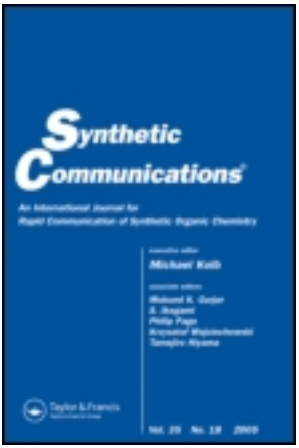

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Synthesis of Anthracyclinone Precursor: 5,12-Dihydroxy-1,3,4-trihydronap

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Synthesis of Anthracyclinone Precursor: 5,12-Dihydroxy-1,3,4-trihydronaphthacene-2,6,11-quinone

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ABSTRACT

Two practical and efficient approaches for preparing large quantities of 5,12-dihydroxy-1,3,4-trihydronaphthacene-2,6,11-quinone **9** are described. Both synthetic approaches involve a simple route with a fewer number of steps and utilize readily available and inexpensive starting materials. Large-scale production of this precursor may prove to be useful for further research involving the synthesis of antineoplastic anthracyclines and development of their analogs with increased activity and decreased toxicity.

Key Words: Anthracyclines; Anthracyclinones; Daunorubicin; 4-Demethoxyaglycones; Doxorubicin; Idarubicin.

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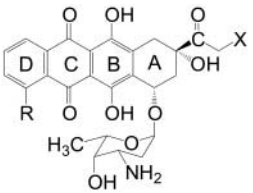
INTRODUCTION

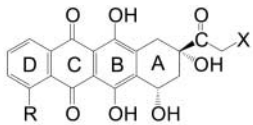
Daunorubicin **1** and doxorubicin **2** are structurally related to the group of glycoside antibiotics called anthracyclines. These agents have shown a very high activity against a wide variety of human cancers. However, chemotherapy employing these anthracyclines is hampered by various undesired side effects, the most notable and serious one of which is dose-related cardiotoxicity.[1]

This important class of antineoplastic agents has been obtained only by fermentation of different fungi belonging to the genus *Streptomyces*.[1] They cannot be produced economically by known synthetic methods; thus, the cost of the drugs is extremely high. These factors have prompted a great interest in development of synthetic routes to these compounds and their analogs with improved therapeutic indices.

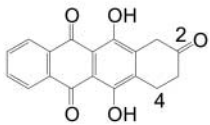


1 R = OCH_3, X = H
2 R = OCH_3, X = OH
3 R = H, X = H
4 R = H, X = OH

In a search for superior analogs, it was established by Arcamone and coworkers that the two unnatural anthracyclines, 4-demethoxydaunorubicin **3** and 4-demethoxydoxorubicin **4**, possess increased activity and decreased toxicity.[1] Currently, 4-demethoxydaunorubicin, called idarubicin, is clinically available in the United States. Clinical studies indicate that the drug possesses higher affinity for lipids than both parent drugs, which suggests possible oral administration of the drug, and thus provides a distinct advantage over the parent drugs.[2,3]



5 R = OCH_3, X = H
6 R = OCH_3, X = OH
7 R = H, X = H
8 R = H, X = OH



9

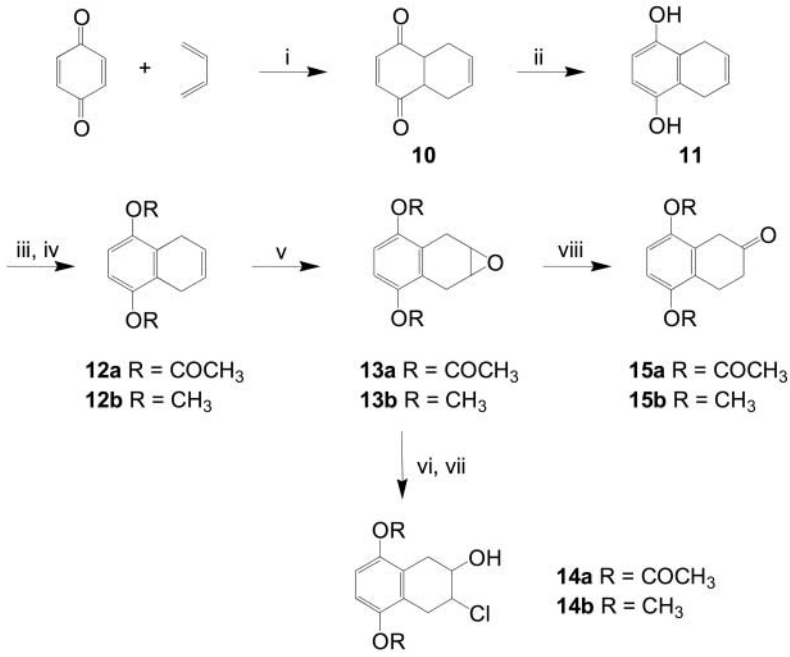
The majority of anthracycline syntheses has been concentrated on the total syntheses of the aglycones such as daunorubicinone **5**, adriamycinone

6, and 4-demethoxy aglycones **7** and **8**. Methodologies employed in these syntheses include (a) Friedel-Crafts acylation and alkylation; (b) Marschalk reaction; (c) Diels-Alder reaction; (d) Claisen rearrangement; and (e) 1,4-dipole-metalated quinone strategy.[4] Although different approaches have been reported, they involve a considerable number of steps and the yields are too low for economical preparation. Herein we report two alternative routes that provide a practical and efficient approach for larger scale preparation of 4-demethoxyaglycones. Our objectives are to develop an approach that involves fewer steps with simpler reactions and uses inexpensive and readily available starting materials. In order to avoid stereochemical problems of the hydroaromatic ring A in the early stage of synthesis, we were particularly intrigued in the preparation of a well-known aglycone precursor, 5,12-dihydroxy-1,3,4-trihydronaphthacene-2,6,11-quinone **9**. Different functionalities at C-2 and C-4 of the aglycone precursor, followed by isomeric resolution, can be subsequently introduced by several well-known reactions to produce desirable 4-demethoxyaglycones **7** and **8**.[5]

RESULTS AND DISCUSSION

According to our methodology, the Diels-Alder reaction was used to construct the AB ring synthon. As illustrated in Sch. 1, we started with the reaction between 1,4-benzoquinone and 1,3-butadiene to give an excellent yield of the tetrahydro-1,4-naphthoquinone **10**, which was aromatized with glacial AcOH in the presence of concentrated HBr as a catalyst to afford 5,8-dihydro-1,4-dihydroxynaphthalene **11** (91%). Diacetylation by Ac_2O and dimethylation by Me_2SO_4 in NaOH solution of compound **11** yielded the diacetoxy compound **12a** (98%) and the dimethoxy compound **12b** (68%), respectively. Epoxidation of **12a, b** with *m*-CPBA in CH_2Cl_2 gave the epoxides **13a, b** with 97% and 91% yields, respectively. It is notable that the quinone **10** could also be diacetylated and dimethylated in a similar manner to that described for the dihydroxy compound **11** to afford excellent yields of compounds **12a** and **12b**, respectively.

Several attempts to rearrange the epoxides **13a** and **13b** in the presence of a Lewis acid such as BF_3 etherate or $AlCl_3$ under different conditions[6] failed to produce the corresponding disubstituted 2-tetralones **15a** and **15b**. It appeared that BF_3 etherate and $AlCl_3$ were too reactive and the resulting sticky materials could not be purified and identified. A very low yield of one product obtained from the reaction of **13b** with $AlCl_3$ in dry toluene was characterized as 5,8-dimethoxy-3-chloro-2-hydroxy-1,2,3,4-tetrahydronaphthalene **14b**. Other acid catalysts such as *p*-TsOH, dry HCl gas, and methane sulfonic acid were also employed.[7] The results indicated that the epoxides underwent nucleophilic

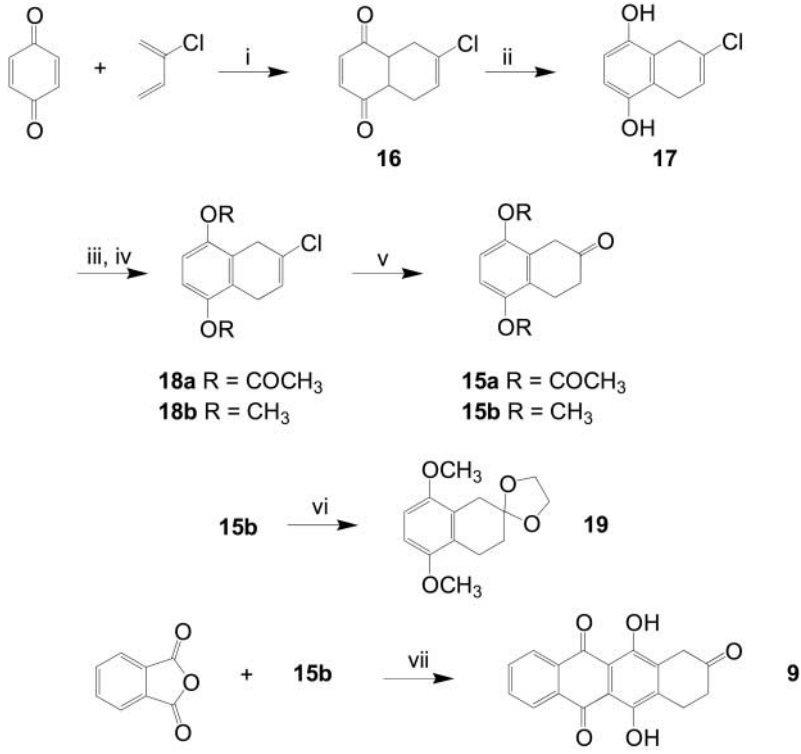


Scheme 1. (i) Toluene, rt, 5 days; (ii) glacial AcOH, conc. HBr, 80° and then rt, 15 min; (iii) Ac_2O, conc. H_2SO_4, rt, 15 min; (iv) Me_2SO_4, $NaOH/H_2O$, 10° and then rt, 12 hr; (v) *m*-CPBA, CH_2Cl_2, rt, 12 hr; (vi) dry HCl gas, anhydrous ethylene glycol dimethyl ether, $(-20) - (-10)°$, overnight; (vii) refluxed, $AlCl_3$, dry toluene, 2 hr; (viii) refluxed, $MgBr_2$ etherate, dry toluene, 6 hr.

addition instead of the rearrangement. For example, the reaction of the epoxide **13a** with dry HCl gas, in CH_2Cl_2 or in anhydrous ethylene glycol dimethyl ether gave the chlorohydrin **14a** in a very good yield. It is possible that the conditions were not dry enough for a hydride shift to occur. The acid-catalyzed rearrangement of the epoxide **13b** was eventually achieved when the epoxide was refluxed with excess $MgBr_2$ etherate in dry toluene for 6 hours, resulting in the 5,8-dimethoxy-2-tetralone **15b** in a 60% yield. The rearrangement of the epoxide **13a** in the presence of $MgBr_2$ etherate in dry toluene also yielded the corresponding 2-tetralone **15a**. Attempts to isolate and purify compound **15a** failed but a ^1H nmr spectrum of its 2,4-dinitrophenyl hydrazone indicated that the tetralone **15a** was actually formed.

A similar approach (Sch. 2) was conducted by utilizing 2-chloro-1,3-butadiene (chloroprene) as a diene. This procedure was modified from the procedure developed by Grob and Jundt in 1952.[8]

As illustrated in Sch. 2, diacetylation and dimethylation of either compound **16** or **17** yielded the vinyl chlorides **18a** and **18b** in good yields. The 5,8-dimethoxy-2-tetralone **15b** was then obtained in 40% yield from the hydrolysis of the corresponding vinyl chloride **18b** with concentrated H_2SO_4. This modified method was able to produce large quantities of the 2-tetralone **15b** in just three steps with less-expensive reagents. Acid hydrolysis of the vinyl chlorides **17** and **18a**, however, failed to give the corresponding 2-tetralones. The ethylene ketal **19** was prepared in order to protect the keto functional group of compound **15b** before condensation with phthalic anhydride; however, this step was unnecessary. Finally, the aglycone precursor, 5,12-dihydroxy-1,3,4-trihydronaphthacene-2,6,11-quinione **9**, was obtained



Scheme 2. (i) refluxed, benzene/xylene, 6 h; (ii) glacial AcOH, conc. HBr, 80° and then rt, 15 min; (iii) Ac_2O, conc. H_2SO_4, rt, 15 min; (iv) Me_2SO_4, $NaOH/H_2O$, 10° and then rt, 12 h; (v) conc. H_2SO_4, 0°, 2.5 h; (vi) refluxed, ethylene glycol, benzene, *p*-TsOH; (vii) $AlCl_3/NaCl$, 180°, 2 min.

in 80% yield by the Friedel-Crafts acylation of **15b** with phthalic anhydride in a single pot procedure.

CONCLUSION

These syntheses may prove to be a practical and efficient approach for preparing large quantities of 5,12-dihydroxy-1,3,4-trihydronaphthacene-2,6,11-quinone **9**, which will be a useful precursor for further research involving the synthesis of anthracycline antibiotics and development of their analogues with increased activity and decreased toxicity.

EXPERIMENTAL

All melting points are uncorrected. All infrared spectra (FT-IR) were recorded with thin film on NaCl plate, except when mentioned in the experimental, and only noteworthy absorptions (cm^{-1}) are listed. ^{1}H and ^{13}C NMR spectra were recorded at 90 MHz and at 400 MHz with TMS as an internal reference. All mass spectra were determined with a gas chromatograph with a mass detector utilizing electron impact ionization. The results of elemental analyses are within $\pm 0.3\%$ of the theoretical values.

4a,5,8,8a-Tetrahydronaphthoquinone-1,4-dione (10)

A gas delivery system consisted of a reaction cylinder, a gas dispersion tube, and a 1, 3-butadiene tank; all were interconnected by a 2-inch tygon tube. The reaction cylinder was charged with 50 g (0.46 mol) of 1,4-benzoquinone and 120 mL of toluene. To the magnetically stirred suspension the 1,3-butadiene gas was added at a slow rate through the gas dispersion tube until the weight of the cylinder increased by the required amount of the diene (24.9 g, 0.48 mol). After the addition was complete, the cylinder was stoppered and the dark green reaction mixture was stirred at room temperature for 5 days. Then the reaction mixture was filtered and the solvent was evaporated to give 65.4 g (88%) of **10** as a pale yellow solid. A part of the crude product was recrystallized from petroleum ether to afford the pure adduct of **10** as pale green needles, mp 56–57° (ref. 55–60°).[9] IR: 1676 (C═O) cm^{-1}; ^{1}H nmr (400 MHz, $CDCl_3$): δ 2.15–2.21 (2H, m), 2.44–2.50 (2H, m), 3.21–3.26 (2H, m), 5.66–5.72 (2H, t, J = 1.5 Hz), 6.66 (2H, s); ^{13}C nmr (90 MHz, $CDCl_3$): δ 24.38, 46.57, 125.12, 140.10, 201.04; GC-MS: m/z 162 ($M^{+\bullet}$),

147, 134, 115, 105, 79, 77, 54; Anal. Calcd. for $C_{10}H_{10}O_2$ (162.18): C, 74.06; H, 6.21; O, 19.73. Found: C, 74.05; H, 6.19.

5,8-Dihydronaphthalene-1,4-diol (11)

A mixture of 24 g (0.15 mol) of the quinone **10** in 60 mL glacial AcOH was heated until the temperature reached 80°. The heating was stopped and a few drops of concentrated HBr were added to the hot solution. A vigorous exothermic reaction occurred, the temperature rapidly increasing to 110–115°. The solution was stirred at room temperature for 15 min and then it was allowed to stand and cool down to room temperature. Upon cooling, a mass of white crystals separated. The precipitate was filtered and dried to give 21.8 g (91%) of **11**. A part of the crude product was recrystallized from benzene/acetone solvent pair to afford pure **11** as white crystals, mp 209–211° (ref. 208–209°).[9] IR: 3258 (OH), 1482, 1424, 1405, 1380 cm^{-1}; ^1H nmr (90 MHz, acetone-d_6): δ 3.24 (4H, d, J = 1.4 Hz), 5.87–5.91 (2H, t, J = 1.4 Hz), 6.54 (2H, s), 7.52 (2H, s); ^{13}C nmr (90 MHz, DMSO-d_6): δ 24.71, 112.59, 122.47, 124.70, 147.98; GC-MS: m/z 162 ($M^{+\bullet}$), 147, 115, 105, 77; Anal. Calcd. for $C_{10}H_{10}O_2$ (162.18): C, 74.06; H, 6.21; O, 19.73. Found: C, 74.01; H, 6.27.

4-Acetyloxy-5,8-dihydronaphthalen-1-yl acetate (12a)

A mixture of 21.2 g (0.13 mol) of compound **11** in 80 mL Ac_2O was stirred at room temperature until a clear solution was obtained. To the solution was added a few drops of concentrated H_2SO_4. The resulting deep red solution was stirred for 15 min and then it was poured onto crushed ice. The reaction mixture was stirred until all the sticky material turned to a solid. The solid was filtered and dried, resulting in 31.3 g (98%) of **12a** as white powder. Recrystallization from 95% EtOH yielded pure **12a** as white needles, mp 130–132° (ref. 133–133.5°).[9] IR: 1757 (C=O), 1471, 1369, 1201 cm^{-1}; ^1H nmr (90 MHz, $CDCl_3$): δ 2.28 (6H, s), 3.17–3.19 (4H, d, J = 1.3 Hz), 5.81–5.84 (2H, t, J = 1.3 Hz), 6.93 (2H, s); ^{13}C nmr (90 MHz, $CDCl_3$): δ 20.86, 24.44, 120.58, 123.52, 128.94, 146.95, 170.00; GC-MS: m/z 204 ($M^{+\bullet}$), 162, 144, 115, 105, 77; Anal. Calcd. for $C_{14}H_{14}O_4$ (246.26): C, 68.28; H, 5.73; O, 25.99. Found: C, 68.26; H, 5.74.

5,8-Dimethoxy-1,4-dihydronaphthalene (12b)

A mixture of 36.8 g (0.23 mol) of the quinone **10** and 37 g (0.92 mol) of NaOH in 400 mL water was cooled to a temperature between 5 and 10° in an

ice-acetone bath. Dimethyl sulfate, 60 mL (0.63 mol), was slowly added and the reaction mixture was stirred at room temperature for 12 h.[10] The precipitate was filtered, washed with NaOH solution and water, and dried. To the filtrate was added an additional 10 mL of Me_2SO_4 and stirred for additional 6 h. The second precipitate was collected and combined with the previous one. The resulting 34.6 g (79%) of a brown solid was extracted with hexane. After the hexane was evaporated, 29.7 g (68%) of a yellow solid was obtained and subsequently recrystallized from MeOH to give relatively pure **12b** as off-white needles. Pure **12b** was obtained from repeated recrystallizations from MeOH, mp 48.5–49 °. IR: 2938, 2832, 1481, 1253 cm^{-1}; ^1H nmr (90 MHz, $CDCl_3$): δ 3.25–3.26 (4H, d, J = 1.3 Hz), 3.76 (6H, s), 5.85–5.88 (2H, t, J = 1.3 Hz), 6.62 (2H, s); ^{13}C nmr (90 MHz, $CDCl_3$): δ 24.76, 55.99, 107.20, 124.0, 124.84, 151.46; GC-MS: m/z 190 ($M^{+\bullet}$), 175, 159, 144, 115; Anal. Calcd. for $C_{12}H_{14}O_2$ (190.24): C, 75.76; H, 7.42; O, 16.82. Found: C, 75.46; H, 7.40.

6-Acetyloxy-1a,2,7,7a-tetrahydronaphtho[2,3-*b*]oxiren-3-yl Acetate (13a)

A solution of 4.5 g (0.02 mol) of *m*-CPBA (77%) in 80 mL CH_2Cl_2 was dried over anhydrous $MgSO_4$ and filtered. This solution was added dropwise to a solution of 4.4 g (0.018 mol) of the alkene **12a** in 20 mL CH_2Cl_2.[11] The reaction mixture was stirred at room temperature for 12 h. The mixture was filtered to remove *m*-chlorobenzoic acid formed during the epoxidation. The CH_2Cl_2 filtrate was first washed with 3 × 40 mL saturated solution of $NaHCO_3$ and then with 3 × 40 mL of 10% $NaHSO_4$ solution to remove residual acid and excess *m*-CPBA, respectively. The organic layer was washed with water and dried over anhydrous $MgSO_4$. After evaporation, the resulting 4.6 g (97%) of a white solid was recrystallized from 95% EtOH to afford pure **13a** as white crystals, mp 165–166°. IR: 3002, 1755 (C═O), 1470, 1371, 1196, 1041 cm^{-1}; ^1H nmr (90 MHz, DMSO-d_6): δ 2.32 (6H, s), 2.70 and 2.90 (2H, 2 br s, ^2J = 18 Hz), 3.10 and 3.30 (2H, 2 br s, ^2J = 18 Hz), 3.45 (2H, br s), 7.02 (2H, s); ^{13}C nmr (90 MHz, PENDANT, $CDCl_3$): δ 20.65, 23.63, 50.44, 120.25, 125.49, 146.32, 168.74; GC-MS: m/z 262 ($M^{+\bullet}$), 220, 178, 160; Anal. Calcd. for $C_{14}H_{14}O_5$ (262.26): C, 64.12; H, 5.38; O, 30.50. Found: C, 64.10; H, 5.33.

3,6-Dimethoxy-1a,2,7,7a-tetrahydronaphtho[2,3-*b*]oxirene (13b)

A solution of 23 g (0.10 mol) of *m*-CPBA (77%) in 150 mL CH_2Cl_2 was added dropwise to a solution of 17.5 g (0.092 mol) of the alkene **12b** in

150 mL CH_2Cl_2. The reaction mixture was stirred at room temperature for 12 h, followed by the work-up in a manner similar to that described for the epoxide **13a**. The resulting 17.2 g (91%) of a white solid was recrystallized from 95% EtOH to afford pure **13b** as white crystals, mp 129–130 °. IR: 2994, 2938, 2834, 1479, 1252, 1093 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ 2.82–2.88 (2H, dd, $^2J = 18.2$ Hz, J = 1.3 Hz), 3.49 and 3.54 (2H, t, $^2J = 18.2$ Hz, J = 1.3 Hz), 3.50–3.51 (2H, t, J = 1.3 Hz), 3.79 (6H, s), 6.66 (2H, s); ^{13}C nmr (400 MHz, $CDCl_3$): δ 23.71, 51.74, 56.04, 107.86, 121.77, 151.81; GC-MS: m/z 206 ($M^{+\bullet}$), 191, 173; Anal. Calcd. for $C_{12}H_{14}O_3$ (206.24): C, 69.89; H, 6.84; O, 23.27. Found: C, 69.67; H, 6.81.

4-Acetyloxy-6-chloro-7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl Acetate (14a)

A solution of 2.5 g (0.0095 mol) of the epoxide **13a** in 15 mL anhydrous ethylene glycol dimethyl ether was cooled in a dry ice-acetone bath to a temperature between −20 and −10°. Dry HCl gas was then delivered into the cooled solution for 1 hour to ensure saturation of the acid. The reaction mixture was kept refrigerated overnight [7] and then the solvent was evaporated to yield 2.5 g (88%) of **14a** as a white solid. Recrystallization from 95% EtOH afforded pure **14a** as white needles, mp 156–158°. IR: 3521 (OH), 1755 (C═O), 1471, 1370, 1201 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ 2.33 (3H, s), 2.34 (3H, s), 2.57–2.64 (1H, td, J = 9.35 Hz), 2.83 (1H, br s), 2.87–2.94 (1H, td, J = 10.36 Hz), 3.20–3.26 (1H, dd, $^2J = 17.2$ Hz, J = 5.8 Hz), 3.32–3.37 (1H, dd, $^2J = 17.2$ Hz, J = 5.8 Hz), 3.96–4.02 (1H, m), 4.10–4.16 (1H, m), 6.98 (2H, s); ^{13}C nmr (400 MHz, $CDCl_3$): δ 20.74, 20.78, 30.86, 32.66, 61.54, 70.40, 120.71, 120.98, 127.43, 127.85, 145.78, 146.33, 169.02, 169.03; GC-MS: m/z 298 ($M^{+\bullet}$), 256, 214, 161; Anal. Calcd. for $C_{14}H_{15}ClO_5$ (298.72): C, 56.29; H, 5.06; Cl, 11.87; O, 26.78. Found: C, 56.10; H, 5.04; Cl, 11.71.

6-Chloro-4a,5,8,8a-tetrahydronaphthalene-1,4-dione (16)

To a stirred suspension of 95.6 g (0.88 mol) 1,4-benzoquinone in 600 mL of benzene/xylene mixture (5:1) was added 156 mL (0.90 mol) of freshly distilled 2-chloro-1,3-butadiene (50% w/v in xylene obtained from Monomer-Polymer & Dajac Labs, Inc.). The reaction mixture was refluxed for 6 h and then it was cooled in an ice-water bath. The residual undissolved solid was filtered and the filtrate was evaporated, resulting in 144.7 g of a yellow solid, which turned gray upon air exposure.[8] A GC-MS on this crude product

showed two major peaks, which were characterized as compound **16** and **17**. Several recrystallizations from petroleum ether did not yield a pure compound.

6-Chloro-5,8-dihydronaphthalene-1,4-diol (17)

Compound **17** was prepared by heating a mixture of 129.2 g (0.66 mol) of the impure quinone **16** in 300 mL glacial AcOH in a manner similar to that described for compound **11**. After the reaction mixture cooled down to room temperature, it was poured onto crushed ice. The precipitate was filtered and dried to give 112 g (87%) of gray powder, which acquired purplish tinge upon air exposure. A part of the crude product was recrystallized from benzene/acetone solvent pair to afford pure **17** as white crystals, which would later turn a pale bluish color, mp 191–192° (ref. 197–199°).[8] IR: 3217 (OH), 1487, 1425 cm^{-1}; ^1H nmr (90 MHz, DMSO-d_6): δ 3.28–3.41(4H, m), 6.02–6.04 (1H, m), 6.54 (2H, s), 8.73 (1H, s), 8.78 (1H, s); ^{13}C nmr (90 MHz, DMSO-d_6): δ 26.58, 31.86, 112.79, 119.95, 120.85, 122.40, 128.84, 147.10, 147.55; GC-MS: m/z 196 ($M^{+\bullet}$), 161, 115; Anal. Calcd. for $C_{10}H_9ClO_2$ (196.63): C, 61.08; H, 4.61; Cl, 18.03; O, 16.27. Found: C, 61.06; H, 4.53; Cl, 18.04.

4-Acetyloxy-6-chloro-5,8-dihydronaphthalen-1-yl Acetate (18a)

Compound **18a** was obtained by diacetylation of 3.1 g (0.016 mol) of the dihydroxy compound **16** with 20 mL Ac_2O in the presence of concentrated H_2SO_4. The resulting 2.98 g (66%) of white powder was recrystallized from 95% EtOH to give 2 g (45%) of **18a** as white needles, mp 127–128°. IR: 1780 (C═O), 1473, 1370, 1180 cm^{-1}; ^1H nmr (90 MHz, $CDCl_3$): δ 2.32 (3H, s), 2.35 (3H, s), 3.32–3.46 (4H, m), 5.94–5.98 (1H, t, J = 1.8 Hz), 6.99 (2H, s); ^{13}C nmr (400 MHz, $CDCl_3$): δ 20.80, 20.85, 26.54, 31.54, 120.29, 120.67, 120.68, 126.32, 127.25, 128.07, 145.72, 146.14, 169.02, 169.05; GC-MS: m/z 280 ($M^{+\bullet}$), 196, 161; Anal. Calcd. for $C_{14}H_{13}ClO_4$ (280.70): C, 59.90; H, 4.67; Cl, 12.63; O, 22.80. Found: C, 60.01; H, 4.59; Cl, 12.34.

2-Chloro-5,8-dimethoxy-1,4-dihydronaphthalene (18b)

To a cooled solution of 100 g (0.51 mol) of compound **16** and 82 g (2.05 mol) of NaOH in 500 mL water was slowly added 145 mL (1.53 mol)

of Me_2SO_4. The reaction mixture was stirred at room temperature for 12 h. The precipitate was collected and dried. To the filtrate was added an additional 45 mL of Me_2SO_4 and the solution stirred for an additional 6 h. The second precipitate was combined with the previous one. The resulting 98.9 g (86%) of a dark brown solid was extracted with hexane. After the hexane was evaporated, 78.5 g (69%) of a green solid was obtained and subsequently recrystallized from MeOH. The resulting 53.1 g (46%) of a relatively pure compound **18b** was ready to use in the next step. An analytical sample was obtained from repeated recrystallizations from MeOH and yielded pure **18b** as yellow needles, mp 77–78° (ref. 77–78°).[8] IR: 2938, 2833, 1481, 1255, 1098 cm^{-1}; ^1H nmr (90 MHz, DMSO-d_6): δ 3.28–3.41 (4H, m), 3.75 (6H, s), 5.99–6.06 (1H, m), 6.78 (2H, s); ^{13}C nmr (90 MHz, DMSO-d_3): δ 26.21, 31.34, 39.53, 55.44, 108.21, 121.96, 128.40, 150.38, 150.87; GC-MS: m/z 224 ($M^{+\bullet}$), 189, 174, 158; Anal. Calcd. for $C_{12}H_{13}ClO_2$ (224.68): C, 64.15; H, 5.83; Cl, 15.78; O, 14.24. Found: C, 64.24; H, 5.80; Cl, 15.62.

5,8-Dimethoxy-3,4-dihydronaphthalen-2(1*H*)-one or 5,8-Dimethoxy-2-tetralone (15b)

Method A

Following the procedure described by Grob and Jundt,[8] 80 g (0.36 mol) of the vinyl chloride **18b** was cooled in an ice-acetone bath to −5 to 0° under N_2 atmosphere. Then 320 mL of cooled concentrated H_2SO_4 was added to the system and the reaction mixture was stirred at −5 to 0° for 2.5 h. The resulting dark brown solution was poured onto crushed ice and the mixture was stirred and additional water was added until all sticky materials turned to a solid. The precipitate was filtered, washed several times with water, and dried to give a light brown solid, which was subsequently extracted with hexane. The hexane was evaporated to obtain 29.4 g (40%) of **15b** as yellow needles. Recrystallization from 95% EtOH afforded 17.8 g (24%) of yellow needles, mp 97–98° (ref. 97–99°).[8,12]

Method B

To 100 mL of toluene dried overnight with Na metal was added 5 g of $MgBr_2$ etherate and the suspension was stirred at room temperature for 15 min. To the suspension was added 3.5 g (0.017 mol) of the epoxide **13b**. The reaction mixture was refluxed for 6 h and then allowed to cool to room temperature. The precipitate was filtered and washed with benzene. The dried solids were added to water to remove $MgBr_2$ and the white residue

was collected and air dried to give 2.1 g (60%) of crude **15b**, which was extracted with hot hexane. The resulting 1.5 g (42%) of light yellow crystals was recrystallized from 95% EtOH. IR: 2952, 2835, 1716 (C═O), 1482, 1260, 1085 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ 2.54–2.57 (2H, t, J = 6.8 Hz), 3.07–3.10 (2H, t, J = 6.8 Hz), 3.52 (2H, s), 3.79 (3H, s), 3.82 (3H, s), 6.70–6.72 (1H, d, J = 8.8 Hz), 6.73–6.75 (1H, d, J = 8.8 Hz); ^{13}C nmr (400 MHz, $CDCl_3$): δ 22.36, 38.55, 38.61, 56.06, 56.26, 108.50, 108.74, 124.16, 126.52, 150.93, 151.12, 211.16; GC-MS: m/z 206 ($M^{+\bullet}$), 164, 149; *Anal.* Calcd. for $C_{12}H_{14}O_3$ (206.24): C, 69.89; H, 6.84; O, 23.27. Found: C, 69.75; H, 6.70.

5′,8′-Dimethoxy-3′,4′-dihydro-1′*H*-spiro[1,3-dioxolane-2,2′-naphthalene] (19)

The reaction mixture containing 4.5 g (0.022 mol) of the tetralone **15b**, 10 mL (0.18 mol) of ethylene glycol, 80 mL of benzene, and 0.25 g of *p*-TsOH was refluxed until approximately 0.4 mL of water was collected in the water separator. After cooling, the reaction mixture was washed first with 3 × 20 mL of 10% NaOH solution and then with 3 × 20 mL of water. The benzene layer was dried over anhydrous $MgSO_4$ and evaporated to give 4.8 g (87%) of a yellow solid, which was recrystallized from 95% EtOH, yielding pure **19** as yellow needles, mp 100–101°. IR: 2945, 2833, 1480, 1250, 1121, 1081 cm^{-1}; ^1H nmr (90 MHz, $CDCl_3$): δ 1.82–1.97 (2H, t, J = 7 Hz), 2.82–2.96 (4H, m), 3.75 (3H, s), 3.76 (3H, s), 4.02 (4H, s), 6.62 (2H, s); ^{13}C nmr (90 MHz, $CDCl_3$): δ 22.21, 30.53, 33.31, 55.42, 64.33, 107.32, 108.25, 125.06, 125.80, 151.60, 151.76; GC-MS: m/z 250 ($M^{+\bullet}$), 164, 149; *Anal.* Calcd. for $C_{14}H_{18}O_4$ (250.29): C, 67.18; H, 7.25; O, 25.57. Found: C, 67.29; H, 7.29.

5,12-Dihydroxy-1,3,4-trihydronaphthacene-2,6,11-quinone (9)

A solid mixture, containing 40.6 g of $AlCl_3$, 8 g of NaCl, 3 g (0.02mol) of finely ground phthalic anhydride, and 4 g (0.019mol) of finely ground tetralone **15b**, was thoroughly mixed and heated in a silicone oil bath at 180°. After the reaction mixture was melted, it was mechanically stirred for 2 min. After cooling, the mixture was treated with 200 mL of a saturated aqueous solution of oxalic acid.[13] The resulting 4.8 g (80%) of a red-orange solid was collected and subjected to column chromatography on silica gel (60–200 mesh), with $CHCl_3$ as the eluting solvent. Yield after removal of $CHCl_3$ was 3.2 g (54%). Recrystallization from glacial AcOH

yielded 2.9 g (48%) of pure **9** as red needles, mp $> 310^{\circ}$ (ref $> 300^{\circ}$).[5] IR (KBr): 1723 (C═O), 1621, 1581, 1372, 1233 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ 2.67–2.7 (2H, t, J = 7.0 Hz), 3.28–3.31 (2H, t, J = 7.0 Hz), 3.70 (2H, s), 7.86–7.88 (2H, dd, J = 5.8 Hz), 8.38–8.40 (2H, dd, J = 5.8 Hz), 13.39 (1H, s), 13.50 (1H, s); *Anal.* Calcd. for $C_{18}H_{12}O_5$ (308.29): C, 70.13; H, 3.92; O, 25.95. Found: C, 70.08; H, 3.90.

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