The Total Synthesis of some Deuterium Labelled Pentaketide Derivatives of Orsellinic Acid

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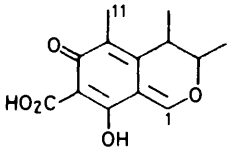
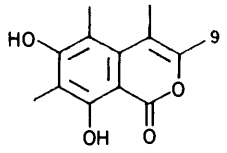
The total syntheses of 4,6-dihydroxy-3,5-dimethyl-2-(1-methyl-2-oxopropyl)benzaldehyde and 6,8-dihydroxy-3,4,5,7-tetramethyl-3,4-dihydroisocoumarin, which allow the insertion of specific deuterium labels, are described.

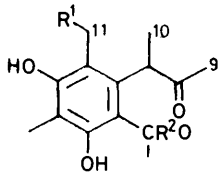
As part of our study of the biosynthesis of the pentaketide antibiotic citrinin (1) we were interested in synthesising the potential advanced biosynthetic intermediates (2), (3), (4), and (5) which are at different oxidation levels and any one of which could be the first enzyme-free intermediate in the biosynthesis. The synthesis of (2) has been described [1] and an incorporation study performed.[2] This paper describes the total synthesis of compounds (3) and (4) by routes which allow insertion of labels at suitable selected sites.



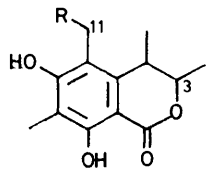
(1)



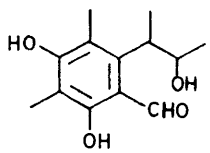
(2)



(3) $R^1 = R^2 = H$
a; $R^1 = H$, $R^2 = D$
b; $R^1 = D$, $R^2 = H$



(4) R = H
b; R = D



(5)

The indanone (6) was chosen as a suitable key intermediate. It has been prepared by two independent routes [1,3] and has been used in the total synthesis of sclerotinin A by oxidative cleavage of the indanone ring.

The dimethyl ether of (3) has been reported as an unstable synthetic intermediate in Tanaka's synthesis of sclerotinin A [3] but was not fully characterised. It was produced by ozonolysis of the indene (8) derived from reduction of (6) followed by dehydration of the resulting alcohol (7). Repetition of these steps but with the vital modification of working up the ozonolysis reaction with dimethyl sulphide, rather than zinc and acetic acid, yielded the ketoaldehyde (9) in a sufficiently pure form for it to be characterised fully. The product is unstable to acid, and is very heat sensitive but can be stored satisfactorily for several days at −18 °C.

The n.m.r. spectrum is interesting, being most easily interpretable in terms of a ketoaldehyde structure in which the aldehyde signal appears at δ 6.7. The protons on the carbon atoms adjacent to the ketone function also resonate at a somewhat higher field. We attribute these values to steric crowding which forces the aldehyde group to lie out of the plane of the benzene ring and the ketone oxygen to lie close to the aldehyde carbon. The i.r. spectrum with a broad carbonyl peak at 1 705—1 715 cm^{-1} is consistent with the assigned structure.

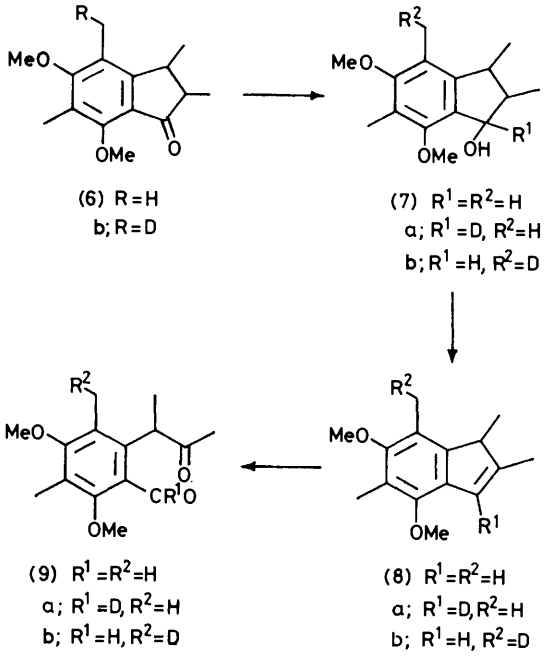
Despite its lability to acid the ketoaldehyde was successfully deprotected using boron tribromide. The borate complex breaks down only very slowly on addition of water and on work-up no trace of (3) was found in the organic extracts but it crystallised slowly from the aqueous mother-liquors at room temperature. Steric crowding is now greatly diminished and a model shows that in this compound it is possible for the aldehyde moiety to be in the plane of the benzene ring. As would be expected the aldehyde proton now appears at *ca.* δ 10 in the ^1H n.m.r. spectrum and the i.r. and u.v. spectra reveal that the aldehyde group is conjugated with the benzene ring. The compound is a crystalline solid and is indefinitely stable at room temperature.

Classically, ^{14}C has been used as a label in incorporation studies with advanced precursors, and in earlier work [1] the isocoumarin (2) was prepared with a ^{14}C label in the C-9 position indicated. This procedure necessitated a multi-step synthesis of tiglic acid, which, in unlabelled form, is commercially available. With the increasing availability of ^2H n.m.r. spectroscopy we were attracted to the possibility of using deuterium rather than ^{14}C as a label. Our synthesis of (3) provides two alternative methods of inserting a deuterium label, in positions which would be easily detectable in citrinin (1).

Firstly in the (a) series of deuterium analogues a deuterium label is introduced in the reduction of the

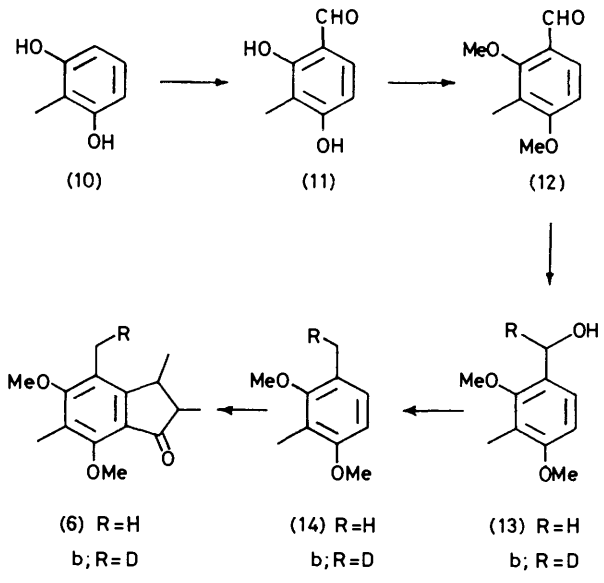
indanone (6) by using lithium aluminium deuteride to give (7a). Subsequent steps of Scheme 1 lead through dehydration to give (8a), ozonolysis to give (9a) which on demethylation gives (3a).

The early steps of the synthetic sequence leading to the



SCHEME 1

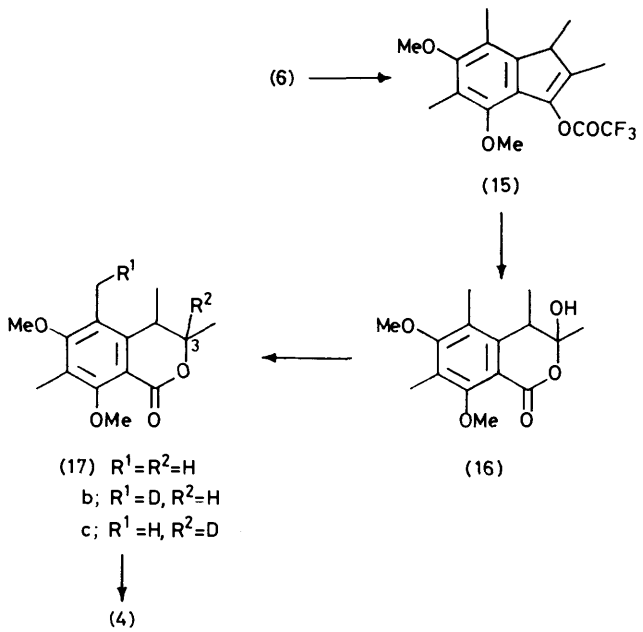
deuterium analogue (3b) are shown in Scheme 2. These are based on a modification of the earlier synthesis [1] of the indanone so as to allow the introduction of a single



SCHEME 2

deuterium label in one of the C-methyl groups. Commercially available 2-methylresorcinol (10) is formylated by the Gattermann reaction [4] to give (11) which forms (12) in high yield on methylation with dimethyl sulphate. In a pilot study this was reduced with sodium borohydride or lithium aluminium hydride to the alcohol (13) which on hydrogenolysis followed by Friedel-Crafts reaction with tiglyl chloride using either of the published methods [1,3] yields the key indanone (6). The (b) series of deuterium analogues is started by using sodium borodeuteride or lithium aluminium hydride in the reduction of (12). The product (13b) is converted *via* (14b) into (6b). The material is then carried through the series of steps illustrated in Scheme 1 to produce eventually the deuterium analogue (3b).

Our first synthesis (Scheme 3) of the lactone (4)

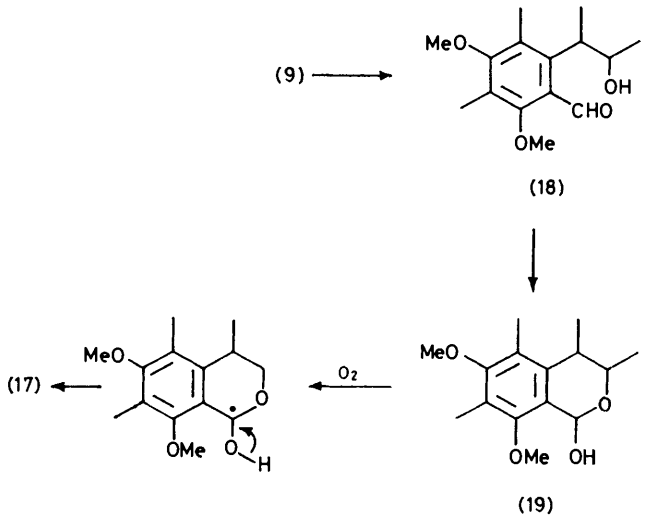


SCHEME 3

followed a published procedure [1] as far as the dimethoxy-analogue of sclerotinin A (16). Treatment of (16) with sodium borohydride in the presence of 0.1M-ethoxide gave the dimethoxylactone (17), which was deprotected with boron tribromide to give (4), as white needles. Citrinin is of *trans*-stereochemistry at C-3 and C-4 and so the *trans*-isomer of (4) was required for feeding experiments. Fortuitously this was the only isomer isolated, the borohydride reduction of (16) having given only the *trans*-isomer of (16). However, this synthesis involves two steps (15) → (16) and (16) → (17) which give very variable yields, and is thus unsatisfactory for use with expensive isotopes. Fortunately a superior synthesis was discovered during unsuccessful attempts to synthesise the aldehydo-alcohol (5).

It was reasoned that because of steric crowding the aldehyde function of the ketoaldehyde (9) would be inaccessible to nucleophilic reagents. However, treatment of (9) with sodium borohydride, instead of giving the aldehydo-alcohol (18), surprisingly gave the lactone (17) in high yield (Scheme 4). Initially we suspected

that a Canizarro reaction might have occurred and accordingly prepared (9a) which has a deuterium label in the aldehyde function (see Scheme 1). Treatment of this compound with sodium borohydride again yielded unlabelled (17). Further, treatment of unlabelled (9) with sodium borodeuteride gave rise to (17c) in which C-3 bears a deuteron. We conclude therefore that borohydride indeed reduced the ketone function of (9) to the alcohol but that the aldehyde group is subsequently oxidised by an external source. Standard measures to exclude air during the reduction did not prevent the formation of (17) (in fact the yield was slightly enhanced). It was, therefore, reasoned that the oxidation was taking place in air during work-up, presumably *via* the benzyl radical of the hemiacetal (19) (Scheme 4). This reaction



SCHEME 4

also yields only the *trans*-isomer of (17); it is reliable and high yielding and so became the method of choice for the preparation of (4).

The lactone (4) can be synthesised with a deuterium label in the aromatic methyl group C-11 *via* the indanone (6b) (Scheme 2). Alternatively a deuterium label may be inserted at C-3 as described above. Both (3) and (4) have been synthesised with a deuterium label in the methyl group, C-11, and their incorporation into citrinin by *Penicillium citrinum* tested.[5] It was found that (4) was not incorporated but (3) showed substantial incorporation. This, together with other evidence,[6] suggests that (3) is an advanced precursor in the biosynthesis of citrinin.

EXPERIMENTAL

General Procedures.—M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected. U.v. spectra were taken on a Unicam SP800B spectrometer; all samples were in 95% ethanol. I.r. spectra were taken on a Perkin-Elmer 257 i.r. spectrometer; all samples were in chloroform solution unless otherwise stated. ^{1}H N.m.r. spectra were determined on either a Varian HA100 spectrometer or a Varian XL100 spectrometer. Samples were dissolved in deuteriochloroform and tetramethylsilane was used as internal standard unless otherwise stated. Preparative layer chromatography was undertaken with plates (20 × 20 cm) coated with Merck Kieselgel GF_{254}. Organic solutions were dried by washing with saturated brine then standing over anhydrous sodium sulphate unless otherwise stated. All solvents and reagents were purified by standard methods.

4-Formyl-2-methylresorcinol (11).—Powdered, anhydrous zinc cyanide (10 g), 2-methylresorcinol (5 g), and dry ether (100 ml) were stirred together vigorously. Dry hydrogen chloride gas was passed through the mixture for 45 min.

The ether was decanted off and the pink aldimine hydrochloride was washed four times with dry ether, then taken up in ice–water (100 ml). The temperature of the solution was slowly raised to 40 °C. The solution was retained at this temperature until all the remaining ether had boiled off and white crystals of the aldehyde were beginning to precipitate. The mixture was allowed to cool and was stored at 4 °C overnight. The aldehyde was filtered off and recrystallised from aqueous ethanol to give white needles (5.55 g, 91%), which turn superficially pink in the air; m.p. 149—151 °C (lit.,[4] 152—153 °C); $\lambda_{max.}$ 285 nm; $\nu_{max.}$ 1 640s and 2 900b cm^{-1}; δ 11.62 (1 H, s, Ar-OH), 9.64 (1 H, s, ArCHO), 7.27 (1 H, d, *J* 8 Hz, ArH), 6.45 (1 H, d, *J* 8 Hz, Ar-H), 5.61 (1 H, d, *J* 8 Hz, Ar-H), 5.61 (1 H, s, ArOH), and 2.14 p.p.m. (3 H, s, $ArCH_3$); *m/e* 152, 151, 137, and 123.

1,4-Dimethoxy-3-methylbenzaldehyde (12).—4-Formyl-2-methylresorcinol (5 g) was dissolved in dry acetone (150 ml) and anhydrous potassium carbonate (25 g) was added slowly, with vigorous stirring. Dimethyl sulphate (5 ml) was added carefully and the solution was stirred at reflux for 5 h, until t.l.c. (silica, 3 : 1 chloroform–ether) showed that the reaction was complete. The solution was cooled, filtered, and evaporated and the resulting solid recrystallised from ethanol containing a few drops of triethylamine–water to give colourless needles (5.45 g, 92%), m.p. 53—54 °C (lit.,[7] 54—55 °C); $\lambda_{max.}$ 285 (nm; $\nu_{max.}$ 1 695s and 1 600m cm^{-1}; δ 10.29 (1 H, s, ArCHO), 7.80 (1 H, d, *J* 9 Hz, ArH), 6.90 (1 H, d, *J* 9 Hz, ArH), 3.83 (3 H, s, $ArOCH_3$), 3.80 (3 H, s, $ArOCH_3$), and 2.14 p.p.m. (3 H, s, $ArCH_3$); *m/e* 180 (M^+).

2,4-Dimethoxy-3-methylbenzyl Alcohol (13).—1,4-Dimethoxy-3-methylbenzaldehyde (4.5 g) was dissolved in dry ether (20 ml) and lithium aluminium hydride (400 mg) added. The solution was stirred at room temperature for 3 h, then poured into ice–concentrated sulphuric acid (50 ml : 2 ml). The aqueous layer was extracted with chloroform (3 × 20 ml) and the combined organic layers were washed with brine, dried, and evaporated to give a colourless liquid on distillation (yield 3.5 g, 78%), b.p. 80—90 °C, at 0.3 Torr (Found: M^+, 182.0944. $C_{10}H_{14}O_3$ requires *M*, 182.0942); $\nu_{max.}$ 3 380s,b, 2 817m, and 1 603m cm^{-1}; δ 7.20 (1 H, d, *J* 8 Hz, ArH), 6.5 (1 H, d, *J* 8 Hz, ArH), 4.75 (2 H, bs, $ArCH_2OH$), 3.75 (3 H, s, $ArOCH_3$), 3.65 (3 H, s, $ArOCH_3$), 2.70 (1 H, bs, OH), and 2.10 p.p.m. (3 H, s, $ArCH_3$); *m/e* 182, 181, 167, 153, 151, and 149.

2,4-Dimethoxy-3-methyl[α-^{2}H]benzyl Alcohol (13b).—The method used to prepare this was as above, lithium aluminium deuteride replacing lithium aluminium hydride; δ 7.10 (1 H, d, *J* 8 Hz, ArH), 6.59 (1 H, d, *J* 8 Hz, ArH), 4.60 (1 H, t, *J* 2 Hz, C*H*DOH), 3.80 (3 H, s, $ArOCH_3$), 3.76 (3 H, s, $ArOCH_3$), and 2.16 p.p.m. (3 H, s, $ArCH_3$); *m/e* 183, 168, and 166.

1,3-Dimethoxy-2,4-dimethylbenzene (14).—Palladium oxide (0.1 g) was suspended in glacial acetic acid (10 ml), and the

suspension was hydrogenated for 1 h until hydrogen uptake ceased. 2,4-Dimethoxy-3-methylbenzyl alcohol (13) (2.5 g) in glacial acetic acid (20 ml) was added, and the solution was hydrogenated until hydrogen uptake ceased. The solution was filtered (Hyflosupercel) and evaporated and the resulting oil was distilled to give a colourless liquid (1.8 g, 79%), b.p. 68—72 °C, τ 0.2 (lit.,[8] 85 °C, τ 3); $\nu_{max.}$ 1 600m cm^{-1}; δ 6.83 (1 H, d, *J* 8.4 Hz, ArH), 6.40 (1 H, d, *J* 8.4 Hz, ArH), 3.69 (3 H, s, $ArOCH_3$), 3.62 (3 H, s, $ArOCH_3$), 2.17 (3 H, s, $ArCH_3$), and 2.10 p.p.m. (3 H, s, $ArCH_3$); *m/e* 166, 151, 135, 120, and 105.

2,4-*Dimethoxy*-3-*methyl*-[α-^{2}H]*toluene* (14b). The method used to prepare this was as above using (13b) instead of (13) (Found: M^+, 167.1059. $C_{10}DH_{13}O_2$ requires *M*, 167.1056); δ 6.95 (1 H, d, *J* 8.5 Hz, ArH), 6.50 (1 H, d, *J* 8.5 Hz, ArH), 3.77 (3 H, s, $ArOCH_3$), 3.70 (3 H, s, $ArOCH_3$), and 2.15 p.p.m. (5 H, br s, $ArCH_3$ and $ArCH_2D$); *m/e* 167, 152, 136, and 92.

5,7-*Dimethoxy*-2,3,4,6-*tetramethylindan*-1-*one* (6).—1,3-Dimethoxy-2,4-dimethylbenzene (13a) (0.83 g, 5 mmol) was dissolved in Analar carbon disulphide (30 ml). Stannic chloride (2 ml, 14 mmol) and *trans*-2-methylbut-2-enoyl chloride (0.5 ml, 4.8 mmol were added and the solution was stirred at reflux for 2 h. The solvent was distilled off at atmospheric pressure and sodium hydroxide (50 ml of a 10% solution) and ether (20 ml) were added. The mixture was stirred vigorously until the residue completely dissolved. The aqueous layer was further extracted with ether (2 × 20 ml) and the combined organic layers were dried and evaporated to give the indanone [3] as a yellow oil which was purified by distillation (125—130 °C at 0.5 Torr) (1.0 g, 80%); $\lambda_{max.}$ 260 and 302 nm; $\nu_{max.}$ 2 040s, 1 695s, 1 585s, and 1 325m cm^{-1}; δ 3.94 (3 H, s, $ArOCH_3$), 3.77 (3 H, s, $ArOCH_3$), 3.4—3.8 (1 H, m, ArCOC*H*Me), 2.70—3.05 (1 H, m, ArCH-Me), 2.29 and 2.27 (each 1.5 H, s, $ArCH_3$—two diastereoisomers in 1 : 1 ratio), 2.21 (3 H, s, $ArCH_3$), and 1.06—1.48 p.p.m. (6 H, m, $ArCHCH_3$ and $ArCOCHCH_3$); *m/e* 248 (M^+).

5,7-*Dimethoxy*-4-[^{2}H]*methyl*-2,3,6-*trimethylindan*-1-*one* (6b).—The method used to prepare this was as above using (14b) instead of (14) and with an excess (1 ml) of *trans*-2-methylbut-2-enoyl chloride. This resulted in the formation of only one diastereoisomer of the indanone (Found: M^+, 249.1474. $C_{15}DH_{19}O_3$ requires *M*, 249.1475); δ 3.93 (3 H, s, $ArOCH_3$), 3.77 (3 H, s, $ArOCH_3$), 3.39—3.65 (1 H, m, COC*H*Me), 2.87 (1 H, quintet, *J* 7.8 Hz, ArC*H*Me), 2.26 (2 H, t, *J* 2.1 Hz, $ArCH_2D$), 2.20 (3 H, s, $ArCH_3$), 1.22 (3 H, d, *J* 7.8 Hz, $ArCHCH_3$), and 1.09 p.p.m. (3 H, d, *J* 6.5 Hz, $ArCOCHCH_3$); *m/e* 249, 234, 220, and 167.

5,7-*Dimethoxy*-2,3,4,6-*tetramethylindan*-1-*ol* (7).—5,7-Dimethoxy-2,3,4,6-tetramethylindan-1-one (6) (440 mg) was dissolved in dry ether (10 ml). Lithium aluminium hydride (100 mg) was added slowly and the suspension was stirred at room temperature for 3 h and then poured into ice–concentrated sulphuric acid (25 ml : 1 ml). The organic layer was separated, the aqueous layer extracted with ether (2 × 10 ml) and the combined organic layers washed with water (10 ml) then dried, and evaporated to give a pale yellow oil (440 mg, 99%), which was used without further purification; $\nu_{max.}$ 3 430, 2 950, 1 595, and 1 115 cm^{-1}; δ 4.84 (1 H, d, *J* 2 Hz, ArC*H*OH), 3.80 (3 H, 2 × s, $ArOCH_3$ of two diastereoisomers), 3.67 (3 H, s, $ArOCH_3$), 3.20 (2 H, m, CHMe), 2.70 (1 H, s, OH), 2.18 (6 H, s, $ArCH_3$), and 0.95—1.31 p.p.m. (6 H, m, $CHCH_3$ of two diastereoisomers); *m/e* 250, 249, and 235.

5,7-*Dimethoxy*-4-[^{2}H]*methyl*-2,3,6-*tetramethylindan*-1-*ol* (7b).—This was prepared as above using (6b) instead of (6) (Found: M^+, 251.1624. $C_{15}DH_{21}O_3$ requires *M*, 251.1631); δ 4.84 (1 H, br s, ArC*H*OH), 3.80 (3 H, 2 × s, $ArOCH_3$ of two diastereoisomers), 3.67 (3 H, s, $ArOCH_3$), 3.20 (2 H, m, CHMe), 2.70 (1 H, s, OH), 2.21 (3 H, s, $ArCH_3$), 2.18 (2 H, t, *J* 1.4 Hz, partly obscured), and 0.95—1.31 p.p.m. (6 H, m, $CHCH_3$ of two diastereoisomers); *m/e* 251, 250, 233, and 218.

5,7-*Dimethoxy*-2,3,4,6-*tetramethyl*[1-^{2}H]*indan*-1-*ol* (7a).—This was prepared as for (7) with lithium aluminium deuteride replacing lithium aluminium hydride (Found: M^+, 251.1617. $C_{15}DH_{21}O_3$ requires *M*, 251.1631); 3.80 (3 H, 2 × s, $ArOCH_3$ of two diastereoisomers), 3.67 (3 H, s, $ArOCH_3$), 3.20 (2 H, m, C*H*Me), 2.70 (1 H, s, OH), 2.18 (6 H, s, $ArCH_3$), and 0.95—1.31 p.p.m. (6 H, m, $CHCH_3$ of two diastereoisomers); *m/e* 251, 233, and 218.

5,7-*Dimethoxy*-2,3,4,6-*tetramethylindene* (8).—A trace of toluene-*p*-sulphonic acid was dissolved in (7) (250 mg, 1 mmol), which was then distilled under reduced pressure (130—140°, 0.4 Torr) to give a yellow oil (179 mg, 77%), $\lambda_{max.}$ 267 nm; $\nu_{max.}$ 2 950, 1 603, 1 273, and 1 110 cm^{-1}; δ 6.48 (1 H, q, *J* 1.0 Hz, ArC*H*=CHMe), 3.81, 3.70 (each 3 H, s, $ArOCH_3$), 3.24 (1 H, q, *J* 0.75 Hz, ArC*H*CH_3), 2.29, 2.22 (each 3 H, s, $ArCH_3$), 2.04 (3 H, d, *J* 1.0 Hz, ArCH=CCH_3), and 1.28 p.p.m. (3 H, d, *J* 8 Hz, $ArCHCH_3$); *m/e* 232 and 217.

5,7-*Dimethoxy*-4-[^{2}H]*methyl*-2,3,6-*tetramethylindene* (8b).—This was prepared as for (8) with (7b) replacing (7) (Found: M^+, 233.1530. $C_{15}DH_{19}O_2$ requires *M*, 233.1526); δ 6.46 (1 H, q, *J* 1 Hz, ArC*H*=CHMe), 3.81, 3.70 (each 3 H, s, $ArOCH_3$), 3.24 (1 H, q, *J* 8 Hz, ArCHMe), 2.38 (2 H, t, *J* 3 Hz, $ArCH_2D$), 2.23 (3 H, s, $ArCH_3$), 2.06 (3 H, d, *J* 1.0 Hz, ArCH=CCH_2), and 1.29 p.p.m. (3 H, d, *J* 8 Hz, $ArCHCH_3$); *m/e* 233, 218, and 167.

5,7-*Dimethoxy*-2,3,4,6-*tetramethyl*[1-^{2}H]*indene* (8a).—This was prepared as for (8) with (7a) replacing (7) (Found: M^+, 233.1522. $C_{15}DH_{19}O_2$ requires *M*, 233.1526); δ 3.83, 3.73 (each 3 H, s, $ArOCH_3$), 3.24 (1 H, q, *J* 8 Hz, ArCHMe), 2.30, 2.25 (each 3 H, s, $ArCH_3$), 2.06 (3 H, s, ArCD=CCH_3), and 1.26 p.p.m. (3 H, d, *J* 8 Hz, $ArCHCH_3$); *m/e* 233, 218, and 190.

4,6-*Dimethoxy*-3,5-*dimethyl*-2-(1-*methyl*-2-*oxopropyl*)*benzaldehyde* (9).[3]—The indene (8) (65 mg) was dissolved in dry ethyl acetate (50 ml) and cooled to −78 °C. The solution was flushed with dry nitrogen, then ozone was passed through until a blue colouration was obtained. The solution was left at −78 °C for 10 min and then flushed with dry nitrogen until no positive starch–iodide test was obtained. Dimethyl sulphide (0.5 ml) was added and the solution allowed to warm towards room temperature over 10 min. The solvent was removed under reduced pressure to leave a pale yellow oil which was used without further purification the same day, or stored at −18 °C; b.p. 200—210 °C at 0.3 Torr; (Found: M^+, 264.1366. $C_{15}H_{20}O_4$ requires *M*, 264.1362); $\lambda_{max.}$ 255w and 276w nm; $\nu_{max.}$ 1 718 and 1 700 cm^{-1}; δ 6.69 (1 H, s, CHO), 3.75, 3.71 (each 3 H, s, $ArOCH_3$), 2.95 (1 H, q, *J* 7 Hz, ArC*H*Me), 2.21, 2.18 (each 3 H, s, $ArCH_3$), 1.72 (3 H, s, $COCH_3$), and 1.24 p.p.m. (3 H, d, *J* 7 Hz, $ArCHCH_3$); *m/e* 264, 248, 233, and 221.

4,6-*Dimethoxy*-3,5-*di*[3-^{2}H]*methyl*-2-(1-*methyl*-2-*oxopropyl*)*benzaldehyde* (9b).—This was prepared as above, (8b) replacing (8) (Found: M^+, 265.1429. $C_{15}DH_{19}O_4$ requires *M*, 265.1424); δ 6.68 (1 H, s, CHO), 3.73, 3.70 (each 3 H, s, $ArOCH_3$), 2.94 (1 H, q, *J* 7 Hz, ArCHMe), 2.21 (3 H, s, $ArCH_3$), 2.16 (2 H, t, *J* 2.5 Hz, $ArCH_2D$), 1.70 (3 H, s,

$COCH_3$), and 1.24 p.p.m. (3 H, d, *J* 7 Hz, ArCHCH_3); *m/e* 265, 253, 249, 235, 222.

4,6-*Dimethoxy*-3,5-*dimethyl*-2-(1-*methyl*-2-*oxopropyl*)-*benz*[^{2}H]*aldehyde* (9a).—This was prepared as for (9), (8a) replacing (8), δ 3.75, 3.71 (each 3 H, s, $ArOCH_3$), 2.95 (1 H, q, *J* 7 Hz, ArC*H*Me), 2.21 2.18 (each 3 H, s, $ArCH_3$), 1.72 (3 H, s, $COCH_3$), and 1.24 p.p.m. (3 H, d, *J* 7 Hz, ArCHCH_3).

4,6-*Dihydroxy*-3,5-*dimethyl*-2-(1-*methyl*-2-*oxopropyl*)-*benzaldehyde* (3).—4,6-Dimethoxy-3,5-dimethyl-2-(1-methyl-2-oxopropyl)benzaldehyde (9) [from (8), 200 mg], was dissolved in dry dichloromethane (30 ml), and cooled to −78 °C. Boron tribromide (1 ml) was added and the solution was allowed to warm to room temperature overnight with stirring. Ether (30 ml) then water (30 ml) were added cautiously. The aqueous layer was washed with ether (30 ml) and then left at room temperature for 24 h during which time white crystals began to form. It was then kept at 4 °C for 2 days. The very pale yellow needles (100 mg, 50% over two steps) were recrystallised from methanol, m.p. 186—186.5 °C (Found: C, 66.25; H, 6.9. $C_{13}H_{16}O_4$ requires C, 66.08; H, 6.83%); $\lambda_{max.}$ 298 and 391 nm; $\nu_{max.}$ 3 370, 1 700, and 1 605 cm^{-1}; δ(acetone) 13.03 (1 H, s, OH), 9.97 (1 H, s, CHO), 8.50 (1 H, br s, OH), 4.43 (1 H, q, *J* 7 Hz, ArCHMe), 2.20 (3 H, s, $ArCH_3$, 2.17 (3 H, s, $ArCH_3$), 2.05 (3 H, s, ArCHMeCOCH_3), and 1.46 p.p.m. (3 H, d, *J* 7 Hz, ArCHCH_3); *m/e* 236, 221, 218, 194, and 193.

4,6-*Dihydroxy*-3,5-di[3-^{2}H]*methyl*-2-(1-*methyl*-2-*oxopropyl*)*benzaldehyde* (3b).—This was prepared as for (3), (9b) replacing (9) (Found: M^+, 237.1109. $C_{13}DH_{15}O_4$ requires *M*, 237.1112); δ(acetone) 13.03 (1 H, s, OH), 9.97 (1 H, s, CHO), 8.50 (1 H, s, OH), 4.43 (1 H, q, *J* 7 Hz, ArCHMe), 2.20 (5 H, br s, $ArCH_3$ and $ArCDH_2$), 2.05 (3 H, s, ArCHMeCOCH_3), and 1.46 p.p.m. (3 H, d, *J* 7 Hz, ArCHCH_3); *m/e* 237, 219, and 194.

6,8-*Dimethoxy*-3,4,5,7-*tetramethyl*-3,4-*dihydroisocoumarin* (17).—*Method* 1. At −78 °C butyl-lithium (3 ml of a 1.6M-solution in hexane) was added to absolute alcohol (6 ml). The solution was stirred for 10 min and then 3-hydroxy-6,8-dimethoxy-3,4,5,7-tetramethyl-3,4-dihydroisocoumarin [1] [from 100 mg of (6)] in ethanol (5 ml) was added. The solution was allowed to warm to room temperature and then sodium borohydride (60 mg) was added. The solution was stirred at reflux under nitrogen for 6 h. It was then evaporated to dryness and partitioned between water and ether. The aqueous layer was washed with ether (20 ml) and then acidified (conc. hydrochloric acid) and extracted with ether (3 × 20 ml). These ether extracts were combined, dried, and evaporated. Further purification could be achieved by p.l.c. [silica chloroform–ether (3 : 1),]; yield 58 mg (49% over three steps).

Method 2. 4,6-Dimethoxy-3,5-dimethyl-2-(1-methyl-2-oxopropyl)benzaldehyde (9) (90 mg) was dissolved in ethanol (95%, 20 ml), and sodium borohydride (45 mg) was added. The solution was stirred overnight under nitrogen and then evaporated to dryness. The residue was partitioned between water and ether. The aqueous layer was washed with ether (20 ml) and then acidified (conc. hydrochloric acid) and extracted with ether (5 × 15 ml). These combined extracts were washed with brine, dried, and evaporated to give a colourless oil (70 mg, 77.5%), b.p. 105—115° at 0.2 Torr) (Found: M^+, 264.1359. $C_{15}H_{20}O_4$ requires *M*, 264.1362); $\lambda_{max.}$ 251 and 295 nm; $\nu_{max.}$ 1 680 and 1 580 cm^{-1}; δ 4.59 (1 H, q, *J* 6.5 Hz, ArCOOC*H*CH_3), 3.86, 3.76 (each 3 H, s, $ArOCH_3$), 2.94 (1 H, q, *J* ArC*H*CH_3), 2.25, 2.22 (each 3 H, s, $ArCH_3$), 1.32 (3 H, d, *J* 7 Hz, ArCHCH_3), and 1.25 p.p.m. (3 H, d, *J* 6.5 Hz, ArCOOCH-CH_3); *m/e* 264.

6,8-*Dimethoxy*-5-[^{2}H]*methyl*-3,4,7-*trimethyl*-3,4-*dihydroisocoumarin* (17b).—This was prepared as above with (9b) replacing (9); δ 4.63 (1 H, q, *J* 6.5 Hz, ArCOOC*H*Me), 3.84, 3.74 (each 3 H, s, $ArOCH_3$), 3.02 (1 H, q, *J* 7 Hz, ArC*H*Me), 2.24 (3 H, s, $ArCH_3$), 2.18 (2 H, t, *J* 2 Hz, $ArCH_2D$), 1.35 (3 H, d, *J* 7 Hz, ArCHCH_3), and 1.25 p.p.m. (3 H, d, *J* 6.5 Hz, ArCOOCHCH_3); *m/e* 265.

6,8-*Dimethoxy*-3,4,5,7-*tetramethyl*-3,4-*dihydro*[3-^{2}H]*isocoumarin* (17c).—This was prepared as for (17) (method 2) with sodium borodeuteride replacing sodium borohydride (Found: M^+, 265.1447. $C_{15}DH_{19}O_4$ requires *M*, 265.1435); δ 3.81, 3.70 (each 3 H, s, $ArOCH_3$), 2.92 (1 H, q, *J* 7 Hz, ArC*H*Me), 2.20, 2.18 (each 3 H, s, $ArCH_3$), 1.37 (3 H, d, *J* 7 Hz, ArCHCH_3), and 1.27 p.p.m. (3 H, s, ArCOOCDCH_3); *m/e* 265, 250, 235, 232, and 204.

6,8-*Dihydroxy*-3,4,5,7-*tetramethyl*-3,4-*dihydroisocoumarin* (4).—Compound (17) (250 mg) was dissolved in dry dichloromethane (40 ml) and cooled to −78 °C. Boron tribromide (2 ml) was added and the solution was stirred overnight and allowed to warm to room temperature during that time. Ether (30 ml) was added cautiously, followed by water (50 ml). The organic layer was extracted once more with water (50 ml) and the combined aqueous layers were re-extracted with ether (2 × 30 ml). All the combined organic layers were dried and evaporated to give dirty white crystals which were recrystallised from methanol as needles (120 mg, 53.7%), m.p. 163—164 °C (Found: C, 65.95; H, 6.8. $C_{13}H_{16}O_4$ requires C, 66.08; H, 6.83%), $\lambda_{max.}$ 275 and 314 nm; $\nu_{max.}$ 3 580, 3 300br, 2 920, 1 650, 1 615, and 1 580w cm^{-1}; δ 11.74 (1 H, s, OH), 5.46 (1 H, br s, OH), 4.73 (1 H, q, *J* 6.6 Hz, $ArCO_2CH$Me), 3.02 (1 H, q, *J* 7.0 Hz, ArC*H*Me), 2.20, 2.18 (each 3 H, s, $ArCH_3$), 1.38 (3 H, d, *J* 6.6 Hz, $ArCO_2CHCH_3$), and 1.35 p.p.m. (3 H, d, *J* 7.0 Hz, ArCHCH_3); *m/e* 236.

6,8-*Dihydroxy*-5-[^{2}H]*methyl*-3,4,7-*trimethyl*-3,4-*dihydroisocoumarin* (4b).—This was prepared as for (4) with (17b) replacing (17); δ 11.74 (1 H, s, OH), 5.46 (1 H, br s, OH), 4.73 (1 H, q, *J* 6.6 Hz, $ArCO_2CH$Me), 3.02 (1 H, q, *J* 7.0 Hz, ArC*H*Me), 2.20 (3 H, s, $ArCH_3$), 2.18 (2 H, t, *J* 2 Hz, $ArCDH_2$), 1.38 (3 H, d, *J* 6.6 Hz, ArCOOCHCH_3), and 1.35 p.p.m. (3 H, d, *J* 7.0 Hz, ArCHCH_3); *m/e* 237.

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REFERENCES

[1] R. H. Carter, M. J. Garson, R. A. Hill, J. Staunton, and D. C. Sunter, *J. Chem. Soc., Perkin Trans. 1*, 1981, 471.
[2] R. H. Carter, M. J. Garson, and J. Staunton, *J. Chem. Soc., Chem. Commun.*, 1979, 1097.
[3] A. K. Tanaka, A. Kobayashi, and K. Yamashita, *Agric. Biol. Chem.*, 1973, **37**, 669.
[4] W. Baker, H. F. Bondy, J. W. F. McOmie, and H. R. Tunnicliff, *J. Chem. Soc.*, 1949, 2834.
[5] J. Barber and J. Staunton, *J. Chem. Soc., Chem. Commun.*, 1980, 552.
[6] J. Barber and J. Staunton, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2244.
[7] I. Godfrey, M. Sargent, and J. Elix, *J. Chem. Soc., Perkin Trans. 1*, 1974, 1353.
[8] T. Sassa, H. Aoki, and K. Munakata, *Tetrahedron Lett.*, 1968, 5703.