Anthracyclines. Part 2. Investigations relating to the Synthesis of 4-Demethoxyanthracyclinones

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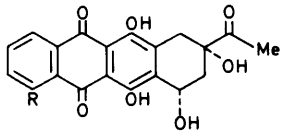
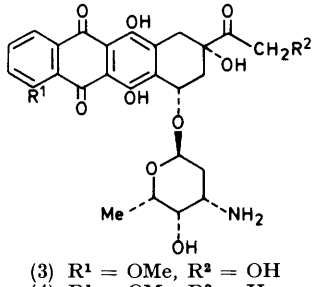
Three strategies for the synthesis of suitably substituted tetrahydronaphthacenequinones related to the 4-demethoxyanthracyclinone series have been investigated. The first, involving conventional Friedel–Crafts annelation required 7-substitution processes at a late stage and proved unsuitable for larger scale preparations. The second and third procedures utilised cyclisation on appropriately substituted, preformed A,B-bicyclic systems; they employed a benzeneboronic acid–phthalaldehyde condensation and a Diels–Alder reaction, respectively. The latter process used *trans*-1,2-diacetoxy-1,2-dihydrobenzocyclobutene to give the appropriate diene *in situ*. A practicable synthesis of (±)-4-demethoxydaunomycinone has been achieved by this route.

THE preceding paper [1] described exploratory studies on several regiochemically controlled syntheses of tetrahydronaphthacenequinones culminating in an efficient procedure for the preparation of (±)-daunomycinone (1), a key intermediate for the preparation of the clinically important antitumour agents adriamycin (3), daunomycin (4), and carminomycin (5).[2] When it was shown that synthetic 4-demethoxyanthracyclines such as (6) and (7) were more potent [3] and less cardiotoxic [4] than the related, substituted natural products, we undertook the development of a synthesis of the 4-demethoxy-series that could be applied to large-scale preparation and to the investigation of analogues for the study of structure–activity relationships.



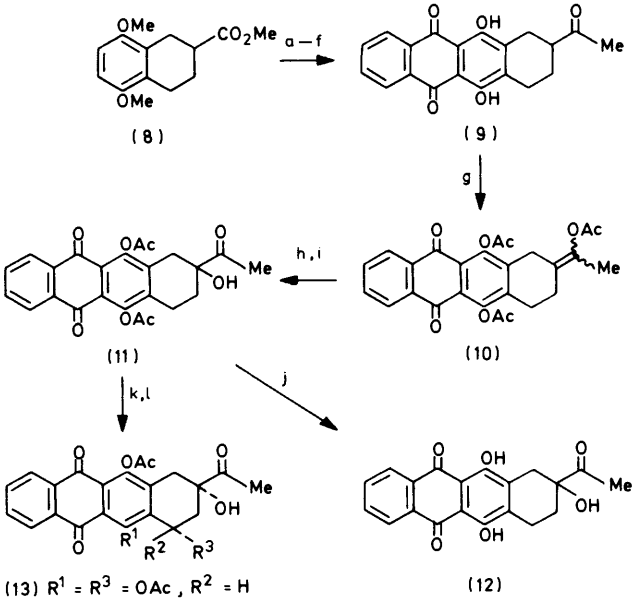
(1) R = OMe
(2) R = H



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

There have been various approaches to the synthesis of the 4-demethoxyanthracycline aglycones; most of this work has been described recently in an excellent review.[5] For some of these studies the synthesis was incomplete; moreover, only a few of the total syntheses reported have given material in sufficient quantity to enable a full biological evaluation.[3,4,6] Even with knowledge of these cases, we concluded that alternative procedures, capable of producing, economically, larger quantities of material, should be investigated.

Initially, our route to 4-demethoxyanthracyclinones utilised Friedel–Crafts condensations; other workers have investigated related procedures for the preparation of the tetracyclic system.[7-10] Our sequence (Scheme 1)

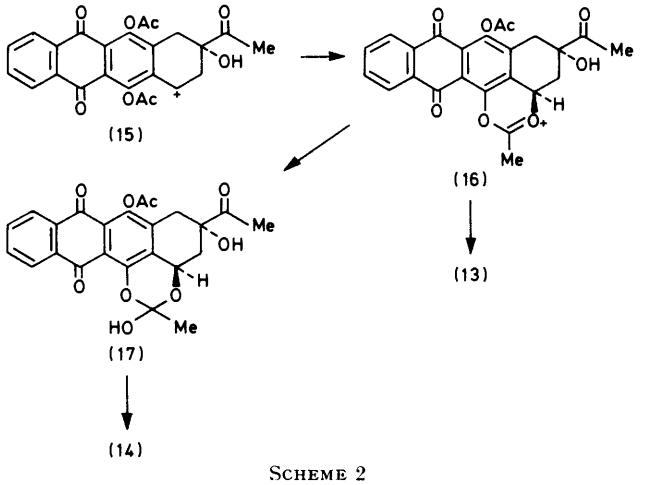


(8) (9) (11) (10) (13) R^1 = R^3 = OAc, R^2 = H (14) R^1 = OH, R^2 = OAc, R^3 = H (12)

SCHEME 1 *Reagents:* a, monomethyl phthalate; b, OH^-; c, H_2SO_4; d, $(COCl)_2$; e, $EtOMgCH(CO_2Et)_2$; f, HBr; g, Ac_2O; h, *m*-$ClC_6H_4CO_3H$; i, H^+; j, BCl_3; k, NBS; l, AgOAc

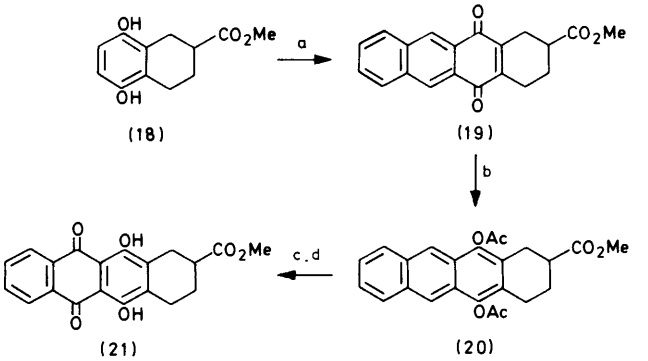
involved the condensation of the bicyclic ester (8) with a phthalic-acid half-ester using trifluoroacetic acid, followed by conventional reactions, to give the ketone (9) in high yield. This was hydroxylated through the enol acetate (10).[22] The introduction of the C-7 hydroxy-group, using methods which have been well documented,[7,8,11,12] gave poor yields when applied to the ketone (12); separation procedures were required in order to obtain pure material. A similar hydroxylation procedure was applied to the acetate (11). The first-formed mixture of bromides after treatment with silver

acetate gave two major products (19 and 33% yield respectively) with structures (13) and (14), determined by *X*-ray diffraction and n.m.r. spectroscopy. We attribute the formation of these products (13) and (14) to a reaction sequence in which the benzylic carbonium ion (15) reacts intramolecularly to give the oxonium ion (16) (Scheme 2). This may then give rise to compound



SCHEME 2

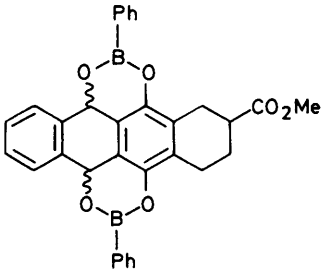
(13), with inversion, by interaction with acetate ion, or may interact with water to give the alternative product (14) through the orthoacetate (17). The latter process is reminiscent of the acetate-transfer reactions observed by Woodward [13] and by Winstein.[14] The low overall yield obtained by this Friedel–Crafts route discouraged its use for larger scale preparations.



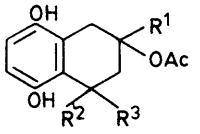
SCHEME 3 *Reagents:* a, phthalaldehyde, $PhB(OH)_2$; b, Zn, Ac_2O; c, CrO_3; d, BCl_3

Use of the Benzeneboronic Acid–Phthalaldehyde Condensation.—The initial work established that introduction of the C-7 and -9 hydroxy-substituents late in the synthesis should be avoided. We have investigated alternative syntheses utilising A,B-ring precursors which incorporate C-7 and -9 substituents, preferably with the appropriate chirality. There is one published route based on this strategy,[15] but we considered that alternative procedures deserved investigation.

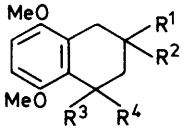
The condensation of aldehydes with phenols using benzeneboronic acid under mild conditions was applied in our earlier synthesis of anthracyclinones.[1] When this was applied to the reaction of phthalaldehyde with the model hydroquinone (18), the tetracyclic quinone (19) was obtained rather than the bisboronate (22). Similar



quinones have been synthesised in other approaches to anthracyclinones.[16–18] The quinone (19) was, however, converted readily (Scheme 3) in excellent yield into the relevant hydroxyquinone (21). A similar procedure was applied to the substituted hydroquinones (23), (24), and (25) which were prepared in excellent yields through the corresponding esters (8) and (28) by hydroxylation of the enolate. The esters (29) and (30) were converted into the ketones (34) and (32) by the action of sodium methylsulphinyl methide followed by reduction with aluminium amalgam.[19] In each case demethylation of



(23) $R^1 = CO_2Me$, $R^2 = R^3 = H$
(24) $R^1 = CO_2Me$, $R^2,R^3 = SCH_2CH_2S$
(25) $R^1 = COMe$, $R^2,R^3 = SCH_2CH_2S$

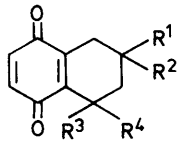


(26) $R^1 = CO_2Me$, $R^2 = OH$, $R^3 = R^4 = H$
(27) $R^1 = CO_2Me$, $R^2 = OAc$, $R^3 = R^4 = H$
(28) $R^1 = CO_2Me$, $R^2 = H$, $R^3,R^4 = OCH_2CH_2O$
(29) $R^1 = CO_2Me$, $R^2 = OH$, $R^3,R^4 = OCH_2CH_2O$
(30) $R^1 = CO_2Me$, $R^2 = OH$, $R^3,R^4 = SCH_2CH_2S$
(31) $R^1 = CO_2Me$, $R^2 = OAc$, $R^3,R^4 = SCH_2CH_2S$
(32) $R^1 = COMe$, $R^2 = OH$, $R^3,R^4 = SCH_2CH_2S$
(33) $R^1 = COMe$, $R^2 = OAc$, $R^3,R^4 = SCH_2CH_2S$
(34) $R^1 = COMe$, $R^2 = OH$, $R^3,R^4 = OCH_2CH_2O$
(35) $R^1 = COMe$, $R^2 = OAc$, $R^3,R^4 = OCH_2CH_2O$
(36) $R^1 = CO_2Me$, $R^2 = H$, $R^3,R^4 = SCH_2CH_2S$

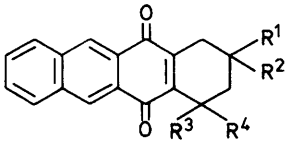
the methylated hydroquinone was achieved by oxidation with ammonium ceric nitrate, followed by reduction to the hydroquinone. The use of the ceric salt in this way was based on the little-exploited observation of Castagnoli and co-workers in their work on psychotomimetic agents.[20] It was the determining factor in achieving near-quantitative yields. None of the alternative oxidising agents investigated were as specific or effective.

The condensation of the 7-substituted bicyclic hydro-

quinones (24) and (25) with phthalaldehyde gave the required products (44) and (45), but yields were disappointing and could not be improved by modification of the reaction conditions. Similar behaviour has been observed with other reactions involving more highly substituted hydroquinones.[21,22] The route did not, therefore, provide a satisfactory basis for the synthesis of larger quantities of 4-demethoxyanthracyclinones, although it does give excellent yields of related compounds unsubstituted at C-7.



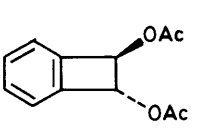
(37) $R^1 = CO_2Me$, $R^2 = R^3 = R^4 = H$
(38) $R^1 = CO_2Me$, $R^2 = OAc$, $R^3 = R^4 = H$
(39) $R^1 = CO_2Me$, $R^2 = OAc$, $R^3,R^4 = SCH_2CH_2S$
(40) $R^1 = COMe$, $R^2 = OAc$, $R^3,R^4 = SCH_2CH_2S$
(41) $R^1 = COMe$, $R^2 = OAc$, $R^3,R^4 = OCH_2CH_2O$
(42) $R^1 = CO_2Me$, $R^2 = H$, $R^3,R^4 = SCH_2CH_2S$



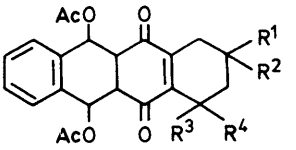
(43) $R^1 = CO_2Me$, $R^2 = OAc$, $R^3 = R^4 = H$
(44) $R^1 = CO_2Me$, $R^2 = OAc$, $R^3,R^4 = SCH_2CH_2S$
(45) $R^1 = COMe$, $R^2 = OAc$, $R^3,R^4 = SCH_2CH_2S$
(46) $R^1 = COMe$, $R^2 = OAc$, $R^3,R^4 = OCH_2CH_2O$
(47) $R^1 = CO_2Me$, $R^2 = H$, $R^3,R^4 = SCH_2CH_2S$

Use of trans-1,2-*Diacetoxy*-1,2-*dihydrobenzocyclobutene*.—Sammes and co-workers [23] have reported the thermal ring-opening of 1,2-dihydrobenzocyclobutenes to the corresponding *o*-quinonedimethides which serve as excellent dienes in Diels–Alder reactions. We have investigated the application of this process to the synthesis of anthracyclinones. When *trans*-1,2-diacetoxy-1,2-dihydrobenzocyclobutene (48) [23] was refluxed in xylene with the quinone (40) the product (49) was formed initially, but was in turn converted readily, by heating or by treatment with mild base or silica gel, into the quinone (45). Unfortunately, all attempts to dehydrogenate compound (49) or the related compounds (50), (51), and (52) failed to give products with the required oxidation level of anthracyclinones; either unchanged material or one of the quinones (45), (46), (47), or (19) was recovered. Consequently, an alternative sequence based on the use of the bicyclic diol (54) was investigated. This has resulted in a practicable procedure for the total synthesis of (±)-4-demethoxydaunomycinone.

Evidently, to achieve a practicable synthesis of the tetracyclic system with the C-7- and -9-functionality of the A,B-ring precursor maintained, protection of both ring A hydroxy-functions must be introduced. Exploratory experiments utilising 7-acetoxy- or 7,9-dihydroxybicyclic intermediates confirmed this. We have prepared a suitable bicyclic intermediate (53) from the 9-

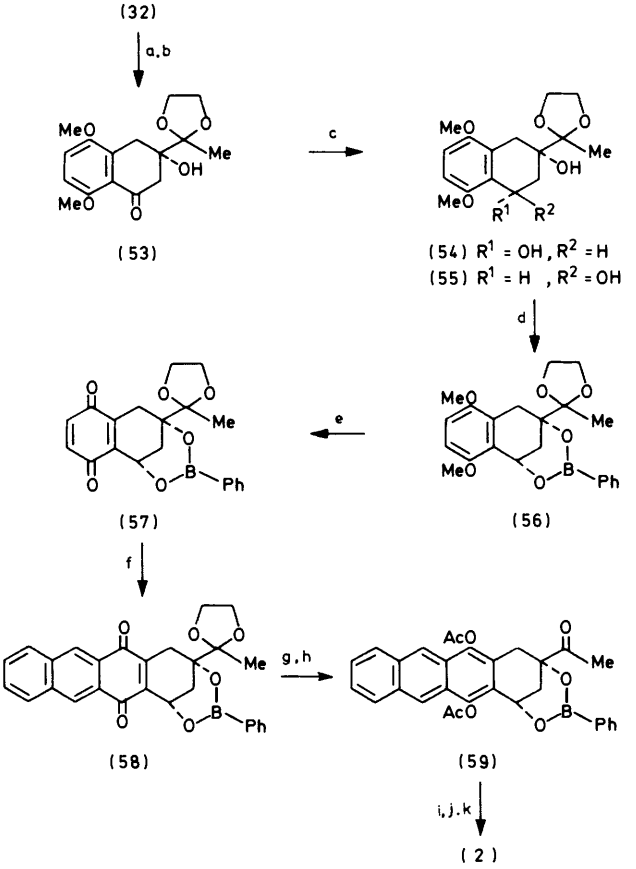


(48)



(49) $R^1 = COMe$, $R^2 = OAc$, $R^3,R^4 = SCH_2CH_2S$
(50) $R^1 = COMe$, $R^2 = OAc$, $R^3,R^4 = OCH_2CH_2O$
(51) $R^1 = CO_2Me$, $R^2 = H$, $R^3,R^4 = SCH_2CH_2S$
(52) $R^1 = CO_2Me$, $R^2 = R^3 = R^4 = H$

keto-thioacetal (32). This was converted into a mixture of the diols (54) and (55), and treatment of this mixture with benzeneboronic acid in the presence of toluene-4-sulphonic acid gave the *cis*-benzeneboronate (56) (Scheme 4); the *trans*-diol (55) in the mixture was epimerised under these conditions. This provides a novel method for achieving the *cis*-stereochemistry of the 7- and 9-hydroxy-functions and, simultaneously, introducing



SCHEME 4 *Reagents:* a, $HOCH_2CH_2OH$; b, HgO, $HgCl_2$; c, $LiBH_4$; d, $PhB(OH)_2$, H^+; e, $(NH_4)_2Ce(NO_3)_6$; f, (48); g, H^+; h, H_2, Pd–C, Ac_2O; i, CrO_3; j, BCl_3; k, $(CH_3)_2C(OH)$-$CH_2CH(OH)CH_3$

suitable protection. The bicyclic intermediate (56) was converted into the quinone (57), which reacted with *trans*-1,2-diacetoxy-1,2-dihydrobenzocyclobutene (48) to give the tetracyclic quinone (58). Deacetalisation and reductive acetylation to the naphthacene (59), followed by oxidation with chromium trioxide under anhydrous conditions and deprotection with boron trichloride and

with 2-methylpentane-2,4-diol (to remove the benzeneboronate function), gave (±)-4-demethoxydaunomycinone (2), which had the reported characteristics.[16,24-26] Anhydrous conditions were essential in the oxidation of the benzeneboronate (59). Treatment with chromic oxide under the usual aqueous conditions resulted in concomitant oxidation at position 7.

This synthetic route to 4-demethoxydaunomycinone compares favourably with other procedures with respect to length and overall yield. Moreover, difficult or tedious separations of reaction products by column or preparative t.l.c. are avoided so that large scale preparations are practicable. In subsequent publications we shall report the application of this synthetic route to the preparation of various optically active 4-demethoxyanthracyclines.

EXPERIMENTAL

M.p.s were determined on a Büchi melting point apparatus. Unless otherwise stated i.r. spectra were recorded on a Unicam SP 1000 spectrophotometer for Nujol mulls, u.v. and visible spectra were recorded for chloroform solutions with a Unicam SP 8000 spectrophotometer and ^{1}H n.m.r. spectra were recorded on either a Varian T 60 or XL 100 spectrometer for deuteriochloroform solutions with tetramethylsilane as internal reference. Mass spectra were recorded using an A.E.I. MS 902 mass spectrometer with a direct insertion probe. Microanalyses were carried out by Mr. M. R. Cottrell. Organic solutions were dried ($MgSO_4$) and evaporated using a rotary evaporator Silica gel used for column chromatography was Kiesel gel 60, 70—230 mesh (Merck). Ether refers to diethyl ether throughout.

Methyl 1,2,3,4-*Tetrahydro*-5,8-*dimethoxynaphthalene*-2-*carboxylate* (8).—Methyl 1,2,3,4-tetrahydro-5,8-dimethoxy-1-oxonaphthalene-3-carboxylate [1] (6.0 g) was suspended in methanol (500 ml) and 10% Pd–C catalyst (1.0 g) was added. The mixture was shaken in a hydrogen atmosphere until uptake ceased, and the catalyst was filtered off (Celite) and the filtrate evaporated to give the *ester* (8) (5.68 g, 100%) as colourless crystals. Recrystallisation from aqueous methanol gave colourless crystals, m.p. 65—65.5 °C (Found: C, 67.0; H, 7.35. $C_{14}H_{18}O_4$ requires C, 67.2; H, 7.25%); M^+, 250; $\nu_{max.}$ 1 735 and 1 605 cm^{-1}; δ 6.64 (2 H, s, ArH), 3.78 (6 H, s, 2 OMe), 3.72 (3 H, s, OMe), and 3.3—1.4 (7 H, m, 3 CH_2 and CH).

2-*Acetyl*-1,2,3,4,6,11-*hexahydro*-5,12-*dihydroxynaphthacene*-6,11-*quinone* (9).—(*a*) A mixture of the ester (8) (25 g), monomethyl phthalate (50 g) and trifluoroacetic anhydride (50 ml) in dichloromethane (60 ml) was heated under reflux in a nitrogen atmosphere for 5 h. The solution was then cooled and poured into 10% aqueous potassium carbonate (1 l). The product was extracted into dichloromethane (3 × 250 ml) and the combined extracts washed with 10% aqueous potassium carbonate (4 × 100 ml) and then evaporated to give a pale yellow gum. The gum was dissolved in methanol (200 ml), aqueous sodium hydroxide (40 g in 200 ml of water) was added and the mixture heated under reflux for 3.5 h. Most of the methanol was evaporated off and the residue was then diluted with water (300 ml). The solution was washed with ether (2 × 100 ml) and then acidified with concentrated hydrochloric acid. The mixture was extracted with ethyl acetate (3 × 200 ml) and the combined ethyl acetate extracts dried and evaporated to give a white solid (35.0 g) which was powdered and added with stirring to concentrated sulphuric acid (300 ml). After being stirred at room temperature for 8 h the deep red solution was poured with stirring onto crushed ice (1 500 g) and left overnight. The precipitated product was filtered off, washed with water, and dried *in vacuo* at 30 °C. Recrystallisation from methanol gave 1,2,3,4,6,11-*hexahydro*-5,12-*dimethoxy*-6,11-*dioxonaphthacene*-2-*carboxylic acid* (31.0 g, 84.7%) as orange-yellow crystals, m.p. 225—225.5 °C (Found: C, 68.65; H, 4.95. $C_{21}H_{18}O_6$ requires C, 68.85; H, 4.95%; M^+, 366; $\nu_{max.}$ 1 705, 1 675, 1 595, and 1 555 cm^{-1}; δ 8.6 (1 H, br s, CO_2H), 8.2 (2 H, m, ArH), 7.8 (2 H, m, ArH), 3.96 (6 H, s, 2 OMe), and 3.45—1.6 (7 H, m, 3 CH_2 and CH).

(*b*) The above acid (10.0 g) was suspended in dichloromethane (200 ml) and oxalyl dichloride (20 ml) added. The mixture was stirred at room temperature for 20 h and the yellow solution obtained was evaporated. The product was dissolved in benzene (100 ml) and re-evaporated. This procedure was repeated and the crude acid chloride thus obtained was used directly without further purification. The acid chloride in benzene (100 ml) was added dropwise with stirring to a solution of ethoxymagnesium malonic ester [prepared from diethyl malonate (12.5 g)] in benzene (40 ml) at 0 °C. The red solution was then heated under reflux for 35 min, allowed to cool, and left at room temperature overnight. The mixture was then poured onto 2M-hydrochloric acid (500 ml) and the product extracted with ethyl acetate (3 × 200 ml). The combined extracts were washed with water (3 × 200 ml), dried, and evaporated to give an orange gum. Crystallisation from methanol gave *diethyl* 2-[(1,2,3,4,6,11-*hexahydro*-5,12-*dimethoxy*-6,11-*dioxonaphthacen*-2-*yl*)*carbonyl*]*malonate* (13.5 g, 97%) as orange crystals, m.p. 131—132 °C (Found: C, 66.15; H, 5.55. $C_{28}H_{28}O_9$ requires C, 66.15; H, 5.55%); M^+, 508; $\nu_{max.}$ 1 755, 1 730, 1 715, 1 675, 1 630, 1 600, and 1 560 cm^{-1}; $\lambda_{max.}$ 262 and 375 nm (log ε 4.60 and 3.69); δ 8.15 (2 H, m, ArH), 7.66 (2 H, m, ArH), 4.7 [1 H, s, $CH(CO_2Et)_2$], 4.31 (4 H, q, *J* 7 Hz, OCH_2Me), 3.81 (6 H, s, 2 OMe), 3.45—1.5 (7 H, m, 3 CH_2 and CH), and 1.34 (6 H, t, *J* 7 Hz, OCH_2Me).

(*c*) The above diester (25.0 g) was suspended in 48% hydrobromic acid (200 ml) and the mixture heated under reflux with stirring for 2 h. Water (100 ml) was then added and the mixture heated under reflux for 1 h and then allowed to cool. The precipitated product was filtered off, washed with water and dried *in vacuo* at 30 °C. Recrystallisation from ethanol–ethyl acetate gave the quinone (9) (14.4 g, 88%) as red crystals, m.p. 198.5—199.5 °C (lit.,[27] m.p. 180—182 °C) (Found: C, 71.15; H, 4.7. Calc. for $C_{20}H_{16}O_5$: C, 71.45; H, 4.8%); M^+, 336; $\nu_{max.}$ 1 710, 1 630, and 1 595 cm^{-1}; $\lambda_{max.}$ 258, 291, 486, and 521 nm (log ε 4.65, 3.99, 4.06, and 3.89); δ($CDCl_3$–DMSO) 13.48 (1 H, s, ArOH), 13.45 (1 H, s, ArOH), 8.3 (2 H, m, ArH), 8.0 (2 H, m, ArH), 3.3—1.5 (7 H, m, 3 CH_2 and CH), and 2.29 (3 H, s, COMe).

5,12-*Diacetoxy*-2-*acetyl*-1,2,3,4,6,11-*hexahydro*-2-*hydroxynaphthacene*-6,11-*quinone* (11).—The quinone (9) (5.0 g) was suspended in acetic anhydride (300 ml) containing toluene-4-sulphonic acid (2.82 g). The mixture was heated under reflux for 25 h, cooled and the solvent evaporated to give a brown oil which was dissolved in ethyl acetate (300 ml). The ethyl acetate solution was washed with 10% aqueous potassium hydrogen carbonate (300 ml), dried and evaporated to give a brown oil which was passed through a column of silica gel using ethyl acetate–hexane

(1 : 3) for elution. After evaporation of the solvent, crude enol acetate (10) (6.0 g, 87%) was obtained as a yellow gum which was used directly without further purification. The enol acetate (6.0 g) was dissolved in dichloromethane (250 ml), *m*-chloroperbenzoic acid (2.34 g) added and the mixture stirred for 24 h at room temperature. Acetic acid–water–sulphuric acid (600 : 20 : 3; 25 ml) was then added and the mixture stirred for 35 min before addition of water (200 ml). The dichloromethane layer was separated, washed with water (2 × 100 ml), dried and evaporated to give a yellow gum. Column chromatography on silica gel, using ethyl acetate–hexane (1 : 3) as eluant gave the *diacetate* (11) (4.3 g, 66%) as a yellow solid. Recrystallisation from dichloromethane–hexane gave yellow crystals, m.p. 212.5—213 °C (Found: C, 65.8; H, 4.55. $C_{24}H_{20}O_8$ requires C, 66.05; H, 4.6%); M^+, 436; $\nu_{max.}$ 3 480, 1 775, 1 755, 1 710, 1 675, 1 600, and 1 580 cm^{-1}; $\lambda_{max.}$ 262 and 345 nm (log ε 4.69 and 3.80); δ 8.02 (2 H, m, ArH), 7.6 (2 H, m, ArH), 3.67 (1 H, s, OH), 3.2—2.65 (4 H, m, 2 $ArCH_2$), 2.48 (3 H, s, Ac), 2.42 (3 H, s, Ac), 2.27 (3 H, s, Ac), and 2.1—1.6 (2 H, m, CH_2).

2-Acetyl-1,2,3,4,6,11-hexahydro-2,5,12-trihydroxynaphthacene-6,11-quinone (12).—The diacetate (11) (1.0 g) was dissolved in dichloromethane (200 ml) and the solution cooled to −70 °C under nitrogen. Boron trichloride (1.5 g) in dichloromethane (25 ml) was added with stirring and the resulting solution allowed to return to room temperature; it was stirred at this temperature for 45 min, and then poured into ice-cold 2M-hydrochloric acid (500 ml). The dichloromethane layer was separated, washed with water (4 × 200 ml) and saturated aqueous sodium chloride (200 ml), dried and evaporated to give a red solid. Recrystallisation from dichloromethane–hexane gave the quinone (12) (0.8 g, 99%) as red crystals, m.p. 210—211 °C (lit.,[17] 210—212 °C,[16] 160—162 °C) (Found: C, 68.3; H, 4.7. Calc. for $C_{20}H_{16}O_6$: C, 68.2; H, 4.6%); M^+, 352; $\nu_{max.}$ 3 500, 1 700, 1 625, and 1 590 cm^{-1}; $\lambda_{max.}$ 258, 291, 486, and 520 nm (log ε 4.64, 4.01, 4.05, and 3.88); δ 13.45 (1 H, s, ArH), 13.3 (1 H, s, ArH), 8.2 (2 H, m, ArH), 7.75 (2 H, m, ArH), 3.4 (1 H, br s, OH), 3.1—2.5 (4 H, m, 2 $ArCH_2$), 2.32 (3 H, s, COMe), and 2.0—1.7 (2 H, m, CH_2).

cis-*1,5,12-Triacetoxy-3-acetyl-1,2,3,4,6,11-hexahydro-3-hydroxynaphthacene-6,11-quinone* (13) *and* trans-*1,5-Diacetoxy-3-acetyl-1,2,3,4,6,11-hexahydro-3,12-dihydroxynaphthacene-6,11-quinone* (14).—A mixture of the diacetate (11) (1.0 g), *N*-bromosuccinimide (0.62 g) and 2,2′-azo(2-methylpropionitrile) (0.2 g) in carbon tetrachloride (1 l) was heated under reflux with irradiation in a nitrogen atmosphere for 3.5 h. The solution was allowed to cool and the solvent evaporated to give a yellow residue which was dissolved in acetic acid (100 ml). Silver acetate (2.0 g) was added and the mixture stirred at room temperature for 18 h. The silver salts were filtered off and the filtrate was evaporated to give a mixture of quinones (13) and (14) as a yellow gum which was separated by chromatography on silica gel, using hexane–ethyl acetate (1 : 1) as eluant. The first material eluted was the *quinone* (14) (0.34 g, 33%) as orange-yellow crystals, m.p. 217—218 °C (from ether) (Found: C, 63.5; H, 4.45. $C_{24}H_{20}O_9$ requires C, 63.7; H, 4.45%); M^+, 452; $\nu_{max.}$ 3 440, 1 765, 1 730, 1 710, 1 680, 1 635, 1 595, and 1 580 cm^{-1}; $\lambda_{max.}$ 257, 328, and 412 nm (log ε 4.41, 3.27, and 3.83); δ 8.3 (2 H, m, ArH), 7.82 (2 H, m, ArH), 6.52 (1 H, t, *J* 7 Hz, C*H*OAc), 3.48 (1 H, br s, OH), 3.3—2.6 (2 H, ABq, *J* 17 Hz, CH_2), 2.5 (3 H, s, Ac), 2.45—2.05 (2 H, m, CH_2), 2.34 (3 H, s, Ac), and 2.08 (3 H, s, Ac). Later fractions gave the *quinone* (13) (0.22 g, 19%) as pale yellow crystals, m.p. 208—208.5 °C (from ethyl acetate) (Found: C, 63.15; H, 4.5. $C_{26}H_{22}O_{10}$ requires C, 63.15; H, 4.5%); M^+, 494; $\nu_{max.}$ 3 500, 1 785, 1 740, 1 720, 1 680, and 1 590 cm^{-1}; $\lambda_{max.}$ 260 and 343 nm (log ε 4.65 and 3.82); δ(DMSO) 8.3 (2 H, m, ArH), 8.15 (2 H, m, ArH), 6.36 (1 H, br s, C*H*OAc), 5.78 (1 H, br s, OH), 3.36—2.92 (2 H, ABq, *J* 18 Hz, CH_2), 2.72 (3 H, s, Ac), 2.58 (3 H, s, Ac), 2.54 (3 H, s, Ac), 2.7—2.3 (2 H, m, CH_2), and 2.26 (3 H, s, Ac).

Methyl 1,2,3,4,5,8-Hexahydro-5,8-dioxonaphthalene-2-carboxylate (37).—A solution of ammonium ceric nitrate (19.74 g, 0.036 mol) in water (120 ml) was added to a stirred solution of methyl 1,2,3,4-tetrahydro-5,8-dimethoxynaphthalene-2-carboxylate (3.00 g, 0.012 mol) in acetonitrile (54 ml). The mixture was stirred at room temperature for 25 min and then diluted with water (150 ml) and extracted with ether (3 × 150 ml). The extracts were washed with water (150 ml), dried and evaporated to give the *quinone* (37) (2.60 g, 98.5%) as a bright yellow crystalline solid, m.p. 41—42 °C (Found: C, 65.3; H, 5.5. $C_{12}H_{12}O_4$ requires C, 65.4; H, 5.5%); M^+, 220; $\nu_{max.}$ 1 720, 1 650, and 1 595 cm^{-1}; δ 6.56 (2 H, s, CH=CH), 3.63 (3 H, s, CO_2Me), 2.9—2.4 (5 H, m, 2 CH_2 and CH), and 2.3—1.7 (2 H, m, CH_2).

Methyl 1,2,3,4-Tetrahydro-5,8-dihydroxynaphthalene-2-carboxylate (18).—A mixture of the quinone (37) (4.00 g, 0.018 mol) and 10% Pd–C catalyst (0.30 g) in methanol (180 ml) was shaken under hydrogen until uptake ceased (429 ml, 18 min). The mixture was filtered and the filtrate was evaporated to give the *hydroquinone* (18) (4.0 g, 99%) as a white crystalline solid, m.p. 135—136 °C (Found: C, 64.8; H, 6.5. $C_{12}H_{14}O_4$ requires C, 64.85; H, 6.35%); M^+, 222; $\nu_{max.}$ 3 400, 1 710, 1 660, 1 620, and 1 600 cm^{-1}; δ[$CDCl_3$–$(CD_3)_2SO$] 7.72 (1 H, s, exch. D_2O, ArOH), 7.63 (1 H, s, exch. D_2O, ArOH), 6.53 (2 H, s, ArH), 3.63 (3 H, s, CO_2Me), 3.2—2.5 (5 H, m, 2 CH_2 and CH), and 2.4—1.7 (2 H, m, CH_2).

Methyl 1,2,3,4,5,12-Hexahydro-5,12-dioxonaphthacene-2-carboxylate (19).—A mixture of the hydroquinone (18) (4.04 g, 0.018 mol), phthalaldehyde (2.44 g, 0.018 mol), benzeneboronic acid (4.44 g, 0.036 mol), and propionic acid (3.0 ml) in benzene (180 ml) was stirred and refluxed under nitrogen for 8.5 h. The mixture was evaporated to dryness and the residue washed with ether (40 ml) and filtered to give the *quinone* (19) (2.80 g). The filtrate was concentrated and cooled to 0 °C to yield a second crop (0.80 g, total yield 62%). The product was recrystallised from chloroform–light petroleum (b.p. 60—80 °C)–ether to give bright yellow crystals, m.p. 173—174 °C (Found: C, 74.6; H, 5.15. $C_{20}H_{16}O_4$ requires C, 75.0; H, 5.0%); M^+, 320; $\nu_{max.}$ 1 730, 1 630, 1 620, and 1 590 cm^{-1}; $\lambda_{max.}$ (EtOH) 246, 277sh, 285, 299, and 408 nm (log ε 4.23, 4.28, 4.30, 4.25, and 3.63); δ 8.60 (2 H, s, ArH), 8.12—8.00 (2 H, m, ArH), 7.74—7.62 (2 H, m, ArH), 3.78 (3 H, s, CO_2Me), 3.2—2.55 (5 H, m, 2 CH_2 and CH), and 2.3—1.6 (2 H, m, CH_2).

Methyl 5,12-Diacetoxy-1,2,3,4-tetrahydronaphthacene-2-carboxylate (20).—A mixture of the quinone (19) (1.60 g, 5 mmol), zinc dust (0.65 g, 10 mmol), and acetic anhydride (20 ml) was stirred at 100 °C for 1 h. The mixture was then cooled, poured into water (200 ml) and extracted with dichloromethane (3 × 100 ml). The combined extracts were washed with 5% sodium hydrogen carbonate solution (250 ml) and water (250 ml), dried, and evaporated. The residue was taken up in ether and light petroleum (b.p.

40—60 °C)–ether was added to precipitate the *diacetate* (20) (1.50 g, 74%) as a pale yellow solid, m.p. 210—211 °C (Found: C, 70.9; H, 5.5. $C_{24}H_{22}O_6$ requires C, 70.9; H, 5.5%); M^+, 406; $\nu_{max.}$ 1 755, 1 740, and 1 635 cm^{-1}; $\lambda_{max.}$ 263, 324, 336, 353, 372, and 392 nm (log ε 4.86, 2.98, 3.42, 3.69, 3.83, and 3.76); δ 8.28 (2 H, s, ArH), 8.05—7.93 (2 H, m, ArH), 7.54—7.42 (2 H, m, ArH), 3.78 (3 H, s, CO_2Me), 3.3—2.7 (5 H, m, 2 CH_2 and CH), 2.60 (3 H, s, OAc), 2.58 (3 H, s, OAc), and 2.4—2.0 (2 H, m, CH_2).

Methyl 1,2,3,4,6,11-*Hexahydro*-5,12-*dihydroxy*-6,11-*dioxonaphthacene*-2-*carboxylate* (21).—(*a*) Chromium trioxide (240 mg, 2.4 mmol) was added to a stirred solution of the diacetate (20) (240 mg, 0.6 mmol) in glacial acetic acid (18 ml) and water (2 ml). The mixture was stirred at room temperature for 3 h and then poured into water (100 ml). The resulting precipitate was collected, washed with water, and dried to give methyl 5,12-diacetoxy-1,2,3,4,6,11-hexahydro-6,11-dioxonaphthacene-2-carboxylate (210 mg, 81.5%) as a pale yellow solid, m.p. 203—205 °C; M^+, 436; $\nu_{max.}$ 1 770, 1 735, 1 670, and 1 600 cm^{-1}; $\lambda_{max.}$ 262, 280, and 335 nm (log ε 4.44, 4.09, and 3.49); δ 8.24—8.12 (2 H, m, ArH), 7.80—7.68 (2 H, m, ArH), 3.77 (3 H, s, CO_2Me), 3.2—2.6 (5 H, m, 2 CH_2 and CH), 2.54 (3 H, s, OAc), 2.52 (3 H, s, OAc), and 2.1—1.6 (2 H, m, CH_2).

(*b*) A solution of the product prepared above (150 mg, 0.34 mmol) in dichloromethane (3.0 ml) was cooled to −78 °C. Boron trichloride (1.0 ml) was added and the solution was stirred and allowed to warm up to room temperature over a period of 45 min. It was then poured into 2M-hydrochloric acid (25 ml) and the mixture extracted with dichloromethane (3 × 20 ml). The combined extracts were washed with water, dried and evaporated to give the *dihydroxyquinone* (21) (120 mg, 99%) as a bright orange solid, m.p. 158—160 °C (Found: C, 68.2; H, 4.8. $C_{20}H_{16}O_6$ requires C, 68.2; H, 4.6%); M^+, 352; $\nu_{max.}$ 1 730, 1 660, 1 625, and 1 590 cm^{-1}; $\lambda_{max.}$ 253, 286, 470sh, 485, and 520 nm (log ε 4.41, 4.07, 3.88, 3.91, and 3.67); δ 13.13 (1 H, s, exch. D_2O, ArOH), 13.09 (1 H, s, exch. D_2O, ArOH), 8.32—8.20 (2 H, m, ArH), 7.81—7.69 (2 H, m, ArH), 3.71 (3 H, s, CO_2Me), 3.1—2.5 (5 H, m, 2 CH_2 and CH), and 2.3—1.5 (2 H, m, CH_2).

Methyl 1,2,3,4-*Tetrahydro*-2-*hydroxy*-5,8-*dimethoxynaphthalene*-2-*carboxylate* (26).—A solution of n-butyl-lithium in hexane (100 ml; 1.6M) was added with stirring to a solution of di-isopropylamine (21 ml) in dry tetrahydrofuran (THF) (500 ml) under argon at −78 °C. After 30 min the ester (8) (25 g) in THF (100 ml) was added and the mixture stirred at −78 °C for 1 h. Powdered diperoxo-oxohexamethylphosphoramidomolybdenum(VI) [28] (69.5 g) was then added and the mixture stirred at −78 °C for 1.25 h and then at 0 °C for 30 min. The reaction was quenched by addition of water (600 ml) and most of the THF evaporated off. The residue was extracted with ethyl acetate (3 × 200 ml), the combined extracts washed with 2M-hydrochloric acid (200 ml), 10% aqueous potassium hydrogen carbonate (2 × 200 ml), dried and evaporated. Column chromatography on silica gel using ethyl acetate–hexane (1 : 1) as eluant gave the *hydroxy-ester* (26) (17.8 g, 67%) as colourless crystals, m.p. 76.5—77 °C (from ether–hexane) (Found: C, 63.4; H, 6.65. $C_{14}H_{18}O_5$ requires C, 63.15; H, 6.8%); M^+, 266; $\nu_{max.}$ 3 550, 1 710, and 1 605 cm^{-1}; δ 6.6 (2 H, s, ArH), 3.78 (3 H, s, OMe), 3.73 (3 H, s, OMe), 3.70 (3 H, s, OMe), 3.02 (1 H, s, OH), 2.8 (4 H, m, 2 $ArCH_2$), and 2.0 (2 H, m, CH_2).

Methyl 2-*Acetoxy*-1,2,3,4-*tetrahydro*-5,8-*dimethoxynaphthalene*-2-*carboxylate* (27).—A mixture of the hydroxy-ester (26) (5.0 g), acetic anhydride (10 ml), 4-dimethylaminopyridine (0.1 g), and pyridine (50 ml) was allowed to stand at 0 °C for 20 h. The solution was poured into water (250 ml) and the product extracted into ethyl acetate (3 × 200 ml). The combined ethyl acetate extracts were washed with 5M-hydrochloric acid (400 ml), water (400 ml), 10% aqueous potassium hydrogen carbonate (400 ml) and water (400 ml), dried, and evaporated to give a white solid. Recrystallisation from ether gave the acetate (27) (5.6 g, 96%) as colourless crystals, m.p. 155.5—156 °C (Found: C, 62.35; H, 6.4. $C_{16}H_{20}O_6$ requires C, 62.35; H, 6.55%); M^+, 308; $\nu_{max.}$ 1 740 and 1 605 cm^{-1}; δ 6.61 (2 H, s, Ar H), 3.77 (9 H, s, 3 OMe), 3.3—1.8 (6 H, m, 3 CH_2), and 2.0 (3 H, s, Ac).

Synthesis of Quinones (38), (39), (40), (41), *and* (42).—A solution of ammonium ceric nitrate (4.8 g) in water (40 ml) was added rapidly to a stirred solution of the acetate (27) (1.2 g) in acetonitrile (40 ml). After being stirred for 25 min at room temperature, the solution was diluted with water (300 ml) and extracted with ethyl acetate (3 × 150 ml). The combined extracts were dried and evaporated to give the quinone (38) (0.95 g, 87%) as a yellow oil which was used directly. Similar procedures were employed in the preparation of the following: *methyl* 3′-*acetoxy*-1′,2′,3′,4′-5′,8′-*hexahydro*-5′,8′-*dioxospiro*[1,3-*dithiolan*-2,1′-*naphthalene*]-3′-*carboxylate* (39) (75%), obtained as an orange powder, m.p. 185—186 °C (from ether) (Found: C, 52.0; H, 4.35; S, 17.1. $C_{16}H_{16}O_6S_2$ requires C, 52.15; H, 4.4; S, 17.4%); M^+, 368; δ 6.67 (2 H, s, CH=CH), 3.78 (3 H, s, OMe), 3.5 (4 H, m, SCH_2CH_2S), 3.4—2.5 (4 H, m, 2 CH_2), and 2.1 (3 H, s, Ac); 3′-*acetoxy*-3′-*acetyl*-1′,2′,3′,4′,5′,8′-*hexahydro*-5′,8′-*dioxospiro*[1,3-*dithiolan*-2,1′-*naphthalene*] (40) (95%), obtained as orange crystals, m.p. 214—215 °C (from ethyl acetate–isopropyl alcohol) (Found: C, 54.5; H, 4.75; S, 17.85. $C_{16}H_{16}O_5S_2$ requires C, 54.55; H, 4.6; S, 18.2%); M^+, 352; $\nu_{max.}$ 1 735, 1 710, 1 665, 1 655, 1 625, and 1 590 cm^{-1}; δ 6.66 (2 H, s, CH=CH), 3.95—3.45 (4 H, m, SCH_2-CH_2S), 3.45—2.55 (4 H, m, 2 CH_2), 2.17 (3 H, s, Ac), and 2.12 (3 H, s, Ac); 3-*acetoxy*-3-*acetyl*-1,1-*ethylenedioxy*-1,2,3,4,5,8-*hexahydro*-5,8-*dioxonaphthalene* (41) (93%), obtained as yellow crystals, m.p. 169—171 °C (Found: C, 59.85; H, 5.0. $C_{16}H_{16}O_7$ requires C, 60.0; H, 5.05%); M^+, 320; δ 6.66 (2 H, s, CH=CH), 4.4—3.7 (4 H, m, OCH_2-CH_2O), 2.9—2.2 (4 H, m, 2 CH_2), 2.14 (3 H, s, Ac), and 2.02 (3 H, s, Ac); and *methyl* 1′,2′,3′,4′,5′,8′-*hexahydro*-5′,8′-*dioxospiro*[1,3-*dithiolan*-2,1′-*naphthalene*]-3′-*carboxylate* (42) (86%), obtained as an orange crystalline mass which was recrystallised from ether to give yellow crystals, m.p. 140—141 °C (Found: C, 54.0; H, 4.7. $C_{14}H_{14}O_4S_2$ requires C, 54.2; H, 4.55%); M^+, 310; $\nu_{max.}$ 1 730 and 1 655 cm^{-1}; δ 6.70 (2 H, s, CH=CH), 4.10—3.30 (4 H, m, SCH_2CH_2S), 3.77 (3 H, s, CO_2Me), and 3.12—2.10 (5 H, m, 2 CH_2 and CH).

Synthesis of Hydroquinones (23), (24), *and* (25).—The quinone (38) (0.95 g) was dissolved in ethyl acetate (200 ml) and 10% Pd–C catalyst (0.2 g) added. The mixture was shaken under hydrogen until uptake ceased, after which the catalyst was filtered off (Celite) and the filtrate evaporated to give a colourless oil. Trituration with benzene gave the hydroquinone (23) (0.9 g, 82%) as a colourless powder (sufficiently pure to be used in subsequent reactions), M^+, 280; δ 6.4 (2 H, s, ArH), 3.66 (3 H, s, CO_2Me), 3.1—1.8 (6 H, m, 3 CH_2), and 1.98 (3 H, s, Ac). Hydrogenation of the quinone (39) over 5% rhodium-on-alumina

catalyst gave *methyl 3'-acetoxy-1',2',3',4'-tetrahydro-5',8'-dihydroxyspiro*[1,3-*dithiolan*-2,1'-*naphthalene*]-3'-*carboxylate* (24) (96%) as a colourless powder, m.p. 208—210 °C (Found: C, 51.8; H, 4.7; S, 17.2. $C_{16}H_{18}O_6S_2$ requires C, 51.9; H, 4.9; S, 17.3%); M^+, 370; δ(DMSO) 8.74 (1 H, s, ArOH), 8.4 (1 H, s, ArOH), 6.5 (2 H, ABq, *J* 10 Hz, ArH), 3.64 (3 H, s, OMe), 3.4 (4 H, m, SCH_2CH_2S), 3.1—2.8 (4 H, m, 2 CH_2), and 1.98 (3 H, s, Ac); hydrogenation of the quinone (40) over 10% Pd–C catalyst gave 3'-acetoxy-3'-acetyl-1',2',3',4'-tetrahydro-5',8'-dihydroxyspiro[1,3-dithiolan-2,1'-naphthalene] (25) (88%) as an off-white powder, m.p. 239—240 °C, M^+, 354.

Reaction of Hydroquinones (23), (24), *and* (25) *with Phthalaldehyde*.—A suspension of the hydroquinone (23) (140 mg, 0.5 mmol), phthalaldehyde (67 mg, 0.5 mmol) and benzeneboronic acid (122 mg, 1.0 mmol) in a mixture of benzene (12.5 ml) and propionic acid (0.1 ml) was refluxed under nitrogen for 17 h. The mixture was evaporated and the residue was taken up in dichloromethane (25 ml) and filtered to remove a trace of insoluble material. 2-Methylpentane-2,4-diol (0.5 ml) and glacial acetic acid (0.1 ml) were added to the filtrate and the solution was stirred at room temperature for 2 h. It was then washed with water (4 × 30 ml), dried and evaporated to give the crude product as a bright yellow solid. This was chromatographed on a column of silica gel (10 g), with ether–light petroleum (b.p. 40—60 °C) (1 : 2 v/v), ether–light petroleum (1 : 1 v/v), and ether as eluants. *Methyl 2-acetoxy-1,2,3,4,5,12-hexahydro-5,12-dioxonaphthacene-2-carboxylate* (43) (156 mg, 82.5%) was obtained as a bright yellow solid, m.p. 205—206 °C (Found: C, 69.8; H, 4.75. $C_{22}H_{18}O_6$ requires C, 69.8; H, 4.8%); M^+, 378; $\nu_{max.}$ 1 745, 1 735, 1 660, 1 630, 1 620, and 1 590 cm^{-1}; $\lambda_{max.}$ 244, 276sh, 285, 298, and 410 nm (log ε 4.38, 4.41, 4.43, 4.39, and 3.73); δ 8.60 (2 H, s, ArH), 8.10—7.98 (2 H, m, ArH), 7.75—7.62 (2 H, m, ArH), 3.81 (3 H, s, CO_2Me), 3.0—2.4 (3 H, m, 2 CH_2), 2.08 (3 H, s, OAc), and 2.3—2.0 (2 H, m, CH_2).

Reaction of the hydroquinone (24) with phthalaldehyde under similar conditions gave *methyl 3'-acetoxy-1',2',3',4',-5',12'-hexahydro-5',12'-dioxospiro*[1,3-*dithiolan*-2,1'-*naphthacene*]-3'-*carboxylate* (44) (26%) and unchanged hydroquinone (24) (69%). The quinone (44) was recrystallised from ether to give bright yellow crystals, m.p. 234—235 °C (Found: C, 61.4; H, 4.1. $C_{24}H_{20}O_6S_2$ requires C, 61.5; H, 4.3%); M^+, 468; $\nu_{max.}$ ($CHCl_3$) 1 745, 1 670, 1 620, and 1 600 cm^{-1}; $\lambda_{max.}$ 245, 285sh, 292, 304, and 416 nm (log ε 4.28, 4.15, 4.16, 4.17, and 3.58); δ 8.72 (1 H, s, ArH), 8.68 (1 H, s, ArH), 8.08—7.96 (2 H, m, ArH), 7.72—7.60 (2 H, m, ArH), 4.05—3.76 (2 H, m, CH_2), 3.84 (3 H, s, CO_2Me), 3.65—3.45 (2 H, m, CH_2), 3.40—3.18 (2 H, m, CH_2), 3.00—2.76 (2 H, m, CH_2), and 2.14 (3 H, s, OAc).

Similarly, reaction of the hydroquinone (25) with phthalaldehyde gave 3'-*acetoxy*-3'-*acetyl*-1',2',3',4',5',12'-*hexahydro*-5',12'-*dioxospiro*[1,3-*dithiolan*-2,1'-*naphthacene*] (45) (24%) as bright yellow crystals, m.p. 239—241 °C (Found: C, 63.7; H, 4.8. $C_{24}H_{20}O_5S_2$ requires C, 63.7; H, 4.5%); M^+, 452; $\nu_{max.}$ 1 740, 1 720, 1 665, 1 620, and 1 595 cm^{-1}; $\lambda_{max.}$ 244, 282sh, 290, 302, and 413 nm (log ε 4.33, 4.21, 4.24, 4.24, and 3.68); δ 8.63 (1 H, s, ArH), 8.60 (1 H, s, ArH), 8.10—7.98 (2 H, m, ArH), 7.72—7.60 (2 H, m, ArH), 4.05—3.75 (2 H, m, CH_2), 3.65—3.35 (2 H, m, CH_2), 3.3—2.5 (4 H, m, 2 CH_2), 2.5 (3 H, s, Ac), and 2.16 (3 H, s, Ac).

Methyl 1,1-*Ethylenedioxy*-1,2,3,4-*tetrahydro*-5,8-*dimethoxynaphthalene*-3-*carboxylate* (28).—A mixture of methyl 1,2,3,4-tetrahydro-5,8-dimethoxy-1-oxonaphthalene-3-carboxylate (40 g), ethylene glycol (100.8 g), trimethyl orthoformate (17.68 g), and toluene-4-sulphonic acid (0.5 g) was stirred at room temperature for 4 h and then diluted with dichloromethane (100 ml). It was then washed with 10% aqueous potassium hydrogen carbonate (2 × 100 ml) and water (100 ml), and then dried and evaporated to give a creamy white solid. Trituration with ether gave the *acetal* (28) (40.7 g, 87%) as colourless crystals, m.p. 139—140 °C (Found: C, 62.35; H, 6.55. $C_{16}H_{20}O_6$ requires C, 62.35; H, 6.55%); M^+, 308; $\nu_{max.}$ 1 725 and 1 600 cm^{-1}; δ 6.75 (2 H, s, ArH), 4.17 (4 H, m, OCH_2CH_2O), 3.78 (3 H, s, OMe), 3.75 (3 H, s, OMe), 3.71 (3 H, s, OMe), and 3.45—1.6 (5 H, m, 2 CH_2 and CH).

Methyl 1,1-*Ethylenedioxy*-1,2,3,4-*tetrahydro*-3-*hydroxy*-5,8-*dimethoxynaphthalene*-3-*carboxylate* (29).—A solution of n-butyl-lithium in hexane (115 ml; 1.6M) was added with stirring to a solution of di-isopropylamine (24 ml) in dry THF (320 ml) under argon at −78 °C. After 45 min the acetal (28) (39.36 g) in THF (320 ml) was added and the mixture stirred at −78 °C for 1 h. Triethyl phosphite (45 ml) was added and a stream of oxygen passed through the mixture for 2 h with stirring at −78 °C. The reaction mixture was quenched by addition of acetic acid (35 ml) and water (500 ml) and most of the THF was evaporated off. The residue was extracted with ethyl acetate (4 × 100 ml) and the combined extracts washed with 10% aqueous potassium hydrogen carbonate (100 ml), and then dried and evaporated to give a yellow oil. The oil was dissolved in ether (240 ml) and allowed to crystallise at 0 °C. The *hydroxy-ester* (29) (36 g, 85%) was obtained as colourless crystals, m.p. 74—75 °C (Found: C, 59.2; H, 6.35. $C_{16}H_{20}O_7$ requires C, 59.25; H, 6.2%); $\nu_{max.}$ ($CHCl_3$) 3 500, 1 735, and 1 600 cm^{-1}; δ 6.7 (2 H, s, ArH), 4.17 (4 H, m, OCH_2CH_2O), 3.78 (6 H, s, 2 OMe), 3.73 (3 H, s, OMe), 3.08 (2 H, m, CH_2), and 3.33 (2 H, m, CH_2).

Methyl 1',2',3',4'-*Tetrahydro*-3'-*hydroxy*-5',8'-*dimethoxyspiro*[1,3-*dithiolan*-2,1'-*naphthalene*]-3'-*carboxylate* (30).—Freshly distilled boron trifluoride–ether (4 ml) was added rapidly to a stirred solution of the hydroxy-ester (29) (10.0 g) and ethane-1,2-dithiol (4 ml) in dichloromethane (20 ml) at 0 °C. After 15 min the mixture was poured into ether (200 ml) and the solution washed with 5% aqueous sodium hydroxide (2 × 40 ml) and water (40 ml). It was then dried and evaporated to give a yellow oil which was purified by column chromatography on silica gel, using ether–hexane (1 : 2) as eluant. The *hydroxy-ester* (30) (9.4 g, 85%) was obtained as colourless crystals, m.p. 103.5—104 °C (from ether–hexane) (Found: C, 53.95; H, 5.55; S, 17.9. $C_{16}H_{20}O_5S_2$ requires C, 53.9; H, 5.65; S, 18.0%); M^+, 356; $\nu_{max.}$ 3 420, 1 720, and 1 590 cm^{-1}; δ 6.73 (2 H, s, ArH), 3.83 (3 H, s, OMe), 3.76 (3 H, s, OMe), 3.72 (3 H, s, OMe), 3.48 (4 H, m, SCH_2CH_2S), 3.3 (1 H, s, OH), 3.04 (2 H, s, CH_2), and 2.8 (2 H, s, CH_2).

Methyl 3'-*Acetoxy*-1',2',3',4'-*tetrahydro*-5',8'-*dimethoxyspiro*[1,3-*dithiolan*-2,1'-*naphthalene*]-3'-*carboxylate* (31).—A mixture of the hydroxy-ester (30) (2.0 g), acetic anhydride (2.5 ml), 4-dimethylaminopyridine (0.04 g), and pyridine (20 ml) was left at 0 °C for 20 h. It was then poured into water (200 ml) and the product extracted with ethyl acetate (3 × 150 ml). The combined ethyl acetate extracts were washed with 5M-hydrochloric acid (400 ml), water (400 ml), 10% aqueous potassium hydrogen carbonate (400 ml), and water (400 ml), dried and evaporated to give a white solid. Recrystallisation from ether–hexane gave the *acetate* (31) (2.0 g, 89%) as colourless crystals, m.p. 151—152 °C

(Found: C, 54.2; H, 5.5; S, 16.0. $C_{18}H_{22}O_6S_2$ requires C, 54.25; H, 5.5; S, 16.1%); M^+, 398; δ 6.76 (2 H, s, ArH), 3.84 (3 H, s, OMe), 3.75 (6 H, s, 2 OMe), 3.44 (4 H, m, SCH_2CH_2S), 3.4—2.6 (4 H, m, 2 CH_2), and 2.03 (3 H, s, Ac).

3'-Acetoxy-3'-acetyl-1',2',3',4'-tetrahydro-5',8'-dimethoxyspiro[1,3-*dithiolan*-2,1'-*naphthalene*] (33).—A 50% dispersion of sodium hydride in mineral oil (2.55 g) was suspended in dry dimethyl sulphoxide (DMSO) and the mixture stirred at 65 °C under nitrogen until evolution of hydrogen ceased. It was then cooled to 0 °C and diluted with dry THF (30 ml). A solution of the hydroxy-ester (30) (4.0 g) in THF (30 ml) was then added dropwise during 10 min. After being stirred at 0 °C for 15 min, the mixture was poured into water (200 ml) and hydrochloric acid added until the solution was at pH 3. It was then extracted with dichloromethane (5 × 100 ml) and the combined extracts washed with water (200 ml), dried and evaporated to give crude β-keto-sulphoxide as a yellow solid. This material was dissolved, without purification, in THF (150 ml) and water (15 ml) and the solution cooled to 12 °C with stirring under nitrogen. Aluminium amalgam (3.5 g) was added and the mixture was stirred at 12 °C for 2 h; it was then filtered and the solvent evaporated. The residue was dissolved in ethyl acetate (100 ml), washed with water (100 ml), dried, and evaporated to give a cream solid. Recrystallisation from dichloromethane–ether gave the *hydroxy-ketone* (32) (2.5 g, 66%) as colourless crystals, m.p. 152.5—153 °C (Found: C, 56.3; H, 5.95; S, 18.75. $C_{16}H_{20}O_4S_2$ requires C, 56.45; H, 5.9; S, 18.85%); M^+, 340; $\nu_{max.}$ 3 460, 1 700, and 1 590 cm^{-1}; δ 6.73 (2 H, s, ArH), 3.85 (3 H, s, OMe), 3.73 (3 H, s, OMe), 3.47 (4 H, m, SCH_2CH_2S), 3.1—2.5 (4 H, m, 2 CH_2), and 2.33 (3 H, s, Ac).

From the hydroxy-ketone (32), as described for the preparation of compound (31), the acetate (33) (97%) was obtained as colourless crystals, m.p. 162—163 °C (from dichloromethane–ether) (Found: C, 56.45; H, 5.9; S, 16.45. $C_{18}H_{22}O_5S_2$ requires C, 56.6; H, 5.8; S, 16.75%); M^+, 382; $\nu_{max.}$ 1 740, 1 720, and 1 590 cm^{-1}; δ 6.7 (2 H, s, ArH), 3.83 (3 H, s, OMe), 3.71 (3 H, s, OMe), 3.42 (4 H, m, SCH_2CH_2S), 3.4—2.4 (4 H, m, 2 CH_2), 2.17 (3 H, s, Ac), and 2.05 (3 H, s, Ac).

3-Acetoxy-3-acetyl-1,1-ethylenedioxy-1,2,3,4-tetrahydro-5,8-dimethoxynaphthalene (35).—From the hydroxy-ester (29), as described for the preparation of compound (32), the *hydroxy-ketone* (34) (66%) was obtained as colourless crystals, m.p. 59—60 °C (Found: C, 62.3; H, 6.5. $C_{16}H_{20}O_6$ requires C, 62.35; H, 6.55%); M^+, 308; δ 6.6 (2 H, s, ArH), 4.1 (4 H, m, OCH_2CH_2O), 3.68 (3 H, s, OMe), 3.62 (3 H, s, OMe), 2.9 (2 H, m, CH_2), 2.24 (3 H, s, Ac), and 2.2 (3 H, m, CH_2 and OH).

From the hydroxy-ketone (34), using the procedure described for the preparation of compound (31), the acetate (35) was obtained as colourless crystals, m.p. 144—146 °C.

Reaction of the Quinones (40), (41), (42), *and* (37) *with* trans-1,2-*Diacetoxy*-1,2-*dihydrobenzocyclobutene*.—A solution of the quinone (40) (234 mg, 0.66 mmol) and *trans*-1,2-diacetoxy-1,2-dihydrobenzocyclobutene (48) (220 mg, 1.0 mmol) in xylene (15 ml) was refluxed under nitrogen for 40 min. The mixture was evaporated and the residue was suspended in ether (15 ml), cooled to 0 °C overnight, and filtered to give *3',6',11'-triacetoxy-3'-acetyl-1',2',3',4',5',5a',6',11',11a',12'-decahydro-5',12'-dioxospiro*[1,3-*dithiolan*-2,1'-*naphthacene*] (49) (298 mg, 78%) as a pale yellow solid, m.p. 135—145 °C (solidifies at *ca.* 170 °C, remelts at 240 °C) (Found: C, 58.6; H, 4.8. $C_{28}H_{28}O_9S_2$ requires C, 58.7; H, 4.9%); M^+ − 2 AcOH, 452; $\nu_{max.}$ 1 735, 1 675, and 1 600 cm^{-1}; $\lambda_{max.}$ 252 and 304 nm (log ε 3.89 and 3.18); δ 7.6—7.3 (4 H, m, ArH), 6.30—6.18 (2 H, m, 6'- and 11'-H), 3.85—3.30 (6 H, m, 5a'-, 11a'-H and SCH_2CH_2S), 3.10—2.32 (4 H, m, 2'- and 4'-H_2), 2.19 (3 H, s, Ac), 2.17 (3 H, s, Ac), 2,07 (3 H, s, Ac), and 2.04 (3 H, s, Ac).

Similar reaction of the diacetoxy-compound (48) with the dithiolan (40) during a longer period (18 h) gave the quinone (45) in 80% yield.

An analogous reaction of the quinone (41) with compound (48) gave *3,6,11-triacetoxy-3-acetyl-1,1-ethylenedioxy-1,2,3,4,5,5a,6,11,11a,12-decahydronaphthacene-5,12-quinone* (50) (42%) as a pale yellow solid, m.p. 133—143 °C (solidifies at *ca.* 165 °C, remelts at 221—225 °C) (Found: C, 62.2; H, 5.5. $C_{28}H_{28}O_{11}$ requires C, 62.2; H, 5.2%); M^+, 540; $\nu_{max.}$ 1 735, 1 690, and 1 660 cm^{-1}; $\lambda_{max.}$ 242 and 300 nm (log ε 4.18 and 3.48); δ 7.56—7.32 (4 H, m, ArH), 6.34—6.15 (2 H, m, 6- and 11-H), 4.3—3.8 (4 H, m, OCH_2CH_2O), 3.68—3.56 (2 H, m, 5a- and 11a-H), 3.10—2.34 (4 H, m, 2- and 4-H_2), 2.15 (3 H, s, Ac), 2.08 (3 H, s, Ac), and 2.02 (6 H, s, 2 Ac); after a longer reaction time *3-acetoxy-3-acetyl-1,1-ethylenedioxy-1,2,3,4,5,12-hexahydronaphthacene-5,12-quinone* (46) (57%) was obtained as a bright yellow solid, m.p. 232—236 °C (Found: C, 68.8; H, 4.8. $C_{24}H_{20}O_7$ requires C, 68.6; H, 4.8%); M^+, 420; $\nu_{max.}$ 1 725, 1 665, 1 620, and 1 590 cm^{-1}; $\lambda_{max.}$ 243, 260, 291, 302, and 415 nm (log ε 4.42, 4.28, 4.16, 4.18, and 3.61); δ 8.62 (2 H, s, ArH), 8.14—8.00 (2 H, m, ArH), 7.77—7.64 (2 H, m, ArH), 4.55—3.95 (4 H, m, OCH_2CH_2O), 3.62—2.30 (4 H, m, 2- and 4-H_2), 2.25 (3 H, s, Ac), and 2.10 (3 H, s, Ac).

Similarly reaction of compound (48) with the quinone (42) gave *methyl 6',11'-diacetoxy-1',2',3',4',5',5a',6',11',11a',12'-decahydro-5',12'-dioxospiro*[1,3-*dithiolan*-2,1'-*naphthacene*]-*3'-carboxylate* (51) (58.5%) as a pale yellow crystalline solid, m.p. 186—188 °C (Found: C, 58.6; H, 4.9. $C_{26}H_{26}O_8S_2$ requires C, 58.85; H, 4.9%); M^+, 530; $\lambda_{max.}$ 250 and 310 nm (log ε 4.09 and 3.30); δ 7.62—7.30 (4 H, m, ArH), 6.28—6.18 (2 H, m, 6'- and 11'-H), 3.9—3.3 (6 H, m, 5a'-, 11a'-H and SCH_2CH_2S), 3.76 (3 H, s, CO_2Me), 3.15—2.15 (5 H, m, 3'-H and 2-, 4'-H_2), 2.06 (3 H, s, Ac), and 2.05 (3 H, s, Ac); on prolonged reaction the *quinone* (47) (60%) was obtained as bright orange crystals, m.p. 216 °C (Found: C, 64.4; H, 4.3. $C_{22}H_{16}O_4S_2$ requires C, 64.4; H, 4.4%); M^+, 410; $\nu_{max.}$ 1 725, 1 665, 1 620, and 1 590 cm^{-1}; $\lambda_{max.}$ 246, 282sh, 290, 302, and 415 nm (log ε 4.38, 4.21, 4.21, 4.19, and 3.65); δ 8.65 (1 H, s, ArH), 8.62 (1 H, s, ArH), 8.11—7.99 (2 H, m, ArH), 7.73—7.61 (2 H, m, ArH), 4.25—3.5 (4 H, m, SCH_2CH_2S), 3.80 (3 H, s, CO_2Me), and 3.5—2.2 (5 H, m, 2'-, 4'-H_2 and 3'-H). The quinone (37) gave *methyl 6,11-diacetoxy-1,2,3,4,5,5a,6,11,11a,12-decahydro-5,12-dioxonaphthacene-2-carboxylate* (52) (45%) as a pale yellow solid, m.p. 130—135 °C (Found: C, 65.7; H, 5.5. $C_{24}H_{24}O_8$ requires C, 65.45; H, 5.5%); M^+ − 2 AcOH, 320; $\lambda_{max.}$ 254 and 297 nm (log ε 4.11 and 3.33); δ 7.58—7.32 (4 H, m, ArH), 6.35—6.20 (2 H, m, 6- and 11-H), 3.78—3.60 (5 H, m, 5a-, 11a-H and CO_2Me), 2.8—2.4 (5 H, m, 2 CH_2 and CH), 2.2—1.6 (2 H, m, CH_2), 2.03 (3 H, s, Ac), and 2.00 (3 H, s, Ac); after longer reaction times the quinone (19) was obtained in 81% yield.

3-[1-(1,1-Ethylenedioxy)ethyl]-1,2,3,4-tetrahydro-3-hydroxy-5,8-dimethoxynaphthalenone (53).—A mixture of the hydroxy-ketone (32) (2.0 g), ethylene glycol (15 ml), and toluene-4-sulphonic acid (0.1 g) in benzene (150 ml) was

heated under reflux, using a Dean-Stark water separator, for 6 h. The solution was allowed to cool and was then washed with 10% aqueous potassium hydrogen carbonate (2 × 100 ml) and water (2 × 100 ml), dried and evaporated. Crystallisation of the residue from dichloromethane–ether gave 3′-[1-(1,1-*ethylenedioxy*)*ethyl*]-1′,2′,3′,4′-*tetrahydro*-3′-*hydroxy*-5′,8′-*dimethoxyspiro*[1,3-*dithiolan*-2,1′-*naphthalene*] (2.04 g, 90%) as colourless crystals, m.p. 162.5—163 °C (Found: C, 56.25; H, 6.5; S, 16.65. $C_{18}H_{24}S_2O_5$ requires C, 56.25; H, 6.3; S, 16.7%); M^+, 384; $\nu_{max.}$ 3 530 and 1 600 cm^{-1}; δ 6.66 (2 H, s, ArH), 4.0 (4 H, s, OCH_2CH_2O), 3.81 (3 H, s, OMe), 3.72 (3 H, s, OMe), 3.63—3.2 (4 H, m, SCH_2CH_2S), 3.0—2.4 (5 H, m, 2 CH_2 and OH), and 1.4 (3 H, s, Me). A solution of the above product (2.0 g) in THF (20 ml) was added rapidly to a stirred mixture of yellow mercuric oxide (6.4 g) and mercuric chloride (6.4 g) in methanol (200 ml) and water (18 ml). After stirring at room temperature for 1.25 h, the solvent volume was reduced by *ca.* one half by evaporation under reduced pressure and dichloromethane (300 ml) was added. The suspended inorganic salts were filtered off (Celite) and the filtrate washed with water (3 × 200 ml), dried, and evaporated to give a white solid. Recrystallisation from dichloromethane–ether gave the *ketone* (53) (1.42 g, 89%) as colourless crystals, m.p. 177.5—178 °C (Found: C, 62.35; H, 6.55. $C_{16}H_{20}O_6$ requires C, 62.15; H, 6.5%); $\nu_{max.}$ 3 410, 1 685, and 1 590 cm^{-1}; δ 6.82 (2 H, ABq, *J* 9 Hz, ArH), 3.98 (4 H, s, OCH_2CH_2O), 3.81 (3 H, s, OMe), 3.77 (3 H, s, OMe), 3.1 (2 H, m, CH_2), 2.77 (2 H, m, CH_2), 2.23 (1 H, s, OH), and 1.4 (3 H, s, Me).

cis-3-[1-(1,1-*Ethylenedioxy*)*ethyl*]-1,2,3,4-*tetrahydro*-5,8-*dimethoxynaphthalene*-1,3-*diyl Benzeneboronate* (56).—Lithium borohydride (0.12 g) was added to a stirred solution of the ketone (53) (0.75 g) in THF (40 ml). The mixture was stirred at room temperature for 3 h and the solvent evaporated. The residue was dissolved in 10% aqueous ammonium chloride (100 ml) and the solution extracted with ethyl acetate (3 × 100 ml). The combined extracts were washed with water (200 ml), dried, and evaporated to give a mixture of the diols (54) and (55) (0.75 g, 100%) as a colourless gum. This mixture was dissolved in toluene (50 ml) and benzeneboronic acid (0.35 g) and toluene-4-sulphonic acid (0.03 g) were added. The solution was stirred at room temperature for 18 h and was then washed with 5% aqueous potassium hydrogen carbonate, dried, and evaporated to give a colourless gum. Crystallisation from ether–hexane gave the *benzeneboronate* (56) (0.78 g, 81%) as colourless crystals, m.p. 149—149.5 °C (Found: C, 66.9; H, 6.1. $C_{22}H_{25}BO_6$ requires C, 66.7; H, 6.35%); M^+, 396; $\nu_{max.}$ 1 600 cm^{-1}; δ 7.4 (2 H, m, ArH), 7.23 (3 H, m, ArH), 6.64 (2 H, s, ArH), 5.6 (1 H, t, *J* 3 Hz, CH), 4.05 (4 H, s, OCH_2CH_2O), 3.84 (3 H, s, OMe), 3.75 (3 H, s, OMe), 3.05 (2 H, m, CH_2), 2.7—1.8 (2 H, m, CH_2), and 1.56 (3 H, s, Me).

cis-3-[1-(1,1-*Ethylenedioxy*)*ethyl*]-1,2,3,4,5,8-*hexahydro*-5,8-*dioxonaphthalene*-1,3-*diyl Benzeneboronate* (57).—A solution of ammonium ceric nitrate (21.10 g, 0.038 mol) in water (370 ml) was added over 5 min to a stirred solution of the dimethyl ether (56) (7.60 g, 0.019 mol) in acetonitrile (370 ml). The mixture was stirred for 5 min and then diluted with water (1.83 l) and extracted with dichloromethane (4 × 500 ml). The combined extracts were washed with water (500 ml), dried, and evaporated to give the *quinone* (57) as a yellow gum which was used without purification for the next reaction.

cis-3-[1-(1,1-*Ethylenedioxy*)*ethyl*]-1,2,3,4,5,12-*hexahydro*-5,12-*dioxonaphthacene*-1,3-*diyl Benzeneboronate* (58).—A solution of the crude quinone (57) and the benzocyclobutene (48) (4.39 g, 0.020 mol) in xylene (397 ml) was refluxed under nitrogen for 3 h. The solvent was evaporated off and the residue was triturated with ether (50 ml) and filtered to give the *quinone* (58) (7.10 g, 79%) as a bright yellow crystal, line solid, m.p. 239—241 °C (Found: C, 72.05; H, 5.05. $C_{28}H_{23}BO_6$ requires C, 72.1; H, 4.95%); M^+, 466; $\nu_{max.}$ 1 665, 1 640, 1 600, and 1 590 cm^{-1}; δ 8.70 (1 H, s, ArH), 8.62 (1 H, s, ArH), 8.1 (2 H, m, ArH), 7.7 (4 H, m, ArH), 7.3 (3 H, m, ArH), 5.72 (1 H, t, *J* 3 Hz, CH), 4.12 (4 H, s, OCH_2CH_2O), 3.4—2.88 (2 H, m, CH_2), 2.56—1.88 (2 H, m, CH_2), and 1.58 (3 H, s, Me).

cis-5,12-*Diacetoxy*-3-*acetyl*-1,2,3,4-*tetrahydronaphthacene*-1,3-*diyl Benzeneboronate* (59).—(*a*) A solution of the quinone (58) (7.00 g, 0.015 mol) in dioxan (1.51 l) was stirred at 18 °C and ice-cold 6M-hydrochloric acid (1.12 l) added during 7 min. The mixture was stirred at room temperature for 4 h and then diluted with water (1.69 l). The solution was extracted with dichloromethane (3 × 560 ml) and the combined extracts were washed with 10% aqueous potassium hydrogen carbonate (1.09 l), dried and evaporated. The residue was triturated with ether and filtered to give cis-3-*acetyl*-1,2,3,4,5,12-*hexahydro*-5,12-*dioxonaphthacene*-1,3-*diyl benzeneboronate* (5.55 g, 88%) as a bright yellow solid, M^+ 422.

(*b*) A solution of the product prepared above (5.45 g, 0.013 mol) in a mixture of pyridine (300 ml) and acetic anhydride (150 ml) was hydrogenated over 10% Pd–C catalyst (0.59 g) at atmospheric pressure for 40 min. The catalyst was filtered off and the filtrate evaporated. The residue was suspended in ether (120 ml), cooled to 0 °C for 18 h, and filtered to give the *diacetate* (59) (5.95 g, 91%) as a light brown solid, M^+ 508.

cis-3-*Acetyl*-1,2,3,4,6,11-*hexahydro*-1,3,5,12-*tetrahydroxynaphthacene*-6,11-*quinone* [(±)-4-*Demethoxydaunomycinone*] (2).—(*a*) A suspension of the diacetate (59) (2.75 g, 5.4 mmol) in a mixture of acetic anhydride (53 ml) and glacial acetic acid (160 ml) was stirred, and finely ground chromium trioxide (2.16 g, 21.6 mmol) was added. The mixture was stirred at room temperature for 20 h and then poured into water (500 ml) and extracted with dichloromethane (5 × 250 ml). The combined extracts were washed with water (4 × 500 ml), dried, and evaporated. The resulting orange gum was suspended in ether (100 ml), cooled to −20 °C for 18 h, and filtered to give cis-5,12-*diacetoxy*-3-*acetyl*-1,2,3,4,6,-11-*hexahydro*-6,11-*dioxonaphthacene*-1,3-*diyl benzeneboronate* (1.46 g, 50%) as a light brown solid, M^+ 538

(*b*) A solution of the quinone prepared above (1.42 g, 2.6 mmol) in dichloromethane (330 ml) was cooled to −70 °C and a solution of boron trichloride (6.0 ml) in dichloromethane (24 ml) was added. The mixture was stirred and allowed to warm to 10 °C during 1.5 h; it was then poured into ice-cold 2M-hydrochloric acid (330 ml) and the layers were separated. The aqueous phase was further extracted with dichloromethane (2 × 300 ml) and the combined dichloromethane solutions were washed with water (2 × 500 ml), dried, and evaporated to give cis-3-*acetyl*-1,2,3,4,6,11-*hexahydro*-5,12-*dihydroxy*-6,11-*dioxonaphthacene*-1,3-*diyl benzeneboronate* (1.15 g, 96%) as a red gum, M^+ 454.

(*c*) A solution of the benzeneboronate prepared above (160 mg, 0.35 mmol) in a mixture of dichloromethane (18 ml), 2-methylpentane-2,4-diol (4.5 ml) and glacial acetic acid (0.75 ml) was stirred at room temperature for 42 h.

The solution was then washed with water (3 × 40 ml), dried, and evaporated. The residue was crystallised from a mixture of dichloromethane and ether to give (±)-4-demethoxydaunomycinone (2) (115 mg, 89%) as a bright red solid, m.p. 174—178 °C (lit.,[25] 183 °C; variable m.p. between 167—170 °C and 197—200 °C [24]) (Found: C, 65.35; H, 4.5. Calc. for $C_{20}H_{16}O_7$: C, 65.2; H, 4.4%); M^+, 368; $\nu_{max.}$ 3 600—2 400, 1 730, 1 635, and 1 600 cm^{-1}; δ 13.54 (1 H, s, exch. D_2O, ArOH), 13.26 (1 H, s, exch. D_2O, ArOH), 8.40—8.28 (2 H, m, ArH), 7.91—7.79 (2 H, m, ArH), 5.30 (1 H, br s, 1-H), 4.55 (1 H, s, exch. D_2O, 3-OH), 3.78 (1 H, d, J 6 Hz, exch. D_2O, 1-OH), 3.19 (1 H, dd, $J_{4\text{-}eq,2\text{-}eq}$ 2 Hz, $J_{4\text{-}eq,4\text{-}ax}$ 19 Hz, 4-*eq*-H), 2.96 (1 H, d, $J_{4\text{-}eq,4\text{-}ax}$ 19 Hz, 4-*ax*-H), 2.45 (3 H, s, Ac), 2.36 (1 H, dt, $J_{4\text{-}eq,2\text{-}eq} = J_{2\text{-}eq,1}$ = 2 Hz, $J_{2\text{-}eq,2\text{-}ax}$ 15 Hz, 2-*eq*-H), and 2.18 (1 H, dd, $J_{2\text{-}ax,1}$ 5 Hz, $J_{2\text{-}ax,2\text{-}eq}$ 15 Hz, 2-*ax*-H).

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