An Efficient Synthesis of *peri*-Hydroxy Aromatic Compounds via a Strong-Base-Induced [4+2] Cycloaddition of Homophthalic Anhydrides with Enolizable Enones

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An efficient synthesis of *peri*-hydroxy aromatic compounds has been accomplished via a strong-base-induced [4+2] cycloaddition of homophthalic anhydrides with α-sulfinyl-substituted derivatives of enolizable enones. The unsubstituted enones did not undergo an efficient [4+2] cycloaddition reaction with homophthalic anhydrides, presumably due to their enolization under the basic reaction conditions. The sulfinyl group not only promotes the cycloaddition reaction but also undergoes in situ elimination under the reaction conditions to afford the *peri*-hydroxy aromatic compounds in a single step. The application of this methodology for the synthesis of a key intermediate of antitumor antibiotic fredericamycin A is described. PM3 calculations of various 2-substituted cyclopentenones as well as the mechanism of the cycloaddition are also discussed.

Introduction

In the past two decades, considerable effort has been devoted to the synthesis of biologically important polycyclic *peri*-hydroxy aromatic compounds such as the anthracyclines,[1] fredericamycin A,[2] granaticin,[3] bostrycin,[4] olivin,[5] and other related polycyclic antibiotics (Figure 1). The available methods for the construction of the key *peri*-hydroxy aromatic frameworks include (a) reaction of phthalide[6] or substituted phthalides[3,5,7] with enones followed by cyclization and aromatization; (b) condensation of orsellinate with enones;[8] (c) benzannulation of Fischer chromium carbene complexes with functionalized alkynes;[2,9] (d) [4+2] cycloaddition of appropriate ketene silyl acetals to naphthoquinone derivatives;[10] (e) tandem Claisen rearrangement/Diels−Alder reaction of substituted aryl allyl ethers;[11] (f) construction from tetralone derivatives;[12] (g) Reformatsky reaction of isocoumarin or naphthopyran derivatives;[13] and (h) the strong-base-induced [4+2] cycloaddition reaction of homophthalic anhydrides to dienophiles.[14] Among these methods, the last one, viz. the strong-base-induced [4+2] cycloaddition of homophthalic anhydrides to dienophiles, is perhaps most general and efficient as well as having readily available starting materials.[14] Another advantage is that the *peri*-hydroxy functional group is directly obtained in a single step. The applicability of this methodology has already been realized in the total synthesis of a variety of natural products such as the anthracyclines,[1c,15] galtamycinone,[16] and dynemicin A.[17] Despite these successful applications, this methodology

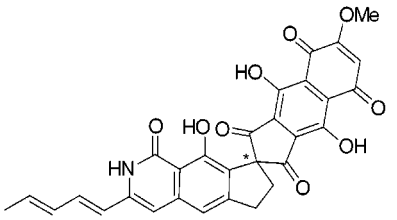

Figure 1.

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Scheme 1

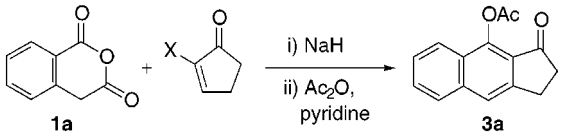


Table 1. Reaction of Homophthalic Anhydride 1a with Substituted Cyclopentenone in the Presence of NaH under Various Reaction Conditions

entry	X	reaction conditions	**3a** (%)[a]
1	Br	THF, rt, 6 h, then reflux 22 h	11
2	Br	1,4-dioxane, reflux, 7 h	7
3	S(O)Ph	THF, rt, 25 h	20
4	S(O)Ph	THF, reflux, 15 min	41
5	S(O)Ph	1,4-dioxane, reflux, 20 min	62
6	S(O)Ph	1,2-diethoxyethane, reflux, 20 min	45
7	S(O)-C_6H_4-*p*-NO_2	THF, reflux, 7 h	9
8	SO_2Ph	THF, rt, 1 h	–
9	H	1,4-dioxane, reflux, 20 min	–

[a] Isolated yields after column chromatography.

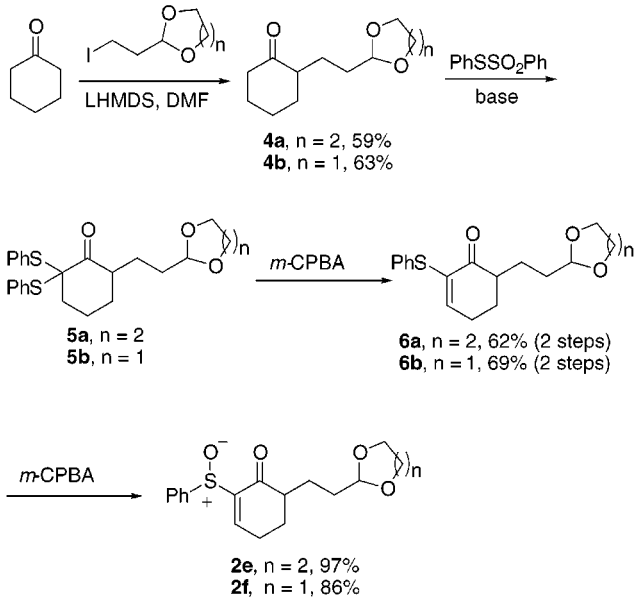
was not found to be efficient for enolizable enones such as 2-cyclohexenone or its β-substituted deriatives, except in some cases where the yields were low.[18] It is likely due to extensive enolization of the dienophile under the basic reaction conditions, which in turn might decrease the dienophile's reactivity.

Recently, we have briefly communicated that an efficient [4+2] cycloaddition of homophthalic anhydride could be accomplished by introducing a sulfinyl group at the α-position of the enolizable enones.[19] In this article, we report a full acount of our findings in this area including its application to the synthesis of a key intermediate of antitumor antibiotic fredericamycin A.

Results and Discussion

The starting homophthalic anhydrides **1a**−**d** were prepared as per our previously reported procedures.[14,20] In line with our earlier research, NaH was used as a preferred base. To identify the best activating group, cyclopentenone derivatives substituted at the α-position with Br,[21] S(O)Ar,[22] and SO_2Ph[22] were individually treated with homophthalic anhydride **1a** in the presence of NaH under different reaction conditions (Scheme 1). The results summarized in Table 1 reveal that an efficient [4+2] cycloaddition of homophthalic anhydride could indeed be achieved in a practical yield, with 2-sulfinyl-substituted cyclopentenone derivative in refluxing dioxane in the presence of 1.1 equiv of NaH (entry 5). Reactions with other derivatives such as bromo- or sulfonyl-substituted or unsubstituted cyclopentenone were largely unsuccessful (entries 1, 2, 7−9).

Scheme 2



To establish the generality of this reaction, various sulfinyl-substituted enones **2a**−**f** were synthesized. Enones **2a**−**d** were prepared as per the literature procedures.[22,23] Enones **2e** and **2f**, possessing a side chain at the 6-position, were synthesized starting from cyclohexanone according to Scheme 2. Alkylation of cyclohexanone with the propylene glycol acetal of 3-iodopropanal[24] in the presence of LHMDS afforded the monoalkylated cyclohexanone **4a** in 59% yield. Double phenylsulfenylation of **4a** followed by oxidation with *m*-CPBA produced the substituted 2-phenylthiocyclohexenone **6a** in 62% yield from **4a**. Exposure of **6a** to another equivalent of *m*-CPBA furnished the enone **2e** in 97% yield. Using the same protocol, enone **2f** was prepared from cyclohexanone and the ethylene glycol acetal of 3-iodopropanal[24] in 37% overall yield (5 steps).

The strong-base-induced [4+2] cycloaddition reaction was found to be general for a range of substituted homophthalic anhydrides **1a**−**d** with different sulfinyl substituted cyclic enones **2a**−**c** as well as with acyclic enone **2d**, affording the respective products in 41−70% yield. Although the reaction times are longer with the acyclic enone **2d**, the desired products **3j**−**l** could be isolated in 41−49% yield. This is a rewarding result given the report that the cycloaddition reaction of homophthalic anhydride with methyl crotonate was unsuccessful.[18a] The reaction was also extended to the enone **2e**, bearing a side chain with an acetal group, as a model study in our efforts toward the synthesis of a key intermediate of the antitumor antibiotic fredericamycin A (Figure 1). The reaction proceeded smoothly in this case also, providing the respective *peri*-hydroxy aromatic compounds **3m**,**n** in 63% and 57% yield, respectively.

Synthesis of a Key Intermediate of Fredericamycin A. Encouraged by the success of the reaction in our model experiment, attention was focused on the synthesis of **12**, a key intermediate in the synthesis of fredericamycin A. The required hetero homophthalic anhydride

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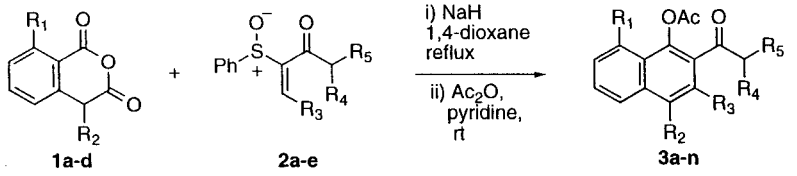
Scheme 3



1a-d + **2a-e** → **3a-n**

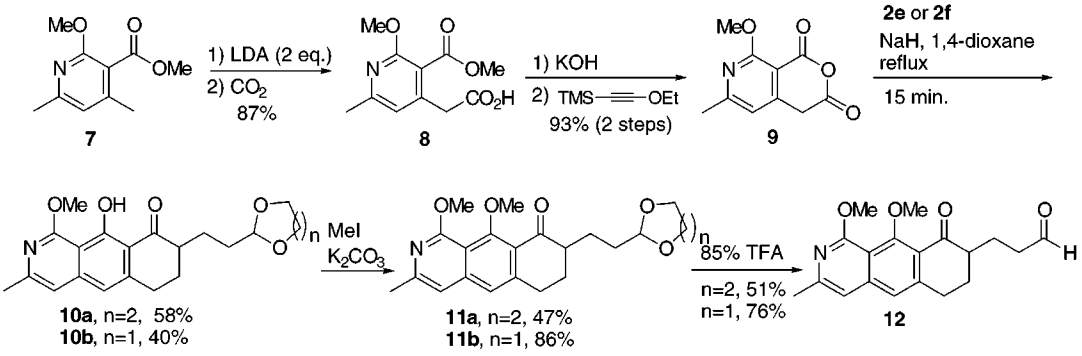
	R_1	R_2
1a	H	H
1b	H	SPh
1c	H	OMe
1d	OBn	H

	R_3 R_4	R_5
2a	$-CH_2-$	H
2b	$-(CH_2)_2-$	H
2c	$-(CH_2)_3-$	H
2d	Ph H	H
2e	$-(CH_2)_2-$	$-(CH_2)_2X$

	Yield (%)	R_1	R_2	R_3 R_4	R_5
3a	62	H	H	$-CH_2-$	H
3b	58	H	SPh	$-CH_2-$	H
3c	59	H	OMe	$-CH_2-$	H
3d	56	OBn	H	$-CH_2-$	H
3e	70	H	H	$-(CH_2)_2-$	H
3f	58	H	SPh	$-(CH_2)_2-$	H
3g	62	H	OMe	$-(CH_2)_2-$	H
3h	60	H	H	$-(CH_3)_3-$	H
3i	52	H	SPh	$-(CH_3)_3-$	H
3j	49	H	H	Ph H	H
3k	48	H	SPh	Ph H	H
3l	41	H	OMe	Ph H	H
3m	63	H	H	$-(CH_2)_2-$	$-(CH_2)_2X$
3n	57	H	SPh	$-(CH_2)_2-$	$-(CH_2)_2X$

Yield refers to isolated yields after column chromatography
X = 1,3-dioxan-2-yl

Scheme 4



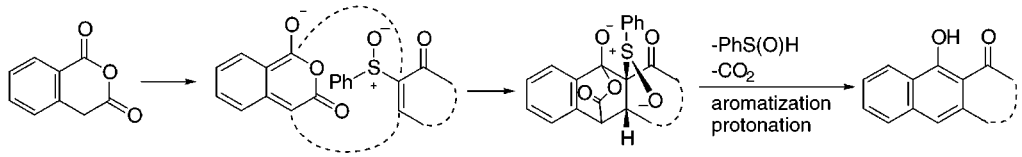
7 → **8** → **9**

10a, n=2, 58%
10b, n=1, 40%

11a, n=2, 47%
11b, n=1, 86%

12

Scheme 5



[4+2]cycloaddition
or
Michael-type addition

13

9 was synthesized starting from methyl 2-methoxy-4,6-dimethylnicotinate **7**.[25] Treatment of **7** with LDA and CO_2 afforded the monocarboxylic acid **8**. Hydrolysis of the ester group of **8** followed by cyclization using trimethylsilyl(ethoxy)acetylene[26] furnished the required hetero homophthalic anhydride **9**, which also underwent the [4+2] cycloaddition reaction with the enones **2e** and **2f**, in the presence of NaH, to afford the *peri*-hydroxy aromatic products **10a** and **10b** in 58% and 40% yield, respectively. Methylation of the hydroxyl groups of **10a** and **10b** followed by hydrolysis of the acetal moiety released the aldehyde **12** (Scheme 4), a key intermediate in the asymmetric total synthesis of fredericamycin A, reported recently from our group.[25] The overall yield of the reactions from **9** to **12** was found to be higher with the enone **2f** than that of enone **2e**.

Mechanism. The mechanism of this reaction can be considered to involve an initial [4+2] cycloaddition (Diels−Alder type) of the enolate (or the enol) or a base-catalyzed Michael addition type reaction of homophthalic anhydride to give the cycloadduct **13**, which then could undergo *syn*-elimination followed by decarboxylation[27] or vice versa to afford the final product. This reaction also took place in the absence of any base, but with a relatively low yield (45%). Clearly, the reaction was found to be accelerated in the presence of a base. It is relevant to mention here that oxyanion-accelerated *peri*-cyclic reactions have been reported in the literature,[28] and the present reaction can be considered as an example of such kind. Initial thermal- or base-induced decarboxylation

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Table 2. HOMO and LUMO Level Values of 2-substituted Cyclopentenones Using PM3 Calculation

	HOMO	LUMO
X = H	−10.440	−0.125
X = Cl	−9.611	−0.362
X = Br	−10.200	−0.406
X = S(O)Ph	−9.222	−0.648

prior to cycloaddition has been ruled out by the fact that refluxing homophthalic anhydride **1a** in dioxane under identical reaction conditions as above resulted in the recovery of **1a** in quantitative yield. Also refluxing **1a** with 1.1 equiv of NaH in dioxane followed by quenching with aqueous NH_4Cl solution afforded a mixture in which **1a** was found to be the major component.

The highlight of the reaction is the rapid *syn*-elimination of the phenylsulfinyl moiety under the reaction conditions, a unique feature of this functional group. In addition, PM3 calculations reveal that the LUMO level of the 2-sulfinylcyclopentenone is considerably lower than that of the corresponding unsubstituted or bromo-substituted derivatives[29] (Table 2). From these observations, it can be concluded that the low LUMO level and, more significantly, the rapid thermal *syn*-elimination of the phenylsulfinyl moiety are the driving forces for the success of the reaction.

In conclusion, we have accomplished an efficient strong-base-induced [4+2] cycloaddition of homophthalic anhydride to enolizable enones, by a simple modification at the enone moiety. A salient feature is that *peri*-hydroxy aromatic compounds were obtained in a single step. Synthesis of a key intermediate of the antitumor antibiotic fredericamycin A using this methodology demonstrates its synthetic potentiality. Further extension and synthetic utility of this methodology is currently under progress.

Experimental Section

General Considerations. All commercial reagents were used as such without purification. Wherever necessary, solvents were dried as per the standard procedures. Unless otherwise stated, all ^1H NMR measurements were carried out at 300 MHz and ^{13}C NMR at 75 MHz using TMS as the internal standard. Column chromatographic purifications were performed using silica gel with either 70−230 or 200−400 mesh size.

General Procedure for the [4+2] Cycloaddition Reaction of Homophthalic Anhydrides 1 with Enones 2. In a flame-dried two-necked flask, fitted with a reflux condenser under nitrogen atmosphere, was taken NaH (1.1 equiv), and dry dioxane was added to it. Homophthalic anhydride **1** (1 equiv) dissolved in dioxane was added dropwise through a cannula. The resulting slurry was stirred at room temperature for 30 min and then for 20 min each at 80 and 120 °C (bath temperature). Sulfinyl-substituted enone **2** (1 equiv) dissolved in dioxane was then injected through a cannula, and the reaction mixture was stirred at 120 °C for the specified time (see Table 2), cooled, quenched with aqueous NH_4Cl solution, and extracted with AcOEt. The organic layer was washed with aqueous NH_4Cl solution, then with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude reaction mixture was then treated with Ac_2O and pyridine and stirred at room temperature overnight. Purification by column chromatography (hexane/AcOEt, 4:1) afforded the *peri*-hydroxy aromatic compounds as their acetates **3**.

9-Acetoxybenz[*f*]indan-1-one (3a). Compound **3a** was obtained in 62% yield (74 mg) as a light brown solid by the reaction of homophthalic anhydride **1a** (81 mg, 0.5 mmol) with enone **2a** (103 mg, 0.5 mmol) in the presence of NaH (18.5 mg of 60% in paraffin oil, 0.55 mmol) in 5 mL of dioxane: mp 108 °C (CH_2Cl_2/hexane); IR (KBr) 1770, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.08 (1H, d, J = 8.5 Hz), 7.83 (1H, d, J = 8.5 Hz), 7.72 (1H, s), 7.61−7.48 (2H, m), 3.25 (2H, dd, J = 6.7, 6.0 Hz), 2.74 (2H, dd, J = 6.7, 6.0 Hz), 2.55 (3H, s); ^{13}C NMR ($CDCl_3$) δ 204.1, 168.9, 148.1, 144.1, 138.3, 129.0, 127.6, 126.3, 126.1, 124.1, 123.1, 122.3, 37.2, 25.0, 20.7. Anal. Calcd for $C_{15}H_{12}O_3$: C, 74.93; H, 5.15. Found: C, 74.99; H, 5.03.

9-Acetoxy-4-phenylthiobenz[*f*]indan-1-one (3b). Compound **3b** (81 mg, 58%) was obtained as a white solid by the reaction of homophthalic anhydride **1b** (108 mg, 0.4 mmol) with enone **2a** (82.4 mg, 0.4 mmol) in the presence of NaH (15 mg of 60% in paraffin oil, 0.44 mmol) in 5 mL of dioxane: mp 124−126 °C (CH_2Cl_2/hexane); IR (KBr) 1780, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.55 (1H, d, J = 8.0 Hz), 8.19 (1H, d, J = 8.0 Hz), 7.70−7.54 (2H, m), 7.20−6.98 (5H, m), 3.30−3.26 (2H, m), 2.77−2.59 (2H, m), 2.59 (3H, s); ^{13}C NMR ($CDCl_3$) δ 204.0, 168.6, 155.1, 145.7, 139.9, 136.6, 130.4, 129.1, 127.3, 126.9, 126.6, 126.0, 125.5, 124.5, 123.9, 123.7, 37.0, 26.0, 20.8; Anal. Calcd for $C_{21}H_{16}O_3S$: C, 72.39; H, 4.63; S, 9.20. Found: C, 72.45; H, 4.79; S, 9.07.

9-Acetoxy-4-methoxybenz[*f*]indan-1-one (3c). Compound **3c** was obtained in 59% yield (48 mg) as a pale yellow solid by the reaction of homophthalic anhydride **1c** (57.6 mg, 0.3 mmol) with enone **2a** (61.8 mg, 0.3 mmol) in the presence of NaH (11.2 mg of 60% in paraffin oil, 0.33 mmol) in 4 mL of dioxane: mp 106 °C (CH_2Cl_2/hexane); IR (KBr) 1770, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.17 (1H, d, J = 8.5 Hz), 8.08 (1H, d, J = 8.5 Hz), 7.64 (1H, m), 7.54 (1H, m), 4.04 (3H, s), 3.31 (2H, m), 2.77 (2H, m), 2.54 (3H, s); ^{13}C NMR ($CDCl_3$) δ 204.0, 169.2, 150.1, 139.8, 136.4, 132.2, 128.8, 127.5, 126.7, 124.7, 123.4, 122.0, 61.0, 37.1, 22.3, 20.7. Anal. Calcd. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 70.96; H, 5.28.

9-Acetoxy-8-benzyloxybenz[*f*]indan-1-one (3d). Compound **3d** was obtained as a light brown solid in 56% yield (78 mg) by the reaction of homophthalic anhydride **1d** (107.2 mg, 0.4 mmol) with enone **2a** (82.4 mg, 0.4 mmol) in the presence of NaH (15 mg of 60% in paraffin oil, 0.44 mmol) in 5 mL of dioxane: mp 202 °C (CH_2Cl_2/hexane); IR (KBr) 1760, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.68 (1H, s), 7.52−7.38 (7H, m), 6.90 (1H, m), 5.09 (2H, m), 3.22 (2H, m), 2.72 (2H, m), 1.78 (3H, s); ^{13}C NMR ($CDCl_3$) δ 204.0, 169.7, 157.4, 148.9, 145.5, 140.8, 136.0, 129.3, 129.0, 128.7, 128.5, 125.0, 122.5, 120.5, 118.6, 106.3, 71.1, 37.4, 24.5, 20.1. Anal. Calcd for $C_{22}H_{18}O_4$: C, 76.29; H, 5.24. Found: C, 76.03; H, 5.26.

10-Acetoxy-3,4-dihydroanthracen-1(2*H*)-one (3e). Compound **3e** was obtained as a white solid in 70% yield (88 mg) by the reaction of homophthalic anhydride **1a** (81 mg, 0.5 mmol) with enone **2b** (110 mg, 0.5 mmol) in the presence of NaH (18.5 mg of 60% in paraffin oil, 0.55 mmol) in 5 mL of dioxane: mp 146−148 °C (Ch_2Cl_2/hexane); IR (KBr) 1770, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.94 (1H, d, J = 8.5 Hz), 7.68 (1H, d, J = 8.5 Hz), 7.52−7.38 (3H, m), 3.04 (2H, t, J = 6.0), 2.64−2.60 (2H, dd, J = 6.7, 6.4 Hz), 2.47 (3H, s), 2.10−2.02 (2H, m); ^{13}C NMR ($CDCl_3$) δ 197.3, 169.6, 147.7, 139.7, 136.2, 129.1, 127.0, 126.5, 126.4, 124.5, 123.2, 120.8, 40.8, 30.7, 22.7, 21.1. Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.40; H, 5.65.

10-Acetoxy-5-phenylthio-3,4-dihydroanthracen-1(2*H*)-one (3f). Compound **3f** was obtained in 58% yield (84 mg) as a pale yellow solid by the reaction of homophthalic anhydride **1b** (108 mg, 0.4 mmol) with enone **2b** (88 mg, 0.4 mmol) in the presence of NaH (15 mg of 60% in paraffin oil, 0.44 mmol) in 4 mL of dioxane: mp 134−135 °C (CH_2Cl_2/hexane); IR (KBr)

(28) For recent reviews on oxy anion accelerated *peri*-cyclic reactions see: (a) Cope rearrangement: Paquette, L. A. *Tetrahedron* **1997**, *53*, 13971. (b) retro Diels−Alder reaction: Bunnage, M. E.; Nicolaou, K. C. *Chem. Eur. J.* **1997**, *3*, 187.

(29) PM3 calculations were done using the PM3 Hamiltonian in Spartan (ver. 3.1.2) program.

1780, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.60 (1H, d, J = 9.0 Hz); 8.12 (1H, d, J = 9.0 Hz), 7.66−6.93 (7H, m), 3.37 (2H, dd, J = 6.2, 5.8 Hz), 2.68 (2H, dd, J = 6.9, 6.2 Hz), 2.57 (3H, s); 2.11−2.07 (2H, m); ^{13}C NMR ($CDCl_3$) δ 197.4, 169.4, 149.3, 146.4, 138.6, 137.7, 130.4, 129.1, 127.2, 127.0, 126.6, 126.1, 125.2, 123.7, 121.9, 40.2, 29.9, 22.0, 21.2. Anal. Calcd for $C_{22}H_{18}O_3S$: C, 72.90; H, 5.01; S, 8.85. Found: C, 72.63; H, 5.09; S, 8.87.

10-Acetoxy-5-methoxy-3,4-dihydroanthracen-1(2*H*)-one (3g). Compound **3g** was obtained as white needles in 62% yield (53 mg) by the reaction of homophthalic anhydride **1c** (57.6 mg, 0.3 mmol) with enone **2b** (66 mg, 0.3 mmol) in the presence of NaH (11.2 mg of 60% in paraffin oil, 0.33 mmol) in 4 mL of dioxane: mp 127 °C (CH_2Cl_2/hexane); IR (KBr) 1770, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.10−8.02 (2H, m); 7.63 (1H, dd, J = 8.0, 7.0 Hz), 7.52 (1H, m), 3.91 (3H, s), 3.14 (2H, bs), 2.68 (2H, m), 2.54 (3H, s), 2.15−2.02 (2H, m); ^{13}C NMR ($CDCl_3$) δ 197.3, 169.8, 150.2, 143.9, 130.9, 130.5, 129.1, 127.2, 126.7, 123.6, 121.9, 121.1, 61.3, 40.6, 23.8, 22.1, 21.1. Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 71.67; H, 5.68.

11-Acetoxy-1-naphthosuberone (3h). Compound **3h** was obtained in 60% yield (65 mg) as a waxy white solid by the reaction of homophthalic anhydride **1a** (65 mg, 0.4 mmol) with enone **2c** (94 mg, 0.4 mmol) in the presence of NaH (15 mg of 60% in paraffin oil, 0.44 mmol) in 4 mL of dioxane: mp 76 °C (CH_2Cl_2/hexane); IR (KBr) 1767, 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.94−7.47 (5H, m), 2.93 (2H, dd, J = 6.5, 6.0 Hz), 2.68 (2H, dd, J = 6.5, 5.0 Hz), 2,40 (3H, s), 1.91−1.67 (4H, m); ^{13}C NMR ($CDCl_3$) δ 206.6, 169.6, 143.2, 135.3, 135.1, 129.8, 127.8, 127.2, 126.3, 125.8, 124.7, 122.3, 41.3, 32.5, 26.3, 21.4, 20.9. Anal. Calcd for $C_{15}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 75.85; H, 6.01.

11-Acetoxy-6-phenylthio-1-naphthosuberone (3i). Compound **3i** was obtained as a white solid in 52% yield (59 mg) by the reaction of homophthalic anhydride **1b** (81 mg, 0.3 mmol) with enone **2c** (70.2 mg, 0.3 mmol) in the presence of NaH (11.2 mg of 60% in paraffin oil, 0.33 mmol) in 4 mL of dioxane: mp 132 °C (CH_2Cl_2/hexane); IR (KBr) 1775, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.56 (1H, d J = 7.5 Hz), 8.02 (1H, d, J = 7.5), 7.60−7.51 (2H, m), 7.17−6.92 (5H, m), 3.31 (2H, bs), 2.66 (2H, bs), 2.43 (3H, s), 1.73 (4H, bs); ^{13}C NMR ($CDCl_3$) δ 206.4, 169.4, 144.4, 142.0, 138.1, 137.3, 130.4, 129.1, 128.9, 127.1, 126.9, 126.7, 125.9, 125.1, 124.6, 122.8, 40.6, 30.2, 25.2, 21.0, 20.4. Anal. Calcd for $C_{23}H_{20}O_3S$: C, 73.38; H, 5.35; S, 8.52. Found: C, 73.32; H, 5.44; S, 8.48.

1-Acetoxy-2-acetyl-3-phenylnaphthalene (3j). Compound **3j** was obtained as a colorless oil in 49% yield (90 mg) by the reaction of homophthalic anhydride **1a** (97.2 mg, 0.6 mmol) with acyclic enone **2d** (163 mg, 0.6 mmol) in the presence of NaH (23 mg of 60% in paraffin oil, 0.66 mmol) in 6 mL of dioxane: IR (KBr) 1770, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.91−7.87 (2H, m), 7.79 (1H, s), 7.59−7.42 (7H, m), 2.44 (3H, s), 1.97 (3H, s); ^{13}C NMR ($CDCl_3$) δ 203.1, 169.5, 142.9, 139.7, 136.6, 134.2, 131.4, 128.9, 128.8, 128.1, 128.0, 127.9, 127.2, 126.9, 125.9, 122.1, 31.4, 20.7; HRMS calcd for $C_{20}H_{16}O_3$ (M^+) 304.1099, found 304.1102.

1-Acetoxy-2-acetyl-3-phenyl-4-phenylthionaphthalene (3k). Compound **3k** was obtained by the reaction of homophthalic anhydride **1b** (108 mg, 0.4 mmol) with enone **2d** (108 mg, 0.4 mmol) in the presence of NaH (15 mg of 60% in paraffin oil, 0.44 mmol) in 5 mL of dioxane, as an oil in 48% yield (79 mg): IR (KBr) 1770, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.57 (1H, m), 7.94 (1H, m), 7.60 (2H, m), 7.35−7.21 (5H, m), 7.10−7.01 (3H, m), 6.84−6.81 (2H, m), 2.44 (3H, s), 1.86 (3H, s); ^{13}C NMR: δ 202.3, 169.1, 143.7, 142.9, 138.4, 138.2, 136.0, 133.3, 130.1, 129.0, 128.8, 128.1, 127.9, 127.64, 127.61, 127.2, 127.1, 126.7, 125.1, 122.5, 31.1, 20.8; HRMS calcd for $C_{26}H_{20}O_3S$ (M^+) 412.1133, found 412.1134.

1-Acetoxy-2-acetyl-4-methoxy-3-phenylnaphthalene (3l). Compound **3l** was obtained by the reaction of homophthalic anhydride **1c** (57.6 mg, 0.3 mmol) with enone **2d** (81 mg, 0.3 mmol) in the presence of NaH (11.2 mg of 60% in paraffin oil, 0.33 mmol) in 4 mL of dioxane, as an oil in 41% yield (36 mg): IR (KBr) 1765, 1700 cm^{-1}; ^1H NMR δ: 8.21 (1H, m), 7.86 (1H, m), 7.64−7.39 (7H, m), 3.49 (3H, s), 2.41 (3H, s), 1.87 (3H, s); ^{13}C NMR δ: 202.6, 169.6, 151.4, 138.5, 135.3, 132.8, 130.3, 129.2, 128.5, 128.0, 127.7, 127.5, 127.4, 127.1, 122.9, 122.3, 61.3, 31.3, 20.7; HRMS calcd for $C_{21}H_{18}O_4$ (M^+) 334.1205, found 334.1206.

2-[2-(1,3-Dioxan-2-yl)ethyl]cyclohexanone (4a). Under a nitrogen atmosphere, to a solution of cyclohexanone (1.7 mL, 16.4 mmol) in DMF (30 mL) was added LHMDS (1.0 M in THF, 17.0 mL, 17 mmol) at 0 °C. After being stirred for 30 min, a solution of 2-(2-iodoethyl)-1,3-dioxane (4.25 g, 17.6 mmol) in DMF (20 mL) was added slowly. The reaction mixture was stirred for 2.5 h, then quenched with aqueous NH_4Cl solution and extracted with Et_2O, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (hexane/AcOEt, 3:1) to give **4a** (2.04 g, 59%) as a colorless oil: IR (KBr) 1713, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.52 (1H, t, J = 5.0 Hz), 4.11−4.05 (2H, m), 3.79−3.30 (2H, m), 2.36−1.30 (15H, m); HRMS calcd for $C_{12}H_{20}O_3$ (M^+) 212.1412, found 212.1426.

6-[2-(1,3-Dioxan-2-yl)ethyl]-2,2-bisphenylthiocyclohexanone (5a). Under a nitrogen atmosphere, to a solution of **4a** (1.72 g, 8.09 mmol) in THF (20 mL) was added LHMDS (1.0 M in THF, 9.2 mL, 9.2 mmol) at −78 °C. After being stirred for 1 h, a solution of $PhSSO_2Ph$ (2.12 g, 8.47 mmol) in THF (10 mL) was added. The reaction mixture was allowed to warm to room temperature over a period of 2 h, then quenched with aqueous NH_4Cl solution and extracted with AcOEt. The extract was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (hexane/AcOEt, 5:1 to 2:1) to give monophenylthio product in 71% yield (1.84 g) as a colorless oil. A solution of this product (1.84 g, 5.73 mmol) in THF (12 mL) was added dropwise to a slurry of ^{t}BuOK (683 mg, 6.09 mmol) in THF (20 mL), at 0 °C, under a nitrogen atmosphere. The reaction mixture was stirred for 30 min, and a solution of $PhSSO_2Ph$ (1.44 g, 5.76 mmol) in THF (10 mL) was added. The reaction mixture was stirred for 2 h, quenched with saturated aqueous NH_4Cl solution, extracted with AcOEt, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography (hexane/AcOEt, 5:1) afforded **5a** as a white solid in 97% yield (2.39 g): mp 84−87 °C; IR (KBr) 1705, 1582 cm^{-1}; ^1H NMR ($CDCl_3$) (500 MHz) δ 7.65−7.60 (4H, m), 7.39−7.31 (6H, m), 4.42 (1H, dd, J = 5.5, 5.0 Hz), 4.09−4.05 (2H, m), 3.75−3.68 (2H, m), 3.26 (1H, ddt, J = 12.0, 6.0, 6.0 Hz), 2.22−2.00 (5H, m), 1.80−1.65 (2H, m), 1.47−1.23 (5H, m); HRMS calcd for $C_{24}H_{28}O_3S_2$ (M^+) 428.1480, found 428.1474.

6-[2-(1,3-Dioxan-2-yl)ethyl]-2-phenylthio-2-cyclohexen-1-one (6a). To a solution of **5a** (2.39 g, 5.57 mmol) in CH_2Cl_2 (50 mL) was added *m*-CPBA (80% purity, 1.2 g, 5.57 mmol) at −65 °C. After being stirred for 2.5 h, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ solution and extracted with CH_2Cl_2. The extract was washed with saturated aqueous $NaHCO_3$ solution, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (hexane/AcOEt, 3:1) to give **6a** (1.6 g, 88%) as a colorless oil: IR (KBr) 1680, 1674, 1582 cm^{-1}; ^1H NMR ($CDCl_3$) (500 MHz) δ 7.42−7.29 (5H, m), 6.41 (1H, dd, J = 5.0, 4.0 Hz), 4.54 (1H, dd, J = 6.0, 5.0 Hz), 4.10−4.06 (2H, m), 3.78−3.72 (2H, m), 2.45−2.31 (3H, m), 2.12−1.94 (3H, m), 1.81−1.49 (4H, m), 1.33 (1H, br d, J = 13.5 Hz); HRMS calcd for $C_{18}H_{22}O_3S$ (M^+) 318.1290, found 318.1293.

6-[2-(1,3-Dioxan-2-yl)ethyl]-2-phenylsulfinyl-2-cyclohexen-1-one (2e). To a solution of **6a** (1.5 g, 4.71 mmol) in CH_2Cl_2 (50 mL) was added *m*-CPBA (80% purity, 1.02 g, 4.71 mmol), at −50 °C. After being stirred at the same temperature for 1 h, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ solution and extracted with CH_2Cl_2. The extract was washed with saturated aqueous $NaHCO_3$ solution, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (hexane/AcOEt, 1:1 to 1:3) to give **2e** as colorless crystals: mp 76−77 °C (AcOEt/hexane); IR (KBr) 1675, 1610, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.73−7.64 (3H, m), 7.44−7.42 (3H, m), 4.49 (1/2H, t, J = 4.5 Hz), 4.39 (1/2H, t, J = 4.5 Hz), 4.07−4.00 (2H, m), 3.76−3.63 (2H, m), 2.77−1.28 (11H, m). Anal. Calcd for $C_{18}H_{22}O_4S$: C, 64.65; H, 6.63; S, 9.59. Found: C, 64.43; H, 6.46; S, 9.44.

10-Acetoxy-2-[2-(1,3-dioxan-2-yl)ethyl]-3,4-dihydroanthracen-1(2*H*)-one (3m). Compound **3m** was obtained as an oil in 63% yield (91 mg) by the reaction of homophthalic anhydride **1a** (65 mg, 0.4 mmol) with enone **2e** (134 mg, 0.4 mmol) in the presence of NaH (15 mg of 60% in paraffin oil, 0.44 mmol) in 4 mL of dioxane, following the general procedure described earlier: IR (KBr) 1770, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) (270 MHz) δ 7.98 (1H, d, J = 9.0 Hz), 7.74 (1H, d, J = 8.0 Hz), 7.57−7.43 (3H, m), 4.55 (1H, dd, J = 5.1, 4.7 Hz), 4.11−4.05 (2H, m), 3.80−3.69 (2H, m), 3.18−3.11 (2H, m), 2.53 (3H, s), 2.29−1.57 (8H, m), 1.34−1.25 (1H, m); ^{13}C NMR ($CDCl_3$) (67.5 MHz) δ 198.8, 169.4, 147.4, 139.2, 135.9, 128.8, 126.8, 126.3, 126.2, 124.3, 123.0, 121.0, 102.2, 66.8, 48.8, 32.5, 29.2, 27.7, 25.8, 24.3, 21.2; HRMS calcd for $C_{22}H_{24}O_5$ (M^+) 368.1624, found 368.1619.

10-Acetoxy-2-[2-(1,3-dioxan-2-yl)ethyl]-5-phenylthio-3,4-dihydroanthracen-1(2*H*)-one (3n). Compound **3n** was obtained by the reaction of homophthalic anhydride **1b** (108 mg, 0.4 mmol) with enone **2e** (134 mg, 0.4 mmol) in the presence of NaH (15 mg of 60% in paraffin oil, 0.44 mmol) in 57% yield (108 mg) as a waxy white solid, following the general procedure described earlier: mp 91−92 °C (CH_2Cl_2/hexane); IR (KBr) 1780, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.57 (1H, d, J = 8.0 Hz), 8.08 (1H, J = 8.0 Hz), 7.63−7.51 (2H, m), 7.18−6.92 (5H, m), 4.53 (1H, m), 4.09−4.06 (2H, m), 3.78−3.64 (3H, m), 3.13−3.02 (1H, m), 2.56−2.50 (4H, m), 2.32−1.25 (8H, m); ^{13}C NMR ($CDCl_3$) δ 199.1, 169.4, 149.0, 146.0, 138.4, 137.0, 130.2, 129.0, 127.2, 126.9, 126.4, 125.9, 125.1, 125.0, 123.6, 122.2, 102.2, 66.8, 48.1, 32.4, 28.7, 27.2, 25.7, 24.1, 21.2. Anal. Calcd for $C_{28}H_{28}O_5S$: C, 70.56; H, 5.92; S, 6.73. Found: C, 70.42; H, 5.89; S, 6.72.

2-[2-(1,3-Dioxolan-2-yl)ethyl]cyclohexanone (4b). Under a nitrogen atmosphere, to a solution of cyclohexanone (3.1 mL, 29.9 mmol) in DMF (60 mL) was added LHMDS (1.0 M in THF, 33 mL, 33.0 mmol) at 0 °C. After being stirred at 0 °C for 30 min, the reaction mixture was warmed to room temperature and stirred for 1 h. It was then cooled to −50 °C, and a solution of 2-(2-iodoethyl)-1,3-dioxolane (7.50 g, 32.9 mmol) in DMF (20 mL) was added slowly. The reaction mixture was allowed to warm to room temperature and stirred for 15 h, then quenched with aqueous NH_4Cl solution and extracted with Et_2O, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (hexane/AcOEt, 4:1) to give **4b** (3.73 g, 63%) as a colorless oil: IR (KBr) 1713, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.85 (1H, t, J = 5.0 Hz), 4.01−3.78 (4H, m), 2.43−2.24 (3H, m), 2.16−1.59 (8H, m), 1.45−1.27 (2H, m); ^{13}C NMR ($CDCl_3$) δ 212.9, 104.5, 64.8, 50.3, 42.0, 34.0, 31.3, 28.0, 24.9, 23.8; HRMS calcd for $C_{11}H_{18}O_3$ (M^+) 198.1256, found 198.1266.

6-[2-(1,3-Dioxolan-2-yl)ethyl]-2,2-bisphenylthiocyclohexanone (5b). Under a nitrogen atmosphere, to a solution of **4b** (100 mg, 0.504 mmol) in THF (10 mL) was added LHMDS (1.0 M in THF, 2.0 mL, 2.0 mmol) at −50 °C. After being allowed to warm to room temperature over a period of 1 h, it was again cooled to −50 °C and a solution of $PhSSO_2Ph$ (500 mg, 2.0 mmol) in THF (10 mL) was added. The reaction mixture was allowed to warm to room temperature over a period of 1.5 h, then quenched with aqueous NH_4Cl solution and extracted with AcOEt. The extract was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (hexane/AcOEt, 5:1) to give **5b** (172 mg, 82%) as a colorless oil: IR (KBr) 1705, 1582 cm^{-1}; ^1H NMR ($CDCl_3$) (500 MHz) δ 7.66−7.63 (4H, m), 7.41−7.31 (6H, m), 4.75 (1H, t, J = 5.0 Hz), 3.95−3.77 (4H, m), 3.31−3.25 (1H, m), 2.23−2.04 (4H, m), 1.83−1.75 (1H, m), 1.70−1.66 (1H, m), 1.54−1.24 (4H, m); ^{13}C NMR ($CDCl_3$) (125 MHz) δ 204.9, 137.3, 134.0, 131.1, 131.1, 129.1, 128.9, 128.5, 128.3, 104.4, 73.8, 64.8, 64.8, 46.2, 42.0, 34.0, 31.0, 24.0, 22.3. Anal. Calcd for $C_{23}H_{26}O_3S_2$: C, 66.63; H, 6.33; S, 15.47. Found: C, 66.81; H, 6.48; S, 15.20.

6-[2-(1,3-Dioxolan-2-yl)ethyl]-2-phenylthio-2-cyclohexen-1-one (6b). To a solution of **5b** (765 mg, 1.85 mmol) in CH_2Cl_2 (60 mL) was added *m*-CPBA (80% purity, 398 mg, 1.85 mmol) at −60 °C. After being stirred for 1 h, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ solution and extracted with CH_2Cl_2. The extract was washed with saturated aqueous $NaHCO_3$ solution, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (hexane/AcOEt, 3:1) to give **6b** (470 mg, 84%) as a pale yellow oil: IR (KBr) 1678, 1674, 1597, 1584 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.43−7.28 (5H, m), 6.41 (1H, t, J = 4.5 Hz), 4.87 (1H, t, J = 4.5 Hz), 3.99−3.81 (4H, m), 2.51−2.36 (3H, m), 2.16−1.95 (2H, m), 1.86−1.48 (4H, m); ^{13}C NMR ($CDCl_3$) δ 197.0, 143.9, 137.0, 133.7, 132.2, 129.3, 128.1, 104.3, 64.8, 64.8, 46.9, 31.1, 27.8, 26.2, 23.6. Anal. Calcd for $C_{17}H_{20}O_3S$: C, 67.08; H, 6.62; S, 10.53. Found: C, 66.89; H, 6.58; S, 10.55.

6-[2-(1,3-Dioxolan-2-yl)ethyl]-2-phenylsulfinyl-2-cyclohexen-1-one (2f). To a solution of **6b** (1.52 g, 5.00 mmol) in CH_2Cl_2 (40 mL) was added *m*-CPBA (80% purity, 1.08 g, 5.00 mmol) at −45 °C. After being stirred at the same temperature for 20 min, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ solution and extracted with CH_2Cl_2. The extract was washed with saturated aqueous $NaHCO_3$ solution, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (hexane/AcOEt, 1:1 to 1:2) to give **2f** (1.37 g, 86%) as an oil: IR (KBr) 1674, 1617, 1582, 1136, 1080, 1045 cm^{-1}; ^1H NMR ($CDCl_3$) (500 MHz) δ 7.74−7.65 (3H, m), 7.45−7.43 (3H, m), 4.83 (1/3H, t, J = 4.5 Hz), 4.73 (2/3H, t, J = 4.5 Hz), 3.95−3.76 (4H, m), 2.77−1.33 (9H, m). Anal. Calcd for $C_{17}H_{20}O_4S$: C, 63.73; H, 6.29; S, 10.01. Found: C, 63.62; H, 6.27; S, 9.80.

2-[2-Methoxy-3-(methoxycarbonyl)-6-methyl-4-pyridinyl]acetic Acid (8). Under a nitrogen atomosphere, LDA was prepared from diisopropylamine (4.5 mL, 32.1 mmol) and n-BuLi (1.59 M in hexane, 20 mL, 31.8 mmol) at 0 °C. To a solution of LDA in THF (70 mL) was added a solution of **7** (2.94 g, 15.0 mmol) in THF (30 mL) at −78 °C. After being stirred at the same temperature for 30 min, CO_2 gas was bubbled over it for 20 min. The reaction mixture was then warmed to room temperature and stirred for 30 min. After addition of CH_2Cl_2 at 0 °C, the cooled aqueous layer was acidified (pH 2−3) with 10% HCl and extracted with CH_2Cl_2. The extract was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give **8** (3.14 g, 87%) as pale yellow crystals: mp 113−115 °C; IR (CH_2Cl_2) 3200−2542 br, 1759, 1721, 1676, 1599, 1572 cm^{-1}; ^1H NMR ($CDCl_3$) (270 MHz) δ 11.02−8.83 (1H, br), 6.69 (1H, s), 3.96 (3H, s), 3.89 (3H, s), 3.69 (2H, s), 2.45 (3H, s); HRMS calcd for $C_{11}H_{13}NO_5$ (M^+) 239.0793, found 239.0785.

8-Methoxy-6-methyl-1*H*-pyrano[3,4-*c*]pyridine-1,3(4*H*)-dione (9). To a solution of **8** (970 mg, 4.05 mmol) in EtOH (40 mL) were added solid KOH (6.90 g, 123 mmol) and water (8 mL). After being stirred at room temperature for 1 h, the reaction mixture was concentrated and the residual aqueous layer was acidified (pH 2−3) with 10% HCl and extracted with AcOEt. The combined extract was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residual solid was washed with hexanes/Et_2O to give 4-(carboxymethyl)-2-methoxy-6-methylnicotinic acid (900 mg, 99%) as pale yellow crystals: mp 145−146 °C; IR (CH_2Cl_2) 3400−2800 br, 1734, 1714, 1601, 1561 cm^{-1}; ^1H NMR ($CDCl_3$−CD_3OD) δ 6.73 (1H, s), 4.02 (3H, s), 3.80 (2H, s), 2.46 (3H, s); HRMS calcd for $C_{10}H_{11}NO_5$ (M^+) 225.0637, found 225.0657. To a suspension of 4-(carboxymethyl)-2-methoxy-6-methylnicotinic acid (358 mg, 1.59 mmol) in CH_2Cl_2 (5 mL) was added trimethylsilyl(ethoxy)acetylene (0.50 mL, ca. 3.50 mmol) at room temperature, and the mixture was stirred for 1 h. After concentration of the reaction mixture, the residual solid was washed with hexane/benzene and dried in vacuo to give **9** (308 mg, 94%) as yellow crystals: mp 128−129 °C; IR (CH_2Cl_2) 1804, 1761, 1599, 1582 cm^{-1}; ^1H NMR ($CDCl_3$) (500 MHz) δ 6.70 (1H, s), 4.11 (3H, s), 3.98 (2H, s), 2.52 (3H, s); HRMS calcd for $C_{10}H_9O_4N$ (M^+) 207.0531. Found: 207.0524.

8-[2-(1,3-Dioxan-2-yl)ethyl]-10-hydroxy-1-methoxy-3-methyl-6,7-dihydrobenz[*g*]isoquinolin-9(8*H*)-one (10a). Under a nitrogen atomosphere, to a suspension of NaH (48.5 mg of 60% in paraffin oil, 1.21 mmol) in dioxane (5 mL) was added a solution of **9** (237 mg, 1.15 mmol) in dioxane (5 mL). After being stirred for 30 min at room temperature, the reaction mixture was stirred at 80 °C for 20 min and at 120

°C for 15 min. A solution of **2e** (341 mg, 1.02 mmol) in dioxane (5 mL) was added at 120 °C. After being stirred at the same temperature for 20 min, the reaction mixtutre was quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2. The extract was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (hexane/AcOEt, 4:1) to give **10a** (167 mg, 45%) as an oil: IR (KBr) 1625, 1575 cm^{-1}; ^1H NMR ($CDCl_3$) (500 MHz) δ 15.25 (1H, s), 6.81 (1H, s), 6.76 (1H, s), 4.57 (1H, m), 4.16−4.06 (2H, m), 4.14 (3H, s), 3.80−3.73 (2H, m), 3.06−2.90 (2H, m), 2.64−2.60 (1H, m), 2.48 (3H, s), 2.22−2.02 (3H, m), 1.96−1.62 (4H, m), 1.33 (1H, br d, J = 12.7 Hz); HRMS calcd for $C_{21}H_{25}NO_5$ (M^+) 371.1732, found 371.1759.

8-[2-(1,3-Dioxolan-2-yl)ethyl]-10-hydroxy-1-methoxy-3-methyl-6,7-dihydrobenz[*g*]isoquinolin-9(8*H*)-one (10b). Under a nitrogen atomosphere, to a suspension of NaH (9.3 mg of 60% in paraffin oil, 0.277 mmol) in dioxane (2 mL) was added a solution of **9** (53 mg, 0.254 mmol) in dioxane (2 mL). After being stirred for 30 min at room temperature, the reaction mixture was stirred at 80 °C for 20 min and at 120 °C for 15 min. A solution of **2f** (74.0 mg, 0.231 mmol) in dioxane (2 mL) was added at 120 °C. After being stirred at the same temperature for 20 min, the reaction mixtutre was quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2. The extract was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (hexane/AcOEt, 4:1) to give **10b** (33 mg, 40%) as a yellow oil: IR (KBr) 1634, 1622, 1615, 1565, 1559 cm^{-1}; ^1H NMR ($CDCl_3$) δ 15.23 (1H, s), 6.81 (1H, s), 6.77 (1H, s), 4.91 (1H, t, J = 4.0 Hz), 4.13 (3H, s), 4.00−3.83 (4H, m), 3.09−2.88 (2H, m), 2.70−2.60 (1H, m), 2.48 (3H, s), 2.27−2.07 (2H, m), 1.95−1.62 (4H, m); ^{13}C NMR ($CDCl_3$) δ 205.9, 166.1, 162.1, 154.3, 145.2, 143.9, 114.3, 112.2, 107.2, 104.3, 64.9, 64.9, 54.0, 46.7, 31.1, 28.7, 27.4, 24.2, 24.0. Anal. Calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.10; H, 6.41; N, 3.87.

8-[2-(1,3-Dioxan-2-yl)ethyl]-1,10-dimethoxy-3-methyl-6,7-dihydrobenz[*g*]isoquinolin-9(8*H*)-one (11a). Under a nitrogen atomosphere, to a solution of **10a** (51.4 mg, 0.138 mmol) in DMF (2 mL) were added K_2CO_3 (381 mg, 2.76 mmol) and MeI (0.11 mL, 1.79 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 3 h, then quenched with water and extracted with CH_2Cl_2. The extract was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by preparative TLC (hexane/AcOEt, 3:1) to give **11a** (25 mg, 47%) as an oil: ^1H NMR ($CDCl_3$) (500 MHz) δ 7.15 (1H, s), 6.88 (1H, s), 4.56 (1H, t, J = 4.9 Hz), 4.11 (3H, s), 4.09−4.06 (2H, m), 3.95 (3H, s), 3.78−3.72 (2H, m), 3.10−2.96 (2H, m), 2.56−2.51 (1H, m), 2.49 (3H, s), 2.24−2.19 (1H, m), 2.11−2.00 (2H, m), 1.85−1.55 (4H, m), 1.32 (1H, br d, J = 13.6 Hz).

8-[2-(1,3-Dioxolan-2-yl)ethyl]-1,10-dimethoxy-3-methyl-6,7-dihydrobenz[*g*]isoquinolin-9(8*H*)-one (11b). Under a nitrogen atomosphere, to a solution of **10b** (30.6 mg, 0.0856 mmol) in DMF (3 mL) were added K_2CO_3 (247 mg, 1.79 mmol) and MeI (0.06 mL, 0.964 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 3 h, then quenched with water and extracted with CH_2Cl_2. The extract was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (hexane/AcOEt, 2:1) to give **11b** (27.2 mg, 86%) as pale yellow crystals: mp 115−116 °C (AcOEt); IR (KBr) 1688, 1684, 1615, 1549 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.16 (1H, s), 6.89 (1H, s), 4.90 (1H, t, J = 5.0 Hz), 4.11 (3H, s), 3.96 (3H, s), 4.00−3.71 (4H, m), 3.10−2.98 (2H, m), 2.49 (3H, s), 2.61−2.46 (1H, m), 2.26−2.20 (1H, m), 2.10−2.03 (1H, m), 1.87−1.58 (4H, m); ^{13}C NMR ($CDCl_3$) δ 199.1, 160.9, 160.5, 151.7, 145.2, 143.3, 124.5, 120.0, 112.2, 111.9, 104.4, 64.9, 64.8, 63.5, 54.9, 49.0, 31.3, 29.4, 28.0, 24.9, 24.0; HRMS calcd for $C_{21}H_{25}NO_5$ (M^+) 371.1732, found 371.1727.

3-(1,10-Dimethoxy-3-methyl-9-oxo-6,7,8,9-tetrahydrobenz[*g*]isoquinolin-8-yl)propanal (12). To a solution of **11b** (15.8 mg, 0.0425 mmol) in THF (3.8 mL) was added 85% aqueous TFA (11 mL) at 0 °C. After being stirred for 4 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The extract was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by preparative TLC (hexane/AcOEt, 4:1) to give **12** (10.6 mg, 76%) as orange crystals: mp 130 °C; IR (KBr) 1725, 1686, 1615, 1547 cm^{-1}; ^1H NMR ($CDCl_3$) (270 MHz) δ 9.80 (1H, s), 7.15 (1H, s), 6.87 (1H, s), 4.10 (3H, s), 3.95 (3H, s), 3.07−3.02 (2H, m), 2.65−2.51 (3H, m), 2.48 (3H, s), 2.22−2.12 (2H, m), 1.92−1.82 (2H, m); ^{13}C NMR ($CDCl_3$) (67.5 MHz) δ 202.1, 198.6, 160.8, 160.6, 151.9, 144.9, 143.4, 124.3, 120.2, 112.1, 111.9, 63.5, 53.9, 48.4, 41.6, 29.5, 28.5, 24.0, 23.1. Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.54; H, 6.41; N, 4.30.

A similar reaction of compound **11a** with TFA afforded the product **12** only in 51% yield.

Supporting Information Available: Copies of ^1H NMR and ^{13}C NMR spectra for compounds **3j**, **3k**, **3l**, **3m**, **4b**, and **11b** and ^1H NMR spectra for compounds **4a**, **5a**, **6a**, **8**, **9**, **10a**, and **11a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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