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Synthesis of Atovaquone

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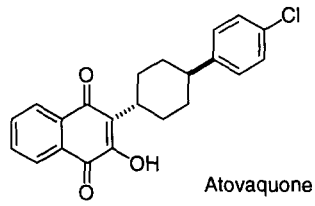
Abstract: A short synthesis of atovaquone 1 is achieved via the radical coupling of the trans-1,4-substituted cyclohexyl mono-oxalate 2 and 2-chloronapthoquinone under phase transfer conditions.

The formation of substituted quinones has received considerable attention in medicinal chemistry. Numerous studies of anthraquinones, benzoquinones, and napthoquinones have demonstrated biological potency as antibiotics, antitumor agents, vitamin E and K analogs, and radical scavengers.[1] Atovaquone **1** is approved and marketed as a prescription drug for the treatment of *Pneumocystis carinii* pneumonia (PCP), a common parasitic lung infection of immunocompromised patients.[2,3] It is not only used for the treatment of PCP, but also displays potent activity as an antimalarial agent, and has been used in the treatment of toxoplasmosis and babesiosis.[4] The mechanism of action for atovaquone involves the inhibition of mitochondrial electron transport in cytochrome complex bc, which is linked to pyrimidine biosynthesis.[5] Herein, we have described a concise route for the preparation of atovaquone, which promises generality for the construction of related napthoquinones.



Atovaquone (**1**)

As illustrated in Scheme 1,[6] our efforts utilized formation of the key intermediate *trans*-1,4-disubstituted cyclohexane **2**, beginning with commercially available 1,4-cyclohexanedione-*mono*-ethylene ketal (**3**). Halogen-metal exchange of 1-iodo-4-chlorobenzene at –60 °C provided the aryl lithium for clean nucleophilic carbonyl addition. The corresponding Grignard reagent also formed readily in THF although yields of the tertiary alcohol **4** (mp 147-149 °C) were considerably reduced (45 to 55% yields).[7] Mild acid hydrolysis in aqueous acetone afforded nearly quantitative production of the ketone **5** (mp 135-136 °C) with no evidence of competing elimination,[8] and diphosphorus tetraiodide deoxygenation[9] of the benzylic alcohol gave cyclohexanone **6**. The order of these operations can be reversed. However, the P_2I_4 reduction of ketal **4** gave lower yields (70-75%), and extended reaction times resulted in mixtures with partial conversion to ketone **6**. Borohydride reduction yielded *trans*-4-(4-chlorophenyl)-1-cyclohexanol, and acylation with excess oxalyl chloride (3 equivs) followed by an aqueous quench produced the desired oxalate acid **2**.[6]

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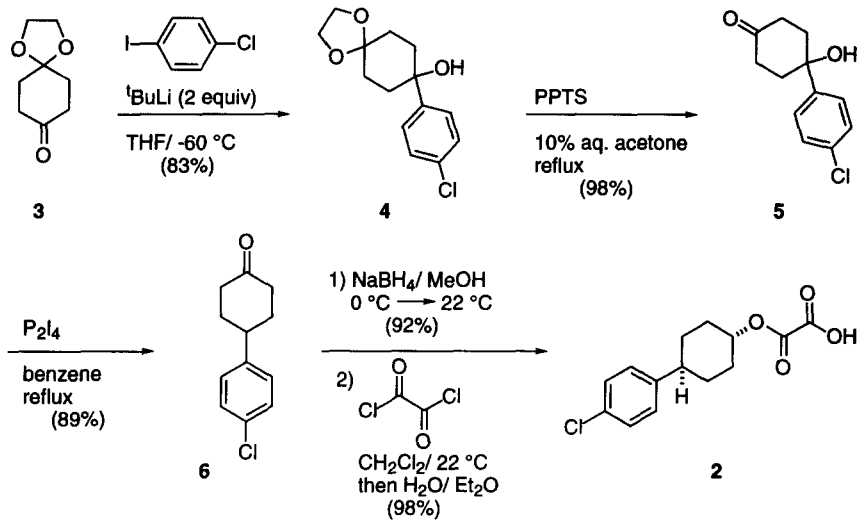
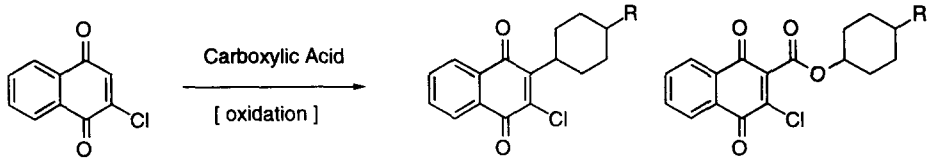
Scheme 1



In 1974 Jacobsen and coworkers[10] reported on the radical-based conjugate addition to 2-methylnapthoquinone through a Hunsdiecker decarboxylation of cyclohexane carboxylic acid using silver nitrate and peroxydisulfate. This procedure, as applied by the Glaxo-Wellcome researchers,[3] describes the coupling of 4-(4-chlorophenyl)cyclohexane-1-carboxylic acid (**13**) with **8**, resulting in low yields of quinone **9** as a mixture of diastereomers (1.3:1 ratio).[11] Minisci and coworkers[12] have recently shown that the oxidative alkylation of quinones from precursor oxalate *mono*-acids affords a preparatively useful source of cyclohexyl radicals. The initial conjugate addition intermediate undergoes further *in situ* transformation to the alkylated quinones. A rationale for this secondary oxidative process has been previously discussed.[12]

Our initial experiments for the coupling of cyclohexyl *mono*-oxalate and 2-chloronapthoquinone (see Table: entry **3**) were conducted in acetonitrile at reflux with ammonium persulfate (2.0 equivs) in the presence of a catalytic amount of silver nitrate (0.1 equiv). Capture of the intermediate acyl radical led to exclusive formation of ester **12** (84% yield). These same conditions applied to oxalate acid **2** (entry **6**) failed to provide any quinone **9** or ester **10**. The two phase solvent system of CH_2Cl_2 and aqueous CH_3CN, as previously prescribed by Minisci,[12] when applied to cyclohexyl *mono*-oxalate and 2-chloronapthoquinone (entry **2**), gave the desired **11** and **12** in approximately 93% yield as a 1.4:1 mixture, respectively. When this biphasic solvent system was utilized with oxalate acid **2** (entry **5**), the desired quinone **9** and ester **10** were formed in approximately 20% yield as a 1:3 mixture, respectively. The low yielding alkylation of starting quinone **8** from the desired carboxylic acid **2** was attributed to the poor solubility of **2** in the oxidative aqueous phase. This reduces the effective concentration of the desired cyclohexyl radical. Substantial improvement was observed by inclusion of the phase transfer catalyst, Adogen® 464.[13] This resulted in the isolation of 43% yield of **9** (1.3 to 1 ratio of *trans/cis*-isomers), and an additional 38% yield of side product **10** (entry **7**).

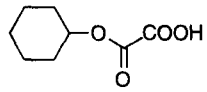
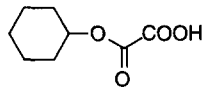
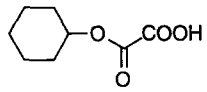
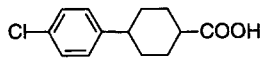
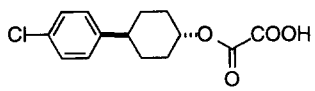
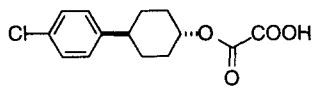
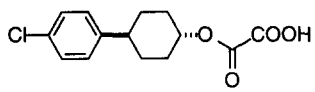


8

9 R = C_6H_4Cl
11 R = H

10 R = C_6H_4Cl
12 R = H

Table: Cyclohexyl Radical Couplings to 2-Chloronapthoquinone

Entry	Carboxylic Acid	Oxidant	Conditions	Yield[a] (9/11)	Yield[a] (10/12)
1		$Na_2S_2O_8$	CH_2Cl_2 / CH_3CN / H_2O (1:1:2), reflux	28%[b]	36%
2		$(NH_4)_2S_2O_8$	CH_2Cl_2 / CH_3CN / H_2O (1:1:2), reflux	55%	38%
3		$(NH_4)_2S_2O_8$	CH_3CN, reflux	0%	84%
4		$(NH_4)_2S_2O_8$	CH_2Cl_2 / CH_3CN / H_2O (1:1:2), reflux	14%	–
5		$(NH_4)_2S_2O_8$	CH_2Cl_2 / CH_3CN / H_2O (1:1:2), reflux	5%[b]	15%
6		$(NH_4)_2S_2O_8$	CH_3CN, reflux	0%[b]	0%
7		$(NH_4)_2S_2O_8$	CH_2Cl_2 / CH_3CN / H_2O (1:1:2), reflux Adogen® 464	43%	38%

a) Yields of purified products were determined following flash silica chromatography using EtOAc/ hexanes.
b) Quantities of the starting 2-chloronapthoquinone were recovered unaltered in several cases: entry **1** (16%); entry **5** (60%); entry **6** (95%).

Finally, the conversion to atovaquone was effected upon treatment of **9** with potassium hydroxide in methanol at reflux (94%), and subsequent recrystallization from hot acetonitrile selectively provided *trans*-**1** as described in the patent procedure.[3] Our synthetic atovaquone proved to be identical in all spectral comparisons to a sample kindly provided by the Glaxo-Wellcome laboratories.[14]

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2. (a) Cirioni, O.; Giancometti, A.; Balducci, M.; Burzacchini, F.; Scalise, G. *J. Antimicrob. Chemother.* **1995**, *36*, 740. (b) Comley, J. C. W.; Yeates, C. L.; Frend, T. J. *Antimicrob. Agents Chemother.* **1995**, *39*, 2217.
3. Atovaquone is a prescription pharmaceutical manufactured by Glaxo-Wellcome under the trade name Mepron®. Hudson, A. T.; Yeates, C. L. E.P. Patent 445141, **1996**. Hudson, A. T.; E.P. Patent 634996 A1, **1996**.
4. (a) Antimalarial agent: Looareesuwan, S.; Viravan, C.; Webster, H.; Kyle, D. E.; Hutchinson, D. B.; Canfield, C. J. *Am. J. Trop. Med. Hyg.* **1996**, *54*, 62. (b) Toxoplasmosis: Araujo, F. G.; Suzuki, Y.; Remington, J. S. *Eur. J. Clin. Microbiol. Infect.* **1996**, *15*, 394. (c) Babesiosis: Hughes, W. T.; Oz, H. S. *J. Infect. Dis.* **1995**, *172*, 1042.
5. Hammond, D. J.; Burchell, J.R.; Pudney. M. *Mol. Biochem. Parasitol.* **1985**, *14*, 97.
6. All yields are reported for purified samples, characterized by infrared, ^{1}H NMR, ^{13}C NMR and high resolution mass spectral data. NMR data for characterization of **2** as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (dd, J = 8.4, 2.0 Hz, 2H), 7.14 (dd, J = 8.4, 2.0 Hz, 2H), 4.97 (dddd, J = 10.8, 10.8, 4.4, 4.4 Hz, 1H), 2.55 (dddd, J = 11.6, 11.6, 3.2, 3.2 Hz, 1H), 2.20 (m, 2H), 1.99 (m, 2H), 1.70 (dddd, J = 12.8, 3.2, 3.2, 3.2 Hz, 2H), 1.58 (dddd, J = 13.2, 3.2, 3.2, 3.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 157.7, 144.0, 131.9, 128.6, 128.1, 77.3, 42.4, 31.9, 31.4.
7. For related studies: Cory, R. M.; Walker, J. R.; Zabel, P. D. *Synth. Commun.* **1994**, *24*, 799.
8. Stronger acids and/or higher reaction temperatures will contribute to the elimination (TsOH; toluene at reflux).
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10. Jacobsen, N.; Goldman, J.; Torssell, K. *Acta Chemica Scandinavica* **1974**, *B28*, 492.
11. Our efforts for coupling of 4-(4-chlorophenyl)cyclohexane-1-carboxylic acid (**13**) and **8** gave yields of **9** ranging from 10 to 14%. Reference 3 describes the oxidation of **13** to yield 7% of **9**.
12. Minisci, F.; Lazzarini, E.; Fontana, F.; Coppa, F. *Chem. Lett.* **1992**, 1299.
13. Adogen® 464 is a methyltrialkyl(C_8–C_{10}) ammonium chloride (Aldrich). One drop of phase-transfer catalyst was used per 5 mL of solution.
14. We gratefully acknowledge the assistance of Dr. Martin Osterhout (Glaxo-Wellcome) in obtaining a sample of atovaquone as well as NMR spectra for our comparisons.