^{1}H NMR signals in agrobactin A and, most dramatically, in the precursor 4 in which Me_2SO-d_6 spectra lacked any sign of the conformers present in $CDCl_3$ at 23 °C. This effect on the ^{1}H NMR of 4, on changing between Me_2SO and $CDCl_3$, is of additional interest in view of the fact that the *tert*-butoxy group is not able to form as many hydrogen bonds as the 2,3-dihydroxybenzoyl group. This suggests that an even greater solvent effect may be experienced by agrobactin A and its related siderophores, producing much higher T_c and E_a values in nonpolar solvents for these compounds. However, due to agrobactin A's poor solubility in all but the most polar solvents, a comprehensive determination of T_c's in other solvents is essentially not possible.

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Registry No. 1, 86748-77-8; 2, 83392-11-4; 3, 86748-78-9; 4, 86748-79-0; 5, 86748-81-4; 6, 86783-92-8; 7, 83392-12-5; 8, 86748-82-5; 9, 86748-84-7; 10, 86748-85-8; 11, 86748-86-9; D,L-threonine, 80-68-2; 2,3-dihydroxybenzoic acid, 303-38-8; succimimidyl *N*-*tert*-butyloxycarbonyl-D,L-threoninate, 86783-93-9; 2,3-dimethoxybenzoic acid, 1521-38-6; D,L-N^4-threonyl-N^1,N^8-bis(2,3-dihydroxybenzoyl)spermidine hydrobromide, 86783-94-0.

Phthalide Annulation: The Synthesis of Kalafungin, Pachybasin, and Chrysophanol

George A. Kraus,* Hidetsura Cho, Steven Crowley, Bruce Roth, Hirohiko Sugimoto, and Susan Prugh

Department of Chemistry, Iowa State University, Ames, Iowa 50011

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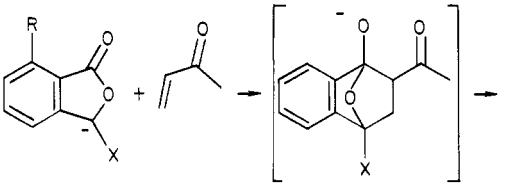
The anions of 3-cyano- or 3-(phenylthio)phthalide react with Michael acceptors to afford functionalized naphthydroquinones in good yield. The cyano and phenylthio groups function both as activating groups and as leaving groups. An alternative involves the use of protected *o*-(carboxymethyl)cyanohydrins. The use of phthalide anions in synthesis is exemplified by total syntheses of kalafungin, pachybasin, and chrysophanol. This methodolgy consititutes a direct and regiospecific approach to polycyclic systems.

Introduction

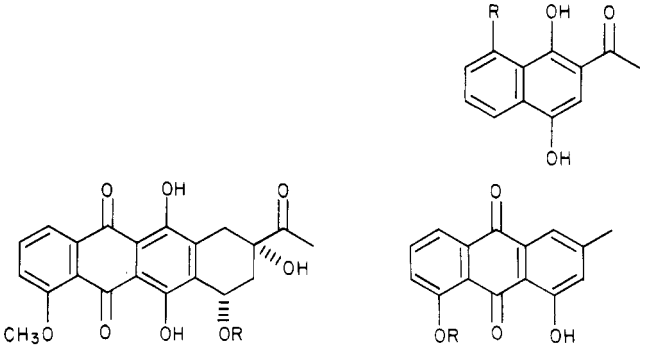
Michael addition followed by base-induced cyclization consitutes a versatile method for the construction of carbocyclic rings. Several variants of this concept have been developed.[1] A common feature of these reactions is that four carbons of the newly formed cyclohexenone ring are supplied by the Michael acceptor. A generally useful Michael addition sequence in which four carbons of the newly formed cyclohexane ring originate from the Michael donor would represent a valuable contribution to synthetic methodology.

In this paper we report the use of functionalized phthalides and ortho-substituted benzoates to effect an annulation reaction. The hydroquinone products of this reaction can be readily oxidized to quinones. Quinones are important subunits in physiologically active molecules such as daunomycin[2] (1), chrysophanol[3] (2), and kalafungin[4] (3). One advantage of this methodology over sequential Friedel–Crafts acylations is that the regiochemistry of the product is unambiguous. In Friedel–Crafts reactions, certain rearrangements such as the Hayashi rearrangement can produce mixtures of isomeric products. This method should complement the Diels–Alder reaction as a useful method for the construction of polycyclic quinones.

Conceptually related cyclizations have recently been described. Hauser and co-workers have investigated the chemistry of anions of sulfonylphthalides and have reported a clever synthesis of kidamycinone.[5] Sammes[6] has studied the reactions of phthalide anions with Michael acceptors. The yields of naphthols obtained by his procedure were modest. VanLeusen and co-workers[7] have

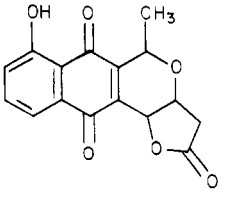


I



1, R = daunosamine

2, chrysophanol, R = H

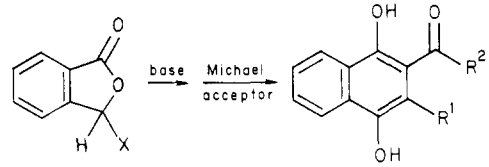


3

(1) Jung, M. E. *Tetrahedron* **1976**, *32*, 3.
(2) Arcamone, F. *Lloydia* **1977**, *40*, 45.
(3) Oli, T.; Matsuzawa, Y.; Yoshimoto, A.; Numata, K.; Kitamura, I.; Hori, S.; Takamatsu, A.; Umezawa, H.; Ishizuka, M.; Naganawa, H.; Suda, H.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1978**, *23*, 830.
(4) Bergy, M. E. *J. Antibiot.* **1976**, *29*, 454.
(5) Hauser, F. M.; Rhee, R. P. *J. Am. Chem. Soc.* **1979**, *101*, 1628.
(6) Broom, N. J. P.; Sammes, P. G. *J. Chem. Soc., Chem. Commun.* **1978**, 162.

0022-3263/83/1948-3439$01.50/0

Table I

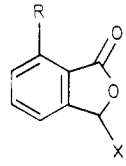


entry	X	Michael acceptor	R_1	R_2	yield, % LDA	yield, % *t*-BuOK/Me_2SO
1	CN	$CH_3CH{=}CHCOCH_3$	CH_3	CH_3	85	
2	CN	CH_2CHCO_2Et	H	OEt	60	
3	CN		$-CH_2O-$		50	
4	CN	PhCH=CHCOPh	Ph	Ph	72	
5	SPh	cyclohexenone	$-CH_2CH_2CH_2-$		38[a]	48
6	SPh	5-(trimethylsilyl)cyclohexenone	$-CH_2CH(SiMe_3)CH_2-$		70	
7	SPh	5-methylcyclohexenone	$-CH_2CH(CH_3)CH_2-$		66	64
8	SPh	$CH_3CH{=}CHCOCH_3$	CH_3	CH_3	30	60
9	CN	cyclohexenone	$-CH_2CH_2CH_2-$			60[b]

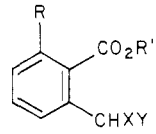
[a] 32% Michael addition product also isolated. [b] The anthraquinone was obtained.

reported preliminary results of the reaction between *o*-sulfonylmethyl carboxylates and various Michael acceptors. Li[8] has observed that cyanophthalides were superior to sulfonyl-substituted phthalides for the synthesis of a key intermediate for anthracycline synthesis.

Synthesis of Reactants. The preparation of functionalized phthalides **4a–4d** and esters **5a–5d** is described

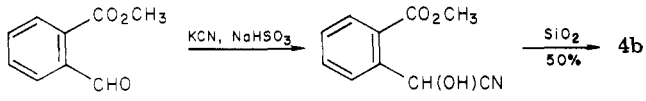


4a, R = H, X = SPh
b, R = H, X = CN
c, R = OCH_3, X = SPh
d, R = OCH_3, X = CN

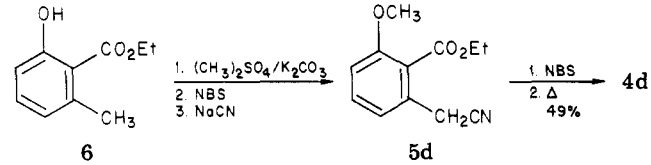


5a, R = OCH_3, X = Y = H; R' = C_2H_5
b, R = H, X = CN, Y = OSi-*t*-$BuMe_2$; R' = CH_3
c, R = H, X = CN, Y = $OCH(CH_3)OEt$; R' = CH_3
d, R = OCH_3, X = CN, Y = H; R' = C_2H_5

below. The one-step transformation of *o*-formylbenzoic acid to **4a** and **4b** has already been described.[9] However, the large scale preparation of **4b** afforded widely varying yields. The two-step preparation of **4b** from methyl *o*-formylbenzoate[10] is reproducible and is illustrated below.



More conventional lactonization procedures (CF_3CO_2H, CH_2Cl_2; pTSA, benzene) furnished **4b** in reduced yields and lower purity. Phthalide **4c** was synthesized from 7-methoxyphthalide[11] by deprotonation at–78 °C with lithium diisopropylamide (LDA) and reaction with diphenyl disulfide. Phthalide **4d** was prepared from **6**[12] by the following five-step sequence depicted below.[13] The



structure of **4d** is supported by an NMR absorption at δ6.58. Ester **5a**[14] was synthesized by methylation of **6** with potassium carbonate and dimethyl sulfate in refluxing acetone. Compounds **5b** and **5c** were prepared from the cyanohydrin of methyl *o*-formylbenzoate in analogy with literature procedures[15] for the protection of aromatic cyanohydrins.

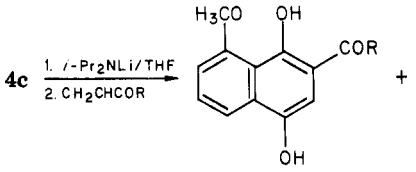
Annelation Results and Discussion

Initial experiments were conducted with phthalides **4a** and **4b**. The anions were generated with LDA at –78 °C. Although hydroquinones were obtained by reaction of Michael acceptors with the anion of **4b**, only Michael addition products were isolated on reaction with the anion of **4a**.[9] The presence of the characteristic phthalide absorption in the infrared spectrum at 1780 cm^{-1} was diagnostic of the Michael adducts. The use of hexamethylphosphoric triamide (HMPA), 1.5 equiv of LDA, and longer reaction times at 0 °C resulted in good yields of annelation products from **4a** with only minor amounts (5–10%) of uncyclized products. We next examined reaction conditions that would generate the anion of **4a** or **4b** under equilibrium conditions in the presence of a Michael acceptor. The optimal conditions, 3 equiv of potassium *tert*-butoxide in Me_2SO at ambient tempera-

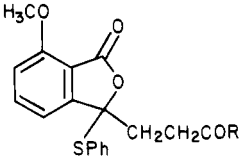
(7) VanLeusen, A. M., Terpstra, J. W. *Tetrahedron Lett.* **1981**, *22*, 5097. For sulfone esters: Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1978**, *43*, 178.
(8) Li, T. Walsgrove, T. C. *Tetrahedron Lett.* **1981**, 3741.
(9) Kraus, G. A.; Sugimoto, H. *Tetrahedron Lett.* **1978**, 2263. Kraus, G. A.; Sugimoto, H. *Synth. Commun.* **1977**, 515.
(10) Brown, C.; Sargent, M. V. *J. Chem. Soc. C* **1969**, 1818.
(11) Trost, B. M.; Rivers, G. T.; Gold, M. M. *J. Org. chem.* **1980**, *45*, 1835. Uemura, M.; Tokuyama, S.; Sakan, T. *Chem. Lett.* **1975**, 1195.
(12) Gerhard, A.; Muntwyler, R.; Keller-Schierlein, W. *Helv. Chim. Acta* **1975**, *58* 1323.
(13) Li, T.; Wu, Y. L. *J. Am. Chem. Soc.* **1981**,*103*, 7007.
(14) For the acid: Anslow, W. K.; Raistrick, H. *Biochem. J.* **1931**, *25*, 39.
(15) Silyl ethers: Hunig, S.; Wehrner, G. *Synthesis* **1975**, 391. Acetals: Stork, G.; Maldonado *J. Am. Chem. Soc.* **1971**, *93*, 5286.

ture, afforded good yields of hydroquinones and no trace of uncyclized products. The results of reactions with **4a** and **4b** are illustrated in Table I. In some cases (entry 9) the anthraquinone was obtained. This probably originated from the reaction of the hydroquinone product with oxygen in the basic media.

Extension of our investigation to substituted phthalides was initated with **4c** and **4d**. Although **4c** afforded mixtures of annelation product **7** and Michael adduct **8** when reacted with methyl vinyl ketone, the reaction with ethyl acrylate produced only adduct **9**. The reaction of 7-

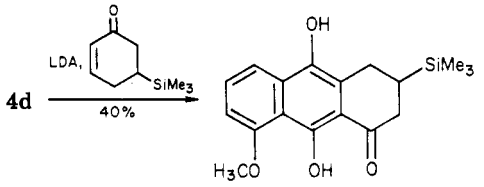


7, R = CH_3, 43%
9, R = OEt, 50%

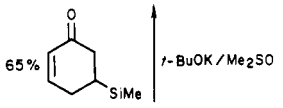


8, 20%

methoxy-3-cyanophthalide with 5-(trimethylsilyl)-3-cyclohexen-2-one produced hydroquinone **10** in 40% isolated yield.

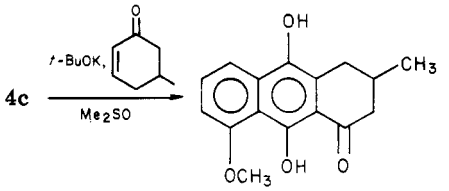


10



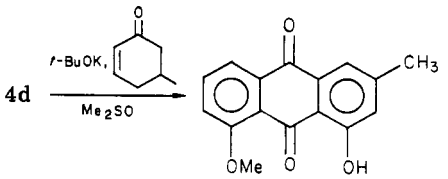
4d

The reaction of 5-methylcyclohexenone with **4c** afforded tricyclic ketone **11** in 65% yield after chromatography.



11

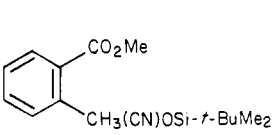
The reaction with **4d** provided *O*-methylchrysophanol directly in 51% isolated yield. The methyl absorptions



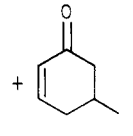
2, R = CH_3

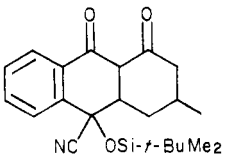
at δ2.40 and 4.02 in the NMR spectrum support the assigned structure.

Benzoates **5b** and **5c** were also prepared (vide supra) and reacted with Michael acceptors. Although anions of

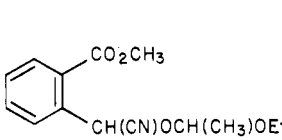


5b

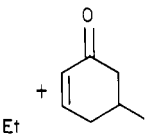


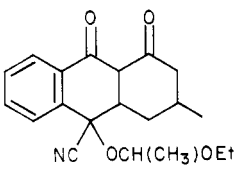


21%



5c





46%

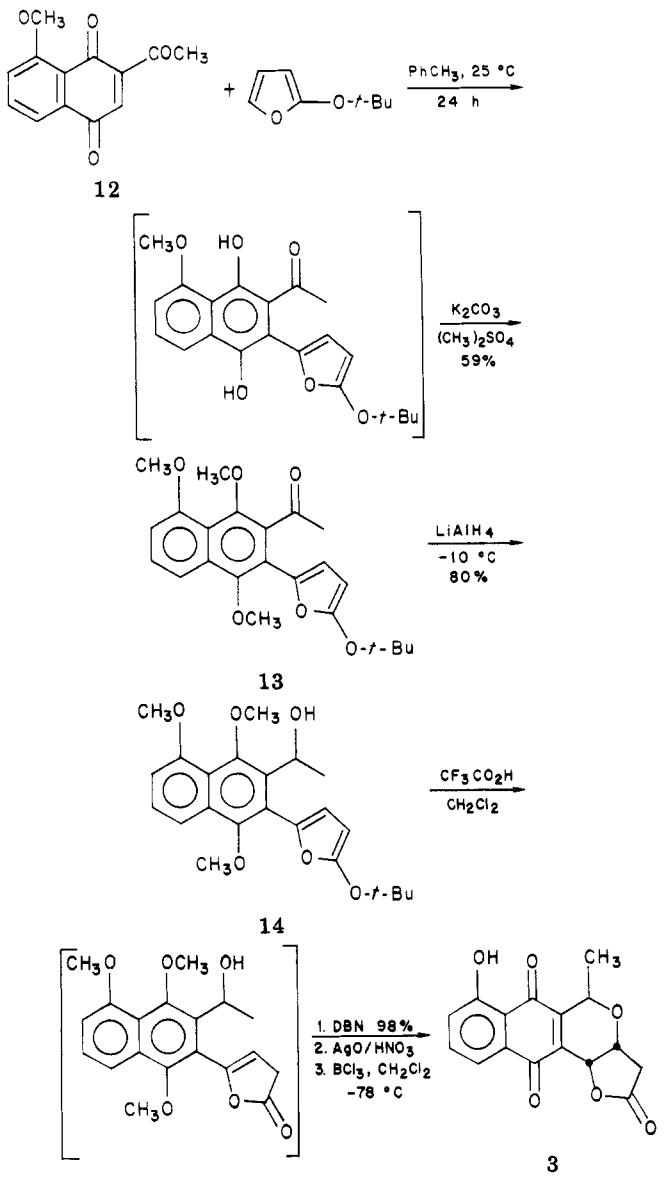
protected aromatic cyanohydrins are well-known and a few Michael additions have been performed, no examples of cyanohydrin anions containing an *o*-carbonyl group have been reported. The reaction of **5b** with 5-methyl-2-cyclohexenone under conditions analogous to the phthalide cyclization produced tricyclic β-diketone in 21% yield. The remainder of the silylated cyanohydrin appeared to have decomposed. The anion of cyanohydrin acetal **5c** was more stable under the reaction conditions and furnished tricyclic product in 46% isolated yield. Although this represents an improvement over the reaction involving **5b**, it is still inferior to the reaction involving **4a**.

Previous work in our laboratory[16] showed that 9-deoxykalafungin could be prepared from 2-acetyl-1,4-naphthoquinone and *tert*-butoxyfuran. The analogous 8-methoxy-2-acetyl-1,4-naphthoquinone had been reported;[17] however, it had been made by a multistep synthesis with low overall yield. Although the reaction of 7-methoxy-3-thiophenylphthalide and methyl vinyl ketone followed by oxidation produces **12** in modest yield, it is certainly much more direct. The route to kalafungin is depicted in Scheme I. In contrast to the rapid reaction of 2-acetyl-1,4-naphthoquinone with *tert*-butoxyfuran (−78 °C), the addition to **12** required 24 h at room temperature.

Unexpectedly, the deprotection–cyclization sequence, which proceeded in only modest yield in the model system, afforded cyclized product in excellent yield. This compound was an epimeric mixture at C-1. Oxidation afforded 9-*O*-methylkalafungin as a *single* isomer (mp 203–210 °C, lit. 205–215 °C), as evidenced by proton and carbon NMR. Reaction of 9-*O*-methylkalafungin with borontrichloride at low temperature furnished synthetic (±)-kalafungin as the sole product. All spectral data for synthetic kalafungin were in accord with available data. Kalafungin has previously been synthesized by Li and co-workers.[18] Our

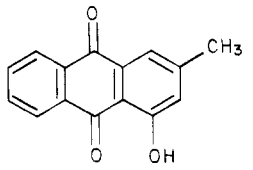
(16) Kraus, G. A.; Roth, B. *J. Org. Chem.* **1978**, *43*, 4923.
(17) Bossard, P.; Fumagalli, S.; Good, R.; Treub, W.; v. Philipsborn, W.; Eugster, C. H. *Helv. Chim. Acta* **1964**, *47*, 796.
(18) Li, T.; Ellison, R. H. *J. Am. Chem. Soc.* **1978**, *100*, 6263.

Scheme I



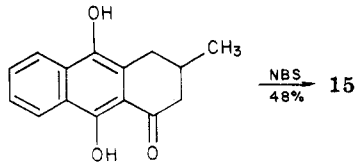
route is more direct than the Li route and proceeds in better overall yield.

Pachybasin (15) was isolated by Japanese workers in 1955. It possesses the tricyclic aromatic subunit of 4-



15

deoxyaclacinomycin and has been used as a model system to test methods for the preparation of 11-deoxyanthracyclines.[19] Hydroquinone 16 can be oxidized with



16

(19) Jung, M. E.; Lowe, J. A. *J. Chem. Soc., Chem. Commun.* **1978**, 95.

N-bromosuccinimide to pachybasin in one step. Alternatively, it can be isolated directly from the reaction of **4b** and 5-methyl-2-cyclohexenone.

The phthalide annulation sequence provides a direct entry to substituted hydroquinones. An alternate sequence employing protected cyanohydrins of *o*-(carbomethoxy)-benzaldehyde affords comparable yields and should be useful in cases where the corresponding phthalide would be difficult to prepare.[20]

Experimental Section

General. Diethyl ether and THF were distilled from lithium aluminum hydride. All organic extracts were dried over Na_2SO_4. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were determined on a Beckman IR-4250 spectrometer. Nuclear magnetic resonance spectra were determined on a Varian EM-360 instrument in $CDCl_3$ with absorptions recorded in ppm downfield from internal Me_4Si. Ultraviolet spectra were recorded with a Cary Model 14 spectrometer. High-resolution mass spectra were recorded on an AEI MS-902 high-resolution mass spectrometer.

Ethyl 2-Hydroxy-6-methylbenzoate (6). To a solution of 9.1 g (50 mmol) of ethyl 6-methyl-2-oxo-cyclohex-3-enecarboxylate[21] in 100 mL of CCl_4 was added 8.9 g (50 mmol) of *N*-bromosuccinimide and a few crystals of benzoyl peroxide. The mixture was refluxed for 18 h. After the reaction mixture had cooled to ambient temperature, it was filtered and the solvent was evaporated in vacuo. The residue was chromatographed on silica gel using 30:1 hexane:ethyl ether as solvent. Chromatography provided an 80% yield of **6**: NMR($CDCl_3$) δ 1.40 (t, 3 H), 2.53 (s, 3 H), 4.38 (q, 2 H), 6.58–7.38 (m, 3 H), 11.21 (s, 1 H); IR (nujol mull) 3400, 1655, 1605 cm^{-1}; mp 39–40 °C.

Ethyl 2-Methoxy-6-methylbenzoate (5a). To a solution of 11.0 g (61 mmol) of **6** in 800 mL of acetone was added 12.6 g (91.5 mmol) of potassium carbonate and 8.65 mL (91.5 mmol) of dimethyl sulfate. The mixture was heated at reflux for 16 h. After the reaction mixture had cooled to room temperature, it was filtered and concentrated in vacuo. The residue was chromatographed on silica gel using 30:1 hexane:ethyl ether as solvent. Chromatography provided a 92% yield of **5a**: NMR ($CDCl_3$) δ 1.34 (t, 3 H), 2.29 (s, 3 H), 3.80 (s, 3 H), 4.35 (q, 2 H), 6.6–7.3 (m, 3 H); IR (nujol mull) 1725, 1585 cm^{-1}.

Ethyl 2-Cyanomethyl-6-methoxybenzoate (5d). To a solution of 22.6 g (116.4 mmol) of **5a** in 230 mL of CCl_4 was added 20.8 g (117 mmol) of NBS and a few crystals of benzoyl peroxide. The mixture was refluxed for 8 h. After cooling to room temperature, the mixture was filtered and the solvent evaporated under reduced pressure to give the crude benzylic bromide: NMR ($CDCl_3$) δ 1.40 (t, 3 H), 3.81 (s, 3 H), 4.49 (s, 2 H), 6.75–7.55 (m, 3 H). To a solution of the crude benzylic bromide in 60 mL of 95% EtOH was added a solution of 6.88 g (140.4 mmol) of NaCN in 70 mL of H_2O. The resulting solution was refluxed for 4 h. The EtOH was evaporated under reduced pressure and the aqueous residue was extracted with ether. The ethereal solution was washed with brine and dried over Na_2SO_4. After the ether was evaporated under reduced pressure, the residue was chromatographed on silica gel using hexane/ethyl ether (10:1) as solvent. The reaction produced 7.64 g (39.4 mmol) of unreacted **5a** and 14.12 g (63.9 mmol) of **5d**. The corrected yield was 83%: NMR($CDCl_3$) δ 1.40 (t, 3 H), 4.75 (s, 2 H), 4.83 (s, 3 H), 4.40 (q, 2 H), 6.82–7.50 (m, 3 H); IR (film) 2225, 1725, 1580 cm^{-1}.

3-Cyano-7-methoxyphthalide (4d). To a solution of 6.57 g (30 mmol) of **5d** in 60 mL of CCl_4 was added 5.34 g (30 mmol) of NBS and a few crystals of benzoyl peroxide. The mixture was refluxed for 16 h. After cooling to room temperature, the mixture was filtered and the solvent evaporated under reduced pressure to give the crude bromide: NMR ($CDCl_3$) δ 1.40 (t, 3 H), 3.85 (s, 3 H), 4.40 (q, 2 H), 5.88 (s, 1 H), 6.82–7.50 (m, 3 H). The crude bromide was placed in a one-necked flask equipped with a stirring bar and the pressure was reduced to 10 mm. The flask was then

(20) This rearrangement involves the formation of a spirocyclic intermediate which partitions to form isomeric products.

(21) Mukherjee, S.; Bhattacharyya, S. *Indian J. Chem. Soc.* **1946**, *23*, 451.

immersed in a preheated silicone oil bath (bath temperature 155 °C) and heated for 45 min. After cooling, the crude product was chromatographed on silica gel using hexane/ethyl acetate (3:2) as solvent. The reaction produced 2.78 g (14.7 mmol, 49%) of crystalline **4d**: NMR (acetone-d_6/Me_2SO-d_6) δ 4.03 (s, 3 H), 6.58 (s, 1 H), 7.21–8.02 (m, 3 H); IR (Nujol mull) 1785 cm^{-1}; mp 147–148.5 °C.

7-Methoxy-3-(phenylthio)phthalide (4c). To a solution of LDA–HMPA complex[22] (from 7.4 mmol of diisopropylamine, 6.7 mmol of *n*-butyllithium, and 6.7 mmol of HMPA) in THF (7 mL), cooled to −78 °C under nitrogen, was added 7-methoxyphthalide in THF (12 mL). The resultant orange solution was stirred 15 min and diphenyl disulfide in 7 mL of THF was added all at once. The cooling bath was removed and replaced with an ice bath. Stirring was continued at 0 °C for 30 min. Then the reaction was quenched by slow addition of 1 N HCL with vigorous stirring. Water (10 mL) was added and the whole extracted with ether (3 × 50 mL). The combined ether layers were washed with 1 N HCl (15 mL), 1 N NaOH (2 × 10 mL), water (10 mL), and brine. The dried (Na_2SO_4) solution was filtered, concentrated, and chromatographed, affording 0.81 g (2.98 mmol, 49%) of **4c** as a light yellow solid. Recrystallization from benzene afforded off-white crystals (mp 113–116 °C): IR (KBr) 1770, 1615, 1595 cm^{-1}; NMR ($CDCl_3$) δ 4.05 (s, 3 H), 6.70 (s, 1 H), 7.0–8.0 (m, 8 H).

General Procedure for the Reaction of 4a with Michael Acceptors. A solution of the lithium diisopropylamide (LDA)–hexamethylphosphoric triamide (HMPA) complex[22] was prepared by adding 10 mL (60.0 mmol) of HMPA in 20 mL of tetrahydrofuran (THF) to a 1 THF solution of LDA (60 mL) at −78 °C under N_2. After the solution had been stirred for 20 min at −78 °C, a solution of 7.26 g (30.0 mmol) of (phenylthio)phthalide in 30 mL, THF was added dropwise to afford a reddish-brown solution. After 30 min at −78 °C, a solution of 3.3 g (30.0 mmol) of 5-methyl-2-cyclohexenone in 30 mL THF was added dropwise. The solution was stirred for 1 h at −78 °C and then 72 h at 0 °C. The reaction mixture was then diluted with water, neutralized with dilute acetic acid, and extracted with ethyl acetate. The organic layer was washed once with brine, dried over sodium sulfate, and concentrated in vacuo. The residue was chromatographed on silica gel using 5:1 hexane/ethyl acetate to afford a 66% yield of product.

Adduct from 5-methyl-2-cyclohexenone: mp 164–166 °C; NMR ($CDCl_3$) δ 1.15 (d, 3 H), 2.0–3.45 (m, 5 H), 7.1–8.4 (m, 4 H); IR (nujol mull) 3220, 1610 cm^{-1}.

Adduct from 5-(trimethylsilyl)-2-cyclohexenone: mp 150–152 °C; NMR ($CDCl_3$) δ 0.10 (s, 9 H), 2.4–3.6 (m, 5 H), 7.4–8.6 (m, 4 H); IR (nujol mull) 3400, 1605 cm^{-1}.

Adduct from 2-cyclohexenone: mp 169–171 °C; NMR ($CDCl_3$) δ 1.9–3.2 (m, 6 H), 7.0–8.4 (m, 4 H); IR (nujol mull) 3320, 1620 cm^{-1}.

Adduct from 3-penten-2-one: mp 134–136 °C; NMR ($CDCl_3$) δ 2.57 (s, 3 H), 2.68 (s, 3 H), 7.3–8.6 (m, 4 H); IR (nujol mull) 3410, 1620 cm^{-1}. The NMR spectrum reported here is identical to material prepared by an independent method.[23]

Adduct from 5-methyl-2-cyclohexenone and 5b: NMR ($CDCl_3$) δ 0.35 (s, 6 H), 0.98 (s, 9 H), 1.25 (d, 3 H), 1.30–2.90 (m, 7 H), 6.90–7.75 (m, 4 H); IR ($CHCl_3$) 2400, 1600 cm^{-1}.

Adduct from 5-methyl-2-cyclohexenone and 5c: NMR ($CDCl_3$) δ 1.00 (d, 3 H), 1.28 (t, 3 H), 1.30–3.30 (m, 7 H), 3.60 (q, 2 H), 5.22 (q, 1 H), 7.20–8.15 (m, 4 H); IR ($CHCl_3$) 2400, 1600 cm^{-1}.

Ethyl 8-Methoxy-1,4-dihydroxy-2-naphthoate (9). A solution of **4c** (0.27 g, 1.0 mmol) in anhydrous THF (2.0 mL) was added dropwise to a suspension of LDA–HMPA complex (1.1 mmol) in 1 mL THF cooled to −78 °C under nitrogen. Stirring was continued for 15 min and ethyl acrylate (0.10 g, 1.0 mmol) was then added as a 1 M THF solution. The mixture was allowed to warm slowly to ambient temperature over approximately 2.5 h and then quenched by addition of 2.5 mL of 1 N HCl. The whole was extracted with ether (2 × 50 mL), and the combined ether layers were washed with water (10 mL) and brine (10 mL). The dried solution was filtered and concentrated. Silica gel chromatography (hexane/ether) provided 140 mg (0.53 mmol, 53%) of **9** as light orange crystals: mp 143–145 °C dec (ether); IR (Nujol) 3500, 1670 cm^{-1}; NMR ($CDCl_3$) δ 1.40 (t, 3 H, J = 7 Hz), 4.13 (s, 3 H), 4.46 (q, 2 H, J = 7 Hz), 6.9–8.0 (m, 4 H), 12.24 (s, 1 H). High-resolution mass spectrum for $C_{14}H_{14}O_5$ required m/e 262.08411; found, m/e 262.08252.

2-Acetyl-8-methoxy-1,4-dihydroxynaphthalene (7). 7-Methoxy-(3-phenylthio)phthalide was reacted with methyl vinyl ketone, in the manner described for **9** to provide **7**: IR (Nujol) 3500, 1640, 1600 cm^{-1}; NMR ($CDCl_3$) δ 2.57 (s, 3 H), 4.14 (s, 3 H), 6.9–7.8 (m, 4 H), 13.60 (s, 1 H).

Silver(I) Oxide Oxidation of Naphthydroquinone 7. The requisite hydroquinone, as a 0.2 M ether solution, was stirred with 1.5 equiv of silver(I) oxide for 3 H. The suspension was filtered and concentrated to afford the quinones in quantitative yield: IR ($CHCl_3$) 1705, 1670, 1595, 1295, 1233 cm^{-1}; NMR ($CDCl_3$) δ 2.67 (s, 3 H), 4.12 (s, 3 H), 7.12 (s, 1 H), 7.3–7.9 (m, 3 H).

2-*tert*-Butoxyfuran. The literature procedure[24] was manipulatively awkward, affording low to moderate yield at best. Using a modified procedure, detailed below, we have been able to generate large quantities in yields significantly higher than was possible employing the literature procedure.

Fifty-seven milliliters (0.125 mol) of a 2.2 M commericial hexane solution of *n*-butyllithium was added dropwise to a solution of furan (13.6 g, 0.15 mol) in anhydrous ether (75 mL) cooled to 0 °C under dry nitrogen. The solution was warmed to ambient temperature over 1 h to yield a white suspension of 2-lithiofuran. After it was cooled to 0 °C, the slurry was transferred under positive nitrogen pressure, through tygon tubing having glass pipets at each end, to a suspension of $MgBr_2$ (prepared from 3.9 g of magnesium turnings and 26.3 g of 1,2-dibromoethane) in anhyd THF (40 mL). To the resultant red-brown solution, *tert*-butyl perbenzoate (19.4 g, 0.10 mol) was added over approximately 30 min. Stirring was continued at 0 °C for 1 h. Then saturated aqueous bicarbonate solution (50 mL) was added with vigorous stirring. A precipitate formed, which was suction filtered (Celite), providing a two-phase system. The layers were separated and the aqueous layer was extracted with ether (2 × 50 mL). The combined layers were washed with brine and dried (Na_2SO_4). The dried solution was filtered and distilled at 1 atm pressure. The residue was distilled at reduced pressure, providing 6.38 g (45%) of **28a** as a colorless liquid (bp 60–64 °C/(55 mmHg) [lit. 44 °C/(16 mmHg)].

1,4,8-Trimethoxy-2-acetyl-3-(5-*tert*-butoxy-2-furyl)-naphthalene (13). A 1.0 M toluene solution of 2-*tert*-butoxyfuran (0.14 g, 1.0 mmol) was added to a solution of 2-acetyl-8-methoxy-1,4-naphthoquinone in 1.0 mL of toluene at 0 °C under nitrogen. The resulting light orange solution was allowed to warm to room temperature, where it was stirred 24 h. The solvent was removed at reduced pressure and replaced with 5 mL of anhydrous acetone. Potassium carbonate (0.55 g, 4 mmol) and dimethyl sulfate (0.29 mL, 3.0 mmol) were added, and the whole was refluxed for 8 h. The cooled solution was filtered and concentrated. Silica gel chromatography (10:1/hexane–ether) yielded 0.224 g (0.563 mmol, 59%) of **13** as a light yellow oil: IR (film) 2980, 2940, 2850, 1710, 1610 cm^{-1}; NMR ($CDCl_3$) δ 1.48 (s, 9 H), 2.67 (s, 3 H), 3.93 (s, 3 H), 3.96 (s, 3 H), 4.17 (s, 3 H), 5.78 (d, 1 H, J = 3 Hz), 7.09 (d, 1 H, J = 3 Hz), 7.1–8.1 (m, 3 H). High-resolution mass spectrum for $C_{23}H_{26}O_6$ required m/e 398.17295; found, m/e 398.17565.

1,4,8-Trimethoxy-2-(1-hydroxyethyl)-3-(5-*tert*-butoxy-2-furyl)naphthalene (14). To a stirred solution of lithium aluminum hydride (15 mg, 0.40 mmol) in ether (1.0 mL), cooled to −10 °C under nitrogen, was added **13** (224 mg, 0.563 mmol) in 1.0 mL of ether. The solution was stirred for 30 min at −10 °C and then quenched by addition of one drop of water, one drop of 15% NaOH, and three drops of water. After 10 min, the solution was filtered to remove precipitated aluminum salts. The filtrate was dried and concentrated to provide 181 mg (0.45 mmol, 80%) of **14** as a colorless oil: IR (film) 3490, 2980, 2940, 1615 cm^{-1}; NMR ($CDCl_3$) 1.45 (s, 9 H), 1.63 (d, 3 H, J = 7 Hz), 3.72 (s, 3 H), 4.02 (s, 3 H), 4.10 (s, 3 H), 4.30 (q, 1 H, J = 7 Hz), 5.2 (br s, 1 H), 5.70 (d, 1 H, J = 3Hz), 6.48 (d, 1 H, J= 3 Hz), 6.9–8.0 (m, 3 H). High-resolution mass spectrum for $C_{23}H_{28}O_6$ required m/e

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400.18860; found, m/e 400.18855.

9-*O*-Methylkalafungin. Trifluoroacetic acid (two drops) was added to a solution of **14** (120 mg, 0.30 mmol) in dichloromethane (1.0 mL) cooled to 0 °C under nitrogen. The cooling bath was removed and the red solution stirred 1 h at ambient temperature. Toluene (10 mL) was added and the solvents were removed at reduced pressure (repeated 3 times). The residue was dissolved in benzene (3 mL) and then cooled to 5 °C. Diazabicyclononane (2 drops) was added and stirring continued for 10 min. Ether (10 mL) was added and the solution transferred to a separatory funnel, where it was washed with ice-cold 0.25 N HCl (2 × 5 mL) and brine (10 mL). The dried (Na_2SO_4) solution was filtered and concentrated to afford a yellow oil. The oil (95 mg) was dissolved in THF (3 mL), and argentic oxide (150 mg, 1.15 mmol) was added followed by 0.3 mL of 6 N HNO_3. Stirring was continued for 10 min. Then 4:1 $CHCl_3/H_2O$ (10 mL) was added. After transfer to a separatory funnel, the whole was extracted with $CHCl_3$ (2 × 50 mL), and the organic layer was then washed with water (2 × 5 mL) and brine (5 mL). The dried solution was filtered and concentrated. The residue was chromatographed (silica gel, 1:1 hexane/ethyl acetate) to afford 42 mg of an orange solid: mp 203–210 °C dec (from acetone); R_f (1:1 hexane/ethyl acetate) 0.15; IR (Nujol) 1780, 1665 cm^{-1}; 90-MHz NMR ($CDCl_3$) δ 1.55 (d, 3 H, J = 7 Hz), 2.63 (d, 1 H, J = 18 Hz), 2.98 (dd, 1 H, J = 18 and 5 Hz), 4.02 (s, 3 H), 4.68 (dt, 1 H, J = 5 and 3 Hz), 5.05 (q, 1 H, J = 7 Hz), 5.27 (d, 1 H, J = 3Hz), 7.2–8.0 (m 3 H); 90-MHz C 13 NMR ($CDCl_3$) δ 18.636, 36.947, 56.504, 66.417, 66.905, 68.909, 118.208, 119.563, 132.510, 133.865, 135.598, 151.038, 160.139, 174.062, 182.513, 203.371; UV (CH_3OH) 211, 253 nm. High-resolution mass spectrum for $C_{17}H_{14}O_6$ required m/e 314.07904; found, m/e 314.07856.

Kalafungin (3). Excess boron trichloride was added to 9-*O*-methylkalafungin in 1 mL of anhydrous dichloromethane cooled to −78 °C under nitrogen. When addition was complete, the cooling bath (dry ice–acetone) was removed and the bright purple solution was allowed to warm to ambient temperature. Ten minutes after removing the cooling bath, water was added with vigorous stirring. The yellow-orange solution was diluted with dichloromethane (50 mL) and washed with water (2 × 10 mL) and brine (10 mL). The dried solution was filtered and concentrated to provide **3** as light orange crystals.

Pachybasin (15). To a solution of 0.97 g (4.0 mmol) of the hydroquinone **16** in 20 mL of CCl_4 was added 0.71 g (4.0 mmol) of NBS and a catalytic amount of benzoyl peroxide. The mixture was refluxed for 10 $^1/_2$ h. On cooling to room temperature, a solid precipitated out of solution. The reaction mixture was diluted with ethyl acetate, washed with water and then brine, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel using 2:1 hexane/CH_2Cl_2 as solvent to give 0.46 g (1.92 mmol), 48%) of pachybasin (**15**): NMR ($CDCl_3$) δ 2.40 (s, 3 H), 7.00–8.40 (m, 6 H); IR (Nujol) 1670, 1640, 1590 cm^{-1}; mp 178–180 °C (lit.[25] 176–177 °C).

General Procedure for Annulations with *t*-BuOK. To a solution of 1.0 equiv of the requisite phthalide and 1.0 equiv of the α,β-unsaturated ketone in dry Me_2SO (0.25 M) was added 3.0 equiv of potassium *tert*-butoxide/*tert*-butyl alcohol complex in three equal portions over 4 h from 0 °C to 25 °C. The reaction mixture was then acidified with aqueous HCl and extracted 4 times with ether. The organic layer was washed with water and brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The crude product was chromatographed on silica gel.

1-Hydroxy-8-methoxy-3-methylanthraquinone: mp 186 °C; NMR ($CDCl_3$) δ 2.40 (s, 3 H), 4.02 (s, 3 H), 6.97–8.00 (m, 5 H).

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Registry No. **3**, 11048-15-0; **4a**, 51287-54-8; **4a** 2-cyclohexenone adduct, 80301-48-0; **4a** 5-(trimethylsilyl)-2-cyclohexenone adduct, 86823-73-6; **4a** 5-methyl-2-cyclohexenone adduct, 80301-50-4; **4a** 3-penten-2-one adduct, 40420-49-3; **4b**, 27613-27-0; **4c**, 73318-26-0; **4d**, 81060-27-7; **5a**, 6520-83-8; **5b**, 86823-74-7; **5b** 5-methyl-2-cyclohexenone adduct, 86823-75-8; **5c**, 86823-76-9; **5c** 5-methyl-2-cyclohexenone adduct, 86823-77-0; **5d**, 81625-31-2; **6**, 6555-40-4; **7**, 83662-31-1; **9**, 86823-78-1; **13**, 86823-79-2; **14**, 86823-80-5; **15**, 2549-78-2; **16**, 80301-50-4; PhCH=CHCOPh, 94-41-7; ethyl 6-methyl-2-oxocyclohex-3-encarboxylate, 78073-67-3; ethyl 2-(bromomethyl)-6-methoxybenzoate, 86823-81-6; ethyl 2-(bromocyanomethyl)-6-methoxybenzoate, 86823-82-7; 7-methoxyphthalide, 28281-58-5; 5-methyl-2-cyclohexenone, 7214-50-8; 5-(trimethylsilyl)-2-cyclohexenone, 56917-71-6; 2-cyclohexenone, 930-68-7; 3-penten-2-one, 625-33-2; ethyl acrylate, 140-88-5; methyl vinyl ketone, 78-94-4; 2-acetyl-8-methoxy-1,4-naphthoquinone, 81418-42-0; furan, 110-00-9; 2-*tert*-butoxyfuran, 32460-41-6; 9-*O*-methylkalafungin, 23125-83-9; 1-hydroxy-8-methoxy-3-methylanthraquinone, 3300-25-2; 2(5*H*)-furanone, 497-23-4; ethyl 1,4-dihydroxynaphthalene-2-carboxylate, 66928-23-2; 4,9-dihydroxynaphtho[2,3-*c*]furan-1(3*H*)-one, 68726-79-4; 2-benzoyl-3-phenyl-1,4-naphthalenediol, 1169-61-5; 3,4-dihydro-2*H*-anthracene-1,9,10-trione, 52422-35-2; chrysophanol, 481-74-3.

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Formation of OH Radicals from Radical Cations of Some Substituted Benzenes in Aqueous Solutions at 80 °C and at Room Temperature. Effect of Oxygen[1]

Manfred K. Eberhardt* and Anselmo Fuentes-Aponte

Puerto Rico Cancer Center, Medical Sciences Campus, University of Puerto Rico, San Juan, Puerto Rico 00936

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The reactions of a number of simple substituted-benzene radical cations with water at 80 °C and at room temperature have been investigated. The radical cations were produced by thermal decomposition of $Na_2S_2O_8$. We searched for the formation of OH radicals, which we identified by their reaction with nitrobenzene to give nitrophenols. The thermal decomposition of peroxydisulfate in deoxygenated, nitrobenzene-saturated aqueous solutions of chlorobenzene, bromobenzene, and *tert*-butylbenzene gave *o*- and *p*-nitrophenols, whereas fluorobenzene, iodobenzene, phenol, and chlorophenols gave no nitrophenols. With nitrobenzene alone, no nitrophenols were obtained. The structural requirements for the reaction of aromatic radical cations with water to produce OH radicals are discussed. In the presence of oxygen, the yield of chlorophenols and bromophenols increased dramatically, producing mainly the para isomer, but in the bromobenzene case also significant amounts of *m*-bromophenol. The mechanism of this oxidation is discussed.

We have recently reported a reaction between benzene radical cations and water to give OH radicals.[2,3] This reaction was found to occur at temperatures as low as 25 °C[3] in the absence of oxygen or oxidizing metal ions. We

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