Synthesis and Regiospecific Deoxygenation of β-Resorcylic Ester Derivatives to 4-Hydroxybenzoates

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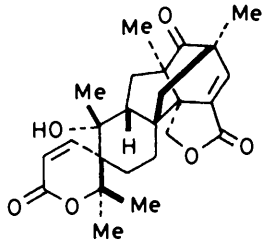
Ethyl [*carboxy*,6-$^{14}C_2$]-4-hydroxy-2-methyl- (6a), and -2,3,5-trimethyl-benzoate (6b), together with ethyl 4-hydroxy-2,3-dimethylbenzoate (6c), have been prepared in satisfactory yields by deoxygenation of the corresponding resorcylate esters, (5a—c), respectively, *via* hydrogenolysis of their 4-benzyloxy-2-(1-phenyl-1*H*-tetrazolyloxy)-derivatives, (8a—c). Ethyl 2,4-dihydroxy-5,6-dimethyl-3-trideuteriomethylbenzoate (5d) has been synthesised by trideuteriomethylation of ethyl 2,3-dimethyl-4,6-dioxocyclohexanecarboxylate (10c), followed by dehydrogenation. Preparations of the requisite resorcylate derivatives are included.

During biosynthetic studies on the polyketide-terpenoid derived fungal metabolites andibenin (1), andilesin (2), austin (3), and terretonin (4), reported elsewhere,[1,2] we have investigated the incorporations of ethyl [*carboxy*,2-$^{14}C_2$]-2,4-dihydroxy-6-methyl- (5a) and -3,5,6-trimethyl-benzoate (5b), the corresponding 3-trideuteriomethyl-5,6-dimethylbenzoate (5d), together with the monohydric phenols ethyl [*carboxy*,6-$^{14}C_2$]-4-hydroxy-2-methyl-(6a) and -2,3,5-trimethyl-benzoates (6b). We have shown that both the trimethylresorcylate (5b) and the trimethyl-*p*-hydroxybenzoate (6b) are efficient precursors of andibenin and andilesin, whereas the mono-*C*-methyl derivatives (5a) and (6a) are not. In the case of austin and terretonin, although the resorcylate derivative (5b) is efficiently incorporated the corresponding *p*-hydroxybenzoate (6b) is not. For each metabolite the specificity of incorporation has been established with the trideuteriomethyl derivative (5d). The significance of these results has been discussed.

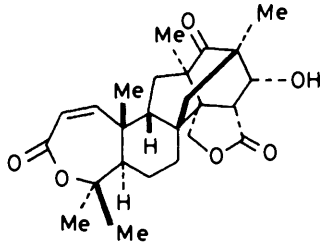
In view of the utility of these [^{14}C]- and [^{2}H]-labelled compounds in the biosynthetic studies, and because the synthesis of some of the compounds contained novel features, we now report fully the synthetic studies.

At the outset, we recognised that having obtained the requisite resorcylate derivatives (5a) and (5b) by conventional routes it would be convenient to derive the corresponding *p*-hydroxybenzoates (6a) and (6b) by regiospecific mono-deoxygenations of the former compounds. Although a number of procedures exist for phenolic deoxygenation, none appear to have been used previously in the regiospecific deoxygenation of polyhydric phenols and many would appear to be unsuitable for the required compounds. Most of the literature procedures are based on the reductive cleavage of the aryl–oxygen bond of appropriate phenolic ethers or esters.[3] A rather different, recent method involves the nucleophilic substitution of an *O*-methoxyaryloxazoline with t-butyl-lithium, followed by hydrolysis of the resultant *C*-t-butyl substituted aryloxazoline.[4]

After some initial experimental investigations we found that the most promising route was that involving the formation and hydrogenolysis of a 1-phenyltetrazolyl ether. This method, due to W. J. Musliner and J. W. Gates,[5] does not appear to have been widely applied, but there are a few interesting examples of its use [6,7] and extension.[8] In the present case, ethyl orsellinate (5a), ethyl 2,4-dihydroxy-3,5,6-trimethylbenzoate (5b), and ethyl 2,4-dihydroxy-5,6-dimethylbenzoate (5c) were readily converted into their 4-monobenzyl ethers (7a—c), respectively, which on treatment with 5-chloro-1-phenyl-1*H*-tetrazole and potassium carbonate in acetone gave high yields of the corresponding 1-phenyl-1*H*-tetrazol-2-yl



(1)



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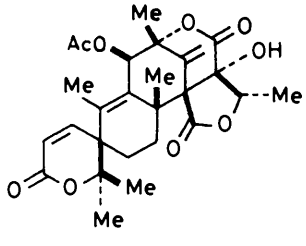

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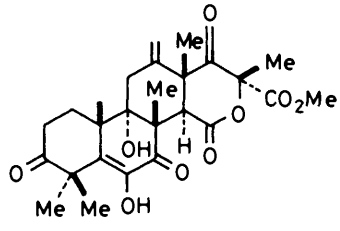
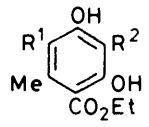
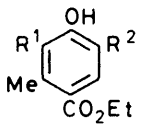


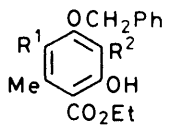
(4)

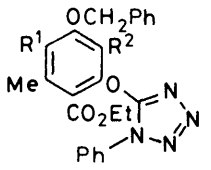
ethers (8a—c), respectively. Removal of the benzyl and tetrazolyloxy-groups from these proceeded smoothly by hydrogenolysis at room temperature and atmospheric pressure in the presence of palladium on carbon to give the requisite 4-hydroxybenzoate derivatives (6a—c), respectively. The experience gained with these heavily substituted aromatic compounds suggests that this method for synthetically useful phenolic deoxygenation is worthy of wider application.

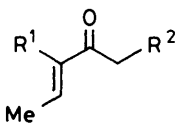
The standard route to the required orsellinate derivatives involves the intermediacy of the dihydro-derivatives derived by base-catalysed condensation between ethyl acetoacetate and the required α,β-unsaturated ester. Despite literature claims[9] we find that this method is unsatisfactory, except for the parent ethyl dihydro-orsellinate (10a). However, the alternative method using diethyl malonate and the requisite α,β-unsaturated ketones, (9a), (9c), and (9b) proceeded satisfactorily to give the substituted dihydroresorcylic esters (10a), (10c), and (10b) respectively, which were then dehydrogenated with bromine, giving the dibromo-, monobromo-, and parent-resorcylic esters, (5e), (5f), and (5b) respectively. Hydrogenolysis of the bromo-compounds (5e) and (5f) in the presence of palladium–carbon catalyst gave high yields of the

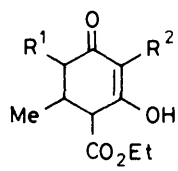

(5a-f)


(6a-c)


(7a-c)


(8a-c)


(9a-c)


(10a-d)

a : $R^1 = R^2 = H$

b : $R^1 = R^2 = Me$

c : $R^1 = Me, R^2 = H$

d : $R^1 = Me, R^2 = CD_3$

e : $R^1 = R^2 = Br$

f : $R^1 = Me, R^2 = Br$

parent esters (5a) and (5c), respectively. Repetition of this work with diethyl [1-^{14}C]malonate gave similar radiochemical yields of the corresponding [*carboxy*, 2-$^{14}C_2$]-derivatives.

The required trideuteriomethyl derivative (5d) was prepared from the dihydroresorcylic ester (10c) by reaction with one equivalent of trideuteriomethyl iodide in the presence of sodium ethoxide, followed by dehydrogenation of the intermediate dihydroresorcylate derivative (10d) with bromine.

A new synthetic route to alkyl β-resorcylates,[10] published since the completion of the present work, does not appear to offer significant advantages for the synthesis of the labelled compounds in the present study.

Experimental

Except where otherwise stated ^{1}H n.m.r. spectra were measured in $CDCl_3$ with $SiMe_4$ as internal standard on a Perkin-Elmer R34 instrument operating at 220 MHz, ^{2}H n.m.r. spectra with a Bruker WH 360 instrument operating at 55.26 MHz, u.v. spectra in ethanol on a Pye-Unicam SP8-100 instrument, and i.r. spectra in CCl_4 on a Perkin-Elmer 257 instrument. Mass spectra were determined with an AEI MS-12 instrument at 70 eV. M.p.s are uncorrected and were measured with a Reichert hot stage. Preparative layer chromatography (p.l.c.) was performed with a 1-mm thick layer of Kieselgel $60PF_{254}$ (Merck) on glass plates (20 × 20 cm), activated at 110 °C for 12 h after air drying. Light petroleum refers to that fraction with b.p. 60—80 °C, and ether refers to diethyl ether.

Ethyl 3,5-*Dibromo*-2,4-*dihydroxy*-6-*methylbenzoate* (5e).—To diethyl malonate (1.58 g) in ethanol (10 ml) containing sodium ethoxide (from 300 mg sodium) was added pent-3-en-2-one (9a) (860 mg) and the whole was heated under reflux under nitrogen for 2 h. After the bulk of the ethanol had been removed, the residue was dissolved in water (25 ml) which was then extracted with ether (2 × 10 ml), the aqueous phase acidified with concentrated hydrochloric acid and again extracted with ether (5 × 10 ml) to give the crude product (10a). After removal of the solvent the residue (1.89 g) in acetic acid (20 ml) was treated with bromine (4.65 g) at room temperature in a stream of dry air to remove most of the hydrogen bromide. After 24 h ether (50 ml) was added and the solution washed successively with saturated sodium hydrogen carbonate (20 × 10 ml), 2M-sodium hydrogen sulphite (5 × 10 ml) and water (2 × 10 ml). After the ether had been removed the residue separated from ethanol in needles (1.39 g) of ethyl dibromo-orsellinate (5e), m.p. 143—144 °C (lit.,[11] m.p. 144 °C) (Found: C, 34.0; H, 2.8. Calc. for $C_{10}H_{10}Br_2O_4$: C, 33.9; H, 2.9%). Under the same conditions diethyl [1-^{14}C]-malonate (1.63 g; 40.29 μC mmol^{-1}) gave ethyl [*carboxy*, 2-$^{14}C_2$]-3,5-dibromo-2,4-dihydroxy-6-methylbenzoate (1.47 g; 39.51 μC mmol^{-1}), m.p. 143—144 °C.

Ethyl 2,4-*Dihydroxy*-6-*methylbenzoate* (5a).—Hydrogenolysis of the above product (1.03 g) in a solution of potassium hydroxide (330 mg) in water (20 ml) containing palladium on carbon (10%, 500 mg) was complete in 36 h at room temperature and atmospheric pressure. After filtration and acidification of the mixture the ethyl ester (5a) was isolated in ether (8 × 10 ml) and crystallised from tetrachloromethane giving platelets (410 mg), m.p. 132 °C (lit.,[11] m.p. 132 °C) (Found: C, 61.1; H, 6.2. Calc. for $C_{10}H_{12}O_4$: C, 61.2; H, 6.2%). Under similar conditions the [^{14}C]-labelled dibromo-ester (1.47 g) gave ethyl [*carboxy*, 2-$^{14}C_2$]-2,4-dihydroxy-6-methylbenzoate (570 mg; 39.75 μC mmol^{-1}), m.p. 132 °C.

Ethyl 3-*Bromo*-2,4-*dihydroxy*-5,6-*dimethylbenzoate* (5f) *and Ethyl* 2,4-*Dihydroxy*-5,6-*dimethylbenzoate* (5c).—Prepared under the above conditions from diethyl malonate (3.17 g) and 3-methylpent-3-en-2-one (9c) (2.12 g), the crude dihydroaromatic ester (10c) (4.48 g) was obtained and a solution in acetic acid (20 ml) was treated with bromine (6.82 g) for 24 h at room temperature as described above. Isolated in the usual way, ethyl 3-bromo-2,4-dihydroxy-5,6-dimethylbenzoate (5f) separated from ethanol as needles (2.45 g), m.p. 66—68 °C (lit.,[9] m.p. 67—69 °C) (Found: C, 43.3; H, 4.9. Calc. for $C_{11}H_{13}BrO_4 \cdot H_2O$: C, 43.0; H, 4.9%).

Prepared from this bromo-ester (590 mg) by hydrogenolysis as described above, ethyl 2,4-dihydroxy-5,6-dimethylbenzoate (5c) separated from tetrachloromethane as pale cream platelets (357 mg), m.p. 115—116 °C (lit.,[9] m.p. 115—117 °C) (Found: C, 62.9; H, 6.8. Calc. for $C_{11}H_{14}O_4$: C, 62.8; H, 6.7%).

Ethyl [carboxy, 2-$^{14}C_2$]-2,4-*Dihydroxy*-3,5,6-*trimethylbenzoate* (5b).—Prepared as described above from diethyl [1-^{14}C]-malonate (1.99 g; 40.29 μC mmol^{-1}) and 4-methylhex-4-en-3-one (9b) (1.51 g), the dihydroaromatic ester (10b) was obtained as a yellow viscous oil (1.79 g) and subsequently dehydrogenated with bromine (1.40 g) in acetic acid (20 ml) by the usual method. The resultant product was shown by ^{1}H n.m.r. spectroscopy to be a mixture of the required product (5b) and 1-bromo-2,4-dihydroxy-3,5,6-trimethylbenzene (*ca.* 3 : 1) which was best separated after hydrogenolysis of the minor component, in the usual way. The resultant mixture was then separated by p.l.c. with chloroform–methanol (98 : 2). The band with R_F 0.48 was crystallised from tetrachloromethane to give microcrystals (1.27 g; 39.70 μC mmol^{-1}) of *ethyl* [carboxy, 2-$^{14}C_2$]-2,4-*dihydroxy*-3,5,6-*trimethylbenzoate* (5b), m.p. 91—92 °C, $\lambda_{max.}$ 270 (ε 14 100) and 218 nm (26 900) $\nu_{max.}$ 3 590, 3 060 (br) and 1 650 cm^{-1}; δ_H 1.39 (3 H, t, *J* 7.1 Hz, CO_2CH_2Me), 2.10 (6 H, s, 3- and 5-Ar*Me*), 2.39 (3 H, s, 6-Ar*Me*), 4.37 (2 H, q, *J* 7.1 Hz, CO_2CH_2 Me), 5.47 (1 H, s, 4-ArO*H*), and 11.55 (1 H, s, 2-ArO*H*); δ_C 7.98 (q, 3-Ar*Me*), 11.81 (q, 5- or 6-Ar*Me*), 14.23 (q, 6- or 5-Ar*Me*), 18.78 (q, CO_2CH_2Me), 61.15 (t, CO_2CH_2Me), 106.22 (s, C-1), 107.20 (s, C-3), 114.70 (s, C-5), 137.35 (s, C-6), 156.46 (s, C-2 or -4),

159.39 (s, C-4 or -2), and 172.04 p.p.m. (s, CO_2CH_2Me) (Found: C, 64.0; H, 7.2%; M^+, 224. $C_{12}H_{16}O_4$ requires C, 64.3; H, 7.2%; *M*, 224).

Ethyl 4-*Benzyloxy*-2-*hydroxy*-6-*methyl*-(7a), -5,6-*dimethyl*-(7c), *and* -3,5,6-*trimethyl-benzoate* (7b) *and their* [^{14}C]-*Labelled Derivatives*.—Monobenzylation of ethyl [*carboxy*, 2-$^{14}C_2$]-orsellinate (5a) (219 mg), ethyl 2,4-dihydroxy-5,6-dimethylbenzoate (5c) (750 mg) and ethyl [*carboxy*, 2-$^{14}C_2$]-2,4-dihydroxy-3,5,6-trimethylbenzoate (5b) (814 mg) were effected with benzyl chloride (220, 660, and 715 mg, respectively) in dry acetone (20 ml) for 18 h under reflux. The mixtures were poured into water, acidified with hydrochloric acid and the following products isolated in ether. The [^{14}C]-labelled ester (7a) separated from light petroleum in microcrystals (272 mg; 39.78 μC mmol^{-1}), m.p. 52—54 °C (lit.,[12] m.p. 53—54 °C) (Found: C, 71.1; H, 6.2. Calc. for $C_{17}H_{18}O_4$: C, 71.3; H, 6.3%); the *ester* (7c) separated from light petroleum in microcrystals (775 mg), m.p. 67—68 °C, $\lambda_{max.}$ 267 (ε 8 900), and 310 nm (5 900); $\nu_{max.}$ 3 160 (br) 1 650 cm^{-1}; δ_H 1.34 (3 H, t, *J* 7.2 Hz, CO_2CH_2Me), 2.10 (3 H, s, 5-Ar*Me*), 2.41 (3 H, s, 6-Ar*Me*), 4.35 (2 H, q, *J* 7.2 Hz, CO_2CH_2Me), 4.98 (2 H, s, $ArCH_2O$), 6.38 (1 H, s, 3 Ar*H*), 7.33 (5 H, m, OCH_2ArH), and 11.42 (1 H, s, 2-ArO*H*) (Found: C, 72.6; H, 6.9%; M^+, 300. $C_{18}H_{20}O_4$ requires C, 72.0; H, 6.7%; *M*, 300); and the [^{14}C]-*labelled ester* (7b) separated from methanol in microcrystals (806 mg; 39.64 μC mmol^{-1}), m.p. 49—50 °C, $\lambda_{max.}$ 216 (40 000), 258 (14 000), and 318 nm (4 600); $\nu_{max.}$ 3 620 (br) 1 650 cm^{-1}; δ_H 1.38 (3 H, t, *J* 7.1 Hz, CO_2CH_2Me), 2.14 (3 H, s, 3-Ar*Me*), 2.16 (3 H, s, 5-Ar*Me*), 2.41 (3 H, s, 6-Ar*Me*), 4.38 (2 H, q, *J* 7.1 Hz, CO_2CH_2Me), 4.72 (2 H, s, $ArCH_2O$), 7.37 (5 H, m, OCH_2ArH), and 11.16 (1 H, s, 2-ArO*H*) (Found: C, 72.4; H, 7.0%; M^+, 314. $C_{19}H_{22}O_4$ requires C, 72.6; H, 7.1%; *M*, 314).

Ethyl 4-*Benzoyloxy*-2-(1-*phenyl*-1*H*-*tetrazol*-2-*yloxy*)-6-*methyl*- (8a),-5,6-*dimethyl*- (8c) and -3,5,6-*trimethyl-benzoate* (8b) *and* [^{14}C]-*Labelled Derivatives*.—The monobenzyl ethers (7a), (7c), and (7b) (271, 521, and 806 mg, respectively) were treated with 5-chloro-1-phenyl-1*H*-tetrazole (171, 320, and 464 mg, respectively) and anhydrous potassium carbonate (262, 500, and 710 mg, respectively) in acetone (10, 20, and 25 ml, respectively) under reflux for 46 h. The following products were isolated in ether after being diluted with water and acidified in the usual way. *Ethyl* [carboxy, 2-$^{14}C_2$]-4-*benzyloxy*-2-(1-*phenyl*-1*H*-*tetrazol*-2-*yloxy*)-6-*methylbenzoate* (8a) (399 mg; 39.86 μC mmol^{-1}) was crystallised from ethyl acetate–light petroleum to give small needles m.p. 98—99 °C; $\lambda_{max.}$ 239 nm (ε 27 000); $\nu_{max.}$ 1 725 cm^{-1}; δ_H 1.05 (3 H, t, *J* 7.2 Hz, CO_2CH_2Me), 2.42 (3 H, s, Ar*Me*), 4.11 (2 H, q, *J* 7.2 Hz CO_2CH_2Me), 5.50 (2 H, s, $ArCH_2O$), 6.81 (1 H, d, *J* 1.9 Hz, 3-Ar*H*), 6.97 (1 H, d, *J* 1.9 Hz, 5-Ar*H*), 7.37 (5 H, m, OCH_2ArH), 7.66 (5 H, m, NAr*H*) (Found: C, 67.0; H, 5.3; N. 13.1; M^+ 430. $C_{24}H_{22}N_4O_4$ requires C, 67.0; H, 5.2; N, 13.0%; *M* 430); *ethyl* 4-*benzyloxy*-2-(1-*phenyl*-1*H*-*tetrazol*-2-*yloxy*)-5,6-*dimethylbenzoate* (8c) formed needles (702 mg) from ethyl acetate–light petroleum, m.p. 112—113 °C, $\lambda_{infl.}$ 248 nm ($\varepsilon_{infl.}$ 15 500); $\nu_{max.}$ 1 725 cm^{-1}; δ_H 1.07 (3 H, t, *J* 7.2 Hz, CO_2CH_2Me), 2.21 (3 H, s, 5-Ar*Me*), 2.29 (3 H, s, 6-Ar*Me*), 4.12 (2 H, q, *J* 7.2 Hz, CO_2CH_2Me), 5.07 (2 H, s, $ArCH_2O$), 7.05 (1 H, s, 3-Ar*H*), 7.39 (5 H, m, $O{\cdot}CH_2ArH$), and 7.68 (5 H, m, NAr*H*) (Found: C, 67.7; H, 5.4; N, 12.8; M^+ 444. $C_{25}H_{24}N_4O_4$ requires C, 67.6; H, 5.4; N, 12.6%; *M*, 444); and *ethyl* [carboxy, 2-$^{14}C_2$], 4-*benzyloxy*-2-(1-*phenyl*-1*H*-*tetrazol*-2-*yloxy*)-3,5,6-*trimethylbenzoate* (8b) formed microcrystals (1.18 g; 39.69 μC mmol^{-1}) from methanol, m.p. 134—135 °C, $\lambda_{max.}$ 256 nm (1 900); $\nu_{max.}$ 1 725 cm^{-1}; δ_H 1.03 (3 H, t, *J* 7.2 Hz, CO_2CH_2Me), 2.15 (3 H, s, 3-Ar*Me*), 2.24 (3 H, s, 5- or 6-Ar*Me*), 2.27 (3 H, s, 5- or 6-Ar*Me*), 4.08 (2 H, q, *J* 7.2 Hz, CO_2CH_2Me), 4.81 (2 H, s, $ArCH_2O$), and 7.61 (10 H, m, OCH_2ArH and NAr*H*) (Found: C, 68.1; H, 5.8; N, 12.3%; M^+ 458. $C_{26}H_{26}N_4O_4$ requires C, 68.1; H, 5.7; N, 12.2%; *M*, 458).

Ethyl 4-*Hydroxy*-2-*methyl*-(6a), -2,3-*dimethyl*- (6c), and 2,3,5-*trimethylbenzoates* (6b) *and* [^{14}C]-*Labelled Derivatives*.—The above compounds (8a), (8c), and (8b) (399 mg, 618 mg, and 1.18 g, respectivley) in ethanol (16, 20, and 40 ml respectively) and acetic acid [2 ml in the case of compound (8b) only] with 10% palladium on carbon (100, 150, and 300 mg, respectively) were hydrogenolysed at room temperature and atmospheric pressure for 24—72 h until hydrogen absorption was complete. After the catalyst and solvent had been removed the residues were purified by p.l.c.; the product from (8a) was obtained as a band, R_F 0.49, with toluene–ether (4 : 1), that from (8c) as a band, R_F 0.38, with light petroleum–ethyl acetate (7 : 3), and that from (8b) as a band, R_F 0.47, with the same solvent mixture.

Ethyl [*carboxy*, 6-$^{14}C_2$]-4-hydroxy-2-methylbenzoate (6a) separated from ethyl acetate–light petroleum in needles (161 mg; 39.82 μC mmol^{-1}), m.p. 98—99 °C (lit.,[13] m.p. 98 °C) (Found: C, 66.7; H, 6.8; M^+, 180. Calc. for $C_{10}H_{12}O_3$: C, 66.7; H, 6.7%; *M*, 180). *Ethyl* 2,3-*dimethyl*-4-*hydroxybenzoate* (6c) separated from tetrachloromethane in microcrystals (219 mg), m.p., 108—109 °C, $\lambda_{max.}$ 259 nm (11 000); $\nu_{max.}$ ($CHCl_3$) 3 580 (sh), 3 290 (br), and 1 705 cm^{-1}; δ_H 1.36 (3 H, t, *J* 7.2 Hz, CO_2CH_2Me), 2.18 (3 H, s, 3-Ar*Me*), 2.49 (3 H, s, 2-Ar*Me*), 4.34 (2 H, q, *J* 7.2 Hz, CO_2CH_2Me), 6.45 (1 H, s, 4-Ar*OH*), 6.66 (1 H, d, *J* 8.8 Hz, 5-Ar*H*), and 7.59 (1 H, d, *J* 8.8 Hz, 6-Ar*H*) (Found: C, 68.1; H, 7.0; M^+, 194. $C_{11}H_{14}O_3$ requires C, 68.0; H, 7.3%; *M*, 194), *Ethyl* [carboxy, 6-$^{14}C_2$]-4-*hydroxy*-2,3,5-*trimethylbenzoate* (6b) separated from tetrachloromethane in microcrystals (284 mg; 39.68 μC mmol^{-1}), m.p. 76—77 °C, $\lambda_{max.}$ 267 nm (9 000); $\nu_{max.}$ 3 605 and 1 710 cm^{-1}; δ_H 1.34 (3 H, t, *J* 7.1 Hz, CO_2CH_2Me), 2.15 (3 H, s, 5-Ar*Me*), 2.19 (3 H, s, 3-Ar*Me*), 2.43 (3 H, s, 2-Ar*Me*), 4.31 (2 H, q, *J* 7.1 Hz, CO_2CH_2Me), 5.62 (1 H, s, 4-ArO*H*), and 7.49 (1 H, s, 6-Ar*H*) (Found: C, 68.7; H, 7.8; M^+, 208. $C_{12}H_{16}O_3$ requires C, 69.2; H, 7.7%; *M*, 208).

Ethyl 2,4-*Dihydroxy*-3-*trideuteriomethyl*-5,6-*dimethylbenzoate* (5d).—The cyclohexanedione (10c) (212 mg) in ethanol (5 ml) containing sodium ethoxide (92 mg) was stirred under dry nitrogen for 3 h at room temperature and then treated with trideuteriomethyl iodide (174 mg) and the mixture heated to 80 °C for 8 h. Further trideuteriomethyl iodide (73 mg) was then added and the heating continued for a further 2 h. The product (10d) (250 mg) was then isolated in the usual way and was dehydrogenated with bromine (0.32 g) in acetic acid (5 ml) as described above. Purified by p.l.c. in chloroform, the *trideuteriomethyl derivative* (5d) was isolated from the band with R_F 0.32 and crystallised from tetrachloromethane giving microcrystals (70 mg), m.p. 90—91 °C, δ_H as listed above for the parent (5b) except that the peak δ_H 2.10 corresponded to only 3 protons; δ_C as listed above for the parent (5b) except for the absence of signals at δ 7.98 and 107.20 p.p.m., δ_{2H} 2.10 p.p.m. (s, 3-CD_3). The band R_F 0.65 was also isolated and the product crystallised from ethanol to give needles of compound (5f) (130 mg), m.p. and mixed m.p. 66—68 °C.

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