Short, High-Yield Syntheses of (±)-Curcuhydroquinone and (±)-Curcuquinone

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The antibacterial sesquiterpenoids (±)-curcuhydroquinone (**6a**) and (±)-curcuquinone (**7**) were prepared in 89% and 70% yields, respectively, from (±)-curcuhydroquinone dimethyl ether (**6b**), which in turn was obtained in a three-step synthesis from 1-bromo-2,5-dimethoxy-4-methylbenzene (**1**) in 77% overall yield.

Curcuquinone (**7**), the simplest monocyclic sesquiterpene benzoquinone found in nature, was recently isolated from the coral *Pseudopterogorgia rigida* together with the corresponding hydroquinone (**6a**; see Chart I) and with curcuphenol.[1] All these compounds show antibacterial activity, and completion of a synthesis of curcuphenol was necessary for structural elucidation.[1]

Due to our interest in sesquiterpene benzoquinones,[2] we describe herein short, high-yield, total syntheses of (±)-curcuquinone (**7**) and (±)-curcuhydroquinone (**6a**), via (±)-curcuhydroquinone dimethyl ether (**6b**). The common intermediate **6b** was synthesized in three steps from the well-known[3] 1-bromo-2,5-dimethoxy-4-methylbenzene (**1**) in 77% overall yield.

Results and Discussion

Grignard reaction of the organomagnesium compound[4] derived from **1** with commercially available 6-methyl-5-hepten-2-one (**2**) allowed the construction[5] of the sesquiterpene skeleton. The reaction product **3** has IR absorptions indicative of a hydroxyl group at 3470 cm^{-1} and of double bonds at 1515 cm^{-1}. Cogent evidence for its structure was readily adduced from inspection of the ^1H and ^{13}C NMR spectra. Thus, singlets at 74.9 ppm in the ^{13}C NMR spectrum and at 1.57 ppm (3 H) in the ^1H NMR spectrum are attributed to a tertiary hydroxy-bearing carbon having, in addition, a methyl group. Other significant absorptions of **3** and the remaining compounds are summarized in Table I and in the Experimental Section.

Removal of the benzylic tertiary hydroxyl group of **3** by catalytic treatment with Amberlyst-15 in benzene afforded a 2:1 mixture of olefins **4** and **5**, as was evident from the ^1H NMR intensity of the terminal methylene group of **4** which appears as an AB (J = 2.5 Hz) pair of doublets at 6.00 and 6.10 ppm and of the H-10 signal of **5** that shows a triplet ($J_{10,11}$ = 7 Hz) of quartets ($J_{9,10}$ = 1.2 Hz) at 5.42 ppm.

Chart I

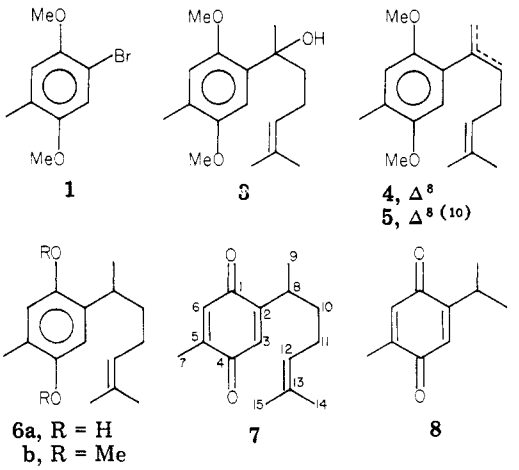

Table I. ^{13}C NMR Chemical Shifts of the Compounds[a]

atom	shift						
	1	2	3	6b	6a	7	8
C-1	149.5		150.1	150.6	146.4	186.7	186.9
C-2	107.9		133.0	133.6	131.7	153.6	154.6
C-3	115.2		109.9	109.5	113.5	130.7	130.1
C-4	151.9		151.5	151.6	147.5	187.8	188.1
C-5	126.9		125.4	123.9	121.9	144.6	144.9
C-6	115.1		114.5	114.0	117.9	133.4	133.6
C-7	16.2		15.9	15.8	15.4	15.0	15.3
C-8		208.2	74.9	31.9	31.5	31.1	26.5
C-9		29.8	27.8	21.1	21.0	19.3	21.4
C-10		43.7	42.0	37.2	37.3	35.6	21.4
C-11		22.6	23.3	26.2	26.0	25.6	
C-12		122.7	124.6	124.6	124.5	123.6	
C-13		132.4	131.0	130.6	131.9	131.5	
C-14		17.6	17.5	17.4	17.6	17.4	
C-15		25.6	25.6	25.5	25.6	25.4	
OMe	56.7		55.9	56.0			
OMe	55.9		55.8	55.7			

[a] Numbering of atoms is the same as for sesquiterpenic benzoquinones (see **7**). Gated decoupled spectra were measured for all compounds except **3**. The shifts are given in parts per million from internal Me_4Si.

The conjugated double bond of each olefin in the mixture of **4** and **5** was saturated[1] by action of sodium in liquid ammonia to produce (±)-curcuhydroquinone dimethyl ether (**6b**) in 89.5% yield. That only the styrene-type

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double bond of **4** and **5** was saturated is evident from the appearance of a secondary methyl doublet (J = 7 Hz) at 1.18 ppm and the presence of the isopropylidene at 5.13 (1 H), 1.61 (3 H), and 1.48 (3 H) ppm.

The synthesis of (±)-curcuhydroquinone (**6a**) was completed by removal of the protecting groups. This was achieved in 89% yield by boron tribromide treatment of **6b**. The spectral data of the synthetic product **6a** are given in the Experimental Section and are in agreement with those of naturally occurring[1] curcuhydroquinone (**6a**), except for the optical rotation, since a racemic mixture has been synthesized.

When solutions of **6a** are stored for several days, the hydroquinone[1] slowly oxidizes to curcuquinone (**7**). In addition, the latter can be prepared in 70% yield directly from curcuhydroquinone dimethyl ether (**6b**) by silver(II) oxide treatment.[6] Synthetic curcuquinone (**7**) was fully characterized in three ways: by comparison of the IR, UV, and ^{1}H NMR data given in the Experimental Section to those data published for the natural product;[1] by comparison of the ^{13}C NMR shifts of the side chain to those of a steroid[7] and other sesquiterpenes[8] having the same unsaturated moiety and of the ring carbons to those of thymoquinone[9] (**8**; see Table I); by direct comparison with a sample obtained after hydrolysis of curcuhydroquinone monoisovalerate (that we very recently isolated from the root of *Perezia carpholepis*[10]), followed by air oxidation.

Experimental Section

Melting points are uncorrected. Infrared (IR) spectra were taken with a Perkin-Elmer 599-B spectrophotometer. Ultraviolet (UV) spectra were determined by using a Hitachi Perkin-Elmer 200 spectrophotometer. ^{1}H NMR spectra were measured with a Varian Associates EM-390 spectrometer in $CDCl_3$ solutions containing tetramethylsilane as the internal standard. Similar solutions were used to determine ^{13}C NMR spectra with a Varian Associates XL-100A-12-FT-16K system. Tetrahydrofuran was distilled from $LiAlH_4$.

(±)-8-Hydroxycurcuhydroquinone Dimethyl Ether (3). A solution of 7 g (30.3 mmol) of 1-bromo-2,5-dimethoxy-4-methylbenzene (**1**)[3,4] in 70 mL of anhydrous tetrahydrofuran was treated with 810 mg (33.75 mol) of magnesium and 1 drop of 1,2-dibromoethane. After being refluxed 30 min, the reaction mixture was cooled and treated with 4.5 g (35.71 mmol) of 6-methyl-5-hepten-2-one (**2**). The reaction mixture was refluxed for an additional 30 min and cooled in an ice bath. A saturated solution (20 mL) of ammonium chloride was added and the mixture extracted with ethyl acetate. The organic layer was washed with a saturated solution of sodium chloride, dried over anhydrous sodium sulfate, and evaporated under vacuum. The residue was chromatographed over silica gel. The fractions eluted with hexane–ethyl acetate (9:1) gave 7.448 g (26.79 mmol, 88.4%) of the product as a viscous oil: IR (neat) 3470 (OH) 1515 cm^{-1} (C=C); UV (methanol) λ_{max} 289 nm (log ϵ 3.56) 224 (3.80) 205 (4.38); ^{1}H NMR δ 6.87 (s, 1 H, H-3), 6.70 (br s 1 H, H-6), 5.10 (t with further unresolved couplings, J_t = 7 Hz, 1 H, H-12), 3.80 and 3.76 (2 s, 3 H each, methoxyls), 2.30 (br, 1 H, OH), 2.20 (s, 3 H, aromatic methyl), 1.63 and 1.54 (2 br s, 3 H each, isopropylidene methyls), and 1.57 (s, 3 H, tertiary methyl); ^{13}C NMR, Table I.

8-Dehydro- (4) and 8(10)-Dehydrocurcuhydroquinone Dimethyl Ether (5). A solution of 650 mg (2.33 mmol) of **3** in 30 mL of anhydrous benzene was treated with a catalytic amount (50 mg) of Amberlyst-15 (Rohm and Hass). The reaction mixture was stirred at room temperature during 36 h. The catalyst was filtered off and the benzene evaporated. The residue was chromatographed over silica gel. The fractions eluted with hexane gave 592 mg (2.28 mmol, 97.4%) of a 2:1 mixture of **4** and **5** (from ^{1}H NMR data) as a viscous oil: IR (neat) 1510 cm^{-1} (C=C); UV (methanol) λ_{max} 298 nm (log ϵ 3.62) 207 (4.25); ^{1}H NMR δ 6.67 (br s, 1 H, H-6), 6.63 (s, 1 H, H-3), 5.42 (tq, J_t = 7 Hz, J_q = 1.2 Hz, 0.33 H, H-10), 5.15 (t with further unresolved couplings, J_t = 7 Hz, 1 H, H-12), 6.10 and 6.00 (2 d, J = 2.5 Hz, 0.66 H each, H-9 and H-9′), 3.78 and 3.75 (2 s, 3 H each, methoxyls), 2.20 (s, 3 H, aromatic methyl), 1.97 (d, J = 1.2 Hz, 0.33 × 3 H, vinyl methyl at C-8), 1.65 and 1.54 (2 br s, 3 H each, isopropylidene methyls).

(±)-Curcuhydroquinone Dimethyl Ether (6b). A solution of 200 mL of liquid ammonia was stirred at −78 °C during 30 min in the presence of 11 g (0.478 mol) of sodium. A solution of 6.77 g (26 mmol) of the mixture of **4** and **5** in 100 mL of ahydrous tetrahydrofuran was slowly added. The reaction mixture was stirred at −78 °C during 1 h. An excess of ammonium chloride (25 g) was added, and the mixture slowly warmed to room temperature overnight. The mixture was treated with water and extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was chromatographed over silica gel. The fractions eluted with hexane–ethyl acetate (19:1) gave 6.103 g (23.3 mmol, 89.5%) of product as a viscous oil: IR (neat) 1510 cm^{-1} (C=C); UV (methanol) λ_{max} 280 nm (log ϵ 3.42) 223 (3.74) 210 (3.85); ^{1}H NMR δ 6.70 (s, 2 H, H-3 and H-6), 5.13 (t with further unresolved couplings, J_t = 7 Hz, 1 H, H-12), 3.78 and 3.75 (2 s, 3 H each, methoxyls), 3.13 (sextet, J = 7 Hz, 1 H, H-8), 2.20 (s, 3 H, aromatic methyl), 1.61 and 1.48 (2 br s, 3 H each, isopropylidene methyls), 1.18 (d, J = 7 Hz, 3 H, secondary methyl); ^{13}C NMR, Table I.

(±)-Curcuhydroquinone (6a). A solution of 173 mg (0.66 mmol) of (±)-curcuhydroquinone dimethyl ether (**6b**) in 25 mL of methylene chloride was treated with 340 mg (0.25 mL, 1.36 mmol) of boron tribromide at 0 °C. The reaction mixture was stored at room temperature during 4 h. After addition of 25 mL of a 5% sodium carbonate solution, the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was chromatographed over silica gel. The fractions eluted with hexane–ethyl acetate (9:1) gave 138 mg (0.59 mmol, 89.3%) of product as a viscous oil: IR (neat) 3370 (OH) 1515 cm^{-1} (C=C); UV (methanol) λ_{max} 294 nm (log ϵ 3.35); ^{1}H NMR δ 6.55 (s, 1 H, H-3), 6.52 (br, s, 1 H, H-6), 5.08 (t with further unresolved couplings, J_t = 7 Hz, 1 H, H-12), 4.25 (br, 2 H, hydroxyls), 2.93 (sextet, J = 7 Hz, 1 H, H-8), 2.15 (s, 3 H, aromatic methyl), 1.67 and 1.53 (2 br s, 3 H each, isopropylidene methyls), 1.17 (d, J = 7 Hz, 3 H, secondary methyl); ^{13}C NMR; Table I.

(±)-Curcuquinone (7). A solution of 262 mg (1 mmol) of (±)-curcuhydroquinone dimethyl ether (**6b**) in 10 mL of dioxane was treated with 445 mg (4 mmol) of silver(II) oxide[6] and 1.2 mL of 7 N nitric acid (6 mmol). The reaction mixture was stirred at room temperature during 10 min. After addition of a 9:1 mixture of chloroform–water, the reaction mixture was diluted with water and extracted with chloroform. The organic layer was washed with a saturated solution of sodium chloride, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was chromatographed over silica gel, and the fractions eluted with hexane–ethyl acetate (19:1) gave 162.2 mg (0.699 mmol, 70%) of product as a yellow viscous oil: IR (neat) 1655 (C=O) 1615 cm^{-1} (C=C); UV (methanol) λ_{max} 253 (log ϵ 4.04) 205 (3.84); ^{1}H NMR δ 6.57 (q, $J_{6,7}$ = 1.7 Hz, 1 H, H-6), 6.50 (s, 1 H, H-3), 5.03 (t with further unresolved couplings, J_t = 7 Hz, 1 H, H-12), 2.87 (sextet, J = 7 Hz, 1 H, H-8), 2.03 (d, $J_{5,6}$ = 1.7 Hz, 3 H, quinone methyl), 1.63 and 1.54 (2 br s, isopropylidene methyls), 1.10 (d, J = 7 Hz, 3 H, secondary methyl); ^{13}C NMR, Table I.

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