Stability of Quinones toward Water. Synthesis of a 1,7-Naphthoquinone[1]

Karl-Hans Menting, Wolfgang Eichel, Klaus Riemenschneider, Horst L. K. Schmand, and Peter Boldt*

Institut für Organische Chemie, Technische Universität Braunschweig, D-3300 Braunschweig, Federal Republic of Germany

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Calculated relative reactivities of the benzo-, naphtho-, and anthraquinones toward water (using perturbation MO theory) reflect well the sequence of stability of the known quinones. This method may be used to predict the stability of unknown quinones toward water or other nucleophiles. A 1,7-naphthoquinone, 3,6-di-*tert*-butyl-8-methyl-1,7-naphthoquinone (**24**), is described for the first time. It is prepared in a 13-step synthesis. On the basis of PMO calculations and analogous cases the alkyl groups in **24** were considered to be adaquate to shield the 1,7-naphthoquinoid system from attack of water and dimerization. **24** shows an unexpected low stability. According to MNDO calculations the alkyl groups cause a high steric strain in the molecule, possibly responsible for the observed low stability.

Quinones are key compounds in some important biochemical processes (e.g., vitamin E and K, coenzyme Q, plastoquinones, anthracyclines[2]) and are widely used as dyes. Nevertheless on the "quinone map" there are many white spots.

For example, out of the family of all possible 17 quinones with a C_{10} perimeter (i.e., 11 azuloquinones, 3 naphthoquinones, 3 [10]anulenoquinones)[3] only four are known (1,2-azuloquinone,[4] 2,6-naphthoquinone,[5] 3,7-di-*tert*-butyl-1,5-naphthoquinone,[6] and the 5,10-methano-bridged 2,4,7,9-cyclodecatetraene-1,6-dione.[7] As has been shown in some cases[1,6,8,9] and may be supposed in others,[10] the reason is the inherent instability of the unknown quinones.

With regard to attempts to synthesize new quinoid systems predictions of the stability on the basis of SCF-MO calculations have been of great interest in the last years. Gleicher et al.[11] suggested that the calculated heat of atomization (ΔH_f) or the value of the π-electron resonance energy may account for the supposed great instability of 2,3-naphthoquinone. We[6] considered two typical reactions which may cause "instability" of quinones, [2 + 4]cycloadditions with themselves and the reaction with water. As in other cases,[12] the HOMO/LUMO gap of the quinones[13] proved to be a good measure for the tendency to undergo cycloadditions. The reactivity with water was related to the LUMO energies[13] of the quinones. This is an oversimplification of the equation (eq 1) for estimating

$$S_r^{(N)} = 2 \sum_i^{unocc} \frac{(c_r^{(i)})^2}{\epsilon_i - \alpha} (-\beta) \qquad (1)$$

relative reactivities of various but similar substrates with *one* nucleophile by using perturbation MO theory[15] and neglecting the numerators and higher unoccupied orbitals.

In eq 1 $S_r^{(N)}$ is a reactivity index, called superdelocalizability. The greater the (negative) value of $S_r^{(N)}$ the faster the reaction of the nucleophile should be. ϵ_i represents the energy of the unoccupied MO i (with i = 1,2, ...), $c_r^{(i)}$ is the AO coefficient at the attacked atom r of the substrate in the ith MO, α is the HOMO energy of the nucleophile (in this case water), and β the resonance integral.

Indeed, there proved to be a good (qualitative) correlation between the stability of the known quinones toward water and their LUMO energies with the exception that the stability of *o*-quinones is greatly overestimated compared with that of the para isomers.[6]

Houk et al.[10] devoted an extended theoretical study to benzo-, naphtho-, and azuloquinones. They took into account the thermodynamic stability (ΔH_f and delocalization energies as calculated by MINDO/3) and, like us,[6] the HOMO/LUMO gap as well as the LUMO energies for predictions of the stability of the azuloquinones. Their MINDO/3 LUMO energies suggest also an inverse stability of the *o*- and *p*-benzo-, and -naphthoquinones toward water.

Results and Discussions

Stability of Benzo-, Naphtho-, and Anthraquinones. Calculation of the stability of quinones toward water (or other nucleophiles, e.g., OH^-) is not only of interest in connection with syntheses of new quinoid systems but is also of central importance for the extrication of new quinoid dyes. Therefore, we tried to get improved predictions for the reactivity of quinones toward water by calculating values for a reactivity index $S_{max}^{(H_2O)}$ (see eq 2), again using only the LUMO energies of the quinones

$$S_{max}^{(H_2O)} = \frac{(c_{max}^{LUMO})^2}{E_{LUMO} - IP_{H_2O}} (-\beta) \qquad (2)$$

(E_{LUMO}) but including the greatest AO coefficient in the LUMO of the quinones, c_{max}^{LUMO}. For α in eq 1 the ionization potential of water (IP_{H_2O} = -12.56 eV) was used. The $S_{max}^{(H_2O)}$ values were calculated in units of the reso-

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(6) Schmand, H.L.K.; Kratzin, H.; Boldt, P. *Justus Liebigs Ann. Chem.* **1976**, 1560.
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(12) Sustmann, R.; Schubert, R. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 840.
(13) The frontier orbital energies were calculated by using a simple SCF-LCAO-MO π-electron method.[14]
(14) Dewar, M. J. S.; Harget, A. J. *Proc. R. Soc. London, Ser. A* **1970**, *315*, 443. Dewar, M. J. S.; Trinajstic, N. *J. Am. Chem. Soc.* **1970**, *92*, 1453.
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Table I. Results of MNDO Calculations[16,17] on Benzoquinones (BQ), Naphthoquinones (NQ), Anthraquinones (AQ), 4,4'-Diphenoquinone, and 1,6-[10]Anulenoquinone

	ΔH_f, kcal/mol	E_{HOMO}, eV	E_{LUMO}, eV	$E_{LUMO} - E_{HOMO}$, eV	$\lvert c_{max}^{LUMO} \rvert$ (at C-atom no.)	$-S_{max}^{(H_2O)} \times 10^{-2}, \beta^{-1}$
1,4-BQ	-33.10	-10.95	-1.51	9.44	0.36 ($C_{2,3,5,6}$)	2.40
1,2-BQ	-33.01	-10.09	-1.46	8.63	0.40 ($C_{3,6}$)	2.90
1,2-NQ	-22.80	-9.54	-1.36	8.18	0.36 (C_{4a})	2.24
1,4-NQ	-22.80	-9.98	-1.36	8.62	0.33 ($C_{4a,8a}$)	1.88
1,5-NQ	-9.47	-9.24	-1.84	7.40	0.40 ($C_{4,8}$)	3.14
1,7-NQ	-8.08	-9.27	-1.88	7.39	0.41 (C_4)	3.32
2,6-NQ	-7.61	-9.62	-1.94	7.68	0.41 ($C_{1,5}$)	3.30
2,3-NQ	-7.35	-8.98	-1.90	7.08	0.41 ($C_{1,4}$)	3.30
9,10-AQ	-10.84	-9.82	-1.25	8.57	0.30 ($C_{4a,8a,9a,10a}$)	1.13
1,2-AQ	-6.62	-8.98	-1.25	7.73	0.32 (C_{4a})	1.68
1,4-AQ	-6.27	-9.08	-1.26	8.62	0.30 ($C_{2,3}$)	1.63
1,10-AQ	1.42	-8.97	-1.71	7.26	0.40 (C_9)	3.08
2,9-AQ	2.89	-8.97	-1.77	7.20	0.41 (C_{10})	3.28
1,5-AQ	14.90	-8.48	-2.07	6.41	0.38 ($C_{4,8}$)	2.86
1,7-AQ	16.31	-8.64	-2.11	7.39	0.39 (C_4)	2.96
2,3-AQ	17.28	-8.37	-2.12	7.08	0.40 ($C_{1,4}$)	3.11
2,6-AQ	17.36	-8.86	-2.16	6.70	0.39 ($C_{1,5}$)	3.00
4,4'-diphenoquinone	12.70	-9.07	-2.14	6.93	0.42 ($C_{1,1'}$)	1.55
1,6-[10]annuleno-quinone	6.50	-9.70	-1.22	8.48	0.30 ($C_{2,3}$)	1.68

Table II. LUMO AO Coefficients ($c_r^{(LUMO)}$) of 1,5- and 1,7-NQ (MNDO Values[16,17])

	C atom							
compd	1	2	3	4	5	6	7	8
1,5-NQ	-0.21	-0.32	0.24	0.40	-0.21	-0.32	-0.24	-0.40
1,7-NQ	0.20	0.32	-0.24	-0.41	0.23	-0.24	-0.23	-0.40

nance integral β, assuming that β is nearly constant for each type of quinone. The AO and MO values for benzoquinones (BQ), naphthoquinones (NQ), and anthraquinones (AQ) were calculated by MNDO[16,17] and are listed in Table I.

Judging from the LUMO energies alone as calculated with MNDO, the *o*-quinones appear nearly as stable toward water as their para isomers (see the values for 1,2-/1,4-BQ; 1,2-/1,4-NQ, and 1,2/1,4-AQ). Furthermore, the extremely low reactivity of 9,10-AQ is not reflected by the LUMO energy value which is the same as that of 1,2- and 1,4-AQ. So again the LUMO energies are not sufficient for an order of reactivity.

However, as may be seen in Figure 1 the superdelocalizabilities ($S_{max}^{(H_2O)}$, in units of β) provide a reasonable order of stability in each class of quinones. As is to be expected, *p*-quinones now appear to be more stable than their ortho isomers; the great instability of 2,6-NQ toward water[5] is documented by its value of $-3.30 \times 10^{-2}\ \beta^{-1}$ for $S_{max}^{(H_2O)}$ and the extreme stability of 9,10-AQ by a value of $-1.13 \times 10^{-2}\ \beta^{-1}$. A good test for the validity of these calculations is that the stability of the extended 4,4'-diphenoquinone and the astonishing stability of the methano-bridged 1,6-[10]anulenoquinone[7] are properly reflected by $S_{max}^{(H_2O)}$ values of -1.55×10^{-2} and $-1.68 \times 10^{-2}\ \beta^{-1}$. The area of -2.5×10^{-2} to $-2.7 \times 10^{-2}\ \beta^{-1}$ may be regarded as a borderline: all known quinones with $S_{max}^{(H_2O)} < -2.5 \times 10^{-2}\ \beta^{-1}$ were prepared in the presence of water (at least at room temperature) whereas for quinones with $S_{max}^{(H_2O)} > -2.7 \times 10^{-2}\ \beta^{-1}$ water has been strictly excluded. The same may be predicted for the still unknown quinones.

Stabilization of 1,7-NQ. There seems to be no chance for a synthesis of 1,7-NQ bearing no shielding groups on a preparative scale. The HOMO–LUMO gap of 7.39 eV

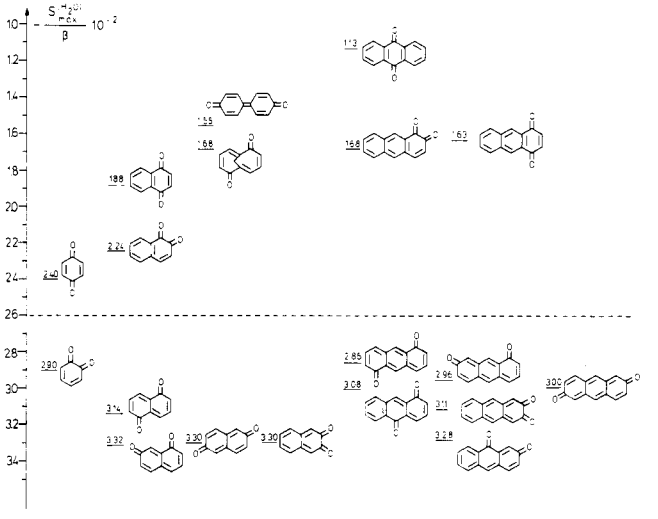


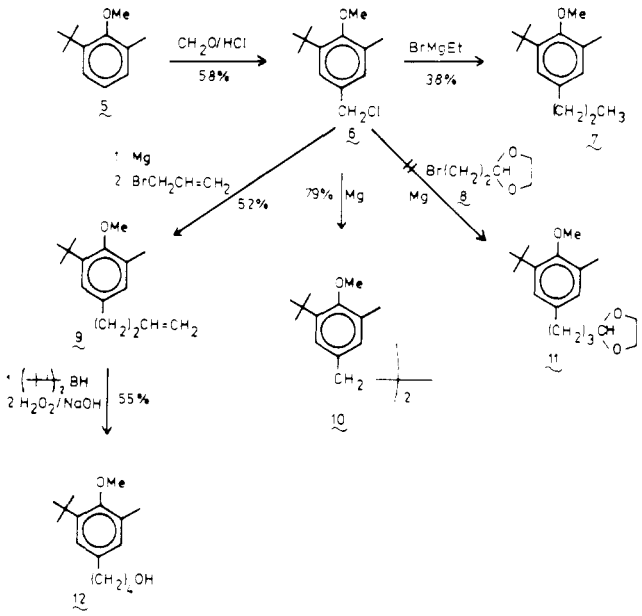
Figure 1. Reactivity index $S_{max}^{(H_2O)}$ (eq 2) for benzo-, naphtho-, and anthraquinones in units of β.

suggests a similar tendency for dimerizations and polymerizations as for 1,5-NQ (7.40 eV). The [4 + 2] cycloadditions in 1,5-NQ could be effectively suppressed by introducing two *tert*-butyl groups in the 3- and 7-positions.

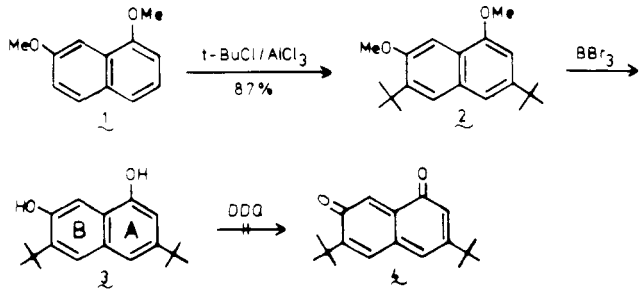
Such bulky alkyl groups exert their stabilizing effect mainly by steric hindrance, thus enhancing the kinetic stability. They have only minor influences on the π-electron system of the quinone. The *tert*-butyl groups also slow down sufficiently the reaction with water which takes place at C-4 and C-8, respectively, in accord with the calculated LUMO/AO coefficients (Table II) with maximum values at these positions. Judging from the LUMO/AO coefficients calculated for 1,7-NQ and following eq 2, attack of water should be expected at C-4 and C-8. C-4 should be shielded sufficiently as with 1,5-NQ by a *tert*-butyl group at C-3. C-8 is not available for shielding by a *tert*-butyl group because of sterical reasons.

(16) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899.
(17) Further MNDO data are collected in ref 18.
(18) Menting, K.-H. Dissertation, Technische Universität Braunschweig, Braunschweig, Federal Republic of Germany, 1981.

Scheme I



Therefore, we tried to synthesize 3,6-di-*tert*-butyl-1,7-naphthoquinone (**4**). As in 1,5-naphthoquinone the two



tert-butyl groups should prevent dimerization reactions effectively. The preparation had to be performed under exclusion of water to avoid reaction of water at C-8. But 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) oxidation of **3**, available by Friedel–Crafts *tert*-butylation of 1,7-dimethoxynaphthalene (**1**) followed by ether cleavage with boron tribromide, yielded a mixture of compounds in which no trace of **4** was detectable. As could be shown, the main reaction path was oxidative coupling of two naphthols **3** via the 8-position.[19] Therefore, this position had to be shielded as well with an alkyl group such as methyl even in the absence of water.

3,7-Di-*tert*-butyl-8-methyl-1,7-naphthoquinone (24). The synthetic aim was therefore **24** by way of the conjugate hydroquinone **23**. All attempts to introduce a methyl group directly into **2** or **3** failed. So a total synthesis of **23** was necessary. At first the introduction of a four-carbon chain at the 4-position of **5** was planned, followed by ring closure, i.e., forming ring A of **23**, dehydrogenation, and introduction of the second *tert*-butyl group in ring A. Also, the di-*tert*-butylation of 8-methyl-1,7-dihydroxynaphthalene should be possible (see reaction **1** → **2**), with 2-methylanisole as the starting material for the total synthesis. But only the *tert*-butyl group in **5** guarantees that the ring closure reaction of a carbon chain in the 4-position takes place in the desired direction. On the other hand, the presence of a *tert*-butyl group excluded strong acidic conditions in all synthetic steps to avoid the splitting off of this group (Scheme I).

Compound **5** could be synthesized by phase-transfer methylation of the conjugate phenol. Chloromethylation yielded **6** (58%). Attempts to couple **6** with the Grignard compound from **8** for the synthesis of **11** failed. In a control experiment with ethyl magnesiumbromide, **7** was formed, although in low yield (38%). So the failure of the reaction with **8** may be due to innermolecular complexation of the magnesium with the acetate oxygen atoms. In an attempt to perform the inverse procedure, coupling of the Grignard compound from **6** with the ethylene acetal of 3-bromo-propanal, no **11** was formed, but the dimerization product **12** was synthesized in good yield (79%). The coupling of the Grignard compound from **6** with allyl bromide was successful, yielding **9** (52%), which, after hydroboration with disiamylborane and oxidation, gave **12** (55%). Oxidation of **12** to the carbonic acid and subsequent cyclization was planned to build up ring A of **23**. But oxidation of **12** with potassium permanganate or chromium trioxide yielded only decomposition products. Therefore, on consideration of the low yields, **6** was dismissed as key precursor for the synthesis of **23**.

Instead, the synthesis was performed as shown in Scheme II. The Grignard compound from **13**, accessable by bromination of **5** (96%), was coupled in tetrahydrofurane with allyl bromide in good yield (92%) to give **14**, which on hydroboration with disiamylborane and oxidation yielded the alcohol **15**. The conversion of **15** to the bromide **16** was performed via the tosylate (not isolated) by reaction with calcium bromide in absolute ethanol (75%). **16** was converted with magnesium and carbon dioxide to acid **17** (68%). The cyclization of **17** with polyphosphoric acid or with sulfuric acid at 0 °C led, judging from the NMR spectra of the reaction mixture, to only ca. 20% **18**. The main product proved to be 7-methoxy-6-methyl-1-tetralone. Obviously the *tert*-butyl group of **17** was split off under these conditions, and the cyclization took place mainly at C-5 of the benzene ring. But cyclization was possible with aluminium trichloride with the acid chloride of **17** without loss of the *tert*-butyl group (85%). Direct dehydrogenation of **18** with sulfur (200 °C) failed, and only a little decomposition was observed. Bromination and dehydrobromination finally yielded **20** in an overall yield of 60%. The dehydrobromination was only possible with lithium bromide/lithium carbonate.[20] When **19** was heated with amines or palladium tetrakis(triphenylphosphine),[21] only decomposition was observed. After phase-transfer etherification of **20** (86%) the introduction of the second *tert*-butyl group was tried by means of an aluminium trichloride catalyzed Friedel–Crafts reaction with *tert*-butyl chloride. Besides decomposition the main product was **2**. Surprisingly the 8-methyl group has been split off under these mild conditions. Quantitative *tert*-butylation was possible with *tert*-butyl alcohol in trifluoroacetic acid with catalytic amounts of sulfuric acid without loss of the methyl group. The ether cleavage to **23** proceeded smoothly (88%) with boron tribromide at 20 °C.

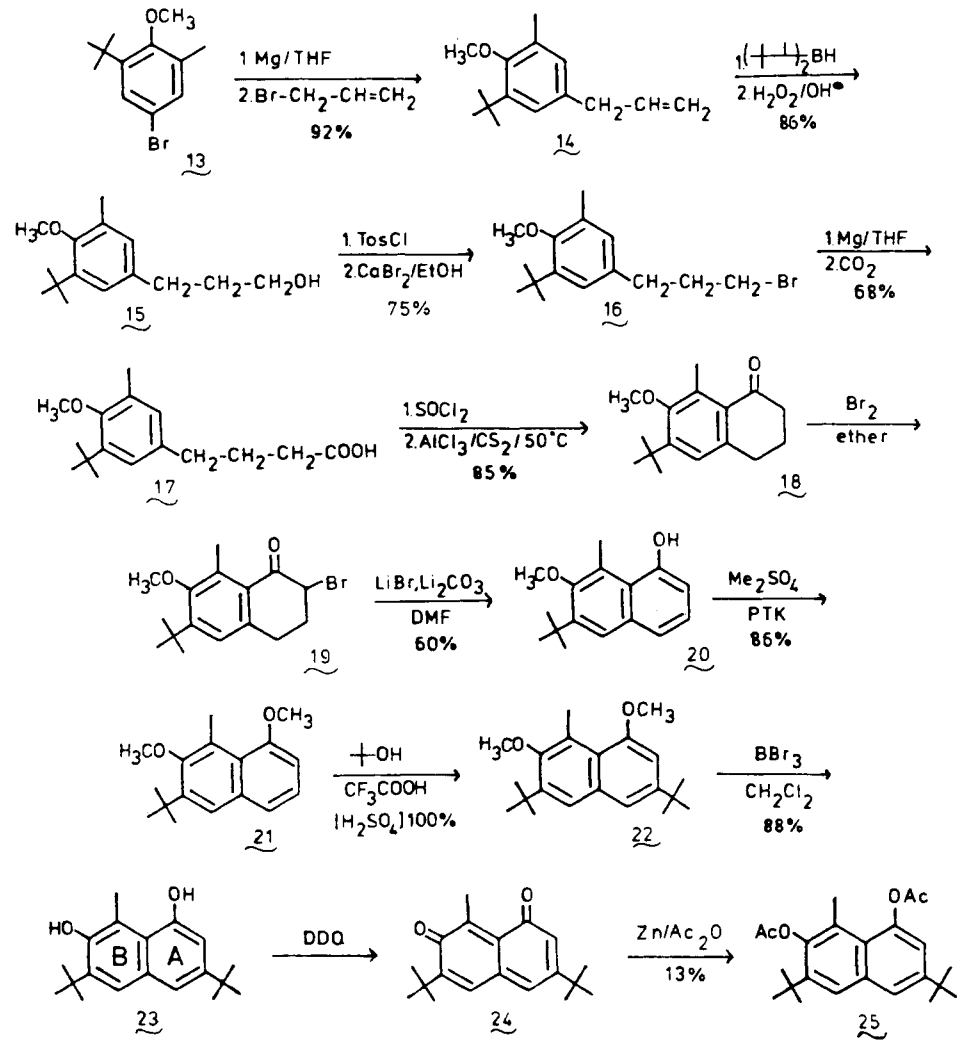
Oxidation of **23** with DDQ gave **24**. The structure follows from the reductive acetylation to **25** and the spectroscopical data. In the mass spectrum (200 °C) there also appears, besides the peak for the molecular ion (*m/e* 284, 12%), a peak for the hydroquinone **23** (*m/e* 286, 15%),

(19) Schmand, H. L. K.; Menting, K.-H., to be submitted for publication.

(20) Fieser, M.; Fieser, L. F. "Reagents for Organic Synthesis"; Wiley: New York, 1967; Vol. I, p 606.

(21) Townsend, J. M.; Reingold, S. D.; Kendall, M. C. R.; Spencer, T. A. *J. Org. Chem.* **1975**, *40*, 2976.

Scheme II

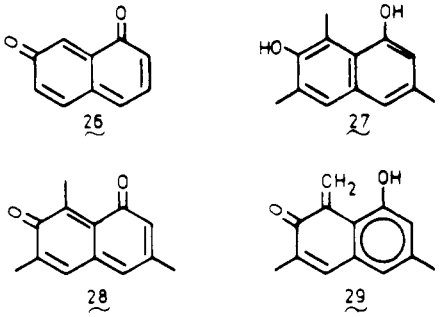


though the quinone contained no **23** (in the NMR spectrum no signals of **23** were observed, and acetylation of the crude quinone yielded no trace of **25**). Hydroquinone peaks are sometimes observed with quinones. They are caused by reaction of the quinone in the mass spectrometer.[22] At 270 °C peaks appear at m/e 566 and 568 which point to a dimerization of **24** at higher temperatures.[23]

In the NMR spectrum the signals of the two *tert*-butyl groups occur at 1.32 ppm and that of the methyl group at 2.48 ppm. Compared with **23** this signal is shifted by 0.32 ppm to higher field. The signals of the quinoid protons are observed at 6.77, 6.93, and 7.04 ppm. In the IR spectrum two bands at 1615 and 1625 cm^{-1} could be assigned to carbonyl stretching frequencies and band at 1690 cm^{-1} to a stretching frequency of a trisubstituted olefine.

The UV absorption band is remarkable which occurs at very short wavelengths (λ_{max} 320 nm) compared with that of, e.g., 1,2-benzoquinone (λ_{max} 385 nm) or 3,7-di-*tert*-butyl-1,5-naphthoquinone (λ_{max} 475 nm[6]) and also remarkable is the instability or reactivity of **24**. Oxidation of **23** at room temperature yielded only decomposition products, and even at -20 to -10 °C and under exclusion of moisture or oxygen no pure **24** could be obtained. So in the NMR spectra of all preparations invariantly two broad singlets at 1.18 and 1.68 ppm and two small singlets at 7.16 and 7.55 ppm were observed, as well as a peak in the mass spectrum at m/e 296. They could not be assigned to any reasonable alternative structure or to decomposition products of **24**.

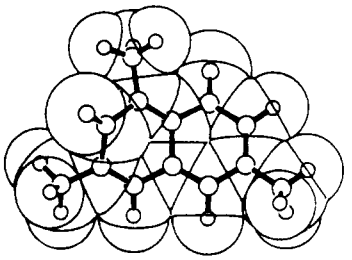
Reasons for the Instability of 24. The instability of **24** is in contrast to our expectations. Steric strain may be envisaged as possible reason: As our calculations showed, 1,7-naphthoquinone (**26**) and 3,6,8-trimethyl-1,7-dihydroxynaphthalene (**27**)[24] possess planar or nearly planar structures, whereas **28** proved to be heavily twisted, the 7-CO group being out of plane by 36°. The geometry of **28** as calculated by MNDO is shown in the SCHAKAL drawing[25] (below) of 3,6,8-trimethyl-1,7-naphthoquinone



(22) Heiss, H.; Zeller, K. P.; Rieker, A. *Org. Mass. Spectrom.* **1969**, *2*, 1325.

(23) The same was observed with 3,7-di-*tert*-butyl-1,5-naphthoquinone.[6]

(24) The MNDO maximum deviations of a carbon atom from the plane are 1.6° and 1.7°, respectively.



(28) as calculated by MNDO.[16,17] 28 was choosen as model compound for the calculations because the capacity of the program was not great enough for the calculations for 24. But if there is any difference in the steric strain, it should be even greater in 24 than in 28. The high steric strain in 28 may be caused by van der Waals repulsion between the nonbonding p electrons of the carbonyl oxygen atom and the methyl group which, in a hypothetical nontwisted molecule, would lay in one plane at very short distances. In 27 the repulsion between the nonbonding electrons of the hydroxy groups and the methyl groups can be minimized by rotation of the hydroxy groups. Thus the angle between the plane formed by the C–O–H atoms of the hydroxy groups and the plane of the naphthalene ring was calculated by MNDO to be 90° at C-7 and at C-1.[16,17]

Thus, in the synthesis of a stable 1,7-naphthoquinone we met with the dilemma that the shielding and stabilizing effect of the alkyl groups inevitably is counterbalanced to some degree by steric strain.

As our MNDO calculations showed, the thermodynamic stability of 29 is greater by 12.5 kcal/mol than that of 28 (ΔH_f(27) = -25.6 kcal/mol, ΔH_f(29) = -38.1 kcal/mol). The formation of the quinone methide instead of 24 should thus be considered in the oxidation of 23. But obviously the oxidation of 23 by DDQ is kinetically controlled because no signal of alkene methylene protons could be detected in the NMR spectrum of the oxidation product of 23.

Experimental Section

1,7-Dimethoxy-3,6-di-*tert*-butylnaphthalene (2). *tert*-Butylchloride (9.25 g, 0.1 mol) was added dropwise to a mixture of 7.7 g (41 mmol) of 1,7-dimethoxynaphthalene (1), 100 mL of carbon disulfide, and 6.6 g (50 mmol) of aluminium chloride. After the mixture was refluxed (72 h), hydrolysis (ice), drying, and evaporation of the solvent the crude oily reaction product yielded, after chromatography from carbon tetrachloride on silica gel 2: 10.7 g (87%); mp 112–113 °C (from ethanol); IR (KBr) 2980, 1600, 1530, 1220 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9 H, *t*-Bu), 1.45 (s, 9 H, *t*-Bu), 4.00 (s, 6 H, OCH_3), 6.78 (d, J = 2 Hz, 1 H, ArH), 7.22 (d, J = 2 Hz, 1 H, ArH), 7.38 (s, 1 H, Ar H), 7.55 (s, 1 H, ArH); MS (70 eV); m/e (relative intensity) 300 (M^+, 100), 285 (M – CH_3, 58%), 57 (*t*-Bu, 10). Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.96; H, 9.39. Found: C, 79.77; H, 9.24.

1,7-Dihydroxy-3,6-di-*tert*-butylnaphthalene (3). To a stirred solution of 2.3 g (7.7 mmol) of 2 in 50 mL of dry dichloromethane was added 5 mL of boron tribromide, and at intervals of 2 and 12 h a further 2 mL of BBr_3 was added. The mixture was stirred for 24 h and evaporated to dryness in vacuo, and the residue was taken up with ether and water. The evaporation residue of the dried etheral phase was recrystallized from cyclohexane to give 3: 1.0 g (48%); mp 162–164 °C; IR (*KBr*) 3265 (OH), 2872, 2905, 29600 (CH), 1638, 1608 cm^{-1}; ^{1}H NMR (acetone-d_6) δ 1.51, 1.34 (2 s, 2 × 9 H, *t*-Bu), 6.89, 7.23 (2 d, J = 1.6 Hz, 2 H, Ar H), 7.48, 7.62 (2 s, 2 H, Ar H), 8.42 (s, 2 H, OH, H/D exchange). Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 78.88; H, 8.72.

1-Methoxy-2-*tert*-butyl-6-methylbenzene (5). To a vigorously stirred mixture of 400 g (2.43 mol) of 2-*tert*-butyl-6-methylphenol, 4.0 g of tetra-*n*-butylammonium iodide, 800 mL of dichloromethane, and 6.3 mol of 50% aqueous sodium hydroxide after 30 min was added dropwise during 1 h 392 g (2.92 mol) of dimethyl sulfate. The temperature of the reaction mixture was held below 45 °C by cooling. After addition of 50 mL of aqueous concentrated ammonia the mixture was stirred 2.5 h at room temperature and poored into water. The organic phase yielded after distillation (15-cm Vigreux column) compound 5: 410.3 g (95%); bp 62 °C (3 Pa). ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 9 H, *t*-Bu), 2.28 (s, 3 H, CH_3–Ar), 3.71 (s, 3 H, CH_3O), 6.7–7.25 (m, 3 H, Ar H); MS (70 eV), m/e (relative intensity) 178 (M^+, 62), 163 (M-CH_3, 100), 149 (M-C_2H_5, 86). Anal. Calcd for $C_{12}H_{18}O$: C, 80.96; H, 10.21. Found: C, 80.85; H, 10.18.

1-Methoxy-4-(chloromethyl)-2-*tert*-butyl-6-methylbenzene (6). After a stirred mixture of 95.5 g (0.55 mol) of 5 and 405 mL of aqueous concentrated hydrochloric acid was saturated with gaseous hydrochloric acid, 21.5 g (0.74 mol) paraformaldehyde was added slowly. At 20 °C further gaseous hydrochloric acid was passed in for 6 h, and afterward stirring was continued for 12 h. The aqueous layer was extracted three times with petroleum ether. The combined organic layers yielded after neutralization with sodium hydrogen carbonate and drying at distillation (15 cm Vigreux column) compound 6: 72.5 g (58%); bp 88–90 °C (13 Pa); ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 9 H, *t*-Bu), 2.28 (s, 3 H, CH_3–Ar), 3.87 (s, 3 H, CH_3O), 4.54 (s, 2 H, CH_2Cl), 7.10, 7.35 (2 d, J = 1.5 Hz, 2 H, Ar H); MS (70 eV), m/e (relative intensity) 228/226 (M^+, 23/72), 213/211 (M – CH_3, 33/100), 191 (M – Cl, 65). Anal. Calcd for $C_{13}H_{19}ClO$: C, 68.84; H, 8.45; Cl, 15.64. Found: C, 68.65; H, 8.33; Cl, 15.42.

1-Methoxy-2-*tert*-butyl-4-propyl-6-methylbenzene (7). To the Grignard reagent from 9.0 g (80 mmol) of ethyl bromide and 2 g (80 mmol) of magnesium in 20 mL of ether was added 15 g (70 mmol) of 6. After addition of ice and aqueous ammonium chloride and distillation of the dried etheral phase, compound 7 was obtained: 8.3 g (38%); bp 93 °C (1 Pa); ^{1}H NMR ($CDCl_3$) δ 0.95 (t, J = 3.5 Hz, 3 H, CH_3CH_2), 1.45 (s, 9 H, *t*-Bu), 1.70 (m, 2 H, $CH_3CH_2CH_2$), 2.35 (s, 3 H, CH_3–Ar), 2.50 (t, J = 3.5 Hz, 2 H, CH_2CH_2–Ar), 3.85 (s, 3 H, CH_3O), 6.85, 7.15 (2 d, J = 1.5 Hz, 2 H, Ar H); MS (70 eV), m/e (relative intensity) 220 (M^+, 85), 205 (M – CH_3, 100), 191 (M – C_2H_5, 33), 177 (M – C_3H_7, 16). Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.83; H, 11.04.

4-(4-Methoxy-3-*tert*-butyl-5-methylphenyl)-1-butene (9). To 3 mL of a solution of 50 g (0.22 mol) of 6 in 50 mL dry tetrahydrofurane was added 5.4 g (0.22 mol) of magnesium. After the reaction had started, the remaining solution of 6 and then 26.7 g (0.22 mol) of 3-bromopropene were added slowly under cooling with ice. After the mixture was stirred (0 °C) for 2 h, addition of ice and aqueous ammonium chloride, extraction with ether, and distillation gave 9: 26.7 g (52%); bp 68–70 °C (1 Pa); ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9 H, *t*-Bu), 2.33 (s, 3 H, CH_3–Ar), 2.37–2.83 (m, 4 H, $ArCH_2CH_2C$=), 4.77–5.07 (m, 2 H, CH=CH_2), 5.67–6.30 (m, 1 H, CH=CH_2) 6.97, 7.07 (2 d, J = 1.5 Hz, 2 H, Ar H); MS (70 eV), m/e (relative intensity) 232 (M^+, 24), 217 (M – CH_3, 9), 191 (M – CH_2 – CH=CH_2, 100). Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.47; H, 10.25.

1,2-Bis(4-methoxy-3-*tert*-butyl-5-methylphenyl)ethane (10). To the Grignard compound from 22.7 g (0.10 mol) of 6 and 2.4 g (0.10 mol) of magnesium in 100 mL tetrahydrofurane were added 10 mL of 0.1 M Li_2CuCl_4 solution in tetrahydrofurane and then, dropwise, 16.8 g (92 mmol) of 3-bromopropanal ethylene acetal. After 3 h of stirring, addition of ice and aqueous ammonium chloride, and extraction with ether the combined and dried organic layers yielded an evaporation residue of 10: 30.0 g (78%); mp 110 °C (from ethanol); ^{1}H NMR ($CDCl_3$) δ 1.45 (s 9 H, *t*-Bu), 2.32 (s, 3 H, CH_3–Ar), 2.85 (s, 2 H, CH_2–Ar), 3.85 (s, 3 H, OCH_3), 6.80, 7.20 (2 d, J = 1.5 Hz, 2 H, Ar H); MS (70 eV), m/e (relative intensity) 382 (M^+, 34), 191 (M/2, 100) 176 (M/2 - CH_3, 6), 161 (M/2 - C_2H_5, 10). Anal. Calcd for $C_{26}H_{38}O_2$: C, 81.62; H, 10.01. Found: C, 81.77; H 9.88.

4-(4-Methoxy-3-*tert*-butyl-5-methylphenyl)butanol (12). To a well-stirred mixture of 100 mL of diglyme, 46.2 g (0.66 mol) of 2-methyl-2-butene, and 9.6 g (0.125 mol) of sodium hydridoborate was added slowly at 0 °C 47.2 g (0.166 mol) of boron trifluoride in ether. Stirring was continued until all the solid had been dissolved (1 h), and 69.6 g (0.30 mol) of 9 was added at 0–5 °C. After 12 h and slow warming to 20 °C, 50 mL of 3 N NaOH and 50 mL of 30% hydrogen peroxide were added while the

(25) Keller, E. *Chem. Unserer Zeit* **1980**, *14*, 56. We thank Dr. Keller, University of Freiburg, for the SCHAKAL program.

temperature was kept below 50 °C. After extraction with ether and distillation 226.1 g (85%) of **12** was obtained; bp 113–123 °C (1 Pa). **12** proved to be free from the 2-butanol isomer up to 99.45% (GC, 220 °C, 4% silicone OV-17 on Chromosorb W): IR (film) 3350 (OH), 2940 (CH), 1470, 1450, 1410 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (s, 9 H, *t*-Bu), 1.45–1.85 (m, 4 H, CH_2), 2.28 (s, 3 H, CH_3–Ar), 2.53 (t, J = 3.5 Hz, 2 H, Ar–CH_2CH$_2$), 3.63 (t, J = 3.5 Hz, 2 H, CH_2CH_2O), 3.76 (s, 3 H, OCH_3), 6.76, 7.06 (2 d, J = 1.5 Hz, 2 H, Ar H); MS (70 eV), *m/e* (relative intensity) 250 (M^+, 100), 235 (M – CH_3, 24), 217 (M – H_2O – CH_3, 10), 191 (M – C_3H_6OH, 35). Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.84; H, 10.39.

1-Methoxy-4-bromo-3-*tert*-butyl-5-methylbenzene (13). To 356 g (2.9 mol) of **5** in 800 mL of carbon tetrachloride was added dropwise at <5 °C 103 mL (2.0 mol) of bromine. After the mixture was washed and distilled, **13** was obtained: 493.4 g (96%); bp 87–91 °C (7 Pa); ^1H NMR ($CDCl_3$) δ 1.38 (s, 9 H, *t*-Bu), 2.30 (s, 3 H, CH_3–Ar), 3.78 (s, 3 H, OCH_3), 7.15, 7.45 (2 d, J = 1.5 Hz, 2 H, ArH); MS (70 eV), *m/e* (relative intensity) 256/258 (M^+, 88/83), 241/243 (M – CH_3, 100/95), 226/228 (M – 2 CH_3, 18/17), 213/215 (M – CO – CH_3, 18/17), 162 (M – CH_3 – Br, 28). Anal. Calcd for $C_{12}H_{17}OBr$: C, 56.04; H, 6.66; Br, 31.07. Found: C, 56.08; H, 6.58; Br, 31.13.

3-(4-Methoxy-3-*tert*-butyl-5-methylphenyl)propene (14). To the Grignard reagent from 59.7 g (2.46 mol) of magnesium and 631.5 g (2.46 mol) of **13** in 250 mL tetrahydrofurane was added dropwise 215 mL (2.48 mol) of 3-bromopropene in 200 mL of tetrahydrofurane. After the mixture was stirred for 12 h at room temperature addition of ice and 2 N NHCl, extraction with ether, and distillation gave **14**: 490.7 g (92%); bp 75° (7 Pa); IR (film) 2970 (CH), 1635 (C=C), 1470, 1410 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (s, 9 H, *t*-Bu), 2.28 (s, 3 H, CH_3–Ar), 3.33 (d, J = 3.5 Hz, 2 H, ArCH_2CH), 3.75 (s, 3 H, OCH_3), 4.85–5.25 (m, 2 H, CH=CH_2), 5.15–6.35 (m, 1 H, CH_2CH=CH_2), 6.81, 7.09 (2 d, J = 1.5 Hz, 2 H, Ar H); MS (70 eV), *m/e* (relative intensity) 218 ($M,^+$ 86), 203 (M – CH_3, 100), 161 (M – *t* – Bu, 10). Anal. Calcd for $C_{15}H_{22}O$: C, 82.50; H, 10.16. Found: C, 82.49; H, 10.07.

3-(4-Methoxy-3-*tert*-butyl-5-methylphenyl)propanol (15). To a mixture of 740 mL of diglyme, 220 mL (3.0 mol) of 2-methyl-2-butene, and 46.2 g (1.18 mol) of sodium hydridoborate were added slowly under stirring at 0 °C 220 g (1.55 mol) of boron trifluoride in ether and, after a nearly clear solution had formed (1 h), 245 g (1.12 mol) of **14** at 0–5 °C. After the mixture was stirred for 12 h and gradually warmed to 20 °C, 465 mL of 3 N NaOH and 465 mL of 30% hydrogen peroxide were added while the temperature was kept below 50 °C. After extraction with ether and distillation **15** was obtained: 226.1 (86%); bp 120–123 °C (1 Pa); IR (film) 3400 (OH), 2940, 2860 (CH), 1470, 1445, 1410 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (s, 9 H, *t*-Bu), 1.65–2.20 (m, 2 H, $CH_2CH_2CH_2$), 2.27 (s, 3 H, CH_3–Ar), 2.65 (t, J = 4 Hz, 2 H, CH_2OH), 3.68 (t, J = 4 Hz, 2 H, CH_2–Ar), 3.77 (s, 3 H, CH_3Ar), 6.81, 7.09 (2 d, J = 1.5 Hz, 2 H, Ar H); MS (70 eV), *m/e* (relative intensity) 236 (M^+, 100), 221 (M – CH_3, 70), 218 (M – H_2O, 8). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.23. Found: C, 76.31; H, 10.05.

3-(4-Methoxy-3-*tert*-butyl-5-methylphenyl)-1-bromopropane (16). To 260 g (1.22 mol) of **15** and 240 g (1.25 mol) of tosyl chloride in 500 mL of dry chloroform was added 152 g (1.9 mol) dry pyridine dropwise at 0–3 °C. After the mixture stirred for 12 h, 700 g of ice and 250 mL of concentrated hydrochloric acid were added. The mixture was extracted with ether. The combined, dried etheral phases yielded an oily evaporation residue which was devolatilized at 1 Pa (room temperature) to give 438.3 g (92%) of 3-(4-methoxy-3-*tert*-butyl-5-methylphenyl)propyltosylate. The tosylate showed no tendency to crystallize, and distillation was not possible without decomposition. It was used without further purification. The raw tosylate (384 g, 0.99 mol) was refluxed for 18 h with 235 g (1.18 mol) of calcium bromide in 700 mL of absolutely dry ethanol. After addtion of water and extraction with ether the evaporation residue of the combined dried etheral phases gave **16** on distillation: 232 g (79%); bp 114–117 °C (1 Pa);[26] ^1H NMR ($CDCl_3$) δ 1.40 (s, 9 H, *t*-Bu), 1.8–2.4 (m, 2 H, $CH_2CH_2CH_2$), 2.28 (s, 3 H, CH_3–Ar), 2.68 (t, J = 3.5 Hz, 2 H, ArCH_2CH_2), 3.35 (t, J = 3.5 Hz, 2 H, CH_2CH_2Br), 3.73 (s, 3 H, OCH_3), 6.78, 7.06 (2 d, J = 1.5 Hz, 2 H, Ar H); MS (70 eV), *m/e* (relative intensity) 300/298 (M^+, 72/74), 285/283 (M – CH_3, 98/100). Anal. Calcd. for $C_{15}H_{23}OBr$: C, 60.20; H, 7.75; Br, 26.70. Found*): C, 61.59; H, 7.92; Br, 24.48.

4-(4-Methoxy-3-*tert*-butyl-5-methylphenyl)butanoic Acid (17). The Grignard compound from 281.7 g (0.94 mol) of **16** and 23.1 g (0.95 mol) of magnesium in 300 mL of tetrahydrofurane (prepared with no further heating after the spontaneous reaction had ceased) was cooled to −5 °C (some precipitated Grignard compound was dissolved by addition of a little dichloromethane), and a stream of dry carbondioxide was passed through until the exothermic reaction ended. After further (1h) passing of carbon dioxide and addition of half-concentrated hydrochloric acid and ice, the mixture was extracted with ether. The combined etheral phases were extracted with 2 N NaOH. After acidification (30% sulfuric acid), extraction with ether, and evaporation of the ether **17** was obtained: 170 g (68%); mp 64–65 °C; IR (KBr) 3340 (OH), 2940, 2860 (CH), 1700 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (s, 9 H, *t*-Bu), 1.6–3.0 (m, 6 H, Ar–(CH_2)$_3$COOH), 2.25 (s, 3 H, CH_3–Ar), 3.75 (s, 3 H, OCH_3), 6.71, 7.09 (2 d, J = 1.5 Hz, 2 H, Ar H), 11.75 (s, 1 H, COOH); MS (70 eV), *m/e* (relative intensity) 264 (M^+, 100), 249 (M – CH_3, 60), 281 (M – CH_3 – CO, 32). Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.87; H, 9.25.

6-*tert*-Butyl-7-methoxy-8-methyl-1-tetralone (18). After 118.9 g (0.45 mol) of **17** was refluxed in 44.1 mL (0.61 mol) of thionyl chloride, the excess thionyl chloride was removed at 0.02 bar, and 400 mL carbon disulfide and 80 g (0.6 mol) dry aluminum chloride were added at 20 °C. After the mixture was refluxed (30 min) and stirred (12 h) at room temperature, addition of ice and concentrated hydrochloride acid, extraction, with carbon tetrachloride, and distillation gave **18**: 94.1 g (85%); bp 120–125 °C (1 Pa); IR (film) 2970 (CH), 1660 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (s, 9 H, *t*-Bu), 2.05 (m, 2 H, $CH_2CH_2CH_3$), 2.55 (t, J = 4 Hz, 2 H, CH_2–Ar), 2.57 (s, 3 H, CH_3–Ar), 2.85 (t, J = 4 Hz, 2 H, CH_2CO), 3.60 (s, 3 H, OCH_3), 6.93 (s, 1 H, Ar H); MS (70 eV), *m/e* (relative intensity) 246 (M^+, 92), 231 (M – CH_3, 100), 189 (M – *t*-Bu, 4). Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.93; H, 8.94.

2-Bromo-6-*tert*-butyl-7-methoxy-8-methyl-1-tetralone (19). To 81.6 g (0.33 mol) of **18** in 1 L of dry ether was added dropwise below 0 °C 18.6 mL (0.365 mol) of bromine. After being stirred (12 h) at room temperature, a strong stream of nitrogen was passed through the mixture to remove the hydrogen bromide. Washing with water and aqueous sodium sulfite, drying, and evaporation of the ether in vacuo yielded 99.9 g (93%) of crude **19**. Distillation of crystallization was not possible without decomposition: ^1H NMR ($CDCl_3$) δ 1.38 (s, 9 H, *t*-Bu), 1.9–3,3 (m, 4 H, ArCH_2CH_2), 2.55 (s, 3 H, CH_3–Ar), 3.71 (s, 3 H, OCH_3), 4.67 (t, J = 2 Hz, 1 H, CHBr), 7.05 (s, 1 H, ArH).

6-*tert*-Butyl-7-methoxy-8-methyl-1-naphthol (20). Crude **19** (192.8 g, 0.593 mol), 140.6 g (1.6 mol) of lithium bromide, and 119.7 g (1.6 mol) of lithium carbonate were refluxed under nitrogen in 1.3 L of freshly distilled, dry *N,N*-dimethylformamide (1.5 h). After the mixture was allowed to stand 12 h at room temperature, addition of concentrated hydrochloric acid, extraction with ether, and distillation gave **20**: 86.8 g (60%); bp 115 °C (1 Pa); mp 110 °C (from *n*-hexane); IR (film) 3330 (OH), 2920 (CH), 1560 cm^{-1}; ^1H NMR ($CHCl_3$) δ 1.47 (s, 9 H, *t*-Bu), 2.88 (s, 3 H, CH_3–Ar), 3.83 (s, 3 H, OCH_3), 5.50 (s, 1 H, Ar OH), 6.54–7.45 (m, 3H, Ar H), 7.53 (s, 1 H, H-5); MS (70 eV), *m/e* (relative intensity) 244 (M^+, 100), 229 (M – CH_3, 75), 214 (M – 2CH_3, 32), 201 (M – CO – CH_3, 14). Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.53; H, 8.22.

6-*tert*-Butyl-1,7-dimethoxy-8-methylnaphthalene (21). To a well-stirred mixture of 142 g (0.58 mol) of **20**, 1 L of dichloromethane, 400 g (5 mol) of 50% sodium hydroxide, and 2 g of tetra-*n*-butylammonium iodide was added 126 g (1 mol) of dimethyl sulfate dropwise. Stirring was continued for 12 h, 200 mL of concentrated ammonia was added, and after further stirring for 30 min the mixture was extracted with dichloromethane. Distillation yielded **21**: 128.0 g (86%); bp 123 °C (13 Pa); mp 73 °C (from ethanol); IR (KBr) 2950 (CH), 2830 (OCH_3), 1590, 1560 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50 (s, 9 H, *t*-Bu), 2.78 (s, 3 H, CH_3–Ar), 3.77 (s, 3 H, OCH_3), 3.87 (5, 3 H, OCH_3), 6.55–7.45 (m, 3 H, Ar H) 7.50 (s 1 H, H-5); MS (70 eV), *m/e* (relative intensity) 258 (M^+,

(26) As indicated by the too low bromine and too high carbon values of the elemental analysis, **16** may still contain a little unreacted **15**.

100), 243 (M - CH_3, 9), 228 (M - $2CH_3$, 6). Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.04; H, 8.58. Found: C, 79.07; H, 8.66.

3,6-Di-*tert*-butyl-1,7-dimethoxy-8-methylnaphthalene (22). Compound **21** (9.6 g, 37.2 mmol), 10 mL of *tert*-butyl alcohol, 50 mL of trifluoroacetic acid, and 3 drops of concentrated sulfuric acid were stirred for 24 h at room temperature, and ether was added. Evaporation of the washed (2 N NaOH, water) and dried ether phase yielded **22**: 11.7 g (99%); mp 114-115 °C (from ethanol); ^1H NMR ($CDCl_3$) δ 1.38, 1.48 (2 s, 2 × 9 H, *t*-Bu), 2.77 (s, 3 H, CH_3-Ar), 3.78, 3.95 (2 s, 2 × 3 H, OCH_3), 6.85, 7.28 (2 d, J = 1.5 Hz, 2 H, Ar H), 7.53 (s, H-5); MS (70 eV), *m/e* (relative intensity) 314 (M^+, 100), 299 (M - CH_3, 22). Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.61. Found: C, 80.38; H, 9.60.

3,6-Di-*tert*-butyl-1,7-dihydroxy-8-methylnaphthalene (23). To a solution of 3 g (9.55 mmol) of **22** in 50 mL of dry dichloromethane was added 5 mL of boron tribromide. After it had been stirred for 2 h at room temperature, a further 2 mL of BBr_3 was added, and after 12 h another 2 mL of BBr_3 was added. The mixture was stirred for 12 h and then evaporated to dryness in vacuo. The residue was taken up with ether and water. After the etheral phase was dried, the evaporation residue was sublimed at 160-200 °C in vacuo to give **23**: 2.4 g (88%); mp 167 °C; IR (KBr) 3580 (OH), 3230 (OH), 2960 (CH), 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27, 1.48 (2 s, 2 × 9 H, *t*-Bu), 2.80 (s, 3 H, CH_3-Ar), 5.20, 5.50 (2 s, 2 H, OH), 6.62, 7.24 (2 d, J = 2 Hz, 2 H, Ar H), 7.52 (s, H-5); MS (70 eV), *m/e* (relative intensity) 286 (M^+, 100), 271 (M - CH_3, 54), 217 (M - CO - C_3H_5, 15). Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.66; H, 9.17. Found: C, 79.73; H, 9.19.

1,7-Diacetoxy-3,6-di-*tert*-butyl-8-methylnaphthalene (25). Compound **23** (1.1 g, 3.85 mmol) was refluxed (0.5 h) in 10 mL of acetic anhydride containing 0.3 g (3.85 mmol) of dry pyridine. After addition of ice and acidification with dilute hydrochloric acid, the solid was purified by preparative TLC (silica gel, Merck 60 PF 254 + 366/dichloromethane) to give **25**: 0.75 g (53%); mp 60-61 °C; ^1H NMR ($CDCl_3$) δ 1.37, 1.40 (2 s, 2 × 9 H, *t*-Bu), 2.33 (s, 6 H, CH_3CO), 2.39 (s, 3 H, CH_3Ar), 7.17, 7.57 (2 d, J = 1.5 Hz, 2 H, Ar H), 7.65 (s, H-5); MS (70 eV), *m/e* 370 (M^+, 17), 328 (M - $COCH_2$, 35), 2.86 (M - $2COCH_2$, 100), 271 (M - CH_3 - $2COCH_2$, 13). Anal. Calcd for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.57; H, 8.07.

3,6-Di-*tert*-butyl-8-methyl-1,7-naphthoquinone (24). After 1.144 g (4 mmol) of **23** and 0.908 g (4 mmol) of DDQ were flushed in an oven-dried closed apparatus with dry, oxygen-free nitrogen for 2 days, 20 mL of ether was added at -40 °C, the mixture was shaken for 10 min, and the ether was evaporated in vacuo below -30 °C. The bright red residue was dried in vacuo (1 Pa) 4 h at -30 °C, 10 mL of absolutely dry deuteriochloroform was added, and the mixture was filtrated. The solution was used directly for measuring the IR, ^1H NMR and UV/vis spectra. For the mass spectra the chloroform was evaporated again. All operations including the measuring of the IR, UV/vis, and ^1H NMR spectra were performed under dry nitrogen and at -30 °C: IR ($CDCl_3$) 2990 (CH), 1615, 1625 (CO), 1690, 1600 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 1.32 (s, 18 H, *t*-Bu), 2.48 (s, 3 H, CH_3), 6.77, 6.93, 7.04 (3 br s, 3 H, =CH); MS (70 eV), *m/e* (relative intensity) 286/284 (M^+ **23**/**24**, 12/11), 271/269 (**23**/**24** - CH_3, metastable peaks at 256.79 and 254.29), a metastable peak at 159.75 makes the fragmentation **24** - 2CO - CH_3 probable; calcd for $C_{19}H_{24}O_2$ *m/e* 284.178, found *m/e* 284.177.

Reductive Acetylation of 24. To 246 mg (0.87 mmol) of **24**, a spatula tipful of dry zinc, and 20 mg of dry sodium acetate was added 10 mL of freshly distilled acetic anhydride. The mixture was refluxed for 15 min, diluted with ether, and filtered. The filtrate was evaporated to dryness in vacuo and the residue purified by preparative TLC (silica gel Merck 60 PF 254 + 366/methylene chloride) to give 42.6 mg (13%) of a substance which proved to be identical with authentic **25**.

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Registry No. **1**, 5309-18-2; **2**, 66952-62-3; **3**, 86392-35-0; **5**, 60772-80-7; **6**, 86392-36-1; **7**, 86392-37-2; **9**, 86392-38-3; **10**, 86392-39-4; **12**, 86392-40-7; **13**, 86392-41-8; **14**, 86392-42-9; **15**, 86392-43-0; **16**, 86392-44-1; **17**, 86392-45-2; **18**, 86392-46-3; **19**, 86392-47-4; **20**, 86392-48-5; **21**, 86392-49-6; **22**, 86392-50-9; **23**, 83021-63-0; **24**, 83021-64-1; **25**, 86392-51-0; 1,4-BQ, 106-51-4; 1,2-BQ, 583-63-1; 1,2-NQ, 524-42-5; 1,4-NQ, 130-15-4; 1,5-NQ, 51583-62-1; 1,7-NQ, 46001-16-5; 2,6-NQ, 613-20-7; 2,3-NQ, 4939-92-8; 1,2-AQ, 655-04-9; 1,4-AQ, 635-12-1; 1,10-AQ, 61391-84-2; 2,9-AQ, 61357-65-1; 1,5-AQ, 61357-66-2; 1,7-AQ, 86409-49-6; 2,3-AQ, 86392-52-1; 2,6-AQ, 61357-67-3; 9,10-AQ, 84-65-1; 4,4'-diphenoquinone, 494-72-4; 1,6-[10]annulenoquinone, 58597-76-5.

Asymmetric 9-Hydroxylation of Anthracyclinones. Total Synthesis of (+)-4-Demethoxydaunomycinone

Domingo Dominguez and Michael P. Cava*

Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104

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A method is described for the synthesis of (*R*)-(-)-4-demethoxy-7-deoxydaunomycinone (**3**) from the readily prepared racemic 4-demethoxy-7,9-dideoxydaunomycinone (**6**). Thus, **6** was converted selectively into its 9-bromo derivative (**9**) by (a) cupric bromide in refluxing chloroform-ethyl acetate or (b) bromine in acetic acid in the presence of hydrogen bromide under equilibrating conditions (100 °C for 20 h). Dehydrohalogenation of **9** by lithium carbonate in dimethylformamide gave the enone **11**, which was converted to diacetate **14** by acetic anhydride. Sodium borohydride reduction of **14** in the presence of ceric chloride gave the racemic allylic alcohol **17**. Asymmetric epoxidation of **17** was carried out by using titanium isopropoxide, (+)-diisopropyl L-tartrate, and 0.6 equiv of *tert*-butyl hydroperoxide to give a mixture of epoxide (-)-**18** and (*R*)-(+)-**17**. Chromic acid oxidation of this mixture, followed by silica chromatography, gave enone **14** (minor product) and epoxy ketone (-)-**20** (major product). Sodium dithionite reduction of (-)-**20** gave (-)-**3** in 82% optically pure form, $[\alpha]^{20}_D$ -71°. The latter compound is an intermediate in the synthesis of (+)-4-demethoxydaunomycinone (**8**).

A large number of syntheses of doxorubicin (**1**) related anthracycline aglycones and glycosides have been achieved during the past few years,[1,2] but only recently has much effort been expended on the synthesis of enantiomerically pure aglycones. The availability of such compounds would avoid the complex and wasteful separation of diastereomeric products in the final glycosidation step and, of course, would require the use of less of the valuable sugar moiety.

Reported procedures make use of an optically active tetralin as an AB synthon, i.e., **2** (Chart I), which can be

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