177 (9), 163 (7), 126 (12), 73 (94); exact mass calcd for $C_{20}H_{38}O_2Si_2$ 366.2409, found 366.2401. Anal. Calcd for $C_{20}H_{38}O_2Si_2$: C, 65.51; H, 10.44; Si, 15.32. Found: C, 65.79; H, 10.63.

1,4-Bis(*tert*-butyldimethylsiloxy)-2-methylbenzene (9) was obtained in a crude yield of 100%. Recrystallization from acetonitrile–chloroform yielded 78% of pure product: mp 38–39 °C; IR (Nujol) 1500–1495 (2 bands), 1400, 1285, 1242, 1215, 1165, 990, 900, 828, 760 cm^{-1}; NMR ($CDCl_3$) δ 7.25 (s, 1 H), 6.51 (m, 2 H), 2.13 (s, 3 H) 0.99 (s, 9 H), 0.96 (s, 9 H), 0.16 (s, 6 H), 0.15 (s, 6 H); mass spectrum, *m/e* (relative intensity) 352 (50, M^+), 295 (99), 237 (7), 119 (5), 73 (45). Anal. Calcd for $C_{19}H_{36}O_2So_2$: C, 64.71; H, 10.29. Found: C, 64.59; H, 10.47.

1,4-Bis(*tert*-butyldimethylsiloxy)-2,5-di-*tert*-butylbenzene (10) was obtained in a crude yield of 97%. Recrystallization from acetonitrile gave an 83% yield of pure product.[8] Anal. Calcd for $C_{26}H_{50}O_2Si_2$: C, 69.27; H, 11.18. Found: C, 69.36; H, 11.24.

1,4-Bis(*tert*-butyldimethylsiloxy)benzene (11) was obtained in a crude yield of 98%. Recrystallization from acetonitrile–chloroform gave a 78% yield of pure product: mp 44–45 °C; IR (Nujol) 1505, 1255–1220 (3 bands), 1238, 910–920, 840, 800, 780, 740–720 (2 bands) cm^{-1}; NMR ($CDCl_3$) δ 6.68 (s, 4 H), 0.96 (s, 18 H), 0.15 (s, 12 H); mass spectrum, *m/e* (relative intensity) 338 (44, M^+), 281 (100), 223 (14), 133 (3), 112 (14), 91 (4), 73 (49); exact mass calcd for $C_{18}H_{34}O_2Si_2$ 338.2096, found 338.2096. Anal. Calcd for $C_{18}H_{34}O_2Si_2$: C, 63.84; H, 10.12. Found: 63.85; H, 10.28.

1,4-Bis(*tert*-butyldimethylsiloxy)-2-chlorobenzene (12) was obtained in a crude yield of 85%. Recrystallization from acetonitrile–chloroform gave a 79% yield of pure product: mp 48–50 °C; IR (Nujol) 1480, 1485, 1455, 1370, 1245, 1195, 1035, 900, 820, 760 cm^{-1}; NMR ($CDCl_3$) δ 6.68 (s, 3 H), 1.00 (s, 9 H), 0.95 (s, 9 H), 0.17 (s, 6 H), 0.15 (s, 6 H); mass spectrum, *m/e* (relative intensity) 374 (5, M^+), 373 (4, M^+), 372 (10, M^+), 338 (9), 315 (62), 281 (27), 279 (12), 257 (29), 199 (4), 165 (6), 149 (3), 129 (7), 93 (20), 73 (100); exact mass calcd for $C_{18}H_{33}ClO_2Si_2$ 372.1706, found 372.1718. Anal. Calcd for $C_{18}H_{33}ClO_2Si_2$: C, 57.95; H, 8.92; Cl, 9.50. Found: C, 57.55; H, 9.10; Cl, 9.34.

1,4-Bis(*tert*-butyldimethylsiloxy)-2-bromobenzene (13) was obtained in a crude yield of 85%. Recrystallization from acetonitrile–chloroform gave a 72% yield of product: mp 42–45 °C; NMR ($CDCl_3$) δ 7.03 (m, 1 H), 6.69 (m, 2 H), 104 (s, 9 H), 0.97 (s, 9 H), 0.22 (s, 6 H), 0.17 (s, 6 H). Anal. Calcd for $C_{18}H_{33}BrO_2Si_2$: C, 51.78; H, 7.97; Br, 19.14. Found: C, 51.94; H, 7.98; Br, 19.31.

Methylation of 13. Methylation of **13** was accomplished in 78% yield according to the *n*-butyllithium–methyl *p*-toluenesulfonate procedure of Syper et al.[1] The product was recrystallized from acetonitrile–chloroform and was identical in all respects with **9**.

Preparative Oxidations. To 0.001 mol of hydroquinone silyl ether dissolved in 8.0 mL of CH_2Cl_2 at 25 °C was added 0.002 mol of PCC (98%, Aldrich). The reaction mixture was stirred for 2 h or until GLC revealed the absence of starting material. The reaction mixture was evaporated to dryness and the residue extracted with 10 mL of anhydrous ether. The extract was passed through a column of Florisil (25-mL buret, 8–10 g of absorbent), eluting with anhydrous ether.

In the case of the bis(trimethylsilyl) ethers (**1–5**), evaporation of the ether elutant yielded the pure quinones. However, with the bis(*tert*-butyldimethylsilyl) ethers (**7–10**), evaporation of the ether elutant yielded a mixture of quinone and the byproduct *tert*-butyldimethylsilanol.[10] The pure quinones were obtained either by recrystallization from heptane or by washing the semisolid residue with ice-cold heptane. The results of the preparative oxidations are summarized in Table II.

Relative Reactivities (k_{rel}). Relative reactivities were determined by allowing a 1:1 molar ratio of a given pair of compounds to compete for a limited quantity of PCC. For instance, 0.5 mmol of **1** and 0.5 mmol of **2** in 8.0 mL of CH_2Cl_2 were reacted with 0.5 mmol of PCC. Prior to the addition of PCC the relative peak areas were determined by GLC analysis. After the addition of PCC the relative concentrations of the starting materials were measured by withdrawing and analyzing 0.5-μL samples at various times.

Acknowledgment. This work was supported by the National Science Foundation and the National Institutes of Health.

Registry No. **1**, 73759-43-0; **2**, 78018-52-7; **3**, 78018-53-8; **4**, 18724-29-3; **5**, 2117-24-0; **6**, 67289-08-1; **7**, 78018-54-9; **8**, 78018-55-0; **9**, 78018-56-1; **10**, 73759-45-2; **11**, 78018-57-2; **12**, 78018-58-3; **13**, 78018-59-4; quinone (R_2 = OCH_3; R_3 = H), 2880-58-2; quinone (R_2 = CH_3; R_3 = CH_3), 137-18-8; quinone (R_2 = CH_3; R_3 = H), 553-97-9; quinone (R_2 = *t*-Bu; R_3 = *t*-Bu), 2460-77-7; quinone (R_2 = H; R_3 = H), 106-51-4; quinone (R_2 = Cl; R_3 = H), 695-99-8; PCC, 26299-14-9.

Assignment of Regiochemistry to Substituted Naphthoquinones by Chemical and Spectroscopic Methods. Amino-, Hydroxy-, and Bromojuglone Derivatives

Kathlyn A. Parker*[1] and Michael E. Sworin

Department of Chemistry, Brown University, Providence, Rhode Island 02912

Received November 13, 1980

Products of the addition of hydrazoic acid to 5-methoxy-, 5-hydroxy-, and 5-acetoxy-1,4-naphthoquinone were determined. Assignment of regiochemistry resolves confusion in the literature, and a correlation between the substitution patterns and chemical shifts in the ^1H NMR spectra was noted.

A retrosynthetic analysis of the structures of the antibiotic kinamycins (**1**)[2] led us to consider a 3-aminojuglone derivative **2** (Chart I) as a building block.

A report by Thomson and co-workers[3] that 3-aminojuglone methyl ether (**2a**) was obtained from the addition of hydrazoic acid to juglone methyl ether (**3**) led us to attempt to repeat this preparation. In our hands, the procedure afforded two products which were separated by

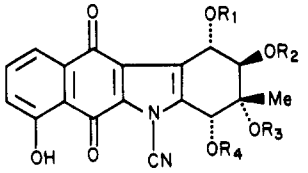
(1) Sloan Fellow, 1977–1981, and Recipient of a Camille and Henry Dreyfus Teacher Scholarship Award, 1979–1984.

(2) A. Furusaki, M. Matsui, T. Watanabe, S. Omura, A. Nakagawa, T. Hata, A Furusaki, and T. Watanabe, *Chem. Pharm. Bull.*, **21**, 931 (1973), and references therein.

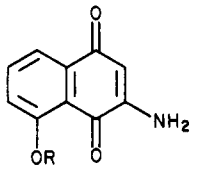
(3) A. R. Forrester, A. S. Ingram, I. C. John, and R. H. Thomson, *J. Chem. Soc., Perkin Trans. 1*, 1115 (1975).

0022-3263/81/1946-3218$01.25/0

Chart I

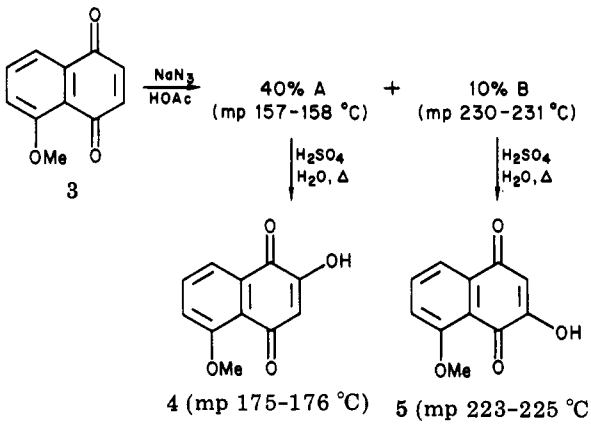


	R_1	R_2	R_3	R_4
kinamycin A (1a)	H	Ac	Ac	Ac
kinamycin B (1b)	H	H	Ac	H
kinamycin C (1c)	Ac	Ac	H	Ac
kinamycin D (1d)	H	Ac	H	Ac

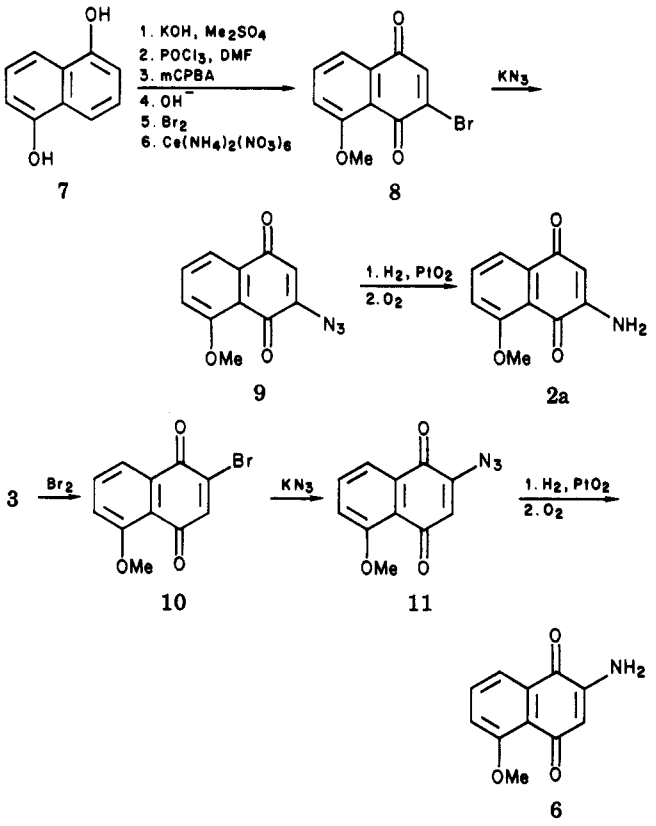


2a, R = Me
b, R = H
c, R = Ac

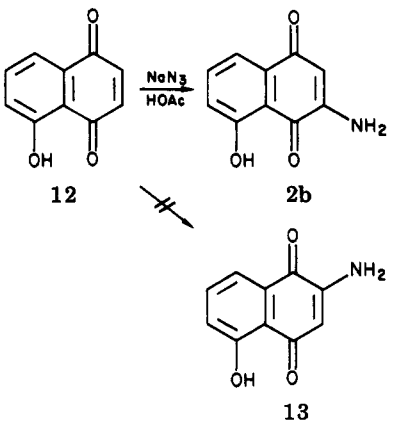
Scheme I



Scheme II



Scheme III



chromatography. The major isomer, obtained in 40% yield and designated by us as isomer A (Scheme I), had a melting point of 157–158 °C, which corresponded to that of the material obtained by Thomson and co-workers.[3] However, the identification of this material as the 3-isomer was thrown into doubt when its hydrolysis was investigated. Aqueous sulfuric acid converted isomer A to the known 2-hydroxyjuglone methyl ether [4, mp 175–176 °C (lit.[4] mp 176–177 °C)] rather than the 3-isomer (lit.[5] mp 211 °C) as reported by Thomson.[6] However, 3-hydroxyjuglone methyl ether (5, mp 223–225 °C) was obtained from hydrolysis of aminojuglone B.

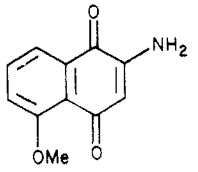
We have therefore undertaken a study of the addition of hydrazoic acid to three juglone derivatives. The regiochemistry of each amino juglone was assigned by comparing it or a derivative with an amino juglone prepared by an independent synthesis.

Preparative Methods

As we had reassigned the structure of isomer A as 6 and assigned the alternative regiochemical possibility 2a as isomer B on the basis of their hydrolysis products 4 and 5, respectively,[7] we felt that it was necessary to confirm these assignments by independent synthesis.

(4) R. G. Cooke and W. Segal, *Aust. J. Sci. Res., Ser. A*, 3, 628 (1950).
(5) J. W. MacLeod and R. H. Thomson, *J. Org. Chem.*, 25, 36 (1960).
(6) Thomson et al.[3] reported that this procedure converted the amino quinone (mp 158–106 °C) to 3-hydroxyjuglone methyl ether.

(7) The literature describing 2- and 3-hydroxyjuglone methyl ether is muddled. Thus, Cooke and Segal[4] treated 5-methoxy-1-tetralone with *p*-nitroso-*N,N*-dimethylaniline in aqueous NaOH and hydrolyzed the product with a 5% H_2SO_4. They report 2-hydroxyjuglone methyl ether (mp 176–177 °C), which was demethylated to 2-hydroxyjuglone, identical with a sample supplied by Thomson and prepared by hydrolysis of 2-anilinojuglone (R. H. Thomson, *J. Org. Chem.*, 13, 870 (1948). D. Molho, C. Mentzer and P. Meunier, *Chem. Abstr.* 52, 1259 (1958), report 2-hydroxy-5-methoxy-1,4-naphthoquinone (mp 232 °C) from aqueous alkaline H_2O_2 and 5-methoxy-1-naphthol. J. W. McLeod and R. H. Thomson[5] report 3-hydroxyjuglone methyl ether (mp 211 °C dec) from hydrolysis of 3-anilinojuglone methyl ether in concentrated H_2SO_4. Finally, Rapoport et al.[8] treated 4-hydroxy-8-methoxy-1-naphthalenecarboxaldehyde with basic peroxide to obtain a hydroxyjuglone methyl ether, mp 160–165 °C. The same product was obtained when juglone methyl ether was submitted to these conditions. Our results (see section on NMR Methods) indicate that the assignments of Cooke and Siegel and of Thomson are correct. It seems likely that Rapoport's product is the 2-substituted compound. The assignment of Molho et al. must be incorrect.



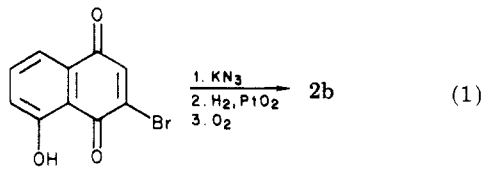
6

The unambiguous method of Rapoport[8] was used to prepare 3-bromojuglone methyl ether (8) from naphthol (7) in good yield (Scheme II) Treatment of quinone 8 with potassium azide in ethanol[9] gave azidoquinone 9 which on reduction with hydrogen followed by air oxidation afforded 3-aminojuglone methyl ether (**2a**), mp 228–230 °C. The regioisomer of 8 (which must therefore be **10**) as assigned by Rapoport[8] and others previously, was prepared by bromination and dehydrobromination of juglone methyl ether. Treatment of **10** with potassium azide, hydrogen/PtO_2, and air converted this material to 2-aminojuglone methyl ether (**6**, mp 156–158 °C).

The synthesis of 3-aminojuglone methyl ether (**2a**) from 8 is convenient (as it originated with the inexpensive and readily available 1,5-dihydroxynaphthalene); nevertheless, addition of hydroazoic acid to juglone or one of its derivatives was viewed as a potentially more attractive route to a kinamycin precursor if this reaction were to proceed in the desired regiochemical sense. Therefore, we have examined the products of the reaction of hydrazoic acid with juglone and with juglone acetate.

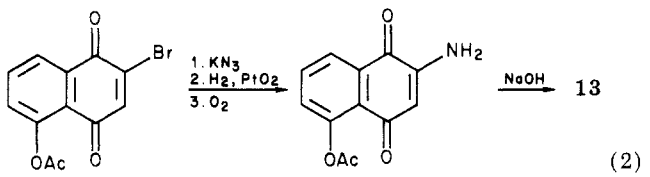
Treatment of juglone (**12**) with sodium azide in acetic acid afforded a 27% yield of a single compound, mp 251–253 °C (Scheme III). This compound was identified as 3-aminojuglone (**2b**) by comparison with an authentic sample; none of the 2-isomer (**13**) could be detected in the product of the hydrazoic acid addition.

The authentic isomeric aminojuglones **2b** and **13** were prepared from the known bromo compounds **14** and **15** (eq 1 and 2). Thus, 3-bromojuglone (**14**)[10] was converted to



(1)

14

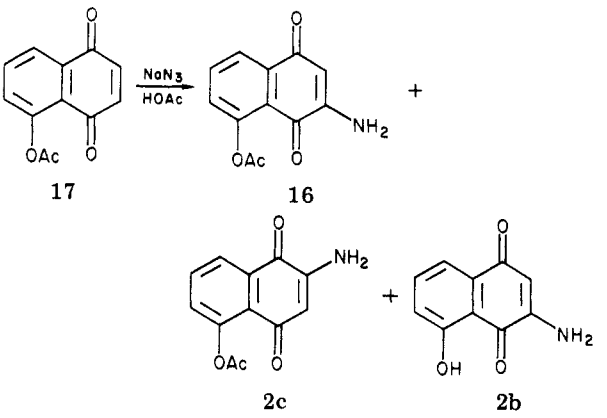


(2)

15 16

2b by treatment with potassium azide in ethanol, followed by hydrogen over platinum and then oxygen gas. The aminojuglone **2b**, a red-orange solid (mp 253–255 °C), was obtained by this unambiguous sequence in 68% yield. By a parallel sequence 2-aminojuglone acetate (**16**, mp 192–193 °C) was prepared in 57% yield from 2-bromojuglone acetate (**15**).[11] Hydrolysis of **16** then afforded 2-aminojuglone **13**, mp 269–270 °C) in 65% yield.

Addition of sodium azide in acetic acid to juglone acetate **17** gave a mixture of three products (eq 3). Partial separation of these products was effected and the yields of products (**16**/**2b**/**2c**, 10%/4%/39%) were determined by integration of the ^1H NMR spectra of the partially purified fractions (see Experimental Section). Preparative liquid chromatography of one fraction afforded 3-aminonaphthoquinone **16** as an orange solid (mp 148–150 °C), identified by hydrolysis to the known **2b**, mp 253–255 °C. 2-Aminojuglone acetate and 3-aminojuglone were identified by comparison with material already in hand. The results of our study are summarized in Table I.



17 16 2c 2b

NMR Methods

As the assignment of regiochemistry to naphthoquinones which bear substituents on both rings has often been ambiguous and/or difficult to prove;[12] the use of NMR to make such assignments should prove both convenient and confidence inspiring.

We noticed that the proton NMR spectra of the 3-amino- and 3-hydroxyjuglone derivatives exhibited noticeable upfield shifts of the signal for the most upfield aromatic proton (a doublet of doublets assigned H-6). In addition, the 2-amino isomers showed an upfield shift on the signal for H-7 (identified by its two large ortho coupling constants). These shift effects were previously noted by Goldstein and co-workers[13] who prepared a large number of 2-substituted 6-protio- and 6-deuterionaphthoquinones and noted substituent effects on each proton in the aromatic ring.[14]

Recognizing the potential of Goldstein's chemical shift parameters for assigning regiochemistry to substituted naphthoquinones, we sought to obtain accurate chemical shifts for the aromatic protons in each of our substituted juglone derivatives and to test the applicability of the Goldstein parameters to the juglone series. In order to

(8) R. L. Hannan, R. B. Barber, and H. Rapoport, *J. Org. Chem.*, **44**, 2153 (1979).

(9) This procedure has been shown to lead to regiospecific substitution for several 5-substituted 2-chlorobenzoquinones: H. W. Moore, H. R. Sheldon, D. W. Deters, and R. J. Wikholm, *J. Am. Chem. Soc.*, **92**, 1675 (1970).

(10) R. H. Thomson, *J. Org. Chem.*, **13**, 377 (1948).

(11) R. H. Thomson, *J. Org. Chem.*, **16**, 1082 (1951).

(12) In addition to the examples discussed in footnote 7 above, one should note the original misassignment of the NH_3/juglone methyl ether adduct[5] and the controversy over the regiochemistry of the 3-halojuglones: K. T. Finley in "The Chemistry of the Quinonoid Compounds", S. Patai, Ed., Wiley, New York, 1974, p 930.

(13) R. W. Crecely, K. M. Crecely, and J. H. Goldstein, *J. Mol. Spectrosc.* **32**, 407 (1969). Note that the chemical shifts and shift parameters were originally expressed in hertz relative to Me_4Si at 60 MHz; also in this paper, an upfield shift was assigned a positive value.

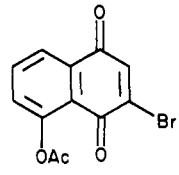
(14) Correlations between quinone substituents and the chemical shifts of *peri*-hydroxyl absorptions have been noted: R. E. Moore, P. J. Scheuer, *J. Org. Chem.*, **31**, 3272 (1966); T. J. Lillie and O. C. Musgrave, *J. Chem. Soc., Perkin Trans. 1*, 355 (1977). There is no obvious relationship between these effects and those observed by Goldstein and ourselves.

Table I.[a] Aminonaphthoquinones Produced by the Addition of Hydrazoic Acid to Naphthoquinones

	substituted position					
	5-methoxy-1,4-naphthoquinone		5-hydroxy-1,4-naphthoquinone		5-acetoxy-1,4-naphthoquinone	
	2	3	2	3	2	3
aminoquinone	**6**	**2a**	**13**	**2b**	**16**	**2c**
% yield	40	10	0	27	10	39[b]
melting point, °C	157-158	230-231	269-270	253-255	192-193	148-150
R_f (EtOAc)	0.39	0.56	0.89	0.78	0.82	0.79
R_f ($CHCl_3$)[c]	0.11	0.13	0.40	0.24	0.15	0.16
R_f (2:1 $CHCl_3$-EtOAc)	0.17	0.21	0.53	0.35	0.36	0.38
hydrolysis product	4	5				
mp, °C	175-176	223-225				

[a] See Experimental Section for details. [b] A 4% yield of 3-amino-5-hydroxy-1,4-naphthoquinone was also recovered. [c] Five developments.

complete Table II, we prepared 3-bromojuglone acetate (**18**).[10]



18

The aromatic protons in juglone acetates **11**, **16**, and **2c** exhibited patterns which could be analyzed as first-order cases at 60 MHz (Table II, entries 1–3). The remaining juglone derivatives had ABC patterns which contained a well-defined AB portion and a distinct C portion at 60 MHz (Table II, entries 4–16). Most of these were expanded to AMX patterns at 270 MHz so that chemical shift assignments and coupling constants could be made by inspection (entries 4–9, 11, 13, 15). The exceptions, juglone methyl ether and its derivatives substituted at the 3-position (entries 10, 12, 14, 16), showed ABX patterns even at 270 MHz. Chemical shifts for the protons in these derivatives were obtained by matching simulated spectra (NMRCAL, 270 MHz) with the measured spectra; in each case, transitions were approximated to within 1 Hz. Parameters used for the NMRCAL simulations are listed in Table II, notes *d–g*.

Inspection of the data in Table II suggests that the chemical shift parameters $\Delta\delta$, which agree at least qualitatively with those derived from spectra of 2-substituted and 2,3-disubstituted naphthoquinones by Goldstein et al.,[13] may be used to assign regiochemistry to various 2- or 3-amino-, hydroxy-, or halojuglone derivatives. (Presumably such assignments might be applied to naphthoquinones which are more highly substituted in the aromatic ring as well. As Goldstein showed that the parameters for substituents at positions 2 and 3 were additive, it seems that this method might be applied to a variety of isomeric pair possibilities where the signals for aromatic protons can be identified and where one of the substituents on the quinone ring is a heteroatom.)

In particular, one should note the parameters for $\Delta\delta_7$ and $\Delta\delta_6$ for the amino and hydroxy substituents and $\Delta\delta_8$ for bromo substituents (footnote *i* in Table II).

From this tabulation is is clear that the upfield shift of H-7 as the result of a 2-amino substituent of H-6 as the result of a 3-amino substituent should be greater than 0.1 ppm; on the other hand, the upfield shift of H-7 when there is a 3-amino substituent or of H-6 when there is a 2-amino substituent should be less than 0.08 ppm. Similarly, a 2-hydroxy substituent shifts H-7 upfield, and it shifts H-6 upfield very slightly or downfield; likewise, a 3-hydroxy shifts H-6 upfield and H-7 only slightly upfield or downfield.

The most pronounced shift in the bromojuglones if the effect of a 2-bromo substituent on H-8 (downfield by approximately 0.1 ppm); a 3-substituent has little or no effect on the chemical shift of H-8.

Conclusion

Chemical interconversions resulted in the unambiguous assignment of regiochemistry to a number of substituted juglone derivatives. The NMR spectra of these compounds were then shown to fit previously observed substituent shift effects. The correlation of substituent position with NMR parameters should allow the straightforward assignment of regiochemistry to new naphthoquinone derivatives.

Experimental Section

All reactions were run under a positive pressure of dry nitrogen or argon unless otherwise stated.

Infrared spectra were obtained by using a Perkin-Elmer 257 grating instrument. Ultraviolet absorption spectra were measured on a Cary 14 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian A-60 or a Bruker WP-60, and chemical shifts are given in parts per million downfield from tetramethylsilane. NMR data are listed in Table II. Mass spectra were recorded at 50 eV on a Hitachi Perkin-Elmer Model RMU-6D spectrometer. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected.

Preparative medium-pressure liquid chromatography separations were performed on a Lobar column (Merck), size B (310 nm × 25 mm), prepacked with Li Chroprep Si 60 silica gel (40–63 μm). Thin-layer chromatography was performed on Merck glass-backed silica gel plates (no. 5765). Spots were examined under shortwave ultraviolet light or by development with iodine. "Flash" chromatography was carried out on Merck silica gel 60 (10–14 mesh).

The term "flash" chromatography applies to a method of rapid purification of a compound or reaction mixture on preparative TLC grade silica gel. It is reduced-pressure column chromatography using a sintered-glass funnel as the glass column and an aspirator as the vacuum source.

The procedure is as follows: (1) pour a slurry of silica gel onto the sintered-glass funnel (while under vacuum); (2) pack down the silica gel with a flat glass stopper (the column should never by allowed to go dry); (3) carefully lower the solvent level to the top of the column (breaking the vacuum helps); (4) load the crude material; (5) elute the column.

Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Inc.

2-Amino-5-methoxy-1,4-naphthoquinone (6) and 3-Amino-5-methoxy-1,4-naphthoquinone (2a). To 940 mg (5.0

Table II. Effect of Substituent at C-2 or C-3 on the Chemical Shifts of H-6, H-7, and H-8 in Juglone Derivatives

entry	compd	substituents of aromatic protons	chemical shifts, δ					coupling constants			other signals, δ
			δ_8	$\Delta\delta_8$	δ_7	$\Delta\delta_7$	δ_6	$\Delta\delta_6$	$J_{7,8}$	$J_{6,7}$	$J_{6,8}$	
1[a]	17	5-OAc	8.01		7.74		7.36		7.6	7.9	1.8	6.90 (s, 2 H), 2.46 (s, 3 H)
2[a]	16	5-OAc, 2-NH_2	7.99	−0.02	7.62	−0.12[i]	7.30	−0.06[i]	7.3	7.9	1.8	5.88 (s, 1 H), 5.02 (s, 2 H), 2.44 (s, 3 H)
3[a]	2c	5-OAc, 3-NH_2	7.98	−0.03	7.70	−0.04[i]	7.24	−0.12[i]	7.6	7.6	1.8	5.98 (s, 1 H), 5.16 (s, 2 H), 2.44 (s, 3 H)
4[b]	15	5-OAc, 2-Br	8.12	0.11[i]	7.79	0.05	7.44	0.08	7.7	8.1	1.1	7.40 (s, 1 H), 2.40 (s, 3 H)
5[b]	18	5-OAc, 3-Br	8.04	0.03[i]	7.81	0.07	7.43	0.07	7.9	8.1	1.3	7.50 (s, 1 H), 2.43 (s, 3 H)
6[b]		5-OH	7.59		7.66		7.28		7.7	8.1	1.1	11.93 (s, 1 H), 6.97 (s, 2 H)
7[b]	13	5-OH, 2-NH_2	7.59	0.00	7.50	−0.16[i]	7.23	−0.05[i]	7.7	8.1	1.1	12.83 (s, 1 H), 5.91 (s, 1 H), 5.30 (s, 2 H)
8[b]	2b	5-OH, 3-NH_2	7.55	−0.04	7.63	−0.03[i]	7.16	0.12[i]	7.3	8.1	1.5	11.56 (s, 1 H), 5.97 (s, 1 H), 5.15 (s, 2 H)
9[b]	14	5-OH, 3-Br	7.62	0.03[i]	7.69	0.03	7.31	0.03	7.3	8.1	1.5	11.7 (s, 1 H), 7.50 (s, 1 H)
10[c,d]	3	5-OMe	7.70		7.70		7.34		7.7	8.1	1.1	6.83 (s, 1 H), 6.82 (s, 1 H), 3.97 (s, 3 H)
11[b]	6	5-OMe, 2-NH_2	7.72	0.02	7.59	−0.11[i]	7.32	−0.02[i]	7.7	8.4	1.1	5.85 (s, 1 H), 5.32 (s, 2 H), 3.94 (s, 3 H)
16[c,e]	2a	5-OMe, 3-NH_2	7.69	−0.01	7.67	−0.03[i]	7.23	−0.11[i]	7.7	8.1	1.1	5.89 (s, 1 H), 5.32 (s, 2 H), 3.98 (s, 3 H)
13[b]	10	5-OMe, 2-Br	7.79	0.09[i]	7.70	0.00	7.36	0.02	7.7	8.1	1.1	7.36 (s, 1 H), 3.98 (s, 3 H)
14[c,f]	8	5-OMe, 3-Br	7.70	0.00[i]	7.73	0.03	7.34	0.00	7.7	8.1	1.1	7.43 (s, 1 H), 4.00 (s, 1 H)
15[b]	4	5-OMe, 2-OH	7.78	0.08	7.67	−0.03[i]	7.39	0.05[i]	7.7	8.4	1.1	7.13 (s, 1 H each in D_2O), 6.18 (s, 1 H), 3.97 (s, 3 H)
16[c,g]	5	5-OMe, 3-OH	7.73	0.03	7.75	0.05[i]	7.30	−0.04[i]	7.7	8.1	1.1	6.27 (s, 1 H), 4.04 (s, 3 H), 1.81 (s, 1 H, each in D_2O)

[a] First-order spectrum at 60 MHz, recorded on a Bruker Model WP-60. [b] First-order spectrum at 270 MHz, recorded on the Bruker Model HX270 at the Southern New England High Field NMR Facility. [c] Non-first-order spectrum at 270 MHz; chemical shifts were obtained to within 1 Hz by matching a simulated spectrum (NMRCAL, 270 MHz) with the measured spectrum. [d] Parameters for NMRCAL, 270 MHz: $\nu(8) = 2078$, $\nu(7) = 2079$, $\nu(6) = 1992$, $J(7,8) = 7.7$, $J(6,8) = 1.1$, $J(6,7) = 8.1$. [e] Parameters for NMRCAL, 270 MHz: $\nu(8) = 2076$, $\nu(7) = 2072$, $\nu(6) = 1951$, $J(7,8) = 7.7$, $J(6,8) = 1.1$, $J(6,7) = 8.1$. [f] Parameters for NMRCAL, 270 MHz: $\nu(8) = 2078$, $\nu(7) = 2086$, $\nu(6) = 1983$, $J(7,8) = 7.7$, $J(6,8) = 1.1$, $J(6,7) = 8.1$. [g] Parameters for NMRCAL, 270 MHz: $\nu(8) = 2088$, $\nu(7) = 2092$, $\nu(6) = 1971$, $J(7,8) = 7.7$, $J(6,8) = 1.1$, $J(6,7) = 8.1$. [h] The δ values are in parts per million relative to Me_4Si, and the Δδ values are in parts per million relative to the 2,3-unsubstituted case. [i] Values of note; see NMR Methods in the text.

mmol) of 5-methoxy-1,4-naphthoquinone (**3**) in 25 mL of glacial acetic acid was added 650 mg (10.0 mmol) of sodium azide in 2 mL of distilled water. After being stirred at room temperature for 48 h, the reaction mixture was poured into 100 mL of water; the resulting solution was stirred for 15 min and filtered. The filtrate was neutralized with solid $NaHCO_3$ and extracted with chloroform. The combined chloroform solution was washed with saturated $NaHCO_3$ and brine, dried (calcium sulfate), and concentrated. Flash chromatography of the residue with chloroform–ethyl acetate (2:1) as eluent provided 505 mg (50%) of an orange solid. Preparative liquid chromatography of an aliquot of this mixture with ethyl acetate afforded both of the regioisomeric aminonaphthoquinones. The ratio of aminonaphthoquinone **6** to aminonaphthoquinone **2a** was 4:1. On the basis of this ratio, the yield of aminonaphthoquinone **6** is 40% and the yield of aminonaphthoquinone **2a** is 10%.

Recrystallization of aminonaphthoquinone **6** from chloroform gave red-orange needles: mp 157–158 °C (lit.[3] mp 158–161 °C); IR ($CHCl_3$) 3480, 3370, 1620, 1280, 1245 cm^{-1}; mass spectrum, *m/e* 203 (M^+).

Recrystallization of aminonaphthoquinone **2a** from chloroform gave red-orange needles: mp 230–231 °C; IR ($CHCl_3$) 3480, 3360, 1615, 1575 cm^{-1}; mass spectrum, *m/e* 203 (M^+).

3-Hydroxy-5-methoxy-1,4-naphthoquinone (5). To a solution of 483 mg (2.38 mmol) of aminonaphthoquinone B (**2a**) in 20 mL of concentrated sulfuric acid was cautiously added 40 mL of water. The solution was gently boiled under reflux for 5 min, cooled, diluted with water, and extracted with chloroform. The combined chloroform solution was washed with brine, dried (calcium sulfate), and concentrated. The distilled (Kugelrohr, bp 190 °C, 0.02 mm) solid was recrystallized from ethanol to provide 215 mg (44%) of golden flakes: mp 223–225 °C (lit.[5] mp 209–211 °C); IR ($CHCl_3$) 1650, 1580, 1390 cm^{-1}.

2-Hydroxy-5-methoxy-1,4-naphthoquinone (4). To a solution of 500 mg (2.46 mmol) of aminonaphthoquinone A (**6**) in 20 mL of concentrated sulfuric acid was cautiously added 40 mL of water. The solution was gently boiled under reflux for 5 min, cooled, diluted with water, and extracted with chloroform. The combined chloroform solution was washed with brine, dried (calcium sulfate), and concentrated. The distilled (Kugelrohr, b 140 °C, 0.02 mm) solid was recrystallized from ethanol–water and dried in a vacuum desiccator to provide 256 mg (51%) of yellow-orange needles: mp 175–176 °C (lit.[4] mp 176–177 °C); IR ($CHCl_3$) 1650, 1630, 1280 cm^{-1}.

3-Amino-5-methoxy-1,4-naphthoquinone (2a). To 200 mg (0.75 mmol) of bromonaphthoquinone **8** in 10 mL of ethanol was added 81 mg (1.0 mmol) of potassium azide. After being stirred at room temperature for 10 h, the solution was diluted with water. The yellow solid which precipitated was washed with water, and 135 mg (79%) of azidonaphthoquinone **9** was isolated: IR ($CHCl_3$) 2110, 1660, 1590, 1580, 1260 cm^{-1}.

To 68.4 mg (0.30 mmol) of azidonaphthoquinone **9** in 10 mL of ethanol was added 14 mg of platinum oxide. The suspension was stirred for 1 h under 1 atm of hydrogen. The catalayst was removed by filtration and O_2 gas bubbled through for 2 h. Concentration afforded a solid which was purified by flash chromatography using chloroform–ethyl acetate (2:1) to give 46 mg (76%) of a red-orange solid: mp 228–230 °C; the spectra were identical with those previously reported for 2a above.

2-Amino-5-methoxy-1,4-naphthoquinone (6). To 400 mg (1.5 mmol) of bromonaphthoquinone **10** in 30 mL of ethanol was added 162 mg (2.0 mmol) of potassium azide. After being stirred at room temperature for 6 h, the solution was diluted with water and filtered, and the yellow solid was washed with water.

To the moist azidonaphthoquinone **11** in 25 mL of ethanol was added 20 mg of platinum oxide. The suspension was stirred for 2 h under 1 atm of hydrogen. The catalyst was removed by filtration and O_2 gas bubbled through the filtrate for 2 h. Concentration afforded a solid which was purified by flash chromatography using chloroform–ethyl acetate (2:1) to give 202 mg (66%) of a red-orange solid: mp 156–158 °C (lit.[3] mp 158–161 °C); the spectra were identical with those previously reported for **6** above.

3-Amino-5-hydroxy-1,4-naphthoquinone (2b). To 870 mg (5.0 mmol) of 5-hydroxy-1,4-naphthoquinone (**12**) in 25 mL of glacial acetic acid was added 650 mg (10.0 mmol) of sodium azide

in 2 mL of distilled water. After being stirred at room temperature for 48 h, the solution was poured into 100 mL of water, neutralized with solid $NaHCO_3$, and extracted with chloroform. The combined chloroform solution was washed with saturated $NaHCO_3$ and brine, dried (calcium sulfate), and concentrated. Flash chromatography of the residue with chloroform–ethyl acetate (2:1) provided 255 mg (27%) of a red solid: mp 251–253 °C; IR (KBr) 3360, 3150, 1580, 1550, 1260 cm^{-1}; mass spectrum, m/e 189 (M^+).

3-Amino-5-hydroxy-1,4-naphthoquinone (2b). To 506 mg (2.0 mmol) of bromonaphthoquinone **14** in 25 mL of ethanol was added 200 mg (2.47 mmol) of potassium azide. After being stirred at room temperature for 20 h, the solution was diluted with water and filtered, and the orange solid was washed with water to provide 408 mg (95%) of the azidonaphthoquinone: IR ($CHCl_3$) 2120, 1635, 1580, 1255 cm^{-1}.

To 317.2 mg (1.48 mmol) of the azidonaphthoquinone in 25 mL of ethanol was added 30 mg of platinum oxide. The suspension was stirred for 8 h under 1 atm of hydrogen. The catalyst was removed by filtration, and O_2 gas was bubbled through for 2 h. Concentration afforded a solid which was purified by flash chromatography using chloroform–ethyl acetate (2:1) to give 200 mg (72%) of a red-orange solid: mp 253–255 °C; the spectra were identical with those reported above for **2b**.

5-Acetoxy-2-amino-1,4-naphthoquinone (16). To 295 mg (1.0 mmol) of bromonaphthoquinone **15** in 15 mL of ethanol was added 100 mg (1.23 mmol) of potassium azide. After stirring at room temperature for 20 h, the solution was diluted with water and filtered. The yellow precipitate was washed with water to provide 214 mg (83%) of the azidonaphthoquinone: IR ($CHCl_3$) 2130, 1760, 1670, 1640, 1595, 1365, 1265, 1180 cm^{-1}.

To 186.7 mg (0.726 mmol) of the azidonaphthoquinone in 20 mL of ethanol was added 20 mg of platinum oxide. The suspension was stirred for 8 h under 1 atm of hydrogen. The catalyst was removed by filtration and O_2 gas bubbled through for 2 h. Filtration gave 50 mg of orange plates. Concentration of the filtrate afforded a solid which was purified by flash chromatography using chloroform–ethyl acetate (2:1) to give 66 mg for a total of 116 mg (69%) of an orange solid: mp 192–193 °C; IR ($CHCl_3$) 3480, 3400, 3360, 1745, 1620, 1260 cm^{-1}; mass spectrum, m/e 231 (M^+).

2-Amino-5-hydroxy-1,4-naphthoquinone (13). To 20 mg (0.087 mmol) of acetoxynaphthoquinone **16** in 2 mL of ethanol was added 5 mL of 5% sodium hydroxide solution. After being stirred for 1 h at room temperature, the solution was diluted with water and extracted with chloroform. The combined chloroform solution was washed with brine, dried (calcium sulfate), and concentrated. Flash chromatography of the residue with chloroform–ethyl acetate (2:1) provided 10.6 mg (65%) of a red solid: mp 269–270 °C; IR (KBr) 3490, 3120, 1610, 1450, 1260 cm^{-1}; mass spectrum, m/e 189 (M^+).

5-Acetoxy-3-amino-1,4-naphthoquinone (2c) and 5-Acetoxy-2-amino-1,4-naphthoquinone (16). To 108 g (5.0 mmol) of 5-acetoxy-1,4-naphthoquinone (**17**) in 25 mL of glacial acetic acid was added 650 mg (10.0 mmol) of sodium azide in 2 mL of distilled water. After being stirred at room temperature for 72 h, the solution was poured into 100 mL of water, stirred for 15 min, and filtered. The filtrate was neutralized with solid $NaHCO_3$ and extracted with chloroform. The combined chloroform solution was washed with saturated $NaHCO_3$ and brine, dried (calcium sulfate), and concentrated. Trituration of the residue with chloroform afforded 281 mg of a mixture of acetoxyaminonaphthoquinone **2c** and aminohydroxynaphthoquinone **2b**. The ratio of **2c** and **2b** was 88:12, as determined by ^1H NMR integration. On the basis of this ratio, the yield of compound **2c** is 21% and the yield of compound **2b** is 4%. Preparative liquid chromatography of an aliquot of this mixture with chloroform provided aminonaphthoquinone **2c** as an orange solid: mp 148–150 °C; IR ($CHCl_3$) 3480, 3360, 1755, 1615, 1345, 1180 cm^{-1}; mass spectrum m/e 231 (M^+).

Preparative liquid chromatography of the trituration washes with chloroform as eluent provided 328 mg of a mixture of aminonaphthoquinone **2c** and aminonaphthoquinone **16**. The ratio **2c** to **16** was 64:36, as determined by ^1H NMR integration. On the basis of this ratio, the yield of compound **2c** is 18%, and the yield of compound **16** is 10%.

3-Amino-5-hydroxy-1,4-naphthoquinone (2b). To 25 mg (0.108 mmol) of acetoxynaphthoquinone **2c** in 2 mL of ethanol was added 5% sodium hydroxide solution. After being stirred for 1 h at room temperature, the solution was diluted with water and extracted with chloroform. The combined chloroform solution was washed with brine, dried (calcium sulfate), and concentrated. Flash chromatography of the residue with chloroform–ethyl acetate (2:1) provided 12.2 mg (60%) of a red solid: mp 253–255 °C; the spectra were identical with those reported above for **2b**.

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Stereospecific Syntheses of Both Diastereomers of (±)-2-Amino-4-methyl-5-hexenoic Acid

Barry B. Snider*[1] and John V. Dunčia

Department of Chemistry, Princeton University, Princeton, New Jersey 08544

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Both diastereomers of 2-amino-4-methyl-5-hexenoic acid (**7** and **16**) have been synthesized stereospecifically from methyl (2*R**,4*S**)-2-bromo-4-methyl-5-hexenoate (**1**), the product of the $EtAlCl_2$-catalyzed ene reaction of methyl α-bromoacrylate and *trans*-2-butene. This synthesis establishes the stereochemistry of the ene reaction and establishes that the amino acid isolated from a *Streptomyces* fermentation is **7**.

A variety of nonprotein amino acids with the 2-amino-4-methylhexanoic skeleton are known. Fowden and Smith isolated (2*S*)-2-amino-4-methyl-4-hexenoic acid and (2*S*,4*S*)-2-amino-4-methylhexanoic acid (**14**) from the seeds of *Aesculus californica*.[2] Kelly et al. isolated (2*S*)-2-amino-4-methyl-5-hexenoic acid, an antimetabolite antibiotic,[3] of unknown configuration at C4 from a *Strepto-*

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(2) Fowden, L.; Smith, A. *Phytochemistry* **1968**, *7*, 809.

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