Total synthesis of moracin C

Graeme D. McAllister,[a] Richard C. Hartley,*[a] Michael J. Dawson[b] and Andrew R. Knaggs[b]

[a] *Department of Chemistry, University of Glasgow, Glasgow, UK G12 8QQ*
[b] *Bioprocessing Group, Glaxo-Wellcome Research and Development, Gunnels Wood Road, Stevenage, Hertfordshire, UK SG1 2NY*

Received (in Cambridge) 30th June 1998, Accepted 21st August 1998

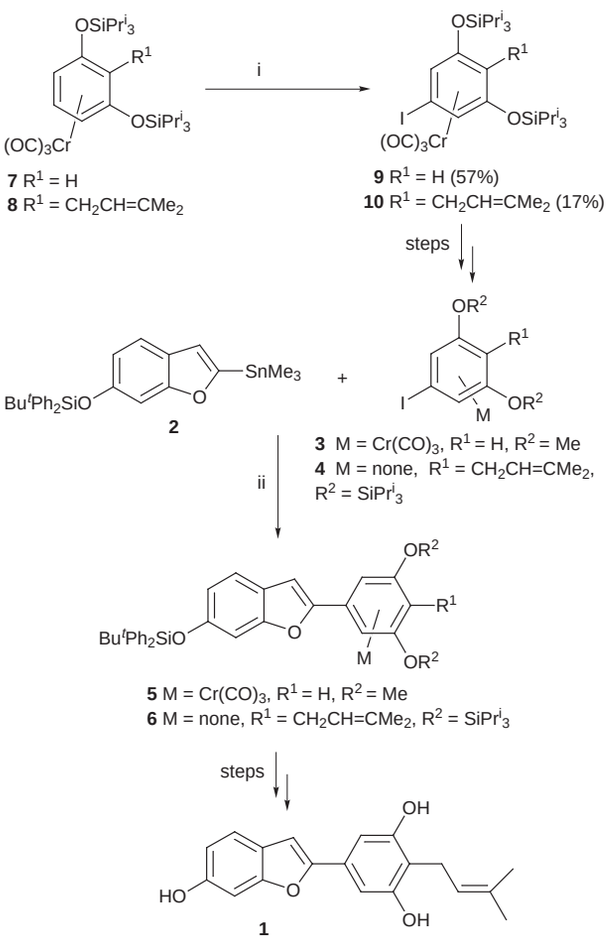
Moracin C has been synthesised by the most efficient route to date (10 steps and 12% overall yield). The relatively unexplored acid-induced, intramolecular migration of an acyl group from an *ortho* phenolic hydroxy to a benzylic hydroxy is used to synthesise *o*-hydroxybenzylphosphonium salts containing ester groups. The phosphonium salts are coupled with 3,5-dimethoxybenzoic acid. Intramolecular Wittig reaction then gives 2-arylbenzo[*b*]furans, bearing the key 1′,3′,5′ substitution pattern on the aryl ring. This discovery provides a concise route to polyphenolic benzo[*b*]furans that we expect to be of general utility.

Introduction

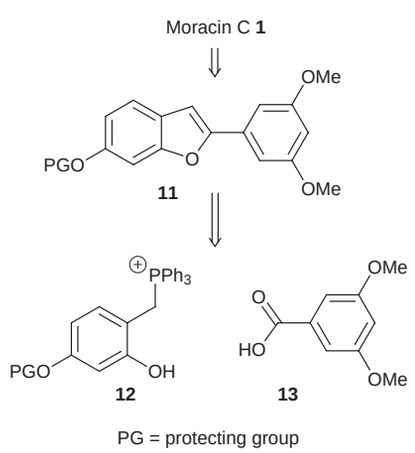
Moracin C **1** is a powerful antifungal produced by the mulberry, *Morus alba*, in response to infection by *Fusarium solani* (Scheme 1).[1] As well as being a defence compound it is also detrimental to the plant as it is an oviposition stimulant that encourages moths (*Glyphodes pyloalis*), whose caterpillars eat the plant, to lay their eggs on its leaves.[2] These properties, together with its unusual biosynthesis and its importance as the natural precursor to a Diels–Alder type adduct,[3] chalcomoracin, make moracin C **1** an attractive synthetic target.

There have been syntheses reported by Mann and Widdowson (12 steps with an overall yield of 4.9% for the longest linear sequence of 9 steps from resorcinol)[4,5] and by Nakamura and co-workers (12 steps with an overall yield of <1% for the longest linear sequence of 9 steps from resorcinol).[2] The approaches were similar. In both cases the 2-arylbenzo[*b*]furan moiety was constructed by coupling stannylated benzofuran **2** with a suitably substituted aryl iodide **3** or **4** to give 2-arylbenzo[*b*]furan **5** or **6** (Scheme 1). The key 1,3,5 relationship in aryl iodides **3** and **4** was set up by lithiation and iodination of triisopropylsilyl protected resorcinols **7** and **8** coordinated to chromium tricarbonyl. This gave the precursor aryl iodides **9** and **10**. In each synthesis the prenyl group was introduced by *ortho*-lithiation.

We required a short and high yielding route to moracin C **1**. Instead of starting with an intact benzofuran we chose to follow Le Corre and Hercouets' approach[6] to benzofuran synthesis and construct the 2-arylbenzo[*b*]furan **11** from a phosphonium salt **12** and commercially available 3,5-dimethoxybenzoic acid **13** (Scheme 2). The starting acid **13** already contains the key 1,3,5 relationship and Mann and Widdowson had demonstrated that 2-arylbenzo[*b*]furan **5**, related to our intermediate **11**, can be converted into moracin C **1**.[4] At first sight the synthesis of phosphonium salt **12** seems to require

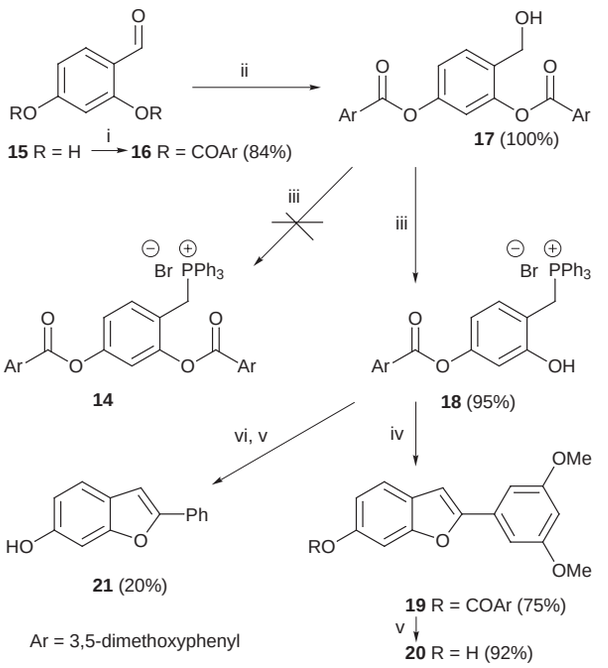


Scheme 1 *Reagents and conditions*: i, (a) BuLi (b) I_2; ii, $Pd(PPh_3)_4$.



Scheme 2 Our retrosynthetic analysis of moracin C.

selective protection of the *p*-hydroxy group. To avoid this, we decided to make diester **14** from the readily available aldehyde **15** (Scheme 3).



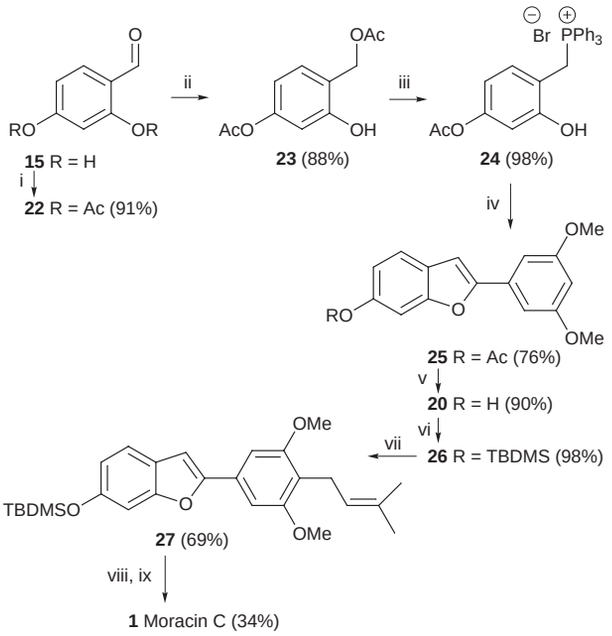
Scheme 3 *Reagents and conditions*: i, **13**, DCC, DMAP, CH_2Cl_2, RT; ii, $NaBH_3CN$, THF–H_2O, pH 3, RT; iii, $Ph_3P{\cdot}HBr$, CH_3CN, reflux; iv, (a) **13**, DCC, DMAP, CH_2Cl_2 (b) solvent removed *in vacuo* (c) Et_3N, dioxane, reflux; v, KOH, EtOH, reflux; vi, (a) $PhCO_2H$, DCC, DMAP, CH_2Cl_2 (b) solvent removed *in vacuo* (c) Et_3N, dioxane, reflux.

Results and discussion

Aldehyde **15** was esterified to give aldehyde **16** which was selectively reduced to alcohol **17** using sodium cyanoborohydride. Treating alcohol **17** with triphenylphosphine hydrobromide[6] gave phosphonium salt **18** rather than the expected diester **14**. Coupling of the phosphonium salt with carboxylic acid **13** and cyclisation using an adaptation of McKittrick and Stevenson's procedure[7] gave benzofuran **19**, which could easily be deprotected to give benzofuran **20**. The structure of the phosphonium salt was confirmed by coupling of the salt with benzoic acid, followed by deprotection to give benzofuran **21** as the only benzofuran product.

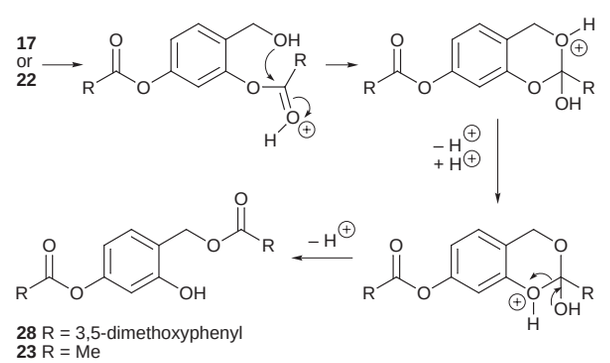
The above synthesis of benzofuran **20** wasted two equivalents of 3,5-dimethoxybenzoic acid **13**. Therefore, we decided to improve our approach by exploiting the selective ester hydrolysis. Aldehyde **15** was protected as the diacetate **22** (Scheme 4).[8] Monoacetylation of this aldehyde is not effective under a variety of conditions.[9,10] Reduction of aldehyde **22** under acidic conditions lead to the formation of phenol **23** rather than 2,4-diacetoxybenzyl alcohol. Ester **23** was converted into the corresponding phosphonium salt **24**, and the latter was coupled with acid **13** to give benzofuran **25**. Hydrolysis of the acetate then gave benzofuran **20**.

Benzofuran **20** was converted into moracin C **1** by a protection–prenylation–deprotection sequence similar to that employed by Mann and Widdowson.[4] We found that coordination to chromium tricarbonyl is not necessary for lithiation of benzofuran **26**, and that the 6-*tert*-butyldimethylsilyloxy group is sufficiently bulky to avoid lithiation at the 7-position. The organocopper reagent, formed from a 1:1 mixture of aryllithium and copper(I) bromide–dimethyl sulfide,[4] was less effective in the prenylation reaction (30–51%) than the higher order cuprate derived from lithium 2-thienylcyanocuprate.[11] Deprotection of benzofuran **27** gave moracin C **1** in 10 steps and 12% overall yield (by either approach to benzofuran **20**).



Scheme 4 *Reagents and conditions*: i, Ac_2O, Et_2O, K_2CO_3, RT; ii, $NaBH_3CN$, THF–H_2O, pH 3, RT; iii, $Ph_3P{\cdot}HBr$, CH_3CN, reflux; iv, (a) **13**, DCC, DMAP, CH_2Cl_2 (b) solvent removed *in vacuo* (c) Et_3N, dioxane, reflux; v, KOH, EtOH–H_2O, reflux; vi, TBDMSCl, imidazole, DMF, RT; vii, (a) BuLi, THF, −78 °C (b) (2-thienyl)Cu(CN)Li, −30 °C (c) prenyl bromide, −30 °C − RT; viii, Ph_2PLi, THF, reflux; ix, Bu_4NF, THF, RT.

We suggest that the selective ester hydrolysis observed in the formation of phosphonium salt **18** results from acyl migration (Scheme 5) followed by S_N2 displacement of the protonated



Scheme 5

ester by triphenylphosphine. The lone pairs of the benzylic oxygen atom are in conjugation with a carbonyl group in the phenol intermediate **28** but not in alcohol **17** and this provides the driving force for the reaction. The acetyl group undergoes migration more readily than the 3,5-dimethoxybenzoyl group, hence the formation of phenol **23** under the mildly acidic reduction conditions. A few similar acid-induced acyl migrations from phenolic to benzylic hydroxys have been observed.[12]

In summary, our syntheses of moracin C **1** are the most efficient to date. Prior to our work, Le Corre and Hercouet's approach[6] to benzo[*b*]furan synthesis had been limited by the requirement for a benzylphosphonium salt bearing a free *o*-hydroxy. We have demonstrated that intramolecular migration of an acyl group from a phenolic to a benzylic hydroxy can be used to synthesise such phosphonium salts. This discovery provides a concise route to polyphenolic benzo[*b*]-furans[4,5,13,14] that we expect to be of general utility.

Experimental

^1H and ^{13}C NMR spectra were obtained on a Bruker AM200-

SY spectrometer operating at 200 and 50 MHz respectively or on a Bruker DPX/400 spectrometer operating at 400 and 100 MHz, respectively. ^{31}P NMR spectra were obtained on a Bruker AM200-SY spectrometer operating at 81 MHz. All coupling constants are measured in Hz. DEPT was used to assign the signals in the ^{13}C NMR spectra as C, CH, CH_2 or CH_3. Mass spectra (MS) were recorded on AEI MS12 or MS902 spectrometers. Infra-red (IR) spectra were obtained from KBr disc or as a solution in chloroform on a Perkin-Elmer 983 spectrophotometer. Ultra-violet (UV) spectra were recorded on a Shimadzu UV-1601 spectrophotometer. Column chromatography was carried out on silica gel, 70–230 mesh. Tetrahydrofuran and diethyl ether were dried over sodium and benzophenone, and dichloromethane was dried over calcium hydride. Dimethylformamide, acetonitrile and triethylamine were distilled from calcium hydride and stored over 4 Å molecular sieves.

Moracin C 1

n-Butyllithium (2.83 cm^3, 1.42 mol dm^{-3} in hexane, 4.01 mmol) was added over 1 h to a stirred solution of diphenylphosphine (0.70 cm^3, 4.01 mmol) in dry THF (5 cm^3) at 0 °C under nitrogen. Benzofuran **27** (0.302 g, 0.668 mmol) in dry THF (2.5 cm^3) was added and the solution was allowed to warm to room temperature. The mixture was heated under reflux for 16 h and was then poured into aqueous NaOH (2.5 mol dm^{-3}), acidified with aqueous HCl (2.5 mol dm^{-3}) and extracted into ethyl acetate. The organic extract was dried with Na_2SO_4 and the solvent removed *in vacuo*. Tetrabutylammonium fluoride (4.1 cm^3, 1 mol dm^{-3} in THF, 4.10 mmol) was added and the resulting solution was stirred under nitrogen at room temperature overnight. Aqueous acetic acid (2 mol dm^{-3}) was added and the mixture extracted into ethyl acetate. The organic layer was extracted with aqueous NaOH (2.5 mol dm^{-3}). The basic aqueous solution was acidified with HCl (2.5 mol dm^{-3}) and extracted into ethyl acetate. The organic extract was washed with water, dried over Na_2SO_4 and the solvent was removed *in vacuo*. Flash column chromatography [SiO_2, CH_2Cl_2–methanol (9 : 1)] of the residue gave moracin C **1** (71 mg, 0.227 mmol, 34%) as plates; mp 196–198 °C (lit.,[1] 198–199 °C); R_f[CH_2Cl_2–MeOH (9 : 1)] 0.30; ν_{max}(soln)/cm^{-1} 3398 (OH), 1624 (Ar), 1560 (Ar), 1508 (Ar), and 1117 (=C–H); δ_H[200 MHz, $(CD_3)_2CO$] 1.57 (3H, s, =CMe), 1.68 (3H, s, =CMe), 3.37 (2H, d, *J* 7.0, CH_2), 5.15 (1H, br t, *J* 7.0, CH=), 6.79 (1H, dd, *J* 2.0 and 8.3, 5-H), 6.91 (2H, s, 2′-H), 6.95 (1H, s, 3-H), 6.97 (1H, s, 7-H), and 7.22 (1H, d, *J* 8.3, 4-H); *m*/*z* (EI) 310 (M$^+$, 67%), 295 (26), 261 (28), 255 (57), 183 (20), 152 (30); (Found: M$^+$, 310.1202. $C_{19}H_{18}O_4$ requires *M*, 310.1205).

2,4-Bis(3′,5′-dimethoxybenzoyloxy)benzaldehyde 16

To a solution of 3,5-dimethoxybenzoic acid **13** (3.00 g, 16.5 mmol) in dry CH_2Cl_2 (80 cm^3) under nitrogen was added sequentially: 4-dimethylaminopyridine (0.29 g, 2.4 mmol), 2,4-dihydroxybenzaldehyde **15** (1.03 g, 7.5 mmol) and a solution of dicyclohexylcarbodiimide (3.92 g, 19.0 mmol) in dry CH_2Cl_2 (10 cm^3). The mixture was stirred at room temperature for 24 h. After this time, dicyclohexylurea was filtered off, and the organic solution washed twice with water, then dried over $MgSO_4$. The solvent was then removed under reduced pressure. Recrystallisation from ethyl acetate gave *aldehyde* **16** (2.910 g, 13.90 mmol, 84%) as needles; mp 145–148 °C; R_f(Et_2O) 0.45; ν_{max}(KBr)/cm^{-1} 1743 (ester C=O), 1695 (aldehyde C=O), and 1608 (Ar); δ_H(200 MHz, $CDCl_3$) 3.86 (6H, s, 2 × OMe), 3.87 (6H, s, 2 × OMe), 6.74 (1H, t, *J* 2.4 , 4′-H), 6.75 (1H, t, *J* 2.4, 4″-H), 7.31–7.36 (6H, m, Ar–H), 8.03 (1H, d, *J* 7.4, 6-H), and 10.20 (1H, s, CHO); δ_C(50 MHz, $CDCl_3$) 55.6, (CH_3), 106.7 (CH), 106.9 (CH), 107.7 (CH), 107.8 (CH), 117.2 (CH), 120.0 (CH), 125.9 (C), 130.0 (C), 130.3 (C), 131.1 (CH), 153.0 (C), 155.8 (C), 160.8 (C), 160.9 (C), 163.9 (C), 164.3 (C), and 187.2 (CH); *m*/*z* (EI) 466 (M$^+$, 23%), and 165 (100); (Found: C, 64.6; H 4.8%; M$^+$, 466.1253. $C_{25}H_{22}O_9$ requires C 64.37; H 4.75%; *M*, 466.1254).

2,4-Bis(3′,5′-dimethoxybenzoyloxy)benzyl alcohol 17

Sodium cyanoborohydride (0.352 g, 5.60 mmol) was added to a suspension of aldehyde **16** (2.610 g, 5.60 mmol) in THF–H_2O (19 : 1, 100 cm^3). The solution was acidified to pH 3 with AcOH–THF–c.HCl (10 : 8 : 1) whereupon the slurry dissolved. The mixture was stirred at room temperature for 1 h, quenched with water, then extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous sodium bicarbonate and brine, then dried over $MgSO_4$. The solvent was removed *in vacuo* to give *alcohol* **17** (5.360 g, 5.54 mmol, 99%) as an amorphous solid; mp 38–40 °C; R_f(Et_2O) 0.3; ν_{max}(KBr)/cm^{-1} 3058 (OH), 1739 (C=O), 1609 (Ar), 1596 (Ar), and 1500 (Ar); δ_H(200 MHz, $CDCl_3$) 2.27 (1H, br s, OH), 3.81 (6H, s, 2 × OMe), 3.82 (6H, s, 2 × OMe), 4.62 (2H, s, CH_2), 6.69 (2H, m, 2 × 4′-H), 7.14–7.18 (2H, m, 3-H, 5-H), 7.29 (2H, d, *J* 2.3, 2′-H), 7.30 (2H, d, *J* 2.3, 2′-H), and 7.56 (1H, d, *J* 9.0, 6-H); δ_C(50 MHz, $CDCl_3$) 55.6 (CH_3), 59.7 (CH_2), 106.5 (CH), 106.6 (CH), 107.6 (CH), 107.7 (CH), 116.1 (CH), 119.7 (CH), 129.6 (C), 130.5 (CH), 130.9 (C), 131.0 (C), 148.7 (C), 150.6 (C), 160.7 (C), 160.8 (C), 164.6 (C), and 164.8 (C); *m*/*z* (EI) 468 (M$^+$, 5%), 182 (75), 165 (100), and 137 (20); (Found: M$^+$, 468.1423. $C_{25}H_{24}O_9$ requires *M*, 468.1420).

[4-(3′,5′-Dimethoxybenzoyloxy)-2-hydroxybenzyl]triphenylphosphonium bromide 18

Alcohol **17** (4.670 g, 9.98 mmol) and triphenylphosphine hydrobromide (3.425 g, 9.98 mmol), were heated under reflux in dry acetonitrile (100 cm^3) under nitrogen for 3 h. The reaction was then allowed to cool to room temperature and stirred overnight. The acetonitrile was removed *in vacuo*, and the residue taken up in CH_2Cl_2 (10 cm^3). Slow addition of diethyl ether gave a precipitate which was collected by filtration and recrystallised from ethanol to give *phosphonium salt* **18** (6.219 g, 9.48 mmol, 95%) as plates; mp 187–190 °C; ν_{max}(KBr)/cm^{-1} 3443 (OH), 1736 (C=O), 1606 (Ar), 1592 (Ar), 1511 (Ar), and 714 (C–P); δ_H(400 MHz, CD_3OD) 3.74 (6H, s, 2 × OMe), 4.69 (2H, br d, *J* 14.0, CH_2-P), 6.45 (1H, s, 3-H), 6.48 (1H, dd, *J* 1.7 and 8.3, 5-H), 6.69 (1H, t, *J* 2.3, 4′-H), 6.88 (1H, dd, *J* 2.7 and 8.3, 6-H), 7.14 (2H, d, *J* 2.3, 2′-H), and 7.54–7.80 (15H, m, 3 × Ph); δ_C(100 MHz, CD_3OD) 25.8 (d, *J* 49.6, CH_2P), 55.6 (CH_3), 107.4 (CH), 109.1 (CH), 110.7 (d, *J* 2.7, CH), 113.1 (d, *J* 8.8, C), 114.7 (d, *J* 3.1, CH), 120.0 (d, *J* 85.7, C), 131.6 (d, *J* 12.5, CH), 132.7 (C), 133.6 (d, *J* 5.0, CH), 135.8 (d, *J* 9.7, CH), 136.7 (d, *J* 2.5, CH), 154.1 (d, *J* 4.0, C), 158.8 (d, *J* 5.0, C), 162.9 (C), and 166.5 (C); δ_P(81 MHz, $CDCl_3$) 21.3; (Found: C, 64.7; H, 4.75%. $C_{34}H_{30}BrO_5P$ requires C, 64.86; H, 4.80).

6-(3″,5″-Dimethoxybenzoyloxy)-2-(3′,5′-dimethoxyphenyl)-benzo[*b*]furan 19

Dicyclohexylcarbodiimide (0.28 g, 1.35 mmol) in dry CH_2Cl_2 (15 cm^3) was added to a solution of phosphonium salt **18** (0.91 g, 1.45 mmol), 4-dimethylaminopyridine (0.021 g, 0.17 mmol), and 3,5-dimethoxybenzoic acid (0.20 g, 1.07 mmol) in dry CH_2Cl_2 (50 cm^3) under nitrogen, and the mixture was stirred overnight at room temperature. The solution was concentrated and the residue dissolved in dioxane (50 cm^3). Triethylamine (0.84 cm^3, 6.03 mmol) was added and the mixture heated under reflux under nitrogen for 12 h. After cooling, the solution was filtered and the solvent removed *in vacuo*. Flash column chromatography (SiO_2, CH_2Cl_2) of the residue gave *benzofuran* **19** (230 mg, 0.803 mmol, 75%) as needles; mp 110–113 °C; R_f(CH_2Cl_2) 0.25; ν_{max}(soln)/cm^{-1} 1752 (C=O), 1602 (Ar), 1573 (Ar), and 1519 (Ar); δ_H(200 MHz, $CDCl_3$) 3.71 (6H, s, 2 × OMe), 3.74 (6H, s, 2 × OMe), 6.33 (1H, t, *J* 2.2, 4′-H), 6.59

(1H, t, *J* 2.3, 4″-H), 6.85 (1H, s, 3-H), 6.86 (2H, d, *J* 2.2, 2″-H), 6.96 (1H, dd, *J* 2.0 and 8.4, 5-H), 7.24 (2H, d, *J* 2.2, 2″-H), 7.29 (1H, d, *J* 1.8, 7-H), and 7.42 (1H, d, *J* 8.4, 4-H); δ_C(50 MHz, $CDCl_3$) 55.4 (CH_3), 55.6 (CH_3), 101.0 (CH), 101.6 (CH), 102.9 (CH), 105.2 (CH), 106.3 (CH), 107.7 (CH), 117.2 (CH), 120.9 (CH), 127.0 (C), 131.3 (C), 131.9 (C), 148.2 (C), 154.6 (C), 156.7 (C), 160.7 (C), 161.1 (C), and 165.2 (C); *m*/*z* (EI) 434 (30%, M^+), 165 (100), and 137 (22); (Found: C, 69.0; H 5.1%; M^+, 434.1364. $C_{25}H_{22}O_7$ requires C, 69.10; H, 5.07%; *M*, 434.1366).

2-(3′,5′-Dimethoxyphenyl)-6-hydroxybenzo[*b*]furan 20

Ester **19** (0.308 g, 0.71 mmol) and potassium hydroxide (0.100 g, 1.71 mmol) were dissolved in ethanol (5 cm^3) and heated under reflux for 2 h. After cooling, the solution was diluted with aqueous NaOH (1 mol dm^{-3}), acidified to pH 2 with aqueous HCl (1 mol dm^{-3}), and then extracted into CH_2Cl_2. The organic solution was washed twice with water, then dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue filtered through a short silica plug (eluting with CH_2Cl_2) to give benzofuran[13] **20** (0.306 g, 0.65 mmol, 92%) as needles; mp 114–116 °C (lit.,[13] 112–115 °C); R_f(CH_2Cl_2) 0.2; ν_{max}(soln)/cm^{-1} 3448 (OH), 1624 (Ar), 1600 (Ar), 1576 (Ar), and 1508 (Ar); δ_H(200 MHz, $CDCl_3$) 3.78 (6H, s, 2 × OMe), 5.42 (1H, br s, OH), 6.37 (1H, t, *J* 2.2, 4′-H), 6.70 (1H, dd, *J* 2.2 and 8.4, 5-H), 6.84 (1H, s, 3-H), 6.88 (2H, d, *J* 2.3, 2′-H), 6.94 (1H, *J* 1.9, d, 7-H), and 7.31 (1H, d, *J* 8.4, 4-H); δ_C(50 MHz, $CDCl_3$) 55.5 (CH_3), 98.2 (CH), 100.6 (CH), 101.7 (CH), 102.6 (CH), 112.2 (CH), 121.2 (CH), 122.6 (C), 132.4 (C), 153.9 (C), 154.9 (C), 155.9 (C), and 160.9 (C); *m*/*z* (EI) 270 (100, M^+); (Found: C, 71.1; H 5.3%; M^+, 270.0983; $C_{16}H_{14}O_4$ requires C, 71.10; H 5.22%; *M*, 270.0982).

In a similar way, a solution of acetate **25** (1.230 g, 3.94 mmol) and potassium hydroxide (0.530 g, 9.46 mmol, 2.4 equiv.) in ethanol–H_2O (5:1, 20 ml) was heated under reflux for 1 h and *benzofuran* **20** (0.958 g, 3.550 mmol, 90%) was then obtained following the same work-up procedure.

6-Hydroxy-2-phenylbenzo[*b*]furan 21

A solution of dicyclohexylcarbodiimide (0.34 g, 1.64 mmol) in dry CH_2Cl_2 (5 cm^3) was added to a solution of phosphonium salt **18** (1.10 g, 1.75 mmol), 4-dimethylaminopyridine (0.030 g, 0.21 mmol), and benzoic acid (0.16 g, 1.30 mmol) in dry CH_2Cl_2 (20 cm^3), under nitrogen, and the mixture stirred overnight. The solution was concentrated and the residue dissolved in dioxane (20 cm^3). Triethylamine (1.02 cm^3, 7.34 mmol) was added and the reaction heated under reflux under nitrogen for 12 h. After cooling, the solution was filtered and the solvent removed *in vacuo*. Flash column chromatography (SiO_2, CH_2Cl_2) gave crude 6-(3″,5″-dimethoxybenzoyloxy)-2-phenylbenzo[*b*]furan (0.82 g). This crude material was dissolved in EtOH (20 cm^3), KOH (0.12 g, 4.4 mmol) was added and the mixture was heated under reflux for 2 h. The reaction was quenched with aqueous NaOH (2.5 mol dm^{-3}), acidified with aqueous HCl (2 mol dm^{-3}) and extracted into CH_2Cl_2. The organic layer was extracted twice with aqueous NaOH (2.5 mol dm^{-3}). The basic aqueous extracts were acidified as before and re-extracted into CH_2Cl_2. The CH_2Cl_2 extract was dried over $MgSO_4$, and concentrated *in vacuo.* The residue was filtered through a short silica column eluting with CH_2Cl_2, the solvent was removed, and the residue was recrystallised from diethyl ether–hexane to give benzofuran **21** (0.90 g, 0.260 mmol, 20%) as pale yellow needles; mp 165–170 °C (lit.,[15] 167 °C); δ_H[200 MHz, $(CD_3)_2$-CO] 6.83 (1H, dd, *J* 2.1 and 8.4, 4-H), 7.02 (1H, d, *J* 1.9, 2′-H), 7.18 (1H, d, *J* 0.8, 3-H), 7.30–7.50 (4H, m, 5-H and 3 × Ph–H), 7.86 (2H, d, *J* 7.1, 2 × Ph–H), and 8.55 (1H, s, OH); [lit.,[13] 60 MHz, $(CD_3)_2CO$].

2,4-Diacetoxybenzaldehyde 22

Following the procedure of Malkin and Nierenstein[8] 2,4-dihydroxybenzaldehyde **15** (5.012 g, 36.32 mmol) gave, after recrystallisation from hexane, aldehyde **22** (7.365 g, 33.05 mmol, 91%) as needles; mp 66–68 °C (lit., 69–70 °C,[9] 65 °C[16]), our ^{1}H NMR data do not completely correspond to those previously reported;[16] ν_{max}(KBr)/cm^{-1} 1767 (ester C=O), 1753 (ester C=O), 1690 (aldehyde C=O), 1606 (Ar), 1585 (Ar) 1545 (Ar), and 1492 (Ar); δ_H(200 MHz, $CDCl_3$) 2.33 (3H, s, OAc), 2.39 (3H, s, OAc), 7.04 (1H, d, *J* 2.2, 3-H), 7.17 (1H, dd, *J* 2.2 and 8.5, 5-H), 7.95 (1H, d, *J* 8.5, 6-H), and 10.07 (1H, s, CHO); δ_C(50 MHz, $CDCl_3$) 20.7 (CH_3), 21.0 (CH_3), 117.0 (CH), 119.6 (CH), 125.5 (C), 132.1 (CH), 152.2 (C), 155.5 (C), 168.2 (C), 168.8 (C), and 187.5 (CH); *m*/*z* (CI) 240 [100%, $(M+NH_4)^+$]; *m*/*z* (EI) 222 (5%, M^+), 180 (35), 179 (15), 138 (100); (Found: C, 59.5; H, 4.6%. $C_{11}H_{10}O_5$ requires C, 59.46; H 4.54%).

4-Acetoxy-2-hydroxybenzyl acetate 23

Sodium cyanoborohydride (1.277 g, 20.28 mmol) was added to a stirred solution of aldehyde **22** (3.001 g, 13.52 mmol) in 19:1 THF–H_2O (60 cm^3). The solution was acidified to pH 3 with AcOH–THF–c.HCl (10:8:1). After stirring at room temperature for 1 h, the mixture was diluted with water (100 cm^3) and extracted into CH_2Cl_2 (3 × 100 cm^3). The organic extract was washed with saturated sodium bicarbonate solution (3 × 100 cm^3) and brine (100 cm^3), then dried ($MgSO_4$) and concentrated *in vacuo* to give *phenol* **23** (2.670 g, 11.92 mmol, 88%) as an oil. R_f[diethyl ether-hexane (2:1)] 0.43; ν_{max}(film)/cm^{-1} 3392 (OH), 1764 (C=O), 1736 (C=O), 1610 (Ar), 1516 (Ar), and 1501 (Ar); δ_H(200 MHz, $CDCl_3$) 2.05 (3H, s, CH_2OAc), 2.23 (3H, s, ArOAc), 5.07 (2H, s, CH_2), 6.57–6.62 (2H, m, 3-H and 5-H), 7.23 (1H, d, *J* 8.9, 6-H), and 8.09 (1H, s, OH); δ_C(50 MHz, $CDCl_3$) 20.8 (CH_3), 20.9 (CH_3), 62.1 (CH_2), 110.0 (CH), 113.2 (CH), 119.8 (C), 131.9 (CH), 151.9 (C), 156.1 (C), 169.8 (C), and 173.0 (C); *m*/*z* (EI) 224 (30, M^+), 182 (30), 164 (20), 122 (100), and 94 (30); (Found: M^+, 224.0862. $C_{11}H_{12}O_5$ requires *M*, 224.0865).

(4-Acetoxy-2-hydroxybenzyl)triphenylphosphonium bromide 24

Triphenylphosphine hydrobromide (1.534 g, 4.47 mmol) was added to a solution of *phenol* **23** (1.002 g, 4.47 mmol) in dry acetonitrile (25 cm^3) under nitrogen and the mixture heated under reflux for 2 h. The solvent was removed *in vacuo* and the residue taken up in CH_2Cl_2 (10 cm^3). Diethyl ether (100 cm^3) was added and the resulting precipitate was filtered off and dried under suction to give the *phosphonium salt* **24** as a white powder (2.231 g, 4.40 mmol, 98%); mp 204–206 °C; ν_{max}(film)/cm^{-1} 3422 (OH), 1763 (C=O), 1603 (Ar), 1588 (Ar), 1511 (Ar), and 689 (C–P); δ_H(400 MHz, CD_3OD) 2.13 (3H, s, OAc), 4.66 (2H, d, *J* 13.9, –CH_2P), 6.33 (1H, s, 3-H), 6.35 (1H, dd, *J* 2.0 and 8.2, 5-H), 6.82 (1H, dd, *J* 2.8 and 8.2, 6-H), and 7.51–7.79 (15H, m, 3 × Ph); δ_C(100 MHz, CD_3OD) 21.3 (CH_3), 25.7 (d, *J* 49.6, CH_2P), 110.6 (d, *J* 2.9, CH) 113.2 (d, *J* 8.8, C), 114.6 (d, *J* 3.0, CH), 120.0 (d, *J* 85.7, C), 131.6 (d, *J* 12.6, CH), 133.5 (d, *J* 5.1, CH), 135.8 (d, *J* 9.8, CH), 136.7 (d, *J* 2.7, CH), 154.0 (d, *J* 4.0, C), 158.7 (d, *J* 5.0, C), and 171.2 (C); δ_P(81 MHz, $CDCl_3$) 21.67; *m*/*z* (EI) 262 (100%, $Ph_3P^{\cdot+}$), 183 (55), 108 (15); (Found: C, 64.0; H, 4.9; Br, 16.0%. $C_{27}H_{24}BrO_3P$ requires C, 63.91; H, 4.73; Br, 15.80).

6-Acetoxy-2-(3′,5′-dimethoxyphenyl)benzo[*b*]furan 25

Dicyclohexylcarbodiimide (5.398 g, 26.20 mmol) in dry CH_2Cl_2 (15 cm^3) was added to a solution of phosphonium salt **24** (10.544 g, 20.80 mmol), 4-dimethylaminopyridine (0.406 g, 3.33 mmol), and 3,5-dimethoxybenzoic acid (3.823 g, 21.00 mmol) in dry CH_2Cl_2 (200 cm^3) under nitrogen, and the mixture was stirred overnight. The solution was concentrated *in vacuo* and the residue dissolved in dry dioxane (100 cm^3). Triethylamine (16.30 cm^3, 117.71 mmol) was added and the mixture heated under reflux under nitrogen overnight. After cooling, the solution was filtered and the solvent removed *in vacuo*. Flash

column chromatography [SiO_2, hexane–diethyl ether (2:1)] of the residue gave *benzofuran* **25** as an amorphous solid (4.874 g, 15.96 mmol, 76%); mp 109–110 °C; R_f[diethyl ether–hexane (1:2)] 0.21; ν_{max}(film)/cm^{-1} 1753 (C=O), 1652 (Ar), 1602 (Ar), 1573 (Ar), and 1518 (Ar); δ_H(200 MHz, $CDCl_3$) 2.35 (3H, s, OAc), 3.87 (6H, s, 2 × OMe), 6.48 (1H, t, *J* 2.2, 4′-H), 6.99–6.93 (4H, m, 2′-H, 3-H and 5-H), 7.30 (1H, s, 7-H), and 7.58 (1H, d, *J* 8.4, 4-H); δ_C(50 MHz, $CDCl_3$) 21.2 (CH_3), 55.5 (CH_3), 101.0 (CH), 101.5 (CH), 102.9 (CH), 105.1 (CH), 117.1 (CH), 121.0 (CH), 127.0 (C), 131.9 (C), 147.9 (C), 154.5 (C), 156.7 (C), 161.0 (C), and 169.8 (C); *m*/*z* (EI) 312 (25%, M^+), 270 (100); (Found: M^+, 312.0994. $C_{18}H_{16}O_5$ requires *M*, 312.0998).

6-(*tert*-Butyldimethylsilyloxy)-2-(3′,5′-dimethoxyphenyl)benzo-[*b*]furan 26

A solution of benzofuran **20** (0.105 g, 0.40 mmol), imidazole (0.060 g, 0.80 mmol), and *tert*-butyldimethylsilyl chloride (0.12 g, 0.80 mmol) in dry DMF (5 cm^3) was stirred under nitrogen at room temperature for 24 h. The mixture was poured into water and extracted into CH_2Cl_2. The organic extract was washed with brine, then with water, dried ($MgSO_4$), and the solvent removed *in vacuo*. The residue was filtered through a short silica column (eluting with CH_2Cl_2) to give the *benzofuran* **26** (0.142 g, 0.372 mmol, 93%) as an oil; R_f(CH_2Cl_2) 0.80; ν_{max}(soln)/cm^{-1} 1600 (Ar), 1570 (Ar), 1508 (Ar), and 1155 (Si–C); δ_H(200 MHz, $CDCl_3$) 0.15 (6H, s, $SiMe_2$), 0.93 (9H, s, Me_3C), 3.77 (6H, s, 2 × OMe), 6.36 (1H, t, *J* 2.2, 4′-H), 6.69 (2H, dd, *J* 2.1 and 8.4, 5-H), 6.84 (1H, s, 3-H), 6.88 (2H, d, *J* 2.3, 2′-H), 6.92 (1H, d, *J* 1.6, 7-H), and 7.30 (1H, d, *J* 8.4, 4-H); δ_C(50 MHz, $CDCl_3$) −4.5 (CH_3), 18.2 (C), 25.7 (CH_3), 55.4 (CH_3), 100.7 (CH), 101.6 (CH), 102.5 (CH), 102.8 (CH), 116.7 (C), 120.7 (C), 123.1 (CH), 132.4 (CH), 153.6 (C), 155.1 (C), 155.6 (C), and 161.0 (C); *m*/*z* (CI) 385 [100%, $(M+H)^+$]; (Found: M^+ 384.1752. $C_{22}H_{28}O_4Si$ requires *M*, 384.1752).

6-(*tert*-Butyldimethylsilyloxy)-2-[3′,5′-dimethoxy-4′-(3″-methylbut-2″-enyl)phenyl]benzo[*b*]furan 27

n-Butyllithium (0.85 cm^3, 1.42 mol dm^{-3} solution in hexane, 1.20 mmol) was added over 1 h to a stirred solution of benzofuran **26** (0.307 g, 0.80 mmol) in dry THF (20 cm^3) under nitrogen at −78 °C. The solution was warmed to −30 °C, stirred for a further 1 h, and then added *via* canula to a solution of lithium 2-thienylcyanocuprate (4.8 cm^3, 0.25 mol dm^{-3} solution in THF, 1.20 mmol) under nitrogen at −30 °C. After 1 h prenyl bromide (0.14 cm^3, 1.20 mmol, 1.5 equiv.) was added. The solution was stirred at −30 °C for 2 h, warmed to room temperature and stirred overnight. The reaction was poured into water and extracted into diethyl ether. The organic solution was washed twice with brine solution and twice with water, dried ($MgSO_4$), and the solvent removed *in vacuo*. Flash column chromatography [SiO_2, hexane–diethyl ether (4:1)] gave the *benzofuran* **27** (0.250 g, 0.553 mmol, 69%), as an amorphous solid; mp 64–67 °C; R_f[hexane–diethyl ether (4:1)] 0.50; ν_{max}(soln)/cm^{-1} 1618 (Ar), 1560 (Ar), 1508 (Ar), 1165 (Si–C), and 972 (=C–H); δ_H(200 MHz, $CDCl_3$) 0.30 (6H, s, $SiMe_2$), 1.08 (9H, s, Me_3C), 1.74 (3H, s, =CMe), 1.85 (3H, s, =CMe), 3.43 (2H, d, *J* 7.0, CH_2), 3.95 (6H, s, 2 × OMe), 5.27 (1H, br t, *J* 7.1, CH=), 6.83 (1H, dd, *J* 2.1 and 8.4, 5-H), 6.95 (1H, s, 3-H), 7.05 (2H, s, 2′-H), 7.10 (1H, d, *J* 1.8, 7-H), and 7.42 (1H, d, *J* 8.4, 4-H); δ_C(50 MHz, $CDCl_3$) −4.5 (CH_3), 17.7 (CH_3), 18.2 (C), 22.3 (CH_2), 25.6 (CH_3), 29.0 (CH_3), 55.8 (CH_3), 100.3 (CH), 100.7 (CH), 102.7 (CH), 116.6 (CH), 118.7 (C), 120.5 (CH), 122.5 (CH), 123.3 (C), 129.2 (C), 131.3 (C), 153.5 (C), 155.4 (C), 155.5 (C), and 158.2 (C); *m*/*z* (EI) 452 (100%, M^+), 437 (117), 395 (12); (Found: M^+, 452.2378. $C_{27}H_{36}O_4Si$ requires *M*, 452.2382).

Acknowledgements

We wish to thank EPSRC and Glaxo-Wellcome for financial support for this project.

References

1 M. Takasugi, S. Nagao, S. Ueno, T. Masamune, A. Shirata and K. Takahashi, *Chem. Lett.*, 1978, 1239.
2 S. Matsuyama, Y. Kuwahara, S. Nakamura and T. Suzuki, *Agric. Biol. Chem.*, 1991, **55**, 1333.
3 Y. Hano, A. Ayukawa, T. Nomura and S. Ueda, *J. Am. Chem. Soc.*, 1994, **116**, 4189 and references 1–4 therein.
4 I. S. Mann and D. A. Widdowson, *Tetrahedron*, 1991, **47**, 7991.
5 I. S. Mann and D. A. Widdowson, *Tetrahedron*, 1991, **47**, 7981.
6 A. Hercouet and M. Le Corre, *Tetrahedron*, 1981, **37**, 2867; A. Hercouet and M. Le Corre, *Tetrahedron Lett.*, 1979, 2145.
7 B. A. McKittrick and R. Stevenson, *J. Chem. Soc.*, *Perkin Trans. 1*, 1984, 709.
8 T. Malkin and M. Nierenstein, *J. Am. Chem. Soc.*, 1931, **53**, 239.
9 Reaction of aldehyde **15** using 1 equivalent of acetic anhydride gave a 1:3:1 mixture of aldehyde **15**, 4-acetoxy-2-hydroxybenzaldehyde and diacetate **23**; L. Noble and R. C. Hartley, unpublished results.
10 G. Nicolosi, M. Piattelli and C. Sanfilippo, *Tetrahedron*, 1993, **49**, 3143.
11 R. J. K. Taylor, *Organocopper Reagents A Practical Approach*, Oxford University Press, Oxford, 1994, 113.
12 V. G. S. Box and D. P. Brown, *Heterocycles*, 1991, **32**, 1273; G. Ferguson, B. L. Ruhl, J. Gilmore, T. Ibrahim and W. B. Whalley, *J. Chem. Res.* (*M*), 1985, 3101; S. Arcamone, G. Cassinelli, F. DiMatteo, S. Forenza, M. C. Ripamonti, G. Rivola, A. Vigevani, J. Clardy and T. McCabe, *J. Am. Chem. Soc.*, 1980, **102**, 1462.
13 M. Watanabe, K. Kawanishi and S. Furukawa, *Chem. Pharm. Bull.*, 1991, **39**, 579.
14 Other examples that illustrate different methods for the synthesis of phenolic 2-arylbenzo[*b*]furans: T. Kinoshita, *Tetrahedron Lett.*, 1997, **38**, 259; T. A. Engler and W. Chai, *Tetrahedron Lett.*, 1996, **37**, 6969; J. F. Cameron, C. G. Willson and J. M. J. Fréchet, *J. Chem. Soc.*, *Chem. Commun.*, 1995, 923; R. C. Larock, E. K. Yum, M. J. Doty and K. K. C. Sham, *J. Org. Chem.*, 1995, **60**, 3270 (only applied to 2-phenylbenzo[*b*]furan) and references 8 and 9 therein; O. Fujimura, G. C. Fu and R. H. Grubbs, *J. Org. Chem.*, 1994, **59**, 4029; M. N. Kanvinde, R. M. Kelkar and M. V. Paradkar, *Synth. Commun.*, 1993, **23**, 961; Z. Yang, H. B. Liu, C. M. Lee, H. M. Chang and H. N. C. Wong, *J. Org. Chem.*, 1992, **57**, 7248; M. Barbier, *Liebigs Ann. Chem.*, 1991, 393; A. Clerici, O. Porta and A. Arnone, *J. Org. Chem.*, 1990, **55**, 1240; J. Guillaumel, N. Boccara, P. Demerseman, R. Royer, J. P. Bideau, M. Cotrait and N. Platzer, *J. Heterocycl. Chem.*, 1990, **27**, 605; G. Pandey, A. Krishna and U. T. Bhalerao, *Tetrahedron Lett.*, 1989, **30**, 1867; T. Ota, S. Hasegawa, S. Inoue and K. Sato, *J. Chem. Soc.*, *Perkin Trans. 1*, 1988, 3029; B. Ledoussal, A. Gorgues and A. Le Coq, *Tetrahedron*, 1987, **43**, 5841; A. Arcadi, F. Marinelli and S. Cacchi, *Synthesis*, 1986, 749.
15 C. Deschamps-Vallet, J.-B. Ilotse, M. Meyer-Dayan and D. Mohlo, *Tetrahedron Lett.*, 1979, 1109.
16 T. Kimachi, K. Tanaka and F. Yoneda, *J. Heterocycl. Chem.*, 1991, **28**, 439.

Paper 8/05026K