From enolates to anthraquinones[1]

David Bailey, Jeffrey N. Murphy, and Vance E. Williams

Abstract: A series of highly reactive cyclopentadienones were prepared in situ from the corresponding hydroxycyclopent-2-enones and trapped with a variety of quinones. Reaction of 1,4-naphthoquinone with 4-hydroxy-3,4-diphenyl-cyclopent-2-enone afforded 2,3-diphenylanthraquinone, whereas reaction of benzoquinone with this same cyclopentadienone precursor yielded a mixture of 6,7-diphenyl-1,4-naphthoquinone and 2,3,6,7-tetraphenylanthraquinone. A number of other 2,3-diarylanthraquinones were likewise prepared in moderate yields from the reaction of 1,4-naphthoquinone with the appropriate 4-hydroxy-3,4-diarylcyclopent-2-enones. This method appears to be generally applicable to the synthesis of anthraquinone derivatives substituted at the 2- and 3-positions from inexpensive starting materials.

Key words: anthraquinone, Diels–Alder, cyclopentadienone, in situ.

Résumé : On a préparé in situ une série de cyclopentadiénones très réactives à partir des hydroxycyclopent-2-énones correspondantes et on les a piégées à l'aide d'une variété de quinones. La réaction de la 1,4-naphtoquinone avec la 4-hydroxy-3,4-diphénylcyclopent-2-énone conduit à la formation de 2,3-diphénylanthraquinone alors que la réaction de la benzoquinone avec la même cyclopentadiénone conduit à un mélange de 6,7-diphényl-1,4-naphtoquinone et de 2,3,6,7-tétraphénylanthraquinone. On a préparé un certain nombre d'autres 2,3-diarylanthraquinones avec des rendements modérés par réaction de la 1,4-naphtoquinone avec des 4-hydroxy-3,4-diarylcyclopent-2-énones appropriées. Le domaine d'application de cette méthode semble général pour la synthèse de dérivés de l'anthraquinone substitués dans les positions 2 et 3, à partir de produits de départs peu coûteux.

Mots clés : anthraquinone, Diels–Alder, cyclopentadiénone, in situ.

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Introduction

> *If you learn nothing else from this class, I want you to remember: "Enolates are nucleophiles."* — Walter Szarek, speaking to his 3rd year organic chemistry class in 1991.

Anthraquinones are a versatile class of compounds that have been exploited as dyes (1), chemical sensors (2), organogelators (3), liquid crystals (4–8), anticancer agents (9), DNA photooxidants (10), and as precursors to substituted anthracenes. Our own interest in the synthesis of anthraquinone derivatives arose out of investigations into the [4+4]-photocycloaddition reactions of peripherally substituted chromophores such as 2,3,6,7-tetraphenylanthracene (11), the logical precursor of which is the anthraquinone (**1**). This quinone could be prepared in a one-pot reaction between 3,4-diphenylthiophene-1,1-dioxide (**2**) and benzoquinone (Scheme 1). Likewise, treatment of compound **2** with 1,4-naphthoquinone afforded 2,3-diphenylanthraquinone (**3**) in 70% yield (12). Although these sulfones are relatively stable and can be prepared from readily accessible thiophenes, the large-scale synthesis of these molecules has, in our hands, proven unreliable. For this reason, we decided to investigate the use of in situ generated cyclopentadienones as synthetic equivalents of sulfones in the construction of anthraquinones.

Cyclopentadienones condense with alkynes to form Diels–Alder adducts, which, upon loss of carbon monoxide, afford highly substituted benzene derivatives (13–16). These cyclones therefore behave in a similar manner to thiophene-1,1-dioxides, although the former tend to be much more reactive than the latter. Unlike sulfones, cyclopentadienones are highly unstable unless substituted at the 2- and 5-positions, and derivatives that lack bulky groups at these sites generally must be generated in situ from precursors such as the corresponding hydroxycyclopent-2-enones (15, 17, 18). Perhaps for this reason, cyclopentadienones have rarely been employed in the synthesis of anthraquinones (15, 19, 20), and only relatively stable derivatives of this type have been used for this purpose. Indeed, while there is some precedent for in situ generated cyclones being used in Diels–Alder reactions with alkynes (15, 19), we are aware of no examples of these compounds being trapped with quinone dienophiles to afford either anthraquinones or naphthoquinones. We therefore wished to explore whether the use of

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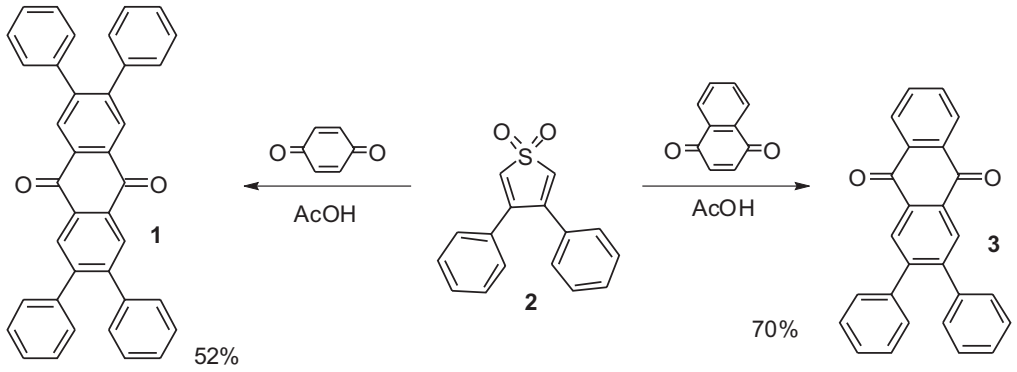
Scheme 1. Diels–Alder synthesis of compounds **1** and **3**. See ref. 12.



hydroxycyclopent-2-enones in the synthesis of anthraquinones was a viable strategy or would merely result in a fiasco.

Experimental

Materials and methods

^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were carried out on a Bruker AMX-400 400 MHz spectrometer; FT-IR spectroscopy was performed on a Thermo Nicolet Nexus 670 FT-IR ESP spectrometer, using KBr pellets. Microanalyses (C, H, N) were performed at Simon Fraser University, Burnaby, British Columbia, by Mr. Miki Yang. Low-resolution EI (70 eV) mass spectrometry was carried out on a Hewlett Packard 5985 mass spectrometer. Melting points were performed on either an Olympus BX50 polarizing microscope with a Linkam 94 heating stage or a MelTempII melting point apparatus and are uncorrected. MALDI-TOF mass spectra were obtained on a Perspective Voyager-DE STR from PE Applied Biosystems with a nitrogen laser (337 nm) and using 2,5-dihydroxybenzoic acid as the matrix.

1,4-Benzoquinone and *p*-toluenesulfonic acid were purchased from the Fisher Scientific Company. 1,4-Napthoquinone was obtained from Eastman Organic Chemicals. Copper sulfate, tetrakis(triphenylphosphine)palladium, copper(I) iodide, diisopropylamine, potassium iodide, benzaldehyde, *p*-anisaldehyde, 2-naphthaldehyde, 4-bromobenzaldehyde, 4-iodoanisole, and phenylacetylene were purchased from the Sigma-Aldrich Chemical Company Inc. The *o*-tolualdehyde was purchased from Matheson, Coleman, and Bell. Silica gel (230–400 mesh ASTM) was purchased from EMD Chemicals Inc. 1,4-Benzoquinone and 1,4-naphthoquinone were sublimed prior to use. Tetrahydrofuran was dried over sodium using benzophenone as an indicator. Benzaldehyde was distilled at reduced pressure. All other reagents were used as received.

Note that in the case of compounds **1**, **3**, **8**, **9**, **11**, **12**, and **24**, fewer peaks were observed in the ^{13}C NMR spectra than were predicted. This is probably due to inadequate peak resolution arising from the similarity in the chemical environments of many of the carbon nuclei. Attempts to resolve these peaks using d_6-benzene as the solvent were unsuccessful.

Synthesis

2,3,6,7-Tetraphenylanthraquinone (1) and 6,7-diphenyl-1,4-naphthaquinone (7)

To a solution of 1,4-benzoquinone (0.71 g, 6.6 mmol) in 180 mL acetic acid was added 0.84 g (3.3 mmol) of 4-hydroxy-3,4-diphenylcyclopent-2-enone (**4**) and 0.065 g (0.38 mmol) of *p*-toluenesulfonic acid. This mixture was refluxed for 49 h, then cooled to room temperature, poured over water (150 mL), and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed in vacuo. The crude product was purified by column chromatography using silica gel with toluene as the eluent. 2,3,6,7-Tetraphenylanthraquinone (**1**) was eluted from the column first, followed by 6,7-diphenylnaphthoquinone (**7**).

2,3,6,7-Tetraphenylanthraquinone (1)

2,3,6,7-Tetraphenylanthraquinone (**1**) was recrystallized from ethanol to afford 0.22 g (0.46 mmol) of a yellow solid; mp: 323 to 324 °C. IR (cm^{-1}): 1672 (C=O stretch). ^{1}H NMR (ppm, acetone-d_6) δ: 8.39 (s, 4H), 7.22–7.29 (m, 20H). ^{13}C NMR (ppm, $CDCl_3$) δ: 182.8, 146.4, 139.6, 132.4, 129.7, 128.2, 127.7 (eight peaks predicted, seven observed). MS (EI) *m*/*z*: 512. HRMS calcd. for $C_{38}H_{24}O_2$: 512.1776; found: 512.1774.

6,7-Diphenyl-1,4-naphthoquinone (7)

6,7-Diphenyl-1,4-naphthoquinone (**7**) was recrystallized from ethanol to afford 150 mg (0.48 mmol) of a yellow solid; mp: 123–125 °C. IR (cm^{-1}): 1668 (C=O stretch). ^{1}H NMR (ppm, CD_2Cl_2) δ: 8.11 (s, 2H), 7.17–7.29 (m, 10H), 7.00 (s, 2H). ^{13}C NMR (ppm, $CDCl_3$) δ: 184.9, 146.2, 139.5, 138.8, 130.6, 129.6 128.8, 128.2, 127.7. MS (EI) *m*/*z*: 310 [M$^+$]. HRMS calcd. for $C_{22}H_{14}O_2$: 310.0994; found: 310.0996.

2,3-Diphenylanthraquinone (3)

To a solution of 1,4-naphthoquinone (0.81 g, 5.2 mmol) in 130 mL acetic acid was added 0.64 g (2.6 mmol) of 4-hydroxy-3,4-diphenylcyclopent-2-enone and 0.090 g (0.52 mmol) of *p*-toluenesulfonic acid. This mixture was then refluxed for 39 h. The solution was then cooled to room temperature, poured over water (150 mL), and then extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent removed in vacuo. The crude product was purified by column chromatography on silica gel with toluene as the eluent and then recrystallized from ethanol to afford 0.39 g (1.1 mmol, 42%) of **3**; mp: 203–206 °C (lit. value (21) mp 211 to 212 °C). IR (cm^{-1}): 1676 (C=O stretch). ^{1}H NMR (ppm, $CDCl_3$) δ: 8.36 (s, 2H), 8.35 (dd, 2H, *J* = 3.36, 5.80 Hz), 7.82 (dd, 2H, *J* =

3.36, 5.80 Hz), 7.30–7.20 (m, 10H). ^{13}C NMR (ppm, $CDCl_3$) δ: 183.0, 146.4, 139.6, 134.1, 132.2, 129.7, 128.3, 127.7, 127.3 (11 peaks predicted, 9 observed). MS (EI) *m/z*: 360 [M^+].

2,3-Di(naphthalen-2-yl)anthraquinone (8)

2,3-Di(naphthalen-2-yl)anthraquinone (**8**) was prepared from 4-hydroxy-3,4-di(naphthalen-2-yl)cyclopent-2-enone (**16**) according to the method described previously. The crude product was eluted through silica gel with a 1:1 mixture of hexanes–toluene, and then recrystallized from ethanol to afford 0.055 g (0.13 mmol, 18%) of **8** as a yellow solid; mp: 238 °C. ^{1}H NMR (ppm, $CDCl_3$) δ: 8.53 (s, 2H), 8.38 (dd, 2H, *J* = 3.3, 5.8 Hz), 7.96 (s, 2H), 7.85 (dd, 2H, *J* = 3.3, 5.8 Hz), 7.81 (dd, 2H, *J* = 3.4, 6.0 Hz), 7.76 (dd, 2H, *J* = 3.4, 6.0 Hz), 7.59 (d, 2H, *J* = 8.6 Hz), 7.48 (dd, 4H, *J* = 3.2, 6.2 Hz), 7.17 (dd, 4H, *J* = 1.7, 8.5 Hz). ^{13}C NMR (ppm, $CDCl_3$) δ: 183.0, 146.4, 137.3, 134.2, 133.8, 133.3, 132.6, 132.4, 130.1, 128.9, 128.3, 127.7, 127.4, 127.3, 126.5, 126.3 (17 peaks predicted, 16 observed). MALDI-TOF *m/z*: 462 [M + 2, 100]. Elemental anal. calcd. for $C_{34}H_{20}O_2$: C 88.67, H 4.38; found: C 88.51, H 4.58.

2,3-Di(o-tolyl)anthraquinone (9)

2,3-Di(*o*-tolyl)anthraquinone (**9**) was prepared from 4-hydroxy-3,4-di(*o*-tolyl)cyclopent-2-enone (**17**) according to the method described previously. The crude product was eluted through silica gel with toluene and recrystallized from ethanol to yield 0.090 g (0.23 mmol, 17%) of **9** as an off-white solid; mp 247 °C. ^{1}H NMR (ppm, $CDCl_3$) δ: 8.34 (dd, 2H, *J* = 3.3, 5.7 Hz), 8.28 (s, 2H), 7.82 (dd, 2H, *J* = 3.3, 5.7 Hz), 7.13–6.91 (broad m, 8H), 2.11 (s, 6H). ^{13}C NMR (ppm, $CDCl_3$) δ: 183.1, 147.3 (broad), 139.1 (broad), 135.3, 134.1, 133.8, 131.9, 130.2, 129.8, 127.8, 127.2, 125.2, 20.2 (broad) (14 peaks predicted, 13 observed). MS (EI) *m/z*: 388.1 [M^+, 100]. Elemental anal. calcd. for $C_{28}H_{20}O_2$: C 86.57, H 5.19; found: C 86.38, H 5.27.

2,3-Bis(4-methoxyphenyl)anthraquinone (10)

2,3-Bis(4-methoxyphenyl)anthraquinone (**10**) was prepared from 4-hydroxy-3,4-bis(4-methoxyphenyl)cyclopent-2-enone (**18**) according to the method described previously. The crude product was eluted through silica gel with a 4:1 mixture of hexanes – ethyl acetate as the eluent. The resulting product was recrystallized from ethanol to afford 0.04 g (0.09 mmol, 7%) of **10** as a brown solid; mp 168 °C. ^{1}H NMR (ppm, $CDCl_3$) δ: 8.34 (dd, 2H, *J* = 3.3, 5.8 Hz), 8.31 (s, 2H), 7.81 (dd, 2H, *J* = 3.3, 5.8 Hz), 7.16 (d, 4H, *J* = 8.7 Hz), 6.82 (d, 4H, *J* = 8.7 Hz), 3.82 (s, 6H). ^{13}C NMR (ppm, $CDCl_3$) δ: 183.0, 159.2, 145.9, 134.0, 133.8, 132.1, 131.9, 130.9, 129.5, 127.2, 113.8, 55.2. MS (CI) *m/z*: 421.2, 422.1 [M + 1, 100] (29%). Elemental anal. calcd. for $C_{28}H_{20}O_4$: C 79.98, H 4.97; found: C 80.13, H 4.90.

2-(4-Methoxyphenyl)-3-phenylanthraquinone (11)

2-(4-Methoxyphenyl)-3-phenylanthraquinone (**11**) was prepared from a mixture of **21a** and **21b** according to the method described previously. The crude product was eluted through a silica gel column using toluene. Recrystallization from ethanol afforded 0.087 g (0.22 mmol, 18%) of **11** as a yellow solid; mp 89–91 °C. ^{1}H NMR (ppm, $CDCl_3$) δ: 8.36–8.34 (m, 4H), 7.82 (dd, 2H, *J* = 3.3, 5.8 Hz), 7.30–7.29 (m, 3H), 7.23 (dd, 2H, *J* = 3.0, 6.7 Hz), 7.14 (d, 2H, *J* = 8.7 Hz), 6.80 (d, 2H, *J* = 8.7 Hz), 3.80 (s, 3H). ^{13}C NMR (ppm, $CDCl_3$) δ: 183.3, 183.2, 159.5, 146.5, 146.3, 140.1, 134.3, 134.3, 134.0, 133.9, 132.5, 132.1, 131.1, 130.0, 129.8, 129.7, 128.5, 127.8, 127.5, 113.9, 55.5 (23 peaks predicted, 21 observed). MS (EI) *m/z*: 390.4 [$C_{27}H_{18}O_3^+$, 100]. Elemental anal. calcd. for $C_{27}H_{18}O_3$: C 83.06, H 4.65; found: C 82.80, H 4.89.

2-(4-Bromophenyl)-3-(4-methoxyphenyl)anthraquinone (12)

2-(4-Bromophenyl)-3-(4-methoxyphenyl)anthraquinone (**12**) was prepared from 3-(4-bromophenyl)-4-hydroxy-4-(4-methoxyphenyl)cyclopent-2-enone/4-(4-bromophenyl)-4-hydroxy-3-(4-methoxyphenyl)cyclopent-2-enone (**23**) according to the method described previously. The product was eluted through silica gel with toluene, then recrystallized from ethanol to afford 0.120 g (0.26 mmol, 21%) of **12** as an orange solid; mp 215 to 216 °C. ^{1}H NMR (ppm, $CDCl_3$) δ: 8.34 (dd, 2H, *J* = 3.1, 5.4 Hz), 8.33 (s, 1H), 8.30 (s, 1H), 7.83 (dd, 2H, *J* = 3.3, 5.8 Hz), 7.43 (d, 2H, *J* = 8.4 Hz), 7.14–7.09 (m, 4H), 6.83 (d, 2H, *J* = 8.7 Hz), 3.82 (s, 3H). ^{13}C NMR (ppm, $CDCl_3$) δ: 183.2, 183.1, 159.6, 146.3, 145.1, 139.0, 134.4, 134.4, 133.9, 132.7, 132.2, 131.8, 131.7, 131.4, 131.1, 129.8, 129.7, 127.5, 122.3, 114.1, 55.5 (23 peaks predicted, 21 observed). MS (CI) *m/z* (relative intensity): 468.2 (80%), 469.2 (60%), 470.2 (100%), 471.2 (58%), 472 (13%). Elemental anal. calcd. for $C_{27}H_{17}BrO_3$: C 69.10, H 3.65; found: C 69.27, H 3.72.

2-(4-Methoxyphenyl)-3,6,7-triphenylanthraquinone (24)

2-(4-Methoxyphenyl)-3,6,7-triphenylanthraquinone (**24**) was prepared from 6,7-diphenyl-1,4-naphthoquinone and a mixture of **21a** and **21b**. The crude product was purified through silica gel with toluene as the eluent. Recrystallization of this product from ethanol afforded 0.14 g (0.26 mmol, 26%) of **24** as an orange solid; mp 230 °C. ^{1}H NMR (ppm, $CDCl_3$) δ: 8.40 (s, 2H), 8.38 (d, 2H, *J* = 2.9 Hz), 7.31–7.23 (m, 15H), 7.17 (d, 2H, *J* = 8.8 Hz), 6.82 (d, 2H, *J* = 8.8 Hz), 3.81 (s, 3H). ^{13}C NMR (ppm, $CDCl_3$) δ: 183.1, 183.0, 159.5, 146.6, 146.6, 146.4, 146.3, 140.1, 139.9, 132.7, 136.7, 132.3, 132.1, 131.2, 130.0, 129.9, 129.8, 129.7, 128.5, 128.4, 127.9, 127.8, 113.9, 55.5 (31 peaks predicted, 24 observed). MALDI-TOF *m/z*: 543 [M^+, 100]. Elemental anal. calcd. for $C_{39}H_{26}O_3$: C 86.32, H 4.83; found: C 85.97, H 5.03.

2,3-Bis(4-methoxyphenyl)-6,7-diphenylanthraquinone (25)

2,3-Bis(4-methoxyphenyl)-6,7-diphenylanthraquinone (**25**) was prepared from 6,7-diphenyl-1,4-napthoquinone (**7**) and 4-hydroxy-3,4-bis(4-methoxyphenyl)cyclopent-2-enone (**18**) according to the method described previously. This mixture of products was then purified through silica gel with a 4:1 mixture of hexanes – ethyl acetate as the eluent. The resulting solid was recrystallized from ethanol to afford 0.050 g (0.09 mmol, 7%) of **25** as an orange solid; mp 235 °C. ^{1}H NMR (ppm, $CDCl_3$) δ: 8.39 (s, 2H), 8.35 (s, 2H), 7.30–7.22 (m, 10H), 7.18 (d, 4H, *J* = 8.8 Hz), 6.83 (d, 4H, *J* = 8.7 Hz), 3.82 (s, 6H). ^{13}C NMR (ppm, $CDCl_3$) δ: 183.1, 159.4, 146.6, 146.1, 139.9, 132.7, 132.4, 132.3, 131.1, 129.9, 129.9, 129.8, 128.4, 127.9, 114.0, 55.5. MALDI-TOF *m/z*: 584

[M + 2, 100]. Elemental anal. calcd. for $C_{40}H_{28}O_4$: C 83.90, H 4.93; found: C 84.20, H 5.16.

General method for the preparation of ethane diones

The aldehyde (32 mmol) and potassium cyanide (1.3 g, 20 mmol) were dissolved in 20 mL of ethanol and 10 mL of water. After refluxing for 24 h, the solution was poured over water and extracted with dichloromethane, yielding the coupled α-hydroxyketone. This product was then dissolved in 25 mL pyridine and 15 mL water, and 5.0 g $CuSO_4$ (35 mmol) was added. This solution was refluxed for 16 h, then cooled to room temperature and extracted with dichloromethane. The combined organic extracts were washed water and the solvent removed to afford the 1,2-dione.

1,2-Di(o-tolyl)ethane-1,2-dione (14)

1,2-Di(*o*-tolyl)ethane-1,2-dione (**14**) was prepared in the manner described in the previous paragraph and was isolated as a pale yellow solid (66% yield); mp 88 to 89 °C (lit. value (22) mp 92 °C). ^{1}H NMR (ppm, $CDCl_3$) δ: 7.66 (d, 2H, *J* = 7.8 Hz), 7.49 (t, 2H, *J* = 7.5 Hz), 7.35 (d, 2H, *J* = 7.6 Hz), 7.28 (m, 2H), 2.71 (s, 6H).

1,2-Bis(4-methoxyphenyl)ethane-1,2-dione (15)

1,2-Bis(4-methoxyphenyl)ethane-1,2-dione (**15**) was prepared in the manner described previously and was isolated as a yellow solid (32% yield); mp obs. 131 °C (lit. value (23) mp 133 °C). ^{1}H NMR (ppm, DCl_3) δ: 7.95 (d, 4H, *J* = 8.8 Hz), 6.97 (d, 4H, *J* = 8.9 Hz), 3.89 (s, 6H).

1,2-Di(naphthalen-2-yl)ethane-1,2-dione (16)

1,2-Di(naphthalen-2-yl)ethane-1,2-dione (**16**) was prepared in the manner described previously, except NaCN was used in place of KCN, and the benzoin condensation was only allowed to proceed for 1.5 h instead of 24 h. Compound **16** was isolated in 64% yield as an off-white solid; mp 155 °C (lit. value (24) mp 155 to 156 °C). ^{1}H NMR (ppm, $CDCl_3$) δ: 8.45 (s, 2H), 8.15 (dd, 2H, *J* = 1.6 8.6 Hz), 7.99 (d, 2H, *J* = 8.7 Hz), 7.90 (d, 4H, *J* = 8.8 Hz), 7.64 (t, 2H, *J* = 7.6 Hz), 7.55 (t, 2H, *J* = 7.6 Hz). ^{13}C NMR (ppm, $CDCl_3$) δ: 194.8, 136.4, 133.6, 132.4, 130.5, 130.0, 129.6, 129.2, 128.0, 127.2, 123.8.

1-(4-Methoxyphenyl)-2-phenylethane-1,2-dione (20)

1-(4-Methoxyphenyl)-2-phenylethane-1,2-dione (**20**) was prepared in the manner described previously and was purified by column chromatography (silica gel, toluene) as a pale yellow solid (22% yield); mp 58.5–60 °C (lit. value (25) mp 61 °C). ^{1}H NMR (ppm, $CDCl_3$) δ: 7.96 (m, 4H), 7.65 (t, 1H, *J* = 7.4 Hz), 7.51 (t, 2H, *J* = 7.8 Hz), 6.98 (d, 2H, *J* = 8.9 Hz), 3.89 (s, 1H).

1-(4-Bromophenyl)-2-(4-methoxyphenyl)ethane-1,2-dione (22)

1-(4-Bromophenyl)-2-(4-methoxyphenyl)ethane-1,2-dione (**22**) was prepared in the manner described previously and was isolated as a yellow solid (46% yield); mp 135 °C (lit. value (26) mp 136 to 137 °C). ^{1}H NMR (ppm, $CDCl_3$) δ: 7.93 (d, 2H, *J* = 8.9 Hz), 7.84 (d, 2H, *J* = 8.6 Hz), 7.65 (d, 2H, *J* = 8.6 Hz), 6.98 (d, 2H, *J* = 8.9 Hz), 3.89 (s, 3H).

Alternate synthesis of 1-(4-methoxyphenyl)-2-phenylethane-1,2-dione (20)

To a dried Schlenk flask was added 4-iodoanisole (3.2 g, 13.8 mmol), tetrakis(triphenylphosphine)palladium (0.059 g, 0.05 mmol), and copper(I) iodide (0.815 g, 4.3 mmol) under nitrogen. To this mixture was added via syringe phenylacetylene (1.75 mL, 16 mmol), 50 mL of dry tetrahydrofuran, and 10 mL of dry diisopropylamine. The resulting mixture was refluxed under nitrogen for 45 h, at which time it was cooled to room temperature and eluted through a short plug of silica gel with dichloromethane. After removing the solvent in vacuo, the crude product was oxidized by treating it with iodine (3.94 g, 15.6 mmol) in dimethylsulfoxide (50 mL) at 145 °C for 44 h. This solution was cooled to room temperature, poured into water, and the resulting mixture was extracted with dichloromethane. The combined organic extracts were washed with brine, then with a saturated aqueous potassium iodide solution, dried ($MgSO_4$), and the solvent removed under reduced pressure. The product was then recrystallized from a methanol–water mixture to **20** as a pale yellow solid (1.7 g, 8.2 mmol, 59% yield).

General method for the preparation of 4-hydroxy-3,4-diarylcyclopent-2-enones

Ethane-1,2-dione (10 mmol) was stirred for 1 week at room temperature in an ethanolic solution of potassium hydroxide (0.56 g, 10 mmol) and acetone (12 mL, 160 mmol). This solution was then poured over water and extracted with dichloromethane, yielding the desired product. Since these compounds proved difficult to purify, they were used directly in the condensation reactions with quinones.

4-Hydroxy-3,4-diphenylcyclopent-2-enone (4)

4-Hydroxy-3,4-diphenylcyclopent-2-enone (**4**) was prepared in the manner described in the previous paragraph as a pale yellow solid (96% yield). ^{1}H NMR (ppm, $CDCl_3$) δ: 7.52–7.50 (m, 2H), 7.47–7.44 (m, 2H), 7.37–7.27 (m, 6H), 6.71 (s, 1H), 3.02 (d, 1H, *J* = 18.5 Hz), 2.90 (d, 1H, *J* = 18.5 Hz).

4-Hydroxy-3,4-di(naphthalene-2-yl)cyclopent-2-enone (16)

4-Hydroxy-3,4-di(naphthalene-2-yl)cyclopent-2-enone **(16)** was prepared in the manner described previously as a brown solid. ^{1}H NMR (ppm, $CDCl_3$) δ: 8.19 (d, 2H, *J* = 11.5 Hz), 7.85–7.40 (m, 12H), 6.90 (s, 1H), 3.13 (d, 1H, *J* = 18.6 Hz), 3.02 (d, 1H, *J* = 18.6 Hz).

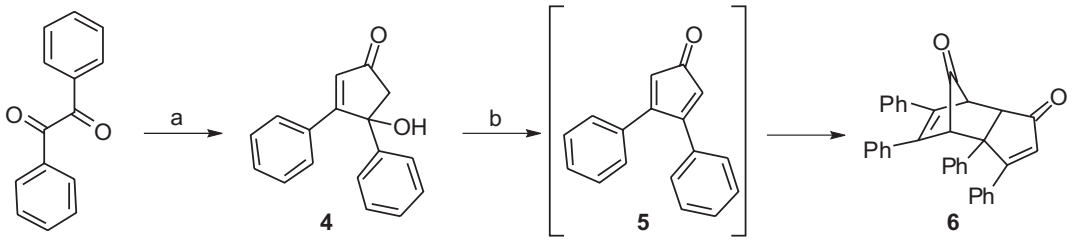
4-Hydroxy-3,4-di(o-tolyl)cyclopent-2-enone (17)

4-Hydroxy-3,4-di(*o*-tolyl)cyclopent-2-enone (**17**) was prepared in the manner described previously as a brown solid. ^{1}H NMR (ppm, $CDCl_3$) δ: 7.55–7.53 (m, 2H), 7.20–7.14 (m, 4H). 6.99–6.97 (m, 2H), 6.40 (s, 1H), 3.07 (d, 2H, *J* = 18.6 Hz), 2.98 (d, 2H, *J* = 18.6 Hz), 2.41 (s, 3H), 2.31 (s, 3H).

4-Hydroxy-3,4-bis(4-methoxyphenyl)cyclopent-2-enone (18)

4-Hydroxy-3,4-bis(4-methoxyphenyl)cyclopent-2-enone (**18**) was prepared in the manner described previously as a brown solid. ^{1}H NMR (ppm, $CDCl_3$) δ: 7.52 (d, 2H, *J* = 9.0 Hz), 7.34 (d, 2H, *J* = 8.8 Hz), 6.83 (dd, 4H, *J* = 8.9, 20.5 Hz),

Scheme 2. Reagents and conditions: (*a*) acetone, KOH, 1 week; (*b*) AcOH, TsOH, reflux 48 h.



6.60 (s, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 2.98 (d, 2H, *J* = 18.5 Hz), 2.85 (d, 2H, *J* = 18.5 Hz).

4-Hydroxy-3-(4-methoxyphenyl)-4-phenylcyclopent-2-enone (21a)

4-Hydroxy-3-(4-methoxyphenyl)-4-phenylcyclopent-2-enone (**21a**) was prepared in the manner described previously and isolated via column chromatography (silica, toluene–EtOAc, 9:1 as eluent) as a white solid. ^{1}H NMR (ppm, $CDCl_3$) δ: 7.51 (dt, 2H, *J* = 9.0, 2.1 Hz), 7.45 (dt, 2H, *J* = 7.3, 1.6 Hz), 7.35 (td, 2H, *J* = 7.6, 1.8 Hz), 7.28–7.25 (m, 1H), 2.88 (d, 1H, *J* = 18.4 Hz), 2.53 (br, 1H).

4-Hydroxy-4-(p-methoxyphenyl)-3-phenylcyclopent-2-enone (21b)

4-Hydroxy-4-(*p*-methoxyphenyl)-3-phenylcyclopent-2-enone (**21b**) was prepared in the manner described previously and isolated via column chromatography (silica, toluene–EtOAc, 7:3 as eluent) as a yellow solid. ^{1}H NMR (ppm, $CDCl_3$) δ: 7.52 (dt, 2H, *J* = 7.1, 1.3 Hz), 7.37–7.35 (m, 3H), 7.30 (td, 2H, *J* = 7.4, 1.5 Hz), 6.87 (dt, 2H *J* = 8.8, 2.5 Hz), 6.66 (s, 1H), 3.79 (s, 3H), 3.00 (d, 1H, *J* = 18.5 Hz), 2.88 (d, 1H, *J* = 18.5 Hz), 2.65 (br, 1H).

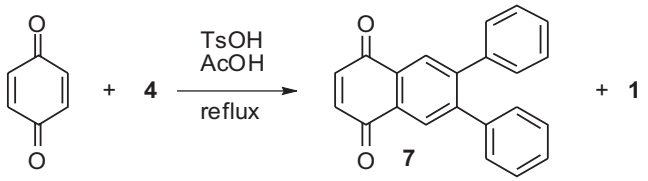
3-(4-Bromophenyl)-4-hydroxy-4-(4-methoxyphenyl)cyclopent-2-enone and 4-(4-bromophenyl)-4-hydroxy-3-(4-methoxyphenyl)cyclopent-2-enone (23)

3-(4-Bromophenyl)-4-hydroxy-4-(4-methoxyphenyl)cyclopent-2-enone and 4-(4-bromophenyl)-4-hydroxy-3-(4-methoxyphenyl)cyclopent-2-enone (**23**) were prepared in the manner described previously as a yellow solid. No attempt was made to separate these isomers. ^{1}H NMR (ppm, $CDCl_3$) δ: 7.52–7.43 (m, 4H), 7.34–7.32 (m, 2H), 6.86 (d, 2H, *J* = 9.0 Hz), 6.82 (d, 2H, *J* = 8.9 Hz), 6.66 (s, 1H), 6.64 (s, 1H), 3.79 (s, 3H), 2.97 (d, 1H, *J* = 18.6 Hz), 2.83 (d, 1H, *J* = 18.5 Hz).

Results and discussion

Our initial studies focused on the construction of 2,3-diphenylanthraquinone (**3**) starting from benzil, which has the advantage of being an inexpensive, commercially available starting material. 4-Hydroxy-3,4-diphenylcyclopent-2-enone (**4**) was synthesized in 96% yield by the condensation of benzil and acetone in the presence of catalytic potassium hydroxide (27). Heating **4** in refluxing acetic acid for 48 h caused no appreciable decomposition of this compound. When this reaction was carried out in the presence of catalytic *p*-toluenesulfonic acid, however, compound **6** was obtained almost quantitatively. The formation of this product, which arises from the dimerization of the highly reactive intermediate **5** (17, 18), demonstrates that this cyclone was indeed being generated under these conditions (Scheme 2).

Scheme 3. Condensation of compound **4** with benzoquinone.



We next turned our attention to trapping this in situ generated cyclone with 1,4-naphthoquinone. When cyclopentadienone **5** was generated in the presence of excess quinone, compound **3** was formed as the major product in 42% yield. Significantly, only trace quantities (<5%) of the dimer **6** were observed under these conditions. More generally, this side product did not arise to an appreciable extent in any subsequent reactions of **4** with quinones, indicating that the dimerization of **5** does not pose a significant problem in these syntheses.

The condensation of **4** with 1,4-benzoquinone was next investigated. This reaction affords two major products: the anthraquinone derivative **1** and the naphthoquinone **7** in an approximately 1:1 ratio (Scheme 3). That significant quantities of the anthraquinone were formed even in the presence of a twofold excess of benzoquinone — conditions that should strongly promote formation of the naphthoquinone **7** — suggests that compound **7** or one of its precursors is a much more reactive dienophile than benzoquinone itself, thus favouring the rapid reaction with a second equivalent of the cyclone. This tendency for benzoquinone to form bisadducts in acetic acid has previously been observed in its reaction with anthracene (28) and 1,1-thiophene dioxides (12).

Far from being an unwanted side product, the naphthoquinone **7** is desirable as a potential dienophile for the subsequent preparation of unsymmetrical anthraquinones. In an attempt to bias the reaction towards the formation of this compound, the condensation of **4** with benzoquinone was carried out in refluxing toluene, which has previously been found to favor formation of monoadducts (12, 28). Once again, catalytic *p*-toluenesulfonic acid was added to activate **4** towards dehydration. Under these conditions, the formation of the cyclopentadienone intermediate **5** is considerably slower than when the reaction was carried out in acetic acid. After 2 days, no appreciable reaction of the starting materials was observed. Allowing this reaction to proceed for 6 days led to only 25% of compound **4** being consumed, although it was gratifying to note that the ratio of naphthoquinone to anthraquinone obtained had increased to 20:1. Addition of a small amount of acetic acid to this reaction

Scheme 4. Reagents and conditions: (*a*) NaCN or KCN, EtOH–H_2O, reflux; (*b*) acetone, KOH, RT, 1 week; (*c*) 1,4-naphthoquinone, AcOH, TsOH, reflux 48 h.

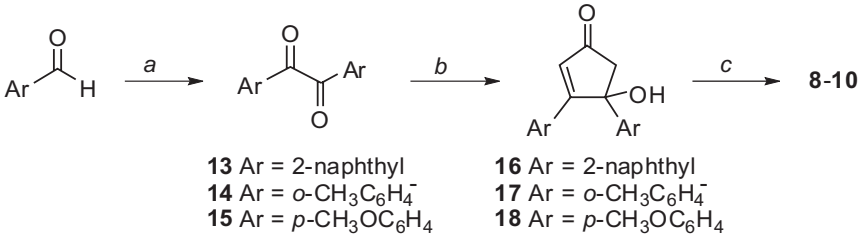
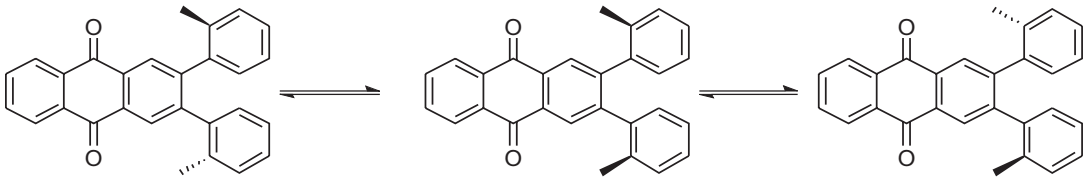


Fig. 1. syn–anti Isomerization of compound **10**.



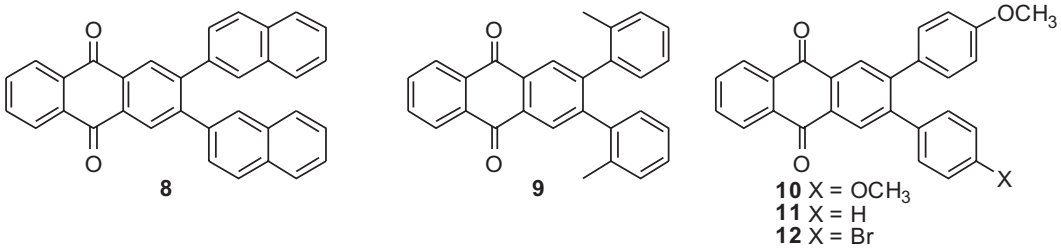
mixture greatly increased the rate; under these conditions, 40% of **4** had reacted after 2 days, but the ratio of naphthoquinone–anthraquinone dropped to 5:1.

The success of the approach described above prompted us to attempt the preparation of other 2,3-disubstituted anthraquinones. Since electronic and steric effects play important roles in the photochemistry of anthracene derivatives (11, 29), we were interested in synthesizing a range of anthraquinones with different pendant aromatic rings. The naphthyl- and *o*-tolyl-substituted derivatives **8** and **9** were therefore targeted as more sterically congested analogs of **3**. On the other hand, the introduction of para-substituents onto the peripheral aromatic rings in compounds **10**–**12** should not appreciably alter lateral bulk of the phenyl rings, but will change electronic properties of these groups. More specifically, methoxy- and bromo-substituents were chosen because they also provide useful points of attachment for the eventual incorporation of these compounds into polymers or other structures.

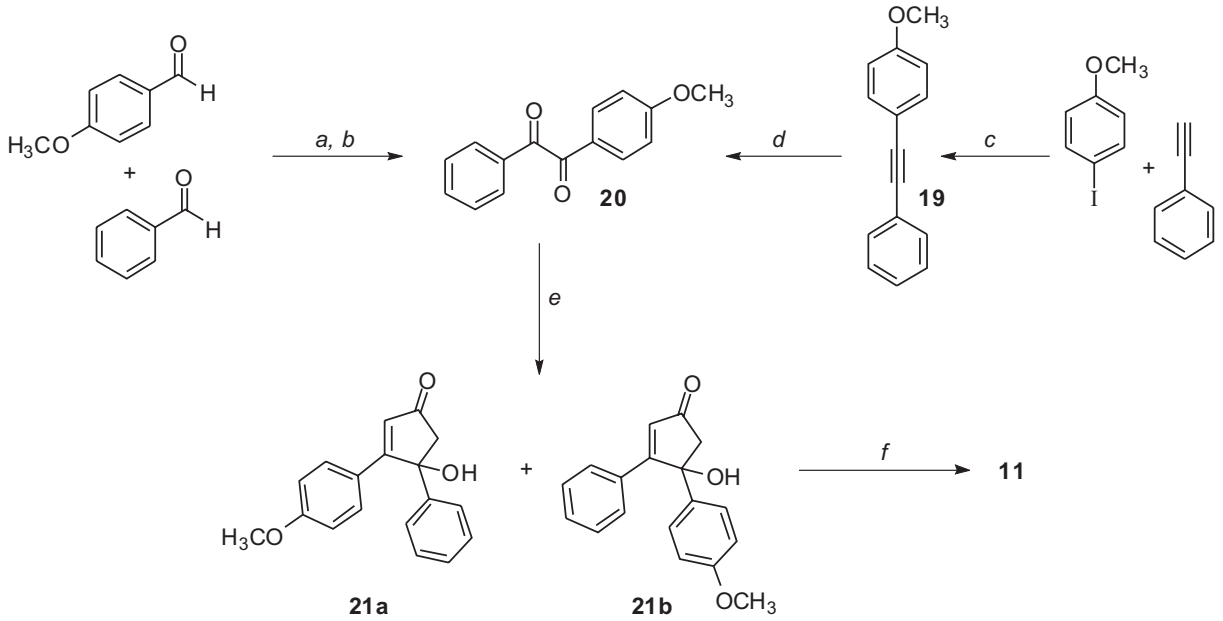
The symmetrical 1,2-diaryl-1,2-ethanediones (**13**–**15**) were synthesized from 2-naphthaldehyde, *o*-tolualdehyde, and *p*-anisaldehyde, respectively, using slightly modified literature procedures (22–24). Like benzil, these compounds are readily converted to the corresponding hydroxycyclopent-2-enones (**16**–**18**). These hydroxy compounds in general proved difficult to purify and were therefore used as obtained in subsequent reactions. Condensation of these compounds with 1,4-naphthoquinone afforded the desired products **8**–**10** in isolated yields that varied from 7%–18% (Scheme 4). It is unclear at this time why the reactions involving these substituted derivatives were much lower than for **4**, although both electronic and steric effects may have been in part responsible.

In the course of characterizing the tolyl derivative **9**, it was noted that several peaks in both the ^1H and ^{13}C NMR spectra of this compound were appreciably broadened. The affected peaks were identified as those associated with the pendant tolyl groups, suggesting that these rings are undergoing conformational syn-/anti-isomerism on the NMR timescale (Fig. 1). This is consistent with the observation that a similar molecule (2,2′-dimethyl-*o*-terphenyl) has a barrier to isomerization of 62 kJ/mol, with an NMR coalescence temperature of 9 °C (30). Although quantitative variable-temperature NMR experiments have not yet been carried out on **9**, the tolyl peaks were observed to sharpen at elevated temperatures, as expected.

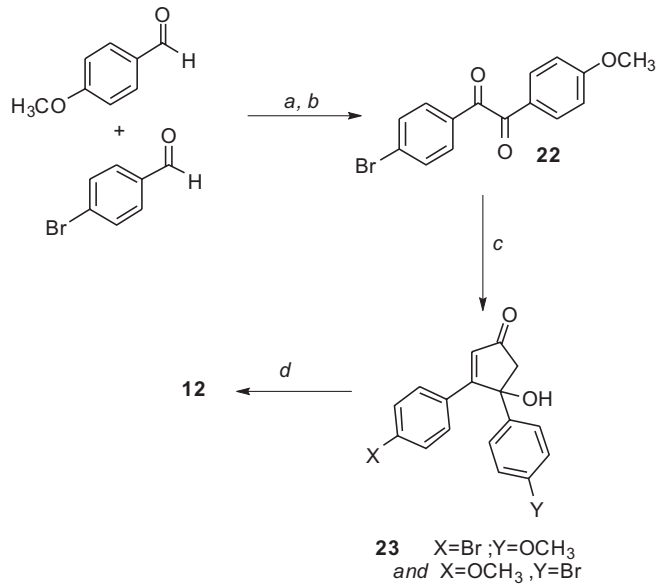
This general synthetic approach can also be employed in the preparation of lower symmetry anthraquinones such as **11** and **12**, which were derived from the corresponding unsymmetrical benzils **20** and **22**, respectively (Schemes 5 and 6). Two routes were explored for the preparation of benzil **20**. This compound can be obtained via the cross-benzoin condensation of benzaldehyde and anisaldehyde (31). Although this synthesis has the advantage of employing relatively inexpensive starting materials, it does yield a mixture of benzil and compound **20** in an approximately 1:3 ratio, with **20** being isolated in only a 22% yield. A more systematic synthesis of this compound proceeds via the oxidation of the diphenylacetylene derivative (**19**), which is easily prepared from phenylacetylene and *p*-iodoanisole using standard Hagihara–Sonagashira conditions. Conversion of this compound to **20** has previously been reported using catalytic



Scheme 5. Reagents and conditions: (*a*) NaCN or KCN, EtOH–H_2O, reflux; (*b*) $CuSO_4$, pyridine–H_2O; (*c*) $Pd(PPh_3)_4$, CuI, $(i\text{-}Pr)_2NH$, THF, reflux 48 h; (*d*) I_2, DMSO, 145 °C; (*e*) acetone, KOH, RT, 1 week; (*f*) 1,4-naphthoquinone, AcOH, TsOH, reflux 48 h.



Scheme 6. Reagents and conditions: (*a*) NaCN or KCN, EtOH–H_2O, reflux; (*b*) $CuSO_4$, pyridine–H_2O; (*c*) I_2, DMSO, 145 °C; (*d*) acetone, KOH, RT, 1 week; (*e*) 1,4-naphthoquinone, AcOH, TsOH, reflux 48 h.



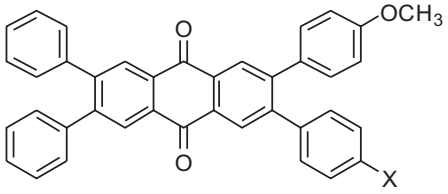
palladium chloride in DMSO (32). We have found that, contrary to this previous report, **19** was also cleanly oxidized to **20** in the presence of I_2/DMSO. The overall yields for this alkyne route are considerably higher (59% vs. 22%) than for the cross-benzoin method, although the use of more costly reagents is required.

Condensation of the unsymmetrical benzil **20** with acetone yields two products that were formed in a 5:2 ratio. These products were readily separated by column chromatography and were identified as the two regioisomers of the hydroxycyclopent-2-enones **21a** and **21b**. To positively identify the two isomers, NOESY spectra were obtained for both compounds. The spectrum of the major product showed a strong NOE between the protons on the anisole ring and the vinylic proton on the cyclopentene ring, which led to the identification of this compound as **21a**. Conversely, a significant cross peak was observed between the phenyl ring and the vinylic proton in the NOESY spectrum of the minor product, confirming the identity of this compound as the second regioisomer **21b**. The formation of **21a** as the major product is consistent with the stabilization of the incipient positive charge on the cyclopentane ring by the electron-donating *p*-methoxy group during the elimination of water. From a practical standpoint, the formation of two isomers is not problematic, since both **21a** and **21b** yield the same cyclopentiadienone upon loss of water. These isomeric hydroxycyclopent-2-enones were therefore not separated prior to carrying out Diels–Alder reactions with naphthoquinone derivatives in subsequent experiments. Condensation of a mixture of these intermediates with 1,4-naphthoquinone afforded **11** in 18% yield.

In a similar manner, the brominated anthraquinone (**12**) was prepared from *p*-bromobenzaldehyde and anisaldehyde (Scheme 6). The two isomers of the cyclone precursor, collectively denoted as **23**, were not separated from one another prior to condensation with 1,4-naphthoquinone.

It is also possible to use these hydroxycyclopent-2-enone intermediates in the synthesis of 2,3,6,7-tetraarylanthraquinones bearing different aromatic rings at one or more of the sites. To demonstrate the feasibility of this approach, we condensed 6,7-diphenyl-1,4-naphthoquione (**7**) with both **21a**, **21b**, and **18**. In this manner, we were able to prepare compounds **24** and **25** in yields of 26% and 7%, respectively.

In conclusion, we have developed a new strategy for synthesizing highly substituted anthraquinone derivatives from in situ generated cyclopentadienones. This approach is complementary to other methods that have commonly been used to prepare anthraquinones, such as the Friedel–Crafts con-



24 X = H
25 X = OCH_3

densation of phthalic anhydrides with benzene derivatives, an approach that is incompatible with functional groups such as pendant aromatic rings. Although the yields of the condensation reactions reported herein were generally low, our approach nonetheless offers several advantages. These compounds were prepared in only four steps from inexpensive starting materials such as acetone, 1,4-naphthoquinone, and commercially available aldehydes. Significantly, these syntheses are also amenable to working at larger scales. The hydroxycyclopent-2-enone precursors reported herein are readily prepared in multigram quantities, and gram-scale reactions of naphthoquinone with these compounds have been routinely carried out in our laboratory. In contrast, the sulfone **2** is synthesized using much more expensive starting materials and catalysts and could not, in our hands, be prepared on large scales. Moreover, the use of cyclopentadienones lends itself to the formation of lower-symmetry derivatives, such as **10**–**12**, **24**, and **25**, which would be more difficult to prepare from the corresponding sulfones. This approach is also tolerant of functional groups such as aryl bromides, which are incompatible with the chemistry used to prepare diarylsulfone analogues of **2**. These cyclopentadienones are therefore viable precursors for the large-scale preparation of anthraquinones that are not otherwise readily accessible. Further work is being carried out in our laboratory in an ongoing attempt to optimize these reactions.

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