Total Synthesis of the Antibiotic WS-5995A Using a Key Reaction of *o*-Toluamide Anions with Homophthalic Anhydrides

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A total synthesis of the anticoccidial antibiotic WS-5995A was achieved by regioselective condensation of *N,N*-diethyl-*o*-toluamide anions into homophthalic anhydrides as a key reaction.

Keywords WS-5995A; *o*-toluamide; lithiation; homophthalic anhydride; anticoccidial antibiotic; 5*H*-benzo[*d*]naphtho-[2,3-*b*]pyran; naphthoquinone

In 1980, three pigments were isolated[1] from *Streptomyces auranticolor* nov. sp., and tentatively named WS-5995A, B, and C (Chart 1). Among these compounds, WS-5995A and B have been shown to possess excellent protective activity against *Eimeria tenella* infection.[1b] The structures of the series of WS-5995 were elucidated by Tanaka and coworkers[2]; they were shown to be members of the naphthoquinone class of antibiotics. Although there are a number of pyranonaphthoquinone antibiotics[3] such as nanaomycin A, eleutherin, and kalafungin, WS-5995A is the first naturally occurring compound possessing 5*H*-benzo[*d*]naphtho[2,3-*b*]pyran as the basic skeleton.[1,2] The first total synthesis of WS-5995A was accomplished by Ikushima and coworkers[2] in 1980 using a coupling reaction between 3-hydroxyjuglone and the diazonium salt of 3-methoxy-5-methylanthranilic acid. This key reaction, based on Neunhoeffer and Weise's procedure[4] for the synthesis of the parent 5*H*-benzo[*d*]naphtho[2,3-*b*]pyran, suffers from the low yield of the coupling step. We wish to report herein a new regioselective total synthesis of WS-5995A, based on a convergent DC+A→DCA→DCBA approach (Chart 2) using the condensation of *o*-toluamide anion[5] with homophthalic anhydrides (HA)[6a,c] as the key reaction.

It was well documented that HA derivatives are versatile synthons in synthetic chemistry,[6] particularly in natural products chemistry. Convergent syntheses of a series of isoquinoline, oxoberbine, benzophenanthridine, indole, and tetrahydroprotoberberine alkaloids through condensation of imines such as 3,4-dihydroisoquinolines or Schiff bases with HA derivatives[6] have been extensively developed by Haimova *et al.*[7] and Cushman *et al.*[8] Tamura and Kita[6a] have elaborated the facile base-induced cycloaddition of HA with a variety of dienophiles to give the linearly condensed *peri*-hydroxy polycyclic compounds, including key intermediates of anthracyclinones[9] and SS-228R.[10] This reaction is regarded as a cycloaddition of *o*-xylylene type dienes, generated from HA by strong bases or by thermal isomerization, with polar multiple bonds[6] such as C≡C, C=C, C=O,[7] and C=N.[7,8] On the other hand, Snieckus *et al.* have reported[11] the synthesis of phthalideisoquinoline alkaloids by using, as the key reaction, the condensation of phenethylamine with bromo-HA derivatives. Various antifungal isocoumarins[12] have also been prepared from HA derivatives with benzaldehydes in the presence of powdered sodium carbonate by Nakajima *et al.*[13] The reaction of HA derivatives with nitrogen nucleophiles to afford dihydroxyisoquinolines has been well established,[14] but little attention has been given to the corresponding reaction with carbon nucleophiles.[15] According to our synthetic design (Chart 2), we initially examined the reactivity of HA with carbon nucleophiles, especially to clarify which carbonyl groups (C-1 or C-3) in HA would be preferentially attacked by the nucleophiles.

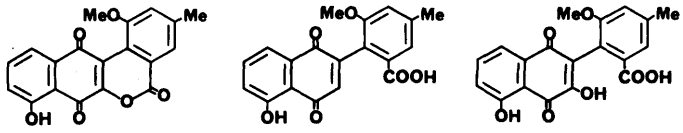

Chart 1

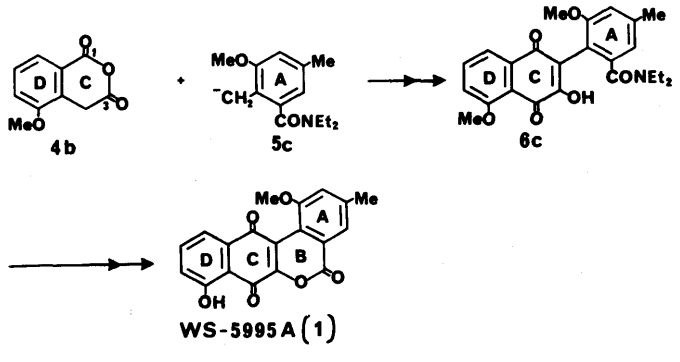

Chart 2

The condensations of HA (**4a**) with carbanions (**7a—c**) derived from phenylmethylsulfone (**8a**), acetophenone (**8b**), and *tert*-butyl acetate (**8c**) were examined as a preliminary study for the synthesis of WS-5995A (**1**) (Chart 3). A tetrahydrofuran (THF) solution of 1.0 eq of **8a** was treated with 1.2 eq of lithium diisopropylamide (LDA) at −78 °C to generate the carbanion **7a**, which was condensed with **4a**. Following standard work-up and chromatographic purification, **9a** was obtained in 10% yield. However, when 2.0 eq of **7a** was employed in the same reaction, the yield of **9a** was increased to 68%. Spectral data were consistent with the proposed structure (see Experimental) although an alternative product in which the C-3 carbonyl is attacked by the carbanion could not be ruled out.

In order to confirm the structure of **9a**, we examined two other reactions (Chart 3). The reaction of the lithio compound **7a** with 3-methoxyisocoumarin (**10**), which is readily available from HA,[16] afforded **9a** in 28% yield

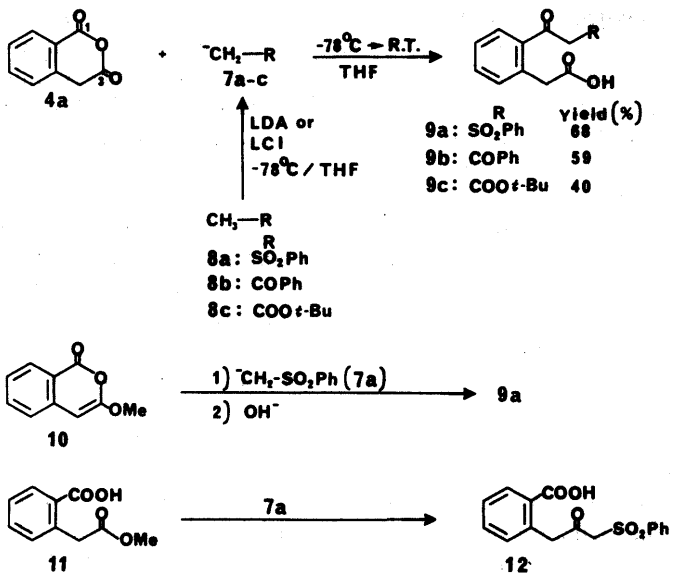

Chart 3

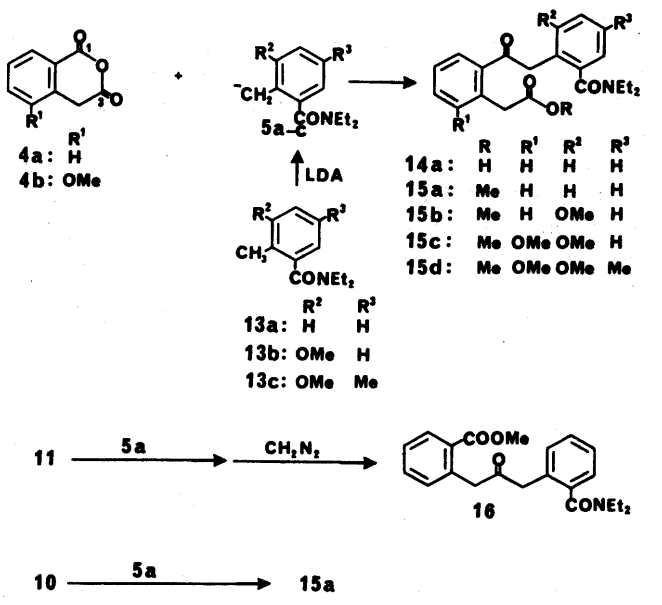

Chart 4

after hydrolysis. On the other hand, methyl 2-carboxyphenylacetate (**11**),[17] which was prepared by application of the procedures of Hauser and Rhee[18] starting from *o*-toluic acid or by partial methanolysis of HA,[17] was treated with **7a** at −78 °C in THF to give 2-(ω-phenylsulfonylacetonyl)benzoic acid (**12**) in 90% yield. A characteristic difference between **9a** and **12** was observed in their proton nuclear magnetic resonance (^{1}H-NMR) spectra (see Experimental). From these observations and the selective syntheses of the two regioisomers, it was clear by analogy that the reaction of HA with **7a** had led regioselectively to 2-(ω-phenylsulfonylacetyl)phenylacetic acid (**9a**) as a result of nucleophilic attack at the C-1 carbonyl group of HA. The corresonding lithio species (**7b, c**), generated from **8b** and **8c** by using 2.0 eq of lithium *N*-isopropylcyclohexylamide (LCI) instead of LDA, were treated with HA in a similar manner to give **9b** and **9c** in 59% and 40% yields, respectively. These results suggest that 1.0 eq of carbanions (**7**) is consumed by proton abstraction from the acidic methylene in HA. To confirm this hypothesis, **4a** was treated with 1.0 eq of NaH at 0 °C in THF for 1 h followed by addition at −78 °C of 1.0 eq of lithio species **7a**, which was generated in another vessel from 1.0 eq of **8a** and 1.0 eq of LDA, to afford **9a** in 48% yield. Physical and spectra data of the condensation products (**9** and **12**) thus obtained are summarized under Experimental.

N,N-Diethyl-*o*-toluamide anions[5,18,19] were easily generated from the corresponding *o*-toluamides by the action of a strong base such as LDA or LCI at low temperature and reacted with a variety of electrophiles. The usefulness of toluamide anions has been demonstrated in convenient syntheses of many compounds, including natural products.[5,19] We have previously applied this approach for the general synthesis of isocoumarins, including natural products such as hydrangenol and phyllodulcin.[20] Our approach to WS-5995A involved the use of *o*-toluamide and HA as convergent building blocks in the A and CD precursors of WS-5995A (Chart 2), respectively.

Lithiation of *N,N*-diethyl-*o*-toluamide (**13a**) with LDA in THF under the standard conditions described for **8** resulted in the formation of *o*-toluamide anion (**5a**) as a burgundy red solution. Treatment with 1.0 eq of HA (**4a**) followed by standard work-up afforded the phenylacetic acid derivative (**14a**), which was not isolated but directly converted by treatment with diazomethane into the corresponding methyl ester (**15a**) in 86% overall yield (Chart 4). The structure of **15a** was again confirmed by synthesis and spectral comparison of two possible regioisomers using the methods described for **9** and **12** (see Experimental). Thus, the isomer, 1-(2-methoxycarbonylphenyl)-3-(2-*N,N*-diethylcarbamoylphenyl)acetone (**16**) was synthesized in 90% yield by the reaction of the half ester (**11**) with **5a** followed by esterification. On the other hand, the reaction of 3-methoxyisocoumarin (**10**) with **5a** directly afforded **15a**, 2-[ω-(2-*N,N*-diethylcarbamoylphenyl)acetyl]phenylacetic acid, in 56% yield (Chart 4). Therefore, it was established that **5a** attacked the C-1 carbonyl group in HA selectively.

Next, the reactions between some other *o*-toluamides (**13b, c**) and HAs (**4a, b**), which include suitably substituted derivatives for WS-5995A, were carreid out (Chart 4) and the results are summarized in Table I. The starting methoxy- or methyl-substituted materials (**4b**, **13b, c**), were all prepared by the directed lithiation strategy[5] of tertiary benzamides. For example, *N,N*-diethyl-2,5-dimethyl-3-methoxybenzamide (**13c**) was regioselectively prepared in 90% yield by lithiation of *N,N*-diethyl-3-methoxy-5-methylbenzamide under the standard conditions (*sec*-BuLi/TMDEA/−78 °C/THF) followed by treatment with methyl iodide. Synthesis of 5-methoxyhomophthalic anhydride (**4b**)[6e] was achieved in 5 steps and 27% overall yield from *N,N*-diethyl-*m*-anisamide using the procedure developed by Snieckus *et al.*[11] As shown in Table I, methoxy-substituted keto esters (**15b, c**) were synthesized in high yields starting from *N,N*-diethyl-3-methoxy-2-methylbenzamide (**13b**) with **4a** and **4b**, respectively (Table I, runs 3—6). The use of 2.0 eq of toluamides (**13**) and 2.2 eq of LDA as opposed to 0.8 and 1.1 eq of these reagents generally improved the yields of the keto esters (**15**) (Table I; compared runs 2, 4, 6, and 7 with runs 1, 3, and 5). The keto ester (**15d**), the key

TABLE I. Reaction of *o*-Toluamides (**13**) with Homophthalic Anhydrides (**4**)

Run	HA (4)	Toluamide (13)	Molar ratio 4:13:LDA	Keto-ester 15	Yield (%)
1	**4a**	**13a**	1:0.8:1.1	**15a**	53
2	**4a**	**13a**	1:2:2.2	**15a**	86
3	**4a**	**13b**	1:0.8:1.2	**15b**	52
4	**4a**	**13b**	1:2:2.2	**15b**	93
5	**4b**	**13b**	1:0.8:1.2	**15c**	28
6	**4b**	**13b**	1:2:2.2	**15c**	61
7	**4b**	**13c**	1:2:2.2	**15d**	80

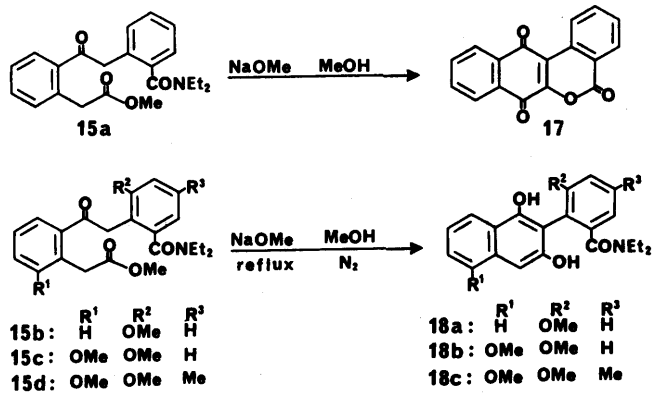

Chart 5

intermediate for the construction of WS-5995A, was synthesized by reaction of **13c** with **4b** in 80% yield (Table I; run 7).

Next, intramolecular cyclization of **15** for construction of the C ring of WS-5995A was examined (Chart 5). The synthesis of aromatic compounds *via* polyketides[21] has been extensively studied as biogenetically modeled routes. Recently, various polycyclic aromatic quinones have been synthesized *via* intramolecular condensation of polyketides in the presence of calcium acetate under mild conditions.[21b,22] However, intramolecular cyclization of **15a** with calcium acetate did not lead to the expected cyclized compound (**18**) and the starting **15a** was completely recovered. When a methanol solution of **15a** was refluxed with 4.0 eq of NaOMe for 18 h under a nitrogen atmosphere, 5*H*-benzo[*d*]naphtho[2,3-*b*]pyran-5,7,12-trione (**17**) was isolated in 10% yield along with unidentified products after standard work-up and chromatographic purification. The formation of **17**, a known compound,[4,12c] is presumably the result of cyclization and subsequent oxidation during work-up. When a methanolic solution of **15a** and 4.0 eq of NaOMe was refluxed without protection from atmospheric oxygen, compound **17** was obtained in 70% yield. On the other hand, cyclization of the methoxy- and methyl-substituted compounds **15b**, **c**, and **d** under anaerobic conditions (4.0 eq of NaOMe/MeOH/refluxed for 18 h/nitrogen atmosphere) gave the desired 2-aryl-1,3-naphthalenediols (**18a**—**c**) in moderate to high yield. The lack of further cyclization of the 2-aryl-1,3-naphthalenediols may be attributable to the steric effect of two *ortho* substituents on the benzene ring, disturbing the coplanarity of the naphthalene and benzene rings.

The conversion of **18** into the corresponding 2-aryl-3-hydroxy-1,4-naphthoquinones (**6a**—**c**) was successfully achieved in high yields by simple aeration of an aqueous alkaline solution[23] of **18** (Chart 6). Compounds **6a**—**c** thus obtained were hydrolyzed in refluxing 15% $HClO_4$ solution[11] to give the corresponding acids (**19a**—**c**) which, without further purification, were treated with trifluoroacetic anhydride (TFAA) in THF to afford the substituted 5*H*-benzo[*d*]naphtho[2,3-*b*]pyran-5,7,12-triones (**20a**—**c**) in high yields. Among the benzonaphthopyrans (**20**) thus synthesized, **20c**, the methyl ether of WS-5995A, was obtained in 60% overall yield from **18c**. These structures were confirmed on the basis of elemental analyses, ultraviolet (UV), infrared (IR), ^{1}H-NMR, and mass spectral data.

Demethylation of **20c** using 6.0 eq of boron tribromide (BBr_3) in dichloromethane at −78 °C gave the completely demethylated product **20d** (mp 189—193 °C) in 87% yield. The structure of **20d** was assigned by comparison of data for the product with the reported melting point (mp 190—192 °C)[2b] and spectral data.[2b] When 3.0 eq of BBr_3 was used under similar conditions, the mono methyl compound **20e** (mp 284—286 °C) was obtained in 33% yield accompanied with unreacted starting material **20c** (5% recovery yield) and **20d** (54%). WS-5995A was not detected under these conditions. Finally, when compound **20c** was treated with LiI[24] in refluxing dimethylformamide (DMF), the desired WS-5995A (**1**, mp 289—291 °C) was obtained in 59% yield accompanied with the isomer **20e** (33% yield). Synthetic WS-5995A thus obtained was shown to be identical with an authentic sample[2] on the basis of melting point, and spectroscopic (^{1}H-NMR, IR, and UV) and thin-layer chromatographic (TLC) comparisons.

In conclusion, we have shown that carbanion nucleo-

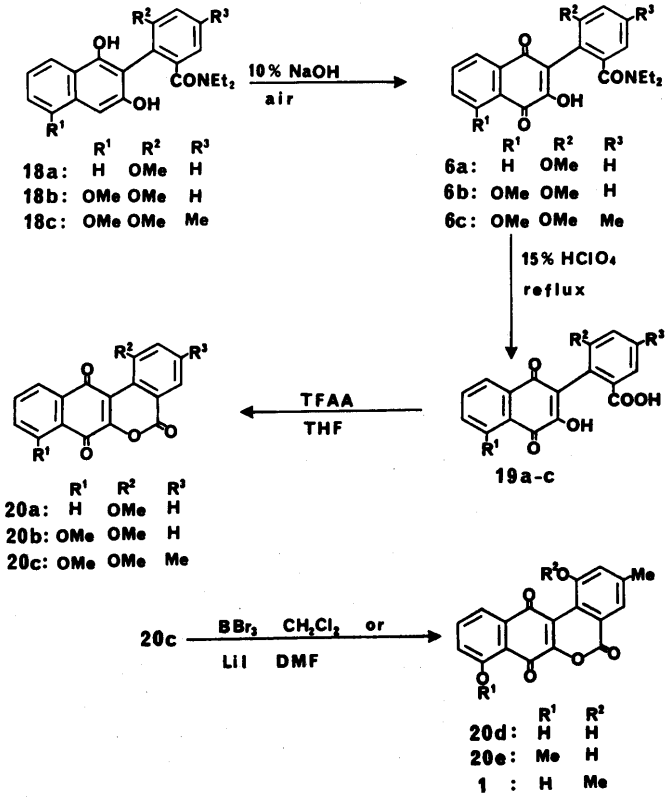

Chart 6

philes undergo regioselective reaction with homophthalic anhydride at the C-1 carbonyl group to give 2-(ω-substituted acetyl)phenylacetic acid derivatives. This regioselective reaction has been successfully applied to a total synthesis of the anticoccidial antibiotic WS-5995A.

Experimental

All melting points are uncorrected. The IR spectra were obtained in KBr disk using a JASCO 810 spectrophotometer. The UV spectra were recorded in 95% ethanol on a Hitachi 323 spectrophotometer. The ^{1}H-NMR spectra were obtained with JEOL FX 90Q, JEOL JNM-PMX 60, and Hitachi R-600 spectrometers using $CDCl_3$ as a solvent and tetramethylsilane as an internal reference. The mass spectra (MS) were determined on a JEOL JMX-DX 303 mass spectrometer. Elemental analyses were performed at the microanalytical laboratory of the Center for Instrumental Analysis in Nagasaki University. All solvents used for lithiation reaction were freshly distilled from sodium benzophenone ketyl before use. Chromatography was carried out by flash chromatography on a column of Kieselgel 60 (230—400 mesh).

Reaction of HA (4a) with Active Methyl Compounds (8a—c); General Procedure for the Syntheses of Phenylacetic Acid Derivatives (9a—c) The following procedures for the synthesis of phenylacetic acid derivative (**9a**) using HA are representative; the other phenylacetic acids (**9b**, **c**) were obtained similarly.

2-(ω-Phenylsulfonylacetyl)phenylacetic Acid (**9a**): i) Using HA (**4a**): Under a nitrogen atmosphere, a hexane solution of *n*-BuLi (1.20 M, 12.30 ml, 14.76 mmol) was injected into a stirred solution of diisopropylamine (2.07 ml, 14.76 mmol) in THF (30 ml) at 0 °C. The mixture was stirred for 30 min at the same temperature and then a solution of methylphenylsulfone (**8a**, 1.90 g, 12.30 mmol) in THF (20 ml) was added. To the resulting solution of **7a**, a solution of HA (**4a**, 1.00 g, 6.20 mmol) in THF (20 ml) was added at −78 °C. Then the dry ice–acetone bath was removed, and the mixture was allowed to warm to room temperature over 8 h. The reaction mixture was quenched with saturated NH_4Cl solution and evaporated. The residue was basified with 10% NaOH and extracted with ether. The aqueous solution was acidified with 10% HCl and extracted with ether. The ether layer was dried over Na_2SO_4 and evaporated to dryness. The residue was purified by recrystallization (CH_2Cl_2) to give **9a** (1.34 g, 68%), mp 183 °C. IR cm^{-1}: 3070 (OH), 1717 (C=O), 1685 (C=O). UV nm (log ε); 258 (3.94), 264 (sh, 3.90), 274 (sh, 3.76), 283 (sh, 3.67). ^{1}H-NMR δ: 3.66 (2H, s), 5.19 (2H, s), 7.25—7.73 (6H, m), 7.81—7.97 (3H, m), 12.01 (1H, br s). MS *m/z*: 318 (M^+). *Anal.* Calcd for $C_{16}H_{14}O_5S$: C, 60.38; H, 4.43; S, 10.05. Found: C, 60.11; H, 4.49; S, 9.95.

ii) Using 3-Methoxyisocoumarin (**10**): A solution of 3-methoxyisocoumarin (**10**, 0.89 g, 5.06 mmol) in THF (20 ml) was injected at −78 °C, under a nitrogen atmosphere, into a solution of lithiated methylphenylsulfone (**7a**), which was prepared in the same manner as described above from LDA (5.57 mmol) and **8a** (0.79 g, 5.06 mmol) in THF (50 ml). The reaction mixture was allowed to warm to room temperature and stirred for 12 h. Standard work-up according to the above description for the reaction of **4a** and **8a** gave the methyl ester which, without purification, was hydrolyzed with 20% NaOH solution (50 ml) on a steam bath for 30 min. After cooling, the solution was acidified with 10% HCl and extracted with ether. The extract was dried (Na_2SO_4) and evaporated to give a crude oil. This oil was chromatographed ($CHCl_3$) to give **9a** (0.43 g, 27%).

2-(ω-Benzoylacetyl)phenylacetic Acid (**9b**): This compound was prepared in 59% yield (1.03 g) starting from acetophenone (**8b**, 1.48 g, 12.30 mmol) and **4a** (1.00 g, 6.20 mmol), mp 89 °C (ether). IR cm^{-1}: 3100—2800 (OH), 1675 (C=O), 1603 (C=O). UV nm (log ε): 318 (5.00). ^{1}H-NMR δ: 4.24 (2H, s), 6.13 (1H, s), 7.26—8.18 (9H, m), 9.47 (1H, s), 15.62 (1H, s). MS *m/z*: 282 (M^+). *Anal.* Calcd for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 72.23; H, 5.15.

2-(ω-*tert*-Butyloxycarbonylacetyl)phenylacetic Acid (**9c**): Compound **9c** was prepared in 40% yield (0.69 g) by the reaction of *tert*-butyl acetate (**8c**, 1.43 g, 12.30 mmol) with **4a** (1.00 g, 6.20 mmol) using LCI (prepared from 1.20 M *n*-BuLi in hexane, 12.30 ml, 14.76 mmol, and *N*-isopropylcyclohexylamine, 2.43 ml, 14.76 mmol), mp 124 °C (ether–hexane). IR cm^{-1}: 3425 (OH), 1735 (C=O), 1690 (C=O). UV nm (log ε): 231 (4.67), 276 (3.89). ^{1}H-NMR δ: 1.52 (9H, s), 2.99 (2H, s), 3.45 (2H, s), 5.31 (1H, br s), 7.18—7.60 (3H, m), 8.06—8.20 (1H, m). MS *m/z*: 278 (M^+). *Anal.* Calcd for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found: C, 64.62; H, 6.45.

Reaction of Methyl 2-Carboxyphenylacetate (11) with 8a; 2-(ω-Phenylsulfonylacetonyl)benzoic Acid (12) A solution of methyl 2-carboxyphenylacetate (**11**, 0.50 g, 2.58 mmol) in THF (20 ml) was injected into a solution of **7a** (5.06 mmol), which was prepared under similar conditions to those described above, at −78 °C. Then the reaction mixture was allowed to warm to room temperature and stirred for 12 h. Standard work-up afforded crude **12**, which was purified by recrystallization (ether) to give **12** (0.72 g, 90%), mp 142 °C. IR cm^{-1}: 3410 (OH), 1718 (C=O), 1678 (C=O). UV nm (log ε): 260 (3.34), 266 (3.38), 273 (3.36). ^{1}H-NMR δ: 4.22 (2H, s), 4.75 (2H, s), 7.13—6.16 (9H, m), 12.79 (1H, br s). MS *m/z*: 318 (M^+). *Anal.* Calcd for $C_{16}H_{14}O_5S$: C, 60.38; H, 4.43; S, 10.05. Found: C, 60.27; H, 4.51; S, 10.12.

Reaction of HA (4a) with *o*-Toluamides (13a—c); General Procedure for Methyl Phenylacetate Derivatives (15a—d) The following procedure for the methyl ester (**15a**) is representative; the other methyl phenylacetate derivatives (**15b—d**) were obtained similarly.

Methyl 2-[ω-(2-*N*,*N*-Diethylcarbamoylphenyl)acetyl]phenylacetate (**15a**): i) Using HA: A solution of **4a** (1.02 g, 6.30 mmol) in THF (10 ml) was injected at −78 °C into a stirred THF solution (50 ml) of the lithiated *N*,*N*-diethyl-*o*-toluamide (**5a**, 5.20 mmol), prepared from **13a** (1.00 g, 5.20 mmol) with LDA (5.24 mmol) at −78 °C under a nitrogen atmosphere, and then the dry ice–acetone bath was removed. The reaction mixture was stirred overnight at room temperature and standard work-up as described above gave crude phenylacetic acid (**14a**), which without purification, was used for esterification. A solution of **14a** in ether was added to dry ethereal diazomethane solution, and the mixture was left overnight in a refrigerator. The ether was removed to give a crude oil. This oil was purified by chromatography (benzene) and recrystallization (ether) to give **15a** (1.62 g, 86%) (Table I, run 2), mp 77 °C. IR cm^{-1}: 1725 (C=O), 1682 (C=O), 1608 (C=O). UV nm (log ε): 243 (4.15), 282 (sh, 3.13). ^{1}H-NMR δ: 1.07 (3H, t, *J*=7.0 Hz), 1.09 (3H, t, *J*=7.3 Hz), 3.16 (2H, q, *J*=7.0 Hz), 3.48 (2H, q, *J*=7.3 Hz), 3.64 (3H, s), 3.89 (2H, s), 4.40 (2H, s), 7.18—7.54 (7H, m), 7.86—7.97 (1H, m). MS *m/z*: 367 (M^+). *Anal.* Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 72.04; H, 6.93; N, 3.78.

ii) Using 3-Methoxyisocoumarin (**10**): A solution of **10** (1.00 g, 5.80 mmol) in THF (20 ml) was injected into a solution of **5a** in THF (50 ml), which was prepared from LDA (5.80 mmol) and *N*,*N*-diethyl-*o*-toluamide (**13a**, 1.00 g, 4.83 mmol), at −78 °C. Then the reaction mixture was allowed to warm to room temperature and stirred overnight at the same temperature. Standard work-up gave crude **15a**. Chromatography (benzene) and recrystallization (ether) gave **15a** (0.99 g, 56%), mp 77 °C.

Methyl 2-[ω-(2-*N*,*N*-Diethylcarbamoyl-6-methoxyphenyl)acetyl]phenylacetate (**15b**): This compound was prepared in 93% yield (2.29 g) from **4a** (1.00 g, 6.20 mmol) and **13b** (2.74 g, 12.40 mmol) using LDA (13.64 mmol), mp 114 °C (ether) (Table I, run 4). IR cm^{-1}: 1720 (C=O), 1678 (C=O), 1620 (C=O). UV nm (log ε): 241 (3.82), 282 (3.31). ^{1}H-NMR δ: 1.04 (3H, t, *J*=7.0 Hz), 1.12 (3H, t, *J*=7.0 Hz), 3.46 (2H, q, *J*=7.0 Hz), 3.65 (2H, q, *J*=7.0 Hz), 3.63 (3H, s), 3.74 (3H, s), 3.86 (2H, s), 4.31 (2H, s), 6.78—6.90 (2H, m), 7.18—7.48 (4H, m), 7.91—8.01 (1H, m). MS *m/z*: 397 (M^+). *Anal.* Calcd for $C_{23}H_{27}NO_5$: C, 69.50; H, 6.85; N, 3.52. Found: 69.57; H, 6.92; N, 3.50.

Methyl 2-[ω-(2-*N*,*N*-Diethylcarbamoyl-6-methoxyphenyl)acetyl]-6-methoxyphenylacetate (**15c**): This compound was prepared from **4b** (1.00 g, 5.21 mmol) and **13b** (2.30 g, 10.42 mmol) using LDA (11.46 mmol). Recrystallization from ether gave **15c** (1.36 g, 61%), mp 93 °C (Table I, run 6). IR cm^{-1}: 1740 (C=O), 1690 (C=O), 1625 (C=O). UV nm (log ε): 245 (3.88), 283 (3.63). ^{1}H-NMR δ: 1.04 (3H, t, *J*=7.2 Hz), 1.14 (3H, t, *J*=7.2 Hz), 3.22 (2H, q, *J*=7.2 Hz), 3.49 (2H, q, *J*=7.2 Hz), 3.62 (3H, s), 3.73 (3H, s), 3.79 (3H, s), 3.88 (2H, s), 4.26 (2H, s), 6.77—7.44 (6H, m). MS *m/z*: 427 (M^+). *Anal.* Calcd for $C_{24}H_{29}NO_6$: C, 67.43; H, 6.84; N, 3.28. Found: C, 67.49; H, 6.88; N, 3.50.

Methyl 2-[ω-(2-*N*,*N*-Diethylcarbamoyl-4-methyl-6-methoxyphenyl)-acetyl]-6-methoxyphenylacetate (**15d**): This compound was prepared from **4b** (1.00 g, 5.21 mmol) and **13c** (2.45 g, 10.42 mmol) using LDA (11.46 mmol). Recrystallization from ether gave pure **15d** (1.84 g, 80%) (Table I, run 7), mp 89 °C. IR cm^{-1}: 1740 (C=O), 1640 (C=O), 1628 (C=O). UV nm (log ε): 248 (3.93), 285 (3.67). ^{1}H-NMR δ: 1.05 (3H, t, *J*=7.0 Hz), 1.15 (3H, t, *J*=7.0 Hz), 2.34 (3H, s), 3.23 (2H, q, *J*=7.0 Hz), 3.63 (3H, s), 3.69 (2H, q, *J*=7.0 Hz), 3.73 (3H, s), 3.81 (3H, s), 3.88 (2H, s), 4.19 (2H, s), 6.67 (2H, s), 7.03—7.43 (3H, m). MS *m/z*: 441 (M^+). *Anal.* Calcd for $C_{25}H_{31}NO_6$: C, 68.00; H, 7.08; N, 3.17. Found: C, 68.16; H, 7.05; N, 3.18.

1-(2-Methoxycarbonylphenyl)-3-(2-*N*,*N*-diethylcarbamoylphenyl)acetone (16) A solution of **11** (0.50 g, 2.58 mmol) in THF (20 ml) was injected at −78 °C, under a nitrogen atmosphere, into a solution of **5a**, prepared from LDA (6.19 mmol) and **13a** (0.98 g, 5.15 mmol) in THF (50 ml). The reaction mixture was allowed to warm to room temperature and stirred for 8 h. After standard work-up, the crude acid was used for esterification. An

ether solution of the acid was treated with diazomethane and then the mixture was left overnight in a refrigerator. Ether was removed to afford a crude oil. This oil was chromatographed (benzene) to give **16** as a colorless viscous oil (0.90 g, 95%). IR cm^{-1}: 1715 (C=O), 1710 (C=O), 1620 (C=O). UV nm (log ε): 241 (sh, 3.98), 268 (3.40), 277 (3.40). ^{1}H-NMR δ: 1.03 (3H, t, J=7.0 Hz), 1.23 (3H, t, J=7.0 Hz), 3.14 (2H, q, J=7.0 Hz), 3.53 (2H, q, J=7.0 Hz), 3.82 (3H, s), 3.96 (2H, s), 4.13 (2H, s), 7.10—7.54 (7H, m), 7.94—8.04 (1H, m). MS *m/z*: 367 (M^+). *Anal.* Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.73; H, 6.88; N, 3.86.

5*H*-Benzo[*d*]naphtho[2,3-*b*]pyran-5,7,12-trione (17) A solution of **15a** (0.30 g, 0.82 mmol) in absolute MeOH (20 ml) was added to a solution of NaOMe (2.46 mmol) in MeOH (40 ml), and the reaction mixture was refluxed for 4 h. After cooling of the reaction mixture, crushed ice and 10% HCl were added and the MeOH was removed under reduced pressure. The residue was extracted with CH_2Cl_2, and the extract was dried over Na_2SO_4 and evaporated. The residue was chromatographed (benzene : AcOEt = 4 : 1) and recrystallized from $CHCl_3$ to give **17** as an orange powder (0.16 g, 70%), mp 257 °C (lit.[4] mp 253 °C and lit.[12c] mp 252 °C). IR cm^{-1}: 1750 (C=O), 1678 (C=O). UV nm (log ε): 227 (4.64), 253 (4.45), 261 (4.44), 282 (sh, 4.42), 291 (4.26), 328 (3.87), 386 (3.51). ^{1}H-NMR δ: 7.64—8.49 (7H, m), 9.26—9.36 (1H, m). MS *m/z*: 276 (M^+). *Anal.* Calcd for $C_{17}H_8O_4$: C, 73.68; H, 2.94. Found: C, 73.65; H, 2.96.

Reaction of 15 with NaOMe; General Procedure for the Syntheses of 2-Phenyl-1,3-naphthalenediols (18a—c) The following procedure for 2-phenyl-1,3-naphthalenediol (**18c**) is representative; the other 2-phenyl-1,3-naphthalenediols (**18a, b**) were obtained similarly.

2-(2-*N*,*N*-Diethylcarbamoyl-4-methyl-6-methoxyphenyl)-5-methoxy-1,3-naphthalenediol (**18c**): An MeOH (10 ml) solution of **15d** (1.00 g, 2.27 mmol) was added to a stirred solution of NaOMe (9.07 mmol) in MeOH (50 ml) under a nitrogen atmosphere. The reaction mixture was refluxed for 18 h. After cooling of the reaction mixture, crushed ice was added, the whole was acidified with 10% HCl, and the MeOH was evaporated off. The aqueous solution was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and evaporated to give a residue. The crude product was purified by chromatography ($CHCl_3$) and recrystallization (ether) to afford **18c** as a white powder (0.70 g, 75%), mp 137 °C. IR cm^{-1}: 3375 (OH), 1625 (C=O). UV nm (log ε): 234 (4.11), 289 (3.51), 302 (3.33). ^{1}H-NMR δ: 0.72 (3H, t, J=7.2 Hz), 0.96 (3H, t, J=7.2 Hz), 2.45 (3H, s), 3.22 (2H, q, J=7.2 Hz), 3.24 (2H, q, J=7.2 Hz), 3.71 (3H, s), 3.97 (3H, s), 6.70—7.64 (6H, m), 7.84 (1H, s), 8.00 (1H, s). MS *m/z*: 409 (M^+). *Anal.* Calcd for $C_{24}H_{27}NO_5$: C, 70.40; H, 6.65; N, 3.42. Found: C, 70.28; H, 6.63; N, 3.41.

2-(2-*N*,*N*-Diethylcarbamoyl-6-methoxyphenyl)-1,3-naphthalenediol (**18a**): This compound was prepared in 89% yield (0.82 g) from **15b** (1.00 g, 2.52 mmol) and NaOMe (10.08 mmol) in the same manner as described above, mp 215 °C (ether). IR cm^{-1}: 3400 (OH), 1628 (C=O). UV nm (log ε): 236 (4.35), 285 (3.98). ^{1}H-NMR δ: 0.68 (3H, t, J=7.0 Hz), 0.98 (3H, t, J=7.0 Hz), 3.16 (2H, q, J=7.0 Hz), 3.21 (2H, q, J=7.0 Hz), 3.68 (3H, s), 6.80—7.58 (7H, m), 8.20 (1H, br s), 8.83 (1H, br s). MS *m/z*: 365 (M^+). *Anal.* Calcd for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34; N, 3.83. Found: C, 72.52; H, 6.37; N, 3.83.

2-(2-*N*,*N*-Diethylcarbamoyl-6-methoxyphenyl)-5-methoxy-1,3-naphthalenediol (**18b**): This compound was prepared in 63% yield (0.58 g) from **15c** (1.00 g, 2.34 mmol) and NaOMe (9.36 mmol), mp 213 °C (ether). IR cm^{-1}: 3340 (OH), 1625 (C=O). UV nm (log ε): 234 (4.73), 289 (4.15), 302 (3.99). ^{1}H-NMR δ: 0.67 (3H, t, J=7.2 Hz), 0.95 (3H, t, J=7.2 Hz), 3.22 (4H, q, J=7.2 Hz), 3.65 (3H, s), 3.91 (3H, s), 6.67—7.73 (7H, m), 8.02 (1H, s), 9.12 (1H, s). MS *m/z*: 395 (M^+). *Anal.* Calcd for $C_{23}H_{25}NO_5$: C, 69.85; H, 6.37; N, 3.54. Found: C, 69.76; H, 6.33; N, 3.39.

General Procedure for the Oxidation of Naphthalenediols (18) The following procedure for the oxidation of **18c** is representative; the other naphthalenediols (**18a, b**) were oxidized similarly.

2-(2-*N*,*N*-Diethylcarbamoyl-4-methyl-6-methoxyphenyl)-3-hydroxy-5-methoxy-1,4-naphthoquinone (**6c**): Air was bubbled through a mixture of **18c** (0.5 g, 1.22 mmol), 10% NaOH (10 ml), and EtOH (10 ml) at room temperature for 24 h. The EtOH was evaporated off to give an aqueous residue, which was acidified with 10% HCl and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The residue was recrystallized from ether–CH_2Cl_2 to afford **6c** as a yellow powder (0.42 g, 82%), mp 214 °C. IR cm^{-1}: 3320 (OH), 1660 (C=O), 1630 (C=O). UV nm (log ε): 280 (4.19), 382 (3.62). ^{1}H-NMR δ: 0.91 (3H, t, J=6.6 Hz), 1.07 (3H, t, J=7.2 Hz), 2.40 (3H, s), 3.25 (2H, q, J=7.2 Hz), 3.29 (2H, q, J=6.6 Hz), 3.76 (3H, s), 4.02 (3H, s), 6.80 (2H, s), 7.17—7.78 (4H, m). MS *m/z*: 423 (M^+). *Anal.* Calcd for $C_{24}H_{25}NO_6$: C, 68.07; H, 5.95; N, 3.31. Found: C, 67.75; H, 6.08; N, 3.26.

2-(2-*N*,*N*-Diethylcarbamoyl-6-methoxyphenyl)-3-hydroxy-1,4-naphthoquinone (**6a**): This compound was prepared from **18a** (0.50 g, 1.37 mmol) in the same manner as described for **6c**. Recrystallization from ether–hexane gave **6a** as a yellow powder (0.53 g, 98%), mp 217 °C. IR cm^{-1}: 3070 (OH), 1675 (C=O), 1640 (C=O). UV nm (log ε): 238 (sh, 3.94), 273 (4.06). ^{1}H-NMR δ: 0.90 (3H, t, J=6.0 Hz), 1.02 (3H, t, J=6.6 Hz), 3.13 (2H, q, J=6.6 Hz), 3.23 (2H, q, J=6.6 Hz), 3.73 (3H, s), 6.84—8.07 (8H, m). MS *m/z*: 379 (M^+). *Anal.* Calcd for $C_{22}H_{21}NO_5$: C, 69.64; H, 5.58; N, 3.69. Found: C, 69.52; H, 5.63; N, 3.35.

2-(2-*N*,*N*-Diethylcarbamoyl-6-methoxyphenyl)-3-hydroxy-5-methoxy-1,4-naphthoquinone (**6b**): This compound was prepared from **18b** (0.50 g, 1.27 mmol). Recrystallization from MeOH gave **6b** as a pure yellow powder (0.50 g, 97%), mp 212 °C. IR cm^{-1}: 3420 (OH), 1660 (C=O), 1630 (C=O). UV nm (log ε): 280 (3.88), 382 (3.62). ^{1}H-NMR δ: 0.90 (3H, t, J=6.0 Hz), 1.02 (3H, t, J=6.6 Hz), 3.08—3.50 (4H, m), 3.76 (3H, s), 4.01 (3H, s), 6.90—7.78 (7H, m). MS *m/z*: 409 (M^+). *Anal.* Calcd for $C_{23}H_{23}NO_6 \cdot 1/2H_2O$: C, 66.01; H, 5.78; N, 3.45. Found: C, 66.21; H, 5.62; N, 3.39.

General Procedure for the Syntheses of 5*H*-Benzo[*d*]naphtho[2,3-*b*]-pyran-5,7,12-triones (20a—c) The following procedure for the synthesis of benzonaphthopyran (**20c**) is representative; the other benzonaphthopyrans (**20a, b**) were obtained similarly.

1,8-Dimethoxy-3-methyl-5*H*-benzo[*d*]naphtho[2,3-*b*]pyran-5,7,12-trione (**20c**): A suspension of **6c** (0.50 g, 1.18 mmol) in 15% $HClO_4$ (50 ml) was refluxed for 8 h. After cooling, 10% NaOH was added to the mixture and the alkaline solution was extracted with ether. After acidification of the aqueous layer with 10% HCl, the aqueous solution was extracted with CH_2Cl_2, and extract was dried over Na_2SO_4 and evaporated to dryness. The residue was chromatographed ($CHCl_3$: MeOH = 9 : 1) to give **19c** as a yellow power (0.41 g, 1.11 mmol), which was used for the next cyclization without further purification. TFAA (1 ml) was added to a solution of **19c** (0.41 g, 1.11 mmol) in THF (5 ml) at room temperature, and the reaction mixture was stirred for 12 h. The reaction mixture was quenched with MeOH and evaporated to dryness. The residue was chromatographed ($CHCl_3$) and the product was recrystallized to afford **20c** as orange needles (0.31 g, 79%), mp 237 °C. IR cm^{-1}: 1750 (C=O), 1680 (C=O). UV nm (log ε): 241 (4.30), 276 (sh, 4.40), 293 (3.82), 350 (3.81), 408 (3.88). ^{1}H-NMR δ: 2.51 (3H, s), 3.95 (3H, s), 4.03 (3H, s), 7.18—7.32 (2H, m), 7.59—7.79 (3H, m). MS *m/z*: 350 (M^+). *Anal.* Calcd for $C_{20}H_{14}O_6 \cdot 1/2H_2O$: C, 66.84; H, 4.21. Found: C, 66.88; H, 4.13.

1-Methoxy-5*H*-benzo[*d*]naphtho[2,3-*b*]pyran-5,7,12-trione (**20a**): This was prepared from **6a** (0.5 g, 1.32 mmol) *via* **19a** (0.42 g, 99%) in the same manner as described for **20c**. Recrystallization from THF gave **20a** as orange yellow needles (0.34 g, 84%), mp 242 °C. IR cm^{-1}: 1750 (C=O), 1675 (C=O). UV nm (log ε): 233 (4.49), 244 (4.49), 274 (sh, 4.22), 292 (4.18), 404 (3.64). ^{1}H-NMR δ: 3.97 (3H, s), 7.31—8.08 (7H, m). MS *m/z*: 306 (M^+). *Anal.* Calcd for $C_{18}H_{10}O_5$: C, 70.59; H, 3.29. Found: C, 70.18; H, 3.57.

1,8-Dimethoxy-5*H*-benzo[*d*]naphtho[2,3-*b*]pyran-5,7,12-trione (**20b**): This was prepared from **6b** (0.50 g, 1.22 mmol) *via* **19b** (0.41 g, 95%) in the same manner as described for the synthesis of **20c**. Recrystallization from THF gave **20b** as orange needles (0.31 g, 79%), mp 241 °C. IR cm^{-1}: 1740 (C=O), 1670 (C=O). UV nm (log ε): 236, 265 (sh), 273 (sh), 288, 313, 345, 400.*) ^{1}H-NMR δ: 3.95 (3H, s), 4.02 (3H, s), 7.18—8.03 (6H, m). MS *m/z*: 336 (M^+). *Anal.* Calcd for $C_{19}H_{12}O_6$: C, 67.85; H, 3.60. Found: C, 67.36; H, 3.86.*) sparing soluble (log ε could not be calculated).

Demethylation of 20c i) Using Excess BBr_3: A solution of **20c** (50 mg, 0.14 mmol) in dry CH_2Cl_2 (10 ml) was cooled to −78 °C under a nitrogen atmosphere. A solution of BBr_3 (1 ml) in CH_2Cl_2 (5 ml) was injected into the solution of **20c** at −78 °C. The reaction mixture was allowed to warm to room temperature, stirred for 1 h, and treated with 5% $NaHCO_3$. The organic layer was separated, dried over Na_2SO_4 and evaporated to dryness. The residue was purified by chromatography ($CHCl_3$) and recrystallization (MeOH) to afford **20d** as purple needles (40 mg, 80%).

1,8-Dihydroxy-3-methyl-5*H*-benzo[*d*]naphtho[2,3-*b*]pyran-5,7,12-trione (**20d**): mp 188—193 °C (lit.[2b] mp 190—192 °C). IR cm^{-1}: 3500—3300 (OH), 1760 (C=O), 1640 (C=O). UV (THF) nm (log ε): 241 (4.15), 246 (4.15), 322 (3.69), 445 (2.94). ^{1}H-NMR δ: 2.47 (3H, s), 7.01—7.43 (2H, m), 7.61—7.91 (3H, m), 11.65 (1H, s). MS *m/z*: 322 (M^+).

ii) Using Three Equivalents of BBr_3: This reaction was carried out with **19c** (220 mg, 0.63 mmol) and BBr_3 (0.18 ml, 1.89 mmol) according to the method as described above. The crude products were chromatographed ($CHCl_3$) to give **20d** (110 mg, 54%) and **20e** (70 mg, 33%).

1-Hydroxy-8-methoxy-3-methyl-5*H*-benzo[*d*]naphtho[2,3-*b*]pyran-5,7,12-trione (**20e**): mp 284—286 °C (THF). IR cm^{-1}: 3340 (OH), 1730 (C=O), 1650 (C=O). UV (THF) nm (log ε): 244 (3.93), 277 (3.67), 304 (sh,

3.44), 341 (3.36), 416 (3.21). ^{1}H-NMR δ: 2.45 (3H, s), 4.06 (3H, s), 7.25—7.45 (2H, m), 7.68—7.92 (2H, m), 12.03 (1H, s). MS *m/z*: 336 (M^+). *Anal.* Calcd for $C_{19}H_{12}O_6 \cdot 1/2H_2O$: C, 66.09; H, 3.80. Found: C, 66.14; H, 3.96.

iii) Using Lithium Iodide: A mixture of anhydrous LiI (36 mg, 0.274 mmol) and **20c** (80 mg, 0.228 mmol) in DMF (1 ml) was refluxed for 5 h. After cooling, DMF was removed under reduced pressure to give the residue, which was purified by chromatography ($CHCl_3$) to afford **20e** (25 mg, 33%) and **1** (45 mg, 59%).

8-Hydroxy-1-methoxy-3-methyl-5*H*-benzo[*d*]naphtho[2,3-*b*]pyran-5,7,12-trione (**1**) (WS-5995A): 289—291 °C (lit.[1,2] mp 289—291 °C). IR cm^{-1}: 3425 (OH), 1750 (C=O), 1670 (C=O), 1640 (C=O). UV (THF) nm (log ε): 242 (4.39), 302 (3.92), 432 (3.76). ^{1}H-NMR δ: 2.53 (3H, s), 3.95 (3H, s), 7.19—7.30 (2H, m), 7.53—7.80 (3H, m), 11.61 (1H, s). MS *m/z*: 336 (M^+). This was identical with an authentic sample,[2] by comparison of spectral data and TLC behavior.

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