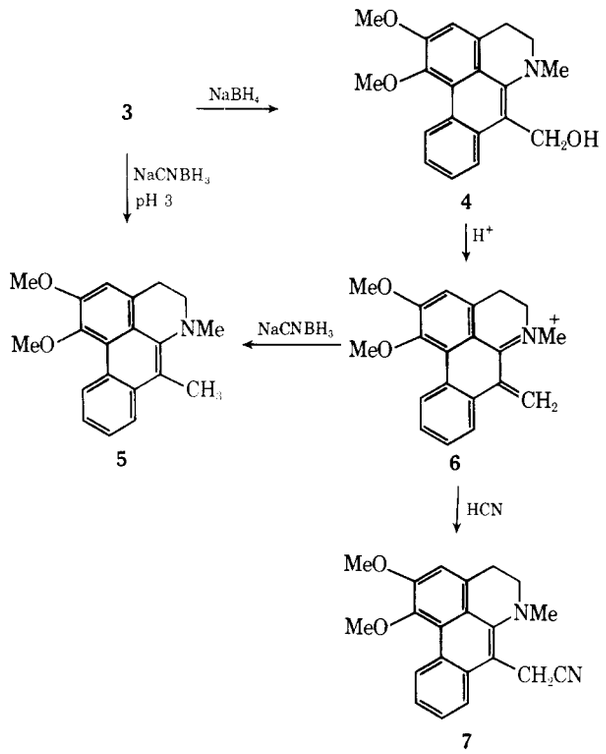

internal standard), ultraviolet spectra (ethanol), infrared spectra (KBr), and mass spectra were determined using JEOL-JNH-PS-100 and Perkin-Elmer 202, 137, and 270 spectrometers, respectively. Microanalyses were performed by Midwest Microlab, Indianapolis, Ind.

Dehydronuciferine-7-carboxaldehyde (3). Aqueous sodium hydroxide (2 ml, 50%) was added to a solution of dehydronuciferine[3] (1, 0.360 g) in chloroform (10 ml) containing a few drops of 30% aqueous tetra-*n*-butylammonium hydroxide, and the mixture was stirred for 4 h (external bath at 55–65 °C). After washing with water, the dried organic phase was evaporated and the residue chromatographed (chloroform eluent) to give recovered 1 (0.144 g) and 0.190 g of aldehyde 3, which crystallized from acetone as dark brown prisms: mp 161–163 °C; ir 6.24 μ; uv λ_{max} 213 nm (ϵ 11 000), 261 (24 000), 280 (17 000), 315 sh (7200), 418 (8000); NMR δ 3.30 (s, 3 H, NMe), 3.74 (s, 3 H, OMe), 3.93 (s, 3 H, OMe), 3.03 (t, 2 H, J = 6.5 Hz), 3.52 (t, 2 H, J = 6.5 Hz), 6.88 (s, 1 H, C-3), 10.13 (s, 1 H, CHO), 7.27–9.31 (m, 4 H); mass spectrum m/e 321 (M^+, 100), 304 (92), 160.5 (1).

Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.76; H, 5.92; N, 4.33. Found: C, 74.86; H, 6.02; N, 4.29.

7-Hydroxymethyldehydronuciferine (4). Excess sodium borohydride was added to a solution of aldehyde 3 (0.050 g) in methanol (10 ml). Examination by TLC after a few minutes showed the absence of any aldehyde. Evaporation, addition of water, and chloroform extraction afforded the alcohol 4 (0.045 g) as a yellow oil which decomposed upon attempted chromatography over silica or alumina. Compound 4 was characterized spectroscopically as follows: uv λ_{max} 260, 325 nm; NMR δ 2.85 (s, 3 H, NMe), 3.21 (t, 2 H, J = 8.5 Hz), 3.28 (t, 2 H, J = 8.5 Hz), 3.86 (s, 3 H, OMe), 4.00 (s, 3 H, OMe), 7.08 (s, 1 H, C-3), 7.46–9.76 (m, 4 H); mass spectrum m/e 323 (M^+, 100), 308 (55), 306 (55), 292 (25), 290 (20), 161.5 (1).

7-Methyldehydronuciferine (5). A. A solution of alcohol 4 (0.040 g) in tetrahydrofuran (10 ml) was brought to pH 3–4 by the addition of a few drops of 5% hydrochloric acid, and excess sodium cyanoborohydride was added in portions, while maintaining the acidity of the solution. After 15 min, TLC showed no starting material to be present. Workup in the usual manner, followed by crystallization from methanol, gave compound 5 as yellow prisms (0.034 g): mp 99–100 °C; uv λ_{max} 254 nm (ϵ 100 000), 264 (100 000), 324 (25 000), 387 sh (4000); NMR δ 2.68 (s, 3 H, C-Me), 2.78 (s, 3 H, NMe), 3.21 (t, 2 H, J = 8.5 Hz), 3.28 (t, 2 H, J = 8.5 Hz), 3.88 (s, 3 H, OMe), 4.00 (s, 3 H, OMe), 7.06 (s, 1 H, C-3), 7.41–9.78 (m, 4 H); mass spectrum m/e 307 (M^+, 100), 292 (43), 153.5 (5).

Anal. Calcd. for $C_{20}H_{21}NO_2$: C, 78.17; H, 6.84; N, 4.56. Found: C, 78.00; H, 6.98; N, 4.48.

B. A solution of aldehyde 3 (0.050 g) in methanol (10 ml) was reduced at pH 3–4 with sodium cyanoborohydride as described above for alcohol 4. Workup afforded 5 in 84% yield.

7-Cyanomethyldehydronuciferine (7). Potassium cyanide (0.060 g) was added to a stirred solution of alcohol 4 (0.200 g) in a mixture of ethanol (5 ml) and 1% hydrochloric acid (15 ml). After stirring for 30 min at room temperature, the mixture was heated on the steam bath for 15 min. The usual workup, followed by filtration in chloroform through silica, gave crude nitrile 7. Crystallization from ethanol–chloroform gave 7 as prisms (0.160 g): mp 195–196 °C; ir 4.40 μ; uv λ_{max} 253 nm (sh) (ϵ 35 000), 262 (50 000), 323 (11 000), 370 (2400); NMR δ 2.98 (s, 3 H, NMe), 3.98 (s, 3 H, OMe), 4.01 (s, 3 H, OMe), 4.45 (s, 2 H, CH_2CN), 7.13 (s, 1 H, C-3), 7.50–9.75 (m, 4 H); mass spectrum m/e 332 (M^+, 100), 317 (57), 292 (49), 166.5 (1).

Anal. Calcd for $C_{21}H_{20}N_2O_2$: C, 75.90; H, 6.02; N, 8.43. Found: C, 76.03; H. 6.12; N, 8.42.

Acknowledgment. We thank the National Institutes of Health for a grant (CA-11445) in support of this work, and the Fundación Juan March for a supporting fellowship to one of us (J. M. Saá).

Registry No.—1, 7630-74-2; 3, 60538-11-6; 4, 60538-12-7; 5, 60538-13-8; 7, 60538-14-9.

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Gnididione, a New Furanosesquiterpene from *Gnidia latifolia*[1]

S. Morris Kupchan,* Yoshikazu Shizuri, Robert L. Baxter, and H. Richard Haynes

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901

Received June 30, 1976

In the course of a continuing search for tumor inhibitors from plant sources, we have isolated the potent antileukemic diterpenoid esters, gnidilatin 20-palmitate and gnidilatidin 20-palmitate, from *Gnidia latifolia* Gilg. (Thymelaeaceae).[2,3] Our isolation procedure also yielded a new sesquiterpene, gnididione (1). Gnididione is the first known guaiane-type sesquiterpenoid with a furan ring.

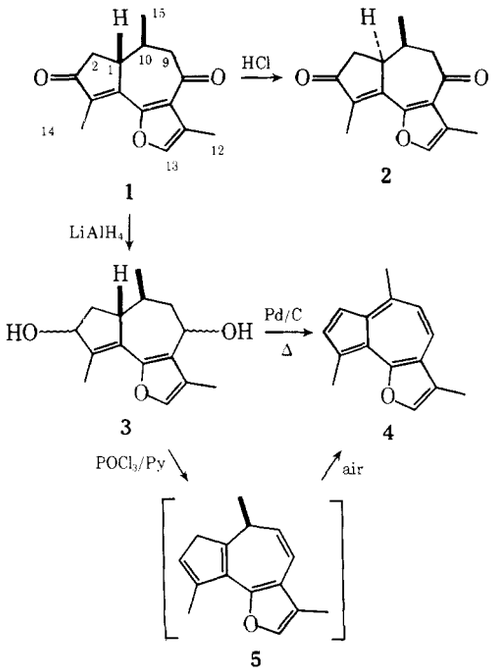
An ethanol extract of *G. latifolia* was partitioned between chloroform and water. The chloroform soluble material was chromatographed on SilicAR CC-7. Crystallization from methanol of the fraction which was eluted with 10% ethyl acetate in benzene gave gnididione (1).

Elemental analysis and mass spectrometry established a molecular formula of $C_{15}H_{16}O_3$ for 1. The ^{13}C NMR spectrum of 1 indicated the presence of two carbonyl groups [δ 206.3 (s) and 195.8 (s)], three double bonds [δ 154.0 (s), 153.6 (s), 142.2 (d), 137.9 (s), 126.5 (s), and 123.4 (s)], two methylene groups [δ 54.1 (t) and 40.7 (t)], two methine groups [δ 46.4 (d) and 32.8 (d)], and three methyl groups [δ 21.8 (q), 10.1 (q), and 9.8 (q)]. Furthermore, the ^1H NMR spectrum showed that one of the methyl groups was attached to a methine group [τ 8.88 (3 H, d, J = 7 Hz)]. The absorptions at 3.22, 6.33, and 6.69 μ in the ir spectrum indicated the presence of a furan ring, and the uv absorption at 338 nm showed that the carbonyl groups, double bond, and furan ring were conjugated. From the above data and from biogenetic considerations, gnididione (1) appeared to belong to the guaiane class of sesquiterpenes and to have either structure 1 or 2. The structure was confirmed by subsequent chemical transformations. Thus, reduction of 1 with lithium aluminum hydride, followed by dehydrogenation over palladium on charcoal, yielded artemazulene (4), which formed a crystalline trinitrobenzene complex. In order to avert possible intramolecular changes during dehydrogenation, the

lithium aluminum hydride reduction product was dehydrated with phosphorus oxychloride in pyridine to give intermediate **5**, which was very unstable and was autoxidized by air to give artemazulene (**4**).

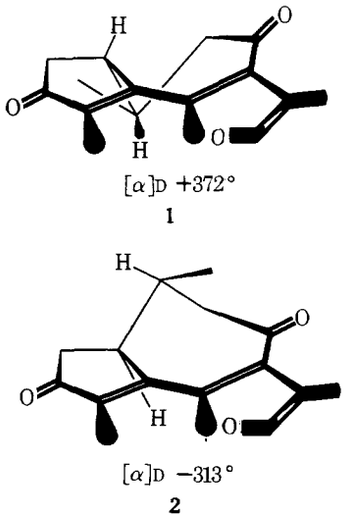
Isomerization of gnididione (**1**) with hydrochloric acid in ethanol yielded isognididione (**2**). In view of the mild conditions employed for the conversion of gnididione (**1**) to isognididione (**2**), epimerization at the C-1 position seemed likely. The uv and ir spectra of **2** were virtually identical with those of **1**, indicating little change in the chromophore during isomerization. Moreover, the $[\alpha]_D$ values of **1** and **2** were +370 and −313°, respectively, a difference which is compatible with isomerization at C-1 (Chart I, **1** → **2**).

Chart I



1 2 3 4 5

The configuration of the C-15 methyl group relative to the C-1 proton was determined by a comparison of the ^1H NMR spectra of **1** and **2**. In **1** the methyl resonance (3 H, d, J = 7 Hz, 15-H) was at τ 8.88, whereas in **2** the methyl resonance was shifted to τ 9.20 as a result of its close proximity to the 6,7 double bond (Figure 1). Thus, H-1 and C-15 are cis in gnididione (**1**) and trans in isognididione (**2**). The absolute configuration of gnididione has not yet been established.



$[\alpha]_D$ +372°

1

$[\alpha]_D$ −313°

2

Figure 1.

Experimental Section

General. Melting points were determined on a Mettler Model FP2 hot stage and are uncorrected. Ultraviolet and visible absorption spectra were determined on a Beckman Model DK-2A recording spectrophotometer. Infrared spectra were determined on Perkin-Elmer Model 257 and Model 337 recording spectrophotometers. Nuclear magnetic resonance spectra were determined on either a Varian HA-100 spectrometer or a JEOL PS-100 pulsed FT NMR spectrometer interfaced to a Texas Instrument JEOL 980A computer, with tetramethylsilane as an internal standard. Mass spectra were determined on Hitachi Perkin-Elmer Model RMU-6E and AEI Model MS-902 spectrometers. Values of $[\alpha]_D$ were determined on a Perkin-Elmer Model 141 automatic polarimeter. Microanalysis was carried out by Spang Microanalytical Laboratory, Ann Arbor, Mich. All thin layer chromatography utilized silica gel 60 precoated glass plates (E. Merck), and visualization of TLC was effected with short wavelength uv and concentrated sulfuric acid–vanillin–ethanol (20:1:3) spray.

Isolation of Gnididione (1) from *Gnidia latifolia*. The dried ground stem wood and stem bark (30 kg) of *Gnidia latifolia* was extracted at room temperature by stirring with 95% ethanol (216 l.) for 24 h. The extraction mixture was filtered and concentrated below 30 °C in vacuo, to a syrupy residue (~900 ml). The residue was partitioned between chloroform (3 × 8 l.) and water (10 l.). The combined chloroform layers were concentrated to give a brown tar (440 g), which was chromatographed on a SilicAR CC-7 (Mallinkrodt) column (5 kg) by eluting with benzene followed by benzene containing increasing amounts of ethyl acetate. Elution with 10% ethyl acetate in benzene gave a fraction (65 g) which gave plates upon crystallization from methanol. Recrystallization from methanol gave gnididione (**1**, 20 g, 0.067%): mp 110–111 °C; $[\alpha]^{29}_D$ +372° (c 0.97, $CHCl_3$); uv max (EtOH) λ (ϵ) 238 (7170), 259 (7650), 338 nm (19 700); ir (KBr) 3.22, 3.41, 5.95, 6.10, 6.22, 6.33, 6.69, 12.58 μ; NMR ($CDCl_3$) τ 8.88 (3 H, d, J = 7 Hz, 15-CH_3), 7.98 (3 H, d, J = 2 Hz, 14-CH_3), 7.85 (3 H, d, J = 1 Hz, 12-CH_3), 7.70–7.00 (6 H, m, 1-, 2-, 9-, and 10-H), 2.65 (1 H, q, J = 1 Hz, 13-H); mass spectrum m/e 244 (M^+), 216, 201, 187, 174, 117, 91, 77.

Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.73; H, 6.75.

Artemazulene (4). Method A. A solution of gnididione (**1**, 1 g) in THF (5 ml) was added to a suspension of lithium aluminum hydride (0.5 g). The mixture was stirred at room temperature for 1 h. Excess reagent was decomposed with saturated sodium potassium tartrate solution, the precipitate was removed, and the filtrate was concentrated at reduced pressure to give a white powder (1.1 g). This was mixed with 10% palladium on charcoal (1 g) and heated at about 300 °C for 10 min. The reaction mixture was extracted with hexane (50 ml) to give a dark blue oil (150 mg), which was chromatographed on alumina (Woelm; neutral, activity II, III) to give artemazulene (**4**, 15 mg). The theoretical amount of 1,3,5-trinitrobenzene was added and the complex, crystallized twice from methanol, was identified as the artemazulene derivative by melting point (188–189 °C, lit.[4] mp 187–188 °C) and uv, visible, and ir spectra.

Method B. Phosphorus oxychloride (1.5 ml) was added to a solution of the lithium aluminum hydride reduction product (1.1 g) in pyridine at 0 °C under nitrogen. After 2 h the reaction mixture was poured into ice water and extracted with chloroform. The chloroform layer was evaporated and chromatographed on alumina (Woelm; 20 g, neutral, activity II, III) to give **5** (430 mg): NMR ($CDCl_3$) τ 8.77 (3 H, d, J = 7 Hz, 15-CH_3), 8.04 (3 H, d, J = 1.5 Hz, 14-CH_3), 7.86 (3 H, br s, 12-CH_3), 7.42 (1 H, d of q, J = 6, 7 Hz, 10-H), 7.07 (2 H, br s, 2-H), 4.93 (1 H, d of d, J = 6, 10 Hz, 9-H), 4.20 (1 H, q, J = 1.5 Hz, 3-H), 3.80 (1 H, d, J = 10 Hz, 8-H), 2.96 (1 H, br s, 13-H). Intermediate **5** was rapidly oxidized by air to give artemazulene (**4**, 380 mg).

Isognididione (2). Hydrochloric acid (2 N, 2 ml) was added to a solution of gnididione (100 mg) in ethanol (3 ml). The mixture was heated at reflux temperature for 18 h, then extracted with chloroform. The chloroform layer was evaporated and separated on silica gel plates to give gnididione (48 mg) and isognididione, as a homogeneous, amorphous solid (**2**, 36 mg): $[\alpha]^{24}_D$ −313° (c 1.365, $CHCl_3$); uv (EtOH) λ (ϵ) 237 (8200), 258 (8800), 336 nm (20 000); ir (KBr) 3.21, 3.42, 5.92, 6.05, 6.23, 6.32, 6.67, 12.50 μ; NMR ($CDCl_3$) τ 9.20 (3 H, d, J = 7 Hz, 15-CH_3), 7.97 (3 H, d, J = 2 Hz, 14-CH_3), 7.86 (3 H, br s, 12-CH_3), ca. 7.9 (1 H, 10-H), 7.29, 7.85 (each 1 H, m, 2-H), 7.01, 7.24 (each 1 H, m, 9-H), 6.68 (1 H, br m, 1-H), 2.73 (1 H, br s, 13-H); mass spectrum m/e 244.1106 (M^+, calcd for $C_{15}H_{16}O_3$, 244.1099).

Registry No.—**1**, 60498-89-7; **2**, 60498-90-0; **4**, 478-51-3; **5**, 60498-91-1.

References and Notes

(1) This investigation was supported by research grants from the National Cancer Institute (CA-11718 and CA-12059) and the American Cancer Society (CI-102K), and contracts with the Division of Cancer Treatment, NCI, National Institutes of Health (N01-CM-12099 and N01-CM-67002).
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Synthesis of Antibacterial *p*-Quinols from Marine Sponges. Synthetic Applications of "Masked" Quinones

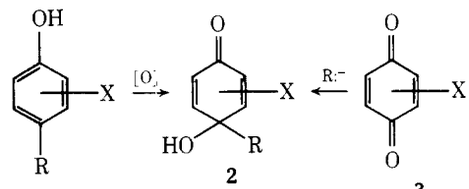
David A. Evans[1] and Rayman Y. Wong

Contribution No. 5359 from the Laboratories of Chemistry, California Institute of Technology, Pasadena, California 91125

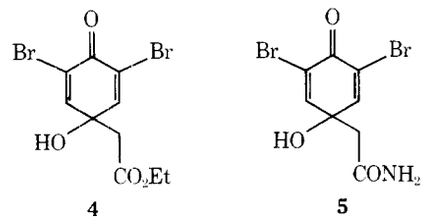
Received June 18, 1976

o- and *p*-quinols, including closely related derivatives, are important intermediates in the biosynthesis and metabolism of phenolic natural products.[2] Recently, research in this laboratory[3] and elsewhere[4] has been directed toward exploiting such versatile intermediates in the synthesis of naturally occurring quinones and alkaloids.

In principle, there are two potentially attractive routes to the synthesis of *p*-quinols such as **2**, one being the oxidation of the appropriately substituted phenol **1**, and the other being the regioselective nucleophilic addition of a carbon nucleophile ($R:^-$) to the quinone moiety **3**. Historically, the use of

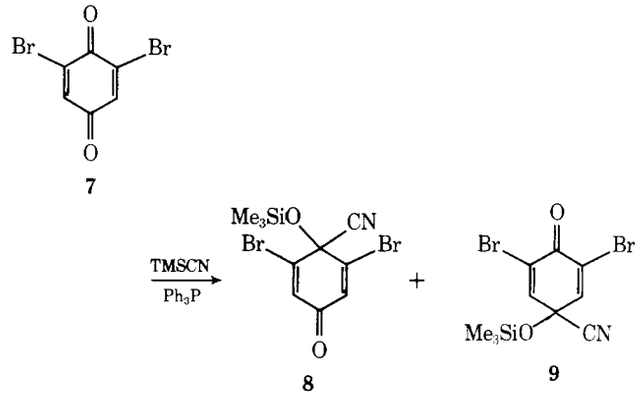


phenol oxidation techniques as an effective means of producing *p*-quinols has been quite disappointing;[5] however, with the recent development of selective oxidants such as thallium(III),[6] these phenol oxidations may now be considered as viable synthetic processes. Recently, we have developed the capability of regioselectively monoprotecting substituted *p*-quinones **3**, and have demonstrated that such substrates are excellent general precursors to *p*-quinols.[7] The purpose of this note is to report on the application of such methodology to the synthesis of *p*-quinol antibiotic metabolites **4** and **5**



recently isolated from the mollusk *Tylodina fungina*, and marine sponges of the genus *Verongia*, respectively.[8]

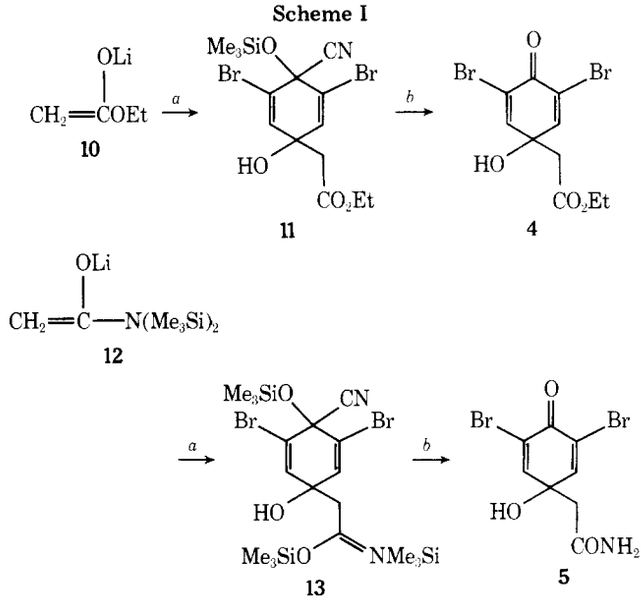
The requisite monoprotected *p*-quinone **8** was readily prepared in two steps from commercially available precursors. 2,4,6-Tribromophenol (**6**) was oxidized with thallium tris(trifluoroacetate), according to the method of Taylor,[9] to 2,6-dibromo-*p*-benzoquinone (**7**) in 67% yield.[10] Regiospecific carbonyl protection of the requisite quinone carbonyl was realized upon treatment of **7** with 1 equiv of trimethylsilyl cyanide (TMSCN) and a catalytic amount of triphenylphosphine in acetonitrile at 0 °C. *Under these conditions the adduct* **8** *was produced in essentially quantitative yield uncontaminated by the isomeric quinone adduct* **9**. A change



in solvent (C_6H_6, CCl_4, $CHCl_3$) or increased reaction temperatures resulted in a loss in regioselectivity of the reaction. For example, the same reaction carried out in chloroform (25 °C, 1 h) afforded an **8**:**9** ratio of 38:62. Tentative conclusions relating to the relative stabilities of the isomeric adducts were obtained from an equilibrium experiment. Treatment of **8** with a catalytic amount of triphenylphosphine at 40 °C (240 h) in acetonitrile resulted in an apparent isomerization to **9** ($K_{eq} \geq 10$).

With the requisite "masked" quinone **8** in hand, the *p*-quinol ester **4** and amide **5** were readily prepared via the enolate carbonyl addition processes outlined in Scheme I. A tetrahydrofuran solution of lithioethyl acetate (**10**) was gen-

Scheme I



a, **8**, −100 °C, NH_4Cl-H_2O; b, AgF, H_2O-THF.

erated according to established procedures,[11] and then cooled to −100 °C, whereupon a tetrahydrofuran solution of blocked quinone **8** was added over a period of a few seconds. The reaction mixture was allowed to warm to 0 °C over a 2-h period, and quenched with 1 equiv of ammonium chloride. The resultant dark crude blocked quinol **11** was immediately deblocked with 1 equiv of silver fluoride in THF–water (10:1).[3] The flocculent mixture was stirred at room temperature for 2.5 h to yield the desired quinol **4**[8b] in a 77% overall yield from masked quinone **8**.