Novel Bioactive Cubé Insecticide Constituents: Isolation and Preparation of 13-*homo*-13-Oxa-6a,12a-dehydrorotenoids

Nianbai Fang and John E. Casida*

Environmental Chemistry and Toxicology Laboratory, Department of Environmental Science, Policy, and Management, University of California, Berkeley, California 94720-3112

Received August 19, 1996[⊗]

Two novel rotenoid-like compounds isolated from cubé resin, used as an insecticide and piscicide, have an unprecedented skeleton consisting of a 1,5-benzodioxepin (A and B rings) and a chromone (C and D rings). Their structures are assigned as (−)-13-*homo*-13-oxa-6a,12a-dehydrorotenone (**5**) and 13-*homo*-13-oxa-6a,12a-dehydrodeguelin (**6**) based on ^{1}H and ^{13}C NMR, MS, UV, and optical rotation. X-ray structure determination confirmed the assignment of **5** and revealed that the 1-methylethenyl group is disordered into two sets of atoms. Compound **5** from cubé resin was identical with a product previously reported as being formed by reaction of rotenone (**1**) with acetyl chloride and DMF and misassigned as "6a,12a-epoxyrotenone" (**7**). A modified procedure was developed for preparation of the new oxarotenoid component of the commercial insecticide. The cubé resin from which **5** and **6** were isolated in equal amounts contains **1** and deguelin (**2**) in a >10:1 ratio; this large difference in ratio indicates that **5** and **6** are not artifacts formed from **1** and **2**, respectively. Rotenoid **5** acts as a respiratory inhibitor with 50% inhibition of NADH:ubiquinone oxidoreductase activity at 0.11 μM, of goldfish survival at 1 ppm, and of the viability of three cell lines at 4–8 μM.

Introduction

Rotenone (**1**) from the roots of cubé (*Lonchocarpus utilis* and *urucu*) or derris (*Derris elliptica*) or from other *Leguminosae* has been an important piscicide for centuries and insecticide for at least 150 years.[1,2] The ground roots or their extracts contain not only **1** but also deguelin (**2**) and numerous *cis*-chromanochromanones, chromanochromones, and related compounds.[2] Their biological activity is generally attributable to inhibition of NADH:ubiquinone oxidoreductase activity and thereby mitochondrial respiration.[3] There is renewed interest in the composition and biological activity of rotenoid-containing plants not only as agrochemicals but also as potential carcinogenesis inhibitors.[4]

The present study examines the composition and toxicology of cubé resin, which is the most commonly-used form of this botanical piscicide and insecticide. Chromatographic separation of cubé resin led to the discovery of two compounds (**5** and **6**) related to rotenoids **1** and **2** and their dehydro derivatives (**3** and **4**) with the same A, D, and E rings but an unexpected B/C ring system (Figure 1). Compound **5** is identical with a substance previously prepared by reaction of **1** with acetyl chloride in DMF and misassigned formula **7** (6a,12a-epoxyrotenone).[5] We report below the isolation, structure elucidation, preparation, and bioactivity of **5** as a novel constituent, along with **6**, of cubé insecticide.

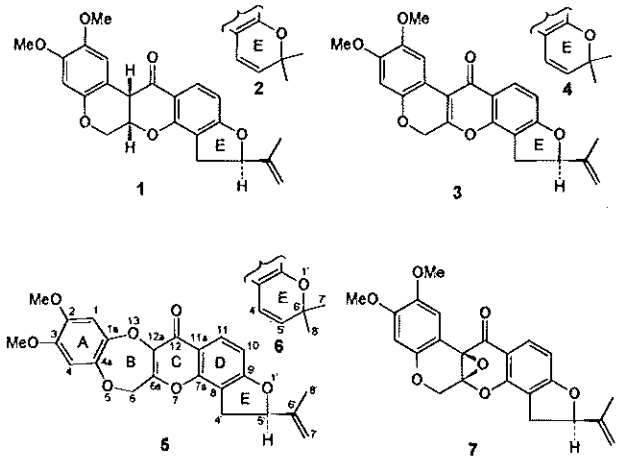


Figure 1. Structures of four known rotenoids (**1**–**4**), two new 13-*homo*-13-oxa-6a,12a-dehydrorotenoids (**5** and **6**), and a compound originally reported as structure **7** but reassigned here as **5**.

Results and Discussion

Cubé Resin Fractionation and Rotenoid Isolation. Fractionation by extraction of the resin with cold methanol and chromatography of the soluble portion on silica gel with hexane:EtOAc:MeOH revealed a large number of compounds including four known rotenoids (**1**–**4**) and two unusual compounds (**5** and **6**). The known rotenoids were identified as **1**, **2**, 6a,12a-dehydrorotenone (**3**), and 6a,12a-dehydrodeguelin (**4**).

Identification of 5. The EI-MS data established a molecular ion at *m/z* 408 as the base peak in accord with a $C_{23}H_{20}O_7$ formula, which is one more oxygen and two less hydrogens than that of **1**. The structure was assigned by comparison of ^{1}H and ^{13}C NMR data for **5** (Tables 1 and 2, respectively) with those for **1** and **3** (refs 6 and 7, respectively). The ^{1}H NMR spectrum of **5** shows characteristic signals assignable to the 1-(methylethenyl)-dihydrofuran ring for protons 4′, 5′, 7′, and 8′ plus signals

* To whom correspondence should be addressed. Tele.: (510) 642-5424. FAX: (510) 642-6497. E-mail: ectl@nature.berkeley.edu.

[⊗] Abstract published in *Advance ACS Abstracts*, January 1, 1997.

(1) Negherbon, W. O. *Handbook of Toxicology. Volume III: Insecticides;* W. B. Saunders Co.: Philadelphia, PA, 1959; p 661.
(2) Fukami, H.; Nakajima, M. In *Naturally Occurring Insecticides;* Jacobson, M., Crosby, D. G., Eds.: Dekker, New York, 1971; p 71.
(3) Hollingworth, R. M.; Ahammadsahib, K. I. *Rev. Pestic. Toxicol.* **1995**, *3*, 277.
(4) Pezzuto, J. M. *Recent Adv. Phytochem.* **1995**, *29*, 19.
(5) Kostova, I.; Ognyanov, I. *F.E.C.S. Int. Conf. Chem. Biotechnol. Biol. Act. Nat. Prod., [Proc.] 3rd;* VCH: Weinheim, 1985 (Pub. 1987); Vol. 4, p 350.

S0022-3263(96)01604-0 CCC: $14.00

Table 1. ^{1}H (300 MHz) Data (δ) in $CDCl_3$ for 5 and 6

proton	5	6
1	6.93 s (1H)	6.94 s (1H)
4	6.63 s (1H)	6.64 s (1H)
6	5.08 s (2H)	5.11 s (2H)
10	6.88 d (J = 8.6 Hz, 1H)	6.84 d (J = 9.8 Hz, 1H)
11	8.12 d (J = 8.6 Hz, 1H)	8.04 d (J = 9.8 Hz, 1H)
4′	3.49 dd (J = 9.9, 15.8 Hz, 1H)	6.72 d (J = 10.1 Hz, 1H)
	3.15 dd (J = 7.9, 15.8 Hz, 1H)	
5′	5.39 dd (J = 7.9, 9.9 Hz, 1H)	5.71 d (J = 10.1 Hz, 1H)
7′	5.12 s (1H)	1.48 s (3H)
	4.97 s (1H)	
8′	1.79 s (3H)	1.48 s (3H)
2-OMe	3.84 s (3H)	3.85 s (3H)
3-OMe	3.84 s (3H)	3.85 s (3H)

Table 2. ^{13}C (75 MHz) NMR Data (δ) in $CDCl_3$ for 5 and 6

carbon	5	6
1	117.9	117.4
1a	150.3	150.4
2	145.4	145.5
3	145.8	145.8
4	104.7	104.7
4a	142.0	142.0
6	69.5	69.5
6a	142.4	142.4
7a	152.1	150.8
8	112.6	108.8
9	165.0	157.4
10	108.5	114.5
11	127.9	126.4
11a	105.4	105.4
12	171.7	171.7
12a	140.5	140.5
4′	31.4	115.1
5′	87.8	130.3
6′	142.7	77.8
7′	112.9	28.1
8′	17.0	28.1
2-OMe	56.3	56.3
3-OMe	56.3	56.3

for four aromatic protons, two methoxyl groups, and two methene protons. This pattern is similar to those of **1** and **3**, suggesting that **5** may be a rotenone derivative. The absence of signals for methine protons at positions 6a and 12a and no additional proton signals in the spectrum of **5** in comparison with that of **1** suggested either a double bond or an epoxy substituent at 6a,12a. In 6a,12a-dehydrorotenoids, H-1 is approximately coplanar with the 12-carbonyl group and strongly deshielded[8] and in **3** the chemical shift of the signal for H-1 appears at δ 8.45.[6] The chemical shift of H-1 of **5** at δ 6.93 ruled out the possibility that it is a 6a,12a-dehydrorotenoid. Comparison of the ^{13}C NMR spectra of **1**, **3**, and **5** indicated that **5** has a double bond between C-6a (δ 142.4) and C-12a (δ 140.5), an interpretation supported by the signal for C-12 at δ 171.7.[9] Moreover, the signals from **5** for 12a and 1a (δ 150.3) at significantly lower field than the corresponding signals of **3** indicated that C-12a and C-1a may be connected by a bridge oxygen. With an oxygen between C-12a and C-1a, H-1 is not coplanar with the 12-carbonyl group as in **3**, and its chemical shift appears at δ 6.93. The UV spectrum of **5** consists of an absorption maximum at 300 nm for the C- and D-rings chromone system and another at 256 nm for the A-ring with four oxygen atoms. These results led to the proposed structure 13-*homo*-13-oxa-6a,12a-dehydrorotenone for **5**.

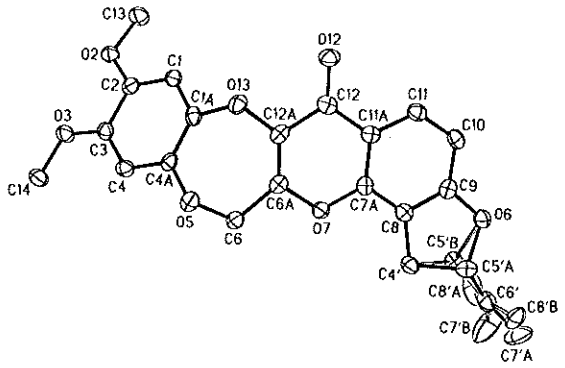


Figure 2. Computer-generated perspective drawing of compound **5**. Hydrogens are omitted for clarity. The molecules displayed statistical disorder in the 1-methylethenyl group, which appears to arise from free rotation about the C5′A–C6′ bond, and it is evidently indifferent during crystallization whether it points one way or another. We view it as one molecule with disorder in the rotational conformation of this group. One set of atoms is (C7′AC8′A), and the other is (C7′BC8′B).

The crystal structure of **5** was determined by X-ray diffraction, thereby confirming the assignment, providing background for relating the three-dimensional structure to the biological activity and establishing that the 1-methylethenyl group is disordered into two sets of atoms (Figure 2). The molecules consist of the chromone (C and D rings) and benzene (A ring) conjugation systems separated by a dioxepin (B ring). The absolute configuration at 5′ follows from the same optical rotation for **5** in comparison with **3** as a standard, i.e., $[\alpha]^{25}_D$ −38.1 ($CHCl_3$, c = 1.33) in each case. Thus, compound **5** was identified as (−)-[5′*R*-(5′α)]-4′,5′-dihydro-2,3-dimethoxy-5′-(1-methylethenyl)[1,5]benzodioxepin[3,4-*b*]furo[2,3-*h*]-[1]benzopyran-12-one.

Preparation of 5. The ^{1}H NMR and EI-MS data for **5** are the same as those reported by Kostova and Ognyanov for a compound misassigned structure **7** (6a,12a-epoxyrotenone) prepared by reaction of **1** with acetyl chloride.[5] The structures of the 8′-hydroxy and 8′-acetoxy derivatives, originally designated by them as analogs of **7**,[5,10] require reassignment as the corresponding derivatives of **5**. The chemical conversion of **1** to **5** further established the absolute configuration of 5′ as *R* in **5** as it is in **1**. Importantly, their procedure provides a means of converting **1** to **5**. On examining variables,

(6) ^{1}H NMR data in $CDCl_3$ (δ, 300 MHz). J values are given in Hz. Compound **1**: 7.84 (1H, d, J = 8.5, H-11), 6.77 (1H, s, H-1), 6.51 (1H, d, J = 8.5, H-10), 6.45 (1H, s, H-4), 5.24 (1H, dd, J = 8.1,9.8, H-5′), 5.07 (1H, s, H-7′), 4.94 (1H, s, H-7′), 4.94 (1H, m, H-6a), 4.62 (1H, dd, J = 3.0,12.0, H-6), 4.18 (1H, d, J = 12.0, H-6), 3.84 (1H, d, J = 4.0, H-12a), 3.81 (3H, s, 2-OMe), 3.77 (3H, s, 3-OMe), 3.32 (1H, dd, J = 9.8,15.7, H-4′), 2.95 (1H, dd, J = 8.1,15.7, H-4′), 1.77 (3H, s, H-8′). Compound **3**: 8.45 (1H, s, H-1), 8.13 (1H, d, J = 8.6, H-11), 6.93 (1H, d, J = 8.6, H-10), 6.55 (1H, s, H-4), 5.41 (1H, dd, J = 7.9,9.8, H-5′), 5.14 (1H, s, H-7′), 5.00 (2H, s, H-6), 4.98 (1H, s, H-7′), 3.96 (3H, s, 2-OMe), 3.87 (3H, s, 3-OMe), 3.53 (1H, dd, J = 9.8,15.8, H-4′), 3.19 (1H, dd, J = 7.9,15.8, H-4′), 1.81 (3H, s, H-8′).

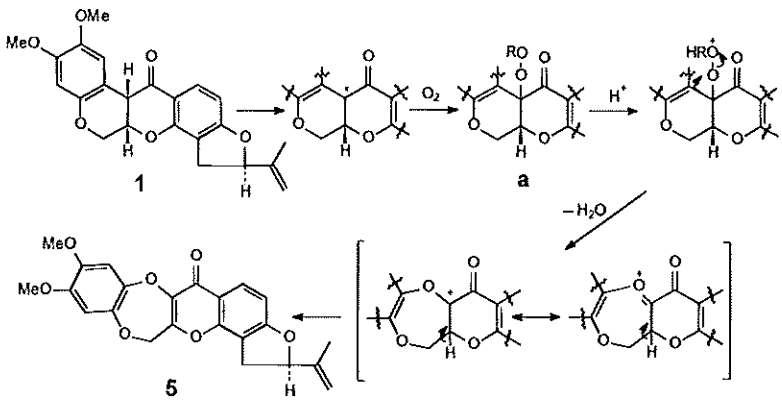
(7) ^{13}C NMR data in $CDCl_3$ (δ, 75 MHz). Compound **1**: 188.7 (C-12), 167.2 (C-9), 157.8 (C-7a), 149.4 (C-3), 147.3 (C-4a), 143.8 (C-2), 142.9 (C-6′), 129.8 (C-11), 113.2 (C-11a), 112.8 (C-8), 112.3 (C-7′), 110.5 (C-1), 104.8 (C-1a), 104.7 (C-10), 100.9 (C-4), 87.7 (C-5′), 72.2 (C-6a), 66.1 (C-6), 56.2 (2-OMe), 55.7 (3-OMe), 44.5 (C-12a), 31.2 (C-4′), 17.0 (C-8′). Compound **3**: 174.1 (C-12), 164.7 (C-9), 155.9 (C-7a), 152.1 (C-6a), 148.3 (C-3), 146.1 (C-4a), 143.9 (C-2), 142.7 (C-6′), 127.7 (C-11), 118.8 (C-1a), 112.9 (C-12a), 112.8 (C-7′), 111.5 (C-11a), 110.5 (C-8), 110.0 (C-10), 108.5 (C-1), 100.3 (C-4), 87.8 (C-5′), 64.7 (C-6), 56.2 (2-OMe), 55.8 (3-OMe), 31.4 (C-4′), 17.0 (C-8′).

(8) Crombie, L.; Lown, J. W. *J. Chem. Soc.* **1962**, 775.

(9) Crombie, L.; Kilbee, G. W.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1497.

(10) Kostova, I.; Mollova, N.; Ognyanov, I. *Izv. Khim.* **1988**, *21*, 236.

Scheme 1



the reaction requires acetyl chloride, and yields are enhanced with oxygen consistent with autoxidation. Our preferred procedure changed their method (60 °C, 1 h, air)[5] to a more oxidative condition (60 °C, 8 h, continuous bubbling of O_2) with 3-fold higher yield. Under these conditions compound **5** was not produced from **3** or 12a-hydroxyrotenone (rotenolone), giving mostly rotenolone acetate in the latter case, ruling out these compounds as intermediates.

Speculation for the mechanism of formation of **5** in the reaction between **1** and acetyl chloride in DMF is shown in Scheme 1. The process has some analogy to the well-known autoxidation of cumene to phenol. The first step is proposed to be autoxidation of the benzylic 12a position, which is also facilitated by the adjacent carbonyl group. 12a-Hydroperoxide **a** (or its acetate; R = H or acetyl) then eliminates with rearrangement under the acidic conditions.

Identification of 6. The NMR spectral data for **5** and **6** (Tables 1 and 2) indicate that they bear the same structural relationship as **1** and **2**;[11] i.e., **6** is the dimethylpyran analog of **5**. The EI-MS data established a $C_{23}H_{20}O_7$ formula with the major fragmentation pathway involving cleavage to the *m/z* 191 and 187 fragment ions characteristic of the D/E rings of **2**[11,12] plus fragments at *m/z* 206 and 178 from the A/B rings. The *m/z* 206 and 178 fragment ions observed with both **5** and **6** are useful in characterizing the 13-*homo*-13-oxadehydrorotenoids. Therefore, the structure of the new compound is 2,3-dimethoxy-6′,6′-dimethyl[1,5]benzodioxepin[3,4-*b*]pyran-[2,3-*h*][1]benzopyran-12-one (**6**).

Rotenoids 5 and 6 Are Probably Natural Products. Compounds **5** and **6** are described here for the first time from cubé resin produced as a plant extract. There is some indication that **5** and **6** are natural products rather than formed as artifacts from **1** and **2**, respectively, on extraction and processing of cubé resin. Thus, the ratio of **1**:**2** is >10, whereas that of **5**:**6** is 1.0, favoring the proposal that **5** and **6** are present in the plant at the time of extraction.

Bioactivity. 13-*homo*-13-Oxadehydrorotenone (**5**) is a biologically-active compound. Rotenone (**1**) is a classical inhibitor of mitochondrial respiration,[3] and **5** appears to act at the same target inhibiting NADH: ubiquinone oxidoreductase activity by 50% at 0.11 μM. It gives 50% mortality of goldfish at 1 ppm and is toxic to three cell lines with 50% inhibition of viability at 4−8 μM.

(11) Luyengi, L.; Lee, I.-S.; Mar, W.; Fong, H. H. S.; Pezzuto, J. M.; Kinghorn, A. D. *Phytochemistry* **1994**, *36*, 1523.
(12) Ollis, W. D.; Rhodes, C. A.; Sutherland, I. O. *Tetrahedron* **1967**, *23*, 4741.

Experimental Section

Material. Cubé resin (Shipping Reference 14873, Lot Number 3526−158) extracted from *Lonchocarpus utilis* and *urucu*[1] and containing 46.4% **1** was provided by Don Maciver of AgrEvo Environmental Health (Montvale, NJ). The roots from Peru (the Apurimac River Valley in the Ayacucho or Jeveros Northern rain forest regions) were extracted in France (SARPAP company of Bergerac) to obtain the original "brittle" sold for crop protection in the United States.

Isolation. The first step in fractionation of the resin was to remove most of the **1** from other components. The resin (650 g) was dissolved in MeOH (3000 mL) at 60 °C by stirring for 6 h and the solution was allowed to stand at 0 °C for 5 h for precipitation of **1**, and this process was repeated two more times. The final precipitate (246 g after drying under vacuum) was >95% **1** based on comparison with standard **1** by HPLC (see below). The combined filtrates were concentrated under reduced pressure and chromatographed on a silica gel column (200−425 mesh) packed in 95% hexane with 5% of a mixture of EtOAc:MeOH (3:1). Compounds were eluted with the same solvent gradually increasing to 100% EtOAc:MeOH (3:1); 20 fractions were collected. Precipitates in the concentrated 6−12th fractions (10 mL each) consisted mostly of **1** and **2**, and the filtrates had more than six additional compounds evident by TLC with two solvent systems [precoated silica on plastic sheets with fluorescent indicator; hexane:EtOAc (6:3) and toluene:acetone (9:1)]. Supernatants of the 6−12th fractions were combined and subjected to HPLC on a semi-preparative silica gel column (Econosil silica 10 μm, 10 mm × 25 cm, Alltech, Deerfield, IL) developed with a linear gradient from 16 to 38% EtOAc in hexane at a flow rate of 4 mL/min over a period of 50 min, monitoring the eluant at 300 nm. The HPLC-isolated compounds and yields were **1** (2600 mg), **2** (1200 mg), **3** (6430 mg), **4** (6200 mg), **5** (106 mg), and **6** (102 mg).

Known Compounds 1−4. Identifications involved direct comparisons of their EI-MS and ^{1}H NMR spectral data with those of authentic standards.

13-*homo*-13-Oxa-6a,12a-dehydrorotenone (5): mp 159−160 °C for crystals from hexane and EtOAc; $[\alpha]^{25}_D$ −38.1 ($CHCl_3$, c = 1.33); UV (MeOH) λ_{max} 256, 300; EI-MS (rel int) 408 $[M]^+$ (100), 393 $[M - 15]^+$ (7), 365 $[M - 43]^+$ (25), 206 (12), 191 (21), 187 (29), and 178 (19). X-ray crystal data: compound **5** crystallizes in the triclinic system, space group $P\bar{1}$, a = 6.8478(10) Å, b = 8.321(2) Å, c = 17.264(2) Å, α = 84.292(13)°, β = 81.178(11)°, γ = 84.204(14)°, V = 963.6(3) Å^3, Z = 2, D_c = 1.408 Mg·m^{-3}, empirical formula $C_{23}H_{20}O_7$, formula weight 408.39, and $F(000)$ = 428 electrons. The atomic coordinates and equivalent isotropic displacement parameters, all bond lengths and angles, anisotropic displacement parameters, and hydrogen coordinates and isotropic displacement

parameters have been deposited with the Cambridge Crystallographic Data Centre.[13]

13-*homo*-13-Oxa-6a,12a-dehydrodeguelin (6): mp 216–217 °C for crystals from CH_2Cl_2 and acetone; UV (MeOH) λ_{max} 264, 295sh, 322; EI-MS (rel int) 408 $[M]^+$ (100), 393 $[M - 15]^+$ (17), 365 $[M - 43]^+$ (12), 206 (6), 191 (6), 187 (36), and 178 (3).

Preparation of 13-*homo*-13-Oxa-6a,12a-dehydrorotenone (5). Acetyl chloride (39.3 g, 500 mmol) in DMF (39.3 mL) was added dropwise to a solution of **1** (19.7 g, 50 mmol) in DMF (197 mL) at 40 °C with constant bubbling of O_2. The mixture was heated at 60 °C for 8 h and then held at room temperature for 16 h, again with O_2 bubbling. The products in solution, after filtering off crystalline material (4.4 g), were recovered by addition of water and extraction with CH_2Cl_2. The crystals were identified as rotenonone[15] by ^1H and ^{13}C NMR and FAB-MS. The two major components of the soluble fraction were isolated by chromatography on silica gel with hexane–EtOAc as above, and 20 fractions (300 mL) were collected and concentrated to 10 mL. Unreacted **1** was crystallized (5.6 g) from the 4–9th fractions and the compound identified as **5** was obtained crystalline (1.8 g, 9%) from the 11–15th fractions. Semisynthetic **5** was identical to the cubé resin **5** in ^1H and ^{13}C NMR, MS, HPLC, and TLC in two solvent systems described above.

The conditions for optimal reaction were examined as above with **1** but on a small scale by comparing air, oxygen, and nitrogen and the presence or absence of acetyl chloride. Other studies compared **1** with **3** and 12a-hydroxyrotenone under the optimized condition.

Assays for inhibition of NADH: Ubiquinone Oxidoreductase Activity and Toxicity to Goldfish and Cultured Cell Lines. The assay procedures involved beef heart mitochondrial electron transport particles for NADH:ubiquinone oxidoreductase activity,[16] goldfish with 24 h exposure in water for piscicidal activity, and three cultured cell lines (NB41A3, MCF7 and Hepa 1C1C7) treated for 3 days prior to determining their viability based on a published procedure.[17]

Acknowledgment. We thank our laboratory colleagues Craig Rowlands, Gary Quistad, and Phillip Jefferies for assistance, Marilyn Olmstead and Dan Nurco (University of California at Davis) for the X-ray crystal structure analysis, Paul Brennan (University of California at Berkeley) for optical rotation measurements, and Thomas Singer (University of California at San Francisco) for supplying the electron transport particles. The project described was supported by Grant P01 ES00049 from the National Institute of Environmental Health Science, NIH.

Supporting Information Available: Copies of proton and carbon NMR spectra of **5** and **6** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO961604H

(13) The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK. The colorless crystal (0.68 × 0.25 × 0.20 mm) selected for data collection was mounted and transferred to a Syntex $P2_1$ diffractometer equipped with a graphite monochromator utilizing Cu Kα radiation from a normal-focus sealed tube where it was maintained in the 130 K cold stream using a locally-modified LT-1 low-temperature apparatus. 3861 Reflections ($-7 \le h \le 7$, $-8 \le k \le 9$, $0 \le l \le 18$) were collected using the $2\theta - \omega$ scan type, 2603 independent reflections, $R_{int} = 0.0165$. Less than 0.5% decay in the intensities of two standard reflections was observed during the data collection. The structure was solved by direct methods (SHELXTL v. 5.03) in the space group $P\bar{1}$ and refined by full-matrix (based on F^2) least-squares methods. The 1-methylethenyl group is statistically disordered into two sets of atoms. These two sets refined to relative occupancies of 0.5:0.5 with a common anisotropic thermal parameter of 0.062 Å^2. The occupancies were fixed in the final cycle of refinement. An empirical absorption correction (XABS2)[14] was applied: maximum and minumum transmission 0.86 and 0.79. Hydrogen atoms were added geometrically and refined using a riding model and isotropic Us tied to those of the bonded atoms. In the final cycles of refinement all non-hydrogen atoms were refined with isotropic thermal parameters. Residual density in the final difference map was less than 0.30 e Å^{-3}. Final R indices are $wR_2 = 0.0713$ (all 2597 data) and $R_1 = 0.0682$ (calculated based on 2522 observed ($> 2s(I)$) data).

(14) Parkin, S.; Moezzi, B.; Hope, H. *J. Appl. Crystallogr.* **1995**, *28*, 53.

(15) Carlson, D. G.; Weisleder, D.; Tallent, W. H. *Tetrahedron* **1973**, *29*, 2731.

(16) Wood, E.; Latli, B.; Casida, J. E. *Pestic Biochem. Physiol* **1996**, *54*, 135.

(17) Cohen, E.; Quistad, G. B.; Casida, J. E. *Life Sci.* **1996**, *58*, 1075.