Anthracyclines. Part 1. The Synthesis of Racemic Daunomycinone and Some Related Tetrahydronaphthacenequinones

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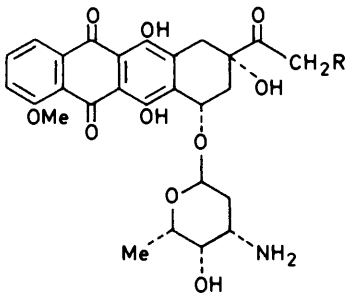
New tetrahydronaphthacenequinones, which are related in structure to the aglycones of the antitumour drugs adriamycin and daunomycin, have been synthesised. Racemic daunomycinone has been prepared by a new, mild procedure utilising a phthalide intermediate for annelation.

OUR earlier studies [1,2] have identified novel procedures for the synthesis of polycyclic quinones related to natural tetracyclines. In view of the continuing importance of daunomycin (1), adriamycin (2), and related glycosides in



(1) Daunomycin, R = H
(2) Adriamycin, R = OH

the treatment of human cancer [3-7] we have studied the application of these and alternative procedures to the synthesis of biologically active anthracyclines. The high cost and limited availability of naturally occurring anthracyclines has made total synthesis of these compounds, or analogues with advantages for use in therapy, an attractive goal. In spite of extensive and elegant investigations in various laboratories,[5,8] a synthesis that provides a practicable and proven basis for preparing large quantities of optically pure anthracyclines for use in human medicine has still to be found.

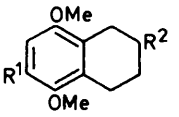
At the outset of this investigation the only published account of a total synthesis of fully functionalised daunomycin analogues was that of Wong and co-workers.[9,10] They utilised the phthalic anhydride procedure which has been employed extensively for anthraquinone synthesis; there was no attempt to achieve regio- or stereo-chemical control. Earlier experience [1,2] with base-catalysed, regiospecific cyclisations yielding anthraquinones encouraged us to investigate similar procedures for the synthesis of anthracyclines. Compound (27), which is unsubstituted in rings A and D, was prepared in excellent yield by treatment of the benzophenone-ester (21) with potassium t-butoxide in dimethyl sulphoxide at 30 °C followed by oxidation of the intermediate (24) with alkaline hydrogen peroxide. Attempts to extend the procedure to the more highly substituted tetrahydronaphthacene derivatives (28) and (29) were discouraged by low yields in the preparation of the intermediate benzophenones by condensation of the substituted benzoic acid with the appropriate tetrahydronaphthalene derivatives (7) and (12) using trifluoroacetic anhydride. To avoid this, the benzophenone (31) was prepared (45% yield) through the ester (20) by rearrangement with boron trifluoride-diethyl ether. When the corresponding diacid (32) was cyclised with sulphuric acid alone, it could be shown by the ^{1}H n.m.r. spectra of the methylation product that there was a mixture of isomers (33) and (34) in the ratio *ca.* 2 : 1 (*cf.* ref. 11). Presumably, under these conditions there is a partial Hayashi rearrangement [12] through the spirocyclic intermediate (35). This rearrangement was prevented by cyclisation using sulphuric acid containing boric acid; [13,14] under these conditions the single product (33) was obtained.

However, this procedure was not investigated further. The limited yield, overall, and the susceptibility of ring A substituents in adriamycin and daunomycin to the reaction conditions discouraged its application to the preparation of more complex anthracyclines.

Two alternative procedures, both utilising phthalides, have been investigated. In the first case, the phthalide (41) was prepared by the interaction of the dilithio-derivative (40) and the aldehyde (8) using procedures which have been established for related compounds.[15-18] This phthalide was converted into the tetracyclic quinone (29) by reduction with zinc followed by acid-catalysed cyclisation and oxidation with hydrogen peroxide or chromium trioxide (Scheme 1).

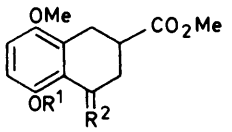
The second procedure for phthalide preparation had the advantages of higher yield and very mild conditions; it employed a little-utilised reagent, benzeneboronic acid, which has been shown to promote the condensation of aldehydes and phenols.[19] When the phenol (57) reacted with the aldehyde (38) in the presence of benzeneboronic acid and propionic acid as catalyst, the boronate (62) was formed. It was converted into the phthalide (44) (83% overall yield) by treatment with an excess of 2-methylpentane-2,4-diol. The regiospecificity of the procedure has been established by showing that the phthalide (44) prepared in this way was converted, as for the previous case, into the corresponding quinone (53), alone. Similarly, the naphthacenequinones (33) and (54) have been prepared from the phenols (15) and (61), respectively.

The utilisation of substituted 1,2,3,4,6,11-hexahydro-

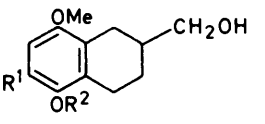


(3) R^1 = CHO, R^2 = H
(4) R^1 = CH_2OH, R^2 = H
(5) R^1 = CH_2CN, R^2 = H
(6) R^1 = CH_2CO_2H, R^2 = H
(7) R^1 = CH_2CO_2Me, R^2 = H

(8) R^1 = CHO, R^2 = CH_2OMe
(9) R^1 = CH_2OH, R^2 = CH_2OMe
(10) R^1 = CH_2CN, R^2 = CH_2OMe
(11) R^1 = CH_2CO_2H, R^2 = CH_2OMe
(12) R^1 = CH_2CO_2Me, R^2 = CH_2OMe

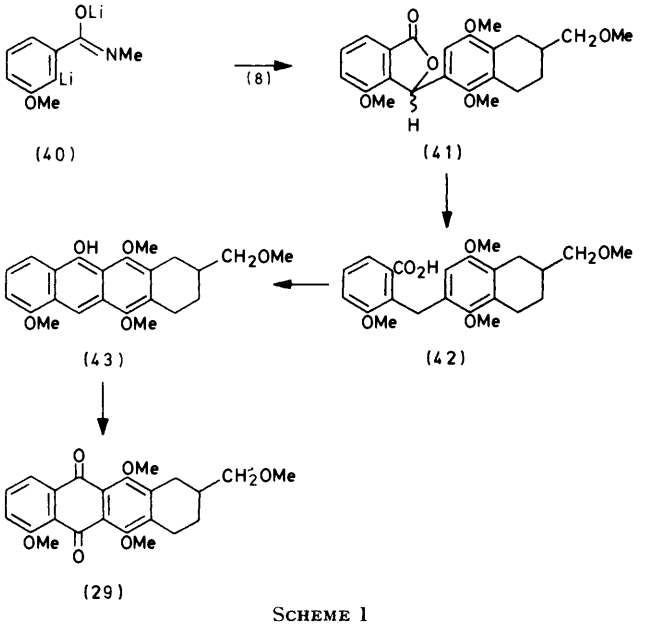


(13) R^1 = Me, R^2 = O
(14) R^1 = H, R^2 = O
(15) R^1 = H, R^2 = H_2
(16) R^1 = $CH_2CH{=}CH_2$, R^2 = H_2
(17) R^1 = CH_2Ph, R^2 = H_2



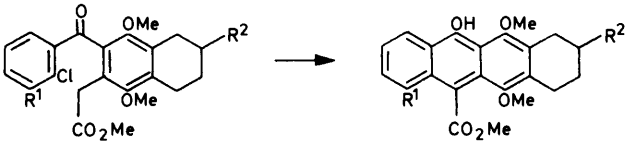
(18) R^1 = H, R^2 = $CH_2CH{=}CH_2$
(19) R^1 = $CH_2CH{=}CH_2$, R^2 = H
(20) R^1 = $CH_2CH{=}CH_2$, R^2 = Me

5,7,12-trimethoxynaphthacene-6,11-quinones for the synthesis of natural anthracyclines requires partial demethylation to give the corresponding 5,12-dihydroxy-derivatives. Earlier studies [9,20,21] suggested that this could be achieved only with difficulty. However, we have found that, using boron trichloride, specific demethylation is accomplished easily and in high yield. By this means, the derivatives (53) and (33) were converted into racemic 7,9-dideoxydaunomycinone (63) [11,20] and the ester (64), respectively. Similarly, after deacetalisation of the intermediate (54), treatment with boron trichloride gave an excellent yield of racemic 7-deoxydaunomycinone (65).

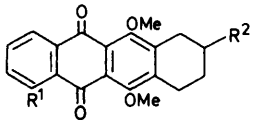


(40) (41) (42) (43) (29)

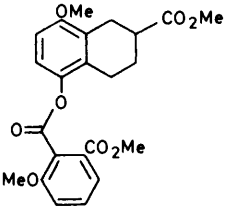
SCHEME 1



(21) R^1 = R^2 = H (24)
(22) R^1 = OMe, R^2 = H (25)
(23) R^1 = OMe, R^2 = CH_2OMe (26)



(27) R^1 = R^2 = H
(28) R^1 = OMe, R^2 = H
(29) R^1 = OMe, R^2 = CH_2OMe



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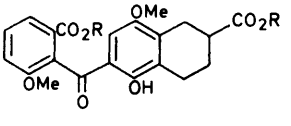
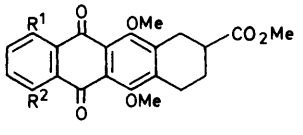
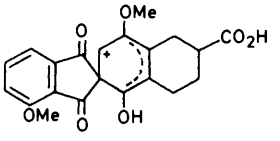


(31) R = Me
(32) R = H



(33) R^1 = H, R^2 = OMe
(34) R^1 = OMe, R^2 = H



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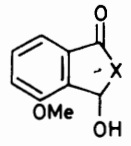
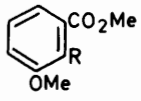
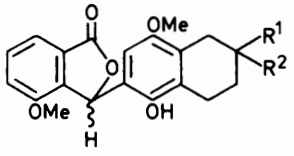


(36) X = NMe
(37) X = O

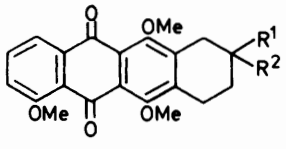


(38) R = CHO
(39) R = CO_2H

In our hands, the reported conversion of racemic 7-deoxydaunomycinone (65) to daunomycin [22] gave poor results. Better results were obtained when the naphthacene (54) was brominated with *N*-bromosuccinimide and the resulting mixture treated with silver acetate in

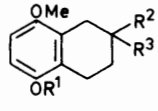


(44) R^1 = COMe, R^2 = H
(45) R^1 = CO_2Me, R^2 = H
(46) R^1 = $C(OCH_2CH_2O)Me$, R^2 = OH

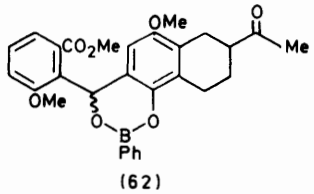


(53) R^1 = COMe, R^2 = H
(54) R^1 = $C(OCH_2CH_2O)Me$, R^2 = OH

acetic acid (Scheme 2). This gave the acetate (66) which has the required *cis*-stereochemistry as the major product (60%), together with a small amount of the *trans*-compound (67) (8%). Deprotection of compound (66) with sodium methoxide followed by hydrochloric acid in dioxan gave a good yield of racemic dimethyl-



(55) R^1 = CH_2Ph, R^2 = CO_2H, R^3 = H
(56) R^1 = CH_2Ph, R^2 = COMe, R^3 = H
(57) R^1 = R^3 = H, R^2 = COMe
(58) R^1 = CH_2Ph, R^2 = CO_2Me, R^3 = OH
(59) R^1 = CH_2Ph, R^2 = COMe, R^3 = OH
(60) R^1 = CH_2Ph, R^2 = $C(OCH_2CH_2O)Me$, R^3 = OH
(61) R^1 = H, R^2 = $C(OCH_2CH_2O)Me$, R^3 = OH



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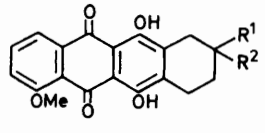
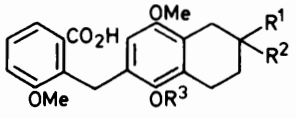


(63) R^1 = COMe, R^2 = H
(64) R^1 = CO_2Me, R^2 = H
(65) R^1 = COMe, R^2 = OH

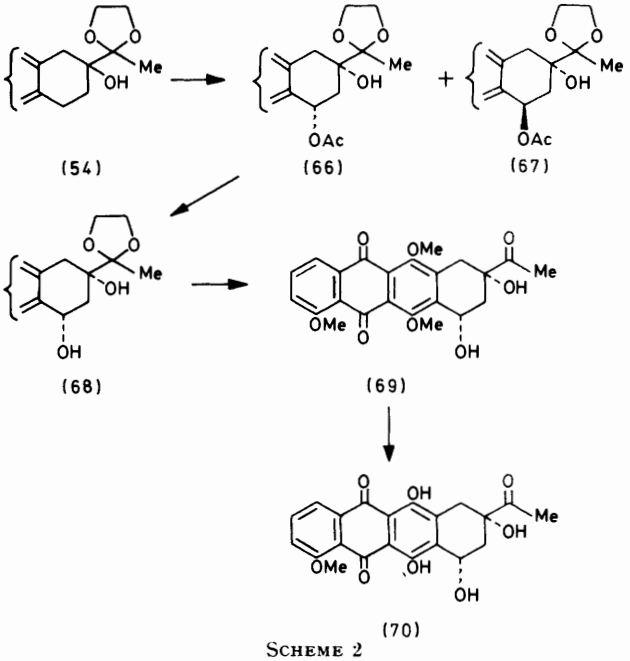
daunomycinone (69) which, on treatment with boron trichloride, gave racemic daunomycinone (70) [22,23] in excellent yield. Optically active intermediates have been obtained by resolution of the carboxylic acid derived from the ester (58) thus allowing the regiospecific synthesis of natural (+)-daunomycinone and related aglycones.

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,



(47) R^1 = COMe, R^2 = R^3 = H
(48) R^1 = CO_2H, R^2 = R^3 = H
(49) R^1 = $C(OCH_2CH_2O)Me$, R^2 = OH, R^3 = H
(50) R^1 = COMe, R^2 = H, R^3 = Me
(51) R^1 = CO_2H, R^2 = H, R^3 = Me
(52) R^1 = $C(OCH_2CH_2O)Me$, R^2 = OH, R^3 = Me



SCHEME 2

u.v. and visible spectra were recorded for chloroform solutions with a Unicam SP 8000 spectrophotometer, and ^1H 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.

For ease of comparison of closely related systems, the numbering of compounds is not in all cases that obtained by the strict application of the I.U.P.A.C. rules of nomenclature.

Tetrahydro-5,8-dimethoxynaphthalene-6-carbaldehyde (3).—A solution of 1,2,3,4-tetrahydro-5,8-dimethoxynaphthalene (4.6 g) in dichloromethane (100 ml) was cooled to 0 °C, treated with titanium tetrachloride (5 ml), and dichloromethyl methyl ether (2.5 ml) then added carefully. After being stirred at 0 °C for 15 min the reaction was quenched by pouring the reaction mixture into 2M-hydrochloric acid (250 ml). The dichloromethane layer was separated, washed with water (2 × 200 ml) and saturated aqueous sodium chloride (200 ml), dried, and evaporated to give an oil which slowly crystallised. Recrystallisation from methanol–water gave the *aldehyde* (3) (4.0 g, 75%) as colourless crystals, m.p. 73—74 °C (Found: C, 70.75; H, 7.25. $C_{13}H_{16}O_3$ requires C, 70.9; H, 7.3%); M^+, 220; $\nu_{max.}$ 1 685 cm^{-1}; δ 10.33 (1 H, s, CHO), 7.10 (1 H, s, ArH), 7.83 (6 H, s, 2 OMe), 2.9—2.5 (4 H, m, 2 $ArCH_2$), and 1.9—1.6 (4 H, m, 2 CH_2).

1,2,3,4-*Tetrahydro-5,8-dimethoxy-6-naphthylmethanol* (4).—The aldehyde (3) (3.8 g) in anhydrous ether (100 ml) was added dropwise with stirring to a suspension of lithium aluminium hydride (1.3 g) in anhydrous ether (100 ml) under nitrogen. After the addition was complete the suspension was stirred at 50 °C under reflux for 1 h and then cooled to 0 °C. The reaction was quenched by careful addition of water (2 ml), 15% sodium hydroxide solution (2 ml), and water (6 ml) with vigorous stirring. The solids were filtered off and the ether was evaporated to give a yellow oil which was purified by column chromatography on silica, using ether–hexane (1 : 1) as eluant. The *alcohol* (4) (3.6 g, 92%) was obtained as colourless crystals, m.p. 65.5—66.5 °C (from methanol–water) (Found: C, 70.1; H, 8.05. $C_{13}H_{18}O_3$ requires C, 70.25; H, 8.15%); M^+, 222; $\nu_{max.}$ 3 350, 3 250, 1 615, and 1 595 cm^{-1}; δ 6.68 (1 H, s, ArH), 4.72 (2 H, s, $ArCH_2OH$), 3.80 (3 H, s, OMe), 3.73 (3 H, s, OMe), 2.90—2.50 (4 H, m, 2 $ArCH_2$), 2.10 (1 H, br s, OH), and 1.9—1.6 (4 H, m, 2 CH_2).

1,2,3,4-*Tetrahydro-5,8-dimethoxy-6-naphthylacetonitrile* (5).—A solution of the alcohol (4) (2.0 g) in anhydrous ether (100 ml) was cooled to 0 °C and a solution of phosphorus tribromide (1 ml) in dry ether (10 ml) added dropwise. After 30 min the solution was washed with aqueous 10% potassium hydrogen carbonate (100 ml), dried and evaporated to give the corresponding bromide as a colourless crystalline solid which was used directly for the next stage. The bromide and potassium cyanide (2 g) were added to ethanol (40 ml) and water (10 ml) and the mixture heated under reflux for 2 h. It was then poured into water (200 ml), extracted with ether, and the ether extracts dried and evaporated. Crystallisation of the residue from ethanol gave the *nitrile* (5) (1.7 g, 82%) as colourless needles, m.p. 77—78 °C (Found: C, 72.5; H, 7.3; N, 5.95. $C_{14}H_{17}NO_2$ requires C, 72.7; H, 7.4; N, 6.05%); M^+ 231; $\nu_{max.}$ 2 240 cm^{-1}; δ 6.70 (1 H, s, ArH), 3.81 (2 H, s, $ArCH_2CN$), 3.78 (6 H, s, 2 OMe), 2.90—2.50 (4 H, m, 2 $ArCH_2$), and 1.9—1.60 (4 H, m, 2 CH_2).

1,2,3,4-*Tetrahydro-5,8-dimethoxy-6-naphthylacetic Acid* (6).—The nitrile (5) (3.0 g) was dissolved in ethanol (20 ml), 10M-sodium hydroxide (20 ml) was added and the mixture heated under reflux with stirring for 7.5 h. The mixture was cooled, most of the ethanol evaporated off, and the remaining solution diluted with water (500 ml). The solution was acidified and extracted with ethyl acetate (3 × 200 ml). The combined extracts were washed with water (300 ml), dried, and evaporated to give the *acid* (6) (2.9 g, 89%) as colourless crystals. Recrystallisation from methanol–water gave needles, m.p. 145—146 °C (Found: C, 66.95; H, 7.35. $C_{14}H_{18}O_4$ requires C, 67.2; H, 7.25%); M^+, 250; $\nu_{max.}$ 1 715 cm^{-1}; δ 10.37 (1 H, br s, exch. D_2O, $ArCH_2CO_2H$), 6.55 (1 H, s, ArH), 3.78 (3 H, s, OMe), 3.70 (3 H, s, OMe), 3.68 (2 H, s, $ArCH_2CO_2H$), 2.90—2.50 (4 H, m, 2 $ArCH_2$), and 1.90—1.50 (4 H, m, 2 CH_2).

Methyl 1,2,3,4-*Tetrahydro-5,8-dimethoxy-6-naphthylacetate* (7).—The acid (6) (1.0 g) was dissolved in methanol (50 ml) and thionyl chloride (0.8 g) added with stirring. After 3 h at room temperature the solvent was evaporated, the residue was taken up in dichloromethane (50 ml) and the solution washed with aqueous 5% potassium hydrogen carbonate (50 ml) and water (50 ml) ; it was then dried and evaporated to yield a pale yellow oil (1.0 g, 95%) which solidified after several weeks. Recrystallisation from methanol–water gave colourless plates, m.p. 48—49 °C (Found: C, 68.2; H, 7.75. $C_{15}H_{20}O_4$ requires C, 68.15; H, 7.65%); M^+, 264; $\nu_{max.}$ 1 740 cm^{-1}; δ 6.56 (1 H, s, ArH), 3.78 (3 H, s, OMe), 3.70 (3 H, s, OMe), 3.67 (3 H, s, OMe), 3.65 (2 H, s, $ArCH_2CO_2Me$), 2.90—2.50 (4 H, m, 2 $ArCH_2$), and 1.90—1.50 (4 H, m, 2 CH_2).

Methyl 7-(2-*Chlorobenzoyl*)-1,2,3,4-*tetrahydro-5,8-dimethoxy-6-naphthylacetate* (21).—A solution of the ester (7) (1.0 g) and 2-chlorobenzoic acid (2.0 g) in trifluoroacetic anhydride (5 ml) was heated at 65 °C for 7 d. The solution was poured into 5% potassium hydrogen carbonate (50 ml) with stirring and the mixture extracted with ethyl acetate (2 × 50 ml). The ethyl acetate extracts were washed with water (50 ml), dried, and evaporated to a gum. Trituration with ether gave the *naphthylacetate* (21) (0.85 g, 56%) as buff crystals. Recrystallisation from dichloromethane–methanol gave colourless prisms, m.p. 118—119 °C (Found: C, 65.6; H, 5.95; Cl, 8.7. $C_{22}H_{23}ClO_5$ requires C, 65.6; H, 5.75; Cl, 8.8%); M^+, 402/404; $\nu_{max.}$ 1 745 and 1 665 cm^{-1}; δ 7.8—7.2 (4 H, m, ArH), 3.79 (2 H, s, $ArCH_2CO_2Me$), 3.77 (3 H, s, OMe), 3.62 (3 H, s, OMe), 3.45 (3 H, s, OMe), 3.0—2.4 (4 H, m, 2 $ArCH_2$), and 1.9—1.6 (4 H, m, 2 CH_2).

Methyl 1,2,3,4-*Tetrahydro-11-hydroxy-5,12-dimethoxynaphthacene-6-carboxylate* (24).—Potassium t-butoxide was added to a stirred solution of the naphthylacetate (21) (2.0 g) in dry dimethyl sulphoxide (40 ml) under nitrogen. The mixture was kept at 30 °C for 10 min and then poured into 2M-hydrochloric acid (200 ml). The suspension was extracted with ethyl acetate (3 × 100 ml) and the extracts were washed with water (3 × 100 ml), dried, and evaporated to give the *naphthacene* (24) (1.2 g, 66%) as yellow crystals, m.p. 149—150 °C (from dichloromethane–ethanol) (Found: C, 71.85; H, 6.05. $C_{22}H_{22}O_5$ requires C, 72.1; H, 6.05%); M^+, 366; $\nu_{max.}$ 3 180, 1 730, 1 625, 1 610, 1 590, and 1 570 cm^{-1}; $\lambda_{max.}$ 272 and 376 nm (log ε 5.02 and 3.89); δ 10.79 (1 H, s, ArOH), 8.42 (1 H, dd, *J* 2 and 8 Hz, ArH), 7.80 (1 H, dd, *J* 2 and 8 Hz, ArH), 7.60—7.28 (2 H, m, ArH), 4.03 (3 H,

s, OMe), 3.93 (3 H, s, OMe), 3.72 (3 H, s, OMe), 4.1—3.8 (4 H, m, 2 $ArCH_2$), and 2.0—1.6 (4 H, m, 2 CH_2).

1,2,3,4,6,11-Hexahydro-5,12-dimethoxynaphthacene-6,11-quinone (27).—The naphthacene (24) (0.6 g) was added to a mixture of ethanol (50 ml), water (5 ml), and sodium hydroxide (0.2 g). Hydrogen peroxide (100 vol; 5 ml) was added and the mixture heated at 70 °C for 1 h. Most of the ethanol was evaporated off, the product dissolved in dichloromethane (50 ml), washed with water (2 × 50 ml), dried and evaporated to give the *naphthacene* (27) (0.37 g, 70%) as yellow crystals, m.p. 171—172 °C (from dichloromethane–ethanol) (Found: C, 74.45; H, 5.65. $C_{20}H_{18}O_4$ requires C, 74.5; H, 5.65%); M^+, 322; $\nu_{max.}$ 1 675, 1 600, and 1 560 cm^{-1}; $\lambda_{max.}$ 264 and 373 nm (log ε 4.53 and 3.73); δ 8.30—8.14 (2 H, m, ArH), 7.82—7.64 (2 H, m, ArH), 3.93 (6 H, s, 2 OMe), 3.0—2.8 (4 H, m, 2 $ArCH_2$), and 1.9—1.7 (2 H, m, 2 CH_2).

Methyl 7-(2-Chloro-3-methoxybenzoyl)-1,2,3,4-tetrahydro-5,8-dimethoxy-6-naphthylacetate (22).—A solution of the ester (7) (1.0 g) and 2-chloro-3-methoxybenzoic acid (1.35 g) in trifluoroacetic anhydride (3 ml) was heated at 60 °C for 6 d. The solution was then poured into 5% potassium hydrogen carbonate (50 ml) with stirring and extracted with ethyl acetate (50 ml). The ethyl acetate extract was washed with water (50 ml), dried, and evaporated to a gum. Crystallisation from methanol gave the *naphthylacetate* (22) (0.8 g, 49%) as tan prisms, m.p. 139—140 °C (Found: C, 63.7; H, 5.7; Cl, 8.35. $C_{23}H_{25}ClO_6$ requires C, 63.8; H, 5.8; Cl, 8.2%); M^+, 432/434; $\nu_{max.}$ 1 735 and 1 695 cm^{-1}; δ 7.4—7.0 (3 H, m, ArH), 3.96 (3 H, s, OMe), 3.80 (2 H, s, $ArCH_2CO_2Me$), 3.77 (3 H, s, OMe), 3.66 (3 H, s, OMe), 3.49 (3 H, s, OMe), 3.0—2.5 (4 H, m, 2 $ArCH_2$), and 1.9—1.7 (4 H, m, 2 CH_2).

Methyl 1,2,3,4-Tetrahydro-11-hydroxy-5,7,12-trimethoxynaphthacene-6-carboxylate (25).—Potassium t-butoxide (0.35 g) was added to a stirred solution of the naphthylacetate (22) (0.4 g) in dry dimethyl sulphoxide (8 ml) under nitrogen at 30 °C. After 10 min the mixture was poured into 2M-hydrochloric acid (50 ml) and extracted with ethyl acetate (3 × 50 ml). The combined extracts were washed with water (3 × 50 ml), dried, and evaporated to give the *naphthacene* (25) (0.23 g, 63%) as yellow crystals, m.p. 175—177 °C (from methanol) (Found: C, 69.6; H, 6.2. $C_{23}H_{24}O_6$ requires C, 69.7; H, 6.1%); M^+, 396; $\nu_{max.}$ 3 200, 1 730, 1 630, 1 610, 1 595, and 1 570 cm^{-1}; $\lambda_{max.}$ 269, 362, 382, 405, and 428 nm (log ε 4.67, 3.50, 3.80, 3.64, and 3.47); δ 10.84 (1 H, s, ArOH), 8.08 (1 H, d, *J* 8 Hz, ArH), 7.30 (1 H, t, *J* 8 Hz, ArH), 6.84 (1 H, d, *J* 8 Hz, ArH), 3.98 (6 H, s, 2 OMe), 3.89 (3 H, s, OMe), 3.72 (3 H, s, OMe), 3.05—2.8 (4 H, m, 2 $ArCH_2$), and 2.0—1.7 (4 H, m, 2 CH_2).

Methyl 1,2,3,4-Tetrahydro-5,8-dimethoxy-4-oxonaphthalene-2-carboxylate (13).—1,2,3,4-Tetrahydro-5,8-dimethoxy-4-oxonaphthalene-2-carboxylic acid [10] (93 g) was suspended in methanol (1.2 l) and the mixture saturated with hydrogen chloride; it was then heated under reflux for 1.5 h. After cooling the solvent was concentrated to 600 ml and the product allowed to crystallise overnight. The *ester* (13) (83.7 g, 85%) was obtained as pale cream needles, m.p. 125.5—126 °C (Found: C, 63.65; H, 6.1. $C_{14}H_{16}O_5$ requires C, 63.65; H, 6.1%); M^+, 264; $\nu_{max.}$ 1 735, 1 685, 1 600, and 1 590 cm^{-1}; δ 7.1 (2 H, ABq, *J* 9 Hz, ArH), 3.87 (3 H, s, OMe), 3.77 (3 H, s, OMe), 3.67 (3 H, s, OMe), and 3.5—2.5 (5 H, m, 2 CH_2 and CH).

Methyl 1,2,3,4-Tetrahydro-5-hydroxy-8-methoxy-4-oxonaphthalene-2-carboxylate (14).—The tetrahydronaphthalene (13) (5.0 g) was dissolved in dichloromethane (50 ml) and the solution cooled to −70 °C under nitrogen. Boron trichloride (5 g) in dichloromethane (40 ml) was added with stirring and the resulting solution allowed to return to room temperature; it was stirred at this temperature for 10 min, and then poured, with stirring, into ice-cold 1M-hydrochloric acid (200 ml). The dichloromethane layer was separated, washed with water (4 × 300 ml) and saturated aqueous sodium chloride (300 ml), dried and evaporated to give a pale yellow crystalline mass. Recrystallisation from dichloromethane–hexane gave the *phenol* (14) (3.0 g, 63%) as pale yellow needles, m.p. 83—83.5 °C (Found: C, 62.45; H, 5.6. $C_{13}H_{14}O_5$ requires C, 62.4; H, 5.65%); M^+, 250; $\nu_{max.}$ 1 730 and 1 660 cm^{-1}; δ 11.71 (1 H, s, ArOH), 6.97 (2 H, ABq, *J* 9 Hz, ArH), 3.82 (3 H, s, OMe), 3.76 (3 H, s, OMe), and 3.5—2.7 (5 H, m, 2 CH_2 and CH).

Methyl 1,2,3,4-Tetrahydro-5-hydroxy-8-methoxynaphthalene-2-carboxylate (15).—The phenol (14) (8 g) was suspended in methanol (500 ml) containing concentrated hydrochloric acid (1 ml). Platinum oxide catalyst (0.6 g) was added and the mixture shaken in hydrogen until uptake ceased. The catalyst was filtered off (Celite) and the filtrate evaporated. The residue was taken up in ether (300 ml) and the solution washed with 5% potassium hydrogen carbonate (50 ml), dried, and evaporated. Trituration of the residue with hexane gave the *phenol* (15) (6.1 g, 81%) as off-white crystals. This was recrystallised from ether–hexane to give colourless crystals, m.p. 129.5—130 °C (Found: C, 66.15; H, 6.9. $C_{13}H_{16}O_4$ requires C, 66.1; H, 6.8%); M^+, 236; $\nu_{max.}$ 3 350, 1 710, and 1 610 cm^{-1}; δ 6.58 (2 H, s, ArH), 5.2 (1 H, s, ArOH), 3.75 (3 H, s, OMe), 3.70 (3 H, s, OMe), and 3.3—1.4 (7 H, m, 3 CH_2 and CH).

Methyl 5-Allyloxy-1,2,3,4-tetrahydro-8-methoxynaphthalene-2-carboxylate (16).—A mixture of the phenol (15) (6 g), allyl bromide (30 ml) and anhydrous potassium carbonate (60 g) in acetone (400 ml) was stirred at 70 °C under nitrogen for 7 h. The solution was cooled, filtered, and evaporated to give a yellow oily residue that was purified by column chromatography on silica gel, using hexane–ether (3 : 1) as eluant. The *allyl ether* (16) (5.9 g, 71%) was obtained as a colourless oil which slowly crystallised. Recrystallisation from ether–hexane gave colourless crystals, m.p. 48.5—49 °C (Found: C, 69.35; H, 7.4. $C_{10}H_{20}O_3$ requires C, 69.45; H, 7.3%); M^+, 276; $\nu_{max.}$ 1 735, 1 655, and 1 605 cm^{-1}; δ 6.62 (2 H, s, ArH), 6.4—5.1 (3 H, m, $OCH_2CH{=}CH_2$), 4.5 (2 H, m, $OCH_2CH{=}CH_2$), 3.8 (3 H, s, OMe), 3.75 (3 H, s, OMe), and 3.3—1.4 (7 H, m, 3 CH_2 and CH).

5-Allyloxy-1,2,3,4-tetrahydro-8-methoxy-2-naphthylmethanol (18).—The allyl ether (16) (55 g) was added to a stirred suspension of lithium aluminium hydride (10 g) in dry ether (1 l). The mixture was heated under reflux for 2 h, cooled, and then quenched by careful addition of water (10 ml), 15% aqueous sodium hydroxide solution (10 ml), and further water (30 ml). The mixture was filtered through magnesium sulphate and the ether evaporated off to give the *alcohol* (18) (47.4 g, 96%) as a white crystalline mass. Recrystallisation from ether–hexane gave colourless crystals, m.p. 66—66.5 °C (Found: C, 72.4; H, 8.05. $C_{15}H_{20}O_2$ requires C, 72.55; H, 8.1%); M^+, 248; $\nu_{max.}$ 3 400, 3 300, and 1 605 cm^{-1}; δ 6.66 (2 H, s, ArH), 6.4—5.1 (3 H, m, $OCH_2CH{=}CH_2$), 4.5 (2 H, (2 H, m, $OCH_2CH{=}CH_2$), 3.82 (3 H, s, OMe), 3.65 (2 H, d, *J* 6 Hz, $CHCH_2OH$), 3.3—1.2 (7 H, m, 3 CH_2 and CH), and 1.74 (1 H, CH_2OH).

6-Allyl-1,2,3,4-tetrahydro-5-hydroxy-8-methoxy-2-naphthylmethanol (19).—A solution of the alcohol (18) (46 g) in

dimethylaniline (200 ml) was heated at 200 °C under nitrogen for 5 h. The mixture was then cooled, the dimethylaniline evaporated off, and the residue dissolved in ethyl acetate (300 ml). The ethyl acetate solution was washed with 2M-hydrochloric acid (4 × 200 ml), water (3 × 200 ml), and saturated aqueous sodium chloride (200 ml). After drying, evaporation of the solvent gave the *phenol* (19) (43 g, 94%) as off-white crystals. Recrystallisation from ethyl acetate–hexane gave colourless crystals, m.p. 110—111 °C (Found: C, 72.5; H, 8.2. $C_{15}H_{20}O_3$ requires C, 72.5; H, 8.1%); M^+, 248; $\nu_{max.}$ 3 330, 1 635, and 1 595 cm^{-1}; δ 6.47 (1 H, s, ArH), 6.3—5.0 (3 H, m, $CH_2CH{=}CH_2$), 4.70 (1 H, s, ArOH), 3.75 (3 H, s, OMe), 3.6 (2 H, d, *J* 5 Hz, $ArCH_2CH{=}CH_2$), 3.38 (2 H, d, *J* 6 Hz, CH_2OH), 3.2—1.0 (7 H, m, 3 CH_2 and CH), and 1.74 (1 H, s, CH_2OH).

6-*Allyl*-1,2,3,4-*tetrahydro*-5,8-*dimethoxy*-2-*naphthylmethanol* (20).—A mixture of the phenol (19) (41 g), anhydrous potassium carbonate (80 g), and methyl iodide (15 ml) in acetone (1 l) was heated under reflux with stirring for 50 h [further methyl iodide (10 ml) was added after 24 h and 48 h]. The mixture was cooled, filtered, and the residue dissolved in toluene (500 ml). The toluene solution was washed with Claisen's alkali (3 × 100 ml), water (300 ml), and saturated aqueous sodium chloride (300 ml), and then dried and evaporated. Trituration of the residue with hexane gave the *alcohol* (20) (40.4 g, 92%) as off-white crystals. Recrystallisation from dichloromethane–hexane gave colourless crystals, m.p. 84—84.5 °C (Found: C, 73.3; H, 8.36. $C_{16}H_{22}O_3$ requires C, 73.25; H, 8.45%); M^+, 262; $\nu_{max.}$ 3 340, 3 240, 1 635, 1 600, and 1 585 cm^{-1}; δ 6.50 (1 H, s, ArH), 6.3—4.9 (3 H, m, $CH_2CH{=}CH_2$), 3.76 (3 H, s, OMe), 3.69 (3 H, s, OMe), 3.63 (2 H, d, *J* 5 Hz, $ArCH_2CH{=}CH_2$), 3.43 (2 H, d, *J* 6 Hz, CH_2OH), 3.1—1.0 (7 H, m, 3 CH_2 and CH), and 1.60 (s, 1 H, CH_2OH).

Tetrahydro-5,8-*dimethoxy*-2-*methoxymethylnaphthalene*-6-*carbaldehyde* (8).—Sodium hydride (6 g) was added to a stirred solution of the alcohol (20) (30 g) in dimethylformamide (DMF) (200 ml) under nitrogen and the mixture was heated at 60 °C for 45 min. Methyl iodide (15 ml) was then added and the mixture heated at 60 °C for a further 1.5 h. The DMF was evaporated off and water (200 ml) added to the residue which was then extracted with ether (3 × 200 ml). The ether extracts were washed with 2M-hydrochloric acid (4 × 200 ml), water (3 × 200 ml), dried and evaporated to give a yellow oil (31 g) which slowly crystallised. This material was dissolved in a mixture of dioxan (250 ml) and ethyl acetate (250 ml) and then added to a solution of osmium tetraoxide (0.2 g) in distilled water (500 ml) at 0 °C. Sodium metaperiodate (50 g) was added and the solution stirred at room temperature under nitrogen for 20 h. The organic layer was separated, washed with water (4 × 300 ml), dried and evaporated to give a brown oil which was purified by column chromatography on silica gel, using hexane–ether (10 : 3) for elution. The *aldehyde* (8) (21.3 g, 66%) was obtained as pale yellow crystals, m.p. 49—50 °C (from ether–hexane) (Found: C, 68.1; H, 7.5. $C_{15}H_{20}O_4$ requires C, 68.15; H, 7.65%); $\nu_{max.}$ 1 680 and 1 600 cm^{-1}; δ 10.38 (1 H, s, CHO), 7.10 (1 H, s, ArH), 3.84 (3 H, s, OMe), 3.4 (3 H, s, OMe), 3.38 (2 H, d, *J* 6 Hz, CH_2OMe), and 3.2—1.05 (7 H, m, 3 CH_2 and CH).

1,2,3,4-*Tetrahydro*-5,8-*dimethoxy*-2-*methoxymethyl*-6-*naphthylmethanol* (9).—Using the aldehyde (8) and a procedure similar to that described for the preparation of compound (4), the *alcohol* (9) was obtained as colourless crystals, m.p. 78—79 °C (Found: C, 67.4; H, 8.35. $C_{15}H_{22}O_4$ requires C, 67.65; H, 8.35%); M^+, 266; $\nu_{max.}$ 3 320, 3 210, 1 610, and 1 590 cm^{-1}; δ 6.73 (1 H, s, ArH), 4.72 (2 H, br s, $ArCH_2OH$), 3.80 (3 H, s, OMe), 3.75 (3 H, s, OMe), 3.4 (3 H, s, OMe), 3.38 (2 H, d, *J* 6 Hz, CH_2OMe), and 3.2—1.05 (8 H, m, 3 CH_2, CH, and CH_2OH).

1,2,3,4-*Tetrahydro*-5,8-*dimethoxy*-2-*methoxymethyl*-6-*naphthylacetonitrile* (10).—Using the procedure described for the preparation of compound (5) and starting with the alcohol (9), the *nitrile* (10) was obtained as colourless crystals, m.p. 51—52 °C (Found: C, 69.8; H, 7.65. $C_{16}H_{21}NO_3$ requires C, 69.8; H, 7.7%); M^+, 275; $\nu_{max.}$ 2 230 cm^{-1}; δ 6.67 (1 H, s, ArH), 3.80 (3 H, s, OMe), 3.73 (2 H, s, $ArCH_2CN$), 3.68 (3 H, s, OMe), 3.39 (3 H, s, OMe), 3.35 (2 H, d, *J* 6 Hz, CH_2OMe), and 3.2—2.05 (7 H, m, 3 CH_2 and CH).

1,2,3,4-*Tetrahydro*-5,8-*dimethoxy*-2-*methoxymethyl*-6-*naphthylacetic Acid* (11).—Using the procedure described for the preparation of compound (6) and starting with the nitrile (10), the *acid* (11) was obtained as colourless crystals, m.p. 138—138.5 °C (Found: C, 65.5; H, 7.5. $C_{16}H_{22}O_5$ requires C, 65.55; H, 7.55%); M^+, 294; $\nu_{max.}$ 1 720, 1 700, 1 610, and 1 595 cm^{-1}; δ 10.52 (1 H, s, CO_2H), 6.60 (1 H, s, ArH), 3.80 (3 H, s, OMe), 3.73 (3 H, s, OMe), 3.70 (2 H, s, $ArCH_2CO_2H$), 3.40 (3 H, s, OMe), 3.38 (2 H, s, CH_2OMe), and 3.2—1.05 (7 H, m, 3 CH_2 and CH). The *ester* (12), obtained as an oil, was prepared from the acid (11) by the method described for the preparation of compound (7) and was used directly for subsequent reactions.

1,2,3,4,6,11-*Hexahydro*-5,7,12-*trimethoxy*-2-*methoxymethylnaphthacene*-6,11-*quinone* (29).—(*a*) A solution of the ester (12) (0.5 g) and 2-chloro-3-methoxybenzoic acid (2.0 g) in trifluoroacetic anhydride (3 ml) was heated at 60 °C for 6 d. The solution was then poured into 5% potassium hydrogen carbonate (50 ml) with stirring and the mixture extracted with ethyl acetate (50 ml). The ethyl acetate extract was washed with water (50 ml), dried, and evaporated to give a gum which was chromatographed on a column of silica gel, using hexane–ether (2 : 1) as eluant. Slightly impure methyl 7-(2-chloro-3-methoxybenzoyl)-1,2,3,4-tetrahydro-5,8-dimethoxy-2-methoxymethyl-6-naphthylacetate (23) (320 mg, 47%) was obtained as a yellow gum which was used directly for the next stage. The naphthylacetate (23) (320 mg) was dissolved in dry dimethyl sulphoxide (5 ml), and potassium t-butoxide (0.25 g) added with stirring. The mixture was heated at 30 °C under nitrogen for 10 min and then poured into 2M-hydrochloric acid (30 ml) and extracted with ethyl acetate (3 × 30 ml). The combined extracts were washed with water (2 × 30 ml), dried, and evaporated to give an orange gum containing the naphthacene (26) which was dissolved in a mixture of ethanol (25 ml), water (2.5 ml), and sodium hydroxide (0.1 g). Hydrogen peroxide (100 vol; 2.5 ml) was added and the solution heated at 70 °C for 1 h. Most of the ethanol was evaporated, the product dissolved in dichloromethane (30 ml) and the solution washed with water (2 × 25 ml), dried, and evaporated to give the *naphthacene* (29) (0.08 g, 12.5%) as yellow crystals, m.p. 142—142.5 °C [from tetrahydrofuran (THF)–isopropyl alcohol (Found: C, 69.65; H, 6.15. $C_{23}H_{24}O_6$ requires C, 69.7; H, 6.1%); M^+, 396; $\lambda_{max.}$ 265 and 378 nm (log ε 4.43 and 3.88); δ 7.78 (1 H, dd, *J* 2 and 8 Hz, ArH), 7.62 (1 H, t, *J* 8 Hz, ArH), 7.24 (1 H, dd, *J* 2 and 8 Hz, ArH), 4.01 (3 H, s, OMe), 3.95 (3 H, s, OMe), 3.92 (3 H, s, OMe), 3.41 (2 H, d, *J* 6 Hz, CH_2OMe), 3.40 (3 H, s, OMe), and 3.3—1.2 (7 H, m, 3 CH_2 and CH).

(*b*) The naphthacene (43) (0.3 g) was suspended in a mixture of ethanol (30 ml), water (15 ml), and sodium hydroxide

(0.3 g). The mixture was heated at 80 °C until all the solid had dissolved and then hydrogen peroxide (100 vol; 10 ml) was added. After heating for 30 min at 80 °C further hydrogen peroxide (100 vol; 10 ml) was added and the mixture heated for an additional 30 min. The mixture was then cooled, the solvent evaporated, and the yellow residue purified by column chromatography, using hexane–ethyl acetate–dichloromethane (3 : 1 : 1) as eluant. The *naphthacene* (29) (0.21 g, 53%) was obtained as yellow crystals, m.p. 142—142.5 °C identical (mixed m.p., t.l.c., n.m.r. and i.r. spectra) with the sample prepared by method (*a*).

1-*Methyl* 2-(1,2,3,4-*Tetrahydro*-8-*methoxy*-2-*methoxycarbonyl*-5-*naphthyl*) 3-*Methoxyphthalate* (30).—A mixture of 2-methoxy-6-methoxycarbonylbenzoic acid [24] (39) (5.65 g) and phenol (15) (5.8 g), in dichloromethane (30 ml) and trifluoroacetic anhydride (30 ml) was stirred at room temperature for 14 h under nitrogen. The mixture was then poured into aqueous 10% potassium hydrogen carbonate (500 ml) and extracted with dichloromethane (3 × 300 ml). The combined extracts were washed with water (2 × 400 ml), dried and evaporated. Trituration of the residue with ether gave the *phthalate* (30) (8.5 g, 81%) as colourless crystals. Recrystallisation from ethyl acetate–hexane gave colourless crystals, m.p. 132—134 °C (Found: C, 64.7; H, 5.6. $C_{23}H_{24}O_8$ requires C, 64.5; H, 5.65%); M^+, 428; $\nu_{max.}$ 1 750, 1 730, 1 715, and 1 590 cm^{-1}; δ 7.72—6.72 (5 H, m, ArH), 3.95 (3 H, s, OMe), 3.02 (3 H, s, OMe), 3.84 (3 H, s, OMe), 3.74 (3 H, s, OMe), and 3.3—1.5 (7 H, m, 3 CH_2 and CH).

Methyl 1,2,3,4-*Tetrahydro*-5-*hydroxy*-8-*methoxy*-6-(2-*methoxy*-6-*methoxycarbonylbenzoyl*)*naphthalene*-2-*carboxylate* (31).—A solution of the phthalate (30) (3.2 g) in boron trifluoride–diethyl ether (14 ml) was heated at 80 °C under nitrogen for 1.5 h. The solution was cooled, poured into water (200 ml), and extracted with ether (3 × 100 ml). The combined ether extracts were washed with water (3 × 100 ml), dried, and evaporated to give an orange gum. Column chromatography on silica gel, using hexane–ether (1 : 1) as eluant, gave the *ketone* (31) (1.36 g, 42.5%) as yellow prisms, m.p. 150—152 °C (from dichloromethane–methanol) (Found: C, 64.35; H, 5.65. $C_{23}H_{24}O_8$ requires C, 64.5; H, 5.65%); M^+ 428; $\nu_{max.}$ 1 730, 1 630, and 1 590 cm^{-1}; $\lambda_{max.}$ 244, 277, 302sh, and 368 nm (log ε 4.04, 4.11, 3.71, and 3.77); δ 12.14 (1 H, s, ArOH), 7.73 (1 H, dd, *J* 1.5 and 8 Hz, ArH), 7.53 (1 H, t, *J* 8 Hz, ArH), 7.22 (1 H, dd, *J* 1.5 and 8 Hz, ArH), 6.31 (1 H, s, ArH), 3.79 (3 H, s, OMe), 3.75 (6 H, s, 2 OMe), 3.51 (3 H, s, OMe), and 3.4—1.6 (7 H, m, 3 CH_2 and CH).

6-(2-*Carboxy*-6-*methoxybenzoyl*)-1,2,3,4-*tetrahydro*-5-*hydroxy*-8-*methoxynaphthalene*-2-*carboxylic Acid* (32).—A mixture of the ketone (31) (0.815 g), methanol (41 ml), water (41 ml), and sodium hydroxide (1.63 g) was heated under reflux for 1 h. The mixture was allowed to cool and most of the methanol evaporated off. The residue was diluted with water (200 ml), acidified by dropwise addition of concentrated hydrochloric acid and allowed to crystallise. The product was collected, washed with water, dried *in vacuo* and recrystallised from acetone–hexane to give the *diacid* (32) (0.728 g, 95.5%) as fine yellow needles, m.p. 263—264 °C (Found: C, 63.05; H, 5.2. $C_{21}H_{20}O_8$ requires C, 63.0; H, 5.05%); M^+, 400; $\nu_{max.}$ 1 690 cm^{-1}; δ (DMSO) 12.6 (2 H, br s, 2 OH), 12.0 (1 H, br s, OH), 7.7—7.4 (3 H, m, ArH), 6.31 (1 H, s, ArH), 3.77 (3 H, s, OMe), 3.46 (3 H, s, OMe), and 3.0—1.5 (7 H, m, 3 CH_2 and CH).

Cyclisation of the Diacid (32).—(*a*) The diacid (32) (0.2 g) was added with stirring to concentrated sulphuric acid (16 ml) at 110 °C under nitrogen. After 40 min the mixture was cooled to 0 °C and quenched by the slow addition of methanol (120 ml) with stirring. The red precipitate was collected and dissolved in DMF (20 ml). Finely ground anhydrous potassium carbonate (1.6 g) and methyl iodide (5 ml) were added and the mixture stirred under nitrogen at 80 °C. After 3.75 h further potassium carbonate (0.5 g) and methyl iodide (5 ml) were added and the mixture stirred for 1.5 h at 80 °C. The mixture was then cooled, filtered through Celite, and the filtrate evaporated to give an orange solid which was purified by column chromatography on silica gel, using ethyl acetate–hexane (1:1) as eluant. The *product* (0.1 g, 49%) was obtained as a bright yellow solid, m.p. 158—172 °C, formulated as a mixture of methyl 1,2,3,-4,6,11-hexahydro-5,7,12-trimethoxy-6,11-dioxonaphthacene-2-carboxylate (33) and methyl 1,2,3,4,6,11-hexahydro-5,10,12-trimethoxy-6,11-dioxonaphthacene-2-carboxylate (34), in the ratio *ca.* 2 : 1, M^+, 410; δ 7.78 (1 H, dd, *J* 2 and 8 Hz, ArH), 7.64 (1 H, t, *J* 8 Hz), 7.14 (1 H, dd, *J* 2 and 8 Hz), 4.01, 3.97, 3.95, 3.93, and 3.91 (total 9 H, all s, 3 OMe), 3.76 (3 H, s, OMe), and 3.4—1.4 (7 H, m, 3 CH_2 and CH).

(*b*) The diacid (32) (300 mg) was added to a stirred mixture of concentrated sulphuric acid (20 ml) and boric acid (8 g) at 110 °C under nitrogen. After 40 min the mixture was cooled and treated as described in (*a*) above. *Methyl* 1,2,3,4,6,11-*hexahydro*-5,7,12-*trimethoxy*-6,11-*dioxonaphthacene*-2-*carboxylate* (33) (0.253 g, 82%) was obtained as bright yellow needles, m.p. 192—193 °C (Found: C, 67.3; H, 5.5. $C_{23}H_{22}O_7$ requires C, 67.3; H, 5.4%); M^+, 410; $\nu_{max.}$ 1 730, 1 675, 1 590, and 1 555 cm^{-1}; $\lambda_{max.}$ 263 and 377 nm (log ε 4.46 and 3.91); δ 7.78 (1 H, dd, *J* 2 and 8 Hz, ArH), 7.64 (1 H, t, *J* 8 Hz, ArH), 7.24 (1 H, dd, *J* 2 and 8 Hz, ArH), 4.01 (3 H, s, OMe), 3.95 (3 H, s, OMe), 3.93 (3 H, s, OMe), 3.77 (3 H, s, OMe), and 3.4—1.4 (7 H, m, 3 CH_2 and CH).

Preparation of the Ester (33) *from the Diacid* (48).—The diacid (48) (0.4 g) was treated in a manner similar to that used for the preparation of compound (53) from acid (47) except that, after cyclisation with sulphuric acid, the mixture was poured into ice-cold methanol and the resulting solution warmed at 60 °C to reform the methyl ester. Oxidation of the product with chromium trioxide was carried out as described for compound (53). The naphthacene (33) (0.165 g, 39%) was obtained as yellow needles, m.p. 192—193 °C, identical (mixed m.p., t.l.c., n.m.r. and i.r. spectra) with the sample prepared by method (*b*) above.

4-*Methoxy*-3-(1,2,3,4-*tetrahydro*-5,8-*dimethoxy*-2-*methoxymethyl*-6-*naphthyl*)*phthalide* (41).—A solution of butyllithium in hexane (25 ml; 1.6M) was added to a stirred solution of 3-methoxy-*N*-methylbenzamide (3.3 g) in dry THF (40 ml) under nitrogen. The mixture was heated under reflux for 30 min, cooled to 0 °C and a solution of the aldehyde (8) (3.0 g) in dry THF (7 ml) added dropwise with stirring. The mixture was stirred at 0 °C for 1 h and for a further 2 h at room temperature. Water (50 ml) was added and the solution warmed at 70 °C for 30 min. The mixture was cooled to room temperature and acidified with 2M-hydrochloric acid and allowed to crystallise at 0 °C for 12 h. The crystalline product was filtered off, washed with methanol and then ether to give the *phthalide* (41) (2.95 g, 65%) as colourless crystals, m.p. 176—179 °C (Found: C, 69.25; H, 6.6. $C_{23}H_{26}O_6$ requires C, 69.35; H, 6.6%); M^+, 398; $\nu_{max.}$ 1 765 and 1 605 cm^{-1}; δ 7.60 (2 H, m, ArH), 7.15 (1 H, m, ArH), 6.82 and 6.80 (total 1H, both s, ArH), 6.05 (1 H, s, Ar_2CHO), 3.86 and 3.80 (total 3 H, both s, OMe),

3.86 (3 H, s, OMe), 3.59 and 3.58 (total 3 H, both s, OMe), 3.42 (3 H, s, OMe), 3.39 (2 H, d, *J* 6 Hz, CH_2OMe), and 3.1—1.2 (7 H, m, 3 CH_2 and CH). The n.m.r. spectrum indicated that the product (41) was obtained as a mixture of diastereoisomers.

6-(2-*Carboxy*-6-*methoxybenzyl*)-1,2,3,4-*tetrahydro*-5,8-*dimethoxy*-2-*methoxymethylnaphthalene* (42).—The phthalide (41) (2.0 g) was suspended in aqueous 10% sodium hydroxide (150 ml) and the suspension heated to reflux with vigorous stirring. Zinc dust (15 g) was added, the mixture was heated under reflux with stirring for 24 h, then cooled and filtered. The filtrate was acidified with 2M-hydrochloric acid and extracted with ethyl acetate (3 × 200 ml). The combined ethyl acetate extracts were washed with water (3 × 200 ml), dried and evaporated to give the *acid* (42) 1.8 g, 90%) as colourless crystals, m.p. 152—153 °C (Found: C, 68.95; H, 7.0. $C_{23}H_{28}O_6$ requires C, 69.0; H, 7.05%); M^+, 400; $\nu_{max.}$ 1 700, 1 600, and 1 580 cm^{-1}; δ 7.59 (1 H, dd, *J* 2 and 8 Hz, ArH), 7.33 (1 H, t, *J* 8 Hz, ArH), 7.07 (1 H, dd, *J* 2 and 8 Hz), 6.12 (1 H, s, ArH), 4.43 (2 H, s, $ArCH_2Ar$), 3.79 (3 H, s, OMe), 3.70 (3 H, s, OMe), 3.57 (3 H, s, OMe), 3.41 (3 H, s, OMe), 3.39 (2 H, d, *J* 6 Hz, CH_2OMe), and 3.2—1.1 (7 H, m, 3 CH_2 and CH).

1,2,3,4-*Tetrahydro*-5,7,12-*trimethoxy*-2-*methoxymethylnaphthacen*-11-*ol* (43).—The acid (42) (1.0 g) was added with stirring to concentrated sulphuric acid (15 ml) under nitrogen. After 15 min the solution was poured onto crushed ice (200 g) and the product extracted with ethyl acetate (3 × 200 ml). The ethyl acetate extracts were combined, washed with water (3 × 300 ml), dried and evaporated to give a yellow-brown residue. Crystallisation from ethyl acetate–hexane gave the *naphthacene* (43) (0.85 g, 89%) as orange crystals, m.p. 136—136 °C (Found: C, 72.35; H, 6.8. $C_{23}H_{26}O_5$ requires C, 72.25; H, 6.85%); M^+, 382; $\nu_{max.}$ 3 320, 1 645, 1 615, and 1 600 cm^{-1}; $\lambda_{max.}$ 267, 359, 378, 396, and 421 nm (log ε 4.77, 3.66, 3.89, 3.71, and 3.55); δ 10.41 (1 H, s, ArOH), 8.48 (1 H, s, ArH), 8.0 (1 H, d, *J* 8 Hz, ArH), 7.30 (1 H, t, *J* 8 Hz, ArH), 6.75 (1 H, d, *J* 8 Hz, ArH), 4.06 (3 H, s, OMe), 3.97 (3 H, s, OMe), 3.95 (3 H, s, OMe), 3.43 (2 H, d, *J* 6 Hz, CH_2OMe), 3.41 (3 H, s, OMe), and 3.2—1.2 (7 H, m, 3 CH_2 and CH).

2,3-*Dihydro*-3-*hydroxy*-4-*methoxy*-2-*methylisoindol*-1-*one* (36).—A solution of butyl-lithium in hexane (25 ml; 1.6M) was added to a stirred solution of 3-methoxy-*N*-methylbenzamide in dry THF (40 ml) under nitrogen. The mixture was heated under reflux with stirring for 30 min, cooled to 0 °C, and a solution of dry DMF (5 ml) in THF (10 ml) added dropwise. The resulting suspension was stirred at 0 °C for 1 h and at room temperature for 1 h. Water (50 ml) was added and most of the THF evaporated off. The residue was diluted with water (50 ml) and the pH adjusted to 7 with 2M-hydrochloric acid. The product was allowed to crystallise at 4 °C for 15 h. The *isoindolone* (36) (2.58 g, 67%) was obtained as white needles, m.p. 181—181.5 °C (from ethyl acetate) (Found: C, 62.0; H, 5.7. $C_{10}H_{11}NO_3$ requires C, 62.15; H, 5.75%); M^+, 193; $\nu_{max.}$ 3 320, 1 675, 1 660, and 1 610 cm^{-1}; δ (pyridine) 7.5—6.78 (3 H, m, ArH), 5.94 (1 H, s, CH), 3.67 (3 H, s, OMe), and 3.17 (3 H, s, NMe).

3-*Hydroxy*-4-*methoxyphthalide* (37).—The isoindolone (36) (10 g) was suspended in 3M-hydrochloric acid (1 l) and the mixture heated under reflux for 10 h. The solution was cooled and extracted with ethyl acetate (5 × 200 ml). The extracts were combined, dried, and evaporated to give the acid (37) (8.8 g, 91.5%) as colourless crystals, m.p. 155—155.5 °C (from ethyl acetate–hexane) (lit.,[25] m.p. 155—157 °C) (Found: C, 59.85; H, 4.45. Calc. for $C_9H_8O_4$: C, 60.0; H, 4.5%); M^+, 180; $\nu_{max.}$ 3 370, 1 730, and 1 615 cm^{-1}; δ ($CDCl_3$–DMSO) 7.6—7.0 (3 H, m, ArH), 6.6 (1 H, s, CH), and 3.90 (3 H, s, OMe).

Methyl 2-*Formyl*-3-*methoxybenzoate* (38).—The acid (37) (0.6 g) was dissolved in water (3 ml) containing potassium carbonate (0.23 g). The mixture was cooled to 0 °C and treated dropwise, with stirring, with a solution of silver nitrate (0.56 g) in water (2 ml). After stirring at 0 °C for 1 h, the white precipitate was filtered off, washed with ethanol–ether (20 ml; 1 : 1) and dried *in vacuo* with protection from light. The silver salt, obtained as an off-white powder (900 mg), was suspended in dry ether (50 ml) and treated with methyl iodide (3 ml). The mixture was refluxed for 5 h, filtered, and evaporated to give the *aldehyde* (38) (0.6 g, 93%) as an oil which slowly solidified at 4 °C (Found: C, 61.6; H, 5.1. $C_{10}H_{10}O_4$ requires C, 61.85; H, 5.2%); M^+, 194; $\nu_{max.}$ 1 720 and 1 690 cm^{-1}; δ 10.3 (1 H, s, CHO), 7.62—7.0 (3 H, m, ArH), and 3.9 (6 H, s, 2 OMe).

Methyl 5-*Benzyloxy*-1,2,3,4-*tetrahydro*-8-*methoxynaphthalene*-2-*carboxylate* (17).—A mixture of the phenol (15) (5.0 g), potassium carbonate (12.0 g), benzyl chloride (5 ml), and DMF (120 ml) was stirred at 80 °C for 4 h under nitrogen. The solvent was evaporated off, the residue dissolved in ethyl acetate (200 ml) and the solution washed with water (3 × 200 ml), dried, and evaporated to give the crude product as pink crystals. Purification by column chromatography on silica gel, using ethyl acetate (1 : 1) as eluant gave the *tetrahydronaphthalene* (17) (5.63 g, 82.5%) as colourless crystals, m.p. 78—80 °C (Found: C, 73.85; H, 6.95. $C_{20}H_{22}O_4$ requires C, 73.6; H, 6.8%); M^+, 326; $\nu_{max.}$ 1 730 and 1 695 cm^{-1}; δ 7.36 (5 H, s, ArH), 6.62 (2 H, s, ArH), 5.0 (2 H, s, $ArCH_2O$), 3.78 (3 H, s, OMe), 3.75 (3 H, s, OMe), and 3.4—1.3 (7 H, m, 3 CH_2 and CH).

5-*Benzyloxy*-1,2,3,4-*tetrahydro*-8-*methoxynaphthalene*-2-*carboxylic Acid* (55).—A mixture of the tetrahydronaphthalene (17) (5.63 g) water (150 ml), methanol (150 ml), and sodium hydroxide (5.0 g) was heated under reflux for 3 h. The methanol was evaporated off and the residue diluted with water (150 ml) and acidified to pH 3 with 2M-hydrochloric acid. The product was extracted with ethyl acetate (3 × 100 ml) and the combined extracts washed with water (2 × 100 ml), dried, and evaporated. Trituration of the residue with ether–hexane gave the acid (55) (5.0 g, 92%) as colourless crystals, m.p. 147—149 °C (Found: C, 72.8; H, 6.35. $C_{19}H_{20}O_4$ requires C, 73.05; H, 6.45%); M^+, 312; $\nu_{max.}$ 1 700 and 1 605 cm^{-1}; δ 8.2 (1 H, br s, CO_2H), 7.28 (5 H, s, ArH), 6.58 (2 H, s, ArH), 3.95 (2 H, s, $ArCH_2O$), 3.70 (3 H, s, OMe), and 3.4—1.5 (7 H, m, 3 CH_2 and CH).

2-*Acetyl*-5-*benzyloxy*-1,2,3,4-*tetrahydro*-8-*methoxynaphthalene* (56).—A solution of methyl-lithium in ether (34 ml; 1.7M) was added to a stirred solution of the acid (55) (7.8 g) in dry ether (500 ml) under nitrogen. The mixture was stirred at room temperature for 4 h and then poured into aqueous 5% ammonium chloride (500 ml). The ether layer was separated, washed with water (200 ml), aqueous 5% potassium carbonate (200 ml), and water (200 ml), and then dried and evaporated to give the *ketone* (56) (6.0 g, 77.5%) as colourless crystals, m.p. 75—76 °C (from ether–hexane) (Found: C, 77.25; H, 7.1. $C_{20}H_{22}O_3$ requires C, 77.4; H, 7.15%); M^+, 310; $\nu_{max.}$ 1 700, 1 595, and 1 580 cm^{-1}; δ 7.34 (5 H, s, ArH), 6.63 (2 H, s, ArH), 5.0 (2 H, s, $ArCH_2O$), 3.79 (3 H, s, OMe), 3.4—1.4 (7 H, m, 3 CH_2 and CH), and 2.25 (3 H, s, COMe).

2-*Acetyl*-1,2,3,4-*tetrahydro*-8-*methoxy*-5-*naphthol* (57).—A

solution of the ketone (56) (1.5 g) in ethyl acetate (100 ml) was shaken with Pd–C (0.2 g; 10%) in hydrogen. After uptake of hydrogen ceased the catalyst was filtered off (Celite) and the filtrate evaporated to give the *phenol* (57) (0.98 g, 91.5%) as colourless crystals, m.p. 143—144 °C (Found: C, 71.1; H, 7.2. $C_{13}H_{16}O_3$ requires C, 70.9; H, 7.32%); $\nu_{max.}$ 3 200, 1 670, and 1 605 cm^{-1}; δ 7.62 (1 H, s, ArOH), 6.55 (2 H, ABq, *J* 8 Hz, ArH), 3.69 (3 H, s, OMe), 3.4—1.3 (7 H, m, 3 CH_2 and CH), and 2.33 (3 H, s, COMe).

3-(2-*Acetyl*-1,2,3,4-*tetrahydro*-5-*hydroxy*-8-*methoxy*-6-*naphthyl*)-4-*methoxyphthalide* (44).—A mixture of the phenol (57) (1.1 g), the aldehyde (38) (1.15 g), benzeneboronic acid (0.7 g), propionic acid (0.5 ml), and benzene (50 ml) was heated under reflux for 20 h. The solvent was evaporated off and the residue dissolved in a mixture of dichloromethane (10 ml), 2-methylpentane-2,4-diol (10 ml) and acetic acid (0.1 ml). The solution was stirred at room temperature for 20 h, and then extracted with dichloromethane (2 × 50 ml). The combined extracts were washed with water (4 × 50 ml), dried, and evaporated to give a yellow oil. Crystallisation from acetone–ether gave the *phthalide* (44) (1.6 g, 83%) as colourless crystals, m.p. 184—187 °C (Found: C, 69.2; H, 5.9. $C_{22}H_{22}O_6$ requires C, 69.1; H, 5.8%); M^+, 382; $\nu_{max.}$ 3 470, 1 760, 1 700, and 1 605 cm^{-1}; δ 7.6 (2 H, m, ArH), 7.15 (1 H, m, ArH), 6.80 and 6.77 (total 1 H, both s, ArH), 6.30 and 6.27 (total 1 H, both s, Ar_2CHO), 5.6 and 5.55 (total 1 H, both br s, ArO*H*), 3.88 (3 H, s, OMe), 3.66 and 3.65 (total 3 H, both s, OMe), 3.2—1.4 (7 H, m, 3 CH_2 and CH), 2.26 and 2.25 (3 H, both s, COMe). The n.m.r. spectrum indicated that compound (44) was obtained as a mixture of diastereoisomers.

2-*Acetyl*-6-(2-*carboxy*-6-*methoxybenzyl*)-1,2,3,4-*tetrahydro*-8-*methoxy*-5-*naphthol* (47).—A mixture of water (50 ml), sodium hydroxide (5.0 g), and zinc powder (5.0 g) was heated under reflux under nitrogen with vigorous stirring. The phthalide (44) (1.0 g) was added to the mixture which was stirred and heated for 2 h. The solution was then cooled, filtered, acidified with 2M-hydrochloric acid, and extracted with ethyl acetate (3 × 50 ml). The combined extracts were washed with water (100 ml), dried, and evaporated to give a pale yellow gum. Trituration with ether–hexane gave the *acid* (47) (0.82 g, 82%) as colourless crystals, m.p. 165—166 °C (Found: C, 68.65; H, 6.3. $C_{24}H_{24}O_6$ requires C, 68.75; H, 6.3%); M^+, 384; $\nu_{max.}$ 3 360, 1 700, 1 685, 1 605, 1 590, and 1 575 cm^{-1}; δ 7.61 (1 H, dd, *J* 2 and 8 Hz, ArH), 7.30 (1 H, t, *J* 8 Hz, ArH), 7.10 (1 H, dd, *J* 2 and 8 Hz, ArH), 6.85 (1 H, br s, ArOH), 6.81 (1 H, s, ArH), 4.38 (2 H, s, Ar_2CH_2) 3.94 (3 H, s, OMe), 3.73 (3 H, s, OMe), 3.1—1.4 (7 H, m, 3 CH_2 and CH), and 2.24 (3 H, s, COMe).

2-*Acetyl*-1,2,3,4,6,11-*hexahydro*-5,7,12-*trimethoxy*-*naphthacene*-6,11-*quinone* (53).—A mixture of the acid (47) (0.5 g), anhydrous potassium carbonate (5.0 g), methyl iodide (2 ml), and acetone (50 ml) was heated under reflux with stirring. Further portions of methyl iodide (2 ml) were added after 3 and 6 h and the mixture was heated and stirred for a total of 24 h. The mixture was cooled, filtered, and the filtrate evaporated. The residue was dissolved in a mixture of methanol (30 ml), water (30 ml), and sodium hydroxide (0.6 g) and heated under reflux for 4 h. Most of the methanol was then evaporated off, and the residue diluted with water (50 ml), acidified with 2M-hydrochloric acid and extracted with ethyl acetate (3 × 50 ml). The combined extracts were washed with water (2 × 50 ml), dried and evaporated to give a yellow gum containing the naphthalene (50) which was dissolved in concentrated sulphuric acid. After 15 min the solution was poured onto crushed ice (50 g) and the product extracted with ethyl acetate (3 × 50 ml). The combined extracts were washed with water (3 × 50 ml) and evaporated to give a brown crystalline residue which was dissolved in acetic acid (40 ml). A solution of chromium trioxide (0.34 g) in aqueous 80% acetic acid (20 ml) was added with stirring, the mixture stirred for 20 min at room temperature, and then poured into water (300 ml). The product was extracted with dichloromethane (3 × 100 ml) and the combined extracts washed with water (2 × 200 ml), and aqueous 10% potassium hydrogen carbonate (3 × 300 ml), dried, and evaporated. Crystallisation of the residue from ethyl acetate–isopropyl alcohol gave the naphthacene (53) (150 mg, 29%) as yellow needles, m.p. 183—184 °C (lit.,[21] m.p. 185—186 °C) (Found: C, 69.8; H, 5.65. Calc. for $C_{23}H_{22}O_6$: C, 70.05; H, 5.6%); M^+, 394; $\lambda_{max.}$ 263 and 378 nm (log ε 4.43 and 3.87); δ 7.8 (1 H, dd, *J* 2 and 7.5 Hz, ArH), 7.64 (1 H, t, *J* 7.5 Hz, ArH), 7.24 (1 H, dd, *J* 2 and 7.5 Hz, ArH), 4.05 (3 H, s, OMe), 3.96 (3 H, s, OMe), 3.94 (3 H, s, OMe), 3.3—1.6 (7 H, m, 3 CH_2 and CH), and 2.30 (3 H, s, COMe).

3-(1,2,3,4-*Tetrahydro*-5-*hydroxy*-8-*methoxycarbonyl*-6-*naphthyl*)-4-*methoxyphthalide* (45).—Using an analogous method to that described for the preparation of compound (44), starting with the phenol (15) (2.36 g), benzeneboronic acid (1.5 g), and the aldehyde (38) (2.2 g), the *phthalide* (45) (2.96 g, 74%) was obtained as colourless crystals, m.p. 206—208 °C (from ethyl acetate–hexane) (Found: C, 66.6; H, 5.6. $C_{22}H_{22}O_7$ requires C, 66.3; H, 5.55%); M^+, 398; $\nu_{max.}$ 3 460, 1 760, 1 715, and 1 600 cm^{-1}; δ 7.6 (2 H, m, ArH), 7.16 (1 H, m, ArH), 6.80 (1 H, m, ArH), 6.30 (1 H, s, Ar_2CHO), 3.9 (3 H, s, OMe), 3.85 (3 H, s, OMe), 3.76 (3 H, s, OMe), and 3.2—1.6 (7 H, m, 3 CH_2 and CH).

6-(2-*Carboxy*-6-*methoxybenzyl*)-1,2,3,4-*tetrahydro*-5-*hydroxy*-8-*methoxynaphthalene*-2-*carboxylic Acid* (48).—Reduction of the phthalide (45) (1.0 g) with zinc dust, as for the preparation of compound (47), gave the *diacid* (48) (0.81 g, 83.5%) as colourless crystals, m.p. 237—240 °C, (from ethyl acetate) (Found: C, 65.3; H, 5.75. $C_{21}H_{20}O_7$ requires C, 65.3; H, 5.75%); M^+, 386; $\nu_{max.}$ 3 480, 1 695, 1 595, and 1 580 cm^{-1}; δ(DMSO) 7.45—7.15 (3 H, m, ArH), 6.0 (1 H, s, ArH), 4.20 (2 H, s, Ar_2CH_2), 3.76 (3 H, s, OMe), 3.44 (3 H, s, OMe), and 3.0—1.4 (7 H, m, 3 CH_2 and CH).

Methyl 5-*Benzyloxy*-1,2,3,4-*tetrahydro*-2-*hydroxy*-8-*methoxynaphthalene*-2-*carboxylate* (58).—A solution of butyllithium in hexane (56.9 ml; 1.6M) was added with stirring to a solution of di-isopropylamine (11.86 ml) in dry THF (160 ml) under argon at − 78 °C. After 30 min the ester (17) (20.4 g) in THF (160 ml) was added and the mixture stirred at −78 °C for 1 h. The resulting solution of lithium enolate was then transferred, by increasing the argon pressure, through a double-ended syringe needle into a flask containing a stirred solution of triethyl phosphite (22.1 ml) in dry THF (160 ml) at −78 °C through which a brisk stream of oxygen was passing. The stream of oxygen was maintained for 80 min before the reaction mixture was quenched by addition of acetic acid (17.4 ml). The mixture was allowed to reach 0 °C and then was stirred for 5 min. Water (600 ml) was added, the solution stirred at 0 °C for 1 h, and then most of the THF was evaporated off. The residue was extracted with ethyl acetate (3 × 200 ml) and the combined extracts washed with aqueous 10% potassium hydrogen carbonate (2 × 100 ml), dried, and evaporated. Column chromatography on silica gel, using ethyl acetate–hexane (1 : 1) as eluant, gave the *hydroxy-ester* (58) (13.75 g, 64%)

as colourless crystals, m.p. 96—97 °C (from ether–hexane) (Found: C, 70.3; H, 6.5. $C_{20}H_{22}O_5$ requires C, 70.15; H, 6.5%); M^+, 342; $\nu_{max.}$ 3 460, 3 390, 1 730, 1 700, and 1 600 cm^{-1}; δ 7.36 (5 H, s, ArH), 6.65 (2 H, s, ArH), 5.0 (2 H, s, ArCH_2O), 3.80 (3 H, s, OMe), 3.74 (3 H, s, OMe), 3.18—2.79 (5 H, m, 2 ArCH_2 and O*H*), and 2.0 (2 H, t, CH_2).

2-*Acetyl*-5-*benzyloxy*-1,2,3,4-*tetrahydro*-8-*methoxy*-2-*naphthol* (59).—A mixture of sodium hydride (9.9 g, 50%) and dimethyl sulphoxide (120 ml) was heated at 70 °C under nitrogen with stirring for 95 min. The mixture was then cooled to 0 °C and dry THF (120 ml) was added, followed by a solution of the hydroxy-ester (58) (14.58 g) in dry THF (120 ml). The mixture was stirred at 0 °C for 45 min, then poured into water (600 ml), acidified to pH 4 with orthophosphoric acid, and extracted with dichloromethane (4 × 300 ml). The combined extracts were washed with water, dried and evaporated to give the crude crystalline β-ketosulphoxide which was used directly for the next step.

The above product was dissolved in a mixture of THF (510 ml) and water (57 ml) and the solution cooled to 10 °C under nitrogen. Aluminium amalgam (prepared from 18.0 g of aluminium foil) was added and the mixture stirred for 4.5 h at 10—12 °C. It was then filtered and evaporated and the oily residue taken up in dichloromethane (200 ml), washed with water (2 × 100 ml), dried and evaporated. Column chromatography on silica gel, using ethyl acetate–hexane (1 : 1) as eluant, gave the *ketone* (59) (10.9 g, 78.4%) as colourless crystals, m.p. 71—72 °C (Found: C, 73.5; H, 6.65. $C_{20}H_{22}O_4$ requires C, 73.6; H, 6.8%); M^+, 326; $\nu_{max.}$ 3 460, 1 710, 1 695, and 1 600 cm^{-1}; δ 7.36 (5 H, s, ArH), 7.66 (2 H, s, ArH), 5.0 (2 H, s, ArCH_2O), 3.79 (3 H, s, OMe), 3.58 (1 H, s, OH), 3.2—2.7 (4 H, m, 2 ArCH_2), 2.32 (3 H, s, COMe), and 2.1—1.7 (2 H, m, CH_2).

5-*Benzyloxy*-2-[1-(1,1-*ethylenedioxy*)*ethyl*]-1,2,3,4-*tetrahydro*-8-*methoxy*-2-*naphthol*(60).—A mixture of the ketone (59) (10.2 g), benzene (790 ml), acetone (27 ml), ethylene glycol (78.5 ml), and toluene-4-sulphonic acid (0.4 g) was heated under reflux, using a Dean-Stark trap, for 6.5 h. The solution was cooled, washed with aqueous 10% potassium hydrogen carbonate (2 × 300 ml), dried, and evaporated. Crystallisation of the product from ether gave the *acetal* (60) (9.85 g, 85%) as colourless crystals, m.p. 99—100 °C (Found: C, 71.3; H, 7.1. $C_{22}H_{26}O_5$ requires C, 71.35; H, 7.05%); M^+, 370; $\nu_{max.}$ 3 460, 1 655, 1 600, and 1 580 cm^{-1}; δ 7.32 (5 H, s, ArH), 6.60 (2 H, s, ArH), 5.0 (2 H, s, ArCH_2O), 4.0 (4 H, s, OCH_2CH_2O), 3.74 (3 H, s, OMe), 3.2—2.6 (4 H, m, 2 ArCH_2), 2.2—1.6 (3 H, m, CH_2 and OH), and 1.40 (3 H, s, Me).

2-[1-(1,1-*Ethylenedioxy*)*ethyl*]-1,2,3,4-*tetrahydro*-8-*methoxynaphthalene*-2,5-*diol* (61).—A solution of the acetal (60) 5.0 g) in ethyl acetate (500 ml) was shaken with Pd–C (0.8 g, 10%) in hydrogen. After hydrogen uptake ceased the catalyst was filtered off (Celite) and the filtrate evaporated to give the *phenol* (61) (3.79 g, 100%) as colourless crystals, m.p. 122—123 °C (Found: C, 64.0; H, 7.25. $C_{15}H_{20}O_5$ requires C, 64.25; H, 7.2%); M^+, 280; $\nu_{max.}$ 3 400 and 1 590 cm^{-1}; δ 6.48 (2 H, s, ArH), 4.89 (1 H, s, OH), 4.0 (4 H, s, OCH_2CH_2O), 3.7 (3 H, s, OMe), 3.0—2.6 (4 H, m, 2 ArCH_2), 2.3—1.8 (3 H, m, CH_2 and OH), and 1.40 (3 H, s, Me).

3-{2-[1-(1,1-*Ethylenedioxy*)*ethyl*]-1,2,3,4-*tetrahydro*-2,5-*dihydroxy*-8-*methoxy*-6-*naphthyl*}-4-*methoxyphthalide* (46).—Using the procedure described for the preparation of compound (44), starting with the phenol (61) (2.5 g), the aldehyde (38) (1.8 g), and benzeneboronic acid (1.75 g), the *phthalide* (46) (2.68 g, 67%) was obtained as a colourless, crystalline mixture of diastereoisomers, m.p. 197—205 °C (from ether–hexane) (Found: C, 64.9; H, 5.9. $C_{24}H_{26}O_8$ requires C, 65.15; H, 5.9%); M^+ 442; $\nu_{max.}$ 3 450, 1 725, and 1 610 cm^{-1}; δ 7.6—6.7 (3 H, m, ArH), 6.15 (1 H, s, ArH), 4.04 (4 H, s, OCH_2CH_2O), 3.80 (3 H, s, OMe), 3.58 (3 H, s, OMe), 3.0—1.6 (7 H, m, 3 CH_2 and OH), and 7.42 (3 H, s, Me).

6-(2-*Carboxy*-6-*methoxybenzyl*)-1,2,3,4-*tetrahydro*-8-*methoxynaphthalene*-2,5-*diol* (49).—Using the procedure described for the preparation of compound (47), starting with the phthalide (46) (2.0 g), the *acid* (49) (1.55 g, 77%) was obtained as a white powder, m.p. 200—202 °C (Found: C, 64.65; H, 6.15. $C_{24}H_{28}O_8$ requires C, 64.85; H, 6.35%); M^+, 444; $\nu_{max.}$ 3 480, 3 250, 1 710, 1 670, 1 615, 1 590, and 1 580 cm^{-1}; δ 7.92 (1 H, dd, *J* 1.5 and 8 Hz, ArH), 7.30 (1 H, t, *J* 8 Hz, ArH), 7.10 (1 H, dd, *J* 1.5 and 8 Hz, ArH), 6.0 (1 H, s, ArH), 4.08 (4 H, s, OCH_2CH_2O), 3.94 (2 H, s, Ar_2-CH_2), 3.89 (6 H, s, 2 OMe), 3.1—2.9 (4 H, m, 2 CH_2), 2.1—1.5 (3 H, m, CH_2 and OH), and 1.45 (3 H, s, Me).

2-[1-(1,1-*Ethylenedioxy*)*ethyl*]-1,2,3,4,6,11-*hexahydro*-2-*hydroxy*-5,7,12-*trimethoxynaphthacene*-6,11-*quinone* (54).—A mixture of the acid (49) (1.0 g), anhydrous potassium carbonate (10 g), methyl iodide (4 ml), and acetone (80 ml) was heated under reflux with stirring. Further portions of methyl iodide (4 ml) were added after 3 and 6 h. The mixture was heated and stirred for a total of 24 h, and then cooled, filtered and the filtrate evaporated. The residue was dissolved in a mixture of methanol (30 ml), water (50 ml), and sodium hydroxide (1.5 g) and heated under reflux for 1.5 h. Most of the methanol was then evaporated off and the residue diluted with water (50 ml), acidified with 2M-hydrochloric acid and extracted with ethyl acetate (3 × 100 ml). The combined extracts were washed with water (2 × 50 ml), dried and evaporated to give a white powder (52) (0.85 g, 82%) which was used for the next step without further purification.

The above product (0.85 g) was suspended in dichloromethane (30 ml) and trifluoroacetic anhydride (5 ml) was added with stirring. The mixture was stirred at room temperature for 30 min and then poured into water (30 ml). The dichloromethane layer was separated, washed with water (2 × 30 ml) and evaporated to give a yellow crystalline residue which was dissolved in a mixture of ethanol (50 ml), water (5 ml), and sodium hydroxide (0.3 g). Hydrogen peroxide (10 ml; 100 vol) was added and the mixture heated at 80 °C. Further portions of hydrogen peroxide (10 ml) were added after 20 and 40 min. The mixture was poured into water (200 ml) and extracted with dichloromethane (3 × 50 ml). The combined dichloromethane extracts were washed with water, dried and evaporated to give a yellow residue which was purified by column chromatography on silica gel using ethyl acetate–hexane (1 : 1) as eluant. The *naphthacene* (54) (490 mg, 58%) was obtained as yellow crystals, m.p. 194—196 °C (from ethyl acetate) (Found: C 66.15; H, 5.8. $C_{25}H_{26}O_8$ requires C, 66.05; H, 5.75%); M^+, 454; $\nu_{max.}$ 3 410, 1 670, 1 585, and 1 550 cm^{-1}; $\lambda_{max.}$ 262 and 379 nm (log ε 4.49 and 3.92); δ 7.77 (1 H, dd, *J* 1.5 and 8 Hz, ArH), 7.62 (1 H, t, *J* 8 Hz, ArH), 7.22 (1 H, dd, *J* 1.5 and 8 Hz, ArH), 4.08 (4 H, s, OCH_2CH_2O), 4.0 (3 H, s, OMe), 3.96 (3 H, s, OMe), 3.92 (3 H, s, OMe), 3.2—2.8 (4 H, m, 2 CH_2), 2.2—1.5 (3 H, m, CH_2 and OH), and 1.45 (3 H, s, Me).

2-*Acetyl*-1,2,3,4,6,11-*hexahydro*-5,12-*dihydroxy*-7-*methoxynaphthacene*-6,11-*quinone* [(±)-7,9-*Dideoxydaunomycinone*]

(63).—Boron trichloride (0.25 g) in dichloromethane (3 ml) was added to a stirred solution of the naphthacene (53) (50 mg) in dichloromethane (20 m) at 0 °C. The solution was stirred for 5 min, then quenched by the slow addition of methanol (5 ml) and poured into water (50 ml). The dichloromethane layer was separated, dried and evaporated to give a red crystalline residue. Recrystallisation from dichloromethane–methanol gave the naphthacene (63) (40 mg, 86%) as red needles, m.p. 243—245 °C (lit.,[11] m.p. 243—245 °C) (Found: C, 68.95; H, 5.0. Calc. for $C_{21}H_{18}O_6$: C, 68.85; H, 4.95%); M^+, 366; $\nu_{max.}$ 1 705, 1 605, 1 580, and 1 570 cm^{-1}; $\lambda_{max.}$ 255, 297, 500, and 536 nm (log ε 4.48, 3.93, 4.08, and 3.87); δ 13.88 (1 H, s, ArOH), 13.53 (1 H, s, ArOH), 8.07 (1 H, dd, *J* 1.5 and 8.0 Hz, ArH), 7.76 (1 H, t, *J* 8 Hz, ArH), 7.36 (1 H, dd, *J* 1.5 and 8 Hz, ArH), 4.08 (3 H, s, OMe), 3.2—1.6 (7 H, m, 3 CH_2 and CH), and 2.27 (3 H, s, COMe).

Methyl 1,2,3,4,6,11-*Hexahydro*-5,12-*dihydroxy*-7-*methoxy*-6,11-*dioxonaphthacene*-2-*carboxylate* (64).—From the naphthacene (33), as for the preparation of compound (63), the *naphthacene* (64) (85%) was obtained as bright red needles, m.p. 262—263 °C (from THF–isopropyl alcohol) (Found: C, 65.9; H, 4.75. $C_{21}H_{18}O_7$ requires C, 65.95; H, 4.75%); M^+, 382; $\nu_{max.}$ 1 715, 1 610, and 1 570 cm^{-1}; $\lambda_{max.}$ 255, 291, 500, and 535 nm (log ε 4.49, 3.95, 4.09, and 3.88); δ 13.88 (1 H, s, ArOH), 13.52 (1 H, s, ArOH), 2.06 (1 H, dd, *J* 1.5 and 8 Hz, ArH), 7.76 (1 H, t, *J* 8 Hz, ArH), 7.36 (1 H, dd, *J* 1.5 and 8 Hz, ArH), 4.09 (3 H, s, OMe), 3.76 (3 H, s, OMe), and 3.2—1.7 (7 H, m, 3 CH_2 and CH).

2-*Acetyl*-1,2,3,4.6,11-*hexahydro*-2,5,12-*trihydroxy*-7-*methoxynaphthacene*-6,11-*quinone* [(±)-7-*Deoxydaunomycinone*] (65).—The naphthacene (54) (36 mg) was dissolved in dioxan (10 ml) and 5M-hydrochloric acid (8 ml) was added with stirring. After 30 min the mixture was poured into water (100 ml) and the product extracted into dichloromethane (2 × 50 ml). The combined extracts were washed with water (2 × 50 ml), dried and evaporated. The yellow residue was redissolved in dichloromethane (10 ml), and boron trichloride (0.2 g) in dichloromethane (3 ml) was added with stirring. After 10 min the red solution was poured into water (50 ml) and shaken. The dichloromethane layer was separated, dried and evaporated to give a red crystalline residue. Recrystallisation from THF–ethyl acetate gave the naphthacene (65) (20 mg, 66%) as red prisms, m.p. 228—229 °C (lit.,[11] m.p. 229—231 °C) (Found: C, 65.9; H, 4.7. Calc. for $C_{21}H_{18}O_7$: C, 65.95; H, 4.75%); M^+, 382; $\nu_{max.}$ 3 490, 1 695, 1 605, 1 580, and 1 570 cm^{-1}; $\lambda_{max.}$ 255, 293, 498, and 536 nm (log ε 4.46 ,3.93, 4.07, and 3.86); δ 13.86 (1 H, s, ArOH), 13.48 (1 H, s, ArOH), 8.05 (1 H, dd, *J* 1.5 and 8.0 Hz, ArH), 7.78 (1 H, t, *J* 8.0 Hz, ArH), 7.38 (1 H, dd, *J* 1.5 and 8.0 Hz, ArH), 4.10 (3 H, s, OMe), 3.73 (1 H, s, OH), 3.2—2.9 (4 H, m, 2 CH_2), 2.38 (3 H, s, OMe), and 2.1—1.9 (2 H, m, CH_2).

cis-1-*Acetoxy*-3-[1-(1,1-*ethylenedioxy*)*ethyl*]-1,2,3,4,6,11-*hexahydro*-3-*hydroxy*-5,10,12-*trimethoxynaphthacene*-6,11-*quinone* (66) *and* trans-1-*Acetoxy*-3-[1-(1,1-*ethylenedioxy*)-*ethyl*]-1,2,3,4,6,11-*hexahydro*-3-*hydroxy*-5,10,12-*trimethoxy-naphthacene*-6,11-*quinone* (67).—To a refluxing solution of the naphthacene (54) (452 mg) in carbon tetrachloride (44 ml) under nitrogen was added *N*-bromosuccinimide (200 mg) and α-azoisobutyronitrile (10 mg). The mixture was stirred under reflux for 1 h and then further amounts of *N*-bromosuccinimide (36 mg) and α-azoisobutyronitrile (5 mg) were added and heating continued for 1 h. After cooling the solvent was evaporated off and the yellow residue obtained was dissolved in glacial acetic acid (50 ml) and silver acetate (0.5 g) added. The mixture was stirred in the dark for 18 h under nitrogen and then the solvent was evaporated off. Dichloromethane (100 ml) was added to the residue, the mixture was filtered and the filtrate washed with 10% potassium hydrogen carbonate solution, dried and evaporated to a yellow gum. Crystallisation from ethyl acetate–ether gave the *naphthacene* (66) (273 mg, 53.8%) as yellow crystals, m.p. 220—222 °C (Found: C, 63.1; H,5.65. $C_{27}H_{28}O_{10}$ requires C, 63.28; H, 5.51); M^+, 512; $\nu_{max.}$ 3 500, 1 735, 1 665, 1 660, 1 580, and 1 565 cm^{-1}; $\lambda_{max.}$ 260 381 nm (log ε 4.45 and 3.92); δ 7.76 (1 H, dd, *J* 2 and 8 Hz, ArH), 7.64 (1 H, t, *J* 8 Hz, ArH), 7.26 (1 H, dd, *J* 2 and 8 Hz, ArH), 6.49 (1 H, q, *J* 2 Hz, CHOAc), 4.06 (4 H, s, OCH_2CH_2O), 4.01 (3 H, s, OMe), 3.95 (3 H, s, OMe), 3.94 (3 H, s, OMe), 3.30 (1 H, dd, *J* 2 and 18 Hz, 4-H), 2.86 (1 H, d, *J* 18 Hz, 4-H), 2.42 (1 H, s, OH), 2.3—1.96 (2 H, m, 2-H_2), 2.10 (3 H, s, OCOMe), and 1.46 (3 H, s, Me).

The mother liquors from the above crystallisation were chromatographed on silica gel, using ethyl acetate as eluant. The *naphthacene* (67) (40 mg, 8%) was obtained as yellow crystals, m.p. 223—224 °C (from THF–methanol)(Found: C, 63.1; H, 5.55. $C_{27}H_{28}O_{10}$ requires C, 63.28; H, 5.51%); M^+, 512; $\nu_{max.}$ 3 575, 1 730, 1 675, 1 640, 1 585, and 1 560 cm^{-1}; $\lambda_{max.}$ 260 and 381 nm (log ε 4.45 and 3.91); δ 7.76 (1 H, dd, *J* 2 and 8 Hz, ArH), 7.62 (1 H, t, *J* 8 Hz, ArH), 7.24 (1 H, dd, *J* 2 and 8 Hz), 6.49 (1 H, t, *J* 7 Hz, CHOAc), 4.06 (4 H, s, OCH_2CH_2O), 4.0 (3 H, s, OMe), 3.92 (3 H, s, OMe), 3.90 (3 H, s, OMe), 3.18 (1 H, dd, *J* 2 and 16 Hz, 4-H), 2.84 (1 H, d, *J* 16 Hz, 4-H), 2.38—1.80 (3 H, m, 2-H_2 and OH), 2.08 (3 H, s, OCOMe), and 1.42 (3 H, s, Me). Further naphthacenedione (66) (25 mg, 5%) was obtained from later fractions.

cis-3-[1-(1,1-*Ethylenedioxy*)*ethyl*]-1,2,3,4,6,11-*hexahydro*-1,3-*dihydroxy*-5,10,12-*trimethoxynaphthacene*-6,11-*quinone* (68).—The naphthacene (66) (100 mg) was dissolved in dichloromethane (2 ml) and the solution diluted with methanol (25 ml). Sodium hydride (30 mg of a 50% dispersion in mineral oil) was added and the mixture stirred at room temperature for 1 h. Acetic acid (0.25 ml) was then added and most of the solvent evaporated off. The residue was dissolved in dichloromethane (50 ml) and water (50 ml) and the organic layer separated, dried and evaporated to give a yellow crystalline product. Trituration with ether gave the *naphthacene* (68) (85 mg, 92.5%) which was recrystallised from THF–methanol to give yellow crystals, m.p. 215—216 °C (Found: C, 63.85; H, 5.6. $C_{25}H_{25}O_9$ requires C, 63.82; H, 5.57%); M^+, 470; $\nu_{max.}$ 3 460, 3 350, 1 660, 1 585, and 1 540 cm^{-1}; $\lambda_{max.}$ 260 and 380 nm (log ε 4.45 and 3.91); δ 7.76 (1 H, dd, *J* 2 and 7 Hz, ArH), 7.63 (1 H, t, *J* 7 Hz, ArH), 7.26 (1 H, dd, *J* 2 and 7 Hz, ArH), 5.27 (1 H, m CHOH), 4.10 (4 H, s, OCH_2CH_2O), 4.09 (3 H, s, OMe), 4.01 (3 H, s, OMe), 3.93 (3 H, s, OMe), 3.26 (1 H, dd, *J* 2 and 18 Hz, 4-H), 2.82 (1 H, d, *J* 18 Hz, 4-H), 2.43 (1 H, dt, *J* 2 and 15 Hz, 2-H), 1.94 (1 H, dd, *J* 5 and 15 Hz, 2-H), and 1.46 (3 H, s, Me).

cis-3-*Acetyl*-1,2,3,4,6,11-*hexahydro*-1,3-*dihydroxy*-5,10,12-*trimethoxynaphthacene*-6,11-*quinone* (69).—The naphthacene (68) (50 mg) was dissolved in warm dioxan (25 ml), the solution was cooled to 0 °C and 5M-hydrochloric acid (25 ml) was added. The mixture was stirred at room temperature for 3.5 h and was then poured into dichloromethane (100 ml). The organic layer was separated, washed with water (2 × 50 ml), dried and evaporated. Trituration with ether gave the *naphthacene* (69) (35 mg, 77%), which was recrystallised from THF–methanol to give yellow crystals, m.p. 214—215 °C

(Found: C, 64.65; H, 5.3. $C_{23}H_{22}O_8$ requires C, 64.78; H, 5.20%); M^+, 426; $\nu_{max.}$ 3 450, 3 380, 1 710, 1 670, 1 660, 1 585, and 1 560 cm^{-1}; $\lambda_{max.}$ 260 and 381 nm (log ε 4.44 and 3.90); δ 7.76 (1 H, dd, *J* 2 and 8 Hz, ArH), 7.64 (1 H, t, *J* 8 Hz, ArH), 7.26 (1 H, dd, *J* 2 and 8 Hz, ArH), 5.30 (1 H, m, C*H*OH), 4.10 (3 H, s, OMe), 4.02 (3 H, s, OMe), 3.92 (3 H, s, OMe), 3.78 (1 H, d, *J* 6 Hz, OH), 3.22 (1 H, dd, *J* 2 and 18 Hz, 4-H), 2.96 (1 H, d, *J* 18 Hz, 4-H), 2.43 (1 H, s, OH), 2.42 (3 H, s, COMe), 2.32 (1 H, dt, *J* 2 and 14 Hz, 2-H), and 2.12 (1 H, dd, *J* 4 and 14 Hz, 2-H).

cis-3-*Acetyl*-1,2,3,4,6,11-*hexahydro*-1,3,5,12-*tetrahydroxy*-10-*methoxynaphthacene*-6,11-*quinone* [(±)-*Daunomycinone*] (70).—The naphthacene (69) (30 mg) was dissolved in dichloromethane (30 ml) and the solution cooled to −70 °C. Boron trichloride (0.5 ml of a 25% v/v solution in dichloromethane) was added and the mixture stirred for 30 min under nitrogen and allowed to warm to room temperature. Methanol (3 ml) was added and the solution was poured into water (50 ml) and shaken vigorously. The dichloromethane layer was separated, washed with water, dried and evaporated to give a red-brown crystalline solid. Recrystallisation from a large volume of THF–methanol gave the *naphthacene* (70) (40 mg, 85%) as red-brown needles, m.p. 286—287 °C (Found: C, 63.2; H, 4.65. $C_{21}H_{18}O_8$ requires C, 63.32; H, 4.55%); M^+, 398; $\nu_{max.}$ 3 480, 1 710, 1 610, 1 580, and 1 570 cm^{-1}; $\lambda_{max.}$ 253, 290, 484, and 534 nm (log ε 4.41, 3.99, 4.08, 4.08, and 3.79); δ[$(CD_3)_2SO$] 8.0—7.6 (3 H, m, ArH), 5.1 (1 H, br s, C*H*OH), 4.03 (3 H, s, OMe), 3.0 (2 H, m, CH_2), 2.32 (3 H, s, COMe), and 2.3—1.9 (2 H, m, CH_2).

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