Synthesis of 8-Fluororhein

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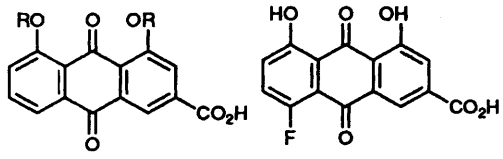
8-Fluoro-5-methoxy-1-tetralone has been formylated, aromatised and alkylated to give 8-fluoro-1-isopropoxy-5-methoxy-2-naphthaldehyde **11**. Condensation of this with a phosphonosuccinate gave, after deprotection, the 4-naphthylbutenoic acid which was cyclised and methylated to give the ethyl 9-fluoro-10-isopropoxy-4,6-dimethoxy-2-carboxylate **12**. Removal of the isopropyl group, dichromate oxidation and deprotection gave 8-fluorohein **3**, an analogue of the osteoarthritis drug rhein.

Osteoarthritis (OA) is a disease of unknown origin which causes great discomfort and pain to millions of people worldwide. Medical treatment of the disease commonly involves the use of non-steroidal anti-inflammatory drugs (NSAIDS) which, realistically, are not a cure, merely a means of pain relief.[1] The anthraquinone carboxylic acid diacetylrhein[2] **1** has been shown[3] to have some efficacy in the treatment of OA. The active metabolite of **1** is rhein **2**.[4] In following up our interest in disease-modifying compounds for the treatment of OA we wished to prepare fluorinated analogues of rhein **2**. Our results on the direct fluorination of anthraquinones have appeared[5] separately; the total synthesis of 8-fluororhein **3** is the subject of this paper.

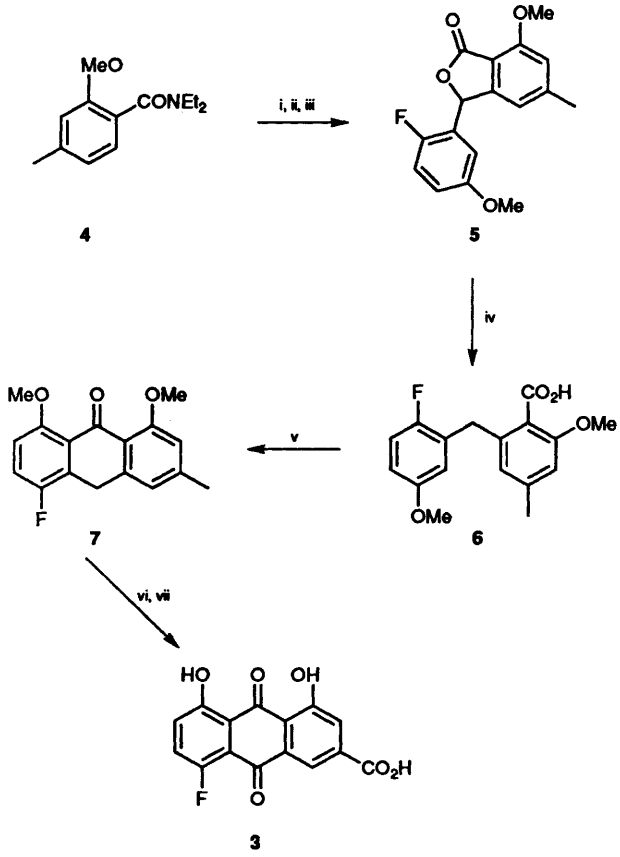


1 R = Ac
2 R = H

3

Our initial route (Scheme 1) to compound **3** was based on the directed metallation techniques developed by Snieckus[6] for the synthesis of anthraquinone natural products. The amide **4** has been metallated and condensed with an aryl aldehyde to give phthalides:[7] condensation with 2-fluoro-5-methoxybenzaldehyde[8] followed by ring closure should give the phthalide **5**. Reduction of **5** by catalytic hydrogenation[6] or another method should give the benzyl benzoic acid **6**, ring closure of which to the anthrone **7** would be expected to proceed readily under Snieckus'[6] conditions. Similar methyl anthrones[9] have been oxidised to anthraquinone carboxylic acids with potassium permanganate in aqueous *tert*-butyl alcohol, and demethylated with hydrobromic acid in these laboratories. An alternative demethylation procedure using aluminium chloride in dichloromethane has been described.[10]

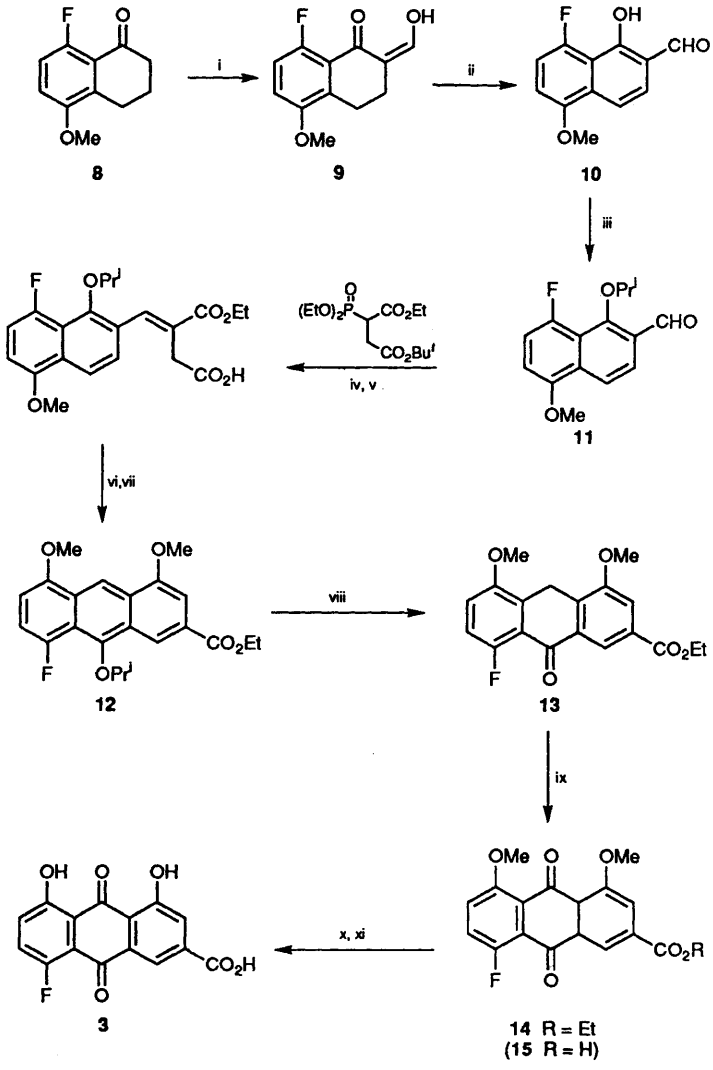
Accordingly, the diethyl amide **4**[7] was lithiated at low temperature and treated with 2-fluoro-5-methoxybenzaldehyde[8] under the literature[6] conditions to give the phthalide **5** in 84% yield. Attempted reduction of **5** by catalytic hydrogenation[6] over 10% palladium-on-charcoal in acetic acid containing a catalytic amount of perchloric acid was completely unsuccessful. Further attempts were made to reduce **5** using triethylsilane in trifluoroacetic acid–carbon tetrachloride,[11] triethylsilane–titanium tetrachloride in carbon tetrachloride,[11] triethylsilane–boron trifluoride–diethyl ether in dichloromethane[12] and zinc–copper couple in refluxing aqueous sodium hydroxide.[20] All of these procedures were equally unsuccessful in producing **6** so this route was abandoned.



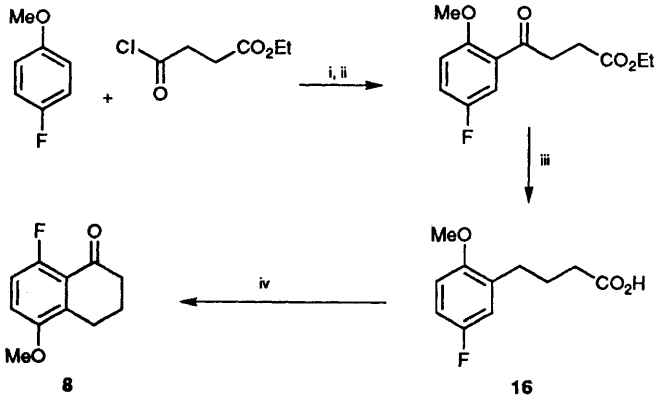
Scheme 1 i, Bu^{s}Li, TMEDA, THF; ii, 2-fluoro-5-methoxybenzaldehyde; iii, PTSA, toluene; iv, H_2, Pd/C, AcOH; v, TFA, TFAA, $CHCl_3$; vi, $KMnO_4$, Bu^{t}OH/H_2O; vii, deprotect

Following this disappointment it was decided to utilise a new synthesis of rhein **2** from 5-methoxy-1-tetralone which has recently[13] been developed in our laboratories. This route (Scheme 2) is longer than our initial route, however, since all the steps had already been proven for very similar materials we felt confident that it would provide the required product.

A synthesis of the required starting material **8** from 4-fluoroanisole *via* succinoylation, reduction and cyclisation, in an overall yield of 13% has been described.[14] Modification of this procedure as shown in Scheme 3 gave **8** in 73% yield in four steps from 4-fluoroanisole. Friedel–Crafts acylation of 4-fluoroanisole with ethyl succinyl chloride in a mixture of dichloromethane and nitromethane in the presence of aluminium chloride, followed by remethylation with dimethyl



Scheme 2 i, NaH, ethyl formate, THF; ii, DDQ, dioxane; iii, Pr^{i}I, K_2CO_3, MeCN; iv, LDA, THF; v, 90% aqueous TFA; vi, NaOAc, Ac_2O; vii, MeI, K_2CO_3, MeCN; viii, BCl_3, CH_2Cl_2; ix $K_2Cr_2O_7$, AcOH; x, LiOH, THF/H_2O; xi $AlCl_3$, CH_2Cl_2



Scheme 3 i, $AlCl_3$, CH_2Cl_2/$MeNO_2$; ii, Me_2SO_4, K_2CO_3, acetone; iii, H_2, 10% Pd/C, AcOH; iv, PPA, 90 °C

sulphate and potassium carbonate in acetone at reflux, gave a product which was essentially pure by TLC. This material was passed through a pad of silica and hydrogenated over 10% palladium-on-charcoal in acetic acid containing a catalytic amount of perchloric acid, to give 4-(5-fluoro-2-methoxyphenyl)butyric acid **16** in 81% yield with respect to 4-fluoroanisole. This material was cyclised with poly(phosphoric acid) at elevated temperature to give **8** in 98% yield. The reaction temperature is crucial to the successful outcome of this step. We found a reaction temperature of 85–90 °C gave the best yield of **8**, the product mixture being essentially one component. Higher temperatures gave lower yields and more complex product mixtures.

With compound **8** in hand we were able to proceed with the sequence (Scheme 2); thus **8** was formylated under the literature[15] conditions, using sodium hydride and ethyl formate in THF, to give **9** in >95% yield. Oxidation of **9** with DDQ in dioxane[16] proceeded smoothly to give **10** in virtually quantitative yield, provided the starting material **9** was of high purity. It was decided to use the isopropyl group for protection at this point: experience with the trimethoxy analogue of **12** had shown that oxidation to the anthraquinone on a scale of >250 mg with chromium reagents gave poor yields, and we speculated that the free hydroxy compound **13** would oxidise more readily. Aryl isopropyl ethers have been cleaved in the presence of aryl methyl ethers by treatment with boron trichloride in dichloromethane.[17] Therefore, compound **10** was alkylated with 2-iodopropane and potassium carbonate in acetonitrile at reflux to give the aldehyde **11** in 99% yield. The aldehyde **11** was then condensed with the lithium enolate of 1-*tert*-butyl 4-ethyl 3-diethylphosphonobutanedioate under the literature[18] conditions. In accordance with the published procedure, no attempt was made to purify the resulting diester, the crude reaction

product being deprotected to give a mixture which was shown by ^{1}H NMR and mass spectroscopy to contain the naphthylbutenoic acid in approximately 80% yield with respect to **11**. This mixture was dissolved in acetic anhydride containing anhydrous sodium acetate and then heated under reflux for 4 h[19] to give, after basic work-up, methylation and column chromatography, compound **12** in moderate yield (*ca* 35% with respect to naphthylbutenoic acid). Removal of the isopropyl protection group with boron trichloride in dichloromethane proved straightforward, and gave compound **13** in 93% yield. Oxidation of **13** with dichromate in acetic acid at reflux[20] gave the protected anthraquinone **14** in near quantitative yield, vindicating the decision to operate at the level of the free anthracenone. Some care is required in choosing deprotection conditions for **14**, as over-vigorous hydrolysis conditions (NaOH/MeOH at reflux) resulted in displacement of the fluorine. Hydrolysis was achieved with a stoichiometric quantity of lithium hydroxide in THF/water (19:1) at room temperature, giving the carboxylic acid **15** in quantitative yield. Demethylation of **15** with aluminium chloride in dichloromethane[10] gave 8-fluororhein **3**. Alternatively compound **14** could be taken directly to **3** with concentrated hydrobromic acid at elevated temperature, although this procedure did not give as clean a product as the two-stage route and **3** is not easily purified.

Experimental

Melting points were determined on a Reichert melting point apparatus and are uncorrected. IR spectra were recorded on KBr discs using a Bruker IFS 48 spectrometer. ^{1}H NMR spectra were determined using a Bruker AM 300 spectrometer. Dilute solutions in deuteriochloroform were used throughout (unless otherwise noted) with tetramethylsilane as internal standard and *J* values are given in Hz . Molecular weights and mass spectra were measured using a VG 707E spectrometer by chemical ionisation (NH_3). THF was dried by distillation from sodium-benzophenone ketyl. Dimethylformamide (DMF), acetonitrile, dioxane and dichloromethane were dried using molecular sieves.

3-(2′-Fluoro-5′-methoxyphenyl)-7-methoxy-5-methylisobenzofuran-1(3H)-one **5**.—*N,N*-Diethyl-2-methoxy-4-methylbenzamide **4**[7] (4.5 g, 20.4 mmol) and *N,N,N′,N′*-tetramethylethylenediamine (2.4 g, 20.6 mmol) were dissolved in dry tetrahydrofuran (100 cm^3) under nitrogen and the solution was cooled in an acetone–solid carbon dioxide bath. *sec*-Butyllithium solution (1.3 mol dm^{-3} in cyclohexane; 28 cm^3, 36 mmol) was added to the reaction mixture which was then stirred and kept at < −70 °C for 1 h. A solution of 2-fluoro-5-methoxybenzaldehyde[8] (3.13 g, 20.3 mmol) dissolved in dry tetrahydrofuran (20 cm^3) was added dropwise with cooling to the reaction mixture which was then stirred at < −70 °C for 1 h. The cooling bath was then removed and the reaction mixture was allowed to come to room temperature overnight. Water (10 cm^3) was added to the reaction mixture which was then concentrated under reduced pressure to provide an oily residue which was partitioned between diethyl ether and dilute aqueous hydrochloric acid. The organic phase was washed with brine, dried ($MgSO_4$), filtered and concentrated to dryness under reduced pressure. The resulting material was taken up in toluene (150 cm^3) and toluene-*p*-sulfonic acid (0.5 g, 2.6 mmol) was added to the mixture. After it had been treated at reflux under Dean-Stark conditions for 15 h the reaction mixture was allowed to cool when it was washed with 1 mol dm^{-3} aqueous hydrochloric acid and saturated aqueous sodium carbonate. The organic phase was dried ($MgSO_4$), filtered and evaporated under reduced pressure to leave a dark oil (9.5 g). The crude product was purified by flash column chromatography on silica gel (eluent hexane–ethyl acetate, 4:1) to give the phthalide **5** as a white solid (5.2 g, 84%), m.p. 120–122 °C (from ethyl acetate–hexane); ν_{max}/cm^{-1} 1770 (C=O); δ_H 2.40 (3 H, s, 5-ArCH$_3$), 3.69 (3 H, s, 5′-OCH$_3$), 3.98 (3 H, s, 7-OCH$_3$), 6.56 (1 H, s, 3-CH), 6.63 (1 H, dd *J* 6,3, 6′-ArH), 6.73 (1 H, d *J* 1,6-ArH), 6.75 (1 H, d *J* 1,4-ArH), 6.81 (1 H, ddd *J* 9,6,3, 4′-ArH) and 7.05 (1 H, t *J* 9,3′-ArH) (Found: MH$^+$, 303.1022. $C_{17}H_{16}FO_4$ requires 303.1033) (Found: C, 67.6; H, 5.0; F, 6.35. $C_{17}H_{15}FO_4$ requires C, 67.54; H, 5.00; F, 6.29%).

4-(5′-Fluoro-2′-methoxyphenyl)butyric Acid **16**.—Nitromethane (20 cm^3) was added to a suspension of anhydrous aluminium chloride (30 g, 225 mmol) in dry dichloromethane (180 cm^3) under nitrogen at room temperature; the aluminium chloride dissolved. 4-Fluoroanisole (15 g, 119 mmol) was added to the reaction mixture followed by ethyl succinyl chloride (19.6 g, 119 mmol). The reaction mixture came to reflux temperature under the reaction exotherm and was then heated to maintain a gentle reflux. After 16 h the reaction mixture was allowed to cool and then poured onto ice containing concentrated orthophosphoric acid. The mixture was extracted with ethyl acetate (3 × 150 cm^3) and the combined organic extracts were dried ($MgSO_4$), filtered and evaporated to dryness under reduced pressure. The resulting oil was dissolved in acetone (150 cm^3) and dimethyl sulphate (15 cm^3) and potassium carbonate (16.6 g, 120 mmol) were added to the solution; the reaction mixture was heated under reflux under nitrogen. After 2 h the reaction mixture was poured into water (1000 cm^3) and extracted into ethyl acetate (3 × 200 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to dryness under reduced pressure. The resulting material was passed through a pad of flash silica (eluent hexane–ethyl acetate, 4:1) and evaporated to dryness under reduced pressure. The resulting oil was dissolved in acetic acid (120 cm^3) containing perchloric acid (60% aq.; 10 cm^3) and hydrogenated at 60 p.s.i. over 10% palladium-on-charcoal. When the theoretical amount of hydrogen had been taken up, the reaction mixture was filtered (Celite) and evaporated under reduced pressure. The crude product was taken up in ethyl acetate (150 cm^3) and washed with saturated aqueous sodium hydrogen carbonate. The organic phase was dried ($MgSO_4$), filtered and evaporated to dryness under reduced pressure to give the acid **16** as a white solid (20.44 g, 81%), m.p. 69–70 °C (from ethyl acetate–hexane) (lit.,[14] 68–70 °C); ν_{max}/cm^{-1} 1734 (C=O); δ_H 1.94 (2 H, m, 3-CH$_2$), 2.38 (2 H, t *J* 7,4-CH$_2$), 2.63 (2 H, t *J* 7,2-CH$_2$), 3.78 (3 H, s, O-CH$_3$), 6.75 (1 H, m, 3′-ArH and 6.83 (2 H, m,4′,6′-ArH) [Found: (M + NH$_4$)$^+$, 230.1185. $C_{11}H_{17}FNO_3$ requires 230.1193].

8-Fluoro-5-methoxy-3,4-dihydronaphthalen-1(2H)-one **8**.—The acid **16** (15.7 g, 74 mmol) mixed with polyphosphoric acid (120 g) was mechanically stirred and heated for 45 min in an oil-bath held at 90 °C; the oil-bath was then removed. The reaction mixture was allowed to cool after which water (200 cm^3) and ethyl acetate (150 cm^3) were added to it with continuous stirring. The organic phase was separated, washed with cold aqueous sodium hydroxide (2 mol dm^{-3}), dried ($MgSO_4$) and filtered. The resulting solution was evaporated to dryness under reduced pressure to give the tetralone **8** as a pale yellow solid (14.11 g, 98%), m.p. 83–84 °C (from ethyl acetate–hexane) (lit.,[14] 82–84 °C); ν_{max}/cm^{-1} 1695 (C=O); δ_H 2.10 (2 H, m, 3-CH$_2$), 2.62 (2 H, t *J* 7, 4-CH$_2$), 2.86 (2 H, t *J* 7, 2-CH$_2$), 3.83 (3 H, s, OCH$_3$), 6.95 (2 H, m, 6,7-ArH) (Found: M$^+$, 194.0735. $C_{11}H_{11}F0_2$ requires 194.0743).

8-Fluoro-5-methoxy-3,4-dihydro-2-hydroxymethylenenaphthalen-1(2H)-one **9**.—A suspension of sodium hydride (50%

disp. in mineral oil; 11.7 g, 244 mmol) in dry THF (200 cm^3) under nitrogen was mechanically stirred and cooled in an ice–water-bath, whilst ethyl formate (28 g, 380 mmol) was added to it. The mixture was stirred at ~ 5 °C for 20 min after which the tetralone **8** (14.1 g, 72.6 mmol) in THF (100 cm^3) was added in one portion to it. The reaction mixture was allowed to warm to room temperature when vigorous hydrogen evolution occurred and a precipitate formed. The reaction mixture was stirred for 15 h after which methanol (10 cm^3) and then water (10 cm^3) were added to it. The mixture was concentrated under reduced pressure and the residue was dissolved in water (200 cm^3) and the solution washed with diethyl ether (2 × 150 cm^3) and acidified with 5 mol dm^{-3} hydrochloric acid. The aqueous phase was extracted with dichloromethane (3 × 150 cm^3) and the combined extracts were dried ($MgSO_4$), filtered and evaporated to dryness under reduced pressure to give a dark oil (16.3 g). This material was taken up in ethyl acetate–hexane (1:5) and treated with activated charcoal (25 g) whilst being heated under reflux for 1 h. The mixture was filtered (Celite) while still hot and the filtrate was cooled to −20 °C to give the hydroxymethylenetetralone **9** as a white solid (15.65 g, 97%), m.p. 66–68 °C; ν_{max}/cm^{-1} 1640, 1608; δ_H 2.43 (2 H, t, *J* 7, 3-CH_2), 2.82 (2 H, t, *J* 7, 4-CH_2), 3.82 (3 H, s) (5-OCH_3), 6.9 (2 H, m) (6,7, ArH) 8.12 (1 H, d *J* 7,=C*H*OH) and 14.65 (1 H, d *J* 7, OH) (Found: M^+, 223.0762. $C_{12}H_{11}FO_3$ requires 223.0771) (Found: C, 64.7; H, 5.25; F, 8.7. $C_{12}H_{11}FO_3$ requires C, 64.86; H, 4.99; F, 8.55%).

8-*Fluoro*-1-*hydroxy*-5-*methoxy*-2-*naphthaldehyde* **10**.—2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (16 g, 70.5 mmol) was added to the hydroxymethylenetetralone **9** (15 g, 67.5 mmol) dissolved in dry dioxane (200 cm^3) and the mixture was heated under reflux for 1 h. The mixture was allowed to cool to room temperature and then filtered. The solids were washed with ethyl acetate and the combined filtrate and washings were concentrated under reduced pressure. The resulting solid was dissolved in ethyl acetate (150 cm^3) and the solution washed with saturated aqueous sodium hydrogen carbonate (150 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness under reduced pressure to give the hydroxynaphthaldehyde **10** as a yellow solid (14.7 g, 99%), m.p. 156–158 °C (from ethyl acetate–hexane); ν_{max}/cm^{-1} 1640 (C=O); δ_H 3.97 (3 H, s, 5-OCH_3), 6.91 (1 H, dd *J* 9,5, 6-ArH), 7.09 (1 H, dd *J* 10,9, 7-ArH), 7.55 (1 H, dd *J* 9,1, 4-ArH), 7.80 (1 H, d *J* 9, 3-ArH), 9.95 (1 H, s, OH) and 12.95 (1 H, s, CHO) (Found: M^+, 221.0614. $C_{12}H_9FO_3$ requires 221.0617) (Found: C, 65.7; H, 4.15; F, 8.7. $C_{12}H_9FO_3$ requires C, 65.45; H, 4.12; F, 8.63%).

8-*Fluoro*-1-*isopropoxy*-5-*methoxy*-2-*naphthaldehyde* **11**.—Anhydrous potassium carbonate (10 g, 72.5 mmol) followed by 2-iodopropane (11.9 g, 70 mmol) were added to the hydroxynaphthaldehyde **10** (14.5 g, 65.9 mmol) dissolved in dry acetonitrile (200 cm^3) and the reaction mixture was stirred and heated under reflux for 15 h under nitrogen. It was then filtered (Celite) and concentrated under reduced pressure. The resulting solid was dissolved in dichloromethane and the solution washed with water, dried ($MgSO_4$), filtered and evaporated to dryness under reduced pressure to give isopropoxynaphthaldehyde **11** as a yellow solid (17.1 g, 99%), m.p. 63–64 °C (from hexane); ν_{max}/cm^{-1} 1685 (C=O); δ_H 1.37 [6 H, d, *J* 6, $CH(CH_3)_2$], 3.99 (3 H, s, 5-OCH_3), 4.45 [1 H, m, $CH(CH_3)_2$], 6.85 (1 H, dd *J* 9,5, 6-ArH), 7.10 (1 H, dd *J* 9,13, 7-ArH), 7.88 (1 H, dd *J* 9,1, 4-ArH), 8.07 (1 H, d *J* 9, 3-ArH) and 10.60 (1 H, s, CHO) (Found: M^+, 263.1076. $C_{15}H_{15}FO_3$ requires 263.1084) (Found: C, 68.9; H, 5.9; F, 7.3. $C_{15}H_{15}FO_3$ requires C, 68.69; H, 5.76; F, 7.25%).

Ethyl 9-*Fluoro*-9-*isopropoxy*-4,6-*dimethoxyanthracene*-2-*carboxylate* **12**.—A solution of 1-*tert*-butyl 4-ethyl 3-diethylphosphonobutanedioate[17] (10.5 g, 31 mmol) dissolved in dry THF (80 cm^3) was stirred under nitrogen in an ice–water bath. Lithium diisopropylamide (1.5 mol dm^{-3} in cyclohexane; 22 cm^3, 33 mmol) was added to the solution which was then stirred for 20 min. The aldehyde **11** (8 g, 30.5 mmol) dissolved in dry THF (20 cm^3) was added to the reaction mixture over 5 min. after which the cooling bath was removed. After the reaction mixture had been stirred under nitrogen for 15 h it was treated with water (3 cm^3) and concentrated under reduced pressure. The residue was taken up in dichloromethane (100 cm^3) and the solution washed with brine (70 cm^3), dried ($MgSO_4$) and evaporated to dryness under reduced pressure to give a dark oil (15.5 g). This material was taken up in trifluoroacetic acid–water (9:1; 25 cm^3) and stirred in an ice–water bath. After 1 h the reaction mixture was poured into water (150 cm^3) and sodium carbonate was added to it until effervescence ceased; the mixture was then extracted with ethyl acetate (3 × 120 cm^3). The combined extracts were dried ($MgSO_4$), filtered and evaporated to dryness under reduced pressure to give a dark oil (12.3 g). This material was dissolved in acetic anhydride (50 cm^3) under nitrogen and treated with anhydrous sodium acetate (6 g, 73 mmol) whilst being heated under reflux. After 4 h the heat was removed and the mixture was allowed to cool before being quenched by addition to ice–water (200 cm^3). Sodium carbonate was added to the reaction mixture until effervescence ceased after which the latter was extracted with ethyl acetate. The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to dryness under reduced pressure. Iodomethane (4g, 28.5 mmol) was added to a solution of the resulting dark oil in acetonitrile (50 cm^3) with potassium carbonate (3.0 g, 21.7 mmol) under nitrogen and the reaction mixture was heated under reflux for 3 h. The mixture was then allowed to cool after which it was filtered (Celite) and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (eluent hexane–ethyl acetate, 4:1) to give the isopropoxyanthracene **12** as a yellow solid (3.54 g, 30%), m.p. 131–133 °C (from ethyl acetate–hexane); ν_{max}/cm^{-1} 1710; δ_H 1.38 [6 H, d *J* 5, $CH(CH_3)_2$], 1.43 (3 H, t *J* 7, CH_2CH_3), 4.05 (3 H, s, OCH_3), 4.13 (3 H, s, OCH_3), 4.45 (2 H, q *J* 7, CH_2CH_3), 4.48 [1 H, m, $CH(CH_3)_2$], 6.62 (1 H, dd *J* 5,9, 7-ArH), 7.01 (1 H, dd *J* 9,9, 8-ArH), 7.32 (1 H, d *J* 2, 3-ArH), 8.76 (1 H, d *J* 2, 1-ArH) and 8.99 (1 H, s, 5-ArH) (Found: MH^+, 387.1617 $C_{22}H_{24}FO_5$ requires 387.1608) (Found: C, 68.5; H, 6.0; F, 4.8. $C_{22}H_{23}FO_5$ requires C, 68.38; H, 6.00; F, 4.92%).

Ethyl 8-*Fluoro*-9,10-*dihydro*-4,5-*dimethoxy*-9-*oxoanthracene*-2-*carboxylate* **13**.—The anthracene **12** (3.0 g, 7.76 mmol) was dissolved in dichloromethane under nitrogen and the solution cooled in an ice–water bath. Boron trichloride solution (1 mol dm^{-3} in dichloromethane; 30 cm^3, 30 mmol) was added to the solution which was then cooled and stirred. After 15 h the reaction mixture was poured into water (150 cm^3) and extracted into dichloromethane (3 × 100 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the anthracenone **13** as a yellow solid (2.50 g, 93%), m.p. 180–181 °C (from ethyl acetate–hexane); ν_{max}/cm^{-1} 1715 and 1688; δ_H(keto tautomer) 1.44 (3 H, t *J* 7, CH_2CH_3), 3.96 (3 H, s, OCH_3), 4.03 (3 H, s, OCH_3), 4.09 (2 H, s 10-CH_2), 4.43 (2 H, q *J* 7, CH_2CH_3), 7.01 (1 H, dd, *J* 5,9, 6-ArH), 7.09 (1 H, dd *J* 9,9, 7-Ar-H), 7.74 (1 H, d *J* 2, 3-ArH) and 8.60 (1 H, d *J* 2,1-ArH) (Found: MH^+, 345.1153. $C_{19}H_{18}FO_5$ requires 345.1138) (Found: C, 66.4; H, 4.9; F, 5.45. $C_{19}H_{17}FO_5$ requires C, 66.27; H, 4.98; F, 5.52%).

Ethyl 8-*Fluoro*-9,10-*dihydro*-4,5-*dimethoxy*-9,10-*dioxoanthracene*-2-*carboxylate* **14**.—The anthracenone **13** (3.1 g, 9.0 mmol) was added to sodium dichromate (3.3 g, 11.2 mmol)

dissolved in hot glacial acetic acid (35 cm^3) and the reaction mixture was heated under reflux for 20 min. After it had been allowed to cool the reaction mixture was poured into water (120 cm^3) to give a green–yellow precipitate. The solid was filtered off, taken up in dichloromethane and the solution washed with water. The organic phase was dried ($MgSO_4$), filtered and evaporated to dryness under reduced pressure to give the anthraquinone **14** as a yellow solid (3.1 g, 96%), m.p. 201–203 °C (from ethyl acetate–hexane); ν_{max}/cm^{-1} 1715 and 1688; δ_H 1.42 (3 H, t *J* 7, CH_2CH_3), 3.96 (3 H, s, OCH_3), 4.05 (3 H, s, OCH_3), 4.43 (2 H, q *J* 7, CH_2CH_3), 7.35 (1 H, dd *J* 4,9, 6-ArH), 7.38 (1 H, dd *J* 9,9, 7-ArH), 7.93 (1 H, d *J* 2, 3-ArH) and 8.40 (1 H, d *J* 2, 1-ArH) (Found: MH^+, 359.0943. $C_{19}H_{16}FO_6$ requires 359.0931) (Found: C, 63.5; H, 4.3; F, 5.0. $C_{19}H_{15}FO_6$ requires C, 63.69; H, 4.22; F, 5.30%).

8-*Fluoro*-9,10-*dihydro*-4,5-*dimethoxy*-9,10-*dioxoanthracene*-2-*carboxylic Acid* **15**.—The ester **14** (0.556 g, 1.5 mmol) was dissolved in tetrahydrofuran–water (19:1; 40 cm^3) at room temperature and lithium hydroxide monohydrate (65 mg, 1.5 mmol) was added to the solution. The mixture was then stirred at room temperature for 3 h. After this, hydrochloric acid (2 mol dm^{-3}; 2 cm^3) was added to the reaction mixture which was then concentrated under reduced pressure and treated with water (40 cm^3) to afford a yellow precipitate. This was filtered off and dried *in vacuo* to give **15** (510 mg, 99%), m.p. 263–265 °C (from ethyl acetate); ν_{max}/cm^{-1} 1685 and 1680; δ_H 3.95 (3 H, s, OCH_3), 4.04 (3 H, s, OCH_3), 7.35 (1 H, dd *J* 5,9, 6-ArH), 7.38 (1 H, dd *J* 9,9, 7-ArH), 7.93 (1 H, d *J* 1, 3-Ar*H*) and 8.40 (1 H, d *J* 1, 3-ArH) (Found: MH^+, 331.0609. $C_{17}H_{12}FO_6$ requires 331.0618) (Found: C, 61.9; H, 3.4; F, 5.7. $C_{17}H_{11}FO_6$ requires C, 61.82; H, 3.36; F, 5.75%).

8-*Fluoro*-9,10-*dihydro*-4,5-*dihydroxy*-9,10-*dioxoanthracene*-2-*carboxylic Acid* **3**.—Aluminium trichloride (450 mg, 3.3 mmol) was added to the carboxylic acid **15** (150 mg, 0.45 mmol) suspended in dry dichloromethane at room temperature under nitrogen and the reaction mixture was stirred at the same temperature for 36 h. The mixture then was poured into ice (150 cm^3) containing orthophosphoric acid (15 cm^3) and the resulting yellow solid filtered off and dried *in vacuo* to give **3** (122 mg, 90%), m.p. 258–260 °C; ν_{max}/cm^{-1} 1700 and 1626 $\delta_H[^2H]_6$ DMSO) 7.48 (1 H, dd *J* 4,9, 6-ArH), 7.73 (1 H, dd *J* 9,9, 7-ArH), 7.74 (1 H, d *J* 1, 3-ArH), 8.06 (1 H, d *J* 1, 3-Ar*H*), 11.75 (1 H, s, OH) 12.12 (1 H, s, O*H*) and 13.58 (1 H, s, CO_2OH) (Found: MH^+, 303.0318. $C_{15}H_8FO_6$ requires 303.0305) (Found: C, 59.7; H, 2.15; F, 6.3. $C_{15}H_7FO_6$ requires C, 59.61; H, 2.33; F, 6.29%).

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