

Synthesis of the aromatic unit of calicheamicin γ_1^1

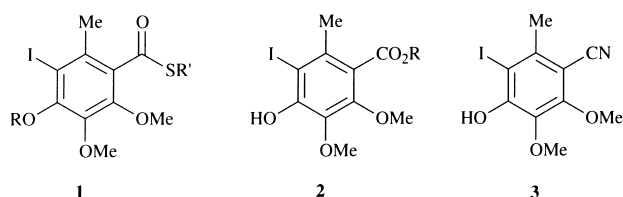
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Yong-Zhou Hu and Derrick L. J. Clive*

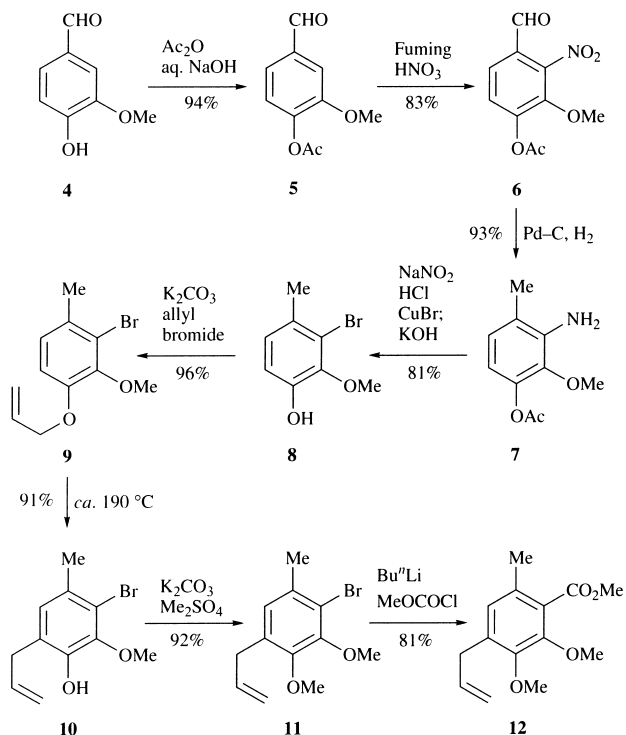
Chemistry Department, University of Alberta, Edmonton, Alberta, T6G 2G2 Canada

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_1^1 .

The aromatic system **1** (R, R' = complex carbohydrate) is a structural unit of the antitumour agent calicheamicin γ_1^1 .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 procedure⁵ (Scheme 1, **4**→**5**†→**6**). Reduction of both the nitro and formyl

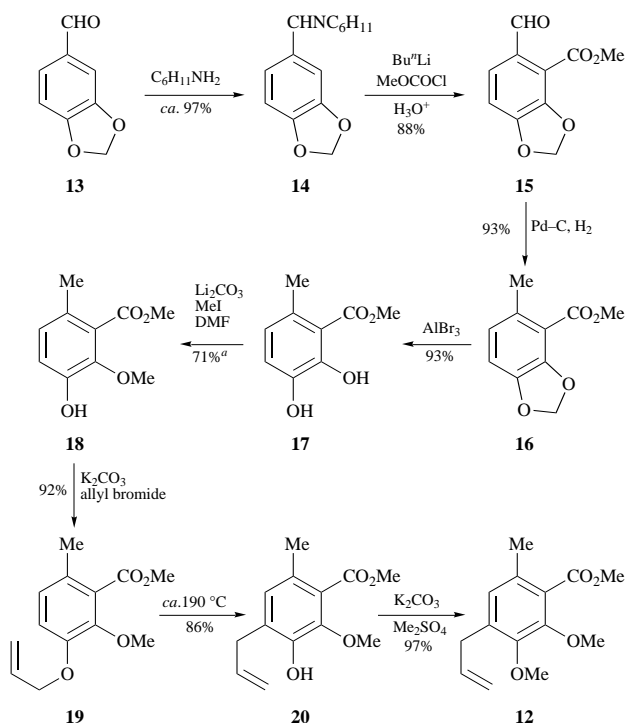


Scheme 1

groups (**6**→**7**, Pd-C, H₂, 93%), followed by Sandmeyer reaction (NaNO₂, HCl, CuBr) and hydrolysis (KOH) afforded bromophenol **8** (81% from **7**). Allylation (**8**→**9**) under classical

† The literature procedure was followed for the preparation of **5**, except that the Ac₂O (4.09 cm³, 43.3 mmol) was dissolved in Et₂O (36 cm³), instead of being used neat. The crude product (94%) was used directly.

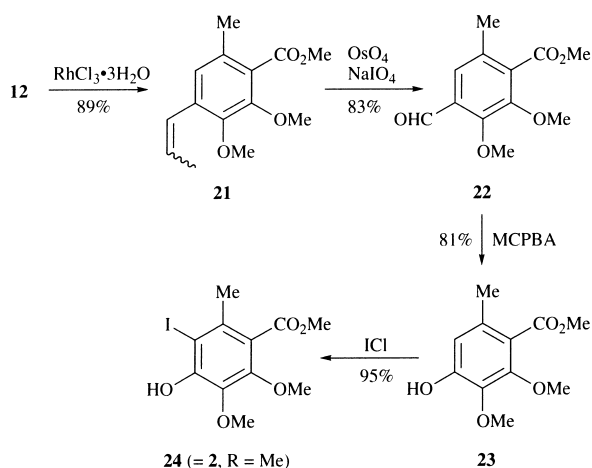
conditions (allyl bromide, K₂CO₃, 96%) and Claisen rearrangement (ca. 190 °C, 91%) served to functionalize the expected position of the aromatic ring (**9**→**10**) and methylation (Me₂SO₄, K₂CO₃, 92%) then gave the fully protected bromide **11**. At this point, halogen-metal exchange (BuⁿLi) and quenching 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).



^aAfter correction for recovered **17** (30%)

Scheme 2

Aldehyde ester **15** was made from piperonal by a literature procedure⁷ (Scheme 2, **13**→**14**→**15**), and then the formyl group was completely reduced⁸ (**15**→**16**, Pd-C, H₂, 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 conditions¹⁰ (DMF, MeI, Li₂CO₃) 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, K₂CO₃, 92%) and then Claisen rearrangement (**19**→**20**, ca. 190 °C, 86%) and subsequent methylation (Me₂SO₄, K₂CO₃, 97%) resulted in formation again of the highly substituted ester



Scheme 3

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

The double bond in the pendant allyl group of **12** was isomerized¹¹ to the geometrical isomers **21** ($\text{RhCl}_3 \cdot \text{H}_2\text{O}$, 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 accomplished¹² by Baeyer–Villiger oxidation (**22**→**23**, MCPBA, 81%). Phenol **23** is a known substance² which, on treatment with iodine chloride,² gave the desired target **24** (*i.e.* **2**, $\text{R} = \text{Me}$) in 95% yield.†

Experimental

General experimental procedures were the same as those used previously.¹³ In the ¹³C 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 cm³) in a 100 cm³ 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 cm³) 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 cm³, 23.23 mmol) and MeOH (150 cm³), 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 cm³). 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; $\nu_{\text{max}}(\text{CH}_2\text{Cl}_2 \text{ cast})/\text{cm}^{-1}$ 3457, 3373, 2968, 2927, 1760, 1618, 1492, 1475, 1250, 1207 and 1061; $\delta_{\text{H}}(400 \text{ MHz}, \text{CDCl}_3)$ 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); $\delta_{\text{C}}(75.5 \text{ MHz}, \text{CDCl}_3)$ 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). $\text{C}_{10}\text{H}_{13}\text{NO}_3$ requires *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 cm³) 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 cm³). 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 cm³). At the end of the addition, stirring was continued for 15 min, and the mixture was then cooled to room temperature and extracted with Et₂O (3 × 25 cm³). The combined extracts were washed with hydrochloric acid (3%; 2 × 125 cm³), water (20 cm³) and saturated aqueous NaHCO_3 (15 cm³). The organic phase (without drying) was evaporated and the residue was diluted with MeOH (50 cm³). KOH (3.0 g, 75.0 mmol) was added, 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 cm³), and the mixture was extracted with Et₂O (3 × 20 cm³), washed with saturated aqueous NaHCO_3 (20 cm³), water (15 cm³) and brine (20 cm³) 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%); $\nu_{\text{max}}(\text{CH}_2\text{Cl}_2 \text{ cast})/\text{cm}^{-1}$ 3422, 2971, 2938, 1603, 1483, 1458, 1276, 1206 and 1037; $\delta_{\text{H}}(300 \text{ MHz}, \text{CDCl}_3)$ 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); $\delta_{\text{C}}(50.3 \text{ MHz}, \text{CDCl}_3)$ 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). $\text{C}_8\text{H}_9^{81}\text{BrO}_2$ requires *M*, 217.9765).

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

Allyl bromide (1.68 cm³, 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 cm³). 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; $\nu_{\text{max}}(\text{CH}_2\text{Cl}_2 \text{ cast})/\text{cm}^{-1}$ 2979, 2933, 1595, 1484, 1458, 1395, 1293, 1268, 1257 and 1049; $\delta_{\text{H}}(300 \text{ MHz}, \text{CDCl}_3)$ 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); $\delta_{\text{C}}(50.3 \text{ MHz}, \text{CDCl}_3)$ 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 150.122 (s′) (Found: M^+ , 258.0077). $\text{C}_{11}\text{H}_{13}^{81}\text{BrO}_2$ 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 cm³) 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; $\nu_{\text{max}}(\text{CH}_2\text{Cl}_2 \text{ cast})/\text{cm}^{-1}$ 3507, 3003, 2976, 2938, 1639, 1459, 1401, 1299, 1210 and 1057; $\delta_{\text{H}}(400 \text{ MHz}, \text{CDCl}_3)$ 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); $\delta_{\text{C}}(50.3 \text{ MHz}, \text{CDCl}_3)$ 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). $\text{C}_{11}\text{H}_{13}^{81}\text{BrO}_2$ requires *M*, 258.0078).

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

Me_2SO_4 (0.78 cm³, 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 cm³). 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 (¹H NMR, 360 MHz), colourless oil; $\nu_{\max}(\text{CH}_2\text{Cl}_2 \text{ cast})/\text{cm}^{-1}$ 3077, 2996, 2976, 1639, 1468, 1422, 1391, 1319, 1243, 1069 and 1015; $\delta_{\text{H}}(360 \text{ MHz, CDCl}_3)$ 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); $\delta_{\text{C}}(50.3 \text{ MHz, CDCl}_3)$ 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. $\text{C}_{12}\text{H}_{15}^{81}\text{BrO}_2$ requires *M*, 272.0235).

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

Bu^tLi (2.5 M in hexane; 1.42 cm³, 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 cm³). Stirring was continued for 15 min, and then MeOCOCl (0.34 cm³, 4.432 mmol) in THF (5 cm³) 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 cm³) was added. The mixture was extracted with Et₂O (2 × 30 cm³) and the extract was washed with saturated aqueous NaHCO₃ (15 cm³) and brine (15 cm³) and dried (Na₂SO₄). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 15 cm), using 1:10 Et₂O–hexane, gave **12** (596 mg, 81%) as a pure (¹H NMR, 400 MHz), colourless oil; $\nu_{\max}(\text{CH}_2\text{Cl}_2 \text{ cast})/\text{cm}^{-1}$ 2977, 2940, 1733, 1605, 1482, 1459, 1315, 1276 and 1054; $\delta_{\text{H}}(300 \text{ MHz, CDCl}_3)$ 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); $\delta_{\text{C}}(75.4 \text{ MHz, CDCl}_3)$ 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. $\text{C}_{14}\text{H}_{18}\text{O}_4$ requires *M*, 250.1205).

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

$\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$ (33 mg, 0.125 mmol) was added to a solution of **12** (403 mg, 1.61 mmol) in dry EtOH (3 cm³) and the mixture was stirred at 70 °C for 8 h. The solvent was then evaporated and the residue was diluted with Et₂O (30 cm³), washed with water (2 × 10 cm³) and brine (10 cm³), dried (Na₂SO₄) 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 (¹H NMR, 300 MHz), colourless oil, which was a 9:1 mixture of *E* and *Z* isomers; $\nu_{\max}(\text{CH}_2\text{Cl}_2 \text{ cast})/\text{cm}^{-1}$ 3034, 2994, 2939, 1732, 1602, 1458, 1448, 1405, 1277, 1154 and 1062; $\delta_{\text{H}}(300 \text{ MHz, CDCl}_3)$ [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); $\delta_{\text{C}}(75.4 \text{ MHz, CDCl}_3)$ [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. $\text{C}_{14}\text{H}_{18}\text{O}_4$ requires *M*, 250.1205).

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

OsO_4 (2.5% w/v in Bu^tOH; 2.10 cm³, 0.34 mmol) was added to a stirred mixture of **21** (710 mg, 2.84 mmol), Bu^tOH (10 cm³), CCl₄ (20 cm³) and water (20 cm³). After 15 min, NaIO₄ (1.52 g, 7.10 mmol) was added in one portion, and stirring was continued for 2 h. Water (20 cm³) was then added and the mixture was extracted with Et₂O (2 × 30 cm³). The combined extracts were washed with water (20 cm³), 10% aqueous NaHSO₃ (20 cm³) and brine (15 cm³), dried (Na₂SO₄) and evaporated. Flash chromatography of the residue over silica gel (2 × 18 cm), using 1:5 Et₂O–hexane, gave **22** (562 mg, 83%) as a pure (¹H NMR, 400 MHz), white solid; mp 49–50 °C; $\nu_{\max}(\text{CH}_2\text{Cl}_2 \text{ cast})/\text{cm}^{-1}$ 2949, 1735, 1692, 1466, 1439, 1280, 1052 and 990; $\delta_{\text{H}}(400 \text{ MHz, CDCl}_3)$ 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); $\delta_{\text{C}}(75.4 \text{ MHz, CDCl}_3)$ 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. $\text{C}_{12}\text{H}_{14}\text{O}_5$ 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 CH₂Cl₂ (8 cm³) and stirring was continued for 3.5 h. Water (15 cm³) was then added and the mixture was extracted with Et₂O (2 × 20 cm³). The combined extracts were washed with saturated aqueous NaHCO₃ (2 × 10 cm³) and brine (10 cm³), dried (Na₂SO₄) and evaporated. The residue was dissolved in MeOH (6.5 cm³) and stirred, and 10% aqueous KOH (1.23 cm³) was added to the resulting solution. After 30 min, the mixture was acidified with 10% aqueous hydrochloric acid and extracted with Et₂O (3 × 15 cm³). The combined extracts were washed with water (10 cm³) and brine (15 cm³), dried (Na₂SO₄) and evaporated. Flash chromatography of the residue over silica gel (2 × 20 cm), using 1:4 Et₂O–hexane, gave **23** (395 mg, 81%) as a pure (¹H NMR, 300 MHz) solid; mp 75–76 °C (lit.,² 76 °C); $\nu_{\max}(\text{CH}_2\text{Cl}_2 \text{ cast})/\text{cm}^{-1}$ 3397, 2970, 2941, 1713, 1580, 1467, 1429, 1291, 1197, 1178 and 962; $\delta_{\text{H}}(300 \text{ MHz, CDCl}_3)$ 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); $\delta_{\text{C}}(75.4 \text{ MHz, CDCl}_3)$ 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. $\text{C}_{11}\text{H}_{14}\text{O}_5$ 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 (¹H NMR, 400 MHz), white solid; mp 134–135 °C (lit.,² 134–135 °C); $\nu_{\max}(\text{CH}_2\text{Cl}_2 \text{ cast})/\text{cm}^{-1}$ 3375, 2994, 2944, 2837, 1714, 1563, 1462, 1420, 1268, 1217, 1095, 1064 and 998; $\delta_{\text{H}}(400 \text{ MHz, CDCl}_3)$ 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); $\delta_{\text{C}}(75.4 \text{ MHz, CDCl}_3)$ 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. $\text{C}_{11}\text{H}_{13}\text{IO}_5$ 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 (¹H NMR, 300 MHz) for use directly in the next step, for which the literature procedure⁷ was modified slightly. Bu^tLi (2.5 M in hexane; 8.20 cm³, 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 cm³). Stirring was continued for 15 min, and then MeOCOCl (2.89 cm³, 37.4 mmol) in THF (30 cm³) 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 cm³) was added. Stirring was continued for 1 h and then the mixture was concentrated to remove the THF and the residue was extracted with Et₂O (2 × 80 cm³). The combined extracts were washed with water (2 × 20 cm³), saturated aqueous NaHCO₃ (2 × 15 cm³) and brine (20 cm³) and dried (Na₂SO₄). Evaporation of the solvent and flash chromatography of the residue over silica gel (4 × 25 cm), using 2:3 Et₂O–hexane, gave **15** (3.42 g, 88%) as a pure (¹H 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 cm³) and MeOH (74 cm³) 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 cm³). 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 (^1H NMR, 400 MHz), white solid; mp 70–71 °C; $\nu_{\text{max}}(\text{CH}_2\text{Cl}_2 \text{ cast})/\text{cm}^{-1}$ 2968, 2953, 1724, 1626, 1470, 1457, 1271, 1127 and 1057; $\delta_{\text{H}}(400 \text{ MHz, CDCl}_3)$ 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); $\delta_{\text{C}}(50.3 \text{ MHz, CDCl}_3)$ 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. $\text{C}_{10}\text{H}_{10}\text{O}_4$ 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 \times 20 cm^3). The combined extracts were washed with water (2 \times 15 cm^3) and brine (15 cm^3), dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 \times 15 cm), using 1 : 5 EtOAc-hexane, gave **17** (880 mg, 93%) as a pure (^1H NMR, 300 MHz), white solid; mp 104–105 °C; $\nu_{\text{max}}(\text{CH}_2\text{Cl}_2 \text{ cast})/\text{cm}^{-1}$ 3478, 1659, 1597, 1445, 1293, 1274 and 799; $\delta_{\text{H}}(300 \text{ MHz, CDCl}_3)$ 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); $\delta_{\text{C}}(50.3 \text{ MHz, CDCl}_3)$ 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. $\text{C}_9\text{H}_{10}\text{O}_4$ 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 \times 20 cm^3). The combined extracts were washed with water (2 \times 15 cm^3) and brine (15 cm^3), dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 \times 20 cm), using 1 : 4 EtOAc-hexane, gave **18** (585 mg, 50%; 71% after allowing for recovered starting material) as a pure (^1H 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 (^1H NMR, 300 MHz), colourless oil, and recovered **17** (324 mg, 30%). Phenol **18** had; $\nu_{\text{max}}(\text{CH}_2\text{Cl}_2 \text{ cast})/\text{cm}^{-1}$ 3387, 3951, 2925, 1731, 1663, 1487 and 1272; $\delta_{\text{H}}(300 \text{ MHz, CDCl}_3)$ 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); $\delta_{\text{C}}(50.3 \text{ MHz, CDCl}_3)$ 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. $\text{C}_{10}\text{H}_{12}\text{O}_4$ 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 \times 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 \times 12 cm), using 1 : 10 EtOAc-hexane, gave **19** (582 mg, 92%) as a pure (^1H NMR, 400 MHz), colourless oil; $\nu_{\text{max}}(\text{CH}_2\text{Cl}_2 \text{ cast})/\text{cm}^{-1}$ 2992, 2949, 1732, 1580, 1490, 1461, 1433, 1297, 1271, 1143 and 1068; $\delta_{\text{H}}(400 \text{ MHz, CDCl}_3)$ 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); $\delta_{\text{C}}(75.4 \text{ MHz, CDCl}_2)$ 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. $\text{C}_{13}\text{H}_{16}\text{O}_4$ requires 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 \times 15 cm), using 1 : 3 Et_2O -hexane, gave **20** (95.2 mg, 86%) as a pure (^1H NMR, 400 MHz), colourless oil; $\nu_{\text{max}}(\text{CH}_2\text{Cl}_2 \text{ cast})/\text{cm}^{-1}$ 3445, 3002, 2977, 2950, 1728, 1614, 1486, 1460, 1434, 1279 and 1195; $\delta_{\text{H}}(400 \text{ MHz, CDCl}_3)$ 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); $\delta_{\text{C}}(50.3 \text{ MHz, CDCl}_3)$ 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. $\text{C}_{13}\text{H}_{16}\text{O}_4$ 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 \times 15 cm), using 1 : 10 Et_2O -hexane, gave **12** (448 mg, 97%) as a pure (^1H NMR, 300 MHz), colourless oil, identical with material made from vanillin, as described above.

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