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TOTAL SYNTHESIS OF SOME NEW 4-DEMETHOXYANTHRACYCLINONES

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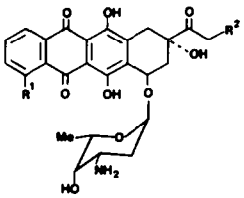
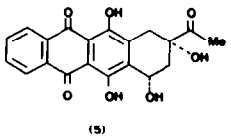
Abstract—Optically active 4-demethoxyanthracyclinones (**39a–g**) bearing a variety of substituents at the 9-position have been synthesised by an analogous route to that previously employed by us for (+)-4-demethoxydaunomycinone (**5**). These novel anthracyclinones have been prepared in sufficient quantity for subsequent glycosidation and biological evaluation.

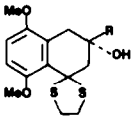
The use of daunomycin (**1**) and, particularly, adriamycin (**2**) for the treatment of certain categories of human cancer has encouraged the search for new anthracyclines with improved potential for therapy.[1–6] There is scope for widening the range of tumour types susceptible to anthracycline chemotherapy and for reducing undersirable side effects of the parent drugs.[7,8] Some structure-activity relationships have been established for the series but these are largely derived from the investigation of analogues of adriamycin and daunomycin prepared by chemical modification of fermentation-derived anthracyclines.[9] This has limited the range of new structures since the natural products have labile functions (as at positions 7, 9) which are essential for good biological activity.[10] For this reason we have undertaken to extend the understanding of structure-activity relationships by utilising a new method of total synthesis[11,12] which has been shown to be capable of producing the substantial quantities of novel anthracycline glycosides which are necessary for good biological evaluation. We have selected as targets for synthesis novel, optically active, 4-demethoxyanthracyclinones with various substituents at position 9. These compounds are converted to the corresponding glycosides and investigated in biological tests. The choice of 4-demethoxyanthracyclinones was influenced by earlier studies. It has been established that 4-demethoxydaunomycin (**3**) and 4-demethoxyadriamycin (**4**) are more potent and less toxic than the parent compounds;[13] they are effective in human therapy.[14,15] Some other 4-demethoxyanthracyclines also appear promising.[16] The choice of position-9 variants of 4-demethoxyanthracyclines is supported by various observations. Some natural compounds such as cinerubin-A[17] and aclacinomycin-A,B,[18] which lack the C-13 oxo-function of adriamycin, have interesting antitumour properties. The 13-deoxy and 13-dihydro analogues of adriamycin and daunomycin, which were obtained from the parent anthracyclines by chemical transformation[19] and as mammalian metabolites,[20,21] respectively, have both been shown to retain antitumour activity. The distinct clinical advantage of adriamycin (**2**) over duanomycin (**1**) must be attributed to the C-14 hydroxyl function.



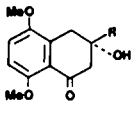
(1) R^1 = OMe, R^2 = H
(2) R^1 = OMe, R^2 = OH
(3) R^1 = R^2 = H
(4) R^1 = H, R^2 = OH



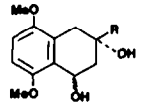
(5)



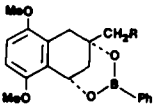
(6) R = $COCH_3$
(7) R = $CH(OH)CH_3$
(8) R = $CH(OSO_2CH_3)CH_3$
(9) R = CH_2CH_3
(10) R = CO_2CH_3
(11) R = CH_2OH
(12) R = CH_2O-SO_2-$C_6H_4CH_3$
(13) R = CH_3
(14) R = CH_2OAc
(15) R = CH_2CN
(16) R = $CH(OAc)CH_3$



(17) R = CH_2CH_3
(18) R = CH_3
(19) R = CH_2OAc
(20) R = CH_2CN
(21) R = $CH(OAc)CH_3$
(22) R = CO_2CH_3



(23) R = CH_2CH_3
(24) R = CH_3
(25) R = CH_2OAc
(26) R = CH_2CN
(27) R = $CH(OAc)CH_3$
(28) R = CO_2CH_3



(29) R = CN
(30) R = CHO
(31) R = CH_2OH

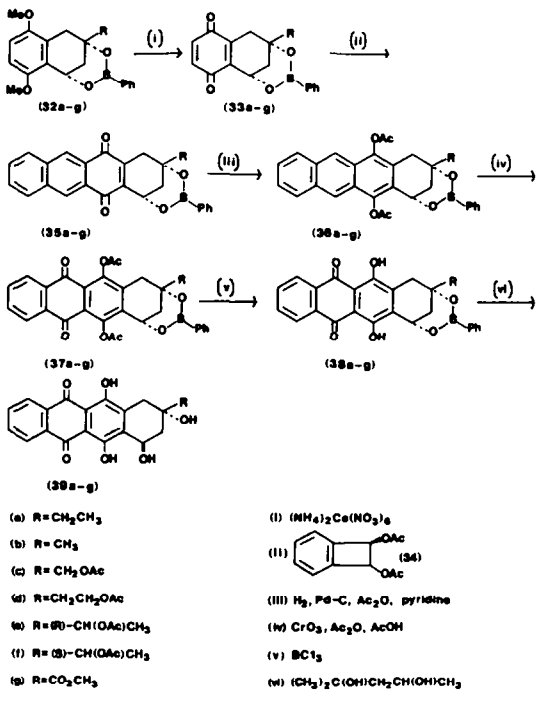
Various approaches to the synthesis of 4-demethoxyanthracyclines have been described. Many lead to 7,9-dideoxy or 7-deoxy anthracyclinones to avoid introduction of the labile 7- and 9-hydroxyl groups at an early stage. Although there are recent improvements in methodology[22] they are not well suited to large scale production. Attempts to introduce 7- and 9-OH substituents at an early stage through Diels–Alder reactions [23–27] or using fully functionalised A,B-ring precursors[28,29] have, as yet, only provided optically active anthracyclinones analogous to 4-demethoxyadriamycinone in one case.[27,30] There are other procedures for the preparation of optically active compounds,[31–35] based largely on Wong's route[36] but these produce 7-deoxyanthracyclinones, with the attendant problems involved in obtaining pure, optically active anthracyclinones conveniently.

The procedure for the synthesis of optically active (+)-4-demethoxydaunomycinone (**5**), 4-demethoxydaunomycin (**3**) and the corresponding 7,9-bis-epi-analogues which we have recently described[11,12] has been applied to the synthesis of new optically active 4-demethoxyanthracyclinones with various 9-substituents. 4-Demethoxy-13-deoxydaunomycinone (**39a**) was prepared through the 9-ethyl substituted bicycle (**9**). This intermediate was converted to a mixture of *cis*- and *trans*-diols (**23**) which gave the *cis*-benzeneboronate (**32a**) alone, on treatment with benzeneboronic acid. The protected intermediate (**32a**) was converted to the 9-ethylanthracyclinone (**39a**) by the procedures which we have already published (Scheme). The 9-methylanthracyclinone (**39b**) was prepared by a similar route.

The preparation of anthracyclinones (**39c–39g**), bearing protected hydroxyl or carboxyl groups on the 9-alkyl side-chain, has been investigated. The 9-acetoxymethylanthracyclinone (**39c**) was readily synthesised from the bicyclic intermediate (**10**)[12] but the homologue (**39d**) was less accessible. Attempted reduction of the nitrile (**15**) under a variety of conditions resulted in aromatisation of ring A. The transformation was achieved, eventually, following conversion to the *cis*-benzeneboronate (**29**) and stepwise reduction to the aldehyde (**30**) and the alcohol (**31**). The bicyclic intermediate (**32d**) was converted to the 9-(2-acetoxymethyl)anthracyclinone (**39d**) according to the Scheme.

Microbial[37] and chemical[38] reduction of 4-demethoxydaunomycin to 13-dihydro analogues has recently been reported, but no information is available concerning the stereochemistry at C-13 in these derivatives. We have now synthesised 13*R*- and 13*S*-dihydroanthracyclinones (**39e** and **39f**), through selective hydride reduction of the ketone (**6**). After investigating various reagents and conditions it was found that lithium aluminium hydride (LAH) at −78° gave a mixture of diols (**7**) (*R*:*S*, 80:20) which could be purified by recrystallisation of the *cis*-benzeneboronates (**32e, 32f**). X-Ray crystallographic analysis established the *R*-configuration of the major component.[39] The preparation of the (*S*)-alcohol was achieved most conveniently by reduction of the ketone (**6**) with the chiral hydride donor[35] derived from the interaction of LAH with (+)-N-methylephedrine and N-methylaniline (*R*:*S*, 40:60). The remaining steps follow procedures already indicated in the Scheme. The anthracyclinone ester (**39g**) was readily prepared from the ester (**10**) through the tetralone (**22**). Reduction of (**22**) to the diols (**28**) utilised sodium cyanoborohydride.

The 4-demethoxyanthracyclinones prepared in this way have been converted to the corresponding 4-demethoxyanthracyclines. Some of the new compounds have shown very interesting antitumour activities in animal models. Details of the biological evaluation of these compounds will be reported elsewhere.



EXPERIMENTAL

M.ps were determined on a Büchi m.p. apparatus. IR spectra were recorded on a Unicam SP 1000 spectrophotometer for Nujol mulls, UV and visible spectra were recorded with a Unicam SP8000 spectrophotometer, and ^{1}H NMR spectra were recorded on a Varian XL 100 spectrometer for $CDCl_3$ solns with TMS as internal reference, unless otherwise stated. Mass spectra were recorded using an AEI MS 902 mass spectrometer with a direct insertion probe. Optical rotations were determined on a Perkin-Elmer 141 MC polarimeter and microanalyses were carried out using a Perkin-Elmer elemental analyser. Organic solns were dried over $MgSO_4$. Silica gel used for column chromatography was Kieselgel 60, 70-230 mesh (Merck).

(S)-3-Ethyl-1,2,3,4-tetrahydro-3-hydroxy-5,8-dimethoxynaphthalenone (**17**)

A suspension of (*S*)-**6**[12] (16.48 g, 0.048 mol) and $NaBH_4$ (3.59 g, 0.095 mol) in THF (1.45 l) was stirred at room temp for 4 hr. The mixture was concentrated *in vacuo* and excess reagent decomposed with 5% NH_4Cl aq (1.5 l). The mixture was extracted with EtOAc (3 × 500 ml) and the combined extracts were washed with water (1.0 l), dried and evaporated to give a mixture of diastereoisomeric alcohols (**7**) as a colourless gum. This was dissolved in pyridine (380 ml) and a soln of methanesulphonyl chloride (5.55 g, 0.048 mol) in pyridine (50 ml) was added. The mixture was kept at 4° overnight and was then concentrated *in vacuo*. The residue was suspended in water (500 ml) and extracted with EtOAc (4 × 250 ml). The combined extracts were washed with water (2 × 500 ml), 2M HCl (2 × 500 ml) and sat $NaHCO_3$ aq (500 ml), dried and evaporated to give a mixture of diastereoisomeric methanesulphonates (**8**) as a colourless gum. This was dissolved in THF (300 ml) and the soln was added over 5 min to a stirred and cooled soln of LAH (3.68 g) in THF (200 ml). The mixture was refluxed for 50 min, and then cooled to 0° and excess reagent decomposed with 10% NH_4Cl aq (110 ml). THF was removed *in vacuo* and the residue was taken up in 2M HCl (1.0 l) and extracted with EtOAc (3 × 500 ml). The combined extracts were washed with sat $NaHCO_3$ aq (500 ml), dried and evaporated to give (*S*)-**9** as a colourless gum, δ 1.02 (3H, t, J = 7.5 Hz, $CH_2\underline{CH_3}$), 1.64 (2H, q, J = 7.5 Hz, $\underline{CH_2}CH_3$), 2.42 (1H, d, J = 19.5 Hz, 4'-ax-H), 2.50 (2H, s, 2'-H_2), 2.60 (1H, broad s, OH), 2.98 (1H, broad d, J = 19.5 Hz, 4'-eq-H), 3.27–3.72 (4H, m, SCH_2CH_2S), 3.76 (3H, s, OMe), 3.87 (3H, s, OMe), 6.77 (2H, s, ArH); M^+ 326. The thioacetal **9** was dissolved in THF (210 ml) and the soln was added to a stirred suspension of mercuric oxide (55.0 g) and mercuric chloride (55.0 g) in a mixture of MeOH (1.8 l) and water (160 ml). The mixture was stirred at room temp for 1.5 hr and the solvent volume was then reduced by approximately 50%. The residue was diluted with

CH_2Cl_2 (2.0 l) and filtered to remove inorganic salts. The filtrate was washed with water (3 × 1.5 l), dried and evaporated. The residue was triturated with ether to give **17** (7.38 g, 61% over 4 steps) as a white solid, m.p. 132–134°; δ 1.00 (3H, t, J = 7.5 Hz, $CH_2C\underline{H}_3$), 1.66 (2H, q, J = 7.5 Hz, $C\underline{H}_2CH_3$), 2.72 (2H, s, 2-H_2), 2.88 (1H, d, J = 18 Hz, 4-ax-H), 3.10 (1H, d, J = 18 Hz, 4-eq-H), 3.84 (3H, s, OMe), 3.88 (3H, s, OMe), 6.82 (1H, d, J = 9 Hz, ArH), 7.00 (1H, d, J = 9 Hz, ArH); ν_{max} 3480, 1670 and 1590 cm^{-1}; M^+ 250.

(S)-cis-3-*Ethyl*-1,2,3,4-*tetrahydro*-5,8-*dimethoxy*-*naphthalene*-1,3-*diyl benzeneboronate* (**32a**)

Reduction of **17** (7.60 g, 0.030 mol) with $LiBH_4$ and treatment of the resulting diols (**23**) with benzeneboronic acid by our earlier procedures[12] gave the benzeneboronate **32a** (8.90 g, 87% over 2 steps) as a white crystalline solid, m.p. 132–133°; $[\alpha]_D^{20}$ + 56.0° (c = 0.5% in $CHCl_3$); δ 1.14 (3H, t, J = 7.5 Hz, $CH_2C\underline{H}_3$), 1.74–1.99 (3H, m, 2-H and $C\underline{H}_2CH_3$), 2.14–2.37 (1H, m, 2-H), 2.68 (1H, d, J = 18 Hz, 4-ax-H), 3.14 (1H, dd, J = 18 Hz and 2 Hz, 4-eq-H), 3.78 (3H, s, OMe), 3.90 (3H, s, OMe), 5.65 (1H, t, J = 3 Hz, 1-H), 6.74 (2H, s, ArH), 7.20–7.40 (3H, m, ArH), 7.72–7.86 (2H, m, ArH); ν_{max} 1600 cm^{-1}; M^+ 338. (Found: C, 70.9; H, 6.9. $C_{20}H_{23}BO_4$ Requires: C, 71.0; H, 6.85%).

(S)-cis-3-*Ethyl*-1,2,3,4,5,12-*hexahydro*-5,12-*dioxonaphthacene*-1,3-*diyl benzeneboronate* (**35a**)

The benzeneboronate **32a** (9.15 g, 0.027 mol) was treated with ammonium ceric nitrate to give the quinone (**33a**) as a yellow gum. This was reacted with *trans*-**34** (7.48 g, 0.034 mol) by our published procedure[12] to give the quinone **35a** (7.96 g, 72% over 2 steps) as a bright yellow crystalline solid, m.p. 225–226°; $[\alpha]_D^{20}$ + 143° (c = 0.1% in $CHCl_3$); δ 1.15 (3H, t, J = 7.5 Hz, $CH_2C\underline{H}_3$), 1.76–2.04 (3H, m, 2-H and $C\underline{H}_2CH_3$), 2.29 (1H, broad d, J = 14 Hz, 2-H), 2.73 (1H, d, J = 20 Hz, 4-ax-H), 3.17 (1H, dd, J = 20 Hz and 1 Hz, 4-eq-H), 5.68 (1H, t, J = 2.5 Hz, 1-H), 7.20–7.38 (3H, m, ArH), 7.58–7.84 (4H, m, ArH), 7.94–8.12 (2H, m, ArH), 8.59 (1H, s, ArH), 8.68 (1H, s, ArH); ν_{max} 1660, 1610 and 1590 cm^{-1}; λ_{max} ($CHCl_3$) 242, 277, 288, 300 and 415 nm (ε 30,844, 18,449, 19,531, 20,194 and 5325); M^+ 408. (Found: C, 76.4; H, 5.2. $C_{26}H_{21}BO_4$ Requires: C, 76.5; H, 5.2%).

(S)-cis-5,12-*Diacetoxy*-3-*ethyl*-1,2,3,4-*tetrahydronaphthacene*-1,3-*diyl benzeneboronate* (**36a**)

Catalytic hydrogenation of the quinone **35a** (7.47 g, 0.018 mol) in a mixture of pyridine and Ac_2O gave **36a** (8.82 g, 98%) as a pale yellow solid, m.p. 274–276°; $[\alpha]_D^{20}$ + 247° (c = 0.1% in dioxan); δ 1.15 (3H, t, J = 7.5 Hz, $CH_2C\underline{H}_3$), 1.76–2.10 (3H, m, 2-H and $C\underline{H}_2CH_3$), 2.35 (1H, broad d, J = 13 Hz, 2-H), 2.56 (3H, s, OAc), 2.67 (3H, s, OAc), 2.82 (1H, d, J = 18 Hz, 4-ax-H), 3.26 (1H, dd, J = 18 Hz and 1 Hz, 4-eq-H), 5.61 (1H, t, J = 3 Hz, 1-H), 7.20–7.36 (3H, m, ArH), 7.38–7.54 (2H, m, ArH), 7.64–7.78 (2H, m, ArH), 7.88–8.04 (2H, m, ArH), 8.26 (1H, s, ArH), 8.35 (1H, s, ArH); ν_{max} 1760, 1740, 1635 and 1595 cm^{-1}; λ_{max} ($CHCl_3$) 263, 320, 336, 351, 370 and 391 nm (ε 151,319, 1559, 2864, 4898, 6858 and 6029); M^+ 494.

(S)-cis-5,12-*Diacetoxy*-3-*ethyl*-1,2,3,4,6,11-*hexahydro*-6,11-*dioxonaphthacene*-1,3-*diyl benzeneboronate* (**37a**)

Treatment of **36a** (8.786 g, 0.018 mol) with CrO_3 in a mixture of Ac_2O and AcOH gave **37a** (5.242 g, 56%) as a pale yellow solid, m.p. 135–143°; $[\alpha]_D^{20}$ + 182° (c = 0.1% in dioxan); δ 1.14 (3H, t, J = 7.5 Hz, $CH_2C\underline{H}_3$), 1.76–2.08 (3H, m, 2-H and $C\underline{H}_2CH_3$), 2.34 (1H, broad d, J = 14 Hz, 2-H), 2.52 (3H, s, OAc), 2.64 (3H, s, OAc), 2.75 (1H, d, J = 19 Hz, 4-ax-H), 3.21 (1H, broad d, J = 19 Hz, 4-eq-H), 5.50 (1H, broad s, 1-H), 7.20–7.39 (3H, m, ArH), 7.62–7.82 (4H, m, ArH), 8.08–8.23 (2H, m, ArH); ν_{max} 1765, 1670 and 1585 cm^{-1}; λ_{max} ($CHCl_3$) 259 and 340 nm (ε 44,700 and 6180); M^+ 524.

(S)-cis-3-*Ethyl*-1,2,3,4,6,11-*hexahydro*-5,12-*dihydroxy*-6,11-*dioxonaphthacene*-1,3-*diyl benzeneboronate* (**38a**)

Treatment of **37a** (5.212 g, 0.010 mol) with BCl_3 gave **38a** (4.09 g, 93%) as a bright orange solid, m.p. 211–224°; $[\alpha]_D^{20}$ + 331° (c = 0.1% in dioxan); δ 1.17 (3H, t, J = 7.5 Hz, $CH_2C\underline{H}_3$), 1.76–2.06 (3H, m, 2-H and $C\underline{H}_2CH_3$), 2.34 (1H, broad d, J = 14 Hz, 2-H), 2.82 (1H, d, J = 19.5 Hz, 4-ax-H), 3.32 (1H, dd, J = 19.5 Hz and 1 Hz, 4-eq-H), 5.77 (1H, t, J = 3 Hz, 1-H), 7.20–7.40 (3H, m, ArH), 7.70–7.92 (4H, m, ArH), 8.24–8.42 (2H, m, ArH), 13.32 (1H, s, ArOH), 13.56 (1H, s, ArOH); ν_{max} 1620 and 1590 cm^{-1}; λ_{max} ($CHCl_3$) 252, 257, 288, 326 sh, 465 sh, 487, 506 sh and 521 nm (ε 43,324, 40,509, 10,824, 2844, 10,094, 11,346, 8268 and 7283); M^+ 440.

(S)-cis-3-*Ethyl*-1,2,3,4,6,11-*hexahydro*-1,3,5,12-*tetrahydroxynaphthacene*-6,11-*quinone* (**39a**)

Treatment of **38a** (4.06 g, 0.009 mol) with 2-methylpentane-2,4-diol by our earlier procedure[12] gave **39a** (2.92 g, 89%) as a bright red solid, m.p. 179–183°; $[\alpha]_D^{20}$ + 136° (c = 0.1% in dioxan); δ [$(CD_3)_2SO$—$CDCl_3$] 1.07 (3H, t, J = 7.5 Hz, $CH_2C\underline{H}_3$), 1.57–1.87 (3H, m, 2-H and $C\underline{H}_2CH_3$), 2.35 (1H, dm, J = 14 Hz, 2-H), 2.53 (1H, d, J = 19 Hz, 4-ax-H), 3.17 (1H, dd, J = 19 Hz and 1.5 Hz, 4-eq-H), 4.35 (1H, s, 3-OH), 4.73 (1H, d, J = 7.5 Hz, 1-OH), 5.10–5.27 (1H, m, 1-H), 7.75–7.91 (2H, m, ArH), 8.23–8.40 (2H, m, ArH), 13.39 (1H, s, ArOH), 13.60 (1H, s, ArOH); ν_{max} 3400–2400, 1615 and 1580 cm^{-1}; λ_{max} ($CHCl_3$) 253, 289, 328 sh, 460 sh, 483 and 517 nm (ε 40.272, 10,270, 2707, 9406, 10,615 and 6431); M^+ 354. (Found: C, 67.4; H, 5.05. $C_{20}H_{18}O_6$ Requires: C, 67.8; 5.1%).

(S)-1',2',3',4'-*Tetrahydro*-3'-*hydroxy*-3'-*methyl*-5',8'-*dimethoxyspiro*[1,3-*dithiolane*-2,1'-*naphthalene*] (**13**)

A soln of ester **10**[12] (30.0 g, 0.084 mol) in THF (1.0 l) was stirred with $NaBH_4$ (30.0 g, 0.79 mol) at room temp for 30 hr. The solvent was evaporated and the residue dissolved in a mixture of EtOAc (250 ml) and water (150 ml). The layers were separated and the aqueous layer extracted with further EtOAc (150 ml). The combined extracts were washed with water (100 ml), dried and evaporated to give alcohol **11** as a colourless gum; δ (60 MHz) 2.20–2.80 (5H, m, 2'-H_2, 4'-H_2 and OH), 3.10–3.70 (7H, SCH_2CH_2S, $C\underline{H}_2OH$ and OH), 3.75 (3H, s, OMe), 3.87 (3H, s, OMe), 6.76 (2H, s, ArH); M^+ 328. The alcohol (**11**) was dissolved in pyridine (300 ml) at 0°C and toluene-4-sulphonyl chloride (44 g, 0.23 mol) added with stirring. The mixture was kept at 4° overnight and was then concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (750 ml) and the soln was washed with water (500 ml), 2M HCl (500 ml) and sat $NaHCO_3$ aq (500 ml), dried and evaporated to give **12** (31.9 g, 78.5% over 2 steps) as a white solid, m.p. 115° (dec.); $[\alpha]_D^{20}$ − 37.5° (c = 0.5% in $CHCl_3$); δ 2.45 (3H, s, CH_3), 2.48 (1H, broad s, OH), 2.48 (1H, d, J = 18 Hz, 4'-ax-H), 2.54 (2H, s, 2'-H_2), 2.91 (1H, broad d, J = 18 Hz, 4'-eq-H), 3.25–3.68 (4H, m, SCH_2CH_2S), 3.73 (3H, s, OMe), 3.87 (3H, s, OMe), 3.98 (2H, s, CH_2), 6.77 (2H, q, J = 9 Hz, ArH), 7.36 (2H, d, J = 8 Hz, ArH), 7.84 (2H, d, J = 8 Hz, ArH); ν_{max} 3480 and 1585 cm^{-1}. (Found: C, 54.75; H, 5.45. $C_{22}H_{26}O_6S_3$ Requires: C, 54.75; H, 5.45%). Compound **12** (3.19 g, 0.066 mol) was dissolved in THF (500 ml) and the soln was added over 15 min to a stirred suspension of LAH (15 g) in THF (400 ml). The mixture was heated under reflux for 3.5 h and then cooled to 0° and excess reagent decomposed with 10% NH_4Cl aq (500 ml). The THF was removed *in vacuo* and the residue was taken up in 2M HCl (2.0 l) and extracted with EtOAc (4 × 500 ml). The combined extracts were washed with sat $NaHCO_3$ aq (1.0 l), dried and evaporated. The residue was triturated with ether to give **13** (20.0 g, 97%) as a white solid, m.p. 152–153°; $[\alpha]_D^{20}$ − 48.0° (c = 0.55% in $CHCl_3$); δ (60 MHz) 1.40 (3H, s, CH_3), 2.33–3.15 (4H, m, 2'-H_2 and 4'-H_2), 2.70 (1H, s, OH), 3.28–3.68 (4H, m, SCH_2CH_2S), 3.76 (3H, s, OMe), 3.86 (3H, s, OMe), 6.79 (2H, s, ArH); ν_{max} 3480 and 1590 cm^{-1}; M^+ 312. (Found: C, 57.7; H, 6.65. $C_{15}H_{20}O_3S_2$ Requires: C, 57.65; H, 6.45%).

(S)-cis-1,2,3,4,5,12-*Hexahydro*-3-*methyl*-5,12-*dioxonaphthacene*-1,3-*diyl benzeneboronate* (**35b**)

The thioacetal **13** (17.25 g, 0.055 mol) was treated with mercuric oxide and mercuric chloride to give **18** (11.0 g, 84%) as a white solid. This was reduced with $LiBH_4$ to give a mixture of

diols **24** as a colourless gum. Treatment of this mixture with benzeneboronic acid and toluene-4-sulphonic acid gave **32b**, δ (60 MHz) 1.59 (3H, s, CH_3), 2.00–2.20 (2H, m, 2-H_2), 2.60 (1H, d, J = 19 Hz, 4-ax-H), 3.21 (1H, broad d, J = 19 Hz, 4-eq-H), 3.76 (3H, s, OMe), 3.88 (3H, s, OMe), 5.63 (1H, t, J = 3 Hz, 1-H), 6.68 (2H, s, ArH), 7.18–7.40 (3H, m, ArH), 7.64–7.85 (2H, m, ArH); M^+ 324. This was oxidised using ammonium ceric nitrate to quinone **33b** which was heated with *trans*-1,2-diacetoxy-1,2-dihydrobenzocyclobutene in xylene to give **35b** (14.3 g, 66% over 5 steps) as a bright yellow crystalline solid, m.p. 275–276°; $[\alpha]_D^{20}$ + 128.3° (c = 0.1% in dioxan); δ 1.66 (3H, s, CH_3), 1.99 (1H, dd, J = 14 Hz and 2.5 Hz, 2-H), 2.30 (1H, broad d, J = 14 Hz, 2-H), 2.72 (1H, d, J = 21 Hz, 4-ax-H), 3.24 (1H, dd, J = 21 Hz and 1.5 Hz, 4-eq-H), 5.70 (1H, t, J = 2.5 Hz, 1-H), 7.16–7.40 (3H, m, ArH), 7.38–7.84 (4H, m, ArH), 7.92–8.13 (2H, m, ArH), 8.61 (1H, s, ArH), 8.70 (1H, s, ArH); ν_{max} 1660, 1615 and 1590 cm^{-1}; λ_{max} ($CHCl_3$) 242, 288, 300 and 419 nm (ε 30,238, 19,087, 20,058 and 5136); M^+ 394. (Found: C, 76.25; H, 4.8. $C_{25}H_{19}BO_4$ Requires: C, 76.15; H, 4.85%).

(S)-cis-5,12-*Diacetoxy*-1,2,3,4-*tetrahydro*-3-*methylnaphthacene*-1,3-*diyl benzeneboronate* (**36b**)

Hydrogenation of a soln of **35b** (6.4 g, 0.016 mol) in pyridine and Ac_2O gave **36b** (7.0 g, 89%) as a pale yellow solid, m.p. 248–251°; δ 1.65 (3H, s, CH_3), 2.26 (2H, m, 2-H_2), 2.57 (3H, s, OAc), 2.67 (3H, s, OAc), 2.83 (1H, d, J = 18 Hz, 4-ax-H), 3.35 (1H, broad d, J = 18 Hz, 4-eq-H), 5.63 (1H, t, J = 3 Hz, 1-H), 7.2–7.36 (3H, m, ArH), 7.40–7.56 (2H, m, ArH), 7.66–7.80 (2H, m, ArH), 7.90–8.06 (2H, m, ArH), 8.28 (1H, s, ArH), 8.36 (1H, s, ArH); M^+ 480. This material was used directly for the next step without further purification.

(S)-cis-5,12-*Diacetoxy*-1,2,3,4,6,11-*hexahydro*-3-*methyl*-6,11-*dioxonaphthacene*-1,3-*diyl benzeneboronate* (**37b**)

The diacetate **36b** (20.35 g, 0.042 mol) was oxidised with CrO_3 to give **37b** (13.4 g, 62%) as a pale yellow solid, m.p. 260–262°; δ 1.65 (3H, s, CH_3), 2.00–2.50 (2H, m, 2-H_2), 2.53 (3H, s, OAc), 2.64 (3H, s, OAc), 2.77 (1H, d, J = 18 Hz, 4-ax-H), 3.30 (1H, broad d, J = 18 Hz, 4-eq-H), 5.54 (1H, broad s, 1-H), 7.24–7.44 (3H, m, ArH), 7.64–7.90 (4H, m, ArH), 8.10–8.30 (2H, m, ArH); M^+ 510. This material was used directly for the next step without further purification.

(S)-cis-1,2,3,4,6,11-*Hexahydro*-1,3,5,12-*tetrahydroxy*-3-*methylnaphthacene*-6,11-*quinone* (**39b**)

The quinone **37b** (12.2 g, 0.024 mol) was treated with BCl_3 to give **38b** (7.9 g, 77.5%) as a red solid, δ 1.67 (3H, s, CH_3), 2.07 (1H, dd, J = 14 Hz and 2.5 Hz, 2-H), 2.32 (1H, broad d, J = 14 Hz, 2-H), 2.82 (1H, d, J = 20 Hz, 4-ax-H), 3.38 (1H, dd, J = 20 Hz and 1.5 Hz, 4-eq-H), 5.78 (1H, t, J = 2.5 Hz, 1-H), 7.20–7.40 (3H, m, ArH), 7.70–7.92 (4H, m, ArH), 8.26–8.43 (2H, m, ArH), 13.00 (1H, s, ArOH), 13.57 (1H, s, ArOH); M^+ 426. This product was then treated with 2-methylpentane-2,4-diol and AcOH to give **39b** (6.2 g, 98%) as a bright red solid, m.p. 214–215°; $[\alpha]_D^{20}$ + 152.5° (c = 0.1% in dioxan); δ [$(CD_3)_2SO$—$CDCl_3$] 1.59 (3H, s, CH_3), 1.88 (1H, dd, J = 14 Hz and 5 Hz, 2-H), 2.37 (1H, dt, J = 14 Hz and 2.5 Hz, 2-H), 2.57 (1H, d, J = 20 Hz, 4-ax-H), 3.27 (1H, dd, J = 20 Hz and 2.5 Hz, 4-eq-H), 3.50 (2H, broad s, 1-OH and 3-OH), 5.17–5.29 (1H, m, 1-H), 7.78–7.93 (2H, m, ArH), 8.26–8.40 (2H, m, ArH), 13.38 (1H, s, ArOH), 13.64 (1H, s, ArOH); ν_{max} 3270, 1620 and 1585 cm^{-1}; λ_{max} ($CHCl_3$) 258, 290 and 486 nm (ε 42,497, 10,438 and 10,704); M^+ 340. (Found: C, 66.95; H, 4.8. $C_{19}H_{16}O_6$ requires C, 67.05; H, 4.8%.

(S)-3-*Acetoxymethyl*-1,2,3,4-*tetrahydro*-3-*hydroxy*-5,8-*dimethoxynaphthalenone* (**19**)

The alcohol **11** (27.6 g, 0.084 mol) was dissolved in a mixture of pyridine (200 ml) and Ac_2O (100 ml). The mixture was allowed to stand at room temp for 18 hr and was then concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (200 ml) and the soln washed with 2M HCl (2 × 100 ml), water (100 ml) and sat $KHCO_3$ (2 × 100 ml), dried and evaporated to give **14** as a colourless gum, δ (60 MHz) 2.14 (3H, s, OAc), 2.36–2.88 (4H, m, 2'-H_2 and 4'-H_2), 3.42–3.66 (4H, m, SCH_2CH_2S), 3.77 (3H, s, OMe), 3.88 (3H, s, OMe), 4.12 (2H, s, CH_2OAc), 6.77 (2H, s, ArH); M^+ 328. This product was treated with mercuric chloride and mercuric oxide to give **19** (19.2 g, 78% over 2 steps) as a pale yellow solid, m.p. 143–145°; $[\alpha]_D^{20}$ + 14.3° (c = 0.5% in $CHCl_3$); δ (300 MHz) 2.14 (3H, s, OAc), 2.74 (1H, s, OH), 2.81 (2H, s, 2-H_2), 2.88 (1H, d, J = 18 Hz, 4-H), 3.17 (1H, d, J = 18 Hz, 4-H), 3.83 (3H, s, OMe), 3.87 (3H, s, OMe), 4.12 (2H, AB_q, J = 12.5 Hz, CH_2OAc), 6.83 (1H, d, J = 9.5 Hz, ArH), 7.05 (1H, d, J = 9.5 Hz, ArH); ν_{max} 3460, 1710, 1665 and 1565 cm^{-1}; M^+ 294.

(S)-cis-3-*Acetoxymethyl*-1,2,3,4,5,12-*hexahydro*-5,12-*dioxonaphthacene*-1,3-*diyl benzeneboronate* (**35c**)

The ketone **19** (19.2 g, 0.065 mol) was dissolved in THF (1.0 l) and $NaBH_4$ (19.2 g, 0.5 mol) added. The mixture was stirred at room temp for 2 hr and then the solvent was evaporated *in vacuo*. The residue was dissolved in a mixture of EtOAc (250 ml) and water (150 ml). The layers were separated and the aqueous layer extracted with further EtOAc (100 ml). The combined extracts were washed with brine (100 ml), dried and evaporated to give a mixture of diols **25** as a colourless gum. This was dissolved in toluene (500 ml) and benzeneboronic acid (8.5 g, 0.071 mol) and toluene-4-sulphonic acid (300 mg) were added and the mixture stirred at room temp for 18 hr. The soln was then washed with 10% $KHCO_3$ aq (2 × 250 ml), dried and evaporated to give **32c** as a colourless gum, δ (60 MHz) 1.80–2.4 (2H, m, 2-H_2), 2.12 (3H, s, OAc), 2.73 (1H, d, J = 18 Hz, 4-ax-H), 3.15 (1H, broad d, J = 18 Hz, 4-eq-H), 3.76 (3H, s, OMe), 3.88 (3H, s, OMe), 4.30 (2H, broad s, CH_2OAc), 5.63 (1H, m, 1-H), 6.70 (2H, s, ArH), 7.15–7.40 (3H, m, ArH), 7.65–7.82 (2H, m, ArH); M^+ 382. The benzeneboronate **32c** was oxidised with ammonium ceric nitrate to **33c** which on reaction with *trans*-1,2-diacetoxy-1,2-dihydrobenzocyclobutene gave **35c** (22.4 g, 76% over 4 steps) as yellow crystals, m.p. 175–176°; $[\alpha]_D^{20}$ + 138.1° (c = 0.1% in $CHCl_3$); δ 2.01 (1H, dd, J = 14 Hz and 2.5 Hz, 2-H), 2.15 (3H, s, OAc), 2.37 (1H, broad d, J = 14 Hz, 2-H), 2.89 (1H, d, J = 21 Hz, 4-ax-H), 3.22 (1H, dd, J = 21 Hz and 1.5 Hz, 4-eq-H), 4.39 (2H, AB_q, J = 10 Hz, CH_2OAc), 5.76 (1H, t, J = 3 Hz, 1-H), 7.22–7.44 (3H, m, ArH), 7.62–7.85 (4H, m, ArH), 7.96–8.16 (2H, m, ArH), 8.64 (1H, s, ArH), 8.72 (1H, s, ArH); ν_{max} 1750, 1630, 1620, 1600 and 1590 cm^{-1}; λ_{max} (dioxan) 240, 285, 296 and 403 nm (ε 20,608, 19,408, 19,210 and 4984); M^+ 452. (Found: C, 71.55; H, 4.7. $C_{27}H_{21}BO_6$ Requires: (C, 71.7; H, 4.7%).

(S)-cis-5,12-*Diacetoxy*-3-*acetoxymethyl*-1,2,3,4-*tetrahydronaphthacene*-1,3-*diyl benzeneboronate* **36c**)

The quinone **35c** (22.35 g, 0.049 mol) was hydrogenated in a mixture of Ac_2O and pyridine to give **36c** (21.3 g 80%) as a pale yellow solid, m.p. 256–258°; $[\alpha]_D^{20}$ + 251.3° (c = 0.1% in dioxan); δ 2.15 (3H, s, OAc), 2.24 (1H, dd, J = 13.5 Hz and 2.5 Hz, 2-H), 2.44 (1H, broad d, J = 13.5 Hz, 2-H), 2.57 (3H, s, OAc), 2.68 (3H, s, OAc), 2.96 (1H, d, J = 19 Hz, 4-ax-H), 3.31 (1H, broad d, J = 19 Hz, 4-eq-H), 4.39 (2H, AB_q, J = 11 Hz, CH_2OAc), 5.68 (1H, t, J = 3 Hz, 1-H), 7.20–7.40 (3H, m, ArH), 7.42–7.60 (2H, m, ArH), 7.64–7.78 (2H, m, ArH), 7.90–8.04 (2H, m, ArH), 8.29 (1H, s, ArH), 8.38 (1H, s, ArH); ν_{max} 1770, 1750, 1730, 1640 and 1600 cm^{-1}; λ_{max} ($CHCl_3$) 264, 352, 371 and 392 nm (ε 190,811, 4969, 7184 and 6048); M^+ 538. (Found: C, 69.25; H, 4.95. $C_{31}H_{27}BO_8$ Requires: C, 69.15; H, 5.05%).

(S)-cis-5,12-*Diacetoxy*-3-*acetoxymethyl*-1,2,3,4,6,11-*hexahydro*-6,11-*dioxonaphthacene*-1,3-*diyl benzeneboronate* (**37c**)

The triacetate **36c** (21 g, 0.039 mol) was oxidised using CrO_3 in a mixture of AcOH and Ac_2O to give **37c** (14.0 g, 63%) as pale yellow crystals, m.p. 204–205°; $[\alpha]_D^{20}$ + 180.3° (c = 0.1% in dioxan); δ 2.12 (1H, dd, J = 14 Hz and 2 Hz, 2-H), 2.16 (3H, s, OAc), 2.39 (1H, broad d, J = 14 Hz, 2-H), 2.56 (3H, s, OAc), 2.65 (3H, s, OAc), 2.88 (1H, d, J = 19 Hz, 4-ax-H), 3.25 (1H, broad d, J = 19 Hz, 4-eq-H), 4.37 (2H, AB_q, J = 11 Hz, CH_2 OAc), 5.56 (1H, broad s, 1-H), 7.16–7.40 (3H, m, ArH), 7.60–

7.82 (4H, m, ArH), 8.11–8.24 (2H, m, ArH); ν_{max} 1765, 1735, 1675 and 1590 cm^{-1}; λ_{max} ($CHCl_3$) 260 and 343 nm (ε 45,902 and 6119); M^+ 568. (Found: C, 65.75; H, 4.35. $C_{31}H_{25}BO_{10}$ Requires: C, 65.5; H, 4.45%).

(S)-cis-3-*Acetoxymethyl*-1,2,3,4,6,11-*hexahydro*-1,3,5,12-*tetrahydroxynaphthacene*-6,11-*quinone* (**39c**)

The quinone **37c** (14.4 g, 0.025 mol) was treated with BCl_3 to give **38c** as a red solid which was subsequently treated with 2-methylpentane-2,4-diol and acetic acid to give **39c** (9.5 g, 94% over 2 steps) as bright orange-red crystals, m.p. 201–203°; $[\alpha]_D^{20}$ + 119.8° (*c* = 0.1% in dioxan); δ 1.93 (1H, dd, J = 14 Hz and 5 Hz, 2-H), 2.20 (3H, s, OAc), 2.43 (1H, dt, J = 14 Hz and 2.5 Hz), 2.66 (1H, d, J = 20 Hz, 4-ax-H), 3.26 (1H, dd, J = 20 Hz and 2.5 Hz, 4-eq-H), 3.65 (1H, d, J = 6 Hz, 1-OH), 3.76 (1H, s, 3-OH), 4.22 (2H, s, CH_2OAc), 5.24–5.41 (1H, m, 1-H), 7.80–7.95 (2H, m, ArH), 8.27–8.44 (2H, m, ArH), 13.34 (1H, s, ArOH), 13.6 (1H, s, ArOH); ν_{max} 3460, 1730, 1625 and 1585 cm^{-1}; λ_{max} 253, 259, 289 and 486 nm (ε 42,259, 39,371, 10,681 and 10,557); M^+ 398. (Found: C, 63.5; H, 4.5. $C_{21}H_{18}O_8$ Requires: C, 63.3; H, 4.55%).

(S)-3′-*Cyanomethyl*-1′,2′,3′,4′-*tetrahydro*-3′-*hydroxy*-5′,8′-*dimethoxyspiro*[1,3-*dithiolane*-2,1′-*naphthalene*] (**15**)

A soln of KCN (10.7 g) in warm water (14.5 ml) was added to a soln of **12** (21.4 g, 0.044 mol) in DMF (285 ml). The mixture was stirred at 90° for 4 hr, and was then poured into water (1.9 l) and extracted with EtOAc (3 × 475 ml). The combined extracts were washed with water (4 × 1.9 l), dried and evaporated. The residue was triturated with ether (100 ml) and filtered to give the nitrile (**15**) (12.55 g, 84%) as a white crystalline solid, m.p. 173–174.5°; $[\alpha]_D^{20}$ − 28.4° (*c* = 0.5% in $CHCl_3$); δ 2.63 (1H, d, J = 18 Hz, 4′-ax-H), 2.64–2.72 (4H, m, 2′-H_2 and CH_2CN), 3.13 (1H, broad d, J = 18 Hz, 4′-eq-H), 3.32–3.74 (5H, m, SCH_2CH_2S and OH), 3.80 (3H, s, OMe), 3.90 (3H, s, OMe), 6.82 (2H, s, ArH); ν_{max} 3440, 2250 and 1580 cm^{-1}; M^+ 337. (Found: C, 57.0; H, 5.7; N, 4.1. $C_{16}H_{19}NO_3S_2$ Requires: C, 56.95; H, 5.7; N, 4.15%).

(S)-3-*Cyanomethyl*-1,2,3,4-*tetrahydro*-3-*hydroxy*-5,8-*dimethoxynaphthalenone* (**20**)

The thioacetal **15** (13.4 g, 0.040 mol) was treated with mercuric oxide and mercuric chloride to give **20** (8.00 g, 77%) as a white crystalline solid, m.p. 160–162°; $[\alpha]_D^{20}$ + 15.0° (*c* = 0.1% in $CHCl_3$); δ [$CDCl_3$—$(CD_3)_2SO$] 2.75 (2H, s, CH_2CN), 2.90 (2H, s, 2-H_2), 3.09 (1H, d, J = 18.5 Hz, 4-H), 3.27 (1H, d, J = 18.5 Hz, 4-H), 3.88 (3H, s, OMe), 3.90 (3H, s, OMe), 6.87 (1H, d, J = 9 Hz, ArH), 7.05 (1H, d, J = 9 Hz, ArH); ν_{max} 3440, 2240, 1655 and 1580 cm^{-1}; M^+ 261. (Found: C, 64.6; H, 5.55; N, 5.2. $C_{14}H_{15}NO_4$ Requires: C, 64.4; H, 5.8; N, 5.4%).

(S)-cis-3-*Cyanomethyl*-1,2,3,4-*tetrahydro*-5,8-*dimethoxynaphthalene*-1,3-*diyl benzeneboronate* (**29**)

The ketone **20** (8.00 g, 0.031 mol) was reduced with $LiBH_4$ and the resulting mixture of diols **26** was treated with benzeneboronic acid and toluene-4-sulphonic acid to give **29** (8.16 g, 76% over 2 steps) as a white crystalline solid, m.p. 124–127°; $[\alpha]_D^{20}$ + 57.3° (*c* = 0.1% in $CHCl_3$); δ 2.14 (1H, dd, J = 14 Hz and 2 Hz, 2-H), 2.34 (1H, dm, J = 14 Hz, 2-H), 2.85 (1H, d, J = 18 Hz, 4-ax-H), 2.89 (2H, s, CH_2CN), 3.27 (1H, dd, J = 18 Hz and 1.5 Hz, 4-eq-H), 3.79 (3H, s, OMe), 3.91 (3H, s, OMe), 5.71 (1H, t, J = 3 Hz, 1-H), 6.77 (2H, s, ArH), 7.20–7.40 (3H, m, ArH), 7.68–7.82 (2H, m, ArH); M^+ 349. (Found: C, 69.1; H, 5.9; N, 4.0. $C_{20}H_{20}BNO_4$ Requires: C, 68.8; H, 5.8; N, 4.0%).

(S)-cis-3-[2-*Acetoxyethyl*]-1,2,3,4-*tetrahydro*-5,8-*dimethoxynaphthalene*-1,3-*diyl benzeneboronate* (**32d**)

Diisobutylaluminium hydride (24.85 ml of a 1.2 M soln in toluene) was added to a stirred soln of **29** (8.70 g, 0.025 mol) in toluene (400 ml) at 0°. The mixture was stirred at 0° for 40 min, and then 2M H_2SO_4 (400 ml) was added to the mixture and the layers were separated. The aqueous soln was extracted with EtOAc (2 × 400 ml) and the combined organic solns were washed with sat $NaHCO_3$ aq (400 ml), dried and evaporated to give **30** as a colourless gum, δ 2.10 (1H, dd, J = 14 Hz and 2 Hz, 2-H), 2.32 (1H, dm, J = 14 Hz, 2-H), 2.79 (1H, d, J = 18 Hz, 4-ax-H), 2.83 (2H, d, J = 2.5 Hz, CH_2CHO), 3.27 (1H, dd, J = 18 Hz and 1.5 Hz, 4-eq-H), 3.76 (3H, s, OMe), 3.88 (3H, s, OMe), 5.66 (1H, t, J = 3 Hz, 1-H), 6.74 (2H, s, ArH), 7.20–7.40 (3H, m, ArH), 7.70–7.84 (2H, m, ArH), 10.14 (1H, t, J = 2.5 Hz, CHO); M^+ 352. The aldehyde was dissolved in THF (240 ml) and $NaBH_4$ (1.17 g) was added. The mixture was stirred at room temp for 1 hr and the solvent was removed *in vacuo*. 2M HCl (215 ml) was added to the residue and the mixture was extracted with CH_2Cl_2 (3 × 200 ml). The combined extracts were washed with water (200 ml), dried and evaporated to give **31** as a colourless gum, δ 1.97 (1H, dd, J = 14 Hz and 1.5 Hz, 2-H), 2.10 (2H, t, J = 6 Hz, CH_2CH_2OH), 2.35 (1H, dm, J = 14 Hz, 2-H), 2.70 (1H, d, J = 19.5 Hz, 4-ax-H), 3.30 (1H, dd, J = 19.5 Hz and 1.5 Hz, 4-eq-H), 3.78 (3H, s, OMe), 3.89 (3H, s, OMe), 3.90–4.25 (2H, m, CH_2CH_2OH), 5.65 (1H, t, J = 3 Hz, 1-H), 6.74 (2H, s, ArH), 7.20–7.40 (3H, m, ArH), 7.64–7.77 (2H, m, ArH); M^+ 354. The alcohol was dissolved in a mixture of pyridine (100 ml) and Ac_2O (13 ml) and the soln was kept at room temp overnight. Ice (370 g) was added and the mixture was acidified with 2M HCl and extracted with CH_2Cl_2 (3 × 450 ml). The combined extracts were washed with 2M HCl (300 ml) and water (450 ml), dried and evaporated. The crude product was purified by chromatography on a column of silica gel (500 g), eluting with EtOAc-hexane (1 : 2, v/v) to give the product (**32d**) (5.99 g, 61% over 3 steps) as a white crystalline solid, m.p. 94–95°; $[\alpha]_D^{20}$ + 52.9° (*c* = 0.1% in $CHCl_3$); δ 1.87–2.40 (4H, m, 2-H_2 and CH_2CH_2OAc), 2.08 (3H, s, OAc), 2.71 (1H, d, J = 18 Hz, 4-ax-H), 3.17 (1H, dd, J = 18 Hz and 1.5 Hz, 4-eq-H), 3.76 (3H, s, OMe), 3.88 (3H, s, OMe), 4.48 (2H, t, J = 7 Hz, CH_2CH_2OAc), 5.62 (1H, t, J = 3 Hz, 1-H), 6.72 (2H, s, ArH), 7.20–7.38 (3H, m, ArH), 7.68–7.81 (2H, m, ArH); ν_{max} 1745 and 1600 cm^{-1}; M^+ 396. (Found: C, 66.7; H, 6.4. $C_{22}H_{25}BO_6$ Requires: C, 66.7; H, 6.4%).

(S)-cis-3-[2-*Acetoxyethyl*]-1,2,3,4,5,12-*hexahydro*-5,12-*dioxonaphthacene*-1,3-*diyl benzeneboronate* (**35d**)

The benzeneboronate **32d** (5.99 g, 0.015 mol) was treated with ammonium ceric nitrate according to our earlier procedure to give **33d** as a brown oil. This was reacted with **34** to give **35d** (5.19 g, 74% over 2 steps) as a yellow solid, m.p. 150–153°; $[\alpha]_D^{20}$ + 135° (*c* = 0.1% in $CHCl_3$); δ 1.88–2.60 (4H, m, 2-H_2 and CH_2CH_2OAc), 2.12 (3H, s, OAc), 2.80 (1H, d, J = 20 Hz, 4-ax-H), 3.26 (1H, dd, J = 20 Hz and 1 Hz, 4-eq-H), 4.50 (2H, dt, J = 2 Hz and 6.5 Hz, CH_2CH_2OAc), 5.70 (1H, t, J = 3 Hz, 1-H), 7.20–7.40 (3H, m, ArH), 7.60–7.84 (4H, m, ArH), 7.96–8.17 (2H, m, ArH), 8.61 (1H, s, ArH), 8.70 (1H, s, ArH); ν_{max} 1740, 1660, 1615 and 1590 cm^{-1}; λ_{max} (MeOH) 242, 276, 287, 300 and 416 nm (ε 37,808, 18,510, 19,357, 20,617 and 5514); M^+ 466. (Found: C, 72.0; H, 4.9. $C_{28}H_{23}BO_6$ Requires: C, 72.1; H, 5.0%).

(S)-cis-5,12-*Diacetoxy*-3-[2-*acetoxyethyl*]-1,2,3,4-*tetrahydronaphthacene*-1,3-*diyl benzeneboronate* (**36d**)

Reductive acetylation of **35d** (5.19 g, 0.011 mol) gave **36d** (4.09 g, 67%) as a light brown solid, m.p. 198–200°; $[\alpha]_D^{20}$ + 224° (*c* = 0.1% in $CHCl_3$); δ 1.92–2.40 (4H, m, 2-H_2 and CH_2CH_2OAc), 2.10 (3H, s, OAc), 2.55 (3H, s, OAc), 2.66 (3H, s, OAc), 2.90 (1H), d, J = 18 Hz, 4-ax-H), 3.36 (1H, broad d, J = 18 Hz, 4-eq-H), 4.50 (2H, t, J = 6.5 Hz, CH_2CH_2OAc), 5.62 (1H, t, J = 3 Hz, 1-H), 7.20–7.36 (3H, m, ArH), 7.39–7.55 (2H, m, ArH), 7.63–7.77 (2H, m, ArH), 7.86–8.05 (2H, m, ArH), 8.26 (1H, s, ArH), 8.36 (1H, s, ArH); ν_{max} 1770, 1760, 1740, 1640 and 1600 cm^{-1}; λ_{max} ($CHCl_3$) 262, 320, 336, 352, 371 and 391 nm (ε 146,816, 1436, 2418, 4396, 6154 and 5348); M^+ 552.

(S)-cis-5,12-*Diacetoxy*-3-[2-*acetoxyethyl*]-1,2,3,4,6,11-*hexahydro*-6,11-*dioxonaphthacene*-1,3-*diyl benzeneboronate* (**37d**)

Oxidation of **36d** (4.09 g, 7.3 mmol) gave **37d** (2.27 g, 53%) as a pale yellow solid, m.p. 162–165°; δ 1.92–2.41 (4H, m, 2-H_2 and CH_2CH_2OAc), 2.10 (3H, s, OAc), 2.52 (3H, s, OAc), 2.64 (3H, s, OAc), 2.83 (1H, d, J = 19 Hz, 4-ax-H), 3.29 (1H, broad d,

J = 19 Hz, 4-eq-H), 4.48 (2H, t, J = 6.5 Hz, CH_2CH_2OAc), 5.51 (1H, broad s, 1-H), 7.20–7.40 (3H, m, ArH), 7.56–7.83 (4H, m, ArH), 8.06–8.23 (2H, m, ArH); ν_{max} 1780, 1740, 1680 and 1590 cm^{-1}; M^+ 582.

(S)-cis-3-[2-*Acetoxyethyl*]-1,2,3,4,6,11-*hexahydro*-1,3,5,12-*tetrahydroxynaphthacene*-6,11-*quinone* (**39d**)

Treatment of **37d** (2.27 g, 3.9 mmol) with BCl_3 gave **38d** as a red amorphous solid, δ 1.96–2.54 (4H, m, 2-H_2 and CH_2CH_2OAc), 2.11 (3H, s, OAc), 2.89 (1H, d, J = 19.5 Hz, 4-ax-H), 3.39 (1H, dd, J = 19.5 Hz and 1.5 Hz, 4-eq-H), 4.52 (2H, dt, J = 2 Hz and 7 Hz, CH_2CH_2OAc), 5.77 (1H, t, J = 2.5 Hz, 1-H), 7.20–7.46 (3H, m, ArH), 7.65–7.93 (4H, m, ArH), 8.24–8.44 (2H, m, ArH), 13.26 (1H, s, ArOH), 13.32 (1H, s, ArOH); ν_{max} 1740, 1620 and 1590 cm^{-1}; M+ 498. The benzeneboronate (**38d**) was treated with 2-methyl-2,4-pentanediol to give **39d** (1.50 g, 93% over 2 steps) as a bright red solid, m.p. 120–125°; $[\alpha]_D^{20}$ +110° (*c* = 0.1% in dioxan); δ 1.78–2.16 (3H, m, 2-H and CH_2CH_2OAc), 2.10 (3H, s, OAc), 2.45 (1H, broad d, J = 14 Hz, 2-H), 2.62 (1H, d, J = 18.5 Hz, 4-ax-H), 3.30 (1H, dd, J = 18.5 Hz and 2 Hz, 4-eq-H), 4.45 (2H, t, J = 6.5 Hz, CH_2CH_2OAc), 5.28 (1H, broad s, 1-H), 7.76–7.94 (2H, m, ArH), 8.28–8.45 (2H, m, ArH), 13.32 (1H, s, ArOH), 13.60 (1H, s, ArOH); ν_{max} 3500–2100, 1740, 1700, 1620 and 1590 cm^{-1}; λ_{max} ($CHCl_3$) 250, 286, 330 sh, 460 sh, 483 and 520 nm (*ε* 38,188, 10,799, 2655, 9087, 10,114 and 6037); M^+ 412. (Found: C, 64.15; H, 5.1. $C_{22}H_{20}O_8$ Requires: C, 64.1; H, 4.9%).

(S)-cis-3-[1(R)-*Acetoxyethyl*]-1,2,3,4-*tetrahydro*-5,8-*dimethoxynaphthalene*-1,3-*diyl benzeneboronate* (**32e**) *and* (S)-cis-3-[1(S)-*acetoxyethyl*]-1,2,3,4-*tetrahydro*-5,8-*dimethoxynaphthalene*-1,3-*diyl benzeneboronate* (**32f**)

A soln of **6** (15.55 g, 46 mmol) in THF (390 ml) was cooled to −78° and a soln of LAH (1.74 g, 47 mmol) in anhyd ether (110 ml) was added. The mixture was stirred at −78° for 15 min, and then further LAH (0.87 g, 23.5 mmol) in ether (50 ml) was added. After stirring for a further 30 min at −78° the reaction was quenched by the careful addition of 2M HCl (390 ml). The mixture was poured into water (1100 ml) and extracted with CH_2Cl_2 (3 × 700 ml). The combined extracts were washed with water (450 ml), dried and evaporated to give a mixture of the diols **7** in the ratio 80:20 as a colourless gum, δ 1.26 and 1.27 (total 3H, doublets, J = 6.5 Hz, $CHCH_3$), 2.30–3.15 (4H, m, 2'-H_2 and 4'-H_2), 3.30–3.90 (5H, m, $CHCH_3$ and SCH_2CH_2S), 3.78 (3H, s, OMe), 3.88 (3H, s, OMe), 6.79 (2H, s, ArH). The diols were dissolved in a mixture of pyridine (155 ml) and Ac_2O (23 ml) and allowed to stand at room temp for 18 hr. Ice (310 g) was added, followed by 6M HCl (300 ml) and the mixture was extracted with CH_2Cl_2 (3 × 300 ml). The combined extracts were washed with 2M HCl (300 ml) and water (300 ml), dried and evaporated to give a mixture of acetates **16** as a colourless gum (17.50 g), δ 1.35 (3H, d, J = 6 Hz, $CHCH_3$), 2.08 and 2.10 (total 3H, singlets, OAc), 2.3–3.2 (4H, m, 2'-H_2 and 4'-H_2), 3.3–3.7 (4H, m, SCH_2CH_2S), 3.78 (3H, s, OMe), 3.88 (3H, s, OMe), 4.86 and 4.89 (total 1H, quartets, J = 6 Hz, $CHCH_3$), 6.78 (2H, s, ArH); M^+ 384. The acetates were treated with mercuric oxide and mercuric chloride to give a mixture of diastereoisomeric ketones **21** as a pale green oil (13.0 g), δ 1.32 and 1.33 (total 3H, doublets, J = 6 Hz, $CHCH_3$), 2.10 (3H, s, OAc), 2.74 (2H, s, 2-H_2), 2.93 (1H, d, J = 17 Hz, 4-ax-H), 3.18 (1H, broad d, J = 17 Hz, 4-eq-H), 3.82 (3H, s, OMe), 3.86 (3H, s, OMe), 4.93 (1H, q, J = 6 Hz, $CHCH_3$), 6.82 (1H, d, J = 9 Hz, ArH), 7.03 (1H, d, J = 9 Hz, ArH). The ketones **21** were reduced with $NaBH_4$ and the resulting diols **27** were treated with benzeneboronic acid and toluene-4-sulphonic acid to give a mixture of diastereoisomeric benzeneboronates (**32e** and **32f**) as a sticky white solid (14.50 g). This was triturated with ether (150 ml), cooled to 0° and filtered to give **32e** (5.87 g). The mother liquor was concentrated and cooled to give second and third crops (1.35 g and 0.65 g) giving **32e** in a total yield of 7.87 g, (43.5% over 5 steps) as a white crystalline solid, m.p. 177.5–180°; $[\alpha]_D^{20}$ +65.5° (*c* = 0.1% in $CHCl_3$) δ 1.48 (3H, d, J = 6 Hz, $CHCH_3$), 2.02–2.16 (2H, m, 2-H_2), 2.06 (3H, s, OAc), 2.84 (1H, d, J = 18.5 Hz, 4-ax-H), 3.12 (1H, broad d, J = 18.5 Hz, 4-eq-H), 3.78 (3H, s, OMe), 3.89 (3H, s, OMe), 5.14 (1H, q, J = 6 Hz, $CHCH_3$), 5.66 (1H, t, J = 3 Hz, 1-H), 6.75 (2H, s, ArH), 7.18–7.40 (3H, m, ArH), 7.69–7.81 (2H, m, ArH); ν_{max} 1740 and 1605 cm^{-1}; M^+ 396. (Found: C, 66.5; H, 6.5. $C_{22}H_{25}BO_6$ Requires: C, 66.7; H, 6.4%).

The mother liquor was concentrated and cooled to give a further crop of crystals (0.70 g) which was shown by NMR spectroscopy and by HPLC to consist mainly of the minor diastereoisomer **32f**. This was recrystallised from ether (10 ml) to give **32f** (250 mg, 1.4%) as a white crystalline solid, m.p. 147–147.5°; $[\alpha]_D^{20}$ + 18.6° (*c* = 0.1% in $CHCl_3$); δ 1.46 (3H, d, J = 6 Hz, $CHCH_3$), 1.91 (1H, dd, J = 13 Hz and 2.5 Hz, 2-H), 2.10 (3H, s, OAc), 2.29 (1H, dm, J = 13 Hz, 2-H), 2.76 (1H, d, J = 18.5 Hz, 4-ax-H), 3.08 (1H, dd, J = 18.5 Hz and 1.5 Hz, 4-eq-H), 3.78 (3H, s, OMe), 3.90 (3H, s, OMe), 5.16 (1H, q, J = 6 Hz, $CHCH_3$), 5.67 (1H, t, J = 3 Hz, 1-H), 6.75 (2H, s, ArH), 7.19–7.40 (3H, m, ArH), 7.70–7.83 (2H, m, ArH); ν_{max} 1735 and 1600 cm^{-1}; M^+ 396. (Found: C, 66.9; H, 6.4%).

Reduction of **6** with the chiral reducing agent derived from reaction of LAH with (+)-N-methylephedrine (1 equiv) and N-methylaniline (2 equiv) gave a mixture of diols **7** in the ratio 40:60. A similar sequence of reactions to that described above then gave **32f** as the major product.

(S)-cis-3-[1(R)-*Acetoxyethyl*]-1,2,3,4,5,12-*hexahydro*-5,12-*dioxonaphthacene*-1,3-*diyl benzeneboronate* (**35e**)

Treatment of **32e** (4.32 g, 0.011 mol) with ammonium ceric nitrate gave **33e** as a yellow oil. This was treated with 1,2-diacetoxy-1,2-dihydrobenzocyclobutene to give **35e** (3.60 g, 71%) as a yellow solid, m.p. 175–184°; $[\alpha]_D^{20}$ + 147.5° (*c* = 0.1% in $CHCl_3$) δ 1.53 (3H, d, J = 6 Hz, $CHCH_3$), 1.91–2.36 (2H, m, 2-H_2), 2.10 (3H, s, OAc), 2.94 (1H, d, J = 20 Hz, 4-ax-H), 3.18 (1H, broad d, J = 20 Hz, 4-eq-H), 5.18 (1H, q, J = 6 Hz, $CHCH_3$), 5.72 (1H, t, J = 3 Hz, 1-H), 7.22–7.42 (3H, m, ArH), 7.59–7.84 (4H, m, ArH), 7.96–8.14 (2H, m, ArH), 8.61 (1H, s, ArH), 8.69 (1H, s, ArH); ν_{max} 1745, 1670 and 1620 cm^{-1}; λ_{max} ($CHCl_3$) 240, 277, 287, 299 and 416 nm (*ε* 36,236, 18,322, 18,994, 19,830 and 5564); M^+ 466. (Found: C, 71.8; H, 5.0. $C_{28}H_{23}BO_6$ Requires: C, 72.1; H, 5.0%).

(S)-cis-5,12-*Diacetoxy*-3-[1(R)-*acetoxyethyl*]-1,2,3,4-*tetrahydronaphthacene*-1,3-*diyl benzeneboronate* (**36e**)

Reductive acetylation of **35e** (3.60 g, 7.7 mmol) gave **36e** (3.71 g, 87%) as a pale brown solid, m.p. 256–259°; δ 1.49 (3H, d, J = 6 Hz, $CHCH_3$), 1.90–2.30 (2H, m, 2-H_2), 2.08 (3H, s, OAc), 2.58 (3H, s, OAc), 2.67 (3H, s, OAc), 3.00 (1H, d, J = 18 Hz, 4-ax-H), 3.26 (1H, broad d, J = 18 Hz, 4-eq-H), 5.22 (1H, q, J = 6 Hz, $CHCH_3$), 5.64 (1H, t, J = 3 Hz, 1-H), 7.22–7.38 (3H, m, ArH), 7.41–7.57 (2H, m, ArH), 7.62–7.77 (2H, m, ArH), 7.89–8.06 (2H, m, ArH), 8.28 (1H, s, ArH), 8.36 (1H, s, ArH); ν_{max} 1770, 1730, 1635 and 1600 cm^{-1}; M^+ 552.

(S)-cis-5,12-*Diacetoxy*-3-[1(R)-*acetoxyethyl*]-1,2,3,4,6,11-*hexahydro*-6,11-*dioxonaphthacene*-1,3-*diyl benzeneboronate* (**37e**)

The triacetate **36e** (7.05 g, 12.8 mmol) was oxidised with CrO_3 to give **37e** (4.34 g, 58%) as a pale yellow solid, m.p. 221–221.5°; δ 1.51 (3H, d, J = 6 Hz, $CHCH_3$), 2.02–2.27 (2H, m, 2-H_2), 2.10 (3H, s, OAc), 2.54 (3H, s, OAc), 2.65 (3H, s, OAc), 2.94 (1H, d, J = 18.5 Hz, 4-ax-H), 3.22 (1H, broad d, J = 18.5 Hz, 4-eq-H), 5.20 (1H, q, J = 6 Hz, $CHCH_3$), 5.55 (1H, broad s, 1-H), 7.19–7.41 (3H, m, ArH), 7.56–7.84 (4H, m, ArH), 8.08–8.25 (2H, m, ArH); ν_{max} 1780, 1735, 1680 and 1590 cm^{-1}; M^+ 582.

(S)-cis-3-[1(R)-*Acetoxyethyl*]-1,2,3,4,6,11-*hexahydro*-1,3,5,12-*tetrahydroxynaphthacene*-6,11-*quinone* (**39e**)

Treatment of **37e** (2.465 g, 4.2 mmol) with BCl_3 gave **38e** as a red gum, δ 1.54 (3H, d, J = 6 Hz, $CHCH_3$), 1.99–2.42 (2H, m, 2-H_2), 2.12 (3H, s, OAc), 3.02 (1H, d, J = 19.5 Hz, 4-ax-H), 3.32 (1H, broad d, J = 19.5 Hz, 4-eq-H), 5.22 (1H, q, J = 6 Hz, $CHCH_3$), 5.78 (1H, t, J = 3 Hz, 1-H), 7.18–7.41 (3H, m, ArH), 7.64–7.91 (4H, m, ArH), 8.22–8.39 (2H, m, ArH), 13.26 (1H, s, ArOH),

13.48 (1H, s, ArOH); M^+ 498. The benzeneboronate **38e** was treated with 2-methyl-2,4-pentanediol to give **39e** (1.70 g, 97% over 2 steps) as a bright red solid, m.p. 199–202°; $[\alpha]_D^{20}$ + 172° (c = 0.1% in dioxan); δ (300 MHz) 1.40 (3H, d, J = 6 Hz, CH C$\underline{H}_3$), 1.88 (1H, dd, J = 5 Hz and 15 Hz, 2-H), 2.14 (3H, s, OAc), 2.30 (1H, d, J = 15 Hz, 2-H), 2.59 (1H, d, J = 18 Hz, 4-$\underline{ax}$-H), 3.21 (1H, dd, J = 18 Hz and 1 Hz, 4-$\underline{eq}$-H), 3.71 (2H, broad s, 1-OH and 3-OH), 4.99 (1H, q, J = 6 Hz, C$\underline{H}$CH$_3$), 5.24 (1H, m, 1-H), 7.80–7.85 (2H, m, ArH), 8.24–8.29 (2H, m, ArH), 13.23 (1H, s, ArOH), 13.45 (1H, s, ArOH); ν_{max} 3460, 1740, 1720, 1625 and 1590 cm^{-1}; λ_{max} ($CHCl_3$) 251, 287, 330 sh, 460 sh, 483 and 518 sh nm (ε 39,878, 10,418, 2719, 9495, 10,461 and 6387); M^+ 412. (Found: C, 64.3; H, 5.2. $C_{22}H_{20}O_8$ Requires: C, 64.1; H, 4.9%).

(S)-cis-3-[1(S)-*Acetoxyethyl*]-1,2,3,4,5,12-*hexahydro*-5,12-*dioxonaphthacene*-1,3-*diyl benzeneboronate* (**35f**)

Treatment of **32f** (4.00 g, 0.010 mol) with ammonium ceric nitrate, and reaction of the resulting quinone **33f** with 1,2-diacetoxy-1,2-dihydrobenzocyclobutene gave **35f** (3.236 g, 69% over 2 steps) as a bright yellow solid, m.p. 172–174°; $[\alpha]_D^{20}$ + 98.7° (c = 0.05% in $CHCl_3$); δ 1.48 (3H, d, J = 6 Hz, CHC$\underline{H}_3$), 1.8–2.5 (2H, m, 2-H$_2$), 2.14 (3H, s, OAc), 2.86 (1H, d, J = 20 Hz, 4-$\underline{ax}$-H), 3.18 (1H, broad d, J = 20 Hz, 4-$\underline{eq}$-H), 5.22 (1H, q, J = 6 Hz, C$\underline{H}$CH$_3$), 5.74 (1H, t, J = 3 Hz, 1-H), 7.25–7.50 (3H, m, ArH), 7.62–7.88 (4H, m, ArH), 8.00–8.16 (2H, m, ArH), 8.64 (1H, s, ArH), 8.72 (1H, s, ArH); ν_{max} 1730, 1670 and 1620 cm^{-1}; λ_{max} ($CHCl_3$) 239, 276, 286, 300 and 417 nm (ε 32,345, 13,879, 14,118, 14,787 and 4180); M^+ 466. (Found: C, 72.1; H, 5.0. $C_{28}H_{23}BO_6$ Requires: C, 72.1; H, 5.0%).

(S)-cis-5,12-*Diacetoxy*-3-[1(S)-*acetoxyethyl*]-1,2,3,4-*tetrahydronaphthacene*-1,3-*diyl benzeneboronate* (**36f**)

Reductive acetylation of **35f** (3.236 g, 6.9 mmol) gave **36f** (3.140 g, 82%) as a pale yellow solid, m.p. 238–240°; $[\alpha]_D^{20}$ + 208° (c = 0.05% in $CHCl_3$); δ 1.46 (3H, d, J = 6 Hz, CHC$\underline{H}_3$), 1.90–2.40 (2H, m, 2-H$_2$), 2.13 (3H, s, OAc), 2.56 (3H, s, OAc), 2.67 (3H, s, OAc), 2.92 (1H, d, J = 18 Hz, 4-$\underline{ax}$-H), 3.24 (1H, dd, J = 18 Hz and 1 Hz, 4-$\underline{eq}$-H), 5.24 (1H, q, J = 6 Hz, C$\underline{H}$CH$_3$), 5.66 (1H, t, J = 3 Hz, 1-H), 7.20–7.38 (3H, m, ArH), 7.42–7.58 (2H, m, ArH), 7.64–7.78 (2H, m, ArH), 7.90–8.06 (2H, m, ArH), 8.28 (1H, s, ArH), 8.37 (1H, s, ArH); M^+ 552.

(S)-cis-5,12-*Diacetoxy*-3-[1(S)-*acetoxyethyl*]-1,2,3,4,6,11-*hexahydro*-6,11-*dioxonaphthacene*-1,3-*diyl benzeneboronate* (**37f**)

Oxidation of **36f** (3.132 g, 5.7 mmol) gave **37f** (2.332 g, 71%) as a pale yellow solid, m.p. 178–180°; $[\alpha]_D^{20}$ + 147° (c = 0.05% in $CHCl_3$); δ 1.46 (3H, d, J = 6 Hz, CHC$\underline{H}_3$), 1.95–2.4 (2H, m, 2-H$_2$), 2.16 (3H, s, OAc), 2.54 (3H, s, OAc), 2.64 (3H, s, OAc), 2.86 (1H, d, J = 18 Hz, 4-$\underline{ax}$-H), 3.18 (1H, broad d, J = 18 Hz, 4-$\underline{eq}$-H), 5.23 (1H, q, J = 6 Hz, C$\underline{H}$CH$_3$), 5.56 (1H, broad s, 1-H), 7.20–7.42 (3H, m, ArH), 7.64–7.84 (4H, m, ArH), 8.10–8.25 (2H, m, ArH); M^+ 582. (Found: C, 66.25; H, 4.7. $C_{32}H_{27}BO_{10}$ Requires: C, 66.0; H, 4.7%).

(S)-cis-3-[1(S)-*Acetoxyethyl*]-1,2,3,4,6,11-*hexahydro*-1,3,5,12-*tetrahydroxynaphthacene*-6,11-*quinone* (**39f**)

The quinone **37f** (2.528 g, 4.3 mmol) was treated with BCl_3 to give **38f** as a red powder, δ 1.50 (3H, d, J = 6 Hz, CHC$\underline{H}_3$), 2.00 (1H, dd, J = 14 Hz and 2 Hz, 2-H), 2.16 (3H, s, OAc), 2.42 (1H, broad d, J = 14 Hz, 2-H), 2.92 (1H, d, J = 19.5 Hz, 4-$\underline{ax}$-H), 3.29 (1H, dd, J = 19.5 Hz and 1 Hz, 4-$\underline{eq}$-H), 5.25 (1H, q, J = 6 Hz, C$\underline{H}$CH$_3$), 5.80 (1H, t, J = 3 Hz, 1-H), 7.20–7.48 (3H, m, ArH), 7.70–7.93 (4H, m, ArH), 8.24–8.44 (2H, m, ArH), 13.28 (1H, s, ArOH), 13.50 (1H, s, ArOH); M^+ 498. Compound **38f** was treated with 2-methyl-2,4-pentanediol to give **39f** (1.709 g, 95% over 2 steps) as a bright red solid, m.p. 199–202°; $[\alpha]_D^{20}$ + 77.4° (c = 0.05% in dioxan); δ 1.41 (3H, d, J = 6 Hz, CHC$\underline{H}_3$), 1.86 (1H, dd, J = 14 Hz and 4 Hz, 2-H), 2.16 (3H, s, OAc), 2.43 (1H, dm, J = 14 Hz, 2-H), 2.60 (1H, d, J = 18.5 Hz, 4-$\underline{ax}$-H), 3.20 (1H, dd, J = 18.5 Hz and 2 Hz, 4-$\underline{eq}$-H), 3.57 (2H, m, 1-OH and 3-OH), 5.00 (1H, q, J = 6 Hz, C$\underline{H}$CH$_3$), 5.30 (1H, m, 1-H), 7.80–7.94 (2H, m, ArH), 8.28–8.43 (2H, m, ArH), 13.36 (1H, s, ArOH), 13.59 (1H, s, ArOH); λ_{max} (dioxan) 251, 286, 330 sh, 460 sh, 482 and 516 sh nm (ε 40,832, 9311, 2617, 9526, 10,514 and 6542); M^+ 412. (Found: C, 63.9; H, 4.8. $C_{22}H_{20}O_8$ Requires: C, 64.1; H, 4.9%).

(S)-cis-1,2,3,4-*Tetrahydro*-5,8-*dimethoxy*-3-*methoxycarbonylnaphthalene*-1,3-*diyl benzeneboronate* (**32g**)

The ester **10** (20 g, 0.056 mol) was treated with mercuric oxide and mercuric chloride to give **22** (12.7 g) as a pale cream solid. The ketone **22** (12.7 g, 0.045 mol) was stirred in a mixture of MeOH (120 ml) and water (2.4 ml) cooled to 15°. A pH meter electrode was inserted into the liquid and sodium cyanoborohydride (3.0 g) added. A soln prepared by diluting conc HCl (5 ml) with MeOH (50 ml) was added dropwise to the mixture at such a rate that a meter reading of between 0.9 and 1.2 pH units was maintained. The temp of the mixture was kept at 15° by external cooling. Further additions of sodium cyanoborohydride (1.2 g, 1.2 g and 0.6 g) were made after 1.25 hr, 2.5 hr and 4.0 hr respectively. After a total of 4.5 hr the soln was adjusted to pH 7 by addition of 15% $KHCO_3$ aq (4 ml). The solvent was removed *in vacuo* and the residue partitioned between brine (75 ml) and EtOAc (75 ml). The aqueous layer was extracted further with EtOAc (3 × 60 ml) and the combined EtOAc extracts dried and evaporated to give a colourless solid. This was dissolved in EtOAc (350 ml) containing AcOH (0.2 ml) and benzeneboronic acid (7.8 g). The mixture was heated under reflux for 1 hr and then the solvent was evaporated *in vacuo* to give a colourless gum that was purified by column chromatography on silica gel using EtOAc-hexane (1 : 1) as the eluant. Compound **32g** (13.1 g, 63% over 3 steps) was obtained as white crystals, m.p. 123–125°; $[\alpha]_D^{20}$ + 46.2° (c = 0.5% in $CHCl_3$); δ (60 MHz), 2.13–2.70 (2H, m, 2-H$_2$), 3.03 (1H, d, J = 19 Hz, 4-$\underline{ax}$-H), 3.42 (1H, broad d, J = 19 Hz, 4-$\underline{eq}$-H), 3.72 (3H, s, OMe), 3.82 (6H, s, 2 OMe), 5.63 (1H, t, J = 3 Hz, 1-H), 6.70 (2H, s, ArH), 7.12–7.40 (3H, m, ArH), 7.66–7.90 (2H, m, ArH); ν_{max} 1730 and 1600 cm^{-1}; M^+ 368. (Found: C, 65.15; H, 5.85. $C_{20}H_{21}BO_6$ Requires: C, 65.25; H, 5.75%).

(S)-cis-1,2,3,4,5,12-*Hexahydro*-3-*methoxycarbonyl*-5,12-*dioxonaphthacene*-1,3-*diyl benzeneboronate* (**35g**)

The benzeneboronate **32g** (13.2 g, 0.036 mol) was oxidised with ammonium ceric nitrate to the quinone (**33g**) which on reaction with *trans*-1,2-diacetoxy-1,2-dihydrobenzocyclobutene gave **35g** (12.5 g, 80% over 2 steps) as yellow crystals, m.p. 237–238°; $[\alpha]_D^{20}$ + 106.7° (c = 0.5% in dioxan); δ 2.28 (1H, dd, J = 14 Hz and 2.5 Hz, 2-H), 2.58 (1H, dm, J = 14 Hz, 2-H), 3.2 (1H, d, J = 21 Hz, 4-$\underline{ax}$-H), 3.46 (1H, d, J = 21 Hz, 4-$\underline{eq}$-H), 3.92 (3H, s, OMe), 5.73 (1H, t, J = 2.5 Hz, 1-H), 7.18–7.5 (3H, m, ArH), 7.56–7.88 (4H, m, ArH), 7.92–8.12 (2H, m, ArH), 8.6 (1H, s, ArH), 8.68 (1H, s, ArH); λ_{max} (dioxan) 285, 296 and 402 nm (ε 19,606, 19,567 and 5228); M^+ 438. (Found: C, 71.3; H, 4.35. $C_{26}H_{19}BO_6$ Requires: C, 71.25; H, 4.35%).

(S)-cis-5,12-*Diacetoxy*-1,2,3,4-*tetrahydro*-3-*methoxycarbonylnaphthacene*-1,3-*diyl benzeneboronate* (**36g**)

A soln of **35g** (12.0 g, 0.027 mol) in pyridine and Ac_2O was hydrogenated to give **36g** (11.6 g, 80%) as pale yellow crystals, m.p. 283–285°; $[\alpha]_D^{20}$ + 238.6° (c = 0.1% in dioxan); δ 2.34–2.80 (2H, m, 2-H$_2$), 2.54 (3H, s, OAc), 2.68 (3H, s, OAc), 3.30 (1H, d, J = 18 Hz, 4-$\underline{ax}$-H), 3.56 (1H, broad d, J = 18 Hz, 4-$\underline{eq}$-H), 5.68 (1H, t, J = 3 Hz, 1-H), 7.16–7.40 (3H, m, ArH), 7.42–7.58 (2H, m, ArH), 7.68–7.82 (2H, m, ArH), 7.88–8.08 (2H, m, ArH), 8.24 (1H, s, ArH), 8.37 (1H, s, ArH); λ_{max} (dioxan) 261, 335, 351, 370 and 391 nm (ε 177,959, 3661, 6467, 8368 and 7322); M^+ 524. (Found: C, 68.55; H, 4.8. $C_{30}H_{25}BO_8$ Requires: C, 68.7; H, 4.8%).

(S)-cis-5,12-*Diacetoxy*-1,2,3,4,6,11-*hexahydro*-3-*methoxycarbonyl*-6,11-*dioxonaphthacene*-1,3-*diyl benzeneboronate* (**37g**)

Oxidation of **36g** (12 g, 0.013 mol) with CrO_3 gave **37g** (7.3 g, 57.5%) as pale yellow crystals, m.p. 176–178°; $[\alpha]_D^{20}$ + 175.6° (c = 0.1% in dioxan); δ 2.25–2.72 (2H, m, 2-H$_2$), 2.52 (3H, s, OAc),

2.63 (3H, s, OAc), 3.23 (1H, d, J = 18 Hz, 4-ax-H), 3.49 (1H, broad d, J = 18 Hz, 4-eq-H), 3.92 (3H, s, OMe), 5.56 (1H, broad s, 1-H), 7.16–7.41 (3H, m, ArH), 7.62–7.84 (4H, m, ArH), 8.06–8.24 (2H, m, ArH); λ_{max} (dioxan) 257 and 339 nm (ε 44,105 and 5879); M^+ 554. (Found: C, 65.0; H, 4.2. $C_{30}H_{23}BO_{10}$ Requires: C, 65.0; H, 4.2%).

(S)-cis-1,2,3,4,6,11-*Hexahydro*-5,12-*dihydroxy*-3-*methoxycarbonyl*-6,11-*dioxonaphthacene*-1,3-*diyl benzeneboronate* (**38g**)

Treatment of **37g** (5.2 g, 0.0094 mol) with BCl_3 gave **38g** (3.48 g, 79%) as a bright orange-red solid, m.p. 238–239°; $[\alpha]_D^{20}$ + 312.1° (c = 0.1% in dioxan); δ 2.35 (1H, dd, J = 14 Hz and 2.5 Hz, 2-H), 2.65 (1H, dm, J = 14 Hz, 2-H), 3.31 (1H, d, J = 19.5 Hz, 4-ax-H), 3.60) 1H, dd, J = 19.5 Hz and 1 Hz, 4-eq-H), 3.95 (3H, s, OMe), 5.82 (1H, t, J = 3 Hz, 1-H), 7.20–7.43 (3H, m, ArH), 7.72–7.96 (4H, m, ArH), 8.24–8.44 (2H, m, ArH), 13.24 (1H, s, ArOH), 13.51 (1H, s, ArOH); λ_{max} 250, 286 and 481 nm (ε 39,701, 8960 and 9686); M^+ 470. (Found: C, 66.2; H, 4.3. $C_{26}H_{19}BO_8$ Requires: C, 66.4; H, 4.05%).

(S)-cis-1,2,3,4,6,11-*Hexahydro*-1,3,5,12-*tetrahydroxy*-3-*methoxycarbonylnaphthacene*-6,11-*quinone* (**39g**)

The benzeneboronate **38g** (1.0 g, 0.002 mol) was treated with 2-methylpentane-2,4-diol and AcOH to give **39g** (0.7 g, 85%) as a bright orange-red solid, m.p. 164–166°; $[\alpha]_D^{20}$ + 146.3° (c = 0.1% in dioxan); δ (300 MHz) 2.33 (1H, dd, J = 14 Hz and 5 Hz, 2-H), 2.52 (1H, dt, J = 14 Hz and 2 Hz, 2-H), 3.02 (1H, d, J = 19 Hz, 4-ax-H), 3.33 (1H, dd, J = 19 Hz and 2.5 Hz, 4-eq-H), 3.92 (3H, s, OMe), 4.03 (2H, broad s, 1-OH and 3-OH), 5.24 (1H, broad s, 1-H), 7.80–7.88 (2H, m, ArH), 8.30–8.37 (2H, m, ArH), 13.28 (1H, s, ArOH), 13.55 (1H, s, ArOH); ν_{max} 3380, 1745, 1740, 1730, 1625 and 1580 cm^{-1}; λ_{max} 251, 288 and 485 nm (ε 39,144, 10,107 and 10,261); M^+ 384. (Found: C, 62.55; H, 4.15. $C_{20}H_{16}O_8$ Requires: C, 62.5; H, 4.2%).

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