Synthesis of the *cis*-3a,8b-Dihydrofuro[3,2-*b*]benzofuran-2(3*H*)-one Ring System *via* a Furofuran Annulation to Activated Benzoquinones[1]

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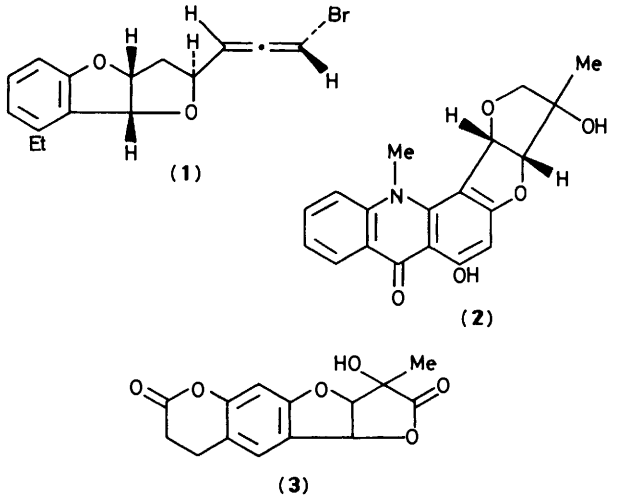
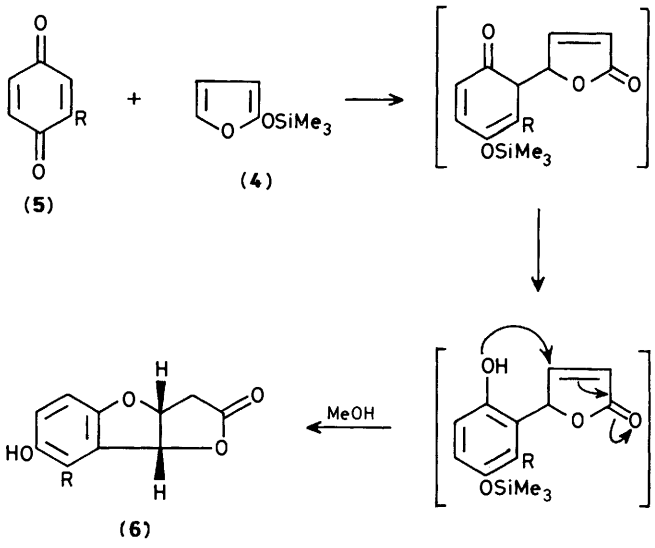
The uncatalysed addition of 2-(trimethylsiloxy)furan (**4**) to the 1,4-benzoquinones (**5a**—**e**) containing electron-withdrawing groups at C-2 gave the *cis*-3a,8b-dihydrofuro[3,2-*b*]benzofuran-2(3*H*)-ones (**6a**—**e**) in 51—76% yields. The 1,4-benzoquinones (**5f, g, h**) without electron-withdrawing groups at C-2 failed to undergo the furofuran annulation, with none of the desired adducts (**6f, g, h**) being isolated. The carboxylic acid adduct (**6i**; R = CO_2H) was prepared indirectly by reductive hydrolysis of either the phenacyl adduct (**6e**) or the trichloroethyl ester adduct (**6d**) using zinc in acetic acid. Treatment of the methyl ketone adduct (**6b**) with acid effected a ring opening to the corresponding (benzofuran-2-yl)acetic acid (**9**).

The *cis*-3a,8b-dihydrofuro[3,2-*b*]benzofuran ring system was first discovered in the potent fish antifeedent panacene (**1**) isolated from the sea hare *Aplysia brasiliana*.[2] Later the alkaloid rutagravine (**2**)[3] and a decomposition product (**3**) of the coumarin micromelin[4] were found to contain this ring system. Previous synthetic routes to the *cis*-3a,8b-dihydrofuro[3,2-*b*]-



benzofuran ring system focussed on a stepwise construction of the desired heterocycle and include the oxidation of a benzofuran with manganese(III) acetate,[5] Fétizon oxidation of a primary β-alkoxycyclopropylalkan-1-ol,[6] reduction of a 5,7-dimethyl-3-oxofuro[2,3-*b*]benzofuran-2-ylacetic acid,[7] and an electrophilic cyclization of an unsaturated alcohol.[8,9] We herein report, in full, an elegant entry to the *cis*-3a,8b-dihydrofuro[3,2-*b*]benzofuran ring system *via* the 1,4-addition of 2-(trimethylsiloxy)furan (**4**) to a range of activated benzoquinones (**5a**—**e**).

It was expected that after the initial 1,4-addition of 2-(trimethylsiloxy)furan (**4**) *ortho* to the activating group on the benzoquinone ring, aromatization, followed by a second 1,4-addition of the resulting phenoxy group onto the neighbouring butenolide moiety, would occur to provide the desired heterocycle (**6**) (Scheme 1). Whilst the 1,4-addition of various nucleophiles to benzoquinones has been demonstrated[10–13] the potential of this addition–aromatization–addition sequence for generating the *cis*-3a,8b-dihydrofuro[3,2-*b*]benzofuran ring system had not been realized. The 1,4-addition of 2-(t-butoxy)-



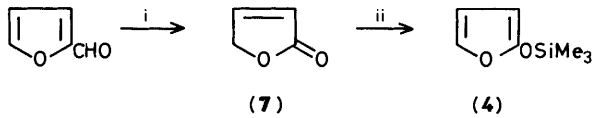
a; R = CO_2Me **e**; R = CO_2CH_2COPh
b; R = COMe **f**; R = SPh
c; R = SOPh **g**; R = Cl
d; R = $CO_2CH_2CCl_3$ **h**; R = H

Scheme 1.

furan to 2-acetyl-1,4-naphthoquinone has been reported by Kraus and Roth.[11]

In this case, the robust nature of the t-butoxy group prevented formation of a butenolide moiety and subsequent cyclization. Thus, the use of a siloxyfuran, being more labile than an alkoxyfuran, was expected to encourage butenolide formation and hence favour the subsequent cyclization.

2-(Trimethylsiloxy)furan (**4**)[14,15] was prepared from but-2-enolide (**7**)[16] using triethylamine and chlorotrimethylsilane (Scheme 2) and was distilled several times before use in order to



Scheme 2. *Reagents and conditions:* i, HCO_2H, H_2O_2, CH_2Cl_2, K_2CO_3 then Et_3N, toluene; ii, Et_3N, $SiMe_3Cl$, O °C

Table 1. *cis*-3a,8b-Dihydrofuro[3,2-*b*]benzofuran-2(3*H*)-ones (**6a**—**e**)

Compound	R	M.p. (°C)	Yield (%)	Formula	Analysis (%)[a] C	H	S
(**6a**)	CO_2Me	171.5—172	75	$C_{12}H_{10}O_6$	57.2 (57.6)	3.9 (4.0)	
(**6b**)	COMe	164—165	72	$C_{12}H_{10}O_5$	61.9 (61.5)	4.3 (4.3)	
(**6c**)	SOPh	154.5—155.5	51	$C_{16}H_{12}O_5S$	60.8 (60.75)	3.7 (3.8)	9.9 (10.1)
(**6d**)	$CO_2CH_2CCl_3$	188—188.5	76	$C_{13}H_9Cl_3O_6$	42.6 (42.5)	2.5 (2.5)	
(**6e**)	CO_2CH_2COPh	204—205	70	$C_{19}H_{14}O_7$	64.3 (64.4)	3.85 (4.0)	

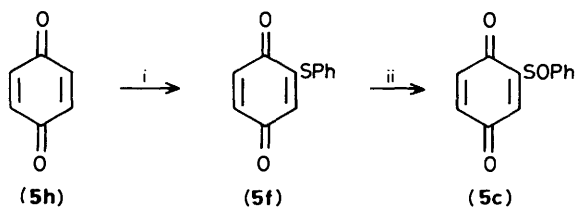
[a] Required values in parentheses.

Table 2. ^1H N.m.r. chemical shifts (δ)[a] and coupling constants (*J*/Hz) of compounds (**6**)

Compd.	3-H, 3-H′	Aromatic H	3a-H	8b-H	OH	Substituent	Conditions
(**6a**)	2.93—3.17 (m)	6.99 (d), *J* 9.0 7.15 (d), *J* 9.0	5.47 (ddd) $J_{3a,8b}$ 5.9 $J_{3a,3}$ 6.1 $J_{3a,3'}$ 1.4	6.44 (d) $J_{3a,8b}$ 5.9	10.51 (s)	R CO_2Me 4.01 (s)	80 MHz; [$^2H_6$]acetone
(**6b**)	3.00—3.07 (m)	7.03 (s)	5.37 (ddd) $J_{3a,8b}$ 6.2 $J_{3a,3}$ 3.6 $J_{3a,3'}$ 1.8	6.26 (d) $J_{3a,8b}$ 6.2	12.44 (s)	R COMe 2.76 (s)	80 MHz; $CDCl_3$
(**6c**)	2.68—3.40 (m)	6.89 (s)	5.47 (ddd) $J_{3a,8b}$ 5.7 $J_{3a,3}$ 6.5 $J_{3a,3'}$ 1.3	6.69 (d) $J_{3a,8b}$ 5.7	*b*	R SOPh 7.45—8.01 (m)	80 MHz; [$^2H_6$]acetone
(**6d**)	3.04—3.07 (m)	7.07 (d), *J* 9.2 7.12 (d), *J* 9.2	5.40 (ddd) $J_{3a,8b}$ 6.0 $J_{3a,3}$ 6.0 $J_{3a,3'}$ 2.1	6.49 (d) $J_{3a,8b}$ 6.0	10.29 (s)	R $CO_2CH_2CCl_3$ 4.81 (d), *J* 12.0 5.34 (d), *J* 12.0	270 MHz; $CDCl_3$
(**6e**)	3.04—3.06 (m)	7.05 (d), *J* 9.2 7.09 (d), *J* 9.2	5.39 (m)	6.62 (d) $J_{3a,8b}$ 6.0	10.30 (s)	R CO_2CH_2COPh 5.99 (d), *J* 16.6 5.43 (d), *J* 16.6 7.52—7.99 (m)	270 MHz; $CDCl_3$
(**6i**)[c]	2.82 (d) $J_{3,3'}$ 18.7 3.18 (dd) $J_{3,3'}$ 18.7 $J_{3,3a}$ 6.3	7.08 (d), *J* 8.8 6.95 (d), *J* 8.8	5.43 (dd) $J_{3a,8b}$ 5.9 $J_{3a,3}$ 6.3	6.43 (d) $J_{3a,8b}$ 5.9	*b*	R CO_2H	270 MHz; [$^2H_6$]acetone

[a] Expressed in p.p.m., downfield from TMS. [b] Not obtained. [c] Prepared from trichloroethyl ester (**6d**).

remove the triethylamine hydrochloride by-product. This was found to be essential to ensure good yields of the furo[3,2-*b*]-benzofuran products in the subsequent step. The 2-substituted benzoquinones (**5a**, **b**, **d**, **e**) were prepared from the corresponding quinols by oxidation with activated manganese dioxide or silver oxide. Oxidation of 2-phenylthio-1,4-benzoquinone (**5f**)[17] using trifluoroperacetic acid (TFPA)[18] provided 2-phenylsulphinyl-1,4-benzoquinone (**5c**) in 93% yield (Scheme 3).



Scheme 3. *Reagents and conditions:* i, PhSH, MeOH; ii, TFA, H_2O_2, 0 °C

A solution of the furan (**4**) (2.0 eq.) in acetonitrile was added to a solution of a quinone (**5a**—**e**) in acetonitrile, cooled to 0 °C under nitrogen, followed by the addition of methanol to ensure complete hydrolysis of the trimethylsilyl group. After an aqueous work-up, purification by flash chromatography[19] afforded the corresponding *cis*-3a,8b-dihydrofuro[3,2-*b*]benzofuran-2(3*H*)-one (**6a**—**e**) in 51—76% yield (Table 1). In all cases, t.l.c. analysis confirmed that the addition reactions took place in a matter of minutes and the use of other solvents such as acetone, methanol, and chloroform resulted in the same products in comparable yields.

This uncatalysed furofuran annulation to a benzoquinone ring system was established from the ^1H n.m.r. spectrum of the adducts (**6a**—**e**) (Table 2). The magnitude of the coupling constants $J_{3a,8b}$ 5.7—6.2 Hz was in agreement with that found in panacene (**1**)[1] ($J_{3a,8b}$ 5.98 Hz) and was indicative of *cis*-fusion of the two furan rings. The more unusual and highly strained *trans*-fusion is seen in the *trans*-isomer of compound (**3**)[4] where the magnitude of the coupling between the bridgehead protons was only 2 Hz. The ^{13}C n.m.r. spectra of the adducts (**6a**—**e**)

Table 3. ^{13}C N.m.r. chemical shifts (δ)[a] of compounds (**6**)

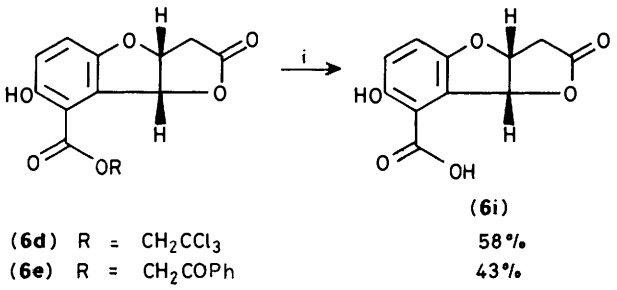
Compd.	C-2	C-3	C-3a	C-4a	C-5, C-6[a]	C-7	C-8	C-8a	C-8b	R	Conditions
(**6a**)	175.1	35.0	82.0	153.7	117.4, 121.1	154.6	110.8	122.6	83.8	R CO_2Me 52.5, 167.9	20 MHz; [$^2H_6$]DMSO
(**6b**)	173.7	35.3	80.7	153.9	119.5, 123.3	158.8	116.3	120.2	84.2	R COMe 30.5, 203.1	20 MHz; $CDCl_3$
(**6c**)	175.1	35.7	81.7	150.6	114.6, 120.9	156.6	127.8	122.4	83.8	R SOPh 126.4, 129.9 132.1, 145.9	20 MHz; [$^2H_6$]acetone
(**6d**)	174.3	35.5	81.3	154.3	119.6, 122.4	158.0	107.9	121.4	84.4	R $CO_2CH_2CCl_3$ 74.9, 83.9, 167.5	67.8 MHz; $CDCl_3$
(**6e**)	174.6	35.5	81.4	154.3	118.9, 121.9	157.4	108.9	122.0	84.8	R CO_2CH_2COPh 66.9, 127.8, 129.0, 133.8, 134.4, 168.3, 191.2	67.8 MHz; $CDCl_3$
(**6i**)[c]	175.8	36.3	83.6	153.5	119.4, 122.4	155.6	117.6	119.6	85.7	R CO_2H 172.2	67.8 MHz; [$^2H_6$]acetone

[a] Expressed in p.p.m. downfield from TMS. [b] Assignment of these resonances to positions 5 and 6 cannot be determined unambiguously. [c] Prepared from trichloroethyl ester (**6d**).

(Table 3) were assigned with the aid of two-dimensional ^1H–^{13}C COSY experiments and the chemical shifts for the bridgehead carbons (C-3a and C-8b) were in excellent agreement with those reported for panacene (**1**).[1]

The addition of furan (**4**) to several unactivated benzoquinones (**5h**), (**5g**), and (**5f**) was also investigated using the conditions already established. In two cases [(**5h**), (**5f**)] a complex mixture of products was obtained and none of the desired adduct was isolated. In the case of 2-chloro-1,4-benzoquinone (**5g**) the ^1H n.m.r. spectrum indicated the presence of unchanged starting material.

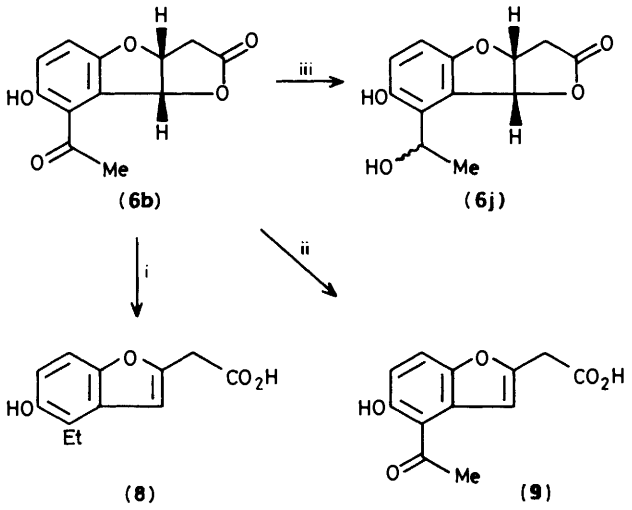
At this point, attention was turned to the chemical modification of the functional groups at C-8 of the adducts. The methyl ester adduct (**6a**) proved to be base sensitive and gave resinous material upon attempted basic hydrolysis of the ester with aqueous sodium hydrogen carbonate in methanol or attempted alkylation of the phenolic oxygen using dimethyl sulphate and potassium carbonate in dimethylformamide. The corresponding carboxylic acid adduct (**6i**; R = CO_2H), however, was easily obtained *via* reductive hydrolysis of the phenacyl ester derivative (**6a**), or in better yield from the trichloroethyl ester derivative (**6d**), using zinc in acetic acid (Scheme 4).



Scheme 4. *Reagents:* i, Zn, HOAc

Attempted reduction of the methyl ketone (**6b**) to an ethyl group [required for panacene (**1**)] using triethylsilane in trifluoroacetic acid (TFA)[20] afforded (4-ethyl-5-hydroxybenzofuran-2-yl)acetic acid (**8**) in 64% yield (Scheme 5).

This ring-opening reaction was quite general under acidic conditions in that treatment of the adduct (**6b**) with a catalytic amount of toluene-*p*-sulphonic acid (PTSA) in methanol under reflux for 3 h, with methanolic acetic acid under reflux for 3 h, and with boron trifluoride–diethyl ether in diethyl ether at 0 °C



Scheme 5. *Reagents and conditions:* i, Et_3SiH, TFA, room temperature; ii, MeOH, PTSA (cat.); iii, $NaBH_4$, MeOH, room temperature

for 1 h, gave (4-acetyl-5-hydroxybenzofuran-2-yl)acetic acid (**9**) in good yield (60—70%). Reduction of the methyl ketone (**6b**) with sodium borohydride in methanol at room temperature, however, did not effect ring opening and gave the lactone alcohol (**6j**) in 57% yield as a mixture of diastereoisomers.

In summary, the addition of 2-(trimethylsiloxy)furan (**4**) to the activated benzoquinones (**5a**—**e**) provides a direct entry to the *cis*-3a,8b-dihydrofuro[3,2-*b*]benzofuran-2(3*H*)-ones (**6a**—**e**). The lability of the furofuran ring under acidic and basic conditions, however, precluded the possibility of reducing the methyl ketone group in adduct (**6b**) to an ethyl group as required for the synthesis of panacene (**1**).

Experimental

M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected. I.r. spectra were recorded on a Pye Unicam SP3-200S spectrophotometer as Nujol mulls between sodium chloride discs. U.v. spectra were recorded on a Shimadzu UV 160 spectrophotometer. ^1H N.m.r. spectra were recorded in the solvents stated using tetramethylsilane as internal standard on either a Varian T-60, Bruker WP-805Y, or a JEOL GX270 spectrometer. ^{13}C N.m.r. spectra were recorded at 20 MHz on

a Bruker WP-80SY or at 67.8 MHz on a JEOL GX270 spectrometer. Mass spectra and accurate mass measurements were recorded on an AEI MS9 spectrometer with an ionization potential of 70 eV. Microanalyses were performed by the microanalytical laboratory, University of Otago. Solvents were purified and dried according to the method of Perrin, Perrin, and Armarego.[21] Column chroamatography was carried out on Merck Kieselgel 60 (230—400 mesh) with the solvents described according to the method of Still *et al.*[19] Activated manganese dioxide was purchased from the Aldrich chemical company.

Furan-2(5H)-*one* (**7**).—Following the procedure of Näsman and Pensar,[16] furan-2(5*H*)-one (**7**) was prepared from 2-furaldehyde as a liquid, b.p. 96—102 °C/20 mmHg (lit.,[16] 95—96 °C/19 mmHg).

2-(*Trimethylsiloxy*)*furan* (**4**).—To furan-2(5*H*)-one (**7**) (11.0 g, 111 mmol), cooled in an ice–salt-bath, under nitrogen was added ice-cold triethylamine (13.8 g, 140 mmol), followed by chlorotrimethylsilane (15.2 g, 140 mmol). After the mixture had been kept for 16 h at ambient temperature, short-path distillation afforded a liquid (16.2 g) which, after several distillations, afforded 2-(trimethylsiloxy)furan (**4**) (7.8 g, 38%) as a liquid, b.p. 44—46 °C/17 mmHg (lit.,[14] 34—35 °C/9—10 mmHg).

2-*Phenylthio*-1,4-*benzoquinone* (**5f**).—To a suspension of finely divided 1,4-benzoquinone (8.6 g, 80 mmol) in methanol (50 ml) was added a solution of thiophenol (4.4 g, 40 mmol) in methanol (10 ml). After 5 min, water (100 ml) was added, and the solid was filtered off and washed with water to yield an orange powder (8.4 g), which was recrystallized from benzene to give 2-phenylthio-1,4-benzoquinone (**5f**) (7.6 g, 87%) as orange-red needles, m.p. 113—114 °C (lit.,[17] 114 °C).

2-*Phenylsulphinyl*-1,4-*benzoquinone* (**5c**).—2-Phenylthio-1,4-benzoquinone (**5f**) (3.0 g, 14 mmol) was dissolved in TFA (10 ml) and the solution was cooled to 0 °C. A solution of TFPA was prepared by mixing 30% aqueous hydrogen peroxide (8.6 ml) with TFA to give a final volume of 25 ml. This solution (3.5 ml, 14 mmol) was added dropwise to the sulphide solution. After the mixture had been kept at 0 °C for 20 h, solvent was removed at reduced pressure. The residue was dissolved in benzene (30 ml), washed with 10% aqueous sodium hydrogen carbonate (2 × 10 ml), and dried ($MgSO_4$). Removal of solvent at reduced pressure gave 2-*phenylsulphinyl*-1,4-*benzoquinone* (**5c**) (3.0 g, 93%) as a red solid, m.p. 118.5—119.5 °C (Found: C, 62.0; H, 3.5; S, 13.6. $C_{12}H_8O_3S$ requires C, 62.1; H, 3.5; S, 13.8%); $\lambda_{max.}$(MeOH) 313 nm (log ε 3.6); $\nu_{max.}$(Nujol) 1 640s (C=O) and 1 050 cm^{-1} (S=O); δ_H[80 MHz; $(CD_3)_2CO$] 6.73—7.00 (2 H, m, 5- and 6-H), 7.24—7.33 (1 H, m, 3-H), 7.47—7.63 (3 H, m, ArH), and 7.70—7.87 (2 H, m, ArH); *m/z* 232 (M^+, 100%) and 216 (M − O, 9).

2,2,2-*Trichloroethyl* 2,5-*Dioxo*-2,5-*dihydrobenzoate* (**5d**).—A mixture of 2,5-dihydroxybenzoic acid (BDH) (1.5 g, 10 mmol) 2,2,2-trichloroethanol (10.0 ml, 104 mmol), PTSA (3.8 g, 20 mmol), and toluene (50 ml) was heated under reflux for 24 h. The solvent was removed on a rotary evaporator and the residue was dissolved in ethyl acetate (100 ml). After being washed successively with water (3 × 25 ml) and brine (25 ml), and then dried ($MgSO_4$), the solution was evaporated at reduced pressure to afford a green solid, which was recrystallized from tetrachloromethane to give the *trichloroethyl ester* of 2,5-*dihydroxybenzoic acid* (1.5 g, 53%) as a powder, m.p. 139—140 °C (Found: C, 37.7; H, 2.4; Cl, 37.0. $C_9H_7Cl_3O_4$ requires C, 37.9; H, 2.5; Cl, 37.25%).

This trichloroethyl ester (1.2 g, 4.2 mmol) was dissolved in dichloromethane (100 ml); activated manganese dioxide (5.4 g, 62 mmol) and anhydrous sodium sulphate (2.0 g) were added, and the mixture was vigorously stirred at room temperature for 0.5 h. The suspension was filtered (Celite) and the filter cake was washed with dichloromethane (2 × 25 ml). Removal of solvent at reduced pressure afforded the *title compound* (**5d**) (1.1 g, 89%) as an orange solid, m.p. 80—82 °C (Found: C, 38.0; H, 1.6; Cl, 37.3. $C_9H_5Cl_3O_4$ requires C, 38.1; H, 1.8; Cl, 37.5%); $\nu_{max.}$(Nujol) 1 740s (C=O, ester) and 1 640s cm^{-1} (C=O, quinone); δ_H(60 MHz; $CDCl_3$) 4.9 (2 H, s, $CO_2CH_2CCl_3$), 6.8 (2 H, m, quinone), and 7.1 (1 H, m, quinone).

Phenacyl 2,5-*Dioxo*-2,5-*dihydrobenzoate* (**5e**).—Phenacyl bromide (2.0 g, 10 mmol) was added to a solution of 2,5-dihydroxybenzoic acid (BDH) (1.5 g, 10 mmol), triethylamine (1.4 ml, 10 mmol), and ethyl acetate (20 ml). After 3 days at room temperature, the triethylamine hydrobromide that had formed was filtered off and the ethyl acetate filtrate was washed successively with 10% aqueous hydrochloric acid (25 ml), water (25 ml), 10% aqueous sodium hydrogen carbonate (25 ml), and brine (25 ml), and dried ($MgSO_4$). Removal of solvent at reduced pressure afforded a pale yellow solid (1.2 g), which was recrystallized from ethyl acetate to give the *phenacyl ester* of 2,5-*dihydroxybenzoic acid* (1.4 g, 51%) as needles, m.p. 176.5—178.5 °C (Found: C, 65.9; H, 4.3. $C_{15}H_{12}O_5$ requires C, 66.2; H, 4.4%).

This phenacyl ester (1.04 g, 3.8 mmol) was dissolved in dichloromethane (100 ml); activated manganese dioxide (5.0 g, 57 mmol) and anhydrous sodium sulphate (2.0 g) were added, and the mixture was vigorously stirred at room temperature for 1 h. The suspension was filtered (Celite) and the filter cake was washed with dichloromethane (2 × 25 ml). Removal of solvent at reduced pressure afforded the *title compound* (**5e**) (906 mg, 88%) as an orange solid, m.p. 123—125 °C (Found: C, 66.2; H, 3.9. $C_{15}H_{10}O_5$ requires C, 66.7; H, 3.7%); $\nu_{max.}$(Nujol) 1 740s and 1 660s cm^{-1}; δ_H(60 MHz; $CDCl_3$) 5.4 (2 H, s, CO_2CH_2-COPh) and 6.7—7.7 (8 H, m, quinone and Ph).

Preparation of the Adducts (**6a—e**): *General Procedure.*—A solution of 2-(trimethylsiloxy)furan (**4**) (770 mg, 5.0 mmol) in acetonitrile (15 ml) was added to an ice-cooled solution of the appropriate quinone (**5a—e**) (2.5 mmol) in acetonitrile (30 ml), under nitrogen. The solution usually changed colour from orange to red. After 0.5 h methanol (5 ml) was added, and the reaction mixture was warmed to room temperature. Following the addition of dichloromethane (100 ml), the reaction mixture was washed successively with 10% aqueous hydrochloric acid (2 × 30 ml) and water (2 × 30 ml), and dried ($MgSO_4$). Removal of solvent at reduced pressure afforded a red oil, which was purified by flash chromatography using hexane–ethyl acetate as eluant to give the appropriate adduct (**6a—e**). Further purification by recrystallisation afforded analytical samples. Analytical data for the adducts (**6a—e**) are given in Table 1, ^1H n.m.r. data in Table 2, and ^{13}C n.m.r. data in Table 3.

Methyl ester adduct (**6a**). Prepared from 2-(trimethylsiloxy)-furan (**4**) (780 mg, 5.0 mmol) and quinone (**5a**)[22] (402 mg, 2.5 mmol) as *needles* (450 mg, 75%), m.p. 171.5—172 °C (from acetone); $\lambda_{max.}$(EtOH) 308 (log ε 3.0) and 349 nm (3.8); $\nu_{max.}$(Nujol) 3 600—3 100 (OH), 1 770s (C=O, γ-lactone), and 1 680s cm^{-1} (C=O *o*-hydroxyaryl ester); *m/z* 250 (M^+, 55%), 218 (M − CH_3OH, 100), 174 (28), and 173 (17).

Methyl ketone adduct (**6b**). Prepared from 2-(trimethylsiloxy)-furan (672 mg, 4.3 mmol) and quinone (**5b**)[23] (320 mg, 2.1 mmol) as *yellow needles* (354 mg, 72%), m.p. 164—165 °C (from chloroform); $\lambda_{max.}$(EtOH) 228 (log ε 4.1) and 365 nm (3.6); $\nu_{max.}$(Nujol) 3 600—3 200 (OH), 1 765s (C=O, γ-lactone), and 1 640s cm^{-1} (C=O, *o*-hydroxyaryl ketone); *m/z* 234 (M^+, 5%), 219 (M − CH_3, 7), 189 (37), and 175 (100).

Phenylsulphinyl adduct (**6c**). Prepared from 2-(trimethyl-

siloxy)furan (**4**) (780 mg, 5.0 mmol) and quinone (**5c**) (580 mg, 2.5 mmol) as *needles* (403 mg, 51%), m.p. 154.5—155.5 °C (from acetone); $\lambda_{max.}$(MeOH) 287 (log ε 3.7) and 327 nm (4.0); $\nu_{max.}$(Nujol) 3 500—3 100 (OH), 1 765s (C=O), and 1 050 cm^{-1} (S=O); *m/z* 316 (M^+, 100%), 300 (M − O, 43), 271 (15), 253 (24), and 245 (25).

Trichloroethyl ester adduct (**6d**). Prepared from 2-(trimethylsiloxy)furan (**4**) (780 mg, 5.0 mmol) and quinone (**5d**) (709 mg, 2.5 mmol) as a *flocculent solid* (696 mg, 76%), m.p. 188—188.5 °C (from ethyl acetate–hexane); $\lambda_{max.}$(MeOH) 220 (log ε 4.0), 235 (3.8), and 395 nm (3.6); $\nu_{max.}$(Nujol) 3 300 (OH), 1 750s (C=O, γ-lactone), and 1 695s cm^{-1} (C=O, *o*-hydroxyaryl ester); *m/z* 365.9475 (M^+, ^{35}Cl, 7%), 218 (100), 219 (27), and 174 (26).

Phenacyl ester adduct (**6e**). Prepared from 2-(trimethylsiloxy)-furan (**4**) (780 mg, 5.0 mmol) and quinone (**6e**) (676 mg, 2.5 mmol) as *needles* (619 mg, 70%), m.p. 204—205 °C (from ethyl acetate–hexane); $\lambda_{max.}$(EtOH) 243 (log ε 3.3) and 349 nm (log ε 2.7); $\nu_{max.}$(Nujol) 3 400s (OH) 1 750s (C=O, γ-lactone), and 1 690, 1 700 cm^{-1} (C=O); *m/z* 354 (M^+, 13%), 272 (52), 218 (23), 136 (100), 105 (92), and 77 (33).

Hydrolysis of the Trichloroethyl Ester Adduct (**6d**) *to the Carboxylic Acid* (**6i**).—A mixture of trichloroethyl ester adduct (**6d**) (192 mg, 0.52 mmol), glacial acetic acid (10 ml), dichloromethane (10 ml), and zinc dust (560 mg) was stirred at room temperature for 15 h. 10% Aqueous hydrochloric acid (10 ml) was added and the reaction mixture was extracted with dichloromethane (3 × 30 ml). The combined extracts were washed successively with water (2 × 20 ml) and brine (20 ml), and dried ($MgSO_4$). Removal of solvent under reduced pressure yielded the *carboxylic acid* (**6i**) (71 mg, 58%) as a solid, m.p. 235 °C (decomp.) (Found: C, 55.7; H, 3.45. $C_{11}H_8O_6$ requires C, 55.9; H, 3.4%); $\lambda_{max.}$(EtOH) 278 (log ε 3.2) and 338 nm (3.6); $\nu_{max.}$(Nujol) 3 600—3 300 (OH), 1 760s (C=O, γ-lactone), and 1 670 cm^{-1} (C=O, aryl acid); *m/z* 236 (M^+, 35%), 218 (M − H_2O, 100), and 173 (30). ^1H N.m.r. and ^{13}C n.m.r. data are reported in Tables 2 and 3 respectively.

(4-*Ethyl*-5-*hydroxybenzofuran*-2-*yl*)*acetic Acid* (**8**).—Triethylsilane (220 mg, 1.9 mmol) was added dropwise to a solution of methyl ketone adduct (**6b**) (200 mg, 0.85 mmol) in TFA (2.0 ml). After 1 h the reaction mixture was diluted with water (15 ml) and extracted with diethyl ether (2 × 20 ml). The combined extracts were dried ($MgSO_4$) and the solvent was removed at reduced pressure to give a red oil, which was purified by flash chromatography. Elution with hexane–ethyl acetate (1:1) gave the *title carboxylic acid* (**8**) (120 mg, 64%) as needles, m.p. 144—146 °C (Found: C, 64.9; H, 5.4. $C_{12}H_{12}O_4$ requires C, 65.4; H, 5.5%); $\nu_{max.}$(Nujol) 3 380 (OH) and 1 700 cm^{-1} (C=O, acid); δ_H(60 MHz; $CDCl_3$) 1.08 (3 H, t, *J* 7 Hz, Me), 2.82 (2 H, q, *J* 7 Hz, CH_2Me), 3.80 (2 H, s, CH_2CO_2H), 6.62 (1 H, s, 3-H), 6.66 (1 H, d, *J* 8 Hz, 6- or 7-H), and 7.04 (1 H, d, *J* 8 Hz, 7- or 6-H); *m/z* 220 (M^+, 100%), 205 (M − CH_3, 91), 176 (M − CO_2, 14), and 175 (M − CO_2H, 65).

(4-*Acetyl*-5-*hydroxybenzofuran*-2-*yl*)*acetic Acid* (**9**).—Methyl ketone adduct (**6b**) (100 mg, 0.43 mmol) was dissolved in methanol (10 ml) and heated under reflux for 3 h with a catalytic amount of PTSA. The solvent was removed at reduced pressure to afford a pale orange solid, which was purified by flash chromatography using ethyl acetate as eluant to give the *title carboxylic acid* (**9**) (68 mg, 68%) as needles, m.p. 172—174 °C (Found: C, 61.3; H, 4.1. $C_{12}H_{10}O_5$ requires C, 61.5; H, 4.3%); $\nu_{max.}$(Nujol) 3 300 (OH), 1 695s (C=O, acid), and 1 610 cm^{-1} (C=O, *o*-hydroxyaryl ketone); δ_H(60 MHz; $CDCl_3$) 2.75 (3 H, s, COMe), 3.85 (2 H, s, CH_2CO_2H), 6.75 (1 H, d, *J* 8 Hz, 6- or 7-H), 6.80 (1 H, s, 3-H), and 7.50 (1 H, d, *J* 8 Hz, 7- or 6-H); *m/z* 234 (M^+, 68%), 219 (M − CH_3, 100), 189 (M − CO_2H, 23), and 175 (M − CH_2CO_2H, 3).

cis-3a,8b-*Dihydro*-7-*hydroxy*-8-(1-*hydroxyethyl*)*furo*[3,2-b]-*benzofuran*-2(3H)-*one* (**6j**).—Sodium borohydride (9 mg, 0.2 mmol) was added to a solution of methyl ketone adduct (**6b**) (100 mg, 0.4 mmol) in methanol (30 ml). After being stirred at room temperature for 1 h, the mixture was treated with 10% aqueous sodium hydroxide (5 ml) and left for 0.25 h. Following acidification with 10% hydrochloric acid (10 ml) the reaction mixture was extracted with ethyl acetate (2 × 30 ml). The combined extracts were dried ($MgSO_4$), and removal of solvent at reduced pressure afforded a pale brown solid, which was purified by flash chromtography. Elution with ethyl acetate afforded the *title alcohol* (**6j**) (58 mg, 58%) as a solid, m.p. 184—186 °C (Found: C, 60.7; H, 5.6. $C_{12}H_{12}O_5$ requires C, 61.0; H, 5.1%); $\lambda_{max.}$(MeOH) 307 nm (log ε 2.9); $\nu_{max.}$(Nujol) 3 350 (OH) and 1 750s cm^{-1} (C=O, γ-lactone); δ_H[80 MHz; $(CD_3)_2CO$] 1.52 (3 H, d, *J* 6.6 Hz, Me), 2.78 (1 H, dd, $J_{3,3'}$ 18.8, $J_{3a,3'}$ 1.5 Hz, 3-H′), 3.19 (1 H, dd, $J_{3,3'}$ 18.8, $J_{3,3a}$ 6.4 Hz, 3-H), 5.15—5.48 (2 H, m, 3a-H and C*H*OH), 6.14 (1 H, d, $J_{3a,8b}$ 5.8 Hz, 8b-H), 6.61 (1 H, d *J* 8.6 Hz, 5- or 6-H), 6.77 (1 H, d, *J* 8.6 Hz, 6- or 5-H), and 8.51 (1 H, s, OH); *m/z* 236 (M^+, 35%), 235 (M − H, 2), 219 (M − OH, 83), and 218 (M − H_2O, 100).

A minor diastereoisomer which was not isolated was detected in the ^1H n.m.r. spectrum of the crude product. Differences in chemical shift were observed for the methyl group, which resonated at δ_H 1.51 instead of δ_H 1.52, and 8b-H, which shifted downfield from δ_H 6.14 to δ_H 6.32 in the minor isomer. All other chemicals shifts are coupling constants were identical.

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References

1 Preliminary communication: M. A. Brimble, J. J. Gibson, R. Baker, M. T. Brimble, A. A. Kee, and M. J. O'Mahoney, *Tetrahedron Lett.*, 1987, **28**, 4891.
2 R. Kinnel, A. J. Duggan, T. Eisner, and J. Meinwald, *Tetrahedron Lett.*, 1977, 3913.
3 A. Nahrstedt, V. Wray, B. Engel, and R. Reinhard, *Planta Med.*, 1985, **44**, 517.
4 S. K. Talapatra, N. C. Ganguly, S. Goswami, and B. Talapatra, *J. Nat. Prod.*, 1983, **46**, 401.
5 A. Kasahara, T. Izumi, A. Suzuki, and T. Takeda, *Bull. Chem. Soc. Jpn.*, 1976, **49**, 3711.
6 E. Wenkert, M. E. Alonso, B. L. Buckwater, and R. L. Sanchez, *J. Am. Chem. Soc.*, 1983, **105**, 2021.
7 P. C. Arora and P. Brassard, *Can. J. Chem.*, 1971, **49**, 3477.
8 K. S. Feldman, C. Crawford Mechem, and L. Nader, *J. Am. Chem. Soc.*, 1982, **104**, 4011.
9 K. S. Feldman, *Tetrahedron Lett.*, 1982, **23**, 2031.
10 P. Kuser, E. F. Frauenfelder, and C. H. Eugster, *Helv. Chim. Acta*, 1971, **54**, 969.
11 G. A. Kraus and B. Roth, *J. Org. Chem.*, 1978, **43**, 4923.
12 H. Uno, *J. Org. Chem.*, 1986, **51**, 350.
13 S. Patai, 'The Chemistry of the Quinonoid Compounds: Part 2,' Wiley, London, 1974, p. 877.
14 M. Asaoka, K. Miyake, and H. Takei, *Chem. Lett.*, 1977, 167.
15 E. Yoshii, T. Koizumi, E. Kitatsuji, T. Kawazoe, and T. Kaneko, *Heterocycles*, 1976, **4**, 1663.
16 J. H. Näsman and K. G. Pensar, *Synthesis*, 1985, 786.
17 O. Dimroth, L. Kraft, and K. Aichinger, *Justus Liebigs Ann. Chem.*, 1940, **545**, 124.
18 C. G. Venier, T. G. Squires, Y. Chen, G. P. Hussmann, J. C. Shei, and B. F. Smith, *J. Org. Chem.*, 1982, **47**, 3773.

19 W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.
20 C. T. West, S. J. Donnelly, D. A. Kooistra, and M. P. Doyle, *J. Org. Chem.*, 1973, **38**, 2675.
21 D. D. Perrin, D. R. Perrin, and W. L. F. Armarego, 'Purification of Laboratory Chemicals,' Pergamon, Oxford, 1966.
22 J. Cason, *Org. React.*, 1948, **4**, 345.
23 M. C. Kloetzel, R. P. Dayton, and B. Y. Abadir, *J. Org. Chem.*, 1955, **20**, 38.

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