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ortho-Directed electrophilic boronation of a benzyl ketone: the preparation, X-ray crystal structure, and some reactions of 4-ethyl-1-hydroxy-3-(4-hydroxyphenyl)-2-oxa-1-boranaphthalene

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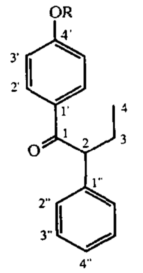
Abstract

4-Ethyl-1-hydroxy-3-(4-hydroxyphenyl)-2-oxa-1-boranaphthalene (**4**) is formed in 78% yield from the reaction of 1-(4-methoxyphenyl)-2-phenylbutan-1-one with an of excess boron tribromide in dichloromethane followed by treatment with water. Reaction of **4** with iodine in aqueous sodium hydroxide gives a second oxaboracycle, 3-ethyl-1-hydroxy-3-(4-hydroxybenzoyl)-2,1-benzoxaborolane (**5**). The X-ray crystal structure determinations of both boron heterocycles are reported. Other new compounds reported are 1-(4-hydroxyphenyl)-2-(1-hydroxyphenyl)-butan-1-one (**6**), formed by reaction of **4** with alkaline hydrogen peroxide, and 1-(4-hydroxyphenyl)-2-(2-biphenyl)-butan-1-one (**8**), formed by coupling of **4** with bromobenzene in the presence of $Pd(PPh_3)_4$.

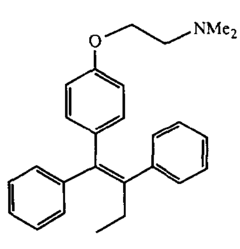
1. Introduction

Derivatives of 1-(4-hydroxyphenyl)-2-phenylbutan-1-one (**1a**) are important [1] as precursors of analogues of the antitumour drug tamoxifen (**2**). Reaction of aryl-Grignard or -lithium reagents with the carbonyl function to form alcohols followed by acid-catalysed dehydration leads to the essential triarylethene structure of tamoxifen. Functionalisation of **1** therefore provides a basis for the synthesis of new compounds with potential antitumour activity. Given that the activity of tamoxifen analogues is dependent on the conformations of the three aryl rings with respect to the double bond [1], there is interest in examining the influence of, in particular, *ortho* substituents

Aryl-boron compounds provide an entry to a variety of types of aryl functionalisation [2,3] through replacement of boron. As a route to aryl-boron compounds, electrophilic aromatic boronation direction by a donor function to an *ortho* position is rare but it has been reported [4] for the reaction of boron tribromide with tosyl hydrazones of aryl aldehydes (*e.g.* eqn. (1)) and for the reaction of boron trichloride with 2-hydroxybiphenyl in the presence of aluminium chloride, which when followed by hydrolysis gives 10-hydroxy-9-oxa-10-boraphenanthrene [5] (eqn. (2)); the 10-bromo compound has more recently been obtained from the sodium salt of 2-hydroxybiphenyl and boron tribromide [6]). Analogous chemistry is established for the reaction of *ortho*-aminobiaryls and -styrenes with boron trichloride or dichlorophenylborane [7,8,9a].



(**1a**) R = H
(**1b**) R = Me



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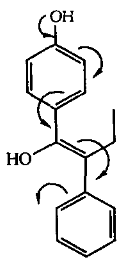

(**3**)

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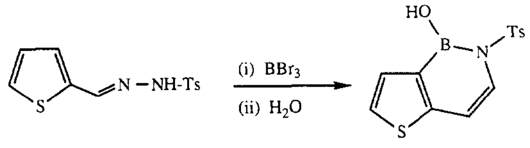

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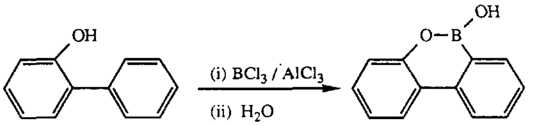

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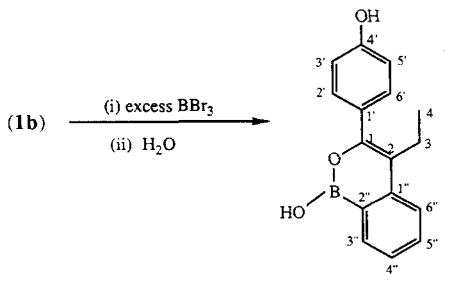
The 2-hydroxybiphenyl system is structurally analogous to the enol form (3) of **1a**, but in **3** there is, as indicated by the electron pair delocalisation arrows, the added potential of the 4-oxy function of the 1-phenyl substituent to provide additional activation at the *ortho* position for electrophilic substitution. We now report facile boronation at such an activated *ortho* site in the reaction (eqn. (3)) of boron tribromide with the methoxy ketone 1-(4-methoxyphenyl)-2-phenylbutan-1-one (**1b**). Also reported are some initial studies of reactions directed towards replacement of boron at the arylcarbon centre of the oxaboranaphthalene product (**4**), as well as the X-ray crystal structure determinations of this and of a second oxaboracycle (**5**), that obtained by reaction of **4** with iodine in aqueous sodium hydroxide (eqn. (4)).



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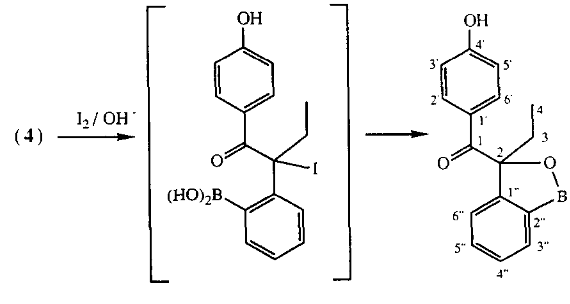

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2. Results and discussion

2.1. Preparation of 4-ethyl-1-hydroxy-3-(4-hydroxyphenyl)-2-oxa-1-boranaphthalene (4)

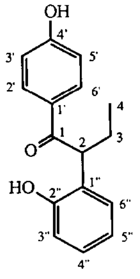
Initially, reaction of 1-(4-methoxyphenyl)-2-phenylbutan-1-one (**1b**) with boron tribromide in dichloromethane followed by treatment with water was found to give a low yield (*ca.* 10%) of a high melting point product that was virtually insoluble in chloroform. When the structure of the product (**4**; eqn. 3) had been tentatively established by NMR spectroscopy, the reaction time and temperature, and the mole ratio of boron tribromide were increased in attempts to improve the yield, and ultimately a yield of 78% was attained as described in the Experimental section. It is not yet established whether the aryl boronation step precedes demethylation of the 4-methoxy group in the 1-phenyl ring of **1b**, but the methoxy group would certainly have more activating potential in accordance with the electron donation implicit in the delocalisation indicated by the arrows in structure **3** than would the demethylated group $OBBr_2$.

2.2. Attempted coupling reactions at the boronated aryl carbon of 4

When the oxaboranaphthalene (**4**) was treated with iodine under alkaline conditions in an attempt to cleave the aryl–boron bond and introduce an iodo substituent into the *ortho* position of the 2-phenyl group, the only product obtained in significant yield was the 5-membered oxaboracycle 3-ethyl-1-hydroxy-3-(4-hydroxybenzoyl)-2,1-benzoxaborolane (**5**), postulated to be formed through enolate iodination followed by substitution of iodide as indicated in eqn. (4). Clearly the attempted iododeboronation at the aryl centre is slow by comparison with reaction at the enolate carbon, making it difficult to achieve under conditions in which it operates effectively at alkenyl [10] and alkanyl [11] centres.

Exploratory studies (not detailed here) of bromination with bromine in methanol both with and without methoxide present demonstrated multiple product formation. This may result from competitive electrophilic attack at the enolic and phenolic ring carbon atoms as well as the arylboron centre, but this chemistry has not been pursued further.

Oxidation of **4** with alkaline hydrogen peroxide gave a quantitative yield of 1-(4-hydroxyphenyl)-2-(2-hydroxyphenyl)-butan-1-one (**6**) if the reaction time was restricted (see Experimental section), but use of longer reaction times resulted in a lower yield and a second product was found whose spectral properties suggested it might be the borate diester **7**. Formation of **7** could be envisaged as arising from the complexing of borate ion with the enolate and phenolate functions of (**6**); there is a precedent in the complex of the enolate form of acetoacetate with borate [12]. However, compound **7** is expected to be formed as an *intermediate* on the pathway from **4** to **6** if the accepted mechanism [13] of HOO^- addition to boron followed by aryl migration to



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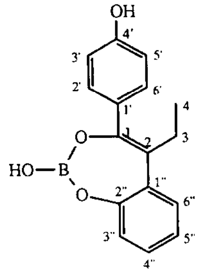
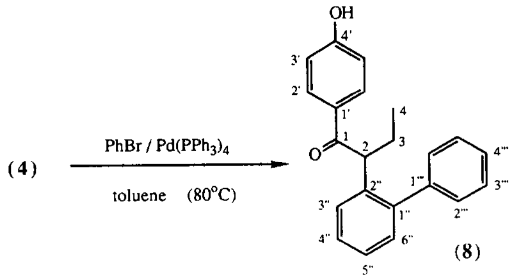


(7)

oxygen applies, so uncertainty will remain until the structure of the compound can be definitely assigned.

The potential for Pd^0-catalysed arylation by aryl halides at the arylboron centres, as originally developed by Suzuki and coworkers [14] and more recently reviewed [15], was tested by treating **4** with bromobenzene in the presence of 3 mol% of tetrakis(triphenylphosphine)palladium(0) in toluene at 80°C for 6 h. This gave the arylated product **8** (eqn. (5)) in 30% yield and recovery of 60% of the reactant. With a reaction time of 18 h, the yield was increased but only to about 40%, with 15% recovered reactant. Clearly conditions need further modification to optimise the yield.



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In summary, the coupling reactions so far studied indicate entry to *ortho*-oxygenation and *ortho*-arylation in the 2-phenyl group of the ketone **1**, but halogenation is apparently not directly accessible because of the potential for electrophilic reaction at the enolate carbon. The latter limitation would not apply to coupling reactions of the 5-membered heterocycle (**5**) which has no α-proton. We are studying the potential of such compounds for the synthesis of 1-(2-hydroxyphenyl)-2-hydroxy-2-(2-substituted-phenyl)-butan-1-ones, compounds not relevant to tamoxifen synthesis but nevertheless of interest in their own right.

2.3. X-Ray crystal structure determinations of the oxaboracycles

Although compounds with heterocyclic rings containing boron are well known [9b], to our knowledge, only four X-ray crystal structure determinations of

TABLE 1. Selected bond lengths (Å) and angles (°) for 4-ethyl-1-hydroxy-3-(4-hydroxyphenyl)-2-oxa-1-boranaphthalene (4)

Bond lengths					
B(1)-O(1)	1.372(3)	B(1)-O(2)	1.378(3)	B(1)-C(6)	1.519(4)
C(1)-O(2)	1.390(3)	C(1)-C(2)	1.354(3)	C(1)-C(11)	1.477(3)
C(2)-C(5)	1.472(3)	C(5)-C(6)	1.417(3)	C(6)-C(7)	1.403(3)
C(7)-C(8)	1.380(4)	C(8)-C(9)	1.393(4)	C(9)-C(10)	1.375(4)
C(5)-C(10)	1.407(3)				
Bond angles					
O(1)-B(1)-O(2)	116.8(2)	O(1)-B(1)-C(6)	124.4(2)	O(2)-B(1)-C(6)	118.8(2)
B(1)-O(2)-C(1)	122.7(2)	O(2)-C(1)-C(2)	121.2(2)	O(2)-C(1)-C(11)	109.0(2)
C(2)-C(1)-C(11)	129.8(2)	C(1)-C(2)-C(3)	121.2(2)	C(1)-C(2)-C(5)	120.6(2)
C(2)-C(5)-C(6)	119.8(2)	C(5)-C(6)-B(1)	116.8(2)		
For 3-ethyl-1-hydroxy-3-(4-hydroxybenzoyl)-1,2-benzoxaborolane (5)					
Bond lengths					
B(1)-O(2)	1.372(3)	B(1)-O(3)	1.358(3)	B(1)-C(6)	1.544(4)
C(1)-O(1)	1.230(3)	C(1)-C(2)	1.540(3)	C(2)-C(5)	1.517(3)
C(5)-C(6)	1.396(3)	C(6)-C(7)	1.389(4)	C(7)-C(8)	1.381(4)
C(8)-C(9)	1.390(4)	C(9)-C(10)	1.379(4)	C(5)-C(10)	1.384(3)
Bond angles					
O(2)-B(1)-O(3)	117.5(2)	O(2)-B(1)-C(6)	109.3(2)	O(3)-B(1)-C(6)	133.2(2)
B(1)-O(2)-C(2)	110.8(2)	O(2)-C(2)-C(5)	104.8(2)	O(2)-C(2)-C(1)	111.6(2)
O(2)-C(2)-C(3)	109.3(2)	C(1)-C(2)-C(3)	110.6(2)	C(1)-C(2)-C(5)	107.3(2)
C(2)-C(5)-C(6)	110.7(2)	C(5)-C(6)-B(1)	104.2(2)		

5-membered C_3BO or 6-membered C_4BO oxaboracycles have been reported (Cambridge Crystallographic Data Centre, October 1992 release). Two of these have 6-membered rings and structures related to phenanthrene [6], a third is saturated, with a cyclohexane-type ring [16], while the final example, with a 5-membered oxonia-borata-cyclopentadienyl ring [17], is a betaine with tetracoordinate boron and is therefore not directly relevant to the new compounds reported in the present study. Given the paucity of crystal structure data, and the additional interest in the potential aromaticity of 4-ethyl-1-hydroxy-3-(4-hydroxyphenyl)-2-oxa-1-boranaphthalene (**4**) in relation to its reactivity in coupling reactions, the crystal structure of **4** was determined. In the case of 3-ethyl-1-hydroxy-3-(4-hydroxybenzoyl)-2,1-benzoxaborolane (**5**), the crystal structure determination was carried out initially to confirm the product's identity, but the structure also provides a basis for assessing the potential reactivity in the synthesis indicated above.

The structure of 4-ethyl-1-hydroxy-3-(4-hydroxyphenyl)-2-oxa-1-boranaphthalene (**4**) is illustrated in Fig. 1 and selected bond parameters are listed in Table 1. Individual molecules in the lattice are linked via H-bonds between the OH(3) group and O(1) on adjacent molecules. The ten atoms that make up the pseudo-naphthalene core are essentially coplanar, with no atom more than 0.04 Å from the least-squares plane. However there appears to be only a small amount of delocalisation of π-electrons over the two rings. In the aryl ring defined by atoms C(5)–C(10), the C(7)–C(8) and C(9)–C(10) bonds are significantly shorter than the other C–C bonds, as is expected from the resonance forms for a naphthalene-like molecule; however the difference is less than in naphthalene itself. In the heterocyclic ring C(1)–C(2) is 1.354(3) Å (typical for an enol-type double bond) and C(2)–C(5) is 1.472(3) Å (essentially normal for a $C(sp^2)$–$C(sp^2)$ single bond, *cf.* the C(1)–C(11) bond in **4** where the dihedral angle precludes delocalised π-electron density). Furthermore the B(1)–O(2) intra-ring bond length is 1.378(3) Å, not significantly different from that of the B(1)–O(1) terminal bond, suggesting no extended delocalisation involving the B and O atoms within the ring. The B(1)–C(6) bond length is 1.519(4) Å, which is at the shorter end of the range found for $B–C_{aryl}$ bonds [18]. These compare with B–O bond lengths of 1.371(7) Å and a B–C single bond length of 1.565(3) Å in $PhB(OH)_2$ [19]. The overall conclusion is therefore that extended delocalisation over the bicyclic framework is small, and that **4** should react more as an arylborane than as an aromatic species.

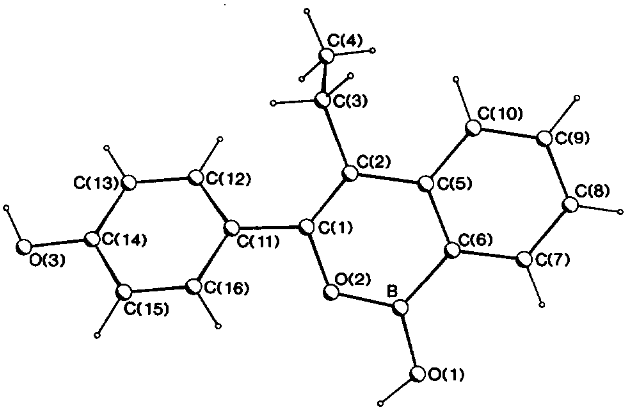

Fig. 1. The structure of 4-ethyl-1-hydroxy-3-(4-hydroxyphenyl)-2-oxa-1-boranaphthalene (4).

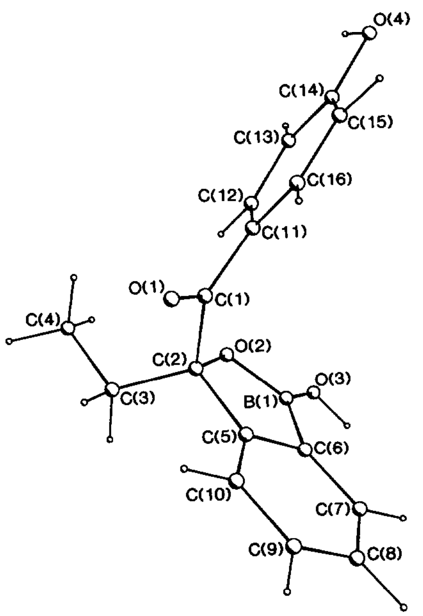

Fig. 2. The structure of 3-ethyl-1-hydroxy-3-(4-hydroxybenzoyl)-2,1-benzoxaborolane (5).

Extended delocalisation in **4** onto the hydroxyphenyl substituent bonded at C(1) is precluded by the twisting of this group out of the plane of the heterocyclic rings, giving rise to a dihedral angle of 36.2° between the two planes. This twisting is no doubt so that steric interactions with the adjacent ethyl group are diminished. The large C(2)–C(1)–C(11) angle of 129.8° is similarly explained.

The structure of **5** is illustrated in Fig. 2, with bond parameters given in Table 1. In the lattice, individual molecules are linked through H-bonds involving the B–OH and the C=O groups of adjacent molecules. For **5**, the bicyclic framework incorporates a five-membered ring with B and O heteroatoms, and can be superficially regarded as a substituted indene. The nine-atom bicyclic unit is essentially planar, with no atom deviating from the least-squares plane by more than 0.09 Å. However there is no indication of any delocalised π-bonding extending from the arene ring onto the C(6)–B(1)–O(2) portion of the molecule. The endo-cyclic B(1)–O(2) bond length of 1.372(3) Å is the same as the equivalent bond in **4**, while the B(1)–C(6) distance is normal for a simple B–C_{aryl} bond. The exo-cyclic B(1)–O(3) bond is noticeably short at 1.358(3) Å, possibly because of strong H-bonding of H(3) to adjacent O(1) atoms in the lattice. The need to maintain H-bonding may also explain the widening of the C(6)–B(1)–O(3) angle to 133.2°, since there are no intra-molecular interactions which would account for marked deviations from 120°. All other parts of the molecule show no remarkable features. Once again, the molecule exhibits little sign of delocalised bonding interactions so that reactivity should be predictable from that established for simpler arylboron compounds. The structures of both **4** and **5** support the conclusions based on spectroscopic and theoretical evidence that boron-oxygen heterocycles are less aromatic than corresponding boron-nitrogen molecules [9].

3. Experimental reaction

The abbreviation 'plc' refers to preparative layer chromatography carried out on 1 mm layers of silica gel (Merck Kieselgel 60 PF_{254}).

^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL FX90Q or a Bruker AC300 spectrometer as indicated and are referenced to TMS. Assignments were made by standard COSY, NOESY, XH correlation and decoupling experiments. ^{11}B-NMR spectra were recorded on a JEOL FX90Q spectrometer at a resonance frequency of 28.69 mHz with an offset of 59 kHz. Generally 5000 scans were recorded using a spectral width of 10 kHz and a 0.7 s recycle time. Chemical shifts were referenced to boron trifluoride etherate.

Elemental analyses were carried out by the University of Otago Microanalytical Laboratory.

3.1. 1-(4-Methoxyphenyl)-2-phenylbutan-1-one

A literature method [20] was modified as follows. Anisole (10.9 g, 0.101 mol) and 2-phenylbutanoyl chloride (15.5 g, 0.085 mol, made from the acid and $SOCl_2$) were dissolved in carbon disulphide (100 ml) in a flask fitted with a reflux condenser. Powdered aluminium chloride (13.26 g) was added in portions during 30 min. The solvent refluxed during the addition, and hydrogen chloride was evolved. The resulting deep-red solution was left to stand overnight. Ice (150 g) was added followed by concentrated hydrochloric acid (20 ml). The orange solvent layer was separated and washed twice with 50 ml portions of hydrochloric acid (3 mol l^{-1}). The solvent was evaporated on a water bath, water (100 ml) was added and steam bubbled through the mixture for 15 min. After cooling to induce crystallisation, the water was decanted, and the solid was recrystallised from 1:6 v/v ethyl acetate/petroleum spirit (b.p. 40–60°C) to give 1-(4-methoxyphenyl)-2-phenylbutan-1-one (**1b**) as white needles, m.p. 42–43°C (lit. [21] 47–48°C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (3H, t, J=7 Hz, CH_3), 1.84 and 2.19 (each 1H, m, CH_2), 3.75 (3H, s, OCH_3), 4.40 (1H, t, J=7 Hz, CH), 6.83 (2H, d, J=9 Hz, H3′, 5′), 7.19–7.31 (5H, m, H2″-5″), 7.95 (2H, d, J=9 Hz, H2′,6′).

3.2. 4-ethyl-1-hydroxy-3-(4-hydroxyphenyl)-2-oxa-1-boranaphthalene (4).

Separate solutions in redistilled dichloromethane (25 ml) of boron tribromide (2.1 ml, 22 mmol) and 1-(4-methoxyphenyl)-2-phenylbutan-1-one (**1b**; 1.85 g, 7.3 mmol) were cooled to −83°C (ethyl acetate slush bath). The boron tribromide solution was then added dropwise to the solution of the ketone (**1b**) at −83°C in a flask fitted with a drying tube.

The now-yellow solution was stirred at −83°C for 60 min, allowed to warm to room temperature and stirred for a further 90 min. The solution was cooled on an ice bath and iced water (40 ml) was added slowly through the condenser. Considerable fuming resulted from the hydrolysis of unchanged boron tribromide and a white solid precipitated out. The two-phase mixture was vigorously stirred for 40 min. The solid was extracted into ether (90 ml) and the separated ether solution extracted twice with sodium hydroxide solution (1 × 75 ml, 1 × 50 ml; 2 mol l^{-1}). Neutralisation of the combined sodium hydroxide layers with hydrochloric acid (2 mol l^{-1}) precipitated a white solid which was taken up in ether (120 ml). The aqueous layer was separated and the ether layer dried ($MgSO_4$) and evaporated under reduced pressure. Purification by flash chromatography on silica gel using 7:3 v/v ethyl acetate-petroleum spirit (b.p. 40–60°C) as eluant gave 4-ethyl-1-hydroxy-3-(4-hydroxyphenyl)-2-oxa-1-boranaphthalene (**4**) as a white crystalline product (0.90 g; 78%) which could be obtained from ethyl acetate by diffusion of chloroform as flat plates of crystallographic quality, m.p. 334–338°C. (Found: C, 72.31; H, 5.89; $C_{16}H_{15}BO_3$ calcd.: C, 72.22; H, 5.68%).

For simplicity of correlation of NMR data with those for the parent ketone and other following compounds, the ^{1}H and ^{13}C assignments are based on the above numbering scheme for **4** (eqn. (3)), which differs from that for the X-ray crystal structure atom labelling.

^{1}H-NMR (300 MHz; $CDCl_3$): δ 1.34 (3H, t, J=7.4 Hz, CH_3), 2.83 (2H, q, J=7.4 Hz, CH_2), 7.10 (2H, d,

J=8.7 Hz, H3′, 5′), 7.54 (1H, m, H4″), 7.56 (2H, d, J=8.7 Hz, H2′,6′), 7.82 (1H, m, H6″), 7.83 (1H, m, H5″), 7.93 (1H, s, B–OH), 8.26 (1H, dt, J=7.5 Hz, J=1.0 Hz, H 3″), 8.73 (1H, s, aryl–OH); ^{13}C NMR (300 MHz; $CDCl_3$): δ 157.1 (C4′), 148.6 (C1 or C1″), 142.7 (C1″ or C1), 132.6 (C3″), 131.6 (C5″), 129.7 (C2′,6′), 128.7 (C1′), 124.9 (C4″), 122.7 (C6″), 115.3 (C2), 114.4 (C3′,5′), 20.4 (CH_2), 14.2 (CH_3); ^{11}B NMR: δ 29.3 (width 8 ppm at half height).

The two singlets in the proton spectrum at 7.93 and 8.73 ppm were assigned to the B–OH and Ar–OH protons respectively, differentiation being made by a more pronounced NOE for the 3′,5′ protons (δ 7.10) when the 8.73 ppm singlet was irradiated as compared to the NOE at 7.10 when the 7.93 ppm singlet was irradiated. Proton exchange between the two hydroxy groups was also indicated by the NOESY spectra. Irradiation of the ethyl protons gave NOE for the signal at 7.56 ppm consistent with assignment of this doublet signal to the (adjacent) H2′,6′ rather than the more remote H3′,5′ (7.10 doublet).

Assignment of the carbons to which the 2′,6′ and 3′,5′ pairs of protons are bonded followed from an XH correlation spectrum. Singlet carbon signals were assigned according to substituent effects for mono- and di-substituted benzenes, alkenes and naphthalenes [22a]. No ^{13}C signal is seen for carbon 2″ due to coupling and quadrupolar broadening by ^{11}B [22b]. Assignments of the remaining doublet carbon signals from the other ring (C3″-C6″), and associated proton signals, were made from X-H correlation and NOESY spectra, as supported by decoupling experiments.

The ^{11}B NMR spectrum showed a peak at 29.3 ppm broadened presumably by proton exchange between boronate and phenol protons. The chemical shift is consistent with an aryl boron linkage with two oxygen substituents [23].

3.3. 1-(4-Hydroxyphenyl)-2-(2-hydroxyphenyl)-butan-1-one (6)

4-Ethyl-1-hydroxy-3-(4-hydroxyphenyl)-2-oxa-1-bora-naphthalene (**4**; 100 mg, 0.376 mmol) was dissolved in sodium hydroxide solution (5 ml; 2 mol l^{-1}). Hydrogen peroxide solution (2ml; 27%) was added dropwise with cooling and stirring during 2 min and the stirring continued for a further 2 min. On neutralisation of the solution by the addition of hydrochloric acid (2 mol l^{-1}), a white solid separated. This was extracted with ether (2 × 20 ml), the combined ether extracts dried, and the solvent evaporated under reduced pressure. The product was separated by plc with 30/70 v/v ethyl acetate/petroleum spirit (b.p. 40–60°C) as the eluant to give 1-(4-hydroxyphenyl)-2-(2-hydroxyphenyl)-butan-1-one (**6**; 96mg; 100%), a white crystalline solid, m.p. 147°C. (Found: C, 74.61; H, 6.39. $C_{16}H_{16}O_3$ calcd.: C, 74.98; H, 6.29%). ^{1}H NMR (90 MHz, d_6-acetone): δ 1.04 (3H, t, J=7.7 Hz, CH_3), 2.01 (2H, m, CH_2), 5.15 (1H, t, J=7.2 Hz, CH), 7.01 (2H, d, J=9.0 Hz, H3′,5′, 8.19 (2H, d, J=9.0 Hz, H2′,6′), 7.1 (4H, m, H3″-6″), 8.95 (1H, s, br, OH), 9.25 (1H, s br, OH); ^{13}C NMR: δ 200.1 (C1), 162.9 (C4′), 155.5 (C2″), 132.2 (C2′,6′), 130.4 (C1″), 129.4 (C6″), 128.9 (C4″), 128.1 (C1′), 121.2 (C5″), 116.9 (C3″), 116.3 (C3′,5′), 48.0 (C2), 27.2 (C3), 12.8 (C4).

When the reaction was repeated but for 30 min, the yield of **6** was only 56% but only one other product could be obtained by plc and in only low yield (*ca.* 2%). Extending the reaction time to 240 min gave a sufficiently increased yield (*ca.* 20%) of this second product, obtained as a colourless oil, for spectral analysis. The data point towards assignment (as follows) as the borate diester **7** (or possibly a condensation [> B–O–B <] dimer of it) but this remains questionable (see Results and discussion section).

^{1}H NMR (90 MHz, d_6-acetone): δ 1.31 (3H, t, J=7.7 Hz, CH_3), 2.89 (2H, q, J=7.7 Hz, CH_2), 6.93 (2H, d, J=9.0 Hz, H3′,5′), 7.65 (2H, d, J=9.0 Hz, H2′,6′), 7.1–7.5 (4H, m, Ph–H), 8.84 (1H, s, OH); ^{13}C NMR: δ 156.5 (C4′), 154.5 (C2″), 151.2 (C1), 131.1 (C1″), 129.2 (C2′,6′), 125.0 (C1′), 124.6 (C6″), 123.0 (C4″), 120.0 (C5″), 117.0 (C3″), 116.6 (C2), 116.4 (C3′,5′), 18.2 (C3), 15.0 (C4).

3.4. 3-Ethyl-1-hydroxy-3-(4-hydroxybenzoyl)-2,1-benzoxaborolane (5) by reaction of 4 with iodine

4-Ethyl-1-hydroxy-3-(4-hydroxyphenyl)-2-oxa-1-bora-naphthalene (**4**) (103 mg, 0.39 mmol) was dissolved in sodium hydroxide solution (5 ml; 2 mol l^{-1}) and a solution of iodine (0.14 g, 0.55 mmol) in ether (5 ml) was added. The iodine colour quickly disappeared and the two-phase solution was vigorously stirred for 30 min. A few drops of saturated aqueous sodium thiosulphate were added to remove any remaining iodine, the aqueous layer was neutralised with aqueous hydrochloric acid, and the organic products were extracted with ether (2 × 10 ml). The combined ether extract was dried and the solvent removed under reduced pressure. The product was purified by plc with using 35 : 65 v/v ethyl acetate/petroleum spirit (b.p. 40–60°C) as eluant to give 3-ethyl-1-hydroxy-3-(4-hydroxybenzoyl)-2,1-benzoxaborolane (**5**; 24 mg, 22%) after recrystallisation from chloroform; m.p. 121–123°C. For X-ray crystal structure data see below. ^{1}H NMR (300 MHz, d_6-acetone): δ 0.92 (3H, t, J=7.3 Hz, H4), 2.13 (1H, dq, J(3a3b) = 13.8 Hz, J(3a4) = 7.3 Hz, H_{3a}), 2.61 (1H, dq, J(3a3b)=13.8 Hz, J(3b4)=7.3 Hz, H_{3b}), 6.97 (2H, d, J=9.0 Hz, H3′,5′), 8.06 (2H, d, J=9.0 Hz, H2′,6′), 7.73 (1H, dt, J(6″5″)=7.8 Hz, J=0.9 Hz, H6″), 7.66 (1H, td,

J=7.8 Hz, J=1.2 Hz, H5″), 7.53 (1H, td, J=7.2 Hz, J=1.2 Hz, H4″), 7.87 (1H, dt, J(3″4″)=7.2 Hz, J=0.9 Hz, H3″), 8.63 (1H, s, OH), 9.25 (1H, s, OH); ^{13}C NMR: δ 200.54 (C1), 162.58 (C4′), 157.60 (C1″), 133.63 (C2′,6′), 132.42 (C3″), 131.36 (C5″), 129.87 (C1′), 129.11 (C6″), 124.32 (C4″), 115.90 (C3′,5′), 95.43 (C2), 34.45 (C3), 8.60 (C4), [C2″ not seen [22b]; ^{11}B NMR (90 MHz): δ 32.8, approximate width at half height: 20 ppm (weak solution).

*3.5. 2-(1-Biphenyl)-1-(4-hydroxyphenyl)-butan-1-one (**8**)*

Pd(PPh$_3$)$_4$ (23 mg, 0.020 mmol; prepared by the standard method [24]), toluene (4 ml), bromobenzene (redistilled, 0.065 ml, 0.62 mmol), aqueous sodium carbonate (2 ml, 2 mol l^{-1}) and 4-ethyl-1-hydroxy-3-(4-hydroxyphenyl)-2-oxa-1-boranaphthalene (**4**; 200 mg, 0.75 mmol in 1 ml MeOH) were placed in a 25 ml flask under N$_2$. The mixture was kept at 80°C for 6 h with vigorous stirring, then cooled. Neutralisation by dropwise addition of hydrochloric and (*ca.* 2 ml, 0.5 mol l^{-1}) resulted in precipitation of a white solid from the aqueous layer. The solid was extracted into ether (1 × 30 ml; 1 × 10 ml). The combined extracts were dried (MgSO$_4$) and the solvent removed under reduced pressure to give the product (300 mg). A portion (80 mg) of the product was separated by plc with 30/70 v/v ethyl acetate/petroleum spirit (b.p. 40–60°C) as the eluant. Two broad bands were extracted. One (R_f 0.4–0.6) was starting material (**4**; 32 mg, 0.120 mmol; 60% recovery). The other band (R_f 0.65–0.8) yielded an oil which was shown by high resolution mass spectroscopy and NMR to be 2-(1-biphenyl)-1-(4-hydroxyphenyl)-butan-1-one (**8**, 16 mg, 0.053 mmol; 30%). (M$^+$ 316.1422; C$_{22}$H$_{20}$O$_2$ calcd: 316.1458). ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.88 (3H, t, J=7 Hz, CH$_3$), 1.85 and 2.33 (each 1H, m, CH$_2$), 4.55 (1H, dd, J=5.7 Hz, CH), 6.66 (2H, d, J=9 Hz, H 3′,5′), 7.28 (9H, m, biphenyl–H), 7.46 (2H, d, J=9 Hz, H2′,6′); ^{13}C NMR (90 MHz): δ 200.1 (C1), 160.6 (C4′), 142.2 (C1‴), 138.2 (C1″), 131.8 (C2′,6′), 131.0 (C4‴), 130.7 (C2″), 130.2 (C2‴,6‴), 129.5 (C1′), 129.0 (C3‴,5‴), 128.6 (C3″), 128.4 (C4″), 128.0 (C6″), 127.3 (C5″), 115.7 (C3′,5′), 50.7 (C2), 28.6 (C3), 13.5 (C4). IR (smear; KBr): 3334s, br, 2966st, 1652s, 1574s cm^{-1}.

When the reaction was repeated but with heating for 18 h, the yield of **8** was increased to 42% but recovery of reactant **4** was only 15%.

3.6. X-ray crystallography

For both **4** and **5** preliminary precession photography defined space groups and crystal quality. Intensity data were collected by ω scans with a Nicolet R3 (for **4**) or an Enraf-Nonius CAD4 (for **5**) diffractometer [λ(Mo Kα)=0.71069 Å]. Cell parameters were determined from 23 reflections ($3 < \theta < 18°$) for **4** and 25 reflections ($10 < \theta < 12°$) for **5**. The intensities were corrected for Lorentz and polarisation effects but not for absorption. The structures were solved by direct methods, and were developed routinely. In the final refinement cycles, all non-hydrogen atoms were treated anisotropically. The OH hydrogen atoms were located in a penultimate difference map and were included with fixed coordinates and temperature factors, while

TABLE 2. Final positional and equivalent thermal parameters for 4-ethyl-1-hydroxy-3-(4-hydroxyphenyl)-2-oxa-1-boranaphthalene (**4**)

Atom	x	y	z	U_{eq}
B(1)	0.8386(2)	−0.0842(5)	0.3455(1)	0.023
O(1)	0.9114(1)	−0.0593(3)	0.3056(1)	0.028
O(2)	0.8506(1)	0.0585(3)	0.4064(1)	0.023
O(3)	0.9400(1)	0.7097(3)	0.6785(1)	0.028
C(1)	0.7810(2)	0.0559(5)	0.4505(1)	0.021
C(2)	0.6966(2)	−0.0885(4)	0.4353(1)	0.022
C(3)	0.6174(2)	−0.0802(5)	0.4809(1)	0.026
C(4)	0.6220(2)	−0.2988(5)	0.5329(1)	0.030
C(5)	0.6786(2)	−0.2558(4)	0.3732(1)	0.023
C(6)	0.7484(2)	−0.2598(4)	0.3273(1)	0.024
C(7)	0.7316(2)	−0.4237(5)	0.2691(1)	0.033
C(8)	0.6490(2)	−0.5822(6)	0.2556(1)	0.039
C(9)	0.5805(2)	−0.5764(5)	0.3006(1)	0.037
C(10)	0.5940(2)	−0.4159(5)	0.3576(1)	0.030
C(11)	0.8171(2)	0.2253(4)	0.5114(1)	0.021
C(12)	0.8080(2)	0.1760(5)	0.5816(1)	0.023
C(13)	0.8475(2)	0.3346(5)	0.6376(1)	0.023
C(14)	0.8986(2)	0.5461(4)	0.6246(1)	0.021
C(15)	0.9093(2)	0.6001(4)	0.5557(1)	0.022
C(16)	0.8688(2)	0.4406(5)	0.5003(1)	0.020

TABLE 3. Final positional and equivalent thermal parameters for 3-ethyl-1-hydroxy-3-(4-hydroxybenzoyl)-2,1-benzoxaborolane (**5**)

Atom	x	y	z	U_{eq}
C(1)	0.7590(2)	0.2663(4)	0.5738(1)	0.033
C(2)	0.6964(1)	0.3747(4)	0.4868(1)	0.033
C(3)	0.6360(2)	0.5267(4)	0.5129(2)	0.044
C(4)	0.6905(3)	0.6917(5)	0.5751(2)	0.063
C(5)	0.6416(1)	0.2170(4)	0.4200(1)	0.032
C(6)	0.6657(2)	0.2125(4)	0.3399(1)	0.034
C(7)	0.6240(2)	0.0743(4)	0.2710(2)	0.042
C(8)	0.5572(2)	−0.0513(4)	0.2810(2)	0.046
C(9)	0.5320(2)	−0.0401(5)	0.3600(2)	0.046
C(10)	0.5742(2)	0.0925(4)	0.4302(2)	0.040
C(1))	0.8592(2)	0.2413(4)	0.5961(2)	0.038
C(12)	0.9162(2)	0.3905(5)	0.5826(2)	0.047
C(13)	1.0103(2)	0.3642(5)	0.6116(2)	0.054
C(14)	1.0487(2)	0.1877(5)	0.6527(2)	0.052
C(15)	0.9929(2)	0.0355(5)	0.6658(2)	0.056
C(16)	0.8990(2)	0.0656(5)	0.6386(2)	0.048
O(1)	0.7192(1)	0.1901(3)	0.6229(1)	0.041
O(2)	0.7490(1)	0.4732(3)	0.4377(1)	0.040
O(3)	0.7757(1)	0.4704(3)	0.2964(1)	0.052
O(4)	1.1409(1)	0.1541(4)	0.6840(2)	0.077
B(1)	0.7339(2)	0.3870(5)	0.3525(2)	0.038

other hydrogen atoms were included in calculated positions (D(C–H) 0.98 Å) with common temperature factors for each type. Programs used were SHELXS-86 and SHELX-76 [25].

3.6.1. *Crystal data for 4*

$C_{16}H_{15}BO_3$, M_r 266.107; monoclinic, a=13.413(5), b=5.425(2), c=19.118(6) Å, β=102.89(3)°, U=1356.2(8) Å^3, d_c=1.30 g cm^{-3}, Z=4, space group $P2_1/c$, μ(Mo Kα)=0.8 cm^{-1}, T=183 K. A total of 2169 unique reflections was measured by ω-scans in the range $0 < 2\theta <$ 50° on a crystal of dimensions 0.8 × 0.5 × 0.1 mm. Of these reflections, 1710 were considered to be observed $[I > 2\sigma(I)]$ and were used in the structure refinement. Refinement converged with R=R_w=0.049, w=$[(\sigma^2(F) + 0.00096F^2]^{-1}$. Largest Δ/σ was 0.01, largest peak in a difference map was 0.3 e Å^{-3}.

3.6.2. *Crystal data for 5*

$C_{16}H_{15}BO_4$, M_r 282.103; monoclinic, a=15.442(4), b=6.720(4), c=15.295(5) Å, β=109.68(2)°, U=1494(1) Å^3, d_c=1.25 g.cm^{-3}, Z=4, space group $P2_1/c$; μ(Mo Kα)=0.8 cm^{-1}, T=293 K. A total of 2962 unique reflections was measured by ω-scans in the range $0 < 2\theta <$ 55° on a crystal of dimensions 0.23 × 0.21 × 0.05 mm. Of these reflections 2199 were considered to be observed $[I > 2\sigma(I)]$ and were used in the structure refinement. Refinement converged with R=0.066, R_w=0.069, w=$[(\sigma^2(F) + 0.00193F^2]^{-1}$. Largest Δ/σ was 0.05, largest peak in a difference map was 0.3 e Å^{-3}.

Final positional parameters for **4** and **5** are given in Tables 2 and 3, and the structures are illustrated in Fig. 1 and 2 respectively. Selected bond parameters are given in Table 1.

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References

1 R. McCague in D.E.V. Wilman (ed.), *Chemistry of Antitumour Agents*, Blackie, Glasgow, 1990, p. 240.
2 F.A. Carey and R.J. Sundberg, *Advanced Organic Chemistry, 3rd Ed., Part B*, Plenum, New York, 1990, pp. 443–464.
3 H.C. Brown, *Organic Synthesis via Boranes*, Wiley, New York, 1975.
4 B.W. Muller, *Helv. Chim. Acta, 61* (1978) 325.
5 M.J.S. Dewar and R. Dietz, *J. Chem. Soc.*, (1960) 1344.
6 W. Maringgele, A. Meller, M. Noltemeyer and G.M. Sheldrick, *Z. Anorg. Allg. Chem., 536* (1986) 24.
7 G.J. Videla and M.A. Molinari, *Argent, Com. Nac. Energ. At.*, (1973) no. 352; (*Chem. Abstr., 80* (1974) 48075).
8 S. Gronowitz and I. Ander, *Chem. Scr., 15* (1980) 23.
9 I. Ander, in A.R. Katritzky and C.W. Rees (eds.), *Comprehensive Heterocyclic Chemistry, Vol. 1*, Pergamon, Oxford, 1984, Ch. 21, (a) p. 648–9; (b) p. 633.
10 H.C. Brown and J.B. Campbell, *J. Org. Chem., 45* (1980) 389.

11 H.C. Brown, M.W. Rathke and M.M. Rogic, *J. Am. Chem. Soc.*, *90* (1968) 5038.
12 S. Neece and I. Fridovich, *Arch. Biochem. Biophys.*, *108* (1964) 240.
13 J. March, *Advanced Organic Chemistry, 3rd Ed*, Wiley, New York, 1985, p. 550.
14 N. Miyaura, T. Yanagi and A. Suzuki, *Synth. Comm.*, *11* (1981) 513.
15 V. Snieckus, *Chem. Rev.*, *90* (1990) 879.
16 C.S. Shiner, C.M. Garner and R.C. Haltiwanger, *J. Am. Chem. Soc.*, *107* (1985) 7167.
17 N.C. Barua, K. Evertz, G. Huttner and R.R. Schmidt, *Chem. Ber.*, *120* (1987) 213.
18 F.H. Allen, O. Kennard, D.G. Watson, L. Brammer, A.G. Orpen and R. Taylor, *J. Chem. Soc., Perkin Trans II*, (1987) S1.
19 S.J. Rettig and J. Trotter, *Can. J. Chem.*, *55* (1977) 3071.
20 J.S. Buck and W.S. Ide, *J. Am. Chem. Soc.*, *54* (1932) 3012.
21 M. Jarman and R. McCague, *J. Chem. Res.*, (1985) (S) 116; (M) 1342.
22 H. Kalinowski, S. Berger and S. Braun, *^{13}C NMR Spectroscopy*, Wiley, New York, 1988 (a) pp. 311–331, 340–345 (b) pp. 250–255.
23 H. Noth and B. Wrackmeyer, Nuclear Magnetic Resonance Spectroscopy of Boron Compounds, in P. Diehl, E. Fluck and R. Kosfeld (eds.), *NMR: Basic Principles and Progress*, Vol. 14 Springer-Verlag, 1978.
24 H.M. Colquhoun, D.J. Thompson and M.V. Twigg, *Carbonylation: Direct Synthesis of Carbonyl Compounds*, Plenum, New York, 1991, p. 237.
25 G. Sheldrick, SHELX-76, University of Cambridge, 1976; SHELXS-86, University of Göttingen, 1986.