Bromination Studies of the 2,3-Dimethylnaphthazarin Core Allowing Easy Access to Naphthazarin Derivatives

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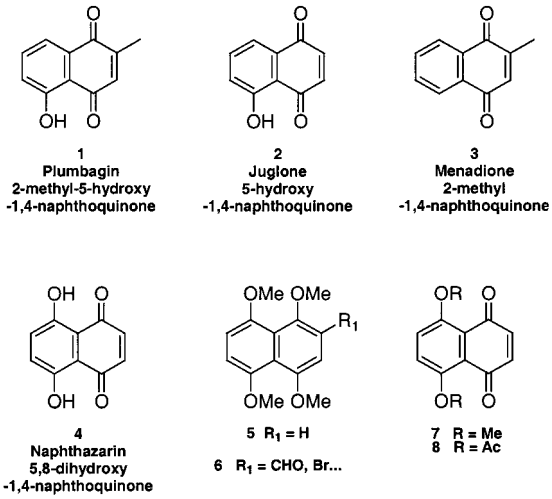
Introduction

1,4-Naphthoquinones are known for their antiinflammatory,[1] antitumor,[1−5] antiparasitic,[6−9] and antimicrobial[1] activities. As part of our ongoing program in the field of trypanocidal drugs, we have reported the synthesis and biological activities of plumbagin **1**, juglone **2**, and menadione **3** derivatives (Chart 1) as potential turncoat inhibitors of trypanothione reductase.[10,11] More recently, we have also extended our range of chemical synthesis to include the production of naphthazarin derivatives as potential thioredoxin reductase inhibitors, since naphthazarin **4** (5,8-dihydroxy-1,4-naphthoquinone) is known to display antiplasmodial[12] and anticancer activities[2−5] and to inhibit both glutathione reductase and thioredoxin reductase.[13,14] Because the attack of the quinone moiety by glutathione is involved in the cytotoxic properties of **4**,[15,16] we designed naphthazarin derivatives

Chart 1



that were alkylated at carbons 2 and 3 to prevent formation of thiol conjugates and to allow introduction of structural diversity.

There are few examples of functionalization of naphthazarin in the literature. So far, the only reactions that led to new compounds involved 1,4,5,8-tetramethoxynaphthalene **5** (Chart 1), which was submitted to a Vilsmeier formylation,[17] and then to an *ortho*-metalation reaction.[18] Sargent et al. showed that both the regioselectivity and the yields for the second lithiation of compound **6** were low. Moreover, the use of this route implied deprotection and oxidation steps that led to an important loss of the newly functionalized derivative **6**,[19] depending on the introduced side chain. Recently, two groups have reported an electrochemical oxidation from analogues of **6** that reveals the naphthazarin core with good yields.[20,21] However, it seemed interesting to determine whether or not the naphthazarin derivatization could be achieved with simple, easily performed chemical reactions and/or without masking the two hydroxyl groups.

In this paper, we describe different approaches with which to functionalize the naphthazarin core to obtain new building blocks for library generation.

Results and Discussion

Because of our previous experience with 1,4-naphthoquinones **1**, **2**, and **3**,[10,11] we first tried to derivatize commercial **4** through the oxidative decarboxylation of carboxylic acids promoted by silver salts in the presence of ammonium peroxydisulfate.[22] All our attempts to add

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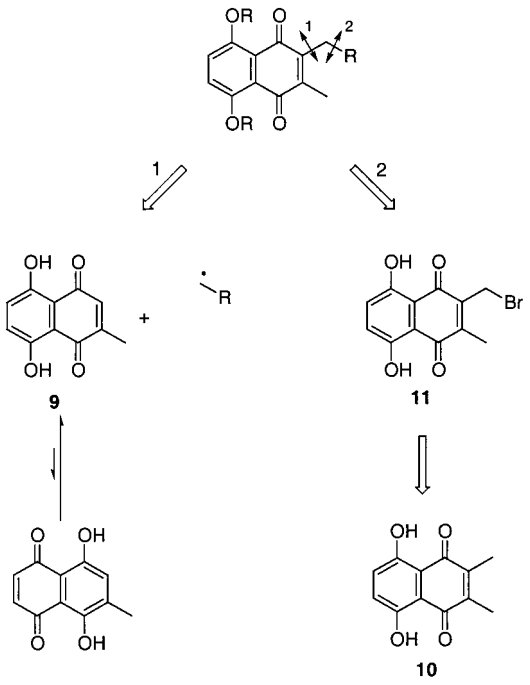
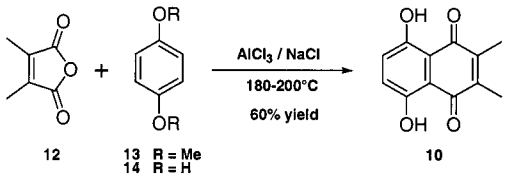
Scheme 1

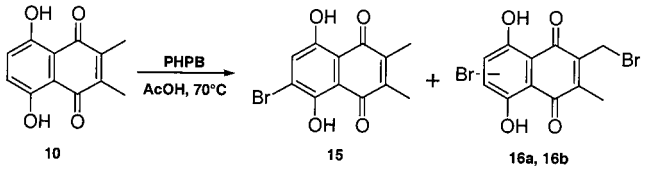


carboxylic acids onto naphthazarin proved unsuccessful, probably due to the tautomerization[23] that occurs in the compound and to its resulting low chemical reactivity,[24] as have been previously reported. To decrease this rapid proton exchange, two 5,8-disubstituted analogues[25] **7** and **8** (Chart 1) were prepared and allowed to react with acids through the oxidative decarboxylation reaction. No reaction occurred, and starting material was recovered, with one exception (R = Ac), where partial deacetylation was observed. Moreover, ring substitution is known to influence the tautomerism of the naphthazarin system.[23] Therefore, we attempted radical alkylation[22] of 2-methylnaphthazarin **9** since the presence of the methyl group resulted in an increase in the alkylated quinoid species (Scheme 1, route 1). The previously reported route to the preparation of large quantities of naphthazarin has been known for years.[26] It involves a three-step synthesis starting from a double-Friedel−Crafts acylation of 1,4-dimethoxybenzene **13** or hydroquinone **14** with dichloromaleic anhydride. A subsequent reductive dechlorination and basic oxidation of the obtained leuconaphthazarin led to naphthazarin with good overall yields.[24,27,28] When it was applied to citraconic anhydride (2-methylmaleic anhydride), production of 2-methylnaphthazarin proved to be difficult and irreproducible, likely because this compound was highly unstable even if stored at low temperature under a nitrogen atmosphere. As an alternative route to access 2,3-disubstituted naphthazarins, we decided to functionalize the 2,3-dimethylnaphthazarin **10** through the bromination of one of its methyl groups to obtain 2-bromomethyl derivative **11** (Scheme 1, route 2). The 2,3-dimethylnaphthazarin **10** and its protected derivative had been previously synthesized from a multistep procedure that included a Diels−Alder reaction, the overall yields being 17 and <12%, respectively.[29,30] In our adopted procedure, compound **10** was obtained in a single step from 2,3-dimethylmaleic anhydride **12** via a straightforward purification process yielding 60% product, along with some unreacted anhydride, which was then recycled for further use (Scheme 2). From these results, it appeared that the use of an excess of anhydride (from 1.5 to 3 equiv) allowed an increase of the obtained naphthoquinone yields. However, when 5 equiv was used, we observed that the reaction mixture became solid. This made stirring the mixture difficult and resulted in a lower yield. Increasing the quantities of fused salts to gain more fluidity did not lead to any improvement. We also showed that the use of hydroquinone **14** instead of 1,4-dimethoxybenzene **13** did not increase the 2,3-dimethylnaphthazarin **10** yield. Optimal conditions were reached using 3 equiv of dimethylmaleic anhydride **12** for 1 equiv of **13**.

Scheme 2. Synthesis of 2,3-Dimethylnaphthazarin 10



Scheme 3. Bromination of 2,3-Dimethylnaphthazarin 10 with PHPB



In contrast to 2-methylnaphthazarin **9**, 2,3-dimethylnaphthazarin **10** proved to be very stable (stored at room temperature, exposed to the light or in solution), facilitating bromination of one of the two methyl groups to derivatize the naphthazarin core. Following a previously reported procedure describing some selectivity toward bromination of the methyl group for menadione **3**,[31] the dimethylnaphthazarin **10** was allowed to react with pyridinium tribromide (PHPB) in acetic acid (Scheme 3). Two brominated species were isolated, the 6-bromomethylnaphthazarin **15** resulting from an electrophilic aromatic substitution, and a mixture of regioisomers **16a** and **16b** obtained from **15** via a side-chain bromination. Due to their similarity in polarity, separation of **16a** and **16b** was impossible. All the isolated compounds were submitted to one- and two-dimensional NMR experiments (HMBC spectra) in order to ascertain their structures and the bromine positions. The reaction time and number of tribromide equivalents were modified in order to reach some selectivity. By changing the reaction conditions, we were able to obtain improved yields of compound **15** and reach a good conversion rate, but 2-bromomethyl derivative **11** was not detected. When the

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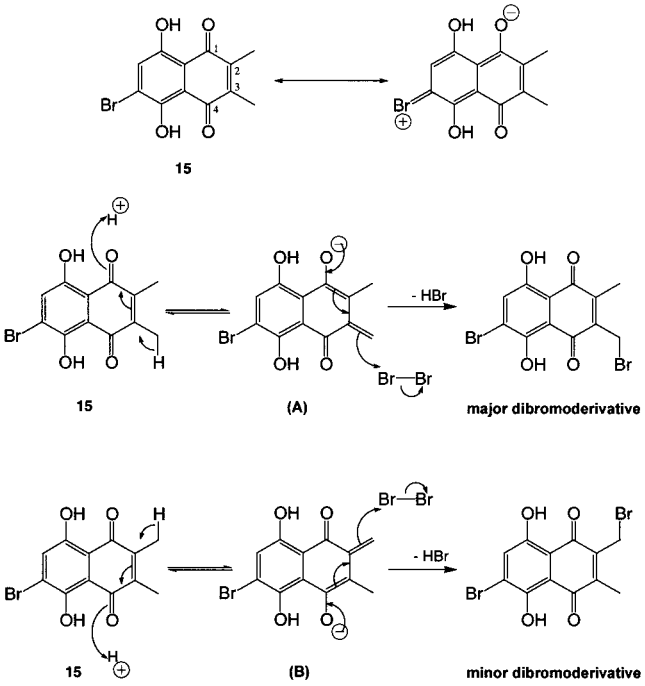
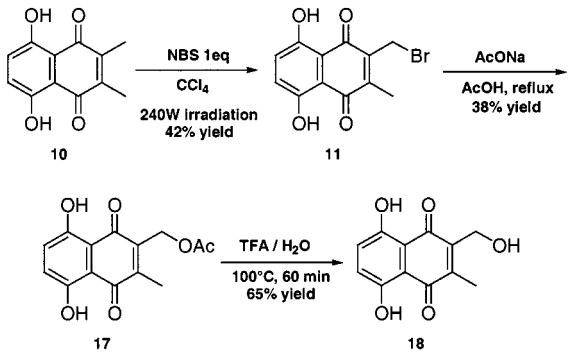
Scheme 4. Influence of the Nuclear Bromine Atom on the Electronic Density of the Carbonyl Groups, and Postulated Mechanism for the Formation of the Dibromo Derivatives 16a and 16b



conversion rate of **10** was poor, a very low yield of dibromo- mixture was obtained. After the formation of the 6-bromo-2,3-dimethylnaphthazarin **15**, the production of compounds **16a** and **16b** was consistent with the addition of Br_2 on the *exo* double bond of each of the postulated intermediates **A** and **B** (Scheme 4). The observed regioselectivity might result from a predominance of intermediate **A** over intermediate **B** due to the mesomeric donor effect of the nuclear bromine atom of **15** increasing the electronegativity of the oxygen atom at carbon 1 of the quinoid moiety, since a ratio of 75:25 had been determined from both an HPLC profile and ^{1}H NMR spectra of the mixture of **16a** and **16b**.

Since PHPB did not lead to the desired 2-bromomethyl-3-methylnaphthazarin **11**, NBS[32] was used in refluxing CCl_4 in the presence or absence of AIBN as a radical initiator. The desired brominated analogue **11** was not obtained by this method, allowing us to conclude that the thermal activation of NBS, with or without a radical initiator, was not efficient enough. Surprisingly, the presence of AIBN was associated with reaction mixture degradation. Finally, the radicals necessary for the side-chain reaction were generated using tungsten lamps (2 × 120 W) placed at a short distance from the reaction vessel to maintain solvent reflux (Scheme 5).[30,33] The conversion rate and the yield of the desired 2-bromomethyl-3-methylnaphthazarin **11** proved to be dependent on the irradiation time. With a reaction time >2 h, some side reaction probably occurred on product **11** because no yield improvement was noticed while the conversion rate increased. However, no 2,3-dibromomethylnaphthazarin was detected as expected, even with higher light intensity (340 W was attempted), while this latter

Scheme 5. Synthesis and Derivatization of Compound 11



compound had been previously reported to be obtained from a protected 2,3-dimethylnaphthazarin derivative.[30]

To complete these studies, we checked that compound **11** could be easily derivatized into the acetoxymethyl compound **17**, which was then hydrolyzed to afford 5,8-dihydroxy-2-hydroxymethyl-3-methyl-1,4-naphthoquinone **18** (Scheme 5). [31]

In summary, data reported in this paper showed that derivatization of the naphthazarin core could be achieved with satisfactory yields via an easy synthetic route without masking or protecting the 5,8-hydroxyl groups. First, the 2,3-dimethylnaphthazarin **10** was easily accessible (60% yield) from inexpensive starting chemicals at the optimal reaction condition. While the use of NBS in the "irradiation reaction" allowed us to brominate one of the two methyl groups of the highly stable 2,3-dimethylnaphthazarin **10** (42% yield), the use of PHPB led to the introduction of a nuclear bromine atom in addition to the side-chain bromination. The utility of bromo derivatives **11**, **16a**, and **16b** as potential starting blocks for library generation was ascertained through the transformation of the 2-bromomethyl-3-methylnaphthazarin **11** into the 2-hydroxymethyl analogue **18**. Work is currently in progress to prepare new building blocks from 5,8-dihydroxy-2-hydroxymethyl-3-methyl-1,4-naphthoquinone **18** and analogues and to introduce structural diversity through versatile reactions to generate focused libraries of naphthazarin derivatives. In particular, use of this hydroxymethyl analogue **18** is being made in the parallel construction of a wide variety of esters, carbamates, or carbonates each bearing groups responsible for specific vectorization into cells or tissues for interaction with their targets.

Experimental Section

All reactions were monitored by thin-layer chromatography carried out on 0.2 mm E. Merck silica gel plates (60F-254) that were visualized by UV light using molybdic acid-cerium sulfate (Ceric dip) as the developing agent. Chromatography was carried out using silica gel 60 (230−400 mesh ASTM) from Macherey-Nagel. Preparative-layer chromatography (PLC) was performed using silica gel from Merck. Melting points were determined on a Büchi melting-point apparatus and were not corrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-300 MHz spectrometer, and chemical shifts were expressed in ppm (δ) relative to TMS; multiplicity was indicated as s (singlet). HRMS (CI) spectra were obtained on a JEOL MS 700. Analytical high-pressure liquid chromatography (HPLC) was performed on a Shimadzu system equipped with a UV detector set at 254 nm. Compounds were dissolved in DCM-EtOH and injected through a 50 μL loop on a Macherey-Nagel C_{18} Nucleosil column (4 × 300 mm, 5 μm, 100 Å) (conditions A). The following solvent

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systems were used: eluent A, 0.05% trifluoroacetic acid (TFA) in H_2O; eluent B, 0.05% TFA, 20% H_2O, and 80% CH_3CN. HPLC retention times (HPLC t_R) were obtained at flow rates of 1 mL/min using the following conditions: a gradient run from 100% eluent A for 5 min, and then increasing to 100% eluent B over the next 25 min. A second injection was performed using a C_{18} Vydac TP 218 column (4 × 300 mm, 10 μm, 300 Å) at flow rates of 2 mL/min (conditions B). The gradient used was a linear gradient of eluents A and B, increasing from 0 to 100% B over a period of 10 min. All chemicals were obtained from Acros and Aldrich and were used without further purification.

5,8-Dihydroxy-2,3-dimethyl-1,4-naphthoquinone (10). A round-bottom flask containing aluminum chloride (6.00 g, 45 mmol) and sodium chloride (1.35 g, 22 mmol) under nitrogen flux was heated with an oil bath to 180 °C at which point a mixture of 1,4-dimethoxybenzene **13** (0.69 g, 5 mmol) and 2,3-dimethylmaleic anhydride **12** (1.90 g, 15 mmol) was carefully added. The temperature was raised to 200 °C and maintained for 5 min until gas evolution ceased. The reaction mixture was allowed to cool to approximately 100 °C, and an ice-cold solution of 10% HCl was added. Hydrolysis was continued overnight at room temperature. The aqueous mixture that was obtained was extracted with CH_2Cl_2 (5 × 20 mL) until the organic extract color turned only slightly red. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The crude red solid (1.96 g) was purified by flash column chromatography using 15:85 acetone/cyclohexane as the eluent. The first fraction afforded the desired compound as a red solid after solvent evaporation (0.64 g, 59% yield). The second fraction consisted of a pink-white solid, and the NMR signal and melting point data confirmed the compound to be unreacted 2,3-dimethylmaleic anhydride (1.11 g). R_f = 0.53 (10:90 acetone/cyclohexane). HPLC: (Nucleosil, conditions A) t_R, 27.9 min; (Vydac, conditions B) t_R, 26.4 min. ^{1}H NMR ($CDCl_3$): δ 2.19 (s, 3H), 7.19 (s, 1H), 12.61 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 12.7, 111.8, 129.4, 144.6, 158.7, 186.6. HRMS (CI, *m/z*): $(M + H)^+$ calcd for $C_{12}H_{11}O_4$, 219.0657; observed, 219.0654.

6-Bromo-5,8-dihydroxy-2,3-dimethyl-1,4-naphthoquinone (15). 5,8-Dihydroxy-2,3-dimethyl-1,4-naphthoquinone **10** (0.10 g, 0.46 mmol) was dissolved with acetic acid (3 mL), pyridinium tribromide (0.16 g, 0.50 mmol) was introduced, and then the mixture was refluxed at 70 °C for 24 h. Acetic acid was removed under reduced pressure, water (10 mL) was added, and the desired compound was extracted with EtOAc (10 mL). The organic layer was washed twice with water (2 × 5 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude red solid (0.15 g) was purified by flash column chromatography using 3:97 acetone/cyclohexane as the eluent. The first eluted fraction (0.09 g) was a mixture of the desired compound and starting material as demonstrated by analytical HPLC and ^{1}H NMR. Preparative HPLC was performed using a C_{18} Vydac column (10 μm, 300 Å, 500 × 20 mm) and a Beckman System Gold apparatus. The first eluted compound proved to be the starting material (0.01 g), and the main fraction was the desired compound **15** (0.08 g, 59% yield). R_f = 0.53 (10:90 acetone/cyclohexane). HPLC: (Nucleosil, conditions A) t_R, 30.7 min; (Vydac, conditions B) t_R, 29.6 min. ^{1}H NMR ($CDCl_3$): δ 2.17 (s, 6H), 7.49 (s, 1H), 12.48 (s, 1H), 13.15 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 13.0, 111.3, 111.7, 125.1, 132.6, 144.0, 145.0, 157.0, 159.6, 184.8, 185.3. HRMS (CI, *m/z*): $(M + H)^+$ calcd for $C_{12}H_{10}O_4Br$, 296.9763/298.9742; observed, 296.9766/298.9751.

The second fraction (0.03 g, 20% yield) obtained by flash chromatography proved to be a mixture of dibromo compounds (see below, compounds **16a**,**b**).

6-Bromo-2-bromomethyl-5,8-dihydroxy-3-methyl-1,4-naphthoquinone (16a) and 6-Bromo-3-bromomethyl-5,8-dihydroxy-2-methyl-1,4-naphthoquinone (16b). The mixture of dibromo isomers was purified during the synthesis of compound **15** as described above. The reported NMR spectra and HPLC chromatogram were obtained for the regioisomeric mixture. Due to overlapping signals, no specific attribution was made for each compound. R_f = 0.48 (10:90 acetone/cyclohexane). HPLC: (Nucleosil, conditions A) t_R, 29.8 and 30.3 min; (Vydac, conditions B) t_R, 28.7 and 29.0 min. ^{1}H NMR ($CDCl_3$): δ 2.32 (s, 3H), 4.49 (s, 2H), 7.57 and 7.58 (s, 1H), 12.52 and 12.53 (s, 1H), 13.05 and 13.09 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 12.7, 21.8, 111.3, 111.7, 125.1, 132.6, 144.0, 145.0, 157.0, 159.6, 184.8, 185.3. HRMS (CI, *m/z*): $(M + H)^+$ calcd for $C_{12}H_9O_4Br_2$, 374.8868/376.8847/378.8827; observed, 374.8863/376.8835/378.8830.

2-Bromomethyl-5,8-dihydroxy-3-methyl-1,4-naphthoquinone (11). 5,8-Dihydroxy-2,3-dimethyl-1,4-naphthoquinone **10** (0.10 g, 0.46 mmol) and *N*-bromosuccinimide (0.08 g, 0.46 mmol) were dissolved with CCl_4 (4 mL) in a 10 mL round-bottom flask equipped with a condenser under nitrogen flux. The two tungsten lamps were placed close to the flask to maintain a vigorous reflux over 2 h. The solvent was removed under reduced pressure, and the solid that was obtained was dissolved in EtOAc (15 mL) and washed three times with water (3 × 5 mL). The organic phase was dried over $MgSO_4$ and concentrated. The crude red solid was purified by flash column chromatography using 2.5:97.5 acetone/cyclohexane as the eluent to afford the unreacted starting material as the first fraction (0.04 g), and then the desired compound **11** as a deep red solid (0.06 g, 42% yield). R_f = 0.46 (10:90 acetone/cyclohexane). HPLC: (Nucleosil, conditions A) t_R, 28.5 min; (Vydac, conditions B) t_R, 26.7 min. ^{1}H NMR ($CDCl_3$): δ 2.29 (s, 3H), 4.48 (s, 2H), 7.22 (s, 1H), 12.53 (s, 1H), 12.58 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 12.5, 21.7, 111.5, 111.9, 130.7, 130.9, 142.3, 146.8, 161.0, 161.2, 182.1, 184.2. HRMS (CI, *m/z*): $(M + H)^+$ calcd for $C_{12}H_{10}O_4Br$, 296.9763/298.9742; observed, 296.9769/298.9755.

(5,8-Dihydroxy-3-methyl-1,4-naphthoquinolyl)methyl Acetate (17). A mixture of 2-bromomethyl-5,8-dihydroxy-3-methyl-1,4-naphthoquinone **11** (0.12 g, 0.40 mmol), AcONa (0.16 g, 1.95 mmol), and 3:1 AcOH/$CHCl_3$ (4.5 mL) was refluxed at 70 °C for 6 h. The solvent mixture was evaporated off, and water (20 mL) was added to the residue. The product was extracted with AcOEt (3 × 50 mL) and dried over $MgSO_4$. After evaporation of the solvent, the crude product was purified by PLC using 19:80:1 acetone/cyclohexane/TFA. **17** was obtained as red crystals (0.04 g, 38% yield). R_f = 0.25 (19:80:1 acetone/cyclohexane/TFA). HPLC: (Nucleosil, conditions A) t_R, 37.3 min; (Vydac, conditions B) t_R, 21.8 min. ^{1}H NMR ($CDCl_3$): δ 2.10 (s, 3H), 2.31 (s, 3H), 5.18 (s, 2H), 7.22 (s, 2H), 12.56 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 12.5, 20.7, 56.6, 111.2, 111.7, 129.9, 130.7, 139.6, 148.3, 160.8, 161.0, 170.48, 183.0, 184.2. HRMS (CI, *m/z*): $(M + H)^+$ calcd for $C_{14}H_{13}O_6$, 277.0713; observed, 277.0715.

5,8-Dihydroxy-2-hydroxymethyl-3-methyl-1,4-naphthoquinone (18). A suspension of 2-acetoxymethyl-5,8-dihydroxy-3-methyl-1,4-naphthoquinone **17** (0.16 g, 0.59 mmol) in 2:1 TFA/H_2O (7.5 mL) was heated at 100 °C for 60 min. The solvent mixture was evaporated off, and water (20 mL) was added to the residue. The product was extracted with AcOEt (3 × 50 mL) and dried over $MgSO_4$. After evaporation of the solvent, the crude product was purified by PLC using 20:80 acetone/petroleum ether. Compound **18** was obtained as red crystals (0.09 g, 65% yield). R_f = 0.33 (20:80 acetone/petroleum ether). HPLC: (Nucleosil, conditions B) t_R, 20.2 min; (Vydac, conditions B) t_R, 17.2 min. ^{1}H NMR ($CDCl_3$): δ 2.28 (s, 3H), 4.71 (s, 2H), 7.25 (s, 2H), 12.50 (s, 1H), 12.61 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 29.8, 57.6, 111.4, 111.5, 130.4, 143.8, 145.7, 160.0, 160.1, 186.0, 186.7. HRMS (CI, *m/z*): $(M + H)^+$ calcd for $C_{12}H_{11}O_5$, 235.0607; observed, 235.0602.

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Supporting Information Available: Tables with the reaction conditions used for syntheses of compounds **10**, **11**, **15**, **16a**, and **16b**, and ^{1}H NMR spectra of compounds **10**, **11**, **15**, **17**, and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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