Synthesis of the aromatic unit of calicheamicin γ_1^I

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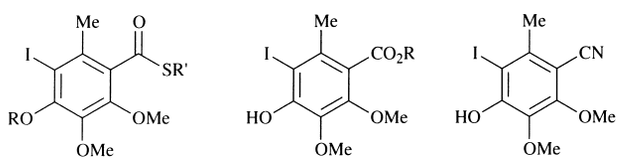
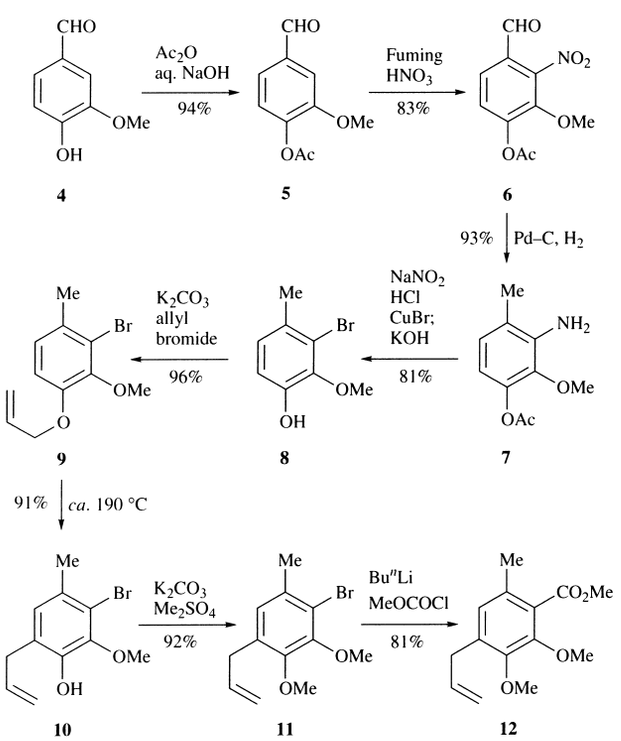
1 PERKIN

Vanillin and piperonal are each converted into methyl 2,3-dimethoxy-6-methyl-4-(prop-2-enyl)benzoate 12, and this is then elaborated into methyl 4-hydroxy-3-iodo-5,6-dimethoxy-2-methylbenzoate 24, which represents the aromatic unit of calicheamicin γ_1^I.

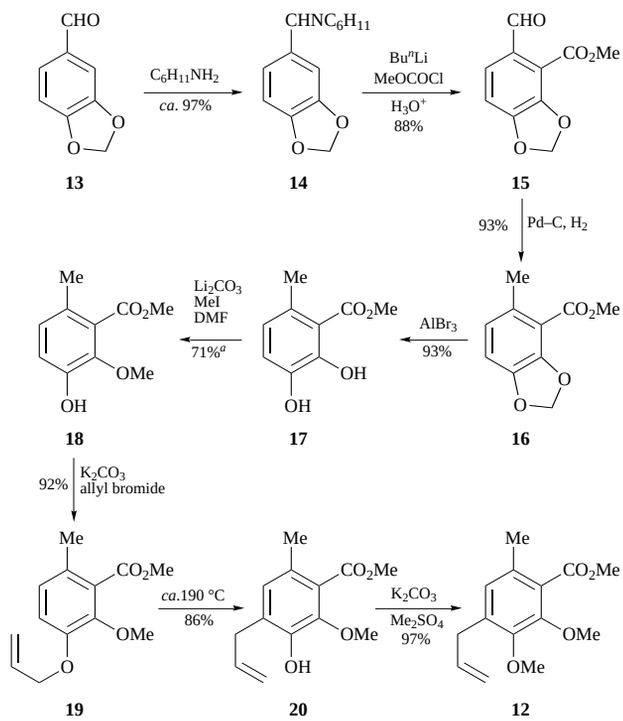
The aromatic system **1** (R, R′ = complex carbohydrate) is a structural unit of the antitumour agent calicheamicin γ_1^I.[1] Methods for making the parent system **2** (R = H)[2] and the corresponding ester (**2**, R = Me)[2,3] and nitrile **3**[4] have been reported. We describe here two further routes to **2** (R = Me).



Our first route begins with the known nitro acetate **6**,[5] which was made from vanillin, according to the literature procedure[5] (Scheme 1, **4**→**5**†,[6]→**6**). Reduction of both the nitro and formyl groups (**6**→**7**, Pd–C, H_2, 93%), followed by Sandmeyer reaction ($NaNO_2$, HCl, CuBr) and hydrolysis (KOH) afforded bromophenol **8** (81% from **7**). Allylation (**8**→**9**) under classical conditions (allyl bromide, K_2CO_3, 96%) and Claisen rearrangement (*ca.* 190 °C, 91%) served to functionalize the expected position of the aromatic ring (**9**→**10**) and methylation (Me_2SO_4, K_2CO_3, 92%) then gave the fully protected bromide **11**. At this point, halogen-metal exchange (Bu^nLi) and quenching with methyl chloroformate yielded ester **12** (81%). This substance is common to both of our routes, as it was also prepared from piperonal, as described below (Scheme 2).



Scheme 1

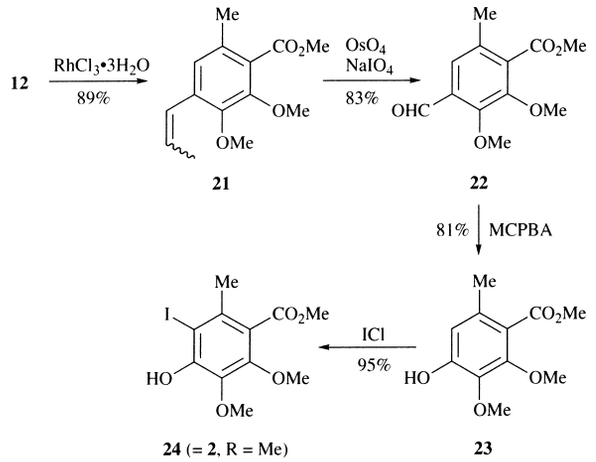


[a]After correction for recovered **17** (30%)

Scheme 2

Aldehyde ester **15** was made from piperonal by a literature procedure[7] (Scheme 2, **13**→**14**→**15**), and then the formyl group was completely reduced[8] (**15**→**16**, Pd–C, H_2, 93%). Deprotection of the phenolic hydroxy groups (**16**→**17**, 93%) was accomplished by the action of aluminum bromide,[9] and the resulting pyrocatechol **17** was then methylated regioselectively under conditions[10] (DMF, MeI, Li_2CO_3) that afforded the monomethyl ether **18** in 50% yield [71%, after allowing for recovered starting material (30%)]. The remaining hydroxy group was then allylated as before (**18**→**19**, allyl bromide K_2CO_3, 92%) and then Claisen rearrangement (**19**→**20**, *ca.* 190 °C, 86%) and subseqent methylation (Me_2SO_4, K_2CO_3, 97%) resulted in formation again of the highly substituted ester

† The literature procedure was followed for the preparation of **5**, except that the Ac_2O (4.09 cm^3, 43.3 mmol) was dissolved in Et_2O (36 cm^3), instead of being used neat. The crude product (94%) was used directly.



Scheme 3

12. This was converted into the target **2** (R = Me), as summarized in Scheme 3.

The double bond in the pendant allyl group of **12** was isomerized[11] to the geometrical isomers **21** ($RhCl_3·H_2O$, EtOH, 70 °C, 89%, $E:Z = 9:1$), and oxidative cleavage (**21**→**22**, OsO_4, $NaIO_4$, 83%) set the stage for the introduction of a hydroxy group. This was accomplished[12] by Baeyer–Villiger oxidation (**22**→**23**, MCPBA, 81%). Phenol **23** is a known substance[2] which, on treatment with iodine chloride,[2] gave the desired target **24** (*i.e.* **2**, R = Me) in 95% yield.‡

Experimental

General experimental procedures were the same as those used previously.[13] In the ^{13}C NMR spectra the symbols s′, d′, t′ and q′ represent 0, 1, 2 and 3 attached protons. *J* Values are given in Hz.

4-Formyl-2-methoxy-3-nitrophenyl acetate 6[5]

Aldehyde **5**†[,6] (7.4 g, 38.1 mmol) was added in portions to stirred and cooled (−10 to −15 °C) fuming HNO_3 (41 cm^3) in a 100 cm^3 flask at such a rate that the temperature did not rise above −10 °C. Stirring was continued for 10 min after the addition and the mixture was then poured onto cracked ice (*ca.* 200 g). The resulting solid was collected, washed with water and recrystallized from a 1:1 mixture of 95% EtOH and water (100 cm^3) to afford **6** (7.53 g, 83%) (lit.,[5] 27%), mp 82–83 °C (lit.,[5] 80 °C).

3-Amino-2-methoxy-4-methylphenyl acetate 7

Aldehyde **6** (3.65 g, 15.27 mmol), in a mixture of AcOH (1.33 cm^3, 23.23 mmol) and MeOH (150 cm^3), was reduced over 10% Pd–C (1.22 g) at 50 psi for 14 h (Parr shaker). The mixture was filtered through a pad of Celite (1.5 × 3 cm) and the pad was washed with MeOH (3 × 10 cm^3). Evaporation of the combined filtrates and flash chromatography of the residue over silica gel (4 × 15 cm), using 1:3 EtOAc–hexane, gave **7** (2.77 g, 93%) as a pure (^1H NMR, 400 MHz) solid, mp 61–62 °C; $\nu_{max}(CH_2Cl_2$ cast)/cm^{-1} 3457, 3373, 2968, 2927, 1760, 1618, 1492, 1475, 1250, 1207 and 1061; δ_H(400 MHz, $CDCl_3$) 2.16 (s, 3 H), 2.34 (s, 3 H), 3.79 (s, 3 H), 3.84 (br s, 2 H), 6.14 (d, *J* 7.9, 1 H) and 6.81 (d, *J* 7.8, 1 H); δ_C(75.5 MHz, $CDCl_3$) 16.77 (q′), 20.51 (q′), 59.69 (q′), 111.02 (d′), 120.85 (s′), 124.91 (d′), 138.10 (s′), 139.15 (s′), 141.72 (s′) and 168.99 (s′) (Found: M^+, 195.0895. $C_{10}H_{13}NO_3$ reqires *M*, 195.0895).

‡ Phenol **23** is also the precursor to the bromide corresponding to **24** (see ref. 2). The bromide represents the aromatic unit of another calicheamicin (see ref. 1).

3-Bromo-2-methoxy-4-methylphenol 8

$NaNO_2$ (1.45 g, 21.03 mmol) in water (4 cm^3) was added dropwise over 30 min to a stirred and cooled (−5 to 0 °C) solution of **7** (4.02 g, 20.61 mmol) in hydrobromic acid (48%; 7.5 cm^3). After the addition, stirring was continued for 25 min, and the solution of the diazonium salt was then added dropwise to a stirred and heated (100 °C) solution of CuBr (1.96 g, 13.60 mmol) in hydrobromic acid (48%; 4.5 cm^3). At the end of the addition, stirring was continued for 15 min, and the mixture was then cooled to room temperature and extracted with Et_2O (3 × 25 cm^3). The combined extracts were washed with hydrochloric acid (3%; 2 × 125 cm^3), water (20 cm^3) and saturated aqueous $NaHCO_3$ (15 cm^3). The organic phase (without drying) was evaporated and the residue was diluted with MeOH (50 cm^3). KOH (3.0 g, 75.0 mmol) was added, the the mixture was stirred at 70 °C (oil bath) for 1.5 h. The mixture was cooled to room temperature, and concentrated. The residue was poured into a mixture of ice (*ca.* 50 g) and concentrated aqueous HCl (30 cm^3), and the mixture was extracted with Et_2O (3 × 20 cm^3), washed with saturated aqueous $NaHCO_3$ (20 cm^3), water (15 cm^3) and brine (20 cm^3) and dried (Na_2SO_4). Evaporation of the solvent and flash chromatography of the residue over silica gel (3 × 20 cm), using 1:6 EtOAc–hexane, gave **8** as a pure (^1H NMR, 300 MHz) oil (3.64 g, 81%); $\nu_{max}(CH_2Cl_2$ cast)/cm^{-1} 3422, 2971, 2938, 1603, 1483, 1458, 1276, 1206 and 1037; δ_H(300 MHz, $CDCl_3$) 2.34 (s, 3 H), 3.88 (s, 3 H), 5.66 (br s, 1 H), 6.82 (d, *J* 7.8, 1 H) and 6.91 (d, *J* 7.9, 1 H); δ_C(50.3 MHz, $CDCl_3$) 22.25 (q′), 60.75 (q′), 114.39 (d′), 118.57 (d′), 126.22 (d′), 130.44 (s′), 144.36 (s′) and 147.51 (s′) (Found: M^+, 217.9769. $C_8H_9{}^{81}BrO_2$ requires *M*, 217.9765).

2-Bromo-3-methoxy-1-methyl-4-(prop-2-enyloxy)benzene 9

Allyl bromide (1.68 cm^3, 9.85 mmol) was added to a stirred mixture of **8** (3.59 g, 16.5 mmol), anhydrous K_2CO_3 (4.12 g, 29.77 mmol) and dry acetone (65 cm^3). The mixture was refluxed with stirring for 7 h, cooled to room temperature and filtered. The solid residue was washed with dry acetone and the combined filtrates were evaporated. Flash chromatography of the residue over silica gel (3.5 × 20 cm), using 1:20 EtOAc–hexane, gave **9** (4.10 g, 96%) as a pure (^1H NMR, 300 MHz), colourless oil; $\nu_{max}(CH_2Cl_2$ cast)/cm^{-1} 2979, 2933, 1595, 1484, 1458, 1395, 1293, 1268, 1257 and 1049; δ_H(300 MHz, $CDCl_3$) 2.34 (s, 3 H), 3.87 (s, 3 H), 4.56 (dt, *J* 6.8, 1.5, 2 H), 5.28 (dq, *J* 10.4, 1.4, 1 H), 5.41 (dq, *J* 17.2, 1.5, 1 H), 5.98–6.11 (m, 1 H), 6.78 (d, *J* 8.3, 1 H) and 6.91 (d, *J* 8.4, 1 H); δ_C(50.3 MHz, $CDCl_3$) 22.34 (q′), 60.11 (q′), 69.70 (t′), 112.92 (d′), 117.33 (t′), 120.29 (s′), 124.92 (d′), 131.02 (s′), 132.97 (d′), 146.75 (s′) and 150.l22 (s′) (Found: M^+, 258.0077. $C_{11}H_{13}{}^{81}BrO_2$ requires *M*, 258.0078).

3-Bromo-2-methoxy-4-methyl-6-(prop-2-enyl)phenol 10

A solution of **9** (2.20 g, 8.56 mmol) in decalin (3 cm^3) was refluxed for 6.5 h under Ar, cooled to room temperature and evaporated. Flash chromatography of the residue over silica gel (3 × 15 cm), using 1:20 EtOAc–hexane, gave **10** (2.01 g, 91%) as a pure (^1H NMR, 400 MHz), colourless oil; $\nu_{max}(CH_2Cl_2$ cast)/cm^{-1} 3507, 3003, 2976, 2938, 1639, 1459, 1401, 1299, 1210 and 1057; δ_H(400 MHz, $CDCl_3$) 2.31 (s, 3 H), 3.34 (dd, *J* 3.5, 1.1, 2 H), 3.88 (s, 3 H), 5.05–5.10 (m, 2 H), 5.59 (s, 1 H), 5.92–6.03 (m, 1 H) and 6.80 (s, 1 H); δ_C(50.3 MHz, $CDCl_3$) 22.24 (q′), 33.79 (t′), 60.86 (q′), 115.80 (s′), 115.91 (t′), 125.69 (s′), 126.91 (d′), 129.61 (s′), 136.10 (d′), 144.10 (s′) and 145.48 (s′) (Found: M^+, 258.0069. $C_{11}H_{13}{}^{81}BrO_2$ requires *M*, 258.0078).

2-Bromo-3,4-dimethoxy-1-methyl-5-(prop-2-enyl)benzene 11

Me_2SO_4 (0.78 cm^3, 8.25 mmol) was added to a stirred mixture of **10** (1.766 g, 6.87 mmol), K_2CO_3 (2.28 g, 16.5 mmol) and dry acetone (55 cm^3). Stirring was continued for 7 h at room temperature and the mixture was then filtered. The insoluble material was washed with dry acetone and the combined fil-

trates were evaporated. Flash chromatography of the residue over silica gel (2.5 × 15 cm), using 1:30 EtOAc–hexane, gave **11** (1.72 g, 92%) as a pure (^{1}H NMR, 360 MHz), colourless oil; ν_{max}(CH_2Cl_2 cast)/cm^{-1} 3077, 2996, 2976, 1639, 1468, 1422, 1391, 1319, 1243, 1069 and 1015; δ_H(360 MHz, $CDCl_3$) 2.17 (s, 3 H), 3.16 (dt, *J* 6.5, 1.3, 2 H), 3.91 (s, 3 H), 3.95 (s, 3 H), 5.01–5.04 (m, 2 H), 5.95–6.00 (m, 1 H) and 6.92 (s, 1 H); δ_C(50.3 MHz, $CDCl_3$) 22.65 (q′), 33.78 (t′), 60.23 (q′), 60.74 (q′), 115.82 (t′), 117.84 (s′), 126.46 (d′), 132.74 (s′), 133.82 (s′), 136.76 (d′), 149.72 (s′) and 150.25 (s′) (Found: M$^+$, 272.0236. $C_{12}H_{15}{}^{81}BrO_2$ requires *M*, 272.0235).

Methyl 2,3-dimethoxy-6-methyl-4-(prop-2-enyl)benzoate 12

Bu^{n}Li (2.5 M in hexane; 1.42 cm^3, 3.546 mmol) was added dropwise over *ca.* 10 min to a stirred and cooled (−78 °C) solution of **11** (801 mg, 2.955 mmol) in THF (30 cm^3). Stirring was continued for 15 min, and then MeOCOCl (0.34 cm^3, 4.432 mmol) in THF (5 cm^3) was added dropwise over *ca.* 5 min. Stirring was continued for 20 min, the cold bath was removed and, when the mixture had reached about 0 °C, water (10 cm^3) was added. The mixture was extracted with Et_2O (2 × 30 cm^3) and the extract was washed with saturated aqueous $NaHCO_3$ (15 cm^3) and brine (15 cm^3) and dried (Na_2SO_4). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 15 cm), using 1:10 Et_2O–hexane, gave **12** (596 mg, 81%) as a pure (^{1}H NMR, 400 MHz), colourless oil; ν_{max}(CH_2Cl_2 cast)/cm^{-1} 2977, 2940, 1733, 1605, 1482, 1459, 1315, 1276 and 1054; δ_H(300 MHz, $CDCl_3$) 2.22 (s, 3 H), 3.33 (dt, *J* 6.5, 1.4, 2 H), 3.81 (s, 3 H), 3.88 (s, 3 H), 3.90 (s, 3 H), 5.02–5.05 (m, 2 H), 5.88–5.98 (m, 1 H) and 6.74 (s, 1 H); δ_C(75.4 MHz, $CDCl_3$) 18.67 (q′), 33.84 (t′), 51.89 (q′), 60.34 (q′), 61.00 (q′), 115.76 (t′), 126.62 (d′), 127.38 (s′), 130.59 (s′), 135.55 (s′), 136.62 (d′), 148.68 (s′), 149.93 (s′) and 168.09 (s′) (Found: M$^+$, 250.1203. $C_{14}H_{18}O_4$ requires *M*, 250.1205).

Methyl (*Z*)- and (*E*)-2,3-dimethoxy-6-methyl-4-(prop-1-enyl)-benzoate 21

$RhCl_3$·$3H_2O$ (33 mg, 0.125 mmol) was added to a solution of **12** (403 mg, 1.61 mmol) in dry EtOH (3 cm^3) and the mixture was stirred at 70 °C for 8 h. The solvent was then evaporated and the residue was diluted with Et_2O (30 cm^3), washed with water (2 × 10 cm^3) and brine (10 cm^3), dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm), using 1:20 EtOAc–hexane, gave **21** (359 mg, 89%) as a pure (^{1}H NMR, 300 MHz), colourless oil, which was a 9:1 mixture of *E* and *Z* isomers; ν_{max}(CH_2Cl_2 cast)/cm^{-1} 3034, 2994, 2939, 1732, 1602, 1458, 1448, 1405, 1277, 1154 and 1062; δ_H(300 MHz, $CDCl_3$) [major (*E*) isomer only] 1.91 (dd, *J* 6.6, 1.6, 3 H), 2.24 (s, 3 H), 3.80 (s, 3 H), 3.88 (s, 3 H), 3.91 (s, 3 H), 6.37 (dq, *J* 16.3, 6.6, 1 H), 6.61 (dq, *J* 15.8, 1.4, 1 H) and 7.00 (s, 1 H); δ_C(75.4 MHz, $CDCl_3$) [major (*E*) isomer only] 18.82 (q′), 18.98 (q′), 52.02 (q′), 60.62 (q′), 61.31 (q′), 122.62 (d′), 124.60 (d′), 127.34 (s′), 128.33 (d′), 130.79 (s′), 133.56 (s′), 147.73 (s′), 150.39 (s′) and 168.15 (s′) (Found: M$^+$, 250.1203. $C_{14}H_{18}O_4$ requires *M*, 250.1205).

Methyl 4-formyl-2,3-dimethoxy-6-methylbenzoate 22

OsO_4 (2.5% w/v in Bu^{t}OH; 2.10 cm^3, 0.34 mmol) was added to a stirred mixture of **21** (710 mg, 2.84 mmol), Bu^{t}OH (10 cm^3), CCl_4 (20 cm^3) and water (20 cm^3). After 15 min, $NaIO_4$ (1.52 g, 7.10 mmol) was added in one portion, and stirring was continued for 2 h. Water (20 cm^3) was then added and the mixture was extracted with Et_2O (2 × 30 cm^3). The combined extracts were washed with water (20 cm^3), 10% aqueous $NaHSO_3$ (20 cm^3) and brine (15 cm^3), dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 × 18 cm), using 1:5 Et_2O–hexane, gave **22** (562 mg, 83%) as a pure (^{1}H NMR, 400 MHz), white solid; mp 49–50 °C; ν_{max}(CH_2Cl_2 cast)/cm^{-1} 2949, 1735, 1692, 1466, 1439, 1280, 1052 and 990; δ_H(400 MHz, $CDCl_3$) 2.27 (s, 3 H), 3.91 (s, 3 H), 3.95 (s, 3 H), 3.98 (s, 3 H), 7.41 (s, 1 H) and 10.36 (s, 1 H); δ_C(75.4 MHz, $CDCl_3$) 18.67 (q′), 52.48 (q′), 61.59 (q′), 62.60 (q′), 124.28 (d′), 130.35 (s′), 131.30 (s′), 135.37 (s′), 150.25 (s′), 153.96 (s′), 167.30 (s′) and 189.29 (d′) (Found: M$^+$, 238.0841. $C_{12}H_{14}O_5$ requires *M*, 238.0841).

Methyl 4-hydroxy-2,3-dimethoxy-6-methylbenzoate 23

MCPBA (80%; 693 mg, 3.214 mmol) was added to a stirred solution of **22** (510 mg, 2.143 mmol) in dry CH_2Cl_2 (8 cm^3) and stirring was continued for 3.5 h. Water (15 cm^3) was then added and the mixture was extracted with Et_2O (2 × 20 cm^3). The combined extracts were washed with saturated aqueous $NaHCO_3$ (2 × 10 cm^3) and brine (10 cm^3), dried (Na_2SO_4) and evaporated. The residue was dissolved in MeOH (6.5 cm^3) and stirred, and 10% aqueous KOH (1.23 cm^3) was added to the resulting solution. After 30 min, the mixture was acidified with 10% aqueous hydrochloric acid and extracted with Et_2O (3 × 15 cm^3). The combined extracts were washed with water (10 cm^3) and brine (15 cm^3), dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 × 20 cm), using 1:4 Et_2O–hexane, gave **23** (395 mg, 81%) as a pure (^{1}H NMR, 300 MHz) solid; mp 75–76 °C (lit.,[2] 76 °C); ν_{max}(CH_2Cl_2 cast)/cm^{-1} 3397, 2970, 2941, 1713, 1580, 1467, 1429, 1291, 1197, 1178 and 962; δ_H(300 MHz, $CDCl_3$) 2.24 (s, 3 H), 3.89 (s, 3 H), 3.91 (s, 6 H), 5.76 (s, 1 H) and 6.56 (s, 1 H); δ_C(75.4 MHz, $CDCl_3$) 19.39 (q′), 52.08 (q′), 60.87 (q′), 61.28 (q′), 112.43 (d′), 120.58 (s′), 132.42 (s′), 137.45 (s′), 150.40 (s′), 150.52 (s′) and 168.13 (s′) (Found: M$^+$, 226.0842. $C_{11}H_{14}O_5$ requires *M*, 226.0841).

Methyl 4-hydroxy-3-iodo-5,6-dimethoxy-2-methylbenzoate 24

Phenol **23** was converted into **24** by the literature procedure,[2] and was obtained (95%) as a pure (^{1}H NMR, 400 MHz), white solid; mp 134–135 °C (lit.,[2] 134–135 °C); ν_{max}(CH_2Cl_2 cast)/cm^{-1} 3375, 2994, 2944, 2837, 1714, 1563, 1462, 1420, 1268, 1217, 1095, 1064 and 998; δ_H(400 MHz, $CDCl_3$) 2.35 (s, 3 H), 3.87 (s, 3 H), 3.91 (s, 3 H), 3.92 (s, 3 H) and 6.31 (br s, 1 H); δ_C(75.4 MHz, $CDCl_3$) 25.21 (q′), 52.42 (q′), 61.02 (q′), 61.33 (q′), 84.00 (s′), 121.75 (s′), 134.05 (s′), 136.56 (s′), 149.61 (s′), 150.47 (s′) and 167.79 (s′); (Found: M$^+$, 351.9801. $C_{11}H_{13}IO_5$ requires *M*, 351.9807).

Methyl 6-formyl-2,3-(methylenedioxy)benzoate 15

Piperonal was converted into its cyclohexyl imine (**14**) by the literature procedure.[7] The crude material (97%) was of adequate purity (^{1}H NMR, 300 MHz) for use directly in the next step, for which the literature procedure[7] was modified slightly. Bu^{n}Li (2.5 M in hexane; 8.20 cm^3, 20.5 mmol) was added dropwise over *ca.* 10 min to a stirred and cooled (−78 °C) solution of the crude imine (4.32 g, 18.7 mmol) in THF (150 cm^3). Stirring was continued for 15 min, and then MeOCOCl (2.89 cm^3, 37.4 mmol) in THF (30 cm^3) was added dropwise over 10 min. Stirring was continued for 10 min, the cold bath was removed and, when the mixture had reached room temperature, 15% aqueous hydrochloric acid (15 cm^3) was added. Stirring was continued for 1 h and then the mixture was concentrated to remove the THF and the residue was extracted with Et_2O (2 × 80 cm^3). The combined extracts were washed with water (2 × 20 cm^3), saturated aqueous $NaHCO_3$ (2 × 15 cm^3) and brine (20 cm^3) and dried (Na_2SO_4). Evaporation of the solvent and flash chromatography of the residue over silica gel (4 × 25 cm), using 2:3 Et_2O–hexane, gave **15** (3.42 g, 88%) as a pure (^{1}H NMR, 400 MHz), white solid; mp 104–105 °C (lit.,[7] 105.5–106.5 °C).

Methyl 6-methyl-2,3-(methylenedioxy)benzoate 16

Aldehyde **15** (1.54 g, 74.0 mmol) in a mixture of AcOH (0.6 cm^3) and MeOH (74 cm^3) was reduced over 10% Pd–C (592 mg) at 50 psi for 9 h (Parr shaker). The mixture was filtered through a pad of Celite (1 × 4 cm) and the pad was washed with MeOH (3 × 10 cm^3). Evaporation of the combined filtrates and flash chromatography of the residue over silica gel (3 × 15 cm), using

1:7 EtOAc–hexane, gave **16** (1.33 g, 93%) as a pure (^{1}H NMR, 400 MHz), white solid; mp 70–71 °C; ν_{max}(CH_2Cl_2 cast)/cm^{-1} 2968, 2953, 1724, 1626, 1470, 1457, 1271, 1127 and 1057; δ_H(400 MHz, $CDCl_3$) 2.42 (s, 3 H), 3.91 (s, 3 H), 6.01 (s, 2 H), 6.67 (dd, *J* 7.9, 0.7, 1 H) and 6.79 (d, *J* 7.9, 1 H); δ_C(50.3 MHz, $CDCl_3$) 20.74 (q′), 51.88 (q′), 101.59 (t′), 110.65 (d′), 113.62 (s′), 123.45 (d′), 131.81 (s′), 146.21 (s′), 147.99 (s′) and 165.90 (s′) (Found: M^+, 194.0578. $C_{10}H_{10}O_4$ requires *M*, 194.0579).

Methyl 2,3-dihydroxy-6-methylbenzoate 17

Ester **16** (1.01 g, 5.20 mmol) was added in one portion to a stirred and cooled (0 °C) mixture of $AlBr_3$ (5.55 g, 20.8 mmol) in EtSH (24 cm^3) contained in a one-necked round-bottomed flask fitted with a drying tube ($CaSO_4$), and stirring at 0 °C was continued for 1 h. The mixture was poured into water (20 cm^3), acidified with 10% hydrochloric acid and extracted with Et_2O (3 × 20 cm^3). The combined extracts were washed with water (2 × 15 cm^3) and brine (15 cm^3), dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 × 15 cm), using 1:5 EtOAc–hexane, gave **17** (880 mg, 93%) as a pure (^{1}H NMR, 300 MHz), white solid; mp 104–105 °C; ν_{max}(CH_2Cl_2 cast)/cm^{-1} 3478, 1659, 1597, 1445, 1293, 1274 and 799; δ_H(300 MHz, $CDCl_3$) 2.46 (s, 3 H), 3.97 (s, 3 H), 5.61 (s, 1 H), 6.63 (d, *J* 8.3, 1 H), 6.97 (d, *J* 8.2, 1 H) and 11.59 (s, 1 H); δ_C(50.3 MHz, $CDCl_3$) 23.20 (q′), 52.23 (q′), 111.77 (s′), 118.48 (d′), 122.12 (d′), 131.40 (s′), 143.20 (s′), 149.94 (s′) and 172.36 (s′) (Found: M^+, 182.0580. $C_9H_{10}O_4$ requires *M*, 182.0579).

Methyl 3-hydroxy-2-methoxy-6-methylbenzoate 18

MeI (1.12 cm^3, 17.97 mmol) was added to a stirred mixture of **17** (1.09 g, 5.99 mmol) and Li_2CO_3 (1.33 g, 17.97 mmol) in dry DMF (15 cm^3) and stirring was continued for 4 days. The mixture was poured into water (30 cm^3), acidified with 10% hydrochloric acid and extracted with Et_2O (3 × 20 cm^3). The combined extracts were washed with water (2 × 15 cm^3) and brine (15 cm^3), dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 × 20 cm), using 1:4 EtOAc–hexane, gave **18** (585 mg, 50%; 71% after allowing for recovered starting material) as a pure (^{1}H NMR 300 MHz), colourless oil, methyl 2-hydroxy-6-methyl-3-methoxybenzoate (199 mg, 17%; 24% after allowing for recovered starting material), also as a pure (^{1}H NMR, 300 MHz), colourless oil, and recovered **17** (324 mg, 30%). Phenol **18** had; ν_{max}(CH_2Cl_2 cast)/cm^{-1} 3387, 3951, 2925, 1731, 1663, 1487 and 1272; δ_H(300 MHz, $CDCl_3$) 2.25 (s, 3 H), 3.84 (s, 3 H), 3.93 (s, 3 H), 5.51 (br s, 1 H), 6.86 (d, *J* 7.9, 1 H) and 6.92 (d, *J* 8.0, 1 H); δ_C(50.3 MHz, $CDCl_3$) 18.70 (q′), 52.28 (q′), 62.02 (q′), 117.19 (d′), 126.26 (d′), 127.32 (s′), 127.63 (s′), 144.23 (s′), 146.63 (s′) and 168.30 (s′) (Found: M^+, 196.0734. $C_{10}H_{12}O_4$ requires *M*, 196.0735).

Methyl 2-methoxy-6-methyl-3-(prop-2-enyloxy)benzoate 19

Allyl bromide (0.27 cm^3, 3.214 mmol) was added to a stirred mixture of **18** (525 mg, 2.678 mmol), anhydrous K_2CO_3 (888 mg, 6.418 mmol) and dry acetone (15 cm^3). The mixture was refluxed with stirring for 7 h, cooled to room temperature and diluted with water (20 cm^3). The mixture was extracted with Et_2O (3 × 20 cm^3) and the combined extracts were washed with water (15 cm^3) and brine (15 cm^3), dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.5 × 12 cm), using 1:10 EtOAc–hexane, gave **19** (582 mg, 92%) as a pure (^{1}H NMR, 400 MHz), colourless oil; ν_{max}(CH_2Cl_2 cast)/cm^{-1} 2992, 2949, 1732, 1580, 1490, 1461, 1433, 1297, 1271, 1143 and 1068; δ_H(400 MHz, $CDCl_3$) 2.22 (s, 3 H), 3.88 (s, 3 H), 3.91 (s, 3 H), 4.56 (dt, *J* 5.2, 1.6, 2 H), 5.26 (dq, *J* 10.5, 1.4, 1 H), 5.28 (dq, *J* 17.2, 1.6, 1 H), 6.01–6.10 (m, 1 H) and 6.85 (s, 2 H); δ_C(75.4 MHz, $CDCl_2$) 18.47 (q′), 52.07 (q′), 61.40 (q′), 69.88 (t′), 115.78 (d′), 117.44 (t′), 125.33 (d′), 127.93 (s′), 129.31 (s′), 133.17 (d′), 146.60 (s′), 149.43 (s′) and 168.33 (s′) (Found: M^+, 236.1048. $C_{13}H_{16}O_4$ requitres *M*, 236.1048).

Methyl 3-hydroxy-2-methoxy-6-methyl-4-(prop-2-enyl)benzoate 20

A solution of **19** (110 mg, 0.466 mmol) in decalin (0.8 cm^3) was refluxed for 8 h under Ar and then cooled to room temperature. Flash chromatography of the mixture (without evaporation) over silica gel (1.5 × 15 cm), using 1:3 Et_2O–hexane, gave **20** (95.2 mg, 86%) as a pure (^{1}H NMR, 400 MHz), colourless oil; ν_{max}(CH_2Cl_2 cast)/cm^{-1} 3445, 3002, 2977, 2950, 1728, 1614, 1486, 1460, 1434, 1279 and 1195; δ_H(400 MHz, $CDCl_3$) 2.23 (s, 3 H), 3.37 (dt, *J* 6.4, 1.2, 2 H), 3.83 (s, 3 H), 3.92 (s, 3 H), 5.06–5.11 (m, 2 H), 5.60 (s, 1 H), 5.92–6.02 (m, 1 H) and 6.73 (s, 1 H); δ_C(50.3 MHz, $CDCl_3$) 18.98 (q′), 34.00 (t′), 52.21 (q′), 62.18 (q′), 116.00 (t′), 124.68 (s′), 126.98 (d′), 127.25 (s′), 128.68 (s′), 135.94 (d′), 144.27 (s′), 144.54 (s′) and 168.16 (s′) (Found: M^+, 236.1047. $C_{13}H_{16}O_4$ requires *M*, 236.1048).

Methyl 2,3-dimethoxy-6-methyl-4-(prop-2-enyl)benzoate 12

Me_2SO_4 (0.21 cm^3, 2.217 mmol) was added to a stirred mixture of **20** (436 mg, 1.847 mmol), K_2CO_3 (600 mg, 4.34 mmol) and dry acetone (20 cm^3). Stirring was continued for 8 h and the mixture was then filtered. The insoluble material was washed with dry acetone and the combined filtrates were evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm), using 1:10 Et_2O–hexane, gave **12** (448 mg, 97%) as a pure (^{1}H NMR, 300 MHz), colourless oil, identical with material made from vanillin, as described above.

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