungal metabolites having antibiotic properties. The existing methods of synthesis for biphenic acids or biphenyls involve either the use of the Ullmann reaction,[8] the Gomberg reaction,[9] or dehydrogenation[10] of cyclohexylbenzenes. Harris *et al.*[11] reported a novel synthesis of 2,4-dihydroxy-6-phenylbenzoic acid by means of a readily occurring aldol cyclisation of 3,5,7-trioxo-7-phenylheptanoic acid. We now report a convenient synthesis of the esters of 6-aryl-2,4-dihydroxybenzoic acids from the readily available 1,5-dimethoxycyclohexa-1,4-diene and phenylpropiolic esters. This methodology has been extended to the synthesis of alternariol (**20a**) and methyl trimethylaltenusin (**21a**).

We have described earlier[12] a general method for the preparation of 6-alkyl-2-hydroxy- and -2,4-dihydroxy-benzoates by an Alder–Rickert reaction between alkylacetylenic esters and 1-methoxycyclohexa-1,3- or -1,4-diene. 1-Methoxycyclohexa-1,4-diene (**1**) is readily available from anisole by Birch reduction and rearranges to the corresponding conjugated 1-methoxycyclohexa-1,3-diene (**3**) on treatment with catalysts such as potassium amide in liquid ammonia or dichloromaleic anhydride. The equilibrium proceeds through the formation of the mesomeric anion (**2**) (Scheme). We have observed that the

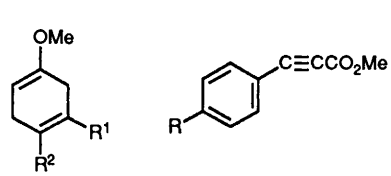


Scheme. *Reagents:* (a) KNH_2–NH_3; (b) NH_4Cl; (c) MeOH.

cycloadditions can be carried out either with the unconjugated or conjugated dienes and the reaction is usually regiospecific with 2- or 3-substituted 1-methoxycyclohexadienes. The regiochemistry of the cycloaddition is generally influenced by the position of the electron-donating substituents such as the methoxy group on the diene. However, a mixture of regioisomers was formed during the reaction of 1-methoxy-4-methylcyclohexa-1,4-diene (**11**) with acetylenic esters. The cycloaddition of 1,5-dimethoxycyclohexa-1,4-diene (**4**) with methyl 3-phenylpropiolate (**5**) and methyl 3-(4′-methoxyphenyl)propiolate (**8**) has now been studied to substantiate the versatility of this method and to investigate the regiochemistry of the products thus formed.

Arylpropiolic esters are readily prepared by a Wittig reaction[13] from an aroyl chloride or by the dehydrobromination[14,15] of dibromocinnamic esters with bases. The latter process invariably results in a mixture of phenylpropiolic acids contaminated with 1-aroyl-2-bromoacetylenes. We have prepared the arylpropiolic acids by the dehydrobromination of dibromocinnamic esters by using ethanolic potassium hydroxide, and we observed that addition of dioxane markedly improved the yield and the purity of the phenylpropiolic acids.

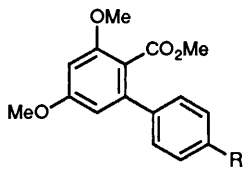
Reaction of 1,5-dimethoxycyclohexa-1,4-diene[16] (**4**) with methyl 3-phenylpropiolate (**5**) at 200 °C in a sealed tube afforded exclusively the adduct (**6**), which aromatised rapidly on further heating at 220 °C to yield methyl 2,4-dimethoxy-6-phenylbenzoate (**7**). Similar reaction of compound (**4**) with 4′-methoxyphenylpropiolate (**8**) gave methyl 2,4-dimethoxy-6-(4′-methoxyphenyl)benzoate (**10**) in 70% yield. The intermediate adducts (**6**) and (**9**) could not be isolated pure as they rapidly decomposed. However, their ^1H NMR spectral data are consistent with the proposed structure, having signals for the methoxy, methoxycarbonyl, methylene, vinyl, and aromatic protons. The structure of the esters (**7**) and (**10**), in particular their regiospecific formation, was deduced from their spectral properties.



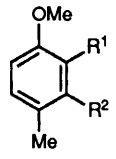
(4) R^1 = OMe, R^2 = H
(11) R^1 = H, R^2 = Me

(5) R = H
(8) R = OMe

(6) R = H
(9) R = OMe



(7) R = H
(10) R = OMe

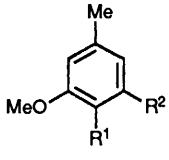


(12) R^1 = CO_2Me, R^2 = Ph
(13) R^1 = Ph, R^2 = CO_2Me

Reaction of the diene (**11**) with methyl 3-phenylpropiolate (**5**) yielded a (3:2) mixture of methyl 6-methoxy-3-methyl-2-phenylbenzoate (**12**) and methyl 3-methoxy-6-methyl-2-phenylbenzoate (**13**), which were separated and characterised from their spectral properties; in particular, the ^1H NMR spectra are significantly different. The formation of these two isomers is mainly due to the non-regiospecific addition of the dienophile to the diene having the two electron-donating substituents at the 1- and 4-position. Such nonspecificity in the cycloaddition has

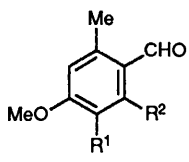
been observed earlier[12] with the diene (**11**) and alkylacetylenic esters.

Having worked out a simple strategy for the construction of biphenic acid derivatives, we next turned our attention to the synthesis of the naturally occurring mould metabolites alternariol and altenusin. These two phenolic compounds, along with their derivatives, have been isolated from the mycelium of *A. alternata*. The structure of alternariol has been established as 3,7,9-trihydroxy-1-methyldibenzo[*a*,*c*]pyran-6-one (**20a**) from degradation experiments and spectral data and confirmed by synthesis.[5] Altenusin (**21b**) has been shown to be 2-(4,5-dihydroxy-2-methylphenyl)-6-hydroxy-4-methoxybenzoic acid from spectral data.[17] We now report a simple, one-pot synthesis of methyl tetra-*O*-methylalternariolate (**19**) and tetramethylaltenusin (**21a**) from 1,5-dimethoxycyclohexa-1,4-diene (**4**) and the appropriate arylacetylenic esters (**18**). Methyl 3-(2,4-dimethoxy-6-methylphenyl)propiolate (**18b**) is prepared from the readily available 2,4-dimethoxy-6-methylbenzaldehyde (**15a**), obtained from 3,5-dimethoxytoluene (**14a**). Reflux of the aldehyde (**15a**) with malonic acid in the presence of pyridine and piperidine afforded the cinnamic acid (**16a**), the ethyl ester (**16b**) of which was brominated to afford the dibromo ester (**17a**). Dehydrobromination was achieved by heating the dibromo ester (**17a**) with aq. KOH in dioxane–ethanol, and resulted in the propiolic acid (**18a**), which was esterified with ethereal diazomethane to afford the methyl ester (**18b**). Similarly the methyl ester (**18d**) of 3-(4,5-dimethoxy-2-methylphenyl)propiolic acid (**18c**) was prepared from 3,4-dimethoxytoluene (**14b**) through the aldehyde (**15b**), the cinnamic ester (**16d**), and the dibromo compound (**17b**). The yields of the acetylenic esters (**18b**) and (**18d**) were excellent and their structures were deduced from their spectral properties (see Experimental section).

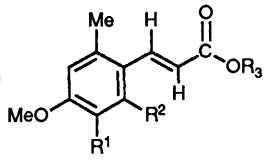


(**14**)

a; R^1 = H, R^2 = OMe
b; R^1 = OMe, R^2 = H

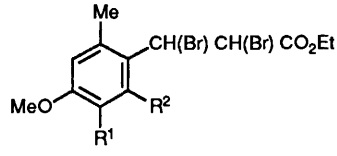


(**15**)



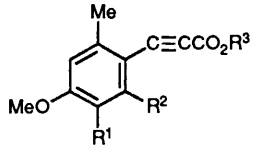
(**16**)

a; R^1 = R^3 = H, R^2 = OMe
b; R^1 = H, R^2 = OMe, R^3 = Et
c; R^1 = OMe, R^2 = R^3 = H
d; R^1 = OMe, R^2 = H, R^3 = Et



(**17**)

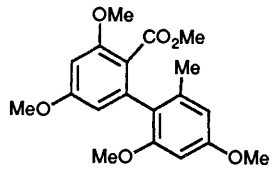
a; R^1 = H, R^2 = OMe
b; R^1 = OMe, R^2 = H



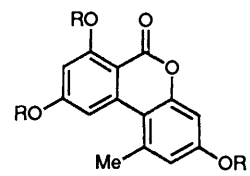
(**18**)

a; R^1 = R^3 = H, R^2 = OMe
b; R^1 = H, R^2 = OMe, R^3 = Me
c; R^1 = OMe, R^2 = R^3 = H
d; R^1 = OMe, R^2 = H, R^3 = Me

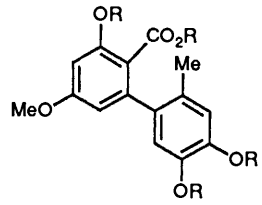
Reaction of the diene (**4**) with the acetylenic dienophile (**18b**) in a sealed tube at 180 °C for 30 h, followed by further heating at 220 °C for 4 h, yielded a product, which was sublimed to give methyl alternariolate tetramethyl ether (**19**) (75%), identical with an authentic specimen.[17] Demethylation with BBr_3 in methylene dichloride gave alternariol (**20a**) which, on treatment with ethereal diazomethane in methanol, afforded trimethylalternariol (**20b**). The compounds (**20a**) and (**20b**) exhibited spectral properties similar to those reported by Coombe *et al.*[17]



(**19**)



(**20**)
a; R = H
b; R = Me



(**21**)
a; R = Me
b; R = H

Cycloaddition of the diene (**4**) with the acetylenic ester (**18d**) at 180 °C for 30 h, followed by further heating at 200 °C for 4 h and sublimation of the resulting reaction mixture, afforded methyl tri-*O*-methylaltenusin (**21a**) in 70% yield. The structure of the ester (**21a**) was deduced from its spectral properties, which indicated the presence of methoxycarbonyl, methoxy, methyl, and aromatic resonances; the structure was confirmed by comparison with an authentic specimen. The synthesis of compound (**21a**) confirms the gross structure assigned for altenusin (**21b**), having the oxygen substitution at appropriate positions.

Thus a one-pot synthesis for biphenic acids has been developed, which was exemplified by the preparation of alternariol (**20a**) and tetramethylaltenusin (**21a**).

Experimental

M.p.s and b.p.s were uncorrected. IR spectra were recorded on a Perkin-Elmer Model 397 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian HA-100D, Varian T-60, or Bruker WH^1-270 MHz spectrometer, with tetramethylsilane as internal reference. Analytical and preparative TLC (PLC) was carried out on glass plates coated with silica gel (*ca.* 0.2 mm; commercial grade containing 10% calcium sulphate binder) activated at 70–90 °C for 12 h prior to use. In all the sealed-tube reactions, the reactants were taken up in a thick walled Pyrex glass tube, which was then sealed under vacuum prior to heating. Hexanes refers to the light petroleum fraction boiling in the range 40–60 °C.

Methyl 2,4-*Dimethoxy*-6-*phenylbenzoate* (**7**).—A mixture of 1,5-dimethoxycyclohexa-1,4-diene (**4**) (1.6 g) and methyl phenylpropiolate (**5**) (1.6 g) was heated in a sealed tube at 200 °C for 25 h. The temperature was raised to 220 °C and maintained at this value for 4 h. The brown viscous liquid obtained was sublimed to furnish *methyl* 2,4-*dimethoxy*-6-*phenylbenzoate* (**7**) (1.5 g, 58%), b.p. 150 °C at 8 mmHg (Found: C, 70.4; H, 5.85. $C_{16}H_{16}O_4$ requires C, 70.59; H, 5.88%); ν_{max} 1 725, 1 610, and 1 590 cm^{-1}; δ 3.65 (s, 9 H, 2 × OMe and CO_2Me), 6.2–6.4 (m, 4 H, ArH), and 6.8–7.2 (m, 3 H, ArH).

Methyl 2,4-*Dimethoxy*-6-(4-*methoxyphenyl*)*benzoate* (**10**).—A mixture of the diene (**4**) (1 g) and methyl 3-(4-methoxyphenyl)propiolate (**8**) (1 g) was heated in a sealed tube, initially at 200 °C for 24 h and then at 220 °C for 4 h. The reaction mixture was sublimed to give the *ester* (**10**) (0.7 g, 40%), b.p. 160 °C at 8 mmHg (Found: C, 67.8; H, 5.9. $C_{17}H_{18}O_5$ requires C, 67.55; H, 5.9%); ν_{max} 1 725, 1 610, and 1 590 cm^{-1}; δ 3.65 (s, 9

H, 3 × OMe), 3.7 (s, 3 H, CO_2Me), 6.2–6.4 (m, 2 H, ArH), and 6.7–7.2 (m, 4 H, ArH).

Methyl 6-Methoxy-3-methyl-2-phenylbenzoate (**12**) *and Methyl 3-Methoxy-6-methyl-2-phenylbenzoate* (**13**).—A mixture of 1-methoxy-4-methylcyclohexa-1,4-diene (**11**) (1.3 g) and methyl 3-phenylpropiolate (**5**) (1.3 g) was heated as before in a sealed tube. Sublimation of the reaction mixture yielded the esters (**12**) and (**13**) in 60% yield. The mixture was chromatographed on neutral alumina. Elution with hexane–benzene (9:1) afforded *methyl 6-methoxy-3-methyl-2-phenylbenzoate* (**12**), b.p. 145 °C at 5 mmHg (Found: C, 74.6; H, 6.1. $C_{16}H_{16}O_3$ requires C, 75.0; H, 6.2%); ν_{max} 1 725, 1 610, and 1 590 cm^{-1}; δ 2.3 (s, 3 H, ArMe), 3.7 (s, 3 H, OMe), 3.9 (s, 3 H, CO_2Me), and 6.8–7.2 (m, 7 H, ArH).

Further elution with hexane–benzene (8:2) yielded the *isomeric ester* (**13**), b.p. 150 °C at 5 mmHg (Found: C, 74.8; H, 6.3%); ν_{max} 1 720, 1 605, and 1 590 cm^{-1}; δ 2.5 (s, 3 H, ArMe), 3.5 (s, 3 H, OMe), 3.92 (s, 3 H, CO_2Me), and 6.8–7.4 (m, 7 H, ArH).

2,4-Dimethoxy-6-methylcinnamic Acid (**16a**).—A mixture of 2,4-dimethoxy-6-methylbenzaldehyde (**15a**) (10 g) and malonic acid (6.5 g) in dry pyridine (20 ml) and piperidine (0.1 ml) was heated on a water-bath for 15 h. The reaction mixture was cooled, poured onto crushed ice (100 g), and conc. hydrochloric acid (40 ml) was added to the stirred mixture. The precipitated acid was filtered off and the product was recrystallised from aqueous ethanol to afford the *acid* (**16a**) (8.9 g, 70%), m.p. 169.5 °C (Found: C, 64.55; H, 6.26. $C_{12}H_{14}O_4$ requires C, 64.87; H, 6.3%); ν_{max}(Nujol) 1 695, 1 605, and 1 590 cm^{-1}; δ 2.4 (s, 3 H, ArMe), 3.7–3.75 (2 s, 6 H, 2 × OMe), 6.39 (s, 2 H, ArH), 6.4 and 8.1 (2 d, *J* 14 Hz, 2 H, CH=CH), and 10.1 (br s, 1 H, CO_2H).

Ethyl 2,4-Dimethoxy-6-methylcinnamate (**16b**).—To a solution of the acid (**16a**) (8.5 g) in absolute ethanol (100 ml) was added conc. sulphuric acid (2 g) and the mixture was refluxed for 6 h. Alcohol was distilled off, and the residue (20 ml) was diluted with water (100 ml) and then extracted with diethyl ether (3 × 50 ml). The combined extracts were washed successively with water, aq. sodium hydrogen carbonate, and again with water, and were then dried. Removal of the solvent from the dried extract, and trituration with hexanes afforded crystals of the *ethyl ester* (**16b**) (7.5 g, 80%), m.p. 56 °C (Found: C, 67.1; H, 7.1. $C_{14}H_{18}O_4$ requires C, 67.2; H, 7.2%); ν_{max}(Nujol) 1 720, 1 600, and 1 580 cm^{-1}; δ 1.1 (t, *J* 8 Hz, 3 H, CH_2Me), 2.4 (s, 3 H, ArMe), 3.8 (s, 3 H, OMe), 3.85 (s, 3 H, OMe), 4.15 (q, *J* 8 Hz, 2 H, OCH_2Me), 6.37 (s, 2 H, ArH), 6.4 (d, *J* 14 Hz, 1 Hz), and 8.1 (d, *J* 14 Hz, 1 H).

Ethyl 2,3-Dibromo-3-(2,4-dimethoxy-6-methylphenyl)propionate (**17a**).—A suspension of ester (**16b**) (7 g) in CCl_4 (30 ml) at 0 °C was treated with a solution of bromine (6.0 g) in CCl_4 (5 ml) in the presence of artificial light. After the addition was complete, the mixture was stirred for 3 h. The solvent was evaporated off and the crude dibromo ester obtained was recrystallised from diethyl ether to give the *dibromo ester* (**17a**) (8.9 g, 80%), m.p. 129 °C (Found: C, 41.3; H, 4.4. $C_{14}H_{18}Br_2O_4$ requires C, 41.2; H, 4.39%); ν_{max}(Nujol) 1 745, 1 605, and 1 580 cm^{-1}; δ 1.15 (t, *J* 8 Hz, 3 H, CH_2Me), 2.55 (s, 3 H, ArMe), 3.8 (s, 6 H, 2 × ArOMe), 4.25 (q, *J* 8 Hz, 2 H, CH_2Me), 4.75–5.75 (2 d, *J* 10 Hz, 2 H, CHBrCHBr), and 6.36 (s, 2 H, ArH).

3-(2,4-Dimethoxy-6-methylphenyl)propiolic Acid (**18a**).—A solution of potassium hydroxide (6 g) in water (5 ml) was diluted with dioxane (15 ml) and ethanol (20 ml). To this mixture was added a solution of the dibromo ester (**17a**) (8 g) in dioxane (5 ml). The mixture was stirred and heated for 7 h at 100 °C and the solvent was then removed under reduced pressure. The residue was dissolved in water (50 ml), treated with animal charcoal, and the mixture was filtered. The filtrate was cooled in an ice–salt-bath and acidified with dil. sulphuric acid. The precipitated propiolic acid was filtered off. Recrystallisation of the crude acid from aqueous alcohol gave the *acid* (**18a**) (3.5 g, 80%), m.p. 152 °C (Found: C, 65.2; H, 5.4. $C_{12}H_{12}O_4$ requires C, 65.46; H, 5.45%); ν_{max}(Nujol) 2 250, 1 700, 1 600, and 1 590 cm^{-1}; δ 2.58 (s, 3 H, ArMe), 3.75 and 3.8 (2 s, 6 H, 2 × ArOMe), 6.25 (s, 2 H, ArH), and 10.2 (br s, 1 H, CO_2H).

Methyl 3-(2,4-Dimethoxy-6-methylphenyl)propiolate (**18b**).—(i) The above acid (**18a**) (2 g) was dissolved in absolute methanol (20 ml). A solution of sodium hydroxide (0.4 g) in methanol (4 ml) was added and the resulting salt was stirred with dimethyl sulphate (1.5 g) for 1 h; methanol was removed under reduced pressure and the residue was diluted with water and extracted with diethyl ether. The extract was stirred with pyridine (0.5 g) for 1 h to remove the excess of dimethyl sulphate. This extract was washed successively with water, aq. sodium hydrogencarbonate, and again with water, then dried, and the solvent was removed to yield a solid, which was recrystallised from alcohol to furnish the methyl ester (**18b**) (1.3 g, 60%), m.p. 135 °C.

(ii) The propiolic acid (**18a**) (1.2 g) was esterified with ethereal diazomethane (0.22 g). After usual work-up the crude ester was recrystallised from alcohol to give pure *methyl 3-(2,4-dimethoxy-6-methylphenyl)propiolate* (**18b**) (1.0 g, 85%), m.p. 135 °C (Found: C, 66.6; H, 6.0. $C_{13}H_{14}O_4$ requires C, 66.67; H, 5.98%); ν_{max}(Nujol) 2 250, 1 720, 1 600, and 1 590 cm^{-1}; δ 2.5 (s, 3 H, ArMe), 3.72 (s, 3 H, ArOMe), 3.8 (s, 3 H, ArOMe), 3.85 (s, 3 H, CO_2Me), and 6.22 (s, 2 H, ArH).

2′,3,4′,5-Tetramethoxy-6′-methylbiphenyl-2-carboxylate (**19**).—Methyl 3-(2,4-dimethoxy-6-methylphenyl)propiolate (**18b**) (1.8 g) was heated with 1,4-dimethoxycyclohexa-1,5-diene (**4**) (1 g) in an evacuated, sealed tube to a temperature of 180 °C. Heating was continued for a period of 30 h; the temperature was then raised to 220 °C and was maintained at this value for 4 h. The brown mixture was then allowed to attain room temperature. The brown viscous liquid was dissolved in chloroform (50 ml) and the solution washed successively with dil. aq. sodium hydroxide and water, then dried (Na_2SO_4), and the solvent was removed. The residue was sublimed at 195 °C at 5 mmHg to yield a viscous liquid from which methyl tetra-*O*-methylalternariolate (**19**) (0.6 g, 35%) was isolated as gum by PLC [ethyl acetate–hexane (2:3)] (0.75 g, 40%). This gum was triturated with methanol and left in a refrigerator for a considerable time in order to effect solidification. The product was recrystallised from methanol, m.p. 125–126 °C (lit.,[5] 124–125 °C) (Found: C, 65.75; H, 6.3. Calc. for $C_{19}H_{22}O_6$: C, 65.9; H, 6.36%); ν_{max}(Nujol) 1 720, 1 600, 1 580, and 1 500 cm^{-1}; δ 2.4 (s, 3 H, ArMe), 3.48 (s, 3 H, ArOMe), 3.67 (s, 3 H, ArOMe), 3.8 (s, 6 H, 2 × ArOMe), 3.84 (s, 3 H, CO_2Me), 6.3 (d, *J* 2 Hz, 1 H, ArH), 6.35 (s, 2 H, ArH), and 6.45 (d, *J* 2 Hz, 1 H, ArH); M^+, 346. This sample was identical with an authentic sample (spectra and mixed m.p.).

Alternariol (**20a**).—A solution of methyl alternariolate tetramethyl ether (**19**) (100 mg) in methylene dichloride (10 ml) was added to a cooled solution of BBr_3 (4 ml) in methylene dichloride (5 ml) under nitrogen and the mixture was stirred for 10 h. The reaction mixture was diluted with water (30 ml), and extracted with chloroform (20 ml), and the extract was thoroughly washed (successively) with brine and water, and was then dried. Removal of the solvent yielded a residue (58 mg), from which alternariol (**20a**) was obtained as a solid, m.p.

345 °C (lit.,[5] 350 °C); ν_{max} 3 450, 1 655, 1 610, and 1 575 cm^{-1}; M^+, 258.

Alternariol Trimethyl Ether (**20b**).—A solution of alternariol (**20a**) (30 mg) in methanol (5 ml) was treated with ethereal diazomethane overnight, after which the solvent was removed and the crude product was purified by PLC (benzene) to afford a pale yellow gum (20 mg) which, on trituration with acetone, yielded a solid, which was recrystallised from acetone to afford the title compound as needles, m.p. 164–165 °C (lit.,[5] 162.5–164 °C) (Found: C, 67.8; H, 5.6. Calc. for $C_{17}H_{16}O_5$: C, 68.1; H, 5.4%); ν_{max}(Nujol) 1 710, 1 610, and 1 590 cm^{-1}; δ 2.7 (s, 3 H, ArMe), 3.82 (s, 3 H, OMe), 3.93 (s, 3 H, OMe), 3.98 (s, 3 H, OMe), 6.35 (s, 2 H, ArH), 6.5 (d, *J* 2.5 Hz, 1 H, ArH), and 7.2 (d, *J* 2.5 Hz, 1 H, ArH); M^+, 300.

4,5-*Dimethoxy*-2-*methylbenzaldehyde* (**15b**).—Freshly distilled phosphorus trichloride oxide (32 g) was added during 30 min to a stirred solution of 3,4-dimethoxytoluene (**14b**) (14.2 g) in dry dimethylformamide (20 ml). After the addition was complete the pale brown reaction mixture was heated on a water-bath for 7 h and was then cooled to room temperature and poured onto stirred, crushed ice (200 g). The mixture was further diluted with water (to 1 l) and kept in an ice-chest for 12 h. The precipitate was filtered off and recrystallised from ethanol to furnish pure 4,5-dimethoxy-2-methylbenzaldehyde (**15b**) (10.5 g, 70%), m.p. 72–73 °C; ν_{max}(film) 1 690 and 1 600 cm^{-1}; δ 2.6 (s, 3 H, ArMe), 3.8 (s, 3 H, ArOMe), 3.85 (s, 3 H, ArOMe), 6.65 (s, 1 H, ArH), 7.3 (s, 1 H, ArH), and 9.25 (s, 1 H, CHO).

4,5-*Dimethoxy*-2-*methylcinnamic Acid* (**16c**).—4,5-Dimethoxy-2-methylbenzaldehyde (**15b**) (10 g) and malonic acid (6.5 g) were dissolved in dry pyridine (20 ml). Piperidine (0.1 ml) was added and the mixture was heated over a water-bath for 15 h, then was cooled and poured onto a mixture of crushed ice (100 g) and conc. hydrochloric acid (40 ml). The precipitated acid was filtered off, washed with water, and dried over Na_2SO_4. Recrystallisation from aq. ethanol afforded the title acid (**16c**)[21] (8.8 g, 75%), m.p. 184 °C; ν_{max}(Nujol) 1 695 and 1 590 cm^{-1}; δ 2.4 (s, 3 H, ArMe), 3.85 (s, 6 H, 2 × ArOMe), 6.25 and 7.9 (2 d, *J* 14 Hz, 2 H, CH=CH), 6.7 (s, 1 H, ArH), 7.1 (s, 1 H, ArH), and 10.2 (br s, 1 H, CO_2H).

Ethyl 4,5-*Dimethoxy*-2-*methylcinnamate* (**16d**).—A mixture of 4,5-dimethoxy-2-methylcinnamic acid (**16c**) (8.5 g), absolute ethanol (100 ml), and conc. sulphuric acid (2 g) was refluxed for 6 h. Alcohol was distilled off and the residue (20 ml) was diluted with water (100 ml) and was extracted with diethyl ether (3 × 50 ml). The extract was washed successively with water, aq. sodium hydrogen carbonate, and again with water. Removal of the solvent from the dried (Na_2SO_4) extract gave a residue, which was triturated with hexanes, when crystals of *ethyl* 4,5-*dimethoxy*-2-*methylcinnamate* (**16d**) were obtained (7.2 g, 75%), m.p. 71 °C (Found: C, 66.9; H, 7.15. $C_{14}H_{18}O_4$ requires C, 67.2; H, 72%); ν_{max}(Nujol) 1 720, 1 600, and 1 580 cm^{-1}; δ 1.15 (t, *J* 8 Hz, 3 H, CH_2Me), 2.4 (s, 3 H, ArMe), 3.85 (s, 6 H, 2 × ArOMe), 4.2 (q, *J* 8 Hz, 2 H, CH_2Me), 6.25 and 7.9 (2 d, *J* 14 Hz, 2 H, CH=CH), 6.7 (s, 1 H, ArH), and 7.1 (s, 1 H, ArH).

Ethyl 2,3-*Dibromo*-3-(4,5-*dimethoxy*-2-*methylphenyl*)*propionate* (**17b**).—A suspension of the ester (**16d**) (7 g) in carbon tetrachloride (30 ml) at 0 °C was slowly treated with a solution of bromine (6.0 g) in carbon tetrachloride (5 ml), in artificial light. After the addition was complete, the mixture was stirred for 3 h. The solvent was evaporated off to afford the dibromo ester, which was crystallised from diethyl ether, to furnish *ethyl* 2,3-*dibromo*-3-(4,5-*dimethoxy*-2-*methylphenyl*)*propionate* (**17b**) (8.2 g, 85%), m.p. 112 °C (Found: C, 41.3; H, 4.45. $C_{14}H_{18}Br_2O_4$ requires C, 41.0; H, 4.39%); ν_{max}(Nujol) 1 745 and 1 605 cm^{-1}; δ 1.18 (t, *J* 8 Hz, 3 H, CH_2Me), 2.5 (s, 3 H, ArMe), 3.85 (s, 6 H, 2 × ArOMe), 4.35 (q, *J* 8 Hz, 2 H, CH_2Me), 4.85 and 5.7 (2 d, *J* 10 Hz, CHBrCHBr), and 6.9 and 7.25 (2 s, 2 H, ArH).

Methyl 3-(4,5-*Dimethoxy*-2-*methylphenyl*)*propiolate* (**18d**).—A mixture of the dibromo ester (**17b**) (8 g) in ethanol (20 ml) and dioxane (25 ml) containing a solution of KOH (6 g) in water (5 ml) was heated at 110 °C and stirred for 7 h. The solvent was removed under reduced pressure, and the residue was diluted with water (50 ml) and was then recrystallised from aq. alcohol to afford the *acid* (**18c**) (3.5 g, 80%), m.p. 147 °C (Found: C, 65.25; H, 5.4. $C_{12}H_{12}O_4$ requires C, 65.45; H, 5.45%); ν_{max}(Nujol) 2 250, 1 700, 1 600, and 1 590 cm^{-1}; δ 2.4 (s, 3 H, ArMe), 3.85 (s, 6 H, 2 × ArOMe), 6.7 (s, 1 H, ArH), and 7.15 (s, 1 H, ArH).

A solution of the acid (**18c**) (1.2 g) in methanol (20 ml) was treated with excess of ethereal diazomethane and the solution was left overnight. Evaporation of the solvent then yielded the ester, which was crystallised from ethanol to yield pure *methyl* 3-(4,5-*dimethoxy*-2-*methylphenyl*)*propiolate* (**18d**) (1.2 g, 85%), m.p. 122 °C (Found: C, 66.5; H, 5.9. $C_{13}H_{14}O_4$ requires C, 66.67; H, 5.9%); ν_{max}(Nujol) 2 250, 1 720, 1 600, and 1 590 cm^{-1}; δ 2.4 (s, 3 H, ArMe), 3.85 (s, 6 H, 2 × ArOMe), 3.9 (s, 3 H, CO_2Me), 6.7 (s, 1 H, ArH), and 7.15 (s, 1 H, ArH).

Methyl Trimethylaltenusin (**21a**).—Methyl 3-(4,5-dimethoxy-2-methylphenyl)propiolate (**18d**) (1.8 g) was heated with 1,5-dimethoxycyclohexa-1,4-diene (**4**) (1 g) in an evacuated, sealed tube to a temperature of 180 °C. Heating was continued for period of 30 h, after which the temperature of the reaction tube was raised to 220 °C and the same temperature was maintained as this value for 4 h. The reaction mixture was allowed to attain room temperature. The brown viscous liquid was dissolved in chloroform (50 ml) and the solution was washed successively with dil. aq. sodium hydroxide and water, dried (Na_2SO_4), and the solvent was distilled off. The residue was sublimed at 195 °C at 5 mmHg to remove impurities. From the viscous liquid obtained, tetramethylaltenusin (**21a**) (0.55 g) was separated by PLC [ethyl acetate–hexane (2:3)]. After being kept for one week in a refrigerator, methyl trimethylaltenusin (**21a**) crystallised slowly from methanol, m.p. 116 °C (lit.,[17] 117–118 °C), identical with an authentic sample (Found: C, 66.2, H, 6.4. Calc. for $C_{19}H_{22}O_6$: C, 65.9; H, 6.36%); ν_{max}(Nujol) 1 725, 1 600, and 1 517 cm^{-1}; δ 2.12 (s, 3 H, ArMe), 3.52, 3.82, and 3.87 (3 s, 12 H, 4 × ArOMe), 3.9 (s, 3 H, CO_2Me), 6.35 (d, *J* 2.5 Hz, 1 H, ArH), 6.48 (d, *J* 2.5 Hz, 1 H, ArH), 6.69 (s, 1 H, ArH), and 6.73 (s, 1 H, ArH).

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