Pergamon

Tetrahedron, Vol. 53, No. 9, pp. 3195-3204, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00030-6

Synthesis of Cytotoxic Furonaphthoquinones: Regiospecific Synthesis of Diodantunezone and 2-Ethylfuronaphthoquinones

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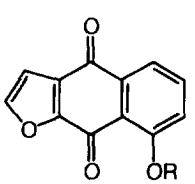
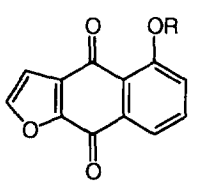
Abstract: Diodantunezone was first isolated from *Lantana achyrantifolia* (Verbenaceae) and originally assigned as 8-hydroxy-4,9-dihydronaphtho[2,3-*b*]furan-4,9-dione **1a** but its structure was later revised to 5-hydroxy-4,9-dihydronaphtho[2,3-*b*]furan-4,9-dione **2a**. The regiospecific synthesis of diodantunezone **2a** and its methyl ether, 5-methoxy-4,9-dihydronaphtho[2,3-*b*]furan-4,9-dione **2b**, is described. The preparation of two 2-ethylfuronaphthoquinones **14a** and **14b** is also described. All four quinones were shown to possess cytotoxic activity against three cell lines (1.3–17.4 μmol dm^{-3}).

INTRODUCTION

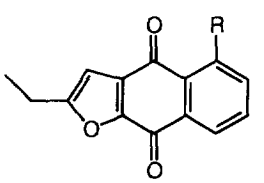
Diodantunezone, a furonaphthoquinone first isolated[1] from the aerial parts of *Lantana achyrantifolia* (Verbenaceae), was originally assigned structure **1a** on spectroscopic grounds. However, the data did not preclude the possibility of the 5-hydroxy regioisomer **2a** (*vide infra*). The authors also referred briefly to the isolation of a second quinone, methyl diodantunezone, presumably 8-methoxy-4,9-dihydronaphtho[2,3-*b*]furan-4,9-dione **1b**, or similarly its 5-methoxy regioisomer **2b**, although no details were given.[1] A more recent examination of *Lantana achyrantifolia* and *L. camara* (Verbenaceae) by Thomson and co-workers[2] led to the isolation of a mixture of the regioisomers **1a** and **2a**. Although structural elucidation of such isomeric pairs may be achieved by a number of methods, such as X-ray crystallography[3] or selective INEPT NMR experiments,[4] unequivocal evidence of regiochemistry is often procured by synthesis.



1a R = H
1b R = Me



2a R = H
2b R = Me



3a R = H
3b R = OH

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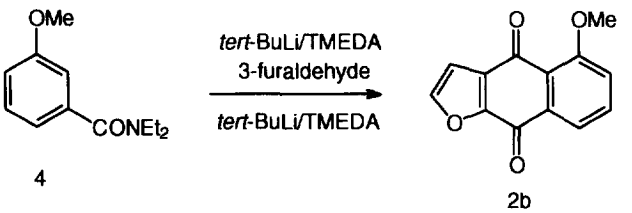
Indeed, unable to separate the two components and thus determine the structures of the two regioisomers **1a** and **2a**, Thomson and co-workers resorted to synthesis.[2] Chloroalkylation of the appropriately substituted dihydroxy-1,4-naphthoquinones followed by cyclisation and subsequent dehydrogenation gave both **1a** and **2a** in poor overall yields (5 and 8% respectively). The sample of diodantunezone originally isolated from *L. achyrantifolia*[1] was found to correspond to 5-hydroxy-4,9-dihydronaphtho[2,3-*b*]furan-4,9-dione **2a**. Accordingly, the structure of diodantunezone was revised to **2a**, with 8-hydroxy-4,9-dihydronaphtho[2,3-*b*]furan-4,9-dione **1a** being referred to as isodiodantunezone.

Given our current interest[5,6] in the synthesis of furonaphthoquinones for biological evaluation, we sought to develop an efficient synthesis of diodantunezone **2a**, as well as a route to analogues of the related naturally occurring 2-ethylfuronaphthoquinones **3a** and **3b**.[7] Herein we describe the regiospecific synthesis of diodantunezone **2a** and its methyl ether, 5-methoxy-4,9-dihydronaphtho[2,3-*b*]furan-4,9-dione **2b**, in 35 and 38% overall yield, respectively. The preparation of two 2-ethylfuronaphthoquinones, **14a** and **14b**, is also described.

RESULTS AND DISCUSSION

Initially a tandem directed metallation technique developed by Snieckus[8] for the one-pot synthesis of polycyclic quinones was investigated. Lithiation of 3-methoxy-*N,N*-diethylbenzamide **4** upon treatment with *tert*-butyllithium/TMEDA may be expected to occur exclusively at the 2-position due to the combined *ortho* directing influences of the methoxy and amide moieties.[9] However, condensation of the lithiated intermediate with 3-furaldehyde followed by a second *in situ* treatment with 4 equivalents of *tert*-butyllithium/TMEDA and subsequent intramolecular cyclisation[10] (scheme 1) gave a complex mixture of products by TLC. Repeated column chromatography of this mixture afforded only a small amount (4%) of the desired quinone **2b**, hence this methodology was not pursued further.

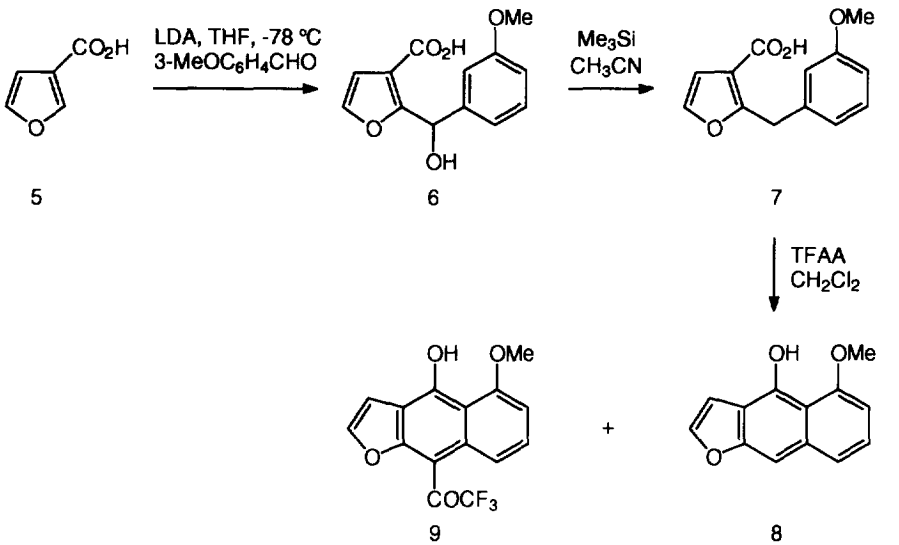
Scheme 1



4 2b

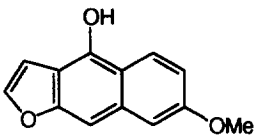
Instead a methodology recently developed[6] in our laboratories for the synthesis of furonaphthoquinones from 3-furoic acid **5** and methoxybenzaldehydes was employed (scheme 2). Regiospecific C-2 lithiation[11] of 3-furoic acid **5** with lithium diisopropylamide (LDA) in THF and subsequent treatment with 3-methoxybenzaldehyde gave the alcohol **6** in 79% yield. Reduction of **6** with iodotrimethylsilane[12] afforded the 2-benzyl-3-furoic acid **7** in near quantitative yield. Friedel-Crafts cyclisation of **7** could be expected to give a mixture of regioisomers owing to the unsymmetrical nature of **7**. Ring closure may occur *ortho* or *para* to the methoxy substituent giving rise to the 5-methoxy or 7-methoxy naphthols, **8** and **10**, respectively. In addition, the facile acylation[6] of naphthols analogous to **8** suggested that the 9-trifluoroacetylnaphthol **9** and its

Scheme 2



5 6 7 9 8

7-methoxy regioisomer **11** may also be formed. Indeed, treatment of **7** with trifluoroacetic anhydride in dry dichloromethane afforded a mixture of two products (13:5 by ^{1}H NMR). Separation by column chromatography on silica gel gave pure samples of the two components (**8**, **9**). The mass spectrum of the major component exhibited a molecular ion at *m/z* 310 and a fragment ion (M^+–CF_3) at *m/z* 241. The infra red spectrum showed strong absorptions at 1670 and 1635 cm^{-1}, characteristic of a 9-trifluoroacetylnaphthol. The ^{13}C NMR spectrum exhibited C-F coupling for the carbonyl (*J* 37 Hz) and CF_3 (*J* 291 Hz) carbons of a trifluoroacetyl group, thus substantiating this structural formulation. The ^{1}H NMR spectrum exhibited a sharp singlet at 10.77 ppm, exchangeable with D_2O, and was assigned to the hydroxyl proton. The aromatic region of the ^{1}H NMR spectrum exhibited a set of two furan protons (7.64 and 7.03 ppm, *J* 2.3 Hz) and a set of three protons characteristic of a 1,2,3-trisubstituted benzene ring. Hence the major component was assigned structure **9**. The minor component was found to be relatively unstable making it difficult to obtain satisfactory analytical data. Such instability is in keeping with that previously reported for analogous anthracenols.[13] However, the ^{1}H NMR spectrum of the minor component was found to be similar to that of **9**. A sharp singlet at 9.84 ppm, exchangeable with D_2O, was again assigned to a hydroxyl proton. The hydroxyl proton signal of 9-trifluoroacetylnaphthols analogous to **9** typically appear *ca.* 1 ppm further downfield in the ^{1}H NMR spectrum than the hydroxyl proton signal of the corresponding unacylated naphthols.[6] Thus the chemical shift of this hydroxyl proton signal indicated that the minor component did not contain a trifluoroacetyl substituent. This structural formulation was substantiated by the aromatic region of the ^{1}H NMR spectrum which was similar to that of **9**, with the addition of a signal at 7.42 ppm (9-H, *J* 1.0 Hz) weakly coupled to the 3-H proton. The ^{13}C NMR spectrum was in full accordance with that of an unacylated naphthol, hence the minor component was assigned structure **8**. No evidence was observed for the formation of the corresponding 7-methoxy regioisomers, **10** and **11**.



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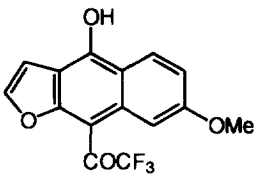
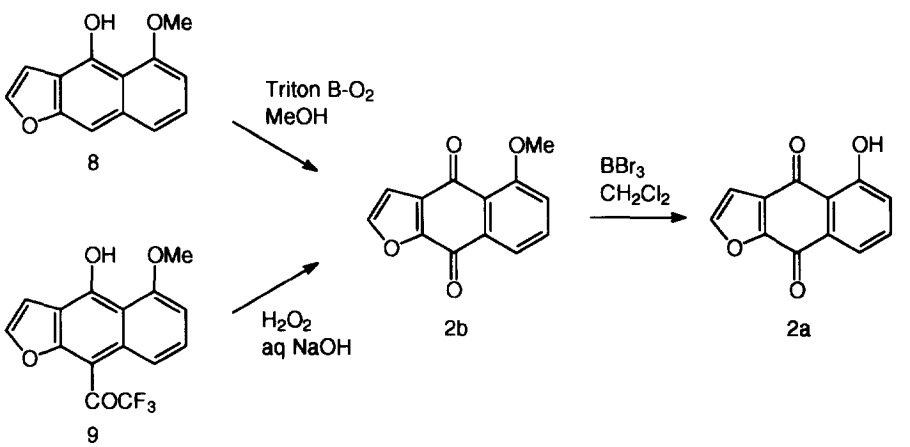


11

Hydrogen peroxide oxidation of **9** in aqueous base (scheme 3) smoothly afforded 5-methoxy-4,9-dihydronaphtho[2,3-*b*]furan-4,9-dione **2b** in excellent yield. Quinone **2b** was shown to exhibit identical spectroscopic properties to those of a semi-synthetic sample[2] obtained from the methylation of natural diodantunezone. Initial attempts to oxidise naphthols analogous to **8** into the corresponding furonaphthoquinones under a variety of conditions were unsuccessful.[6,14] Attempted oxidation of the naphthol **8** with Triton B–O_2 under the conditions described by Kende *et al.*[15] gave a highly complex mixture of products by TLC. However, modification of the above reaction conditions to exclude the presence of light allowed for the smooth conversion of **8** into the corresponding quinone **2b** in good yield. Column chromatography on silica gel gave a pure sample of the quinone **2b** shown to be identical to that prepared by hydrogen peroxide oxidation of **9**. Demethylation of **2b** with boron tribromide smoothly afforded diodantunezone **2a** which was shown to exhibit identical physical and spectroscopic properties to those previously described.[1,2]

Scheme 3

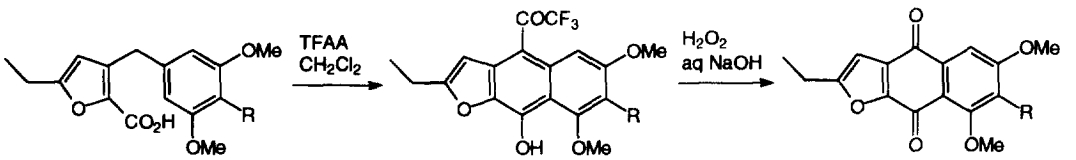


The two 2-ethylfuronaphthoquinones **14a** and **14b** were prepared from the benzylfuroic acids **12a** and **12b** respectively, which in turn were readily prepared from 2-furoic acid in 3 steps as previously described.[16] Friedel-Crafts cyclisations of **12a** and **12b** smoothly afforded the corresponding 4-trifluoroacetylnaphthols **13a** and **13b** respectively which, upon treatment with hydrogen peroxide in aqueous sodium hydroxide, gave the 2-ethylfuronaphthoquinones **14a** and **14b** in near quantitative yield (scheme 4).

The four furonaphthoquinones (**2a**, **2b**, **14a** and **14b**) were tested for cytotoxicity against KB epidermoid nasopharynx, K562 human leukaemia and P388 lymphocytic leukaemia cell lines. All four compounds exhibited cytotoxic activity against all three cell lines (Table 1, ID_{50} 1.3–17.4 μmol dm^{-3}). However, 5-

methoxy-4,9-dihydronaphtho[2,3-*b*]furan-4,9-dione **2b** was shown to exhibit greater cytotoxic activity towards each of the three cell lines than diodantunezone **2a**. These values may be significant inasmuch as lapachol, a biogenetically related prenylnaphthoquinone, has an ID_{50} value of 18.2 μmol dm^{-3} in the KB assay and showed sufficient *in vivo* activity to undergo clinical trials at the National Cancer Institute, Washington, USA.[17]

Scheme 4



12a R = H
12b R = OMe

13a R = H
13b R = OMe

14a R = H
14b R = OMe

Table 1 Effect of compounds **2a**, **2b**, **14a**, and **14b** on the growth of KB, K562 and P388 cell lines. Values shown are the concentrations (μmol dm^{-3}) required to cause a 50% inhibition in cell growth.

Compound	KB	K562	P388
2a	6.76	9.2	7.94
2b	1.3	1.32	1.86
14a	2.85	12.4	17.4
14b	13.0	12.7	17.15

In conclusion, the regiospecific synthesis of both diodantunezone **2a** and its methyl ether, 5-methoxy-4,9-dihydronaphtho[2,3-*b*]furan-4,9-dione **2b**, in good overall yield has been described. This synthesis of diodantunezone confirms the revision of its structure to the 5-hydroxy regioisomer **2a**. The preparation of two 2-ethylfuronaphthoquinones, **14a** and **14b**, has also been described. All four furonaphthoquinones (**2a**, **2b**, **14a** and **14b**) prepared have been shown to possess cytotoxic activity against three cell lines.

EXPERIMENTAL

Mps were determined on a hot-stage microscope and are uncorrected. IR spectra were recorded as potassium bromide disks using a Perkin-Elmer 683 Infrared spectrometer. NMR spectra were recorded on a Bruker AC250 spectrometer at 303.3 K in $CDCl_3$ solution, unless stated otherwise. Chemical shifts (ppm) are given downfield of tetramethylsilane (^1H and ^{13}C) or fluorotrichloromethane (^{19}F). Coupling constants *J* are given in Hz. Electron impact mass spectra were determined on a VG Trio-3 mass spectrometer at an ionisation energy of 70 eV. Organic solutions were dried over magnesium sulphate. Ether refers to diethyl ether. Column

chromatography was performed as previously described[18] on Merck silica gel 60 (230–400 Mesh). Cytotoxicity experiments were carried out as previously described.[19]

5-Methoxy-4,9-dihydronaphtho[2,3-*b*]furan-4,9-dione 2b—To a solution of 3-methoxy-*N*,*N*-diethylbenzamide[9] (1.28 g, 6.2 mmol) and tetramethylethylenediamine (0.75 g, 6.5 mmol) in dry tetrahydrofuran (25 ml) at –78 °C under nitrogen was added *tert*-butyllithium (5 ml of a 1.7 mol dm^{-3} solution in pentane, 8.5 mmol) with stirring. The mixture was stirred at –78 °C for 1 hour and a solution of 3-furaldehyde (0.6 g, 6.2 mmol) in dry tetrahydrofuran (5 ml) was added dropwise. The mixture was allowed to warm slowly to –40 °C over 1 hour before being again cooled to –78 °C. A mixture of *tert*-butyllithium (15 ml of a 1.7 mol dm^{-3} solution in pentane, 25 mmol) and tetramethylethylenediamine (2.95 g, 25 mmol) was added dropwise and the reaction mixture stirred at –78 °C for 1 hour. The reaction mixture was allowed to reach ambient temperature and stirred overnight. The resulting solution was diluted with water (50 ml) and acidified (2 mol dm^{-3} hydrochloric acid). This mixture was extracted with ether (3 x 50 ml) and the combined extracts were washed with brine (25 ml) and dried. Evaporation followed by repeated column chromatography on silica gel with dichloromethane–ethyl acetate gave the title compound **2b** as yellow needles (60 mg, 4%) mp 190–191 °C (lit.,[2] 160–162 °C); (Found: C, 68.5; H, 3.5. Calc. for $C_{13}H_8O_4$: C, 68.4; H, 3.5%); ν_{max}/cm^{-1} 1660 (C=O) and 1590; *m/z* 228 (M^+, 100%), 199 (48), 182 (21), 170 (24), 154 (18), 142 (20), 141 (55) and 75 (30); δ_H 7.93 (1H, dd, *J* 7.6, 1.1, 8-H), 7.75 (1H, d, *J* 1.8, 2-H), 7.70 (1H, dd, *J* 8.5, 7.6, 7-H), 7.35 (1H, dd, *J* 8.5, 1.1, 6-H), 6.98 (1H, d, *J* 1.8, 3-H) and 4.05 (3H, s, OMe); δ_C 179.9, 173.0, 160.45, 150.9, 148.6, 134.9, 134.8, 131.9, 120.4, 119.7, 118.5, 108.9 and 56.4.

2-[(3-Methoxyphenyl)hydroxymethyl]-3-furoic acid 5—To diisopropylamine (7 ml, 50 mmol) (freshly distilled from solid KOH) at –10 °C under nitrogen was added *n*-butyllithium (32 ml of a 1.6 mol dm^{-3} solution in hexanes, 50 mmol) with stirring. After 15 minutes the resulting viscous solution was diluted with dry tetrahydrofuran (50 ml), cooled to –78 °C, and a solution of 3-furoic acid **4** (2.8 g, 25 mmol) in dry tetrahydrofuran (50 ml) was added. The solution was stirred at –78 °C for 30 minutes and a solution of 3-methoxybenzaldehyde (3.4 g, 25 mmol) in dry tetrahydrofuran (50 ml) was added, and the solution allowed to reach ambient temperature over *ca.* 30 minutes. The resulting solution was diluted with water (200 ml) and washed with ether (2 x 50 ml). The aqueous portion was acidified (2 mol dm^{-3} hydrochloric acid) and extracted with ether (3 x 100 ml). The combined extracts were washed with brine, dried, and evaporated to yield the crude product as an oil which was crystallised from light petroleum (40–60 °C)–ether (2:1) giving the title compound **5** as a white solid (4.9 g, 79%) mp 80 °C; (Found: C, 62.7; H, 5.0. $C_{13}H_{12}O_5$ requires C, 62.9; H, 4.9%); ν_{max}/cm^{-1} 3400 (OH), 3200-2900 and 1680 (C=O); δ_H (DMSO) 7.61 (1H, d, *J* 2.0, 5-H), 7.23 (1H, t, *J* 7.8, 5'-H), 6.99 (1H, d, *J* 2.4, ArH), 6.92 (1H, dd, *J* 7.8, 0.8, ArH), 6.81 (1H, ddd, *J* 7.8, 2.4, 0.8, ArH), 6.65 (1H, d, *J* 2.0, 4-H), 6.43 (1H, s, C*H*OH), 3.73 (3H, s, OMe); δ_C (DMSO) 164.5, 161.0, 159.3, 143.6, 142.3, 129.3, 118.2, 114.2, 112.4, 111.8, 110.7, 65.8 and 55.0.

2-(3-Methoxybenzyl)-3-furoic acid 6—To a suspension of sodium iodide (2.25 g, 15 mmol) in dry acetonitrile (10 ml) under nitrogen was added chlorotrimethylsilane (1.93 ml, 15 mmol) with stirring followed by a solution of **5** (620 mg, 2.5 mmol) in dry acetonitrile (50 ml) and the mixture was stirred at room temperature for 5 minutes. The mixture was diluted with water (50 ml) and extracted with ether (3 x 50 ml). The combined extracts were washed with aqueous sodium thiosulphate solution (2 x 50 ml), saturated brine (50 ml) and dried. Evaporation gave the crude product which was recrystallised from methanol to afford the title compound **6** as a white solid (550 mg, 95%) mp 80–82 °C; (Found: C, 67.1; H, 5.2. $C_{13}H_{12}O_4$ requires C, 67.2; H, 5.2%); ν_{max}/cm^{-1} 1680 (C=O); *m/z* 232 (M^+, 91%), 214 (100), 199 (18), 171 (50), 115 (48), 91 (37), 51 (21) and 39 (18); δ_H 7.32 (1H, d, *J* 2.0, 5-H), 7.24 (1H, t, *J* 8.0, ArH), 6.90 (2H, m, ArH), 6.80 (1H, dd, *J* 8.0, 2.5, ArH), 6.76 (1H, d, *J* 2.0, 4-H), 4.39 (2H, s, CH_2), 3.81 (3H, s, OMe); δ_C 169.7, 161.8, 159.7, 141.4, 138.5, 129.5, 121.15, 114.6, 113.2, 112.0, 110.9, 55.1 and 33.5.

4-Hydroxy-5-methoxynaphtho[2,3-*b*]furan 8 and 4-hydroxy-5-methoxy-9-trifluoroacetylnaphtho[2,3-*b*]furan 9—To a stirred solution of 2-(3-methoxybenzyl)-3-furoic acid **6** (1.16 g, 5 mmol) in dry dichloromethane (25 ml) was added trifluoroacetic anhydride (0.71 ml, 5 mmol). After stirring at room temperature for 4 hours, water (10 ml) was added and the mixture stirred for five minutes. The organic phase was separated, washed with brine (10 ml) and dried. Evaporation and column chromatography on silica gel with dichloromethane afforded a mixture of the two products **8** and **9** (5:13 by ^1H NMR) (765 mg, 54%). A second chromatographic separation on silica gel with hexane-ethyl acetate (4:1) afforded pure samples of the title compounds **8** and **9**.

4-Hydroxy-5-methoxynaphtho[2,3-*b*]furan 8. As a yellow oil (160 mg, 15%), R_f = 0.70 (hexane-EtOAc, 4:1); ν_{max} (film)/cm^{-1} 3300 (OH); δ_H 9.84 (1H, s, OH), 7.58 (1H, d, *J* 2.3, 2-H), 7.48 (1H, dd, *J* 8.5, 0.8, 8-H), 7.42 (1H, d, *J* 1.0, 9-H), 7.26 (1H, dd, *J* 8.5, 7.6, 7-H), 7.02 (1H, dd, *J* 2.3, 1.0, 3-H), 6.69 (1H, dd, *J* 7.6, 0.8, 6-H) and 4.11 (3H, s, OMe); δ_C 156.7, 155.35, 147.7, 144.45, 134.4, 124.4, 121.9, 114.6, 110.4, 104.0, 101.2, 98.5 and 55.9.

4-Hydroxy-5-methoxy-9-trifluoroacetylnaphtho[2,3-*b*]furan 9. As yellow needles (600 mg, 39%), mp 127–128 °C (from MeOH); R_f = 0.91 (hexane-EtOAc, 4:1); (Found: C, 58.2; H, 2.9; F, 18.35. $C_{15}H_9O_4F_3$ requires C, 58.1; H, 2.9; F, 18.4%); ν_{max}/cm^{-1} 3300 (OH), 1670 and 1635 (C=O); *m/z* 310 (M^+, 34%), 241 (100), 226 (46), 198 (67) and 170 (27); δ_H 10.77 (1H, s, OH), 8.33 (1H, dd, *J* 9.0, 0.8, 8-H), 7.64 (1H, d, *J* 2.3, 2-H), 7.45 (1H, dd, *J* 9.0, 7.8, 7-H), 7.03 (1H, d, *J* 2.3, 3-H), 6.80 (1H, dd, *J* 7.8, 0.8, 6-H) and 4.10 (3H, s, OMe); δ_C 180.75 (q, *J* 37.0, C=O), 157.0, 156.8, 155.5, 144.7, 134.2, 128.8 and 123.5, 118.85, 114.2 and 109.6 (q, *J* 291.4, CF_3), 118.6, 114.1, 110.9, 103.9, 103.2, 102.2 and 56.3; δ_F –74.0 (s, CF_3).

5-Methoxy-4,9-dihydronaphtho[2,3-*b*]furan-4,9-dione 2b—To a stirred solution of benzyltrimethylammonium hydroxide in methanol (Triton B 40%, 1.6 g, 3.8 mmol) in an additional 2 ml of methanol was added dropwise in the dark a solution of **8** (81 mg, 0.38 mmol) dissolved in dichloromethane (5

ml) over *ca.* 30 minutes whilst oxygen was bubbled through. The solution was stirred and oxygen bubbled through for a further 4 hours. The solution was acidified (2 mol dm^{-3} hydrochloric acid), diluted with water (10 ml) and extracted with dichloromethane (3 x 10 ml). The combined organic extracts were washed with water (10 ml) and dried. Evaporation and column chromatography on silica gel (CH_2Cl_2–EtOAc, 20:1) gave the title quinone **2b** which recrystallised from methanol as yellow needles (71 mg, 82%) with identical physical and spectroscopic properties to those described above.

5-Methoxy-4,9-dihydronaphtho[2,3-*b*]furan-4,9-dione 2b—To a stirred solution of **9** (310 mg, 1 mmol), sodium hydroxide (80 mg, 2 mmol) and sodium carbonate (130 mg, 1.2 mmol) in distilled water (5 ml) at 40 °C was added hydrogen peroxide (0.1 ml, 1.2 mmol, 30% w/w in H_2O) and the mixture stirred at 40 °C for 24 hours. The mixture was acidified (2 mol dm^{-3} hydrochloric acid), extracted with dichloromethane (3 x 20 ml), and dried. Evaporation and recrystallisation from methanol gave the title quinone **2b** as yellow needles (221 mg, 97%) with identical physical and spectroscopic properties to those described above.

5-Hydroxy-4,9-dihydronaphtho[2,3-*b*]furan-4,9-dione (diodantunezone) 2a—To a stirred solution of 5-methoxy-4,9-dihydronaphtho[2,3-*b*]furan-4,9-dione **2b** (91 mg, 0.4 mmol) in dry dichloromethane (35 ml) at –78 °C was added dropwise boron tribromide (0.7 g, 2.8 mmol) and the solution stirred at –78 °C for 30 minutes. The solution was slowly allowed to reach ambient temperature and was stirred for 24 hours. Water (10 ml) was added and the solution stirred for 30 minutes. The solution was extracted with ethyl acetate (3 x 20 ml), dried and evaporated. Recrystallisation from methanol gave the title compound **2a** as orange needles (80 mg, 94%), mp 218 °C (lit.,[2] 217–218 °C); (Found: C, 67.1; H, 3.0. Calc. for $C_{12}H_6O_4$: C, 67.3; H, 2.8%); ν_{max}/cm^{-1} 1665 and 1630 (C=O); *m/z* 214 (M^+, 100%), 186 (48), 158 (33), 130 (52), 129 (38), 102 (24), 92 (22), 75 (35) and 63 (56); δ_H 12.20 (1H, s, OH), 7.78 (1H, d, *J* 1.8, 2-H), 7.76 (1H, dd, *J* 6.4, 1.0, 8-H), 7.62 (1H, dd, *J* 8.6, 6.4, 7-H), 7.28 (1H, dd, *J* 8.6, 1.0, 6-H) and 7.00 (1H, d, *J* 1.8, 3-H).

2-Ethyl-9-hydroxy-6,8-dimethoxy-4-trifluoroacetylnaphtho[2,3-*b*]furan 13a—To a solution of 3-(3,5-dimethoxybenzyl)-5-ethyl-2-furoic acid[16] (1.45g, 5 mmol) in dichloromethane (25 ml) was added trifluoroacetic anhydride (0.71 ml, 5 mmol) at room temperature with stirring. The solution was stirred for 6 hours. Water (10 ml) was added and the mixture stirred for 5 minutes. The organic phase was separated, washed with brine (10 ml) and dried. Evaporation and column chromatography on silica gel with chloroform gave 2-ethyl-9-hydroxy-6,8-dimethoxy-4-trifluoroacetylnaphtho[2,3-*b*]furan **13a** as yellow needles (1.75g, 95%), mp 176 °C; R_f = 0.75 ($CHCl_3$); (Found: C, 58.8; H, 4.0; F, 15.4. $C_{18}H_{15}O_5F_3$ requires C, 58.70; H, 4.10; F, 15.47%); ν_{max} (KBr)/cm^{-1} 3300 (OH), 1680, 1640 (C=O); *m/z* 368 (M^+, 36%), 299 (100); δ_H ($CDCl_3$) 10.31 (1H, s, OH), 7.64 (1H, d, *J* 2.2, 5-H), 6.73 (1H, s, 3-H), 6.54 (1H, d, *J* 2.2, 7-H), 4.13 (3H, s, OMe), 3.94 (3H, s, OMe), 2.93 (2H, q, *J* 7.5, CH_2), 1.42 (3H, t, *J* 7.5, CH_3); δ_C ($CDCl_3$) 182.0, 166.8, 159.4, 158.1, 144.85, 138.2, 135.7, 134.8 (123.6, 119.1, 114.5, 109.8, quartet, *J* 292.4, CF_3), 108.5, 107.3, 101.3, 97.5, 97.2, 56.5, 55.3, 22.0, 11.5; δ_F ($CDCl_3$) -72.0 (s, CF_3).

2-Ethyl-9-hydroxy-6,7,8-trimethoxy-4-trifluoroacetylnaphtho[2,3-*b*]furan 13b—To a solution of 3-(3,4,5-trimethoxybenzyl)-5-ethyl-2-furoic acid[16] (1.60g, 5 mmol) in dichloromethane (25 ml) was added trifluoroacetic anhydride (0.71 ml, 5 mmol) at room temperature with stirring. The solution was stirred for 6 hours. Water (10 ml) was added and the mixture stirred for 5 minutes. The organic phase was separated, washed with brine (10 ml) and dried. Evaporation and column chromatography on silica gel with dichloromethane gave 2-ethyl-9-hydroxy-6,7,8-trimethoxy-4-trifluoroacetylnaphtho[2,3-*b*]furan **13b** as yellow needles (1.90g, 95%), mp 130 °C; (Found: C, 57.2; H, 4.3; F, 14.4. $C_{19}H_{17}O_6F_3$ requires C, 57.29; H, 4.30; F, 14.31%); ν_{max} (KBr)/cm^{-1} 3200 (OH), 1670, 1640 (C=O); *m/z* 398 (M^+, 40%), 329 (100), 299 (30), 286 (36), 271 (29); δ_H ($CDCl_3$) 10.77 (1H, s, OH), 7.94 (1H, s, 5-H), 6.74 (1H, t, *J* 1.0, 3-H), 4.23 (3H, s, OMe), 4.01 (3H, s, OMe), 3.99 (3H, s, OMe), 2.91 (2H, dq, *J* 7.6, 1.0, CH_2), 1.42 (3H, t, *J* 7.6, CH_3); δ_C ($CDCl_3$) 182.0, 166.6, 154.3, 148.7, 143.9, 138.95, 135.2, 129.9, (123.8, 119.2, 114.5, 109.9, quartet, *J* 292.4, CF_3), 109.6, 108.2, 101.7, 101.3, 62.7, 61.2, 55.8, 22.0, 11.4.

2-Ethyl-6,8-dimethoxy-4,9-dihydronaphtho[2,3-*b*]furan-4,9-dione 14a—To a stirred solution of 2-ethyl-9-hydroxy-6,8-dimethoxy-4-trifluoroacetylnaphtho[2,3-*b*]furan **13a** (1.47g, 4 mmol), sodium hydroxide (0.32g, 8 mmol), and sodium carbonate (0.52g, 4.8 mmol) in distilled water (24 ml) at 40 °C was added hydrogen peroxide (0.38 ml, 4.8 mmol, 30% w/w in H_2O). The solution was stirred at 40 °C for 24 hours. The reaction mixture was acidified (2 mol dm^{-3} hydrochloric acid), extracted with dichloromethane (3 x 50 ml), and dried. Evaporation and recrystallisation from methanol afforded 2-ethyl-6,8-dimethoxy-4,9-dihydronaphtho[2,3-*b*]furan-4,9-dione **14a** as orange needles (1.1g, 96%), mp 164 °C; (Found: C, 67.2; H, 4.7. $C_{16}H_{14}O_5$ requires C, 67.13; H, 4.93%); ν_{max} (KBr)/cm^{-1} 1675, 1660, 1580; *m/z* 286 (M^+, 100%), 257 (87), 214 (24), 213 (28), 57 (22); δ_H ($CDCl_3$) 7.39 (1H, d, *J* 2.45, 5-H), 6.74 (1H, d, *J* 2.45, 7-H), 6.54 (1H, s, 3-H), 4.00 (3H, s, OMe), 3.98 (3H, s, OMe), 2.82 (2H, q, *J* 7.6, CH_2), 1.34 (3H, t, *J* 7.6, CH_3); δ_C ($CDCl_3$) 180.4, 172.5, 164.5, 164.3, 162.8, 152.8, 137.6, 128.7, 113.9, 104.8, 103.9, 102.3, 56.4, 55.8, 21.5, 11.5.

2-Ethyl-6,7,8-trimethoxy-4,9-dihydronaphtho[2,3-*b*]furan-4,9-dione 14b—To a stirred solution of 2-ethyl-9-hydroxy-6,7,8-trimethoxy-4-trifluoroacetylnaphtho[2,3-*b*]furan **13b** (1.59g, 4 mmol), sodium hydroxide (0.32g, 8 mmol), and sodium carbonate (0.52g, 4.8 mmol) in distilled water (24 ml) at 40 °C was added hydrogen peroxide (0.38 ml, 4.8 mmol, 30% w/w in H_2O). The solution was stirred at 40 °C for 24 hours. The reaction mixture was acidified (2 mol dm^{-3} hydrochloric acid), extracted with dichloromethane (3 x 50 ml), and dried. Evaporation and recrystallisation from methanol afforded 2-ethyl-6,7,8-dimethoxy-4,9-dihydronaphtho[2,3-*b*]furan-4,9-dione **14b** as yellow needles (1.2g, 95%), mp 139 °C; (Found: C, 64.4; H, 5.2. $C_{17}H_{16}O_6$ requires C, 64.55; H, 5.10%); ν_{max} (KBr)/cm^{-1} 1685, 1660, 1580; *m/z* 316 (M^+, 68%), 301 (76), 287 (20), 243 (19), 105 (100), 77 (88), 43 (35); δ_H ($CDCl_3$) 7.59 (1H, s, 5-H), 6.54 (1H, t, *J* 1.0, 3-H), 4.04 (3H, s, OMe), 3.98 (3H, s, OMe), 3.97 (3H, s, OMe), 2.82 (2H, dq, *J* 7.6, 1.0, CH_2), 1.35 (3H, t, *J* 7.6, CH_3);

δ_C ($CDCl_3$) 180.0, 172.5, 164.7, 156.9, 155.4, 152.4, 147.9, 130.7, 129.3, 119.3, 107.0, 102.6, 61.6, 61.25, 56.3, 21.6, 11.5.

ACKNOWLEDGEMENTS

The authors wish to thank the Cancer Research Campaign and PCFC for financial support, M. Needham for NMR determinations and D. Whittaker for the cytotoxicity experiments.

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(*Received in UK* 15 *November* 1996; *accepted* 9 *January* 1997)