

Table I. Atomic Coordinates ( $\times 10^4$ ) for the Phenyl Ether of 6,14-*exo*-Ethenotetrahydrothebaine

atom	X/A( $\sigma$ )	Y/B( $\sigma$ )	Z/C( $\sigma$ )
C(1)	96 (2)	6129 (1)	4861 (1)
C(2)	-963 (2)	5546 (1)	3978 (1)
C(3)	-1662 (1)	4634 (1)	4211 (1)
C(4)	-1248 (1)	4321 (1)	5329 (1)
C(5)	708 (1)	3335 (1)	7610 (1)
C(6)	2463 (2)	3126 (1)	8552 (1)
C(7)	3865 (2)	3562 (1)	8114 (1)
C(8)	3567 (1)	4732 (2)	7938 (1)
C(9)	1667 (2)	6256 (1)	8071 (1)
C(10)	1578 (2)	6555 (1)	6880 (1)
C(11)	520 (2)	5824 (1)	5978 (1)
C(12)	-105 (1)	4872 (1)	6220 (1)
C(13)	321 (2)	4515 (-)	7439 (1)
C(14)	1973 (1)	5088 (1)	8222 (1)
C(15)	-1200 (2)	4838 (1)	7810 (1)
C(16)	-1432 (2)	6010 (2)	7762 (1)
C(17)	2309 (2)	4736 (2)	9410 (1)
C(18)	2560 (2)	3734 (2)	9582 (1)
C(19)	5693 (2)	3299 (2)	8911 (1)
C(20)	6476 (2)	2323 (2)	8683 (2)
C(21)	-99 (3)	7661 (2)	8364 (2)
C(22)	-3412 (4)	4360 (3)	2305 (2)
C(23)	1661 (3)	1499 (2)	9171 (2)
C(24)	-3736 (1)	3375 (1)	5320 (1)
C(25)	-4408 (2)	2406 (1)	5385 (2)
C(26)	-6153 (2)	2306 (2)	5216 (2)
C(27)	-7226 (2)	3155 (2)	4969 (2)
C(28)	-6550 (2)	4116 (2)	4921 (2)
C(29)	-4794 (2)	4233 (2)	5099 (2)
N(1)	178 (2)	6541 (1)	8388 (1)
O(3)	-2758 (2)	3995 (1)	3428 (1)
O(4)	-1970 (1)	3410 (1)	5538 (1)
O(6)	2780 (1)	2044 (1)	8731 (1)
O(19)	6474 (2)	3864 (2)	9671 (1)

(Woelm, activity grade 1) and excess benzene into a 50-mL buret. To the column was introduced a solution of 0.5 g (1.3 mmol) of crude **4b** and 1.22 mL (1.04 g, 15 mmol, 11.5 equiv) of **2** (dried over molecular sieves) in 10 mL of dry benzene. While the solution was being adsorbed into the alumina, the column became quite hot, especially toward the lower end where there was no coloration. The material was allowed to stand for 40.5 h, the adsorbent washed off with MeOH, and the material concentrated under reduced pressure. The dark red, gummy residue was taken up in  $\text{CHCl}_3$ , filtered, and again concentrated to give 1.45 g of dark reddish brown resin.

This crude product was worked up and then chromatographed as in procedure A to give 0.47 g (80%) of **6b**.

**Crystal Data.** A single crystal of dimensions  $0.4 \times 0.4 \times 0.6$  mm crystallized from acetone was used in the analysis. The crystals were determined to be in the monoclinic space group  $P2_1$  with cell dimensions of  $a = 8.236$  (2) Å,  $b = 12.950$  (1) Å,  $c = 12.745$  (3) Å, and  $\beta = 110.25$  (3)°. Intensities of 2729 independent reflections were measured, of which 2597 had intensities greater than twice their standard deviation ( $\sigma_F$ ). Monitoring of four standard reflections revealed no significant decay of the crystal over the course of intensity collection. Lorentz and polarization corrections were applied to the integrated intensities. Structure determination was achieved through use of the direct-methods program MULTAN.<sup>10</sup>

Hydrogen atoms were introduced at geometrically expected positions. In the final cycles of full-matrix least-squares refinement, positional parameters for all the atoms, anisotropic thermal vibration parameters for the nonhydrogen atoms, and isotropic thermal parameters for the hydrogen atoms were varied.

The quantities  $(1/\sigma_F^2)$ , where  $\sigma_F$  was as defined by Stout and Jensen<sup>11</sup> but with an instrumental instability factor of 0.06, were used to weight the least-squares differences for the observed data;

(10) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. A* 1971, 27, 368.

(11) Stout, G. H.; Jensen, L. H. "X-Ray Structure Determination"; Macmillan: New York, 1968, p 457, eq H14.

differences for data determined to be unobserved  $2\sigma_F$  were given zero weight. The refinement converged to a residual ( $R = \sum |F_o| - |F_c| / \sum |F_o|$ ) of 0.039 for the observed data and 0.042 for all data. Positional parameters are given in Table I.

**Acknowledgment.** This work was supported by a joint development program with Miles Laboratories, Inc., Elkhart, IN. X-ray work was supported by NIH Grant No. RR05716.

**Registry No.** **2**, 78-94-4; **4a**, 63944-52-5; **4b**, 87101-22-2; **6b**, 87101-23-3; bromobenzene, 108-86-1.

### Solvent Dependence of the Conformation and Chiroptical Properties of *trans*-9,10-Dihydroxy-9,10-dihydrophenanthrene and Its Monoglucuronides

Diane I. Cobb, Deborah A. Lewis, and  
Richard N. Armstrong\*

Department of Chemistry, University of Maryland,  
College Park, Maryland 20742

Received April 4, 1983

Vicinal *trans*-dihydro diols are important intermediates in the metabolism of polycyclic aromatic hydrocarbons. Stereoselective enzymatic formation of *trans*-dihydro diols from arene oxides can often influence their subsequent metabolism and biological activity.<sup>1</sup> Hence, considerable interest exists in determining the absolute configurations and preferred solution conformations of these metabolites. Chiroptical techniques often employed to deduce absolute configurations of *trans*-dihydro diols or their derivatives can be extremely sensitive to shifts in conformer populations influenced by stereoelectronic<sup>2,3</sup> and, as demonstrated here, solvent effects. In addition, the previously reported<sup>4</sup> solution conformations (solvent not specified) of *trans*-9,10-dihydroxy-9,10-dihydrophenanthrene (**1**) and the diacetate (**2**) deduced from the chiroptical properties of the 9*S*, 10*S* antipodes (**1b** and **2b**) have been shown inconsistent with both the predicted ORD spectra as well as <sup>1</sup>H NMR data from a series of closely related 9,10-disubstituted-9,10-dihydrophenanthrenes,<sup>2a</sup> raising at least some doubt about the original assignment of absolute configuration.<sup>4</sup> Moreover, although the dramatic solvent dependence of the CD spectrum of **1b**<sup>5</sup> is most reasonably attributed to a shift in conformer populations, additional experimental evidence supporting this conclusion is de-

(1) (a) Koreeda, M.; Moore, P. D.; Wislocki, P. G.; Levin, W.; Conney, A. H.; Yagi, H.; Jerina, D. M. *Science (Washington, D.C.)* 1978, 199, 778. (b) Nakanishi, K.; Kasai, H.; Cho, H.; Harvey, R. G.; Jeffrey, A. M.; Jennette, K. W.; Weinstein, B. I. *J. Am. Chem. Soc.* 1977, 99, 258. (c) Straub, K. M.; Meehan, T.; Burlingame, A. L.; Calvin, M. *Proc. Natl. Acad. Sci. U.S.A.* 1977, 74, 5285. (d) Levin, W.; Buening, M. K.; Wood, A. W.; Chang, R. L.; Kedzierski, B.; Thakker, D. R.; Boyd, D. R.; Gararginamath, G. S.; Armstrong, R. N.; Yagi, H.; Karle, J. M.; Sлага, T. J.; Jerina, D. M.; Conney, A. H. *J. Biol. Chem.* 1980, 255, 9067.

(2) (a) Jerina, D. M.; Selander, H.; Yagi, H.; Wells, M. C.; Davey, J. F.; Mahadevan, V.; Gibson, D. T. *J. Am. Chem. Soc.* 1976, 98, 5988. (b) Lehr, R. E.; Schaefer-Ridder, M.; Jerina, D. M. *J. Org. Chem.* 1977, 42, 736. (c) Buhler, D. R.; Ünlü, F.; Thakker, D. R.; Sлага, T. J.; Conney, A. H.; Wood, A. W.; Chang, R. L.; Levin, W.; Jerina, D. M. *Cancer Res.* 1983, 43, 1541.

(3) (a) Fu, P. P.; Yang, S. K. *Biochem. Biophys. Res. Commun.* 1982, 109, 927. (b) Chiu, P. L.; Fu, P. P.; Yang, S. K. *Ibid.* 1982, 106, 1405.

(4) Miura, R.; Honmaru, S.; Nakazaki, M. *Tetrahedron Lett.* 1968, 5271.

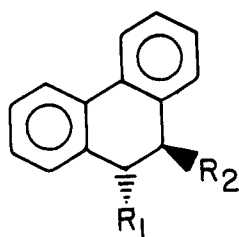
(5) Armstrong, R. N.; Kedzierski, B.; Levin, W.; Jerina, D. M. *J. Biol. Chem.* 1981, 256, 4726.

Table I. Chemical Shifts and Coupling Constants for Benzylic Protons

compd	solvent	chemical shift, ppm	$^3J_{9,10}$ , Hz	$^1J_{H,^{13}C}$ , Hz
1	acetone- $d_6$	4.61	10.4	142.2
1	acetone- $d_6$ / D <sub>2</sub> O (50:50)	4.70	9.2	143.3
1	acetone- $d_6$ / D <sub>2</sub> O (25:75)	4.74	6.8	146.3
1	methanol- $d_4$	4.30	8.4	143.1
2	acetone- $d_6$	6.07	5.6	152.5
3a	methanol- $d_4$	4.81, 4.98	8.9	
3a <sup>a</sup>	D <sub>2</sub> O	4.28, 4.33	4.0	
4a <sup>a</sup>	D <sub>2</sub> O	4.60, 5.16	2.3	

<sup>a</sup> Data from ref 14.

sirable. In order to clarify the above points, we report here our finding of a direct correlation of the chiroptical properties of several metabolically relevant 9,10-disubstituted-9,10-dihydrophenanthrenes 1a–4a to conformer



	R <sub>1</sub>	R <sub>2</sub>
1a	OH	OH
2a	OCOCH <sub>3</sub>	OCOCH <sub>3</sub>
3a	O-β-D-glucuronosyl	OH
4a	S-glutathionyl	OH

populations deduced by <sup>1</sup>H NMR and the observation of a pronounced influence of solvent on the conformer populations of 1 and the diastereomeric 9-β-D-glucuronosyl-10-hydroxy-9,10-dihydrophenanthrenes 3a and 3b, products of the action of the enzyme uridine-5'-diphosphoglucuronosyltransferase on 1.

A direct determination of the vicinal coupling constant  $^3J_{9,10}$  for the benzylic protons of 1 and 2 is possible by measuring the AB coupling in the ABX spectrum associated with the naturally abundant molecules (2.2% of total) containing a single benzylic <sup>13</sup>C nucleus in which the benzylic protons are *not* magnetically equivalent.<sup>6</sup> Coupling constants  $^3J_{9,10}$  and the heteronuclear ( $J_{AX}$ ) coupling constant  $^1J_{H,^{13}C}$  for the benzylic protons determined in this way for 1 and 2 are listed in Table I. The Karplus relationship<sup>7</sup> and the magnitude of  $^3J_{9,10}$  for 1 and 2 in acetone indicates that the preferred conformers are those with the hydroxyl groups equatorial and acetoxy groups axial, respectively. This finding agrees with NMR results on related 9,10-dihydrophenanthrenes<sup>2a</sup> but is clearly and directly inconsistent with the conformations originally suggested<sup>4</sup> for 1b and 2b. In fact, comparison of the ORD spectra<sup>4</sup> of 1b and 2b in organic solvents to that of a related system of known absolute configuration<sup>8</sup> indicates that the biphenyl chromophores of 1b and 2b have the *M* and *P* helicities, respectively. This definition of molecular chirality combined with the conformer populations of 1 and 2 obtained from the <sup>13</sup>C-satellite proton resonances provides an independent determination of the absolute con-

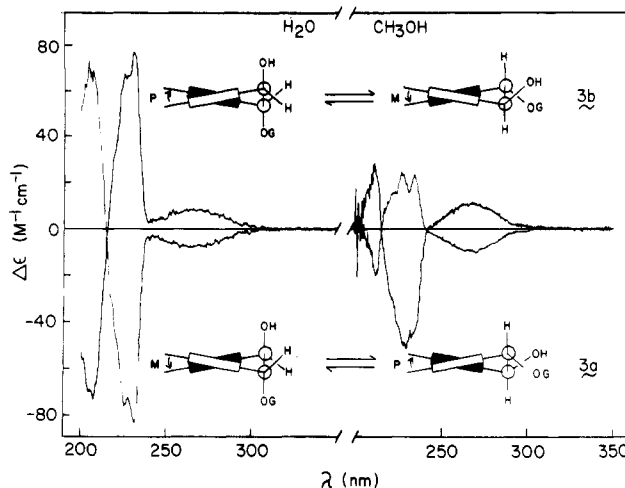


Figure 1. Solvent dependence of the CD spectra of 3a and 3b. Helicities of the biphenyl axes are indicated. G = β-D-glucuronosyl.

figuration of 1b in agreement with the original 9*S*,10*S* configuration assigned by chemical degradation.<sup>4</sup>

A monotonic decrease in  $^3J_{9,10}$  of 1 is seen (Table I) when the solvent composition is changed from acetone to 25% acetone/75% water, providing direct evidence that previously observed solvent-dependent changes in the CD spectrum of 1b<sup>5</sup> are due to shifts in conformer populations. Similarly, the diastereomeric monoglucuronides 3a and 3b exhibit pronounced changes in their CD spectra (Figure 1) below 250 nm associated with the helicity of the biphenyl chromophore as the solvent is changed from CH<sub>3</sub>OH to water. In contrast, CD transitions above 250 nm are relatively insensitive to solvent composition. The mirror-image CD spectra of the two diastereomers in water suggest that, in this solvent, there is little contribution of the glucuronosyl group to the observed ellipticity of 3a and 3b. In CH<sub>3</sub>OH the CD spectra of 3a and 3b are clearly not mirror images, which, as discussed later, probably reflects different conformer populations of the two diastereomers in this solvent. That the solvent-dependent changes in the chiroptical properties of 3a are directly associated with a coupled change in the helicity of the biphenyl chromophore and the conformation of the dihydrophenanthrene is demonstrated by the large difference of  $^3J_{9,10}$  observed in methanol and water (Table I).

For molecules such as 1–4 having two rapidly interconverting conformers A and B, the usual relationship between the observed coupling constant  $^3J_{\text{obsd}}$  and the fraction,  $\alpha$ , of molecules in conformation A is given by eq 1, where  $^3J_A$

$$^3J_{\text{obsd}} = \alpha^3 J_A + (1 - \alpha)^3 J_B \quad (1)$$

and  $^3J_B$  are the expected coupling constants from the Karplus equation for the A and B conformers, respectively.<sup>9</sup> The difficulty in using  $^3J_{\text{obsd}}$  to quantitatively assess  $\alpha$  is the uncertainty in the values of  $^3J_A$  and  $^3J_B$  introduced by electronegativity effects of substituents.<sup>10</sup> A similar relationship should exist between the observed circular dichroic extinction coefficient,  $\Delta\epsilon_{\text{obsd}}$ , of the biphenyl chromophore and  $\alpha$  such that

$$\Delta\epsilon_{\text{obsd}} = \alpha\Delta\epsilon_A + (1 - \alpha)\Delta\epsilon_B \quad (2)$$

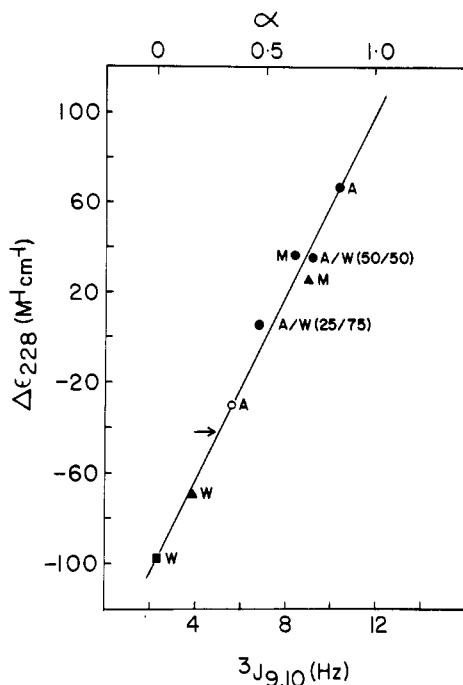
(9) Burton, G. W.; Carr, M. D.; de la Mare, P. B. D.; Rosser, M. J. *J. Chem. Soc., Perkin Trans. 2* 1972, 710.

(10) (a) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon Press: New York, 1969; pp 280–304. (b) Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* 1980, 21, 2783. (c) Altona, C.; Haasnoot, C. A. G. *Org. Magn. Reson.* 1980, 13, 417.

(6) Becker, E. D. "High Resolution NMR Theory and Chemical Applications", 2nd ed.; Academic Press: New York, 1980; p 174.

(7) Karplus, M. *J. Am. Chem. Soc.* 1963, 85, 2870.

(8) Joshua, H.; Gans, R.; Mislow, K. *J. Am. Chem. Soc.* 1968, 90, 4884.



**Figure 2.** Correlation of circular dichroic extinction coefficient ( $\Delta\epsilon_{228}$ ) with  $^3J_{9,10}$  for (9*R*,10*R*)-9,10-disubstituted-9,10-dihydro-phenanthrenes **1a** (●), **2a** (○), **3a** (▲), and **4a** (■). Solvents indicated in the figure are A, acetone; M, methanol; W, water. Solid line is a linear least-squares fit of the data with slope = 20.0, intercept = -143, and correlation coefficient = 0.978. Arrow indicates  $\Delta\epsilon_{228}$  for **1a** in water. Calibration of the  $\alpha$  scale is described in the text.

where  $\Delta\epsilon_A$  and  $\Delta\epsilon_B$  are the CD extinction coefficients for the A and B conformers, respectively, in a given stereochemical series. It is apparent that there should be a linear relationship between  $^3J_{9,10}$  and  $\Delta\epsilon$  for CD transitions sensitive to the helicity of the biphenyl chromophore. Figure 2 shows the empirical correlation of  $^3J_{9,10}$  and  $\Delta\epsilon_{228}$  for the 9*R*,10*R* stereochemical series **1a**–**4a**.

Evaluation of the relationship between  $\Delta\epsilon_{228}$  and  $\alpha$  requires the limiting values  $\Delta\epsilon_A$  and  $\Delta\epsilon_B$  be known. A reasonable value for  $\Delta\epsilon_B$  at 228 nm of  $-98 \text{ M}^{-1} \text{ cm}^{-1}$  can be estimated from **4a** in which the sterically bulky sulfur should prefer almost exclusively the axial position ( $\alpha = 0$ ). If, as expected,<sup>8,11</sup> the dissymmetric biphenyl chromophore dominates the CD spectrum, then  $\Delta\epsilon_A \approx \Delta\epsilon_B$ . Extrapolation of the data of Figure 2 to  $\Delta\epsilon_A = 98 \text{ M}^{-1} \text{ cm}^{-1}$  ( $\alpha = 1$ ) yields  $^3J_{9,10} = 12.0 \text{ Hz}$ , which is within the expected range of 10–14 Hz for axial protons with a dihedral angle of  $\sim 180^\circ$ .<sup>10</sup>

The mutual agreement of the chiroptical and NMR data indicate the  $\Delta\epsilon_{228}$  is a useful and quantitative indicator of conformer populations of substituted 2,2'-bridged biphenyls such as **1**–**4**. For instance, solvent-dependent shifts in the conformer populations of **1a** and **3a** are readily obtained from Figure 2 in terms of  $\alpha$ , the fraction of molecules with substituents diequatorial. For **1a** the  $\alpha$  value ranges from 0.28 in  $\text{H}_2\text{O}$  to 0.68 in  $\text{CH}_3\text{OH}$  and 0.84 in acetone. Similarly, the glucuronide **3a** exhibits  $\alpha$  values of 0.14 and 0.62 in  $\text{H}_2\text{O}$  and  $\text{CH}_3\text{OH}$ , respectively. The larger absolute value of  $\Delta\epsilon_{228}$  for **3b** ( $-51.6 \text{ M}^{-1} \text{ cm}^{-1}$ ) compared to that of **3a** ( $24.8 \text{ M}^{-1} \text{ cm}^{-1}$ ) suggests a slightly greater population ( $\alpha = 0.76$ ) of the diequatorial conformer for the diastereomer **3b** in  $\text{CH}_3\text{OH}$ . The reasons for these dramatic shifts in both cases probably involve stabilization of the conformers with diequatorial substituents through

intramolecular hydrogen bonding<sup>2,12</sup> in organic solvents and, perhaps more importantly, a decrease in the size of the entropically unfavorable aqueous solvation shell about the biphenyl moiety by diaxial substituents in water. The CD spectra of **4a** in  $\text{H}_2\text{O}$  and  $\text{CH}_3\text{OH}$  are essentially identical, a result predicted both from the steric bulk of the sulfur atom and its relatively low potential as an effective hydrogen-bond acceptor. Finally, the large solvent-dependent changes in the CD spectra of **1** and **3** suggests that caution should be exercised in application of chiroptical techniques in deducing absolute configurations of *trans*-dihydro diols and particularly the corresponding glucuronides, which are easily studied in either organic or aqueous solutions. To this point, it appears that the solvent-independent long-wavelength transitions of **1**–**4** centered at  $\sim 270 \text{ nm}$  (Figure 2 and ref 4, 5, and 14) are valuable in reporting the absolute configurations of these molecules whereas the transition at  $\sim 230 \text{ nm}$  is sensitive to the conformation.

### Experimental Section

Racemic **1** was obtained by  $\text{KBH}_4$  reduction of phenanthrene quinone.<sup>13</sup> Antipodes **1a** and **1b** were resolved as previously described.<sup>5</sup> Diacetate **2** was prepared by acetylation of **1** in acetic anhydride/pyridine. Diastereomeric monoglucuronides **3a** and **3b** were synthesized enzymatically.<sup>14</sup>

Proton NMR spectra at 200 MHz were obtained on an IBM WP-200 SY spectrometer. Clear observation of  $^{13}\text{C}$ -satellite resonances in **1** and **2** was possible after ca. 500 pulses for concentrated samples (5–10 mg/mL). Dilute samples (<1 mg/mL) of **1** in acetone- $d_6$ / $\text{D}_2\text{O}$  mixtures required ca. 3000 pulses and decoupling of the residual HDO signal to obtain usable signal to noise. Chemical shifts were referenced to external tetramethylsilane.

Circular dichroism spectra were obtained on a JASCO J500C spectropolarimeter with spectral averaging of 16–64 spectra using a DP-500N data processor. Sample concentrations ranged from 5 to 100  $\mu\text{M}$ . Spectra in acetone solutions were obtained by using a 0.1-cm cell between 235 and 205 nm due to the opacity of the solvent in the UV.

**Acknowledgment.** This work supported in part by NIH Grant GM-30910, American Cancer Society Institutional Grant IN-174, and a Faculty Research Award to R.N.A. from the General Research Board of the University of Maryland.

**Registry No.** **1a**, 64440-29-5; **1b**, 23190-41-2; **2a**, 87206-14-2; **2b**, 23299-68-5; **3a**, 87174-97-8; **3b**, 87206-15-3; **4a**, 84107-69-7.

(12) Jeffrey, A. M.; Yeh, H. J. C.; Jerina, D. M.; Patel, T. R.; Davey, J. F.; Gibson, D. T. *Biochemistry* **1975**, *14*, 575.

(13) Dey, A. S.; Neumeyer, J. L. *J. Med. Chem.* **1974**, *17*, 1095.

(14) Cobb, D.; Boehlert, C.; Lewis, D.; Armstrong, R. N. *Biochemistry* **1983**, *22*, 805.

### Preparation of Grignard Reagents from 3-Halo Ethers

Timothy P. Burns and Reuben D. Rieke\*

Department of Chemistry, University of Nebraska, Lincoln, Nebraska 68588-0304

Received April 4, 1983

The production of cyclopropane from the reaction of magnesium metal with  $\gamma$ -halo ethers is a well-known reaction.<sup>1–3</sup> In fact, this is a standard method of preparing

(11) Harada, N.; Nakanishi, K. *Acc. Chem. Res.* **1972**, *5*, 257.

(1) Paul, R. C. R. *Hebd. Seances Acad. Sci.* **1931**, *192*, 964.