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Benzannulation for the Regiodefined Synthesis of 2-Alkyl/Aryl-1-naphthols: Total Synthesis of Arnottin I

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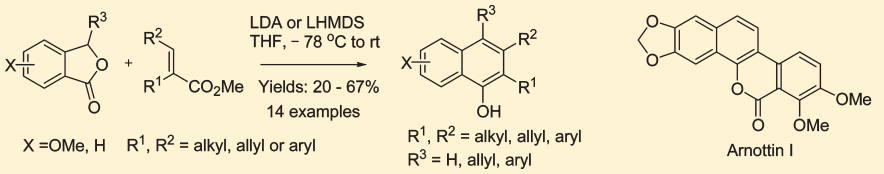
Supporting Information

ABSTRACT:

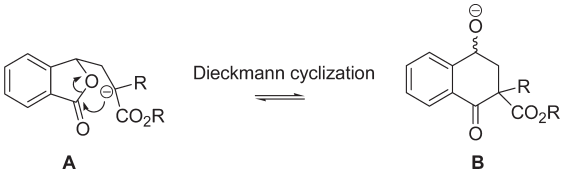


The annulation of phthalides with α-alkyl/arylacrylates in the presence of LDA/LHMDS is shown to directly give alkyl/aryl-1-naphthols. The method involving a novel dealkoxycarbonylation obviates the regiochemical issues in the synthesis of polysubstituted naphthalenes, and it forms the key step in a three-step total synthesis of arnottin I, a naphthobenzopyranone natural product.

INTRODUCTION

The regioselective synthesis of highly substituted naphthalenes is a major challenge in synthetic organic chemistry. Because of the presence of seven chemically nonequivalent positions in a monosubstituted naphthalene, the traditional strategies involving substitutions suffer from regiochemical ambiguities and, hence, efficiencies.[1] Even today a structurally simple 2-methylnaphthol continues to be a subject of rigorous synthetic activities.[2] To a large extent, the regiochemical problems of the arene chemistry are solved by directed metalation technology.[3] Alternatively, benzene rings are constructed by regioselective benzcyclizations[4] and benzannulations,[5] which include (i) cyclotrimerizations,[6] (ii) Dotz annulation,[7] (iii) Hauser annulation,[8] (iv) Asao–Yamamoto annulation,[9] and (v) Danheiser annulation.[10] For the synthesis of substituted 1-naphthols, the lateral lithiation-initiated benzannulations[11] have been found attractive because of the regiochemical integrity and convergence. They have found widespread application in the total synthesis of polycyclic aromatics and natural polyketides.[8] However, these methodologies[12−16] have limitations of incorporating only the directing electron-withdrawing groups of the acceptors in the products. In the synthesis of 1-naphthols, the resulting groups *ortho* to the OH groups are invariably electron-withdrawing groups.[11] Interestingly, such annulations have never been extended to Michael acceptors bearing α-alkyl/aryl substituents.[17] This is perhaps due to the perception that the annulation product formed via the Michael–Dieckmann sequence would be susceptible to ring-opening. In a normal Dieckmann cyclization, the equilibrium is shifted to the forward direction by enolate formation of the initial Dieckmann product with an α-hydrogen.[18] In the present annulation (Scheme 1) with an α-substituted acrylate, the Michael adduct **A** would cyclize under basic conditions to give intermediate **B**. Since there is no active hydrogen in the α-position of the ester group in **B**, it will not form an enolate. Hence, it may revert to the Michael adduct **A**.

Scheme 1. Probable Intermediates of the Proposed Annulation



Herein, we report that α-substituted acrylates react with phthalides regiospecifically to give 2-alkyl/arylnaphthols in a single operation and thereby provide an alternative to the Friedel–Crafts reactions (Scheme 2). For example, 2-methyl-1-naphthol could be prepared directly in one step from commercially available phthalide (**1**) and methyl methacrylate (**2**). We also report a three-step total synthesis of arnottin I, representing a tandem annulation.

RESULTS AND DISCUSSION

This work stemmed from our earlier sporadic observations on the similar anionic annulation routes to carbazoles[17b] and gilvocarcins.[19] In two instances, demethoxycarbonylations occurred to a significant extent, findings which prompted us to study the reactivity profile of the α-alkyl/aryl-substituted acrylates to the phthalide anions. We desired to develop an annulation strategy for the synthesis of 1-naphthols[20] with an alkyl/aryl group at C2. Initial studies were focused on the reaction of

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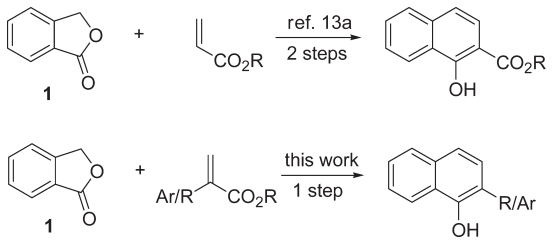
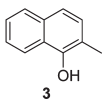
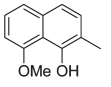
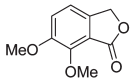
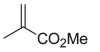
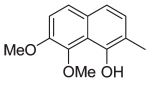
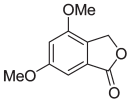
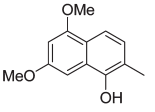
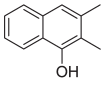
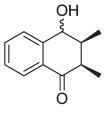
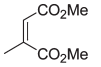
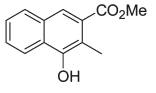
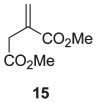
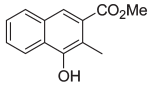
phthalide (**1**) and acrylate **2** under various conditions. When phthalide anion generated with 1.2 equiv of LDA in THF was reacted with methyl methacrylate (**2**) (1.2 equiv), the reaction gave an intractable mixture of products. There was no sign of the proposed annulation, as evident from ^{1}H NMR study of the mixture. Instead, extensive polymerization of the acrylate took place as judged from the formation of an insoluble white solid. Strikingly, when the same reaction was carried out with excess LDA (3 equiv) and the acrylate (3 equiv), methylnaphthol **3**[2] was formed in 30% yield. The probable tetralone intermediate, i.e., 4-hydroxy-2-methyl-α-tetralone (**4**) could not be isolated from the reaction. From a brief optimization study with varied bases, it was apparent that the reaction could be effected by either LDA or LHMDS. On the other hand, KHMDS was found totally ineffective in promoting the reaction.

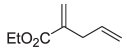
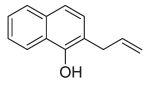
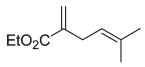
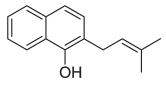
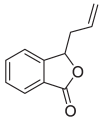
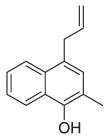
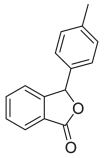
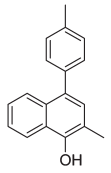
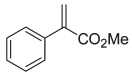
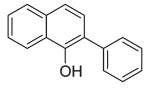
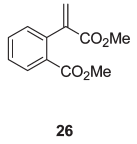
Scheme 2. Epitome of the Present Work



Under the optimized reaction conditions, we investigated the generality of the reaction using different types of substrates. We were particularly interested in the reactivity of the methoxy-substituted phthalides, since a great majority of aromatic polyketides feature methoxy substitutions.[21] Moreover, it was of interest to know if the methoxy groups in a phthalide would complicate the annulation due to nuclear lithiation.[22] As shown in Table 1, phthalide **5** and acrylate **2** reacted efficiently to afford

Table 1. Phthalide Annulation with α-Alkyl/Arylacrylates[a]

Entry	Phthalide	Acrylate	Naphthol	% Yield (base)
1	 **1**	 **2**	 **3**	30 (A) 66 (B)
2	 **5**	 **2**	 **6**	35 (A)
3	 **7**	 **2**	 **9a**	51** (A)
4	 **8**	 **2**	 **10**	55* (A) 45* (B)
5	 **1**	 **11**	 **12**	41*(A) 25 (B)
			 **37**	15 (B)
6	 **1**	 **13**	 **14**	51 (B)
7	 **1**	 **15**	 **14**	41 (B)

Entry	Phthalide	Acrylate	Naphthol	% Yield (base)
8	 **1**	 **16**	 **18**	55 (B)
9	 **1**	 **17**	 **19**	20 (A)
10	 **20**	 **2**	 **21**	52 (A) 35 (B)
11	 **22**	 **2**	 **23**	58* (A)
12	 **1**	 **24**	 **25**	22 (A) 67 (B)
13	 **1**	 **26**	**27**	41 (B)
14	**29**	**26**	**28**	60 (B)

[a] A and B refer to LDA and LHMDS, respectively. Key: *, based on recovery of the starting phthalide; **, the product was fully characterized as its methyl ether **9b**.

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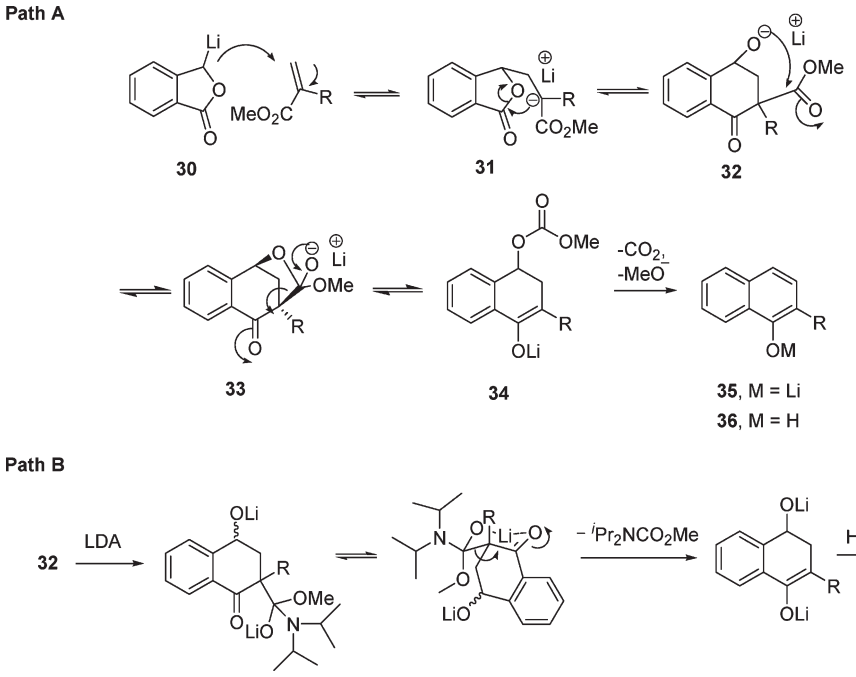
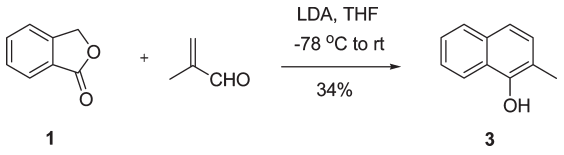
Scheme 3. Proposed Mechanism for the Annulation



Scheme 4. Experimental Support for the Proposed Nucleophilic Fragmentation



the desired product **6** in 35% yield. Similarly, dimethoxyphthalides **7**[23] and **8**[24] afforded methylnaphthols **9a** and **10**,[25] respectively. For the synthesis of naphthols with multiple substituents, we examined the reactivity of dimethylacrylate **11**. Expectedly, its reaction with **1** provided dimethylnaphthol **12**.[26] With methylmaleate **13**, 2,3-disubstituted naphthol **14**[27] was formed. Its formation is presumed to occur via initial Michael addition at the less substituted alkenyl carbon. With acrylate **15**, the product was the same as in the previous case, i.e., **14**, contrary to our expectation of a naphthylacetate. This implies that the isomerization of the acrylate **15** to **13** precedes the annulation. Between two allylacrylates, **16**[28] and **17**,[28] the simpler one, **16**, reacted smoothly to give the desired allylnaphthol **18**.[29] The prenylacrylate **17** had similar reactivity, but the yield of the corresponding product **19**[30] was lower. It is noted that the allyl fragment remained intact under the influence of LDA. Thus, such annulation provides a facile route to installation of prenyl groups in naphthalenes, for which there are fewer methods in the literature.[31] Entries 10 and 11 exemplify the reactivity profile of a phthalide with a C3 substituent. Phthalide **20**[32] gave the desired product **21**[33] in 52% yield with a resulting allyl moiety at C4 of the naphthol. Annulation of phthalide **22**[34] with acrylate **2** installed an aryl group at C4 of the naphthol **23**. Similarly, a phenyl group could be incorporated at C2 of 1-naphthol by annulation of phthalide **1** with phenylacrylate **24**.[35] The desired phenylnaphthol **25**[36] was obtained in 22% yield. When the same reaction was performed with LHMDS, the yield improved to 67%. To explore a tandem annulation for assembly of a benzo[*d*]naphtho[*b*]pyranone motif, **1** was reacted with methylene homophthalate **26**.[37] Expectedly, the reaction afforded benzonaphthopyranone **27**[38] in 41% yield along with side product **28** in 26% yield. To determine the structure of the product **28**, an independent synthesis of **28** was planned by the reaction of carbomethoxyphthalide **29**[39] with homophthalate **26**. Expectedly, the reaction afforded benzonaphthopyranonecarboxylate **28** in good yield.

Mechanism of the Annulation. As shown in Scheme 3, the annulation cascade (path A) is initiated by generation of 3-lithiophthalide **30**, which undergoes Michael addition with methyl methacrylate to form a new carbanion, **31**. This anion then undergoes Dieckmann cyclization, leading to the tetralone **32**. Intramolecular nucleophilic attack[40a] of the alkoxy anion in oxytetralone **32** gives **33**, which fragments to carbonate **34**. Loss of CO_2 and MeO^- from **34** would then generate **35**, eventually forming **36** on acidic workup. The mechanism is supported by a fortuitous finding. In the reaction between **1** and acrylate **11** (entry 5), the possible tetralone intermediate **37** could be isolated in 15% yield with LHMDS. Although the stereochemistry of the hydroxyl group could not be established, the relative stereochemistry of the two methyl groups in **37** is suggested to be *cis* due to the absence of ^3J diaxial coupling in its ^{1}H NMR spectrum. Lastly, the support for the nucleophilic addition induced fragmentation was provided by the designed reaction of **1** with methacrolein. Their reaction in the presence of LDA yielded 2-methylnaphthol (**3**) in 34% yield, implying a nucleophilic addition followed by an induced deformylation step (Scheme 4). Alternatively, LDA-mediated intermolecular demethoxycarbonylation may be proposed to take place via an intermolecular attack of LDA at the methoxycarbonyl group of **32** followed by an appropriate fragmentation[40b] as described in path B (Scheme 3).

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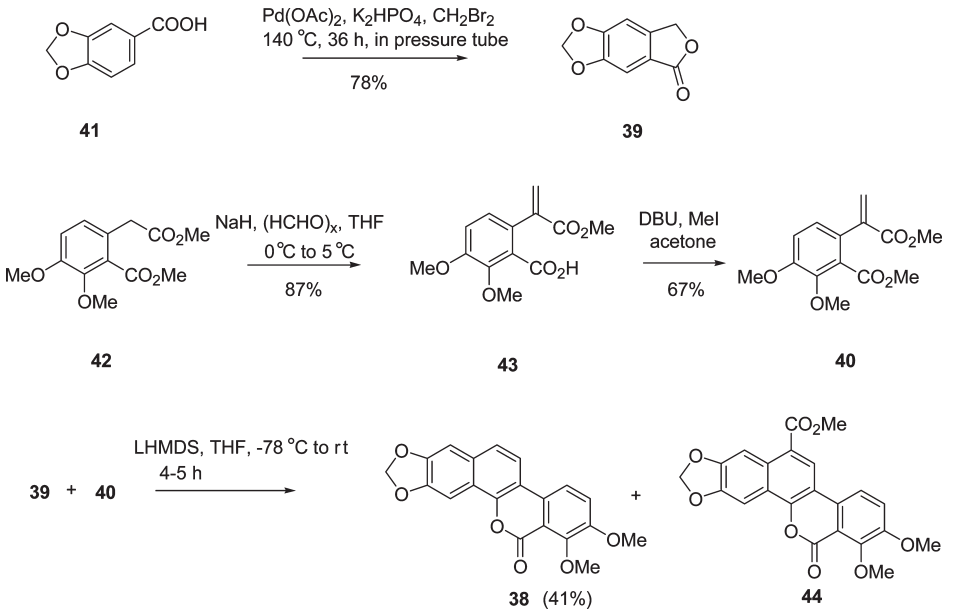
Scheme 5. Total Synthesis of Arnottin I (38)



Total Synthesis of Arnottin I. To demonstrate the potential of this method of hydroxybenzannulation, total synthesis[41] of arnottin I (**38**) was undertaken. As a target, it is attractive because of its biosynthetic relationship with chelerythrine alkaloids. Moreover, it structurally resembles neo-tanshinlactone, which shows potent activity against human breast cancer cell lines.[42] Application of the present methodology as a transform pointed to the annulation between phthalide **39** and homophthalate **40** (Scheme 5). The phthalide **39**[43a] was prepared in one step from commercially available piperonylic acid (**41**) by its reaction[43b] with CH_2Br_2 in the presence of $Pd(OAc)_2$. It should be mentioned that the elaboration of **41** by conventional formylations[44] followed by reduction with $NaBH_4$ was not at all satisfactory. Homophthalate **42**[45] was methylenated with paraformaldehyde and NaH in THF at 0 °C to give half-ester **43**, which was, without purification, converted to diester **40** by interaction with DBU−MeI[46] in acetone. The proposed annulation between donor **39** and acceptor **40** was performed in the presence of LHMDS in THF at −78 °C. It provided an inseparable mixture of two compounds, namely, **38** and **44**. By repeated fractional recrystallizations from chloroform, **38** was obtained in 41% yield. The NMR data of **38**[22] were in good agreement with the reported values. Although compound **44** (purity >90%) could not be fully separated from compound **38** due to their similar TLC behaviors, it was assigned structure **44** on the basis of analysis of the ^1H NMR spectrum. Its formation can be interpreted by intermolecular reaction between a 3-lithiophthalide (cf. **30**) and a methoxycarbonyl intermediate (cf. **34**).

CONCLUSIONS

In conclusion, the reaction of readily accessible phthalides and α-alkyl/arylacrylates in the presence of LDA or LHMDS has given rise to a new annulation. This has paved the way for the regiodefined synthesis of 1-naphthols, in which an alkyl/aryl group can be desirably placed *ortho* to the phenolic OH group. The annulation is applicable to the synthesis of a wide variety of polysubstituted aromatics, including biaryls (entries 11 and 12). The yields tend to be higher for α-arylacrylates than for the alkyl counterparts, probably due to lesser tendency of the former for base-catalyzed polymerization. Further studies on the annulation are under way.

EXPERIMENTAL SECTION

General Procedures. Melting points were determined in open-end capillary tubes and are uncorrected. Solvents were dried and distilled following the standard procedures. TLC was carried out on precoated plates (silica gel 60, GF254), and the spots were visualized with UV and fluorescent lights. Column chromatography was performed on silica gel (60−120 or 230−400 mesh). ^1H and ^{13}C NMR spectra for all the compounds were recorded at 200/400 and 50/100 MHz. IR spectra were recorded on an FT-IR instrument using a KBr pellet. The phrase "usual workup" or "worked up in usual manner" refers to washing of the organic phase with water (2 × 1/3 the volume of the organic phase) and brine (1 × 1/4 the volume of the organic phase), drying (Na_2SO_4), filtration, and concentration under reduced pressure.

The known substrates **5**, **7**, **8**, **16**, **17**, **20**, **22**, **24**, **26**, **29**, and **42** were prepared according to the literature procedures cited in the text.

Method A: General Annulation Procedure with LDA. In a flame-dried flask, LDA (3.2 mmol) was prepared by adding *n*-BuLi (3.2 mmol, 1.6 M in hexane) in a solution of diisopropylamine (3.2 mmol) in THF (10 mL) at −78 °C under a nitrogen atmosphere. After 10 min at −78 °C, an appropriate phthalide (1 mmol) in THF (5 mL) was added dropwise over 15 min. The reaction mixture was stirred at −78 °C for 15 min, and then a solution of the appropriate Michael acceptor (1.2 mmol) in THF (5 mL) was added dropwise over 15 min at −78 °C. The reaction mixture was further stirred for 1 h at the same temperature and allowed to warm under ambient conditions to room temperature over 5−6 h. The solution was then quenched with 10% aq HCl (15 mL) or saturated ammonium chloride solution (15 mL). The resulting mixture was concentrated under reduced pressure and the residue extracted with ethyl acetate (3 × 50 mL). The combined extracts were washed with brine (3 × 1/3 vol), dried (Na_2SO_4), and concentrated to obtain the crude product, which was purified by column chromatography on silica gel.

Method B: General Annulation Procedure with LHMDS. To a stirred solution of lithium hexamethyldisilazide (3.2 mmol) in THF

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(10 mL) at −78 °C under an inert atmosphere was added a solution of phthalide (1 mmol) in THF (5 mL). The resulting yellow solution was stirred at −78 °C for 25 min, after which a solution of a Michael acceptor (1.2 mmol) in THF (5 mL) was added to it. The cooling bath was removed after about 1 h at −78 °C, and the reaction mixture was brought to room temperature over a period of 1 h and further stirred for 5−6 h. The reaction was then quenched with 10% NH_4Cl (15 mL) or 10% aq HCl (15 mL), and the resulting solution was concentrated under reduced pressure. The residue was diluted with ethyl acetate (3 × 50 mL), and the layers were separated. The combined extracts were washed with brine (3 × 1/3 vol), dried (Na_2SO_4), and concentrated to provide the crude product. The crude solid product was purified by column chromatography on silica gel to obtain a pure product.

2-Methylnaphthalen-1-ol (3). Red solid. Mp: 58−61 °C (lit.[2] 60−63 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, 1H, J = 8 Hz), 7.78 (d, 1H, J = 8 Hz), 7.49−7.41 (m, 2H), 7.38 (d, 1H, J = 8.4 Hz), 7.25 (d, 1H, J = 8.8 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 148.6, 133.4, 129.0, 127.6, 125.4, 125.3, 124.2, 120.9, 120.1, 116.3, 15.7.

8-Methoxy-2-methylnaphthalen-1-ol (6). Colorless oil. ν_{max} (KBr, cm^{-1}): 3398, 2927, 1587, 1398, 1251, 1074. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.54 (s, 1H), 7.37 (d, 1H, J = 8.0), 7.27−7.21 (m, 3H), 6.77 (d, 1H, J = 7.6), 4.06 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.8, 151.2, 135.3, 130.5, 124.5, 121.8, 119.1, 118.2, 114.8, 103.9, 56.1 (OCH_3), 15.9 (CH_3). A satisfactory mass spectrum could not be obtained due to its susceptibility to aerial oxidation.

7,8-Dimethoxy-2-methylnaphthalen-1-ol (9a). Colorless oil. ν_{max} (KBr, cm^{-1}): 2356, 1344, 1220, 1027, 771. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.81 (s, 1H), 7.52 (d, 1H, J = 8.8), 7.21−7.12 (m, 3H), 4.07 (s, 3H), 3.98 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.0, 147.2, 142.4, 130.2, 128.5 (CH), 125.1 (CH), 118.9, 118.3 (CH), 117.7, 114.2 (CH), 62.0 (OCH_3), 56.9 (OCH_3), 15.7 (CH_3). LRMS: m/e calcd for $C_{13}H_{15}O_3$ $(MH)^+$ 219.1023, found 219.0887.

1,2,8-Trimethoxy-7-methylnaphthalene (9b). Colorless oil. ν_{max} (KBr, cm^{-1}): 2931, 1452, 1334, 1265, 1070, 1002. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, 1H, J = 8.8), 7.45 (d, 1H, J = 8.4), 7.23 (d, 1H, J = 8.8), 7.16 (d, 1H, J = 8.4), 3.99 (s, 3H), 3.91 (s, 3H), 3.85 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.2, 150.1, 142.2, 130.9, 128.2, 127.4, 124.8 (CH), 124.0 (CH), 123.7, 113.5 (CH), 61.9 (OCH_3), 61.4 (OCH_3), 56.6 (OCH_3), 15.9 (CH_3).

5,7-Dimethoxy-2-methylnaphthalen-1-ol (10). Yellow solid. Mp: 158−160 °C (lit.[25] 162−165 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, 1H, J = 8.4 Hz), 7.08 (d, 1H, J = 8.4 Hz), 6.99 (s, 1H), 6.46 (s, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 158.2, 156.8, 147.8, 125.8, 121.8, 117.8, 114.4, 100.1, 97.4, 91.6, 55.7, 55.6, 16.0.

2,3-Dimethylnaphthalen-1-ol (12)[26]. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06−8.01 (m, 1H), 7.72−7.67 (m, 1H), 7.27 (s, 1H), 5.15 (br s, 1H), 2.44 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.3, 135.9, 132.6, 127.0 (CH), 125.5 (CH), 124.5 (CH), 122.9, 120.7 (CH), 120.3 (CH), 116.7, 21.0 (CH_3), 11.8 (CH_3).

Methyl 4-Hydroxy-3-methylnaphthalene-2-carboxylate (14)[27]. White solid. ν_{max} (KBr, cm^{-1}): 3483, 1707, 1448, 1385, 1298, 1228, 1039, 791. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.16 (d, 1H, J = 8 Hz), 8.06 (s, 1H), 7.85 (d, 1H, J = 7.6 Hz), 7.62−7.46 (m, 2H), 3.96 (s, 3H), 2.61 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.7, 149.5, 131.6, 129.1, 128.7 (CH), 127.5 (CH), 126.3, 125.9, 123.9 (CH), 121.3 (CH), 116.0, 52.2 (CH_3), 12.7 (CH_3).

2-Allylnaphthalen-1-ol (18)[29]. Yellow semisolid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, 1H, J = 7.2 Hz), 7.81−7.77 (m, 1H), 7.51−7.39 (m, 3H), 7.24−7.16 (m, 1H), 6.13−6.05 (m, 1H), 5.57 (s, 1H), 5.29−5.24 (m, 2H), 3.59 (d, 2H, J = 6 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 149.6, 136.1, 133.8, 128.4, 128.3, 127.5, 125.8, 125.3, 121.3, 120.4, 117.8, 117.0, 35.8.

2-Prenylnaphthalen-1-ol (19)[30]. Yellow semisolid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, 1H, J = 7.6 Hz), 7.76−7.75 (m, 1H), 7.46−7.36 (m, 3H), 7.22 (d, 1H, J = 8.4 Hz), 5.79 (br s, 1H), 5.43−5.39 (m, 1H), 3.52 (d, 1H, J = 7.2 Hz), 1.87 (s, 3H), 1.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.6, 135.7, 133.5, 128.2, 127.4, 125.5, 125.2, 124.8, 121.7, 121.3, 120.0, 119.5, 30.5, 25.8, 18.0.

4-Allyl-2-methylnaphthalen-1-ol (21)[33]. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19−8.14 (m, 1H), 7.96−7.91 (m, 1H), 7.50−7.44 (m, 2H), 7.10 (s, 1H), 6.14−6.04 (m, 1H), 5.09 (s, 1H), 5.06 (dd, 1H, J = 1.2 Hz, 8.8 Hz), 3.74 (d, 2H, J = 6 Hz), 2.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.5 (CH), 131.6, 129.4 (CH), 128.1, 125.3 (CH), 125.0 (CH), 124.7, 124.1 (CH), 121.6 (CH), 115.8 (CH_2), 36.8 (CH_2), 15.7 (CH_3).

2-Methyl-4-*p*-tolylnaphthalen-1-ol (23). White solid. Mp: 70−72 °C. ν_{max} (KBr, cm^{-1}): 3435, 2925, 1778, 1691, 1579, 1512, 1456, 1306, 1221, 1169, 1099, 821, 762. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, 1H, J = 8 Hz), 7.88 (d, 1H, J = 8.4 Hz), 7.49 (t, 1H, J = 7.4 Hz), 7.42−7.36 (m, 3H), 7.29 (d, 2H, J = 7.6 Hz), 7.21 (s, 1H), 5.20 (br s, 1H), 2.46 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.9, 137.7, 136.5, 132.7, 131.3, 130.0 (CH), 129.9 (CH), 128.9 (CH), 125.9 (CH), 125.4 (CH), 125.1 (CH), 124.4, 121.1 (CH), 115.7, 21.2 (CH_3), 15.6 (CH_3). HRMS: m/e calcd for $C_{18}H_{17}O$ $(MH)^+$ 249.1209, found 249.1201.

2-Phenylnaphthalen-1-ol (25)[36]. Colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.34−8.29 (m, 1H), 7.87−7.82 (m, 1H), 7.58−7.45 (m, 8H), 7.38 (d, 1H, J = 8.4 Hz), 5.89 (br s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 147.9, 137.5, 134.3, 129.6, 129.5, 127.9, 127.7, 127.6, 126.6, 125.6, 124.5, 122.6, 121.4, 120.3.

Dibenzo[*c*,*h*]chromen-6-one (27). White solid. Mp: 178−180 °C (lit.[38] 182−183 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.61 (d, 1H, J = 9.4 Hz), 8.49 (d, 1H, J = 8 Hz), 8.22 (d, 1H, J = 8 Hz), 8.09 (d, 1H, J = 8.8 Hz), 7.89 (d, 1H, J = 7.2 Hz), 7.87 (d, 1H, J = 6.6 Hz), 7.79 (d, 1H, J = 8.8 Hz), 7.69−7.58 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.2, 147.2, 135.4, 134.9, 134.2, 130.6, 128.6, 127.9, 127.6, 127.1, 124.5, 123.9, 122.3, 122.0, 121.2, 119.1, 113.0.

Methyl 6-Oxo-6*H*-dibenzo[*c*,*h*]chromene-12-carboxylate (28). White solid. Mp: 172 °C. ν_{max} (KBr, cm^{-1}): 2358, 1732, 1259, 1020, 755. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.83 (d, 1H, J = 8.4 Hz), 8.56 (s, 1H), 8.45 (d, 1H, J = 8 Hz), 8.32 (d, 1H, J = 7.6 Hz), 8.02 (d, 1H, J = 8 Hz), 7.78 (t, 1H, J = 7.4 Hz), 7.61−7.52 (m, 3H), 3.99 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.9, 160.4, 149.8, 135.1 (CH), 134.4, 132.0, 130.6 (CH), 129.3 (CH), 129.0 (CH), 127.2 (CH), 125.9 (CH), 124.6 (CH), 124.0, 123.2, 122.5 (CH), 122.0 (CH), 120.9, 111.6, 52.4 (CH_3). HRMS: m/e calcd for $C_{19}H_{12}O_4$ $(MH)^+$ 305.0814, found 305.0810.

4-Hydroxy-2,3-dimethyl-3,4-dihydro-2*H*-naphthalen-1-one (37). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, 1H, J = 7.6 Hz), 7.59 (t, 1H, J = 7.4 Hz), 7.49 (d, 1H, J = 7.6 Hz), 7.43 (t, 1H, J = 7.4 Hz), 4.72 (d, 1H, J = 4.4 Hz), 3.39−3.21 (m, 1H), 2.49−2.38 (m, 1H), 1.22 (d, 3H, J = 3.6 Hz), 0.95 (d, 3H, J = 3.6 Hz). ^{13}C NMR (100 MHz, CDCl3): δ 200.3, 142.0, 134.0, 131.1, 129.1, 128.7, 126.9, 72.7, 42.0, 41.9, 13.0, 11.7.

1,2-Dimethoxy-8,10,12-trioxacyclopenta[*b*]chrysen-13-one (38). White solid. Mp: 295−297 °C (lit.[41] 299−300 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, 1H, J = 9.2 Hz), 7.85 (s, 1H), 7.83 (d, 1H, J = 9.6 Hz), 7.54 (d, 1H, J = 8.8 Hz), 7.45 (d, 1H, J = 8.8 Hz), 7.14 (s, 1H), 6.10 (s, 2H), 4.03 (s, 3H), 3.99 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.7, 153.0, 151.9, 148.8, 148.5, 146.0, 131.1, 129.7, 123.1, 120.2, 119.6, 117.8, 117.7, 115.4, 112.0, 103.9, 101.5, 99.1, 61.5, 56.5. HRMS: m/e calcd for $C_{20}H_{14}O_6$ $(M)^+$ 350.0790, found 350.0796.

7*H*-Furo[3′,4′:4,5]benzo[1,2-*d*][1,3]dioxol-5-one (39)[43a]. This compound was prepared as a white solid by heating piperonylic acid (166 mg, 1 mmol), $Pd(OAc)_2$ (22 mg, 0.1 mmol), and K_2HPO_4 (520 mg, 3 mmol) in dibromomethane (4 mL) in a pressure tube at 140 °C for 36 h. Yield: 78%. R_f: 0.5 (1:5 ethyl acetate/petroleum ether). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.23 (s, 1H), 6.85 (s, 1H,), 6.13 (s, 2H),

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5.19 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.8, 153.9, 149.4, 143.2, 119.6, 104.5 (CH), 102.7 (CH_2), 101.9 (CH), 69.2 (CH_2).

Methyl 2,3-Dimethoxy-6-[1-(methoxycarbonyl)vinyl]benzoate (40). The crude acid **43** (100 mg, 0.38 mmol) was subjected to esterification by the treatment of DBU (0.06 mL, 0.38 mmol) and MeI (0.12 mL, 1.9 mmol) in acetone (5 mL) to furnish pure diester **40** as a colorless oil. Yield: 67% (70 mg). R_f: 0.6 (1:5 ethyl acetate/petroleum ether). ν_{max} (KBr, cm^{-1}): 1726, 1666, 1514, 1446, 1325, 1251, 1028, 748. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.01 (d, 1H, J = 8.4 Hz), 6.95 (d, 1H, J = 8.4 Hz), 6.39 (d, 1H, J = 1 Hz), 5.75 (d, 1H, J = 1 Hz), 3.90 (s, 3H), 3.89 (s, 3H), 3.80 (s, 3H), 3.74 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 166.6, 152.8, 146.7, 139.9, 128.6, 127.9 (CH), 127.8, 125.7 (CH), 113.5 (CH), 61.6 (CH_3), 55.9 (CH_3), 52.1 (CH_3), 52.0 (CH_3). HRMS: m/e calcd for $C_{14}H_{16}O_6$ (M^+) 280.0946, found 280.0939.

2,3-Dimethoxy-6-[1-(methoxycarbonyl)vinyl]benzoic Acid (43). NaH (20 mg, 0.82 mmol) was added to a solution of compound **42** (110 mg, 0.41 mmol) in dry THF. The resulting mixure was cooled to 0 °C and stirred at that temperature for 1 h. Paraformaldehyde (25 mg, 0.82 mmol) was then added to the reaction mixture, maintaining the same temperature for another 3 h. After completion of the reaction, the reaction mixture was concentrated, acidified with 3 N HCl, and worked up in the usual manner. Compound **43** was obtained as a white solid with a purity of ~95%. Yield: ~87%. R_f: 0.1 (1:1 ethyl acetate/petroleum ether). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.04 (s, 2H), 6.37 (d, 1H, J = 1.2 Hz), 5.72 (d, 1H, J = 1.2 Hz), 3.97 (s, 3H), 3.91 (s, 3H), 3.74 (s, 3H).

Methyl 1,2-Dimethoxy-13-oxo-13*H*-8,10,12-trioxacyclopenta[*b*]chrysene-6-carboxylate (44). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.75 (d, 1H, J = 9.4 Hz), 8.53 (s, 1H), 7.80 (s, 1H), 7.61 (s, 1H), 7.46 (d, 1H, J = 9.6 Hz), 6.19 (s, 2H), 4.12 (s, 3H), 4.04 (s, 6H).

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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