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A Regiospecific Synthesis of Anthracyclinones Using Directed Metalation

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Regiospecific and efficient synthesis of anthracyclinones have been achieved by using a directed metalation strategy. The phthalides **5a** and **5b** were prepared by the condensation of metalated *N,N*-diethylbenzamide derivatives (**1′**) with dihydronaphthalene carbaldehydes (**2a** and **2b**) or by the reaction of metalated dihydronaphthalene (**4′**) with a phthalaldehydic amide derivative (**3**). The phthalide (**5**) was then reduced to the acid (**14**), which was readily cyclized with trifluoroacetic anhydride to the tetracyclic quinone (**6**). The tetracyclic quinone (**6**) was converted into the trione (**7**), a key intermediate for the synthesis of daunomycinone, by epoxidation and subsequent rearrangement using *p*-toluenesulfonic acid.

Keywords——directed metalation; anthracyclinone; *N,N*-diethylamide group as directing group; methoxymethoxy group as directing group; regiospecific synthesis of phthalide; zinc–copper couple

The directed metalation reaction[1] of aromatic systems has been developed into a significant method for the regiospecific synthesis of polysubstituted aromatics, especially those which are difficult to prepare by means of classical electrophilic reactions. Among the variety of directing groups, the tertiary amide group on an aromatic ring system was proved to be a useful director[2] for *ortho* metalation. We have already demonstrated the usefulness of *ortho*-lithiated tertiary benzamides for the syntheses of naturally occurring anthraquinones[3] and isocoumarins,[4] polycyclic aromatic hydrocarbons,[5] and several classes of biogenetically diverse alkaloids.[5,6]

Daunomycin and related antibiotics are established antineoplastic agents[7] for the chemotherapeutic treatment of human cancer. We now report a regiospecific synthesis of the key intermediate, 3,4-dihydro-5,7,12-trimethoxynaphthacene-2,6,11(1*H*)-trione (**7**),[8] in the synthesis of *dl*-daunomycinone by using two different types of *ortho*-lithiated species derived from *N,N*-diethylbenzamides and methoxymethoxybenzenes.[9]

Our synthetic design, based on a convergent AB+D→ABD→ABCD approach[10] for the tetracyclic quinone (**6**) and trione (**7**), is illustrated in Chart 1. In the regiospecific construction of the tetracyclic system based upon the directed metalation strategy, we chose two modes of coupling reaction for the synthesis of key intermediate phthalides (**5a** and **5b**): the condensation of the *ortho*-lithiated benzamide D ring (**1′**) with AB ring aldehyde (**2a** and **2b**) and the condensation of *ortho*-lithiated methoxymethoxydihydronaphthalene AB ring (**4′**) with D ring aldehyde-amide (**3**).

The requisite AB ring synthon (**4**), which has the added advantage of being easily convertible into **2b**, was prepared from the readily available tetralone (**8**)[11] in four steps with 74.4% overall yield (Chart 2). Treatment of a solution of the tetralone (**8**) in dichloromethane with 1.5 eq of boron tribromide[12] at −78 °C led to selective demethylation to give 8-hydroxy-5-methoxy-1-tetralone (**9**)[11a] in 95% yield. The tetralone (**9**) was then converted into its *p*-toluenesulfonyl hydrazone (**10**) by reaction with *p*-toluenesulfonyl hydrazide in the presence

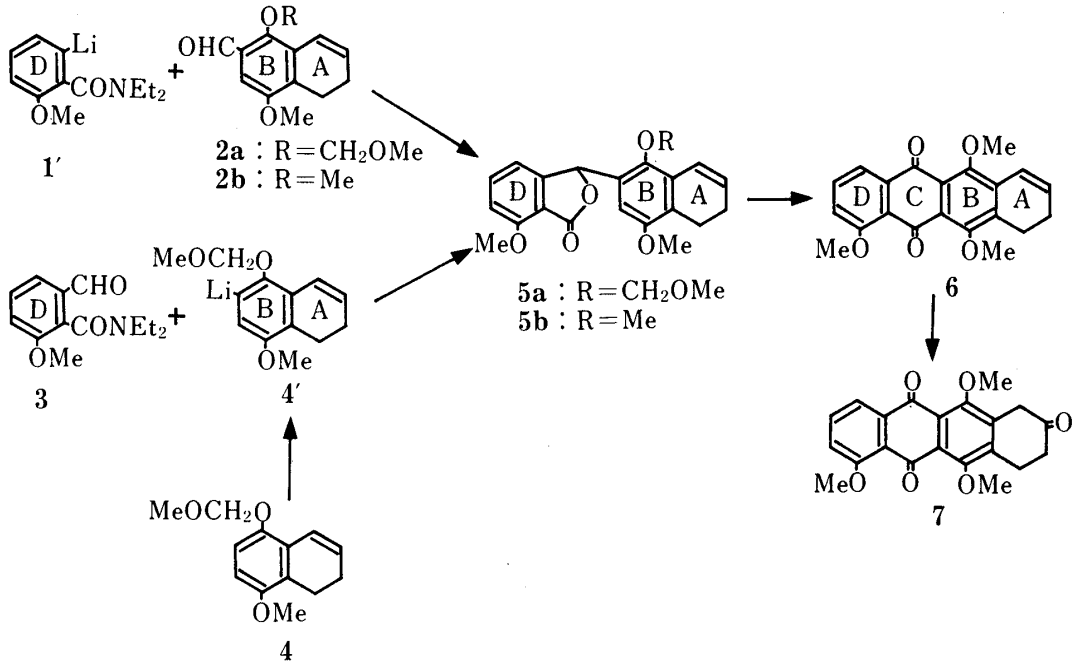

Chart 1

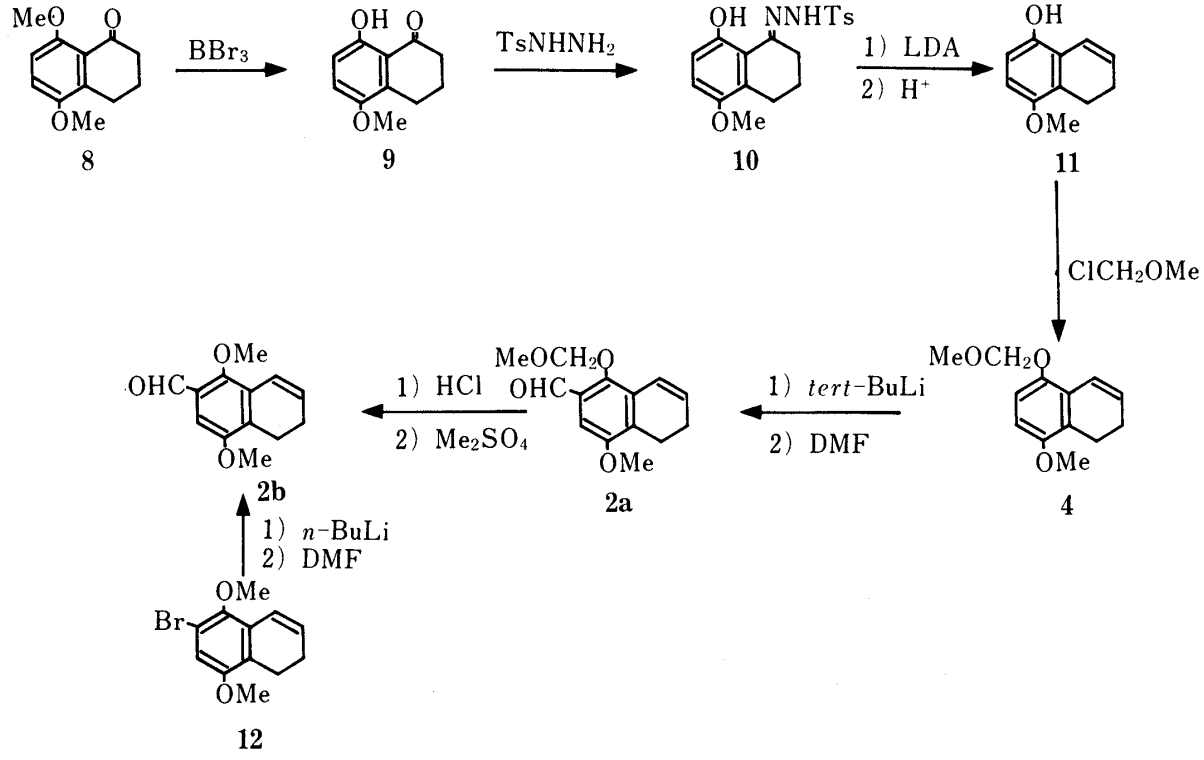

Chart 2

of a catalytic amount of conc. hydrochloric acid. Reaction of the hydrazone (**10**) with lithium diisopropylamide in *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) at 0 °C by the method of Shapiro[13] gave a dihydronaphthalene (**11**), which was methoxymethylated with chloromethyl methyl ether using sodium hydride as a base to produce **4**. According to the model studies of Christensen[14] and Ronald,[15] the reaction of 5-methoxy-8-methoxymethoxy-3,4-dihydronaphthalene (**4**) with 1.2 eq of *tert*-butyllithium in ether at 0 °C for 3 h followed by quenching with *N,N*-dimethylformamide (DMF) gave the desired aldehyde

(**2a**) in 98% yield. The methoxymethoxy group of **2a** was easily cleaved by diluted hydrochloric acid to give the corresponding dihydronaphthol, which was methylated with dimethyl sulfate and potassium carbonate in acetone to afford 5,8-dimethoxy-3,4-dihydronaphthalene-7-carbaldehyde (**2b**) in 95% yield. On the other hand, 7-bromo-5,8-dimethoxy-3,4-dihydronaphthalene (**12**), which can be prepared from 4-(2,5-dimethoxyphenyl)butylic acid in four steps in 58% overall yield according to the method of Braun,[8] was converted into **2b** in 95% yield by halogen-lithium exchange reaction, followed by formylation with DMF.

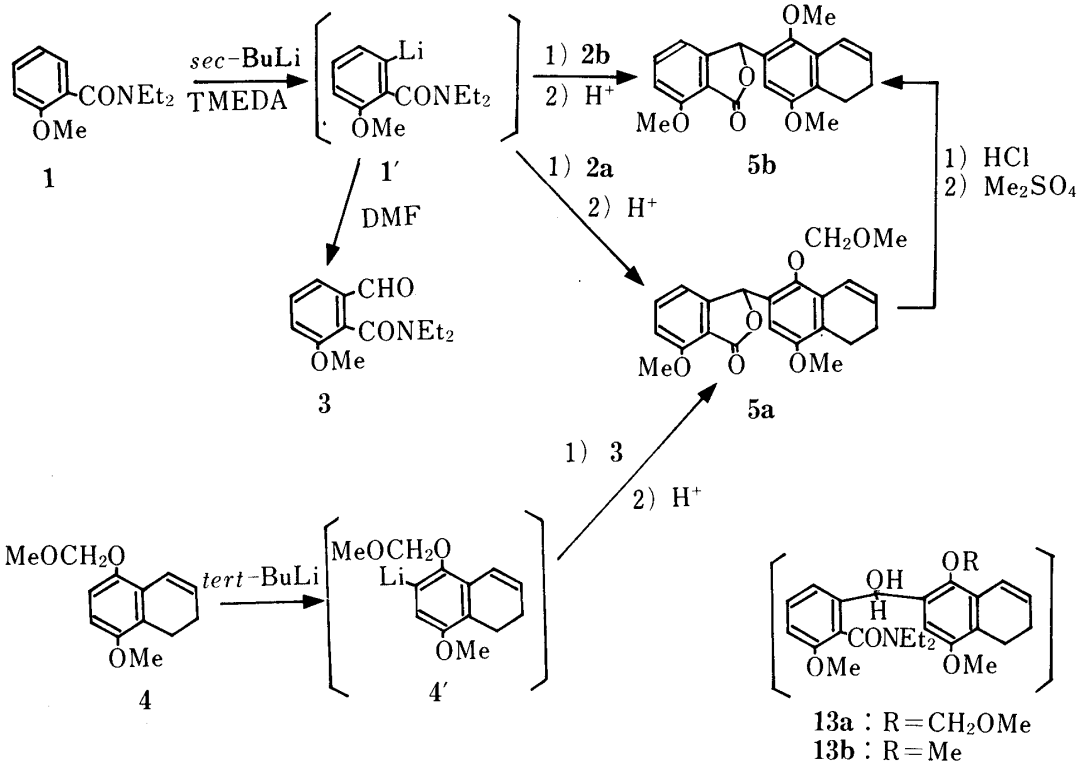

Chart 3

Lithiation[16] of 2-methoxy-*N*,*N*-diethylbenzamide (**1**) with *sec*-butyllithium in tetrahydrofuran at −78 °C followed by treatment with 5,8-dimethoxy-3,4-dihydronaphthalene-7-carbaldehyde (**2b**) afforded the amide alcohol (**13b**) (Chart 3), which was not isolated but was treated with *p*-toluenesulfonic acid in refluxing toluene to give the phthalide (**5b**) in 60% yield. In a similar manner, the lithiated amide (**1'**) was treated with 5-methoxy-8-methoxymethoxy-3,4-dihydronaphthalene-7-carbaldehyde (**2a**) to give the phthalide (**5a**) in 50% yield. Although the methoxymethoxy moiety is known to be labile to acid, no cleavage was observed under the conditions of ring closure using *p*-toluenesulfonic acid in refluxing toluene. The phthalide (**5a**), however, was easily converted into **5b** in quantitative yield by brief treatment with hydrochloric acid in refluxing methanol followed by methylation. The same lithiated amide (**1'**) was also transformed into 2-methoxy-*N*,*N*-diethylbenzamido-6-carbaldehyde (**3**)[16] by reaction with DMF to provide an alternative synthesis of **5a**. The lithiated species (**4'**), obtained by the treatment of **4** with *tert*-butyllithium in ether, was reacted with **3** to give **13a**. The amide alcohol (**13a**) was treated with *p*-toluenesulfonic acid to give the phthalide (**5a**) in 60% overall yield from **4**.[17]

Reduction of **5b** (chart 4) with a suspension of zinc–copper couple, prepared by the method of Shank and Shechter,[18] in a refluxing mixture of pyridine and 10% aqueous potassium hydroxide gave the acid (**14**) in 90% yield. The acid (**14**) was cyclized by treatment with trifluoroacetic anhydride in dichloromethane at room temperature to give the corresponding anthrone, which, without isolation, was air-oxidized during treatment with

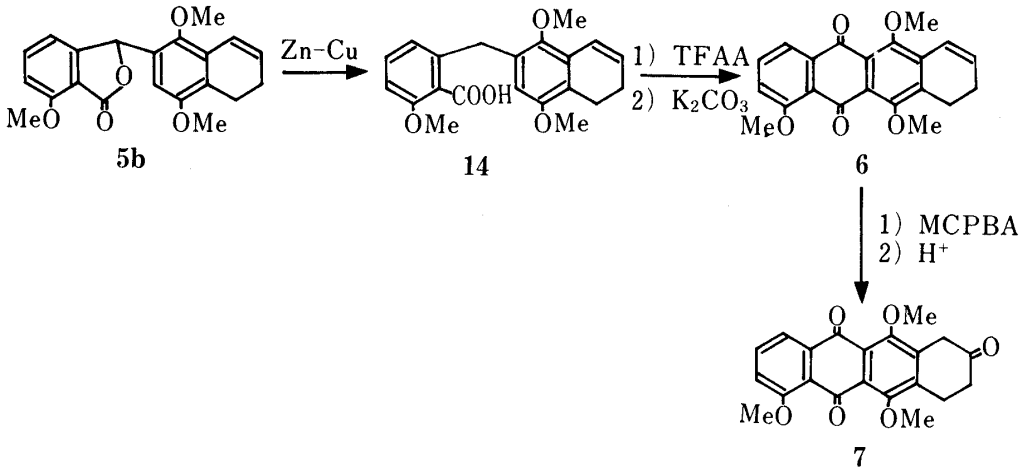

Chart 4

potassium carbonate in methanol for 10 min to yield the quinone (**6**) in 60% overall yield. The conversion of **6** into the trione (**7**) was achieved in 70% yield by epoxidation with *m*-chloroperbenzoic acid and subsequent acid rearrangement by treatment with *p*-toluenesulfonic acid. The synthetic substances **6** and **7** were shown to be identical with authentic samples[8] on the basis of melting point, and spectroscopic (nuclear magnetic resonance (NMR) and infrared (IR)) and thin-layer chromatography (TLC) comparisons.

We have already pointed out that *ortho*-lithiated *N,N*-diethylbenzamide derivatives are useful starting materials for efficient and regiospecific construction of unsymmetrically substituted anthraquinone systems.[3] As the conversion of **7** to *dl*-daunomycinone has already been established,[8] our synthesis of the trione (**7**) constitutes a new formal total synthesis of *dl*-daunomycinone, and it is likely that our strategy could be extended to the synthesis of the related compound, 3,4-dihydro-5,12-dihydroxy-7-methoxynaphthacene-2,6,11(1*H*)-trione,[19] a key intermediate in *dl*-γ-rhodomycinone synthesis.

Experimental

Melting points are uncorrected. IR spectra were determined on JASCO IRA-2 spectrophotometer. UV spectra were recorded on a Hitachi 323 spectrophotometer. NMR spectra were obtained with a JEOL FX 90Q spectrometer and a JEOL JNM-PMX 60 spectrometer using tetramethylsilane as an internal standard. Mass spectra (MS) were determined on a JEOL JMS-01SG mass spectrometer. Chromatography was carried out by flash chromatography on a column of Kieselgel 60 (230—400 mesh).

8-Hydroxy-5-methoxy-1-tetralone (9)——Boron tribromide (0.39 ml, 4.13 mmol) in dry CH_2Cl_2 (1.6 ml) was added dropwise to a stirred solution of 5,8-dimethoxy-1-tetralone (**8**, 1.7 g, 8.24 mmol)[11] in dry CH_2Cl_2 (100 ml) at −78 °C. After 2 h, the dry ice-acetone bath was removed, and the mixture was stirred for 1 h at room temperature. Water (30 ml) and 5% Na_2CO_3 solution (5 ml) were added, and the CH_2Cl_2 layer was separated. The extract was washed with 5% $Na_2S_2O_3$ (5 ml) and water (30 ml), then dried (Na_2SO_4) and evaporated to dryness to give a yellow solid, which, upon chromatography (benzene eluent), furnished **9** (1.5 g, 95%) as yellow needles, mp 96—98 °C (ether (lit.[11a] mp 95 °C). MS *m/e*: 192 (M^+). NMR ($CDCl_3$) δ: 1.89—2.26 (2H, m), 2.50—3.00 (4H, m), 3.70 (3H, s), 6.56 (1H, d, J = 10 Hz), 6.92 (1H, d, J = 10 Hz), 11.6 (1H, s). IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1635 (C=O). UV λ_{max}^{EtOH} nm (log ε): 236 (4.15), 266 (3.92), 370 (3.53). *Anal.* Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.30. Found: C, 68.55; H, 6.37.

8-Hydroxy-5-methoxy-1-tetralone Tosylhydrazone (10)——**9** (3.84 g, 20 mmol) and conc. HCl (3 drops) were added to a solution of tosyl hydrazide (4.1 g, 22 mmol) in EtOH (150 ml), and the mixture was refluxed for 1 h. During the reaction, crystals separated from the reaction mixture. The resulting white solid was collected and washed with cold EtOH to give **10** in quantitative yield, mp 235 °C (dec.) (EtOH). MS *m/e*: 360 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3200, 1600 (C=N). UV λ_{max}^{EtOH} nm (log ε): 224 (4.38), 246 (s) (4.15), 281 (4.18), 310 (s) (3.81), 342 (3.80). *Anal.* Calcd for $C_{18}H_{20}O_4N_2S$: C, 59.99; H, 5.59; N, 7.77; S, 8.89. Found: C, 60,00; H, 5.63; N, 7.65; S, 8.83.

8-Hydroxy-5-methoxy-3,4-dihydronaphthalene (11)——A solution of diisopropylamine (2.27 g, 22.4 mmol) and TMEDA (8 ml) under N_2 was cooled to 0 °C. MeLi in ether (11.7 ml, 14 mmol) was added over a period of 5 min, and

the mixture was stirred for an additional 5 min. To this solution, **10** (1.44 g, 4 mmol) was added. The cold bath was removed, and the mixture was stirred overnight at room temperature. Water was carefully added to dissolve lithium salt. The organic layer was separated, and the aqueous phase was extracted with ether. The combined organic layer was washed with 10% HCl and then with water. The extract was dried (Na_2SO_4) and concentrated. The residual oil was chromatographed with benzene to give **11** (0.65 g, 92%), mp 96—98 °C (ether). MS *m/e*: 176 (M^+). NMR ($CDCl_3$) δ: 2.00—2.50 (2H, m), 2.58—3.00 (2H, m), 3.70 (3H, s), 5.20 (1H, br s), 5.79—6.10 (1H, m), 6.50—7.00 (3H, m). IR ν_{max}^{KBr} cm^{-1}: 3300 (OH). UV λ_{max}^{EtOH} nm (log ε): 217 (4.28), 270 (3.86), 280 (s) (3.64), 323 (3.64). *Anal.* Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 75.01; H, 6.93.

5-Methoxy-8-methoxymethoxy-3,4-dihydronaphthalene (4)——A mixture of **11** (0.88 g, 5 mmol), NaH (0.4 g, 8.3 mmol, 50% in oil) and dry DMF (80 ml) was stirred under N_2 at 0 °C for 1 h, then chloromethyl methyl ether (0.72 g, 9 mmol) in dry DMF (10 ml) was added dropwise, and the mixture was stirred overnight at room temperature. Water was added and the mixture was extracted with $CHCl_3$. The organic layer was evaporated to give a viscous oil, which was distilled to yield **4** (0.95 g, 86%), bp 135 °C (2 mmHg). MS *m/e*: 220 (M^+). UV λ_{max}^{EtOH} nm (log ε): 222 (4.21), 226 (s) (3.90), 270 (3.90), 316 (3.54). NMR ($CDCl_3$) δ: 2.00—2.50 (2H, m), 2.58—3.00 (2H, m), 3.42 (3H, s), 3.73 (3H, s), 5.00 (2H, s), 5.83—6.10 (1H, m), 6.50—6.86 (3H, m). *Anal.* Calcd for $C_{13}H_{16}O_3$: C, 70.88; H, 7.32. Found: C, 70.90; H, 7.30.

5-Methoxy-8-methoxymethoxy-3,4-dihydronaphthalene-7-carbaldehyde (2a)——*tert*-BuLi in pentane (2.66 ml, 5.32 mmol) was added to a solution of **4** (0.9 g, 4.1 mmol) in dry ether (100 ml) under N_2 at 0 °C. The mixture was stirred for 3 h, then DMF (0.5 g, 6.84 mmol) in dry ether (20 ml) was added and the whole was stirred for an additional 2 h at room temperature. Then saturated NH_4Cl solution was added, and the mixture was acidified with cold 10% HCl. The mixture was extracted with ether and the extract was washed with water, dried (Na_2SO_4), and concentrated to leave a viscous oil, which was distilled to give **2a** (1.0 g, 98%), bp 150 °C (0.7 mmHg). MS *m/e*: 248 (M^+). NMR ($CDCl_3$) δ: 2.10—2.50 (2H, m), 2.56—2.96 (2H, m), 3.50 (3H, s), 3.80 (3H, s), 4.93 (2H, s), 5.93—6.26 (1H, m), 6.50—6.80 (1H, m), 7.10 (1H, s), 10.20 (1H, s). IR ν_{max}^{KBr} cm^{-1}: 1680 (C=O). UV λ_{max}^{EtOH} nm (log ε): 250 (4.40), 298 (3.66), 349 (3.49). *Anal.* Calcd for semicarbazone $C_{15}H_{19}N_3O_4$, mp 183—185 °C (benzene): C, 59.01; H, 6.27; N, 13.76. Found: C, 59.09; H, 6.18; N, 13.74.

5,8-Dimethoxy-3,4-dihydronaphthalene-7-carbaldehyde (2b)——a) *n*-BuLi in hexane (20 ml, 24 mmol) was added dropwise to a solution of 7-bromo-5,8-dimethoxy-3,4-dihydronaphthalene (**12**, 2.15 g, 8 mmol) in dry ether (100 ml) under N_2 at −24 °C. The mixture was stirred for 10 min, then dry DMF (2.92 g, 40 mmol) in dry ether (20 ml) was added dropwise to the reaction mixture. The whole was stirred for 20 min at −24 °C then for 40 min at room temperature. The mixture was quenched by the addition of water and 10% HCl, and extracted with ether. The extract was dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave a residue, which was chromatographed (ether eluent) to give **2b** (1.66 g, 95%), mp 86 °C (*n*-hexane–ether).

b) A mixture of **2a** (0.23 g, 0.93 mmol), MeOH (10 ml) and 10% HCl (10 ml) was refluxed for 10 min. MeOH was removed and the acidic solution was extracted with $CHCl_3$. The extract was washed with saturated NaCl solution, dried (Na_2SO_4), and evaporated to give the crude phenol. A mixture of this phenol, K_2CO_3 (15 g), dimethyl sulfate (0.7 g), and acetone (50 ml) was refluxed for 45 min. The filtrate was evaporated to dryness to afford crude **2b**, which was chromatographed ($CHCl_3$ eluent) to give pure **2b** (0.19 g, 95%), mp 85—86 °C (*n*-hexane–ether). MS *m/e*: 218 (M^+). NMR ($CDCl_3$) δ: 2.10—2.50 (2H, m), 2.56—3.00 (2H, m), 3.77 (6H, s), 5.87—6.18 (1H, m), 6.50—6.70 (1H, m), 7.02 (1H, s), 10.15 (1H, s). IR ν_{max}^{KBr} cm^{-1}: 1680 (C=O). UV λ_{max}^{EtOH} nm (log ε): 250 (4.47), 300 (3.73), 350 (3.57). *Anal.* Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.62; H, 6.46.

3-(5-Methoxy-8-methoxymethoxy-3,4-dihydro-7-naphthyl)-7-methoxy-isobenzofuran-1(3*H*)-one (5a)——a) *tert*-BuLi in pentane (3.5 ml, 7 mmol) was added to a stirred solution of **4** (1.1 g, 5 mmol) in dry ether (100 ml) under N_2 at −24 °C and the mixture was stirred for 2 h. A solution of 6-methoxy-*N,N*-diethylbenzamido-2-carbaldehyde (**3**, 1.18 g, 5 mmol)[16] in dry ether (20 ml) was added dropwise to the cloudy reaction mixture and the dry ice–acetone bath was then removed. After being stirred for further 12 h at room temperature, the solution was treated with water and acidified with dilute HCl. The organic layer was separated, washed with saturated NaCl solution, dried (Na_2SO_4), and evaporated to dryness to give the amide alcohol (**13a**) as a viscous oil. A solution of this crude material and *p*-toluenesulfonic acid (100 mg) in toluene (50 ml) was refluxed for 8 h. The mixture was washed with 5% $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated to dryness to afford a crystalline material, which was recrystallized from MeOH to give pure **5a** (1.15 g, 60%), mp 175 °C.

b) A solution of *sec*-BuLi in cyclohexane (3.1 ml, 2.79 mmol) was injected into a stirred solution of 2-methoxy-*N,N*-diethylbenzamide (**1**, 0.48 g, 2.3 mmol) and TMEDA (0.42 ml, 2.78 mmol) in dry ether (100 ml) at −78 °C under N_2. The mixture was stirred for 1 h, then a solution of **2a** (0.57 g, 2.3 mmol) in dry ether (20 ml) was added, and the dry ice-acetone bath was removed. The reaction mixture was stirred for 12 h. **5a** (0.44 g, 50%) was obtained by work-up as described in a), mp 175 °C (MeOH). MS *m/e*: 382 (M^+). NMR ($CDCl_3$) δ: 2.12—2.44 (2H, m), 2.60—2.84 (2H, m), 3.54 (3H, s), 3.60 (3H, s), 4.00 (3H, s), 5.03 (2H, s), 6.00—6.24 (1H, m), 6.28 (1H, s), 6.64—7.64 (5H, m). IR ν_{max}^{KBr} cm^{-1}: 1760 (C=O). UV λ_{max}^{EtOH} nm (log ε): 227 (4.58), 273 (3.93), 284 (s) (3.60), 306 (4.00), 322 (s) (3.35). *Anal.* Calcd for $C_{22}H_{22}O_6$: C, 69.10; H, 5.80. Found: C, 68.67; H, 5.72.

3-(5,8-Dimethoxy-3,4-dihydro-7-naphthyl)-7-methoxy-isobenzofuran-1(3*H*)-one (5b)——a) 2-Methoxy-*N,N*-di-

ethylbenzamide (**1**, 0.71 g, 3.4 mmol) was sequentially treated with *sec*-BuLi (5.2 ml, 4.1 mmol) and **2b** (0.75 g 3.4 mmol) under the same conditions as described for the preparation of **5a**. The same work-up provided a gum, which, upon recrystallization from MeOH and acetone, afforded **5b** (0.72 g, 60%), mp 204—206 °C.

b) **5b** was formed from **5a** in quantitative yield under the conditions as described for the conversion of **2a** into **2b**. MS *m/e*: 352 (M^+). NMR ($CDCl_3$) δ: 2.17—2.43 (2H, m), 2.56—2.89 (2H, m), 3.63 (3H, s), 3.79 (3H, s), 4.00 (3H, s), 5.92—6.23 (1H, m), 6.26 (1H, s), 6.63—7.63 (5H, m). IR ν_{max}^{KBr} cm^{-1}: 1750 (C=O). UV λ_{max}^{EtOH} nm (log ε): 213 (4.72), 226 (s) (3.93), 229 (4.59), 273 (3.95), 286 (s) (3.91), 300 (s) (3.95), 307 (3.97), 322 (s) (3.65). *Anal.* Calcd for $C_{21}H_{20}O_5$: C, 71.58;H, 5.72. Found: C, 71.42; H, 5.72.

2-[(5,8-Dimethoxy-3,4-dihydro-7-naphthyl)methyl]-6-methoxybenzoic Acid (14)——A suspension of **5b** (0.7 g, 2 mmol), Shank and Shechter zinc–copper couple (15 g),[18] and pyridine (6 ml) in 10% KOH solution (60 ml) was refluxed for 96 h. The resulting solid was removed by filtration. The filtrate was acidified with 10% HCl and extracted with ethyl acetate. The organic layer was washed with water and then with saturated NaCl solution, and extracted twice with 5% $NaHCO_3$ solution. The aqueous phase was again acidified with 10% HCl, extracted with $CHCl_3$, dried (Na_2SO_4), and evaporated to leave crude **14**, which was recrystallized from MeOH to give pure **14** (0.63 g, 90%), mp 167—168 °C. MS *m/e*: 354 (M^+). NMR ($CDCl_3$) δ: 2.10—2.39 (2H, m), 2.50—2.82 (2H, m), 3.59 (3H, s), 3.66 (3H, s), 3.83 (3H, s), 4.06 (2H, s), 5.83—6.20 (1H, m), 6.50—7.30 (5H, m), 10.11 (1H, s). IR ν_{max}^{KBr} cm^{-1}: 2900 (OH), 1670 (C=O). UV λ_{max}^{EtOH} nm (log ε): 223 (4.57), 226 (s) (3.97), 273 (4.04), 280 (s) (3.97), 310 (3.50), 320 (s) (3.43). *Anal.* Calcd for $C_{21}H_{22}O_5$: C, 71.17; H, 6.26. Found: C, 71.06; H, 6.31.

9,10-Dihydro-1,6,11-trimethoxynaphthacene-5,12-dione (6)——A solution of **14** (0.55 g, 1.55 mmol) in dry $CHCl_3$ (20 ml) was treated with trifluoroacetic anhydride (2 ml). The mixture was stirred at room temperature for 26 h and evaporated to dryness. The resulting residue was triturated with MeOH to give a crystalline material. A suspension of this solid, K_2CO_3 (0.3 g) and MeOH (20 ml) was stirred for 10 min. The resulting solid was removed by filtration, and the filtrate was evaporated to dryness to give crude **6**, which, upon chromatography (2% acetone in $CHCl_3$ eluent), furnished pure **6** (0.33 g, 60%), mp 154 °C (ether). MS *m/e*: 350 (M^+). NMR ($CDCl_3$) δ: 2.20—2.44 (2H, m), 2.72—3.04 (2H, m), 3.84 (3H, s), 3.88 (3H, s), 3.96 (3H, s), 6.16—6.40 (1H, m), 6.80—6.96 (1H, m), 7.12—7.80 (3H, m). IR ν_{max}^{KBr} cm^{-1}: 1665 (C=O). UV λ_{max}^{EtOH} nm (log ε): 225 (4.38), 240 (4.37), 257 (4.39), 280 (s) (4.41), 287 (4.42), 394 (3.97). *Anal.* Calcd for $C_{21}H_{18}O_5$: C, 71.99; H, 5.18. Found: C, 72.02; H, 5.15.

3,4-Dihydro-5,7,12-trimethoxynaphthacene-2,6,11(1*H*)-trione (7)——A solution of **6** (0.5 g, 1.4 mmol) and *m*-chloroperbenzoic acid (1.0 g, 5.8 mmol) in CH_2Cl_2 (20 ml) was stirred for 72 h at room temperature under shielding from light. The solution was washed with saturated $NaHCO_3$ solution, 3% $NaHSO_3$ solution, and water. The organic phase was dried over Na_2SO_4 and evaporated to give the crude epoxide, which was used without isolation. A solution of this crude material and *p*-toluenesulfonic acid (0.1 g) in toluene (100 ml) was refluxed for 1 h. The solution was washed with 5% $NaHCO_3$ and water, dried (Na_2SO_4), and evaporated to give crude **7**, which, upon chromatography (10% acetone in $CHCl_3$ eluent), furnished pure **7** (0.37 g, 70%), mp 195 °C (ethyl acetate) (lit.[8] mp 196—198 °C). MS *m/e*: 366 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1710 (C=O), 1665 (C=O). NMR ($CDCl_3$) δ: 2.49—2.64 (2H, m), 3.18—3.33 (2H, m), 3.69 (2H, s), 3.90 (3H, s), 3.96 (3H, s), 4.01 (3H, s), 7.19—7.86 (3H, m).

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