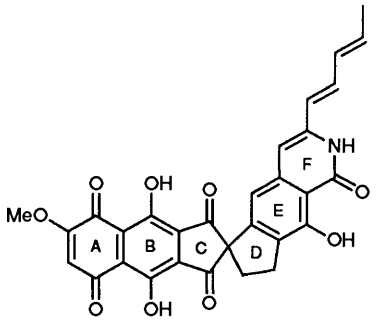
Model Studies Related to the Synthesis of Fredericamycin A

Derrick L. J. Clive,* Ahmad Khodabocus, Peter G. Vernon, A. Gaëtan Angoh, Luc Bordeleau and (in part) Donald S. Middleton, Christopher Lowe and Dorit Kellner
Department of Chemistry, University of Aberta, Edmonton, Alberta, Canada T6G 2G2

A spiro diketone **7** containing a pentamethoxynaphthalene unit, and representing four contiguous rings of the antitumour antibiotic fredericamycin A **1**, was constructed by radical spirocyclization

The fungal metabolite fredericamycin A **1** is a very powerful antitumour agent—as judged mainly by *in vitro* tests—and it also possesses antibiotic properties.[1] Little has been published on its mode of action,[2] or on the way it is formed in Nature,[3] but there is substantial literature[4] on model studies aimed at a synthesis of this complex† substance, and one route to the racemic compound has been reported.[5]



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Our synthetic approach is based on radical spirocyclization,[4h,6] a technique which we have previously tested[4t] by preparing the model compound **3**, along the lines shown in Scheme 1. Compound **3** represents only the four central rings of the natural product, and the next stage of our exploratory work was to apply the radical closure to substances containing a naphthalene unit derived from substrates **4** or **5** [R, R′ = protecting group(s)]. Here we describe the preparation of compounds **4** and **5** (R = R′ = Me) and their use to make the monoketones **6**‡ and then the spiro diketone **7**, representing rings A–D of fredericamycin. These experiments were done in order to gain experience in the preparation of highly oxygenated naphthalenes and in methods for cleaving the exocyclic double bond (see structure **6**) that is always generated by the radical spirocyclization.

We tried several routes (Schemes 2–6) to compounds **4** and **5** (R = R′ = Me) in the knowledge that either structure, or a mixture of the two, would be equally suitable for our purposes. Eventually we were able to devise a practicable method, which had the simplifying feature of giving only product **4** (and not **5**).

All of our early approaches have the quinone **8** as a common intermediate and our first effective attempt to assemble the naphthalene nucleus of this quinone relied on the methodology of directed lithiation (Scheme 2). The diethylamide **9** was readily accessible from the corresponding commercial acid, and the allylation (**9** ⟶ **10**) proceeded smoothly under the standard conditions developed[7] for such a process. Cyclization of the allyl compound (**10** ⟶ **11**) could be carried out in the normal way by treatment of amide **10** with methyllithium, but we obtained better results using lithium diisopropylamide (LDA).[8] The final step, oxidation to quinone **8**, proved difficult and we had to evaluate several reagents.§ Eventually we settled on thallium(III) nitrate,[10] which led to the quinone in *ca.* 50% yield. We used the route of Scheme 2 on a number of occasions, but were later able to replace it by a much more convenient method (see below).

With the quinone in hand, our main effort was then directed to the problem of converting it into one, or both, of the acetylenes represented by structure **18** (see Scheme 3), and a number of trial experiments prompted us to adopt the bromination route shown in Scheme 3. Reaction of quinone **8** with molecular bromine and then triethylamine afforded the monobromide **12**,¶ and further reaction with bromine in acetic acid gave the dibromide **13** (87% overall). From this point, the pentamethoxy dibromide **15** was easily prepared by reduction (dithionite) (**13** ⟶ **14**) and methylation (**14** ⟶ **15**). However, all attempts to replace selectively just one of the halogens by a phenylacetylene group (PhC≡C) were unsuccessful.[11] For this reason we converted the dibromo quinone **13** into the bromo iodides **16**, and then into the bromo(iodo)naphthalenes **17**. The bromide displacement (**13** ⟶ **16**) can be carried out using sodium iodide in refluxing diethyl ketone or in warm acetic acid, the latter giving slightly better yields. In both cases the product is a mixture of the starting dibromide **13**, the corresponding diiodide, and the desired bromo iodides **16** (as a mixture of two regioisomers). This material was used directly for conversion into the bromo(iodo)naphthalenes **17**, and then in the coupling step with copper(I) phenylacetylide. The bromo iodides **17** provided the required bromo acetylenes **18** while the dibromonaphthalene was left unchanged, and the diiodonaphthalene gave the corresponding bisacetylene (PhC≡C in place of each iodine). When acetic acid was used as the solvent for the halogen exchange the yield of bromo acetylenes **18** was 30% (from compound **13**) after crystallization, and the material was mainly (> 90%) one isomer to which we assign structure **19** by comparison with a sample made in a different way (see later).

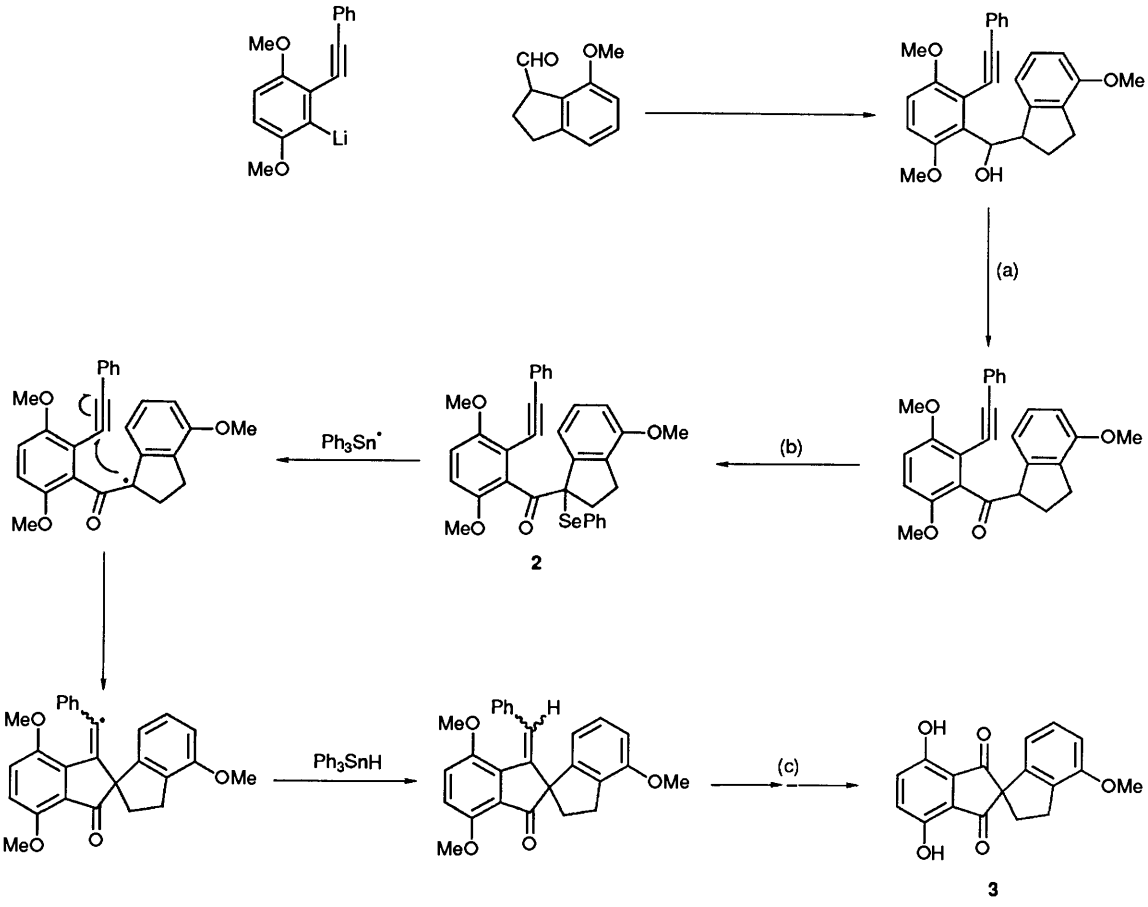
Although the reactions shown in Schemes 2 and 3 provided enough of the bromo acetylenes **18** to allow us to continue further work, it was clearly necessary to improve the synthesis or even to redesign it. At this point we developed an approach

† The structure type appears to be unique (among natural products). See footnote 4 in ref. 5.

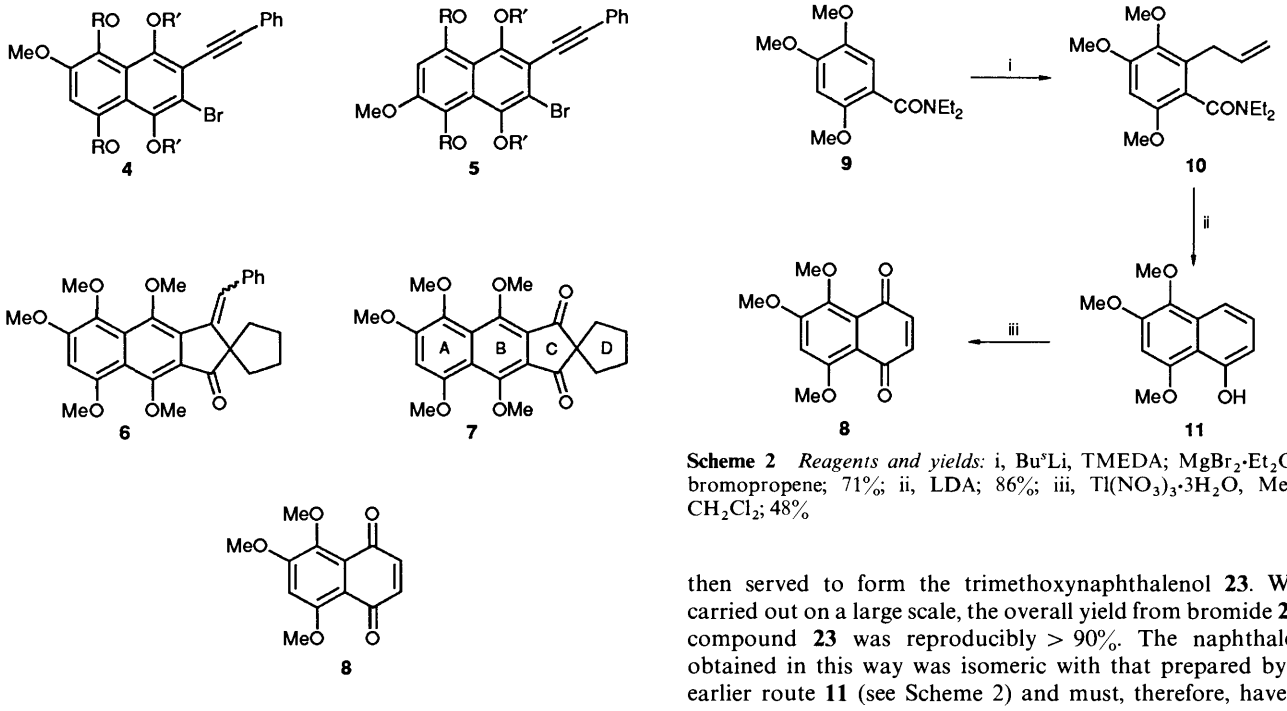
‡ Although we prepared both compounds **4** and **5** (R = R′ = Me), the major isomer by one route (Scheme 3) was that with structure **4**, and this was the exclusive isomer by the second route (Scheme 6). Compound **4** leads to spiro ketone **6** and not ot its regioisomer (carbonyl and CHPh interchanged).

§ Oxidation of the naphthol **11** with oxygen in the presence of a cobalt catalyst (ref. 9) gave quinone **8** in 20% yield. Bromination of the naphthol **11** followed by oxidation under similar conditions gave a bromo quinone, but the yield was no better than that obtained when using thallium(III) nitrate. The monobromo quinone was isomeric with that shown in Scheme 3. Cobalt-catalysed oxygenation gave a very poor result with bromo naphthol **24** (Scheme 5).

¶ A very small amount of the other regioisomer was also formed. See Experimental section.



Scheme 1 (a) Oxidation. (b) Phenylselenenylation. (c) Ozonolysis and demethylation.

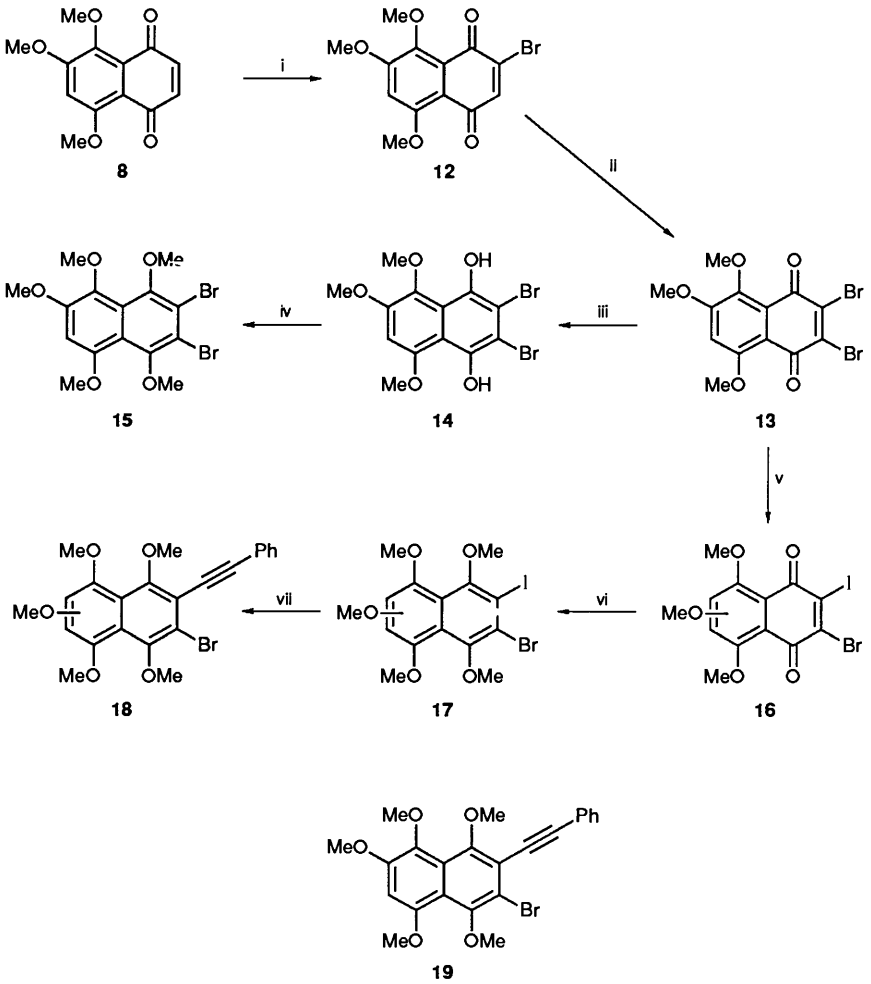


Scheme 2 *Reagents and yields:* i, Bu^{s}Li, TMEDA; $MgBr_2 \cdot Et_2O$; 3-bromopropene; 71%; ii, LDA; 86%; iii, $Tl(NO_3)_3 \cdot 3H_2O$, MeOH, CH_2Cl_2; 48%

based on a trimethoxybenzyne (Scheme 4), which greatly facilitated preparation of quinone **8** in multi-gram quantities.

Commercial 1,2,4-trimethoxybenzene **20** was easily brominated[12] (**20** ⟶ **21**), and treatment with LDA in the presence of a large excess of furan produced the benzyne cycloadduct **22** in nearly quantitative yield. Exposure to a catalytic amount of acid then served to form the trimethoxynaphthalenol **23**. When carried out on a large scale, the overall yield from bromide **21** to compound **23** was reproducibly > 90%. The naphthalenol obtained in this way was isomeric with that prepared by the earlier route **11** (see Scheme 2) and must, therefore, have the indicated structure. This structure is, of course, the one expected on the basis of electronic considerations for the acid-catalysed aromatization of cycloadduct **22**. We oxidized the naphthalenol with thallium(III) nitrate and obtained the desired quinone **8** in 54% yield (on a scale that produced *ca.* 12 g of product).

Although the above method was used to make material that was converted into the spiro diketone **7** (see later), we have



Scheme 3 *Reagents and yields:* i, Br_2, $CHCl_3$; ii, Br_2, AcOH; 87% from **8**; iii, $Na_2S_2O_4$; iv, Me_2SO_4, NaOH; 94% from **13**; v, NaI, AcOH; vi, $Na_2S_2O_4$, Bu_4NBr, Me_2SO_4, NaOH; vii, PhC≡CCu, pyridine; ~ 30% from **13**

developed a more convenient route to appropriate quinone systems. This was accomplished by delaying oxidation to a later part of the sequence (see Scheme 5) and by introducing the acetylene unit at an earlier stage than before (see Scheme 6): Bromination of the naphthalenol **23** afforded the bromonaphthalenol **24** (80%) and oxidation with Jones' reagent then gave the bromo quinone **12** in *ca.* 55% yield. The regiochemical assignment (*i.e.* the location of the bromine atom) to compound **12** followed unambiguously from the mode of formation and we found that the material was identical with the major product (see Scheme 3) generated by monobromination of quinone **8**.

The second modification, which also had the advantage of producing a single bromo acetylene **19**, was achieved (see Scheme 6) by introducing the phenylacetylene unit at the stage of the monobromo quinone **12**. Treatment of this compound with phenylacetylene in the presence of Pd(0) and Cu(I) catalysts[13] led to the acetylenic quinone **25**. Mild reduction (sodium dithionite) (**25** ⟶ **26**) and silylation took the route as far as silyl ether **27**. This compound is very sensitive to bromine, but reaction with pyridinium bromide perbromide afforded the bromonaphthalenol **28**.* Methylation of the free hydroxy group (**28** ⟶ **29**),* desilylation (**29** ⟶ **30**)* and methylation gave compound **19**. All the reactions of Scheme 6 were efficient and the last three steps can be performed without isolation of the intermediates **29** and **30**.

In summary, we were able, by using the reactions of Schemes 3 and 4, to build up an adequate supply of the pentamethoxy bromo acetylenes **18** (mainly of regiochemistry shown in structure **19**), and we had developed satisfactory routes (Schemes 4–6) to the key intermediates.

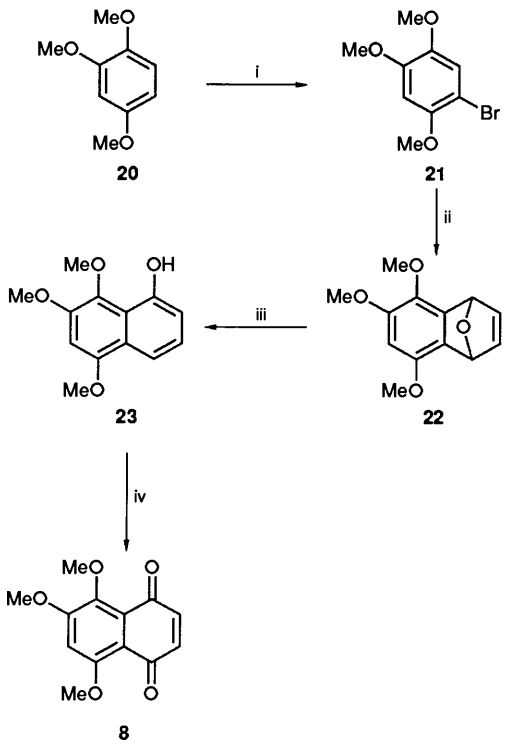
Compounds **18** were converted into the target spiro diketone **7** by the following steps: Halogen–metal exchange (**18** ⟶ **31**; Scheme 7) and treatment with cyclopentanecarbaldehyde[14] gave the expected alcohol **32**.† Some difficulty was then experienced in the oxidation to ketone **33**; however, 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) proved acceptable (50% yield). Direct phenylselenenylation (LDA, PhSeCl) was unpromising, but prior conversion of the ketone into its silyl enol ether (**33** ⟶ **34**), followed by treatment with benzeneselenenyl chloride gave the required material **35**, and radical cyclization to the spiro system could now be attempted.

Rapid addition of triphenyltin hydride in benzene to a refluxing solution of the keto selenide **35** and azoisobutyronitrile (AIBN), in the same solvent, gave rise, *via* the radical **36**, to a mixture of two compounds (Scheme 8). These compounds were separable and could be isolated in yields of 48 and 41% (from **35**). The major product was the desired spiro ketone **6**, which was obtained as a 3:1 mixture of *Z* and *E* isomers.‡ The other product, compound **39**, also a mixture of isomers, must have arisen by a mechanism involving intramolecular 1,7-hydrogen migration (**37** ⟶ **38**). The mass balance in the radical reaction was good (89% yield of **6** plus **39**), and the product

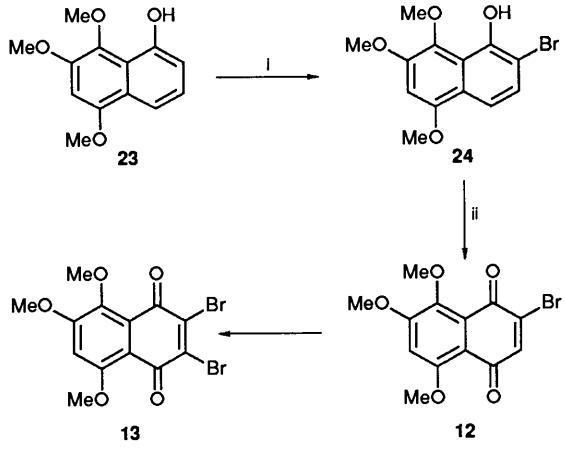
* Regiochemical assignment is arbitrary: we did not ascertain which silyl group was lost

† A single isomer was isolated

‡ We do not know which is the major component



Scheme 4 *Reagents and yields:* i, Br_2, $CHCl_3$; 98%, ii, LDA, furan; iii, $HClO_4$; 95% from **21**; iv, Tl $(NO_3)_3 \cdot 3H_2O$, MeOH, CH_2Cl_2; 58%

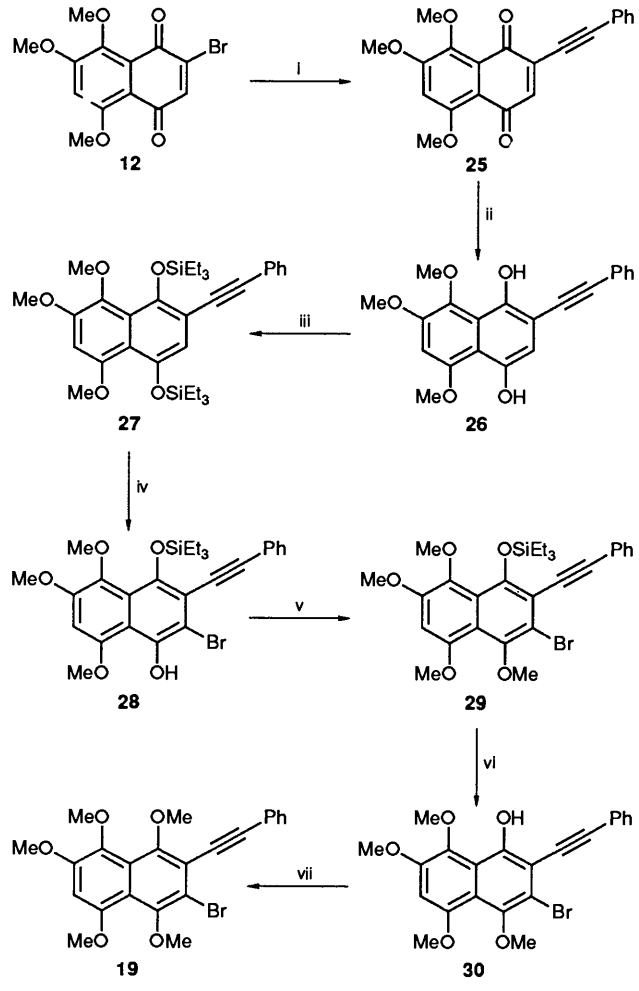


Scheme 5 *Reagents and yields:* i, Pyridinium bromide perbromide; 80%; ii, $Na_2Cr_2O_7$; 55%

distribution suggested that, for optimum results, the oxygen protecting groups should either lack abstractable hydrogen or be held, as in structure **40**, in a position that is inaccessible to the vinyl radical.

It is usual to carry out radical cyclizations by slow addition of the stannane[6] but we had found in earlier work[4t] (see Scheme 1) that application of such radical chemistry to keto selenide **2** gave best results when the stannane was added in one portion. We followed this method in the present case and, in fact, use of slow addition resulted in the undesired product **39** (90% yield). On the other hand, if the concentration of the tin hydride is too high when it is added in one portion, then stannylation of the starting material becomes a serious problem.

The spiro ketones **6** were degraded (Scheme 9) by vicinal hydroxylation (67% yield) of the double bond by use of a stoicheiometric amount of osmium tetraoxide in pyridine.[15] Lastly, periodate cleavage of the diol mixture was easily effected in almost quantitative yield to produce the spiro diketone **7**.



Scheme 6 *Reagents and yields: i,* PhC≡CH, CuI, $(Ph_3P)_4Pd$, Pr^i_2NEt; 77%; ii, $Na_2S_2O_4$, Bu_4NBr; iii, Et_3SiCl, Et_3N, DMAP; 73% from **25**; iv, Pyridinium bromide perbromide; 77%; v, $Na_2S_2O_4$, Bu_4NBr; Me_2SO_4, NaOH; vi, Bu_4NF; vii, Me_2SO_4, NaOH; 95% from **28**

This compound represents four contiguous rings of the natural product, and has the identical oxygenation pattern, but not the same functionality.

Conclusions.—The above experiments have provided us with routes to highly substituted naphthalenes and have served to test the technique of radical spirocyclization. The work has also indicated a number of ways in which our approach to fredericamycin A should be modified. In particular, a very careful choice of protecting group will have to be made for the oxygens located at the *peri* positions of the naphthalene unit.

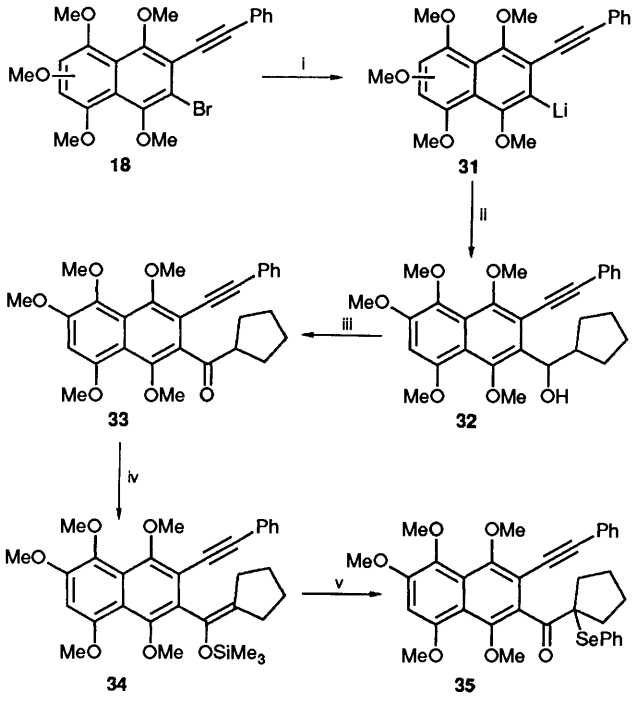
Experimental

Argon was purified by passage through a column (3.5 × 42 cm) of R-311 catalyst* and then through a similar column of Drierite. Glassware was dried in an oven for at least 3 h before use (120 °C) and either cooled in a desiccator over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of argon. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars.

Solvents for chromatography or extractions were distilled before use.

Products were isolated from solution by evaporation under

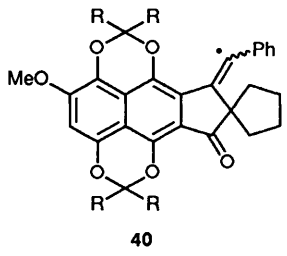
* Supplied by Chemical Dynamics Corp., South Plainfield, NJ.



Scheme 7[a] [a] Although compound **18** is a mixture of regioisomers (mainly **19**), the alcohol **32** was obtained as a single compound. *Reagents and yields:* i, BuLi; ii, cyclopentanecarbaldehyde; 89% from **18**; iii, DDQ; 50%; iv $ZnCl_2$, Me_3SiCl, Et_3N; 89%; v, PhSeCl; 81%

water-pump vacuum at, or below, 30 °C using a rotary evaporator. M.p.s were determined on a Kofler block melting point apparatus. Samples for analysis were usually prepared by crystallization of a portion of the bulk sample.

Commercial TLC plates (silica gel, Merck 60F–254) were used. Spots were detected using iodine, by spraying the plate with 3 mol dm^{-3} sulphuric acid in methanol followed by



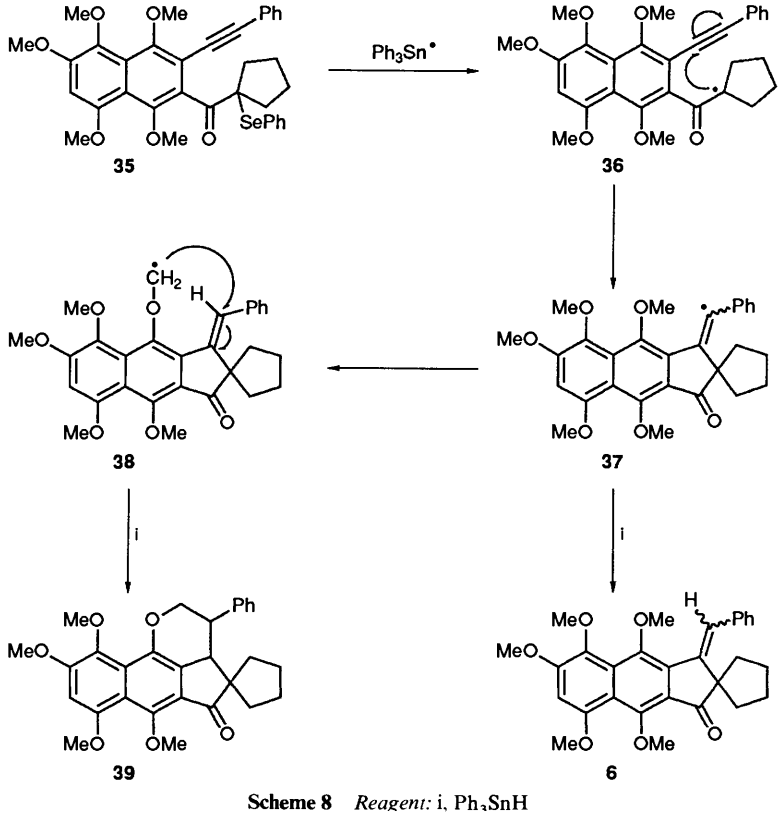
charring on a hot-plate, or by examination under UV light. Silica gel for flash chromatography was Merck type 60 (230–400 mesh).

Dry solvents were prepared under an inert atmosphere and transferred by oven-dried syringes. Dry 1,4-dioxane and tetrahydrofuran (THF) were distilled from sodium and benzophenone ketyl. Dry benzene was distilled from sodium. Dry diisopropylamine, triethylamine, dichloromethane, pyridine, and dimethylformamide (DMF) were distilled from calcium hydride, the last solvent being distilled under water-pump vacuum. Tetramethylethylenediamine (TMEDA) was refluxed for at least 24 h over crushed calcium hydride under argon and then distilled at 1 atm. Commercial (Aldrich) solutions of methyllithium in diethyl ether and butyllithium in hexanes were titrated before use by the diphenylacetic acid method.[16]

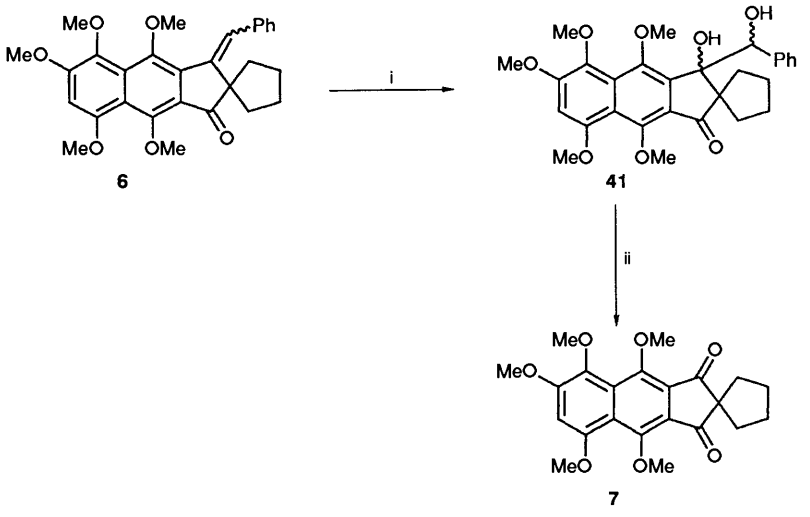
IR spectra were recorded on a Nicolet 7000 FT–IR model. Measurements were made as casts from the specified solvent and using potassium bromide plates.

^1H NMR spectra were recorded with Bruker WP-200 (at 200 MHz), Bruker AM-300 (at 300 MHz) or Bruker AM-400 (at 400 MHz) spectrometers in the specified deuterated solvent with tetramethylsilane as an internal standard, *J* values are given in Hz. ^{13}C NMR spectra were recorded with Bruker AM-300 (at 75.469 MHz) and Bruker AM-400 (at 100.614 MHz) spectrometers using deuterochloroform as an internal standard.

Mass spectra were recorded with an AEI Model MS-12 or MS-50 mass spectrometer at an ionizing voltage of 70 eV.



Scheme 8 *Reagent:* i, Ph_3SnH



Scheme 9 *Reagents and yields:* i, OsO_4, pyridine; 70%; ii, H_3IO_5, MeOH; 100%

Microanalyses were performed by the microanalytical laboratory of this Department.

Reactions of Scheme 2

N,N-*Diethyl*-2,4,5-*trimethoxybenzamide* **9**.[4m]—(*a*) Oxalyl dichloride (18.1 cm^3, 26.3 g, 0.21 mol) was added by syringe pump during 1 h to a magnetically stirred and cooled (ice-bath) suspension of 2,4,5-trimethoxybenzoic acid (20.0 g, 94.3 mmol) in dry benzene (300 cm^3) contained in a 1 dm^3 round-bottomed flask (argon atmosphere). The ice-bath was left in place and the mixture was stirred for 18 h. The solvent was evaporated off (water-pump, protection from moisture) to leave a greenish white solid,[17] which was used directly for the next step.

(*b*) The crude acid chloride from 2,4,5-trimethoxybenzoic acid (19.5 g) was covered (in its original flask) with dry THF (500 cm^3) and the mixture was stirred at −45 °C (acetonitrile–solid carbon dioxide) (argon atmosphere). Reagent grade diethylamine (13.0 cm^3, 9.19 g, 126.0 mmol) was then added by syringe pump during 1 h. The cold-bath was left in place and the mixture was stirred for 18 h. Aqueous sodium hydroxide (150 cm^3; 2 mol dm^{-3}) was added and the resulting mixture was extracted with diethyl ether (3 × 100 cm^3). The combined organic extracts were dried ($MgSO_4$), and evaporation of the solvent gave a beige solid (23.27 g). Crystallization from ethyl acetate–hexane afforded the amide **9** (21.1 g, 86%) as a homogeneous [^{1}H NMR (400 MHz); TLC (silica; ethyl acetate)] solid. In some runs the mother liquors were evaporated, and flash chromatography of the residue over silica gel with ethyl acetate afforded another crop of pure [^{1}H NMR (300 MHz); TLC (silica; ethyl acetate)] material corresponding to an increase in yield of 10%. Compound **9** had m.p. 78–79 °C (from ethyl acetate–hexane) (lit.,[4m] 73–74 °C); ν_{max}/cm^{-1} (FT) ($CHCl_3$ cast) 1628; $\delta_H(CDCl_3$; 300 MHz) 1.06 (3 H, t, *J* 7), 1.24 (3 H, t, *J* 7), 3.19 (2 H, q, *J* 7), 3.55 (2 H, m), 3.80 (3 H, s), 3.84 (3 H, s), 3.90 (3 H, s), 6.55 (1 H, s) and 6.77 (1 H, s); $\delta_C(CDCl_3$; 75.47 MHz) 12.50, 13.67, 38.53, 42.50, 55.71, 56.13, 97.31, 110.97, 117.80, 142.83, 149.26, 149.72 and 168.07 (Found: M^+, 267.1461; C, 63.0; H, 7.9; N, 5.55%. Calc. for $C_{14}H_{21}NO_4$: *M*, 267.1470; C, 62.90; H, 7.92; N, 5.24%).

N,N-*Diethyl*-2,4,5-*trimethoxy*-6-*prop*-2-*enylbenzamide* **10**.—A solution of *N,N*-diethyl-2,4,5-trimethoxybenzamide **9** (4.0 g, 15.0 mmol) in dry THF (50 cm^3) was added rapidly by cannula (under a positive pressure of argon) to a stirred solution, at −78 °C, of *sec*-butyllithium (17.3 cm^3; 1.3 mol dm^{-3} in cyclohexane, 22.5 mmol) and anhydrous TMEDA (3.40 cm^3, 2.62 g, 22.5 mmol) in THF (100 cm^3). The yellow mixture was stirred for 30 min and a freshly prepared solution (see below) of $MgBr_2{\cdot}Et_2O$[18] (17.2 cm^3; 2.62 mol dm^{-3}; 45.1 mmol) in diethyl ether was added as rapidly as possible by cannula (under a positive pressure of argon). The cooling bath was removed and the mixture was allowed to reach room temp (*ca.* 30 min). The resulting clear solution was cooled to −78 °C to produce a suspension, which was stirred for 40 min. 3-Bromopropene (distilled from calcium hydride; 3.9 cm^3, 5.44 g, 45.0 mmol) was added quickly by syringe and the mixture was stirred overnight (20 h), the ice-bath being allowed to reach room temp. The mixture was poured into water (150 cm^3) and extracted with ethyl acetate (3 × 150 cm^3). The combined organic extracts were washed with brine (30 cm^3), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue (4.76 g) over silica gel (15 × 8 cm) with 17:3 ethyl acetate–hexane gave *compound* **10** (3.26 g, 71%) as a homogeneous [^{1}H NMR (400 MHz); TLC (silica; 17:3 ethyl acetate–hexane)], yellowish oil. A small portion was recrystallized from diethyl ether–hexane: m.p. 55.5–56.5 °C; ν_{max}/cm^{-1}(FT) (CCl_4 cast) 3080 and 1628; $\delta_H(CDCl_3$; 300 MHz) 1.03 (3 H, t, *J* 7), 1.23 (3 H, t, *J* 7), 2.97–3.21 (2 H, m), 3.28–3.41 (3 H, m), 3.76–3.84 (10 H, m containing singlets at δ 3.76, 3.77, 3.88), 4.94–5.06 (2 H, m), 5.85–5.99 (1 H, m) and 6.41 (1 H, s); $\delta_C(CDCl_3$; 75.47 MHz) 12.44, 13.36, 31.85, 36.07, 42.71, 55.61, 55.65, 60.50, 95.20, 115.11, 118.72, 131.20, 136.33, 141.21, 151.47, 152.97 and 167.36 (Found: M^+, 307.1791; C, 66.5; H, 8.2; N, 4.6%. $C_{17}H_{25}NO_4$ requires *M*, 307.1783; C, 66.43; H, 8.20; N, 4.56%).

In other runs the oil was distilled [Kugelrohr, b.p. 102 °C (0.12 mmHg)].

When the reaction was carried out on a larger scale [with *N,N*-diethyl-2,4,5-trimethoxybenzamide (11.94 g)] the yield was 81%.

The $MgBr_2{\cdot}Et_2O$ was prepared as follows:[18] 1,2-Dibromoethane (8.9 cm^3, 0.1 mol) was added by syringe pump during *ca.* 1 h to a stirred suspension of magnesium turnings (2.43 g, 0.1 mol) in dry diethyl ether (50 cm^3) (argon atmosphere). The rate of addition was adjusted so as to maintain *gentle* reflux. The mixture was stirred for 2 h at room temp, refluxed for 30 min, and then stirred at room temp. Two layers separated. The lower layer was 2.62 mol dm^{-3} in $MgBr_2{\cdot}Et_2O$. One experiment, in which commercial $MgBr_2{\cdot}Et_2O$ was used, did not work.

5,6,8-*Trimethoxynaphthalen*-1-*ol* **11**.—A solution of diisopropylamine (3.8 cm^3, 2.7 g, 26.8 mmol) in dry THF (100 cm^3)

was kept under a slight static pressure of argon and was cooled to −78 °C. Butyllithium (1.6 mol dm^{-3} in hexanes; 15.3 cm^3, 24.5 mmol) was added dropwise to the stirred mixture during *ca.* 5 min, temporary provision being made for butane to escape *via* an exit bubbler. The mixture was stirred for 30 min and then a solution of the amide **10** (3.4 g, 11.2 mmol) in THF (50 cm^3) was added during 40 min by syringe pump. A further portion of THF (10 cm^3) was used as a rinse in the addition of the amide and this rinse was added during *ca.* 10 min. The cold-bath was left in place and the mixture was stirred for 20 h. The solution was poured into saturated aqueous ammonium chloride (150 cm^3) and extracted with ethyl acetate (4 × 150 cm^3). The combined organic extracts were washed with brine (150 cm^3), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (5 × 15 cm) with 2:3 ethyl acetate–hexane gave *compound* **11** (2.30 g, 86%) as a homogeneous [^1H NMR (400 MHz); TLC (silica; 2:3 ethyl acetate–hexane)], tan solid. A small portion was crystallized once from ethyl acetate–hexane: m.p. 127.5–128.5 °C; ν_{max}/cm^{-1}(FT) (CCl_4 cast) 3380; δ_H($CDCl_3$; 300 MHz) 3.89 (3 H, s), 3.97 (3 H, s), 4.02 (3 H, s), 6.56 (1 H, s), 6.76 (1 H, dd, *J* 7.5, 1), 7.34 (1 H, t, *J* 8), 7.54 (1 H, dd, *J* 7.5, 1) and 9.20 (1 H, s); δ_C($CDCl_3$; 75.47 MHz) 56.34, 57.24, 60.96, 95.24, 108.69, 111.09, 112.20, 128.10, 131.62, 137.61, 147.90, 152.93 and 154.60 (Found: M^+, 234.0897; C, 66.9; H, 6.0%. $C_{13}H_{14}O_4$ requires *M*, 234.0892; C, 66.66; H, 6.02%).

When the reaction was carried out on a larger scale [with *N*,*N*-diethyl-2,4,5-trimethoxy-6-prop-2-enylbenzamide (8.60 g)] the yield was 78%.

5,6,8-*Trimethoxynaphthalene*-1,4-*dione* **8**.[19]—*From* 5,6,8-*trimethoxynaphthalen*-1-*ol* **11**. A solution of the alcohol **11** (4.01 g, 17.14 mmol) in dichloromethane (85 cm^3) was added during *ca.* 20 min to a magnetically stirred and cooled (0 °C) solution of thallium(III) nitrate trihydrate (15.22 g, 34.25 mmol) in methanol (115 cm^3)–dichloromethane (115 cm^3) (argon atmosphere). The dark mixture was stirred for an additional 3 h at 0 °C and was then filtered through a sintered disc. The insoluble material was washed well with dichloromethane (*ca.* 100 cm^3) and the combined filtrates were washed with a mixture of brine (100 cm^3) and water (100 cm^3). The aqueous phase was extracted with dichloromethane (100 cm^3). The combined organic solutions were dried ($MgSO_4$) and evaporated. Flash chromatography of the residual dark oil (5 g) over silica gel (15 × 8 cm) with 9:1 ethyl acetate–hexane gave quinone **8** as a homogeneous [TLC (silica; 4:1 ethyl acetate–hexane)], orange solid (2.02 g, 48%). The spectral properties were identical with those obtained for material derived from the isomeric naphthalenol **23** by the reactions of Scheme 4 (see later). A small portion was crystallized from ethyl acetate–hexane: m.p. 144–146 °C.

Reactions of Scheme 3

2,3-*Dibromo*-5,6,8-*trimethoxynaphthalene*-1,4-*dione* **13**.—(*a*) *Monobromination.* A solution of bromine (1.56 cm^3, 30.16 mmol) in chloroform (15 cm^3) was added during *ca.* 10 min to a stirred and cooled (internal temp. 5 °C) solution of quinone **8** (6.80 g, 27.42 mmol) in chloroform (100 cm^3). The mixture was stirred for an additional 60 min and was then cooled to 0 °C. A stream of dry argon was passed through the solution and triethylamine (4.55 cm^3, 32.64 mmol) was added at a fast dropwise rate. The mixture was stirred for 15 min after the evolution of white fumes had ceased, and then was diluted with dichloromethane (50 cm^3), washed successively with saturated aqueous sodium thiosulphate (2 × 100 cm^3) and brine (1 × 100 cm^3), and dried ($MgSO_4$). Evaporation of the solvent afforded the crude monobromide **12** as an orange-red solid, which was used directly in the next step.

(*b*) *Second bromination.* The above material was dissolved in glacial acetic acid (50 cm^3) and a solution of bromine (3.40 cm^3, 65.88 mmol) in acetic acid (10 cm^3) was added dropwise to the stirred mixture during *ca.* 5 min. The mixture was stirred at room temp. for 4 h. In some runs the acetic acid was then evaporated off at ~ 40 °C (rotary evaporator with solid-CO_2 condenser), but in this particular experiment the solution was diluted with dichloromethane (200 cm^3) and washed successively with water (4 × 200 cm^3), saturated aqueous sodium hydrogen carbonate (2 × 200 cm^3), and brine (1 × 200 cm^3). The organic phase was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (8 × 20 cm) with ethyl acetate–hexane mixtures [containing increasing amounts of ethyl acetate (from 50 to 100%)] gave the *dibromide* **13** as a homogeneous [^1H NMR (200 MHz); TLC (silica; 3:1 ethyl acetate–hexane)] orange solid (9.66 g, 87% over the two steps): m.p. 208–209 °C (from ethyl acetate–hexane); ν_{max}/cm^{-1}(FT) (CH_2Cl_2 cast) 1671; δ_H($CDCl_3$; 300 MHz) 3.89 (3 H, s), 4.01 (3 H, s), 4.02 (3 H, s) and 6.75 (1 H, s); δ_C($CDCl_3$; 75.47 (MHz) 56.42, 56.84, 61.54, 101.45, 111.17, 125.45, 140.31, 143.71, 144.76, 159.03, 160.28, 173.12 and 175.33 (Found: M^+, 407.8894; C, 38.4; H, 2.35%. $C_{13}H_{10}Br_2O_5$ requires *M*, 407.8854; C, 38.46; H, 2.48%).

In one experiment the product from the monobromination was separated into its component regioisomers. The *major isomer* **12** (66% yield) had m.p. 165–169 °C (from ethyl acetate–hexane); ν_{max}/cm^{-1}(FT) ($CHCl_3$ cast) 1675; δ_H($CDCl_3$; 400 MHz) 3.90 (3 H, s), 4.02 (6 H, s), 6.78 (1 H, s) and 7.30 (1 H, s); δ_C($CDCl_3$; 75.47 MHz) 56.27, 56.61, 61.11, 101.51, 111.99, 124.98, 137.24, 141.18, 144.26, 158.05, 159.66, 177.15 and 179.92 (Found: M^+, 327.9777; C, 47.6; H, 3.4; Br, 24.75%. $C_{13}H_{11}BrO_5$ requires *M*, 327.9769; C, 47.70; H, 3.36; Br, 24.46%).

The minor isomer (6% yield) had m.p. 159–161 °C (from ethyl acetate–hexane); ν_{max}/cm^{-1}(FT) ($CHCl_3$ cast) 1663; δ_H($CDCl_3$; 200 MHz) 3.90 (3 H, s), 4.04 (6 H, s), 6.76 (1 H, s) and 7.33 (1 H, s) (Found: M^+, 327.9764).

3-*Bromo*-2-*iodo*-5,6,8-*trimethoxynaphthalene*-1,4-*dione* *and* 2-*Bromo*-3-*iodo*-5,6,8-*trimethoxynaphthalene*-1,4-*dione* **16**.—Sodium iodide (942 mg, 6.28 mmol) was added to a solution of dibromide **13** (2.126 g, 5.24 mmol) in glacial acetic acid (100 cm^3) and the mixture was stirred at 50–60 °C (argon atmosphere and protection from light). After 2 days another batch of sodium iodide (942 mg, 6.28 mmol) was added and the reaction was allowed to proceed for another 2 days under the same conditions. The mixture was cooled and the solvent was evaporated off at 30 °C (water-pump, rotary evaporator with solid-CO_2 condenser). The residue was taken up in dichloromethane (200 cm^3) and washed with water (2 × 75 cm^3). The combined aqueous phase was extracted with dichloromethane (2 × 50 cm^3). The combined organic phases were combined and washed successively with saturated aqueous sodium hydrogen carbonate (1 × 100 cm^3), 10% w/v aqueous sodium thiosulphate (1 × 75 cm^3), and brine (1 × 100 cm^3), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (5 × 20 cm) with 1:49 acetone–dichloromethane gave compounds **16** as an orange solid (1.774 g). The material, which was used directly in the next step, was a mixture of the bromo iodo quinones **16**, the corresponding diiodo quinone, and the starting material **13**. In a typical experiment the proportions were 70:8:22, respectively, and the material had δ_H($CDCl_3$; 200 MHz) 3.90 (3 H, s), 4.02 (6 H, s), 6.75 (0.1 H, s), 6.78 (0.2 H, s) and 6.77 (0.7 H, s) (Found: M^+, 407.8916. $C_{13}H_{10}{}^{81}Br_2O_5$ requires *M*, 407.8854. Found: M^+, 453.8741. $C_{13}H_{10}{}^{81}BrIO_5$ requires *M*, 453.8736. Found: M^+, 499.8620. $C_{13}H_{10}{}^{127}I_2O_5$ requires *M*, 499.8617).

3-*Bromo*-2-*iodo*-1,4,5,6,8-*pentamethoxynaphthalene* *and* 2-*Bromo*-3-*iodo*-1,4,5,6,8-*pentamethoxynaphthalene* **17**.—The

above mixture of halogeno quinones **16** [3.84 g, 8.48 mmol (assuming all the material is the desired bromo iodo quinone)] was dissolved in dichloromethane (100 cm^3). Water (50 cm^3), sodium dithionite (4.42 g, 25.39 mmol) and tetrabutylammonium bromide (50 mg) were added and the mixture was stirred vigorously for 15–30 min (argon atmosphere). During this period the orange organic layer became pale yellow. Dimethyl sulphate (8.0 cm^3, 84.7 mmol) was then added during 2–3 min, followed by aqueous sodium hydroxide (2.5 mol dm^{-3}; 34.0 cm^3, 85.0 mmol) which was added during *ca.* 30 min. The mixture was stirred at room temp overnight, and the aqueous phase was extracted with dichloromethane (2 × 50 cm^3). The organic solutions were combined and washed successively with 10% v/v aqueous ammonia (2 × 50 cm^3, to remove dimethyl sulphate), and brine (1 × 75 cm^3), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (5 × 20 cm) with 1:3 ethyl acetate–hexane gave compounds **17** as an apparently homogeneous [TLC (silica; 1:3 ethyl acetate–hexane)], cream-coloured solid [3.844 g, 94% (assuming all the starting material was the desired bromo iodo quinone)]. The product was a mixture of the required bromo(iodo)pentamethoxynaphthalenes **17** (65% of the material), as well as the corresponding dibromo- and diiodonaphthalenes, and was used directly in the next step without full characterization. The material had $\delta_H(CDCl_3$; 200 MHz) 3.74–4.05 (15 H, series of singlets) and 6.80 (1 H, s) [Found: M^+, 483.9214 (besides molecular ions for dibromide and diiodide). $C_{15}H_{16}{}^{81}BrIO_5$ requires *M*, 483.9205].

3-Bromo-1,4,5,6,8-pentamethoxy-2-(phenylethynyl)-naphthalene and 2-Bromo-1,4,5,6,8-pentamethoxy-3-(phenylethynyl)naphthalene **19**.—A mixture of copper(I) phenylacetylide (1.77, 10.77 mmol), dry pyridine (40 cm^3), and the above bromo iodides (1.30 g, 2.69 mmol*) was refluxed overnight (argon atmosphere). The mixture was cooled, diluted with ethyl acetate (300 cm^3), and washed with ice-cold hydrochloric acid (2 mol dm^{-3}; 2 × 100 cm^3). The combined aqueous phases were extracted with ethyl acetate (2 × 100 cm^3), and the combined organic solutions were washed with dil. hydrochloric acid (2 mol dm^{-3}; 1 × 100 cm^3), 10% w/v aqueous copper(II) sulphate (1 × 100 cm^3), and brine (1 × 100 cm^3), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (3 × 20 cm) with 1:4 ethyl acetate–hexane gave compounds **18** (819 mg, 66% assuming the starting material was free of dibromide and diiodide). Recrystallization from ethyl acetate–hexane (~ 78% recovery) gave a product that was largely (~ 87%) one isomer (**19**) [^1H NMR (200 MHz)]. The recrystallized bromo acetylenes had m.p. 108–109 °C. Spectral data on pure isomer **19** were obtained on material prepared from compound **28** by the method of Scheme 6 (see later).

Reactions of Scheme 4

1-Bromo-2,4,5-trimethoxybenzene **21**.[12]—A solution of bromine (24.85 cm^3, 48.16 mmol) in chloroform (400 cm^3) was added during 4 h to a stirred and cooled (0 °C) solution of 1,2,4-trimethoxybenzene **20** (80.90 g, 481.0 mmol) in chloroform (800 cm^3). The mixture was stirred at 0 °C for 45 min after the end of the addition and the solution was then washed with saturated aqueous sodium thiosulphate (3 × 600 cm^3). The aqueous layer was extracted with dichloromethane (1 × 200 cm^3) and the combined extracts were washed with brine (1 × 800 cm^3), dried ($MgSO_4$), and evaporated to give compound **21** as a blue-purple, apparently homogeneous [^1H NMR (200 MHz)] solid (116.14 g, 98%), which was used directly in the next step.

In another experiment, carried out on a smaller scale [with 1,2,4-trimethoxybenzene **20** (1.151 g)], the crude product was off-white, and flash chromatography of the material over silica gel (3 × 15 cm) with 1:1 diethyl ether–hexane gave compound **21** as a homogeneous [^1H NMR (200 MHz); TLC (silica; 1:1 Et_2O–EtOAc)] solid (1.570 g, 93%); m.p. 56–58 °C; $\delta_H(CDCl_3$; 200 MHz) 3.85 (3 H, s), 3.89 (3 H, s), 3.91 (3 H, s), 6.59 (1 H, s) and 7.06 (1 H, s) (Found: M^+, 247.9869; C, 43.95; H, 4.4%. Calc. for $C_9H_{11}BrO_3$: *M*, 247.9838; C, 43.72; H, 4.45%).

1,4-Epoxy-1,4-dihydro-5,6,8-trimethoxynaphthalene **22**.—Butyllithium (1.6 mol dm^{-3} in hexanes; 234.8 cm^3, 375.7 mmol) was added during 15 min to a stirred and cooled (−25 °C) solution of diisopropylamine (55.2 cm^3, 393.9 mmol) in THF (500 cm^3) (argon atmosphere). The mixture was stirred for 30 min and the resulting solution was cooled to −78 °C and added during 30 min by cannula to a cooled (−78 °C) and stirred solution of the bromide **21** (58.0 g, 234.8 mmol) and furan (freshly distilled from calcium hydride; 509.6 cm^3, 7.01 mol) in THF (900 cm^3). The resulting dark orange solution was then stirred at −78 °C for 4 h. The cold-bath was left in place and the mixture was stirred overnight. Water (250 cm^3) was added dropwise and the mixture was extracted with diethyl ether (2 × 600 cm^3). The combined extracts were washed with brine (1 × 800 cm^3), dried ($MgSO_4$), and evaporated to leave a pale orange solid, which was used immediately in the next step.

In another experiment, carried out on a smaller scale [with the bromide **21** (223 mg)], the crude product was purified by flash chromatography over silica gel (2 × 15 cm) with 1:1 diethyl ether–hexane to obtain *compound* **22** as a homogeneous [^1H NMR (200 MHz)], off-white solid (174 mg, 82%); m.p. 92.5–94 °C; ν_{max}/cm^{-1}(FT) ($CHCl_3$ cast) 1626; $\delta_H(CDCl_3$; 200 MHz) 3.85 (3 H, s), 3.86 (3 H, s), 3.89 (3 H, s), 5.94–5.97 (1 H, m), 5.99–6.01 (1 H, m), 6.18 (1 H, s), 7.00–7.05 (1 H, m) and 7.06–7.11 (1 H, m); $\delta_C(CDCl_3$; 75.47 MHz) 56.40, 56.81, 61.27, 80.16, 80.73, 96.20, 126.15, 138.74, 140.15, 141.64, 143.11, 148.32 and 151.39 (Found: M^+, 234.0897; C, 66.3; H, 6.0%. $C_{13}H_{14}O_4$ requires *M*, 234.0888; C, 66.67; H, 5.98%).

5,7,8-Trimethoxynaphthalen-1-ol **23**.[20]—Aqueous perchloric acid (70%; 5 cm^3) was added during 5 min to a stirred and cooled (0 °C) solution of epoxide **22** in THF (500 cm^3). The cooling bath was then removed and the mixture was stirred for 1.25 h (TLC control; silica; 1:1 diethyl ether–hexane). The solution was poured into diethyl ether (500 cm^3), and the organic phase was washed successively with water (1 × 500 cm^3) and brine (1 × 500 cm^3), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (10 × 40 cm) with diethyl ether–hexane mixtures [containing increasing amounts of Et_2O (from 50 to 100%)] gave the naphthalenol **23** (52.05 g, 95% over the two steps) as a homogeneous [^1H NMR (400 MHz)], pale brown solid, m.p. 95–97 °C; ν_{max}/cm^{-1}(FT) ($CHCl_3$ cast) 3329; $\delta_H(CDCl_3$; 200 MHz) 3.94 (3 H, s), 3.96 (3 H, s), 3.98 (3 H, s), 6.60 (1 H, s), 6.87 (1 H, d, *J* 8.0), 7.21 (1 H, t, *J* 8.0), 7.65 (1 H, d, *J* 8.0) and 9.69 (1 H, s); $\delta_C(CDCl_3$; 75.47 MHz) 55.58, 57.45, 62.15, 95.60, 111.37, 113.14, 118.22, 123.24, 124.92, 136.90, 147.13, 153.08 and 153.35 (Found: M^+, 234.0893; C, 66.7; H, 6.1%. Calc. for $C_{13}H_{14}O_4$: *M*, 234.0888; C, 66.67; H, 5.98%).

5,6,8-Trimethoxynaphthalene-1,4-dione **8**.[19]—*From 5,7,8-trimethoxynaphthalen-1-ol* **23**. 5,7,8-Trimethoxynaphthalen-1-ol **23** (4.16 g, 17.78 mmol) was dissolved in dichloromethane (10 cm^3) (argon atmosphere). The solution was diluted with methanol (100 cm^3) and was then added dropwise during *ca.* 1 h to a stirred and cooled (ice-bath) solution of thallium(III) nitrate

* The amount of bromo iodide was actually less than that indicated because the material contained some dibromide and diiodide

trihydrate (16.19 g, 36.43 mmol) in methanol (140 cm^3). The mixture was stirred at 0 °C for 2 h after the end of the addition. The mixture was filtered and the filtrate was concentrated to near dryness, taken up in dichloromethane (300 cm^3), washed with brine (1 × 100 cm^3), and dried ($MgSO_4$). The solution was filtered and the filtrate was passed through a column of neutral alumina (Grade 1; 1.5 × 10 cm). The column was developed with dichloromethane until the eluate was almost colourless. Evaporation of the eluate and flash chromatography of the residue over silica gel (5 × 20 cm) with 3:1 ethyl acetate–hexane gave *quinone* **8** as a homogeneous [TLC (silica; 3:1 ethyl acetate–hexane)], orange-yellow solid (2.56 g, 58%); ν_{max}/cm^{-1}(FT) ($CHCl_3$ cast) 1649; δ_H($CDCl_3$; 300 MHz) 3.88 (3 H, s), 4.00 (6 H, s), 6.74 (2 H, s) and 6.77 (1 H, s); δ_C($CDCl_3$; 75.47 MHz) 56.26, 56.76, 61.35, 101.44, 113.13, 126.37, 137.58, 139.63, 143.63, 158.07, 159.84, 183.35 and 185.01 (Found: M^+, 248.0684; C, 62.6; H, 4.9%. Calc. for $C_{13}H_{12}O_5$: *M*, 248.0681; C, 62.90; H, 4.87%).

When the reaction was carried out on a larger scale [using the naphthalenol **23** (11.82 g)] the yield was 54%.

Reactions of Scheme 5

2-*Bromo*-5,7,8-*trimethoxynaphthalen*-1-*ol* **24**.—Pyridinium bromide perbromide (21.9 g, 68.5 mmol) was added in small portions during 1 h to a stirred and cooled (0 °C) solution of compound **23** (10.0 g, 42.7 mmol) in dry THF (100 cm^3) (argon atmosphere). The cooling bath was removed and, after 1 h, the solution was diluted with diethyl ether (300 cm^3) and washed successively with 10% w/v aqueous sodium thiosulphate (1 × 200 cm^3) and brine (1 × 200 cm^3), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (9 × 25 cm) with ethyl acetate–hexane mixtures [containing increasing amounts of EtOAc (from 25 to 30%)] gave the bromide **24** (10.6 g, 80%) as a homogeneous [^{1}H NMR (400 MHz)], beige solid; ν_{max}/cm^{-1}(FT) ($CHCl_3$ cast) 3249; δ_H($CDCl_3$; 400 MHz) 3.92 (3 H, s), 3.96 (3 H, s), 3.99 (3 H, s), 6.55 (1 H, s), 7.34 and 7.47 (2 H, AB quartet, *J* 9) and 10.44 (1 H, s); δ_C($CDCl_3$; 75.47 MHz) 55.91, 57.27, 62.34, 95.54, 105.81, 114.27, 118.85, 121.78, 128.41, 136.05, 147.97, 149.39 and 153.14 (Found: M^+, 313.9944; C, 49.7; H, 4.2%. $C_{13}H_{13}BrO_4$ requires *M*, 313.9943; C, 49.86; H, 4.18%).

2-*Bromo*-5,7,8-*trimethoxynaphthalene*-1,4-*dione* **12**.—*Preparation from the alcohol* **24**. A solution of sodium dichromate (30.27 g, 101.57 mmol) in aqueous sulphuric acid (4 mol dm^{-3}; 200 cm^3) was added dropwise during *ca.* 3 h to a stirred and cooled (0 °C) solution of the alcohol **24** (31.79 g, 101.57 mmol) in acetone (600 cm^3). By the end of the addition the temperature of the cooling bath had risen to ~ 4 °C and the mixture was stirred for a further 5 min, by which stage no starting material remained [TLC (silica; 3:2 ethyl acetate–hexane)]. Propan-2-ol (400 cm^3) was then added to the stirred mixture and, after 4 h, the mixture was diluted with ethyl acetate (250 cm^3) and filtered through a pad (~ 10 × 10 cm) of flash chromatography silica gel. The pad was washed with ethyl acetate (~ 500 cm^3) and the combined ethyl acetate solutions were washed with water (3 × 400 cm^3). The organic layer was dried ($MgSO_4$) and evaporated to a small volume. Flash chromatography of the resulting dark orange material over silica gel (7 × 33 cm) with 1:2:2 dichloromethane–ethyl acetate–hexane afforded pure [TLC (silica; 1:50 acetone–dichloromethane)] material (18.55 g, 56%). The compound was identical with the major bromo quinone obtained by the route of Scheme 3 (see above). The present experiment reproducibly gave yields of ~ 55%, the range being 52–69%. In one case the product (15.25 g, 52%) was obtained by crystallization from methanol, after chromatography, and had m.p. 170–172 °C.

Reactions of Scheme 6

5,7,8-*Trimethoxy*-2-(*phenylethynyl*)*naphthalene*-1,4-*dione* **25**.—Phenylacetylene (650 mm^3, 5.92 mmol), copper(I) iodide (118 mg, 0.62 mmol), tetrakis(triphenylphosphine)palladium(0) (170 mg, 0.15 mmol), and diisopropylethylamine (1.07 cm^3, 7.63 mmol) were added in that order, under argon, and in the dark (foil-wrapped flask), to a stirred solution of bromo quinone **12** (1.00 g, 3.06 mmol) in dry DMF (22 cm^3). The mixture was stirred for 18 h, then was diluted with ethyl acetate (150 cm^3) and washed with water (2 × 150 cm^3). The aqueous phase was extracted with ethyl acetate (2 × 150 cm^3) and the combined organic phases were washed with brine (2 × 125 cm^3), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (3 × 15 cm) with 1:49 acetone–dichloromethane gave *compound* **25** as a homogeneous [^{1}H NMR (200 MHz)], orange solid (817 mg, 77%); m.p. 200–202 °C (from ethyl acetate–hexane); ν_{max}/cm^{-1}(FT) ($CHCl_3$ cast) 2198; δ_H($CDCl_3$; 300 MHz) 3.92 (3 H, s), 4.01 (6 H, s), 6.78 (1 H, s), 6.99 (1 H, s), 7.32–7.42 (3 H, m) and 7.55–7.61 (2 H, m); δ_C($CDCl_3$; 75.47 MHz) 56.28, 56.77, 61.47, 82.91, 101.61, 101.98, 113.34, 121.92, 126.48, 128.43, 129.62, 132.27, 133.12, 140.37, 144.04, 157.91, 159.90, 181.38 and 182.41 (Found: M^+, 348.0998; C, 72.0; H, 4.6%. $C_{21}H_{16}O_5$ requires *M*, 348.0993; C, 72.41; H, 4.63%).

Although this experiment has been done a number of times, we find that the corresponding hydroquinone **26** is sometimes obtained as a by-product and the ratio **25**:**26** appears to depend on the batch of palladium catalyst. Compound **26** can, of course, be used directly in the next step.

1,2,4-*Trimethoxy*-7-(*phenylethynyl*)-5,8-*bis*(*triethylsiloxy*)-*naphthalene* **27**.—A solution of quinone **25** (3.10 g, 8.90 mmol) in dichloromethane (100 cm^3) was stirred vigorously with an aqueous solution (100 cm^3) of sodium dithionite (6.2 g, 35.6 mmol) and tetrabutylammonium bromide (50 mg) (argon atmosphere). When the colour of the quinone had disappeared (*ca.* 30 min) the layers were separated and the aqueous phase was extracted with dichloromethane (1 × 100 cm^3). The combined organic solutions were dried ($MgSO_4$) and concentrated to give crude diol **26** as a yellowish foam. This was dissolved in dry dichloromethane (140 cm^3) and the solution was cooled to 0 °C under argon. Chlorotriethylsilane (8.40 cm^3, 50.0 mmol), triethylamine (20.0 cm^3, 143.0 mmol) and 4-(dimethylamino)pyridine (DMAP) (50 mg, 0.41 mmol) were added and the mixture was stirred for 4 h. At that stage, another portion of chlorotriethylsilane (2.80 cm^3, 16.67 mmol) was added. The mixture was stirred overnight, the ice-bath being left in place, and was allowed to attain room temperature. The mixture was then diluted with dichloromethane (200 cm^3), washed successively with water (1 × 400 cm^3) and brine (1 × 300 cm^3), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (5 × 20 cm) with 1:19 ethyl acetate–hexane gave a lemon-yellow solid, which was recrystallized from ethanol to afford the bis(silyl ether) **27** (3.52 g, 73%) as a homogeneous [^{1}H NMR (400 MHz); TLC (silica; 1:19 ethyl acetate–hexane)] solid; m.p. 91–92 °C; δ_H($CDCl_3$; 400 MHz) 0.76–0.87 (21 H, m), 0.96–1.00 (9 H, m), 3.70 (3 H, s), 3.89 (3 H, s), 3.99 (3 H, s), 6.65 (1 H, s), 6.69 (1 H, s), 7.33–7.39 (3 H, m) and 7.57–7.59 (2 H, m); δ_C($CDCl_3$; 75.47 MHz) 5.16, 5.24, 6.75, 6.91, 56.10, 57.12, 61.77, 88.70, 93.24, 97.64, 112.32, 116.44, 117.38, 124.01, 125.71, 127.98, 128.30, 131.52, 137.96, 146.30, 147.20, 149.59 and 153.84 (Found: M^+, 578.2873. $C_{33}H_{46}O_5Si_2$ requires *M*, 578.2884).

The intermediate hydroquinone **26** is an amorphous solid and had ν_{max}/cm^{-1}(FT) ($CHCl_3$ cast) 3406 and 3285 cm^{-1}; δ_H($CDCl_3$; 200 MHz) 4.00 (3 H, s), 4.02 (3 H, s), 4.06 (3 H, s),

6.61 (1 H, s), 6.80 (1 H, s), 7.28–7.39 (3 H, m), 7.56–7.64 (2 H, m), 8.78 (1 H, s) and 10.04 (1 H, s) (Found: M^+, 350.1148. $C_{21}H_{18}O_5$ requires *M*, 350.1154).

2-*Bromo*-5,6,8-*trimethoxy*-3-(*phenylethynyl*)-4-(*triethylsilyloxy*)*naphthalen*-1-*ol* **28**.—Pyridinium bromide perbromide (956 mg, 2.99 mmol) was added in one portion to a stirred and cooled (−78 °C) solution of compound **27** (1.645 g, 2.85 mmol) in dry THF (120 cm^3) (argon atmosphere). After 10 min the cooling bath was removed and the mixture was stirred for 5 h. The mixture was diluted with dichloromethane (400 cm^3) and washed successively with saturated aqueous sodium hydrogen carbonate (2 × 100 cm^3) and brine (1 × 200 cm^3), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4 × 20 cm) with 3:7 ethyl acetate–hexane gave some starting material **27** (210 mg recovery) and the product **28** (1.02 g, 66%; 77% corrected for recovered starting material) as a homogeneous [^{1}H NMR (400 MHz)], yellow-orange solid; m.p. 153–154 °C; ν_{max}/cm^{-1}(FT) ($CHCl_3$ cast) 3295; δ_H($CDCl_3$; 400 MHz) 0.82–0.93 (15 H, m), 3.71 (3 H, s), 4.00 (3 H, s), 4.08 (3 H, s), 6.73 (1 H, s), 7.35–7.42 (3 H, m), 7.63–7.67 (2 H, m) and 9.99 (1 H, s); δ_C($CDCl_3$; 75.47 MHz) 5.21, 6.96, 56.99, 57.46, 61.95, 87.87, 96.18, 97.64, 104.58, 111.82, 115.95, 123.80, 123.89, 128.30, 128.35, 131.56, 139.13, 145.67, 146.15, 149.65 and 151.78 (Found: M^+, 544.1109. $C_{27}H_{31}BrO_5Si$ requires *M*, 544.1104).

2-*Bromo*-1,4,5,6,8-*pentamethoxy*-3-(*phenylethynyl*)*naphthalene* **19**.—*Preparation without isolation of intermediates.* Water (32 cm^3), sodium dithionite (760 mg, 4.4 mmol), and tetrabutylammonium bromide (about 10 mg) were added to a stirred solution of compound **28** (798 mg, 1.47 mmol) in dichloromethane (50 cm^3) (argon atmosphere). (This reduction step is not necessary with freshly prepared **28**.) After 10 min, during which time the mixture became pale yellow, dimethyl sulphate (2.0 cm^3, 21.1 mmol) was added and then aqueous sodium hydroxide (2 mol dm^{-3}; 10.6 cm^3, 21.2 mmol) was injected during 1 h. The mixture was stirred overnight and then tetrabutylammonium fluoride (1.1 mol dm^{-3} in THF; 10.0 cm^3, 11.0 mmol) was added during *ca.* 10 min. The mixture was stirred for 1 h and a further portion of tetrabutylammonium fluoride (1.1 mol dm^{-3} in THF; 2.0 cm^3, 2.2 mmol) was added during *ca.* 1 min. The mixture was stirred for 2 h and more dimethyl sulphate (1.0 cm^3, 10.55 mmol) was added, followed by addition of aqueous sodium hydroxide (2 mol dm^{-3}; 5.3 cm^3, 10.6 mmol) during *ca.* 15 min. The resulting mixture was stirred overnight and diluted with dichloromethane (100 cm^3). The aqueous phase was extracted with dichloromethane (1 × 50 cm^3) and the combined organic solutions were washed with 20% v/v aqueous ammonia (2 × 100 cm^3), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4 × 20 cm) with ethyl acetate–hexane mixtures [containing increasing amounts of ethyl acetate (from 30 to 50%)] gave *compound* **19** (640 mg, 95%) as a homogeneous [^{1}H NMR (400 MHz)], pale yellow solid; δ_H($CDCl_3$; 400 MHz) 3.85 (3 H, s), 3.86 (3 H, s), 3.99 (3 H, s), 4.02 (3 H, s), 4.04 (3 H, s), .680 (1 H, s), 7.36–7.40 (3 H, m) and 7.65–7.67 (2 H, m); δ_C($CDCl_3$; 75.47 MHz) 56.70, 57.31, 61.47, 62.06, 62.27, 85.37, 98.22, 99.01, 114.50, 117.33, 118.55, 123.31, 125.28, 128.33, 128.56, 131.67, 137.00, 150.28, 150.75, 152.87 and 154.34 (Found: M^+, 458.0554; C, 60.4; H, 4.7; Br, 17.8%. $C_{23}H_{21}BrO_5$ requires *M*, 458.0552; C, 60.41; H, 4.63; Br, 17.47%).

In one of several experiments carried out (to the best of our knowledge) by the above procedure, the product was 4-bromo-5,6,8,9-tetramethoxynaphtho[1,2-*b*]furan (40% yield) arising by formal 5-*endo* digonal closure of the phenolic hydroxy group of compound **30** onto the triple bond. Some of us prefered, therefore, to work-up the reaction after the first methylation (as described below). The crude product **29** is used directly for desilylation (to afford compound **30**) and methylation (to compound **19**). This procedure required less tetrabutylammonium fluoride (1.1 mol equiv.) [TLC control (silica; 3:7 ethyl acetate–hexane)]. The *naphthofuran* had δ_H($CDCl_3$;400 MHz) 3.90 (3 H, s), 4.02 (3 H, s), 4.05 (3 H, s), 4.20 (3 H, s), 6.75 (1 H, s), 7.16 (1 H, s), 7.34–7.50 (3 H, m) and 7.95 (2 H, d, *J* 8); δ_C($CDCl_3$; 100.61 MHz) 57.06, 57.40, 61.36, 61.88, 97.91, 102.38, 105.19, 114.17, 119.29, 124.77, 128.18, 128.37, 128.59, 128.90, 130.36, 131.73, 136.09, 144.61, 149.86, 150.62, 153.46 and 156.14 (Found: M^+, 444.0373. $C_{22}H_{19}BrO_5$ requires *M*, 444.0390).

Preparation with isolation of intermediates. Water (10 cm^3), dimethyl sulphate (1.5 cm^3, 15.85 mmol), and tetrabutylammonium bromide (~ 10 mg) were added to a vigorously stirred solution of freshly prepared compound **28** (888 mg, 1.64 mmol) in dichloromethane (20 cm^3) (argon atmosphere). Aqueous sodium hydroxide (2 mol dm^{-3}; 8.0 cm^3, 16.0 mmol) was then added during 40 min and the mixture was stirred overnight. The layers were separated and the aqueous phase was extracted with dichloromethane (2 × 25 cm^3). The combined organic solutions were washed successively with 10% v/v aqueous ammonia and brine (1 × 25 cm^3), and dried ($MgSO_4$). The solvent was evaporated off and the crude residue was dissolved immediately in dichloromethane (12 cm^3) and tetrabutylammonium fluoride (1.1 mol dm^{-3} in THF; 1.5 cm^3, 1.65 mmol) was added during 2 min (stirring; argon atmosphere). When the desilylation was complete [< 5 min; TLC control (silica; 3:7 ethyl acetate–hexane)] dimethyl sulphate (1.5 cm^3, 15.9 mmol), water (10 cm^3), and tetrabutylammonium bromide (~ 10 mg) were added to the stirred mixture. Aqueous sodium hydroxide (2 mol dm^{-3}; ~ 8 cm^3, 16.0 mmol) was then injected during 30 min and the mixture was stirred overnight. The mixture was worked up as before and flash chromatography of the crude product over silica gel (2.5 × 18 cm) with 3:7 ethyl acetate–hexane gave compound **19** (715 mg, 95% overall) as a homogeneous [TLC (silica; 3:7 ethyl acetate–hexane)], pale yellow solid.

Reactions of Scheme 7

α-*Cyclopentyl*-α-[1,4,5,6,8-*Pentamethoxy*-3-(*phenylethynyl*)-2-*naphthyl*]*methanol* **32**.—Butyllithium (1.6 mol dm^{-3} in hexanes; 0.300 cm^3, 0.480 mmol) was added during *ca.* 1 min to a stirred and cooled (−78 °C) solution of the recrystallized acetylenic bromides **18** (111 mg, 0.243 mmol) in dry THF (3.0 cm^3) (argon atmosphere). The resulting dark solution (which was dark yellow to dark red, depending on the amount, if any, of dibromide and diiodide in the starting material) was stirred at −78 °C for *ca.* 10 min and cyclopentanecarbaldehyde[14] (100 mm^3, ~ 1.0 mmol) was injected in one portion. The colour of the solution faded. The mixture was stirred for 30 min and saturated aqueous ammonium chloride (10 cm^3) was added. The mixture was partitioned between ethyl acetate (50 cm^3) and water (25 cm^3) and the aqueous phase was extracted with ethyl acetate (1 × 50 cm^3). The combined organic solutions were washed with brine (1 × 25 cm^3) and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 15 cm) with 3:7 ethyl acetate–hexane gave *compound* **32** as a homogeneous [^{1}H NMR (200 MHz)], yellowish foam (103 mg, 89%), m.p. 96–98 °C (from hexane at −78 °C); ν_{max}/cm^{-1}(FT) ($CHCl_3$ cast) 3530; δ_H($CDCl_3$; 200 MHz) 1.28–1.84 (8 H, m), 2.79 (1 H, m), 3.58 (1 H, d, *J* 12.0), 3.82 (3 H, s), 3.86 (3 H, s), 4.00 (3 H, s), 4.03 (6 H, s), 5.08 (1 H, t, *J* 10), 6.78 (1 H, s), 7.38 (3 H, m) and 7.88 (2 H, m); δ_C($CDCl_3$; 75.47 MHz) 25.60, 29.27, 31.03, 46.97, 56.81, 57.10, 62.07, 62.20, 63.28, 75.24, 85.15, 98.63, 99.43, 114.66, 116.79, 123.18, 125.44, 128.52, 128.63, 131.34, 131.55, 136.98, 150.39,

150.43, 153.11 and 154.56 (Found: M^+, 476.2198. $C_{29}H_{32}O_6$ requires M, 476.2199).

If the starting material was not purified by crystallization then the yield in the present experiment was ~ 60%.

In another experiment [with compound **19** (526 mg), prepared by the method of Scheme 6] the yield was 93% and the material was pure [^{1}H NMR (300 MHz)] and was the same regioisomer as was the material made from the bromine/iodine exchange in acetic acid.

Cyclopentyl-[1,4,5,6,8-*pentamethoxy*-3-(*phenylethynyl*)-2-*naphthyl*]*methanone* **33**.—DDQ (205 mg, 0.90 mmol) was added in one batch to a solution of compound **32** (215 mg, 0.45 mmol) in dry 1,4-dioxane (5 cm^3). The mixture was stirred at 100 °C under argon overnight, cooled, diluted with 1:1 ethyl acetate–hexane (~ 5 cm^3), and filtered through a short column of alumina (Grade III, 2 × 6 cm). The column was washed with 1:1 ethyl acetate–hexane until no more of the desired product was eluted. Evaporation of appropriate fractions and flash chromatography of the residue over silica gel (2 × 15 cm) with 1:4 ethyl acetate–hexane gave ketone **33** as an apparently homogeneous [TLC (silica; 1:4 ethyl acetate–hexane)], yellowish foam (106 mg, 50%), m.p. 100–103 °C (from hexane at −78 °C); ν_{max}/cm^{-1}(FT) ($CHCl_3$ cast) 2380, 2350 and 1700; δ_H($CDCl_3$; 200 MHz) 1.42–2.18 (8 H, m), 3.54 (1 H, q, J 6.4), 3.77 (3 H, s), 3.87 (3 H, s), 3.99 (3 H, s), 4.00 (3 H, s), 4.51 (3 H, s), 6.78 (1 H, s), 7.36 (3 H, m) and 7.42 (2 H, m); δ_C($CDCl_3$; 75.47 MHz) 26.05, 29.21, 53.17, 56.78, 62.12, 62.40, 64.18, 83.89, 97.74, 97.91, 112.67, 116.63, 123.21, 126.31, 128.35, 128.53, 131.60, 133.49, 136.97, 148.93, 151.15, 153.64, 154.04 and 208.24 (Found: M^+, 474.2039; C, 73.7; H, 6.5%. $C_{29}H_{30}O_6$ requires M, 474.2043; C, 73.40; H, 6.37%).

In another experiment [with alcohol **32** (495 mg), prepared from material obtained by the method of Scheme 6] the yield was 62%.

2-[*Cyclopentylidene* (*trimethylsiloxy*)*methyl*]-1,4,5,6,8-*pentamethoxy*-3-(*phenylethynyl*)*naphthalene* **34**.—Anhydrous zinc chloride (~ 20 mg) and chlorotrimethylsilane (0.4 cm^3, 3.15 mmol) were added to a solution of ketone **33** (163 mg, 0.344 mmol) in dry triethylamine (4.0 cm^3) and the mixture was kept overnight at 80 °C (argon atmosphere) before being cooled, diluted with ethyl acetate (~ 5 cm^3), and filtered through a short column (2 × 5 cm) of Florisil. The column was developed with sufficient ethyl acetate (~ 200 cm^3) to elute all the product. Evaporation of the solvent gave *silyl ether* **34** as a yellowish solid (167 mg, 89%) suitable for the next step. A sample was purified by flash chromatography over silica gel with 1:4 ethyl acetate–hexane: m.p. 176–178 °C (from diethyl ether–hexane); δ_H($CDCl_3$; 200 MHz) 0.01 (9 H, s), 1.62 (4 H, m), 1.90 (1 H, m), 2.46 (3 H, m), 3.80 (3 H, s). 3.90 (3 H, s), 3.98 (3 H, s), 4.03 (3 H, s), 4.04 (3 H, s), 6.75 (1 H, s), 7.38 (3 H, m) and 7.52 (2 H, m); δ_C($CDCl_3$; 75.47 MHz) 0.90, 26.62, 27.26, 29.25, 30.14, 56.79, 57.43, 62.06, 62.19, 62.37, 86.18, 96.18, 98.63, 116.96, 117.63, 124.03, 125.90, 126.32, 128.13, 128.35, 129.48, 131.58, 136.31, 136.94, 150.51, 151.54, 153.58 and 153.84 (Found: M^+, 546.2433; C, 70.1; H, 7.15%. $C_{32}H_{38}O_6Si$ requires M, 546.2437; C, 70.33; H, 6.96%).

In another experiment [with ketone **33** (943 mg), prepared from material obtained by the method of Scheme 6] the yield of pure [TLC (silica; 3:7 ethyl acetate–hexane)] product **34** was 84% after flash chromatography.

[1,4,5,6,8-*Pentamethoxy*-3-(*phenylethynyl*)-2-*naphthyl*]-[1-(*phenylseleno*)*cyclopentyl*]*methanone* **35**.—Solid benzeneselenenyl chloride (71 mg, 0.37 mmol) was added in one portion to a stirred and cooled (−78 °C) solution of silyl ether **34** (157 mg, 0.287 mmol) in dry THF (5.0 cm^3) (argon atmosphere). The mixture was stirred for 5–6 h, during which time the cold-bath was allowed to attain room temperature. The solution was diluted with ethyl acetate (100 cm^3), washed successively with saturated aqueous sodium hydrogen carbonate (1 × 25 cm^3) and brine (1 × 25 cm^3), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 × 15 cm) with 1:3 ethyl acetate–hexane gave *ketone* **35** (176 mg, 81% from **33** as a homogeneous [^{1}H NMR (400 MHz); TLC (silica; 1:3 ethyl acetate–hexane)], yellowish foam; ν_{max}/cm^{-1}(FT) ($CHCl_3$ cast) 1734, 1681 and 1653; δ_H($CDCl_3$; 400 MHz) 1.7 (2 H, m), 1.87 (2 H, m), 1.97 (2 H, m), 2.30 (2 H, m), 3.75 (3 H, s), 3.87 (3 H, s), 4.00 (3 H, s), 4.03 (3 H, s), 4.05 (3 H, s), 6.78 (1 H, s), 7.30 (6 H, m), 7.50 (2 H, m), 7.75 (2 H, br d, J *ca.* 8.0); δ_C($CDCl_3$; 75.47 MHz) 24.31, 36.81, 56.77, 57.09, 62.10, 62.28, 63.40, 65.54, 84.64, 97.91, 98.39, 113.20, 116.61, 123.22, 126.20, 128.25, 128.45, 128.51, 128.64, 128.90, 131.62, 131.82, 136.98, 137.63, 148.71, 151.14, 153.68, 154.24 and 206.13 (Found: M^+, 630.1571; C, 66.8; H, 5.6; O, 15.0%. $C_{35}H_{34}O_6Se$ requires M, 630.1520; C, 66.77; H, 5.44; O, 15.24%).

When the reaction was carried out on a larger scale [with compound **34** (808 mg)] the yield was 73%.

Process of Scheme 8

3-*Benzylidene*-4,5,6,8,9-*pentamethoxyspiro*-[2H-*benz*[f]*indene*-2,1′-*cyclopentan*]-1(3H)-*one* **6**.—AIBN (10.0 mg, 0.061 mmol) was tipped into a solution of selenide **35** (416 mg, 0.661 mmol) in dry benzene (10 cm^3) and the solution was maintained under a static pressure of argon. The mixture was lowered into an oil-bath and, as soon as the solution began to reflux, a solution of triphenyltin hydride (348 mg, 0.991 mmol) in dry benzene (2.5 cm^3 plus 0.5 cm^3 as a rinse) was added during 2–3 min. Reflux was continued overnight, and the mixture was then cooled and evaporated. Flash chromatography of the residue over silica gel (2 × 18 cm) with 1:4 ethyl acetate–hexane gave the desired product **6** (150 mg, 48%) and the isomeric material **39** (130 mg, 41.5%), each as an apparently homogeneous [TLC (silica, 1:4 ethyl acetate–hexane)] substance, the former as a yellow foam and the latter as a solid. *Compound* **6** had ν_{max}/cm^{-1}(FT) (CCl_4 cast) 1708; δ_H($CDCl_3$; 300 MHz) 1.35–1.50 (2 H, m), 1.70–2.10 (6 H, m), 3.23 [1 H (Me of minor isomer), s], 3.60 [1 H (Me of minor isomer), s], 3.87–4.08 (13 H, 7 overlapping singlets, 5 of which account for the major isomer), 6.70 (0.25 H, s), 6.75 (overlapping singlets, corresponding in all to 1 H), 7.16–7.41 (5 H, m) and 8.32 (0.75 H, s); δ_C($CDCl_3$; 75.47 MHz) 26.92, 27.01, 56.57, 57.32, 60.20, 60.52, 60.63, 62.10, 62.43, 62.73, 63.33, 65.35, 97.47, 97.73, 117.95, 118.02, 121.18, 123.35, 124.58, 126.56, 126.76, 127.05, 128.00, 128.18, 128.60, 128.91, 130.54, 133.66, 134.71, 137.02, 137.64, 138.21, 139.08, 141.76, 142.52, 147.77, 147.99, 152.74, 152.80, 153.16, 153.77, 156.62, 156.66, 204.03 and 206.83 (Found: M^+, 474.2035. $C_{29}H_{30}O_6$ requires M, 474.2042).

Compound **39** had ν_{max}/cm^{-1}(FT) (CCl_4 cast) 1709; δ_H($CDCl_3$; 300 MHz) 0.80–2.20 (8 H, br m), 3.24 (0.6 H, dt, J 11.0, 3.5), 3.45 (0.4 H, m), 3.73–4.00 (13 H, series of singlets overlapping two small multiplets), 4.30 (0.64 H, t, J 11), 4.55 (1 H, m), 4.77 (0.37 H, dd, J 11.0, 3.0), 6.69–6.71 (1 H, two close singlets) and 7.00–7.40 (5 H, m); δ_C($CDCl_3$; 75.47 MHz) 25.09, 25.24, 25.71, 25.98, 32.94, 33.07, 33.85, 38.31, 39.33, 40.08, 46.14, 47.48, 57.14, 57.27, 61.98, 62.39, 62.55, 63.10, 63.15, 63.38, 72.33, 74.04, 98.18, 98.26, 117.80, 118.01, 121.14, 121.39, 125.72, 125.78, 126.92, 127.40, 127.67, 127.74, 128.14, 128.90, 137.76, 137.82, 139.26, 140.95, 143.04, 143.60, 150.13, 150.48, 152.40, 156.54, 156.68, 206.47 and 207.10 (Found: M^+, 474.2040. $C_{29}H_{30}O_6$ requires M, 474.2042).

Reactions of Scheme 9

3-*Hydroxy*-3-(α-*hydroxybenzyl*)-4,5,6,8,9-*pentamethoxyspiro*-

[2H-*benz*[f]*indene*-2,1′-*cyclopentan*]-1(3H)-*one*.—Osmium tetraoxide (2.5% w/w solution in *tert*-butyl alcohol; 0.60 cm^3, 14.7 mg, 0.058 mmol) was added to a stirred solution of compound **6** (25 mg, 0.053 mmol) in pyridine (2.5 cm^3).[15] After 1 h at room temperature the mixture was diluted with ethyl acetate (30 cm^3) and washed successively with 10% w/v aqueous sodium hydrogen sulphite (2 × 25 cm^3), dil. hydrochloric acid (2 mol dm^{-3}; 1 × 20 cm^{-3}), and brine (1 × 25 cm^3), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 15 cm) with 2:3 ethyl acetate–hexane gave compounds **41** [18 mg, 67%; 70% after correction for recovered starting material (1.0 mg)] as an apparently homogeneous [TLC (silica; 2:3 ethyl acetate–hexane)], yellow oil, ν_{max}/cm^{-1}(FT) ($CHCl_3$ cast) 3475 and 1720; δ_H($CDCl_3$; 300 MHz) 1.55–2.45 (8 H, m), 3.35–4.10 (9 s corresponding to 15 H), 4.35 (0.75 H, br s), 4.75 (0.25 H, br s), 4.96 (0.25 H, br d, *J* 8.0), 5.05 (0.75 H. br s) and 6.65–7.25 (6 H, m including s at δ 6.75) [Found: $M^+ + 1$) (CI) 509. $C_{29}H_{32}O_8$ requires *M*, 508].

4,5,6,8,9-*Pentamethoxyspiro*-[2H-*benz*[f]*indene*-2,1′-*cyclopentane*]-1,3-*dione* **7**.—Periodic acid (15 mg, 0.08 mmol) was added in one batch to a stirred solution of the glycol **41** (10.0 mg, 0.020 mmol) in methanol (1.0 cm^3). After 2 h at room temp [TLC control (silica; 3:7 ethyl acetate–hexane)] the mixture was diluted with ethyl acetate (25 cm^3), washed successively with water (1 × 15 cm^3) and brine (1 × 15 cm^3), and dried ($MgSO_4$). (The reaction must be stopped as soon as it is complete, otherwise the yield is reduced.) Evaporation of the solvent and flash chromatography of the residue over silica gel (Pasteur pipette) with 1:4 ethyl acetate–hexane gave dione **7** (8.0 mg, 100%) as a homogeneous [^{1}H NMR (200 MHz); TLC (silica; 2:3 ethyl acetate–hexane)] foam; m.p. 117–122 °C (from ethyl acetate–hexane); ν_{max}/cm^{-1}(FT) ($CHCl_3$ cast) 1728 and 1702; δ_H($CDCl_3$; 200 MHz) 1.98 (8 H, br s), 3.88 (3 H, s), 4.04–4.06 (12 H, overlapping singlets) and 6.90 (1 H, s); δ_C($CDCl_3$; 75.47 MHz) 27.61, 36.01, 56.58, 57.48, 62.25, 62.44, 63.06, 63.21, 99.91, 121.15, 124.21, 127.29, 130.98, 139.34, 150.61, 153.54, 153.62, 156.83, 201.91 and 203.32 (Found: M^+, 400.1521; C, 65.9; H, 6.15%. $C_{22}H_{24}O_7$ requires *M*, 400.1522; C, 65.99; H, 6.04%).

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