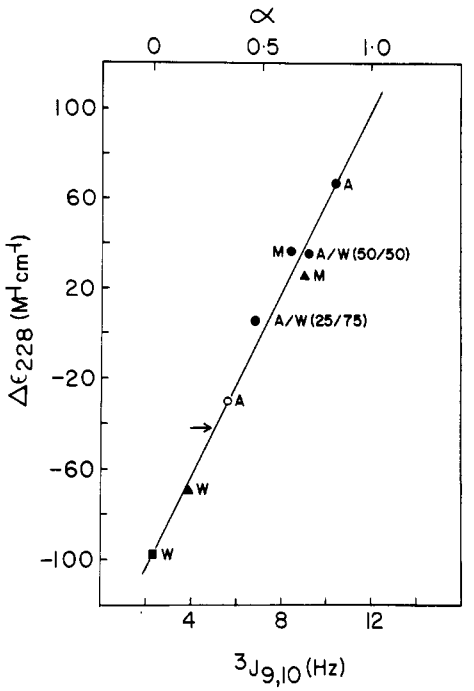

Figure 2. Correlation of circular dichroic extinction coefficient ($\Delta\epsilon_{228}$) with $^3J_{9,10}$ for (9*R*,10*R*)-9,10-disubstituted-9,10-dihydrophenanthrenes **1a** (●), **2a** (○), **3a** (▲), and **4a** (■). Solvents indicated in the figure are A, acetone; M, methanol; W, water. Solid 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 α 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 α 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 M^{-1} cm^{-1} can be estimated from **4a** in which the sterically bulky sulfur should prefer almost exclusively the axial position (α = 0). If, as expected,[8,11] 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 M^{-1} cm^{-1} (α = 1) yields $^3J_{9,10}$ = 12.0 Hz, which is within the expected range of 10–14 Hz for axial protons with a dihedral angle of ~180°.[10]

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 α, the fraction of molecules with substituents diequitorial. For **1a** the α value ranges from 0.28 in H_2O to 0.68 in CH_3OH and 0.84 in acetone. Similarly, the glucuronide **3a** exhibits α values of 0.14 and 0.62 in H_2O and CH_3OH, respectively. The larger absolute value of $\Delta\epsilon_{228}$ for **3b** (−51.6 M^{-1} cm^{-1}) compared to that of **3a** (24.8 M^{-1} cm^{-1}) suggests a slightly greater population (α = 0.76) of the diequitorial conformer for the diastereomer **3b** in CH_3OH. The reasons for these dramatic shifts in both cases probably involve stabilization of the conformers with diequitoral substituents through intramolecular hydrogen bonding[2,12] 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 H_2O and CH_3OH 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 ~270 nm (Figure 2 and ref 4, 5, and 14) are valuable in reporting the absolute configurations of these molecules whereas the transition at ~230 nm is sensitive to the conformation.

Experimental Section

Racemic **1** was obtained by KBH_4 reduction of phenanthrene quinone.[13] Antipodes **1a** and **1b** were resolved as previously described.[5] Diacetate **2** was prepared by acetylation of **1** in acetic anhydride/pyridine. Diastereomeric monoglucuronides **3a** and **3b** were synthesized enzymatically.[14]

Proton NMR spectra at 200 MHz were obtained on an IBM WP-200 SY spectrometer. Clear observation of ^{13}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/D_2O 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 μM. 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.

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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.

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Preparation of Grignard Reagents from 3-Halo Ethers

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The production of cyclopropane from the reaction of magnesium metal with γ-halo ethers is a well-known reaction.[1-3] In fact, this is a standard method of preparing

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0022-3263/83/1948-4141$01.50/0

Table I. Rate of Cyclization in H_2O at 25 °C

substrate	final ring size	K, s^{-1}
$Br(CH_2)_5NH_2$	6	80×10^{-4}
$Br(CH_2)_4NH_2$	5	5000×10^{-4}
$Br(CH_2)_3NH_2$	4	0.08×10^{-4}
$Br(CH_2)_2NH_2$	3	6×10^{-4}

substituted cyclopropanes.[3] However, because of the ease of cyclopropane formation from such systems, it precludes their use in normal Grignard chemistry. We report here a method for the preparation and cross-coupling of the Grignard reagent from 3-bromophenoxypropane by employing highly reactive magnesium. Also, we report here Grignard formation of the higher homologues of the γ-halo ether series.

Results and Discussion

Earlier we had reported a variety of methods for preparing highly reactive magnesium metal powders.[4-8] The most recent of these approaches was to reduce anhydrous magnesium chloride with lithium by using naphthalene as an electron carrier.[8] It occurred to us that using the highly reactive magnesium at low temperatures might allow the formation of Grignard reagents from 3-halo ethers and cross-coupling reactions to be carried out before cyclization and cyclopropane formation. This proved to be the case. When 3-bromophenoxypropane (I) was added to magnesium turnings or highly reactive magnesium powder in THF at room temperature, an exothermic reaction accompanied by copius gas evolution occurred. Upon treatment with CO_2 followed by hydrolysis, the only acidic product isolated was phenol. As the starting material was totally consumed, it can be assumed that cyclopropane formation followed initial Grignard formation.

However, by using activated magnesium (Mg*) prepared according to previously published methods,[8] the reaction can be conducted at −78 °C. When I was added to the highly reactive magnesium in THF at −78 °C, GC analysis indicated that all of the starting material had been consumed in a little over 1 h. Subsequent CO_2 treatment and hydrolysis produced 4-phenoxybutanoic acid (II) in over 70% yield. Thus, when the Grignard reaction is carried out at room temperature, the standard cyclopropane formation can be effected. However, by using highly reactive magnesium powders at low temperatures, cyclization can be stopped and the 3-phenoxypropyl Grignard reagent can be cross-coupled with other acceptors.

The ease of cyclization of the 3-phenoxypropyl Grignard reagent led us to speculate that higher homologues in the series would also cyclize. As a crude model, one might expect the kinetic data on rates of cyclization of bromoalkylamines to be somewhat applicable in our studies. Table I contains cyclization rates for various ring-size formations.[9] From these data one might speculate that five- and six-membered-ring formation might be very facile, while four-membered-ring formation might be expected to be slow. Accordingly, the reactions of 4-bromophenoxybutane (III), 5-bromophenoxypentane (IV), and 6-bromophenoxyhexane (V) with magnesium were examined. Much to our surprise, III–V all formed stable Grignard reagents at low temperatures, but these Grignard reagents did not cyclize at room temperature or even upon extended reflux times in THF. Moreover, after 24 h of relfux in diglyme (162 °C) no cyclization of IV was observed. In all cases, no cyclization products or phenol could be detected by GC. Moreover, upon treatment with CO_2, high yields of the corresponding carboxylic acids were isolated as shown in Table II. There does not appear to be any obvious thermodynamic or kinetic reasons why cyclization should not occur in the case of the Grignard reagents of IV and V. While the lack of cyclization of the Grignard reagents of III–V is disappointing, it can be taken advantage of in the design of synthetic schemes involving these reagents.

Experimental Section

I (98%) and III (97%) were purchased from Aldrich Chemical Co. and used without further purification. IV and V were prepared by literature methods.[10] The course of Grignard reagent formation was followed by removing 1-mL aliquots of the reaction slurry via syringe and hydrolyzing with 1 mL of 3 N HCl. After being partitioned into 1 mL of pentane, the hydrolysis products were analyzed on a Hewlett-Packard 57301 gas chromatograph, using an $^1/_8$ in. × 1.5 m stainless steel column packed with 10% SE-30 on 80/100 mesh Chromosorb P-DMCS. IR data were recorded on a Perkin-Elmer 283 spectrophotometer using KBr pellets or melts and are reported as cm^{-1}. NMR data were collected on a Varian EM-390 90-MHz spectrometer and are reported in the form chemical shift (peak multiplicity, peak area, peak character) relative to tetramethylsilane. Melting points were determined on a Thomas Hoover Unimelt and are corrected. Mg* was prepared as reported previously from magnesium chloride.[11] After reduction was complete, the slurry was allowed to settle at least 3 h, and the supernatant was drawn off with a cannula. Fresh solvent was added, the slurry was stirred and settled, and the process was repeated two or three times. After the first two washings, the slurry settled much faster, usually within an hour. The reactions were carried out in the same 50-mL, two-necked flask used for the reduction. One neck was connected to a condenser that was fitted to an argon inlet. The other neck was equipped with a rubber septum. The moles of Mg* cited in this paper refer to the theoretical amount possible, based on the original amount of magnesium chloride. Reported yields have been corrected for the purity of starting material and aliquots withdrawn.

I with Mg* at 20 °C. I (1.58 mL, 9.83 mmol) was added quickly via syringe to a stirred slurry of Mg* (30.2 mmol) in 25 mL of THF. The very exothermic reaction lasted about 5 min. An aliquot was removed and hydrolyzed with dilute HCl. GC analysis of this aliquot revealed that all of I was consumed and a new peak, presumably corresponding to the Grignard hydrolysis product, had appeared. Later, peak matching and isolation of the final product proved this peak to be that of phenol. The stirring was continued overnight; then the mixture was cannulated onto freshly crushed CO_2. The mixture was hydrolyzed with 3 N HCl, multiply extracted with 10% NaOH, and then reacidified with HCl. This aqueous acid phase was multiply extracted with diethyl ether. The ether layers were combined, dried with sodium sulfate followed by magnesium sulfate, and stripped. Phenol (7.68 mmol, 78%) was isolated as a clear colorless oil, which slowly crystallized: NMR (CCl_4) δ 5.9 (s, 1 H, br), 6.6–7.2 (m, 5 H)[12] (the singlet at δ 5.9 disappeared upon D_2O addition); IR (melt) 3600 cm^{-1}, 3300, 1605, 1595, 1225.[13]

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(12) Matches Sadtler Index no. 3152.
(13) Matches Sadtler Index no. 165.

Table II. Reaction of $C_6H_5O(CH_2)_nBr$ with Mg*

	reagent	temp, °C	time	substrate	product	yield, %
I	$C_6H_5O(CH_2)_3Br$	20	5 min	CO_2	C_6H_5OH	100[a] 71[b]
I		−78	1 h	CO_2	$C_6H_5O(CH_2)_3CO_2H$	71[b]
III	$C_6H_5O(CH_2)_4Br$	20	15 min	CO_2	$C_6H_5O(CH_2)_4CO_2H$	89[b]
IV	$C_6H_5O(CH_2)_5Br$	20	15 min	CO_2	$C_6H_5O(CH_2)_5CO_2H$	73[b]
IV		65	240 h	H^+	$C_6H_5O(CH_2)_4CH_3$	100[a]
V	$C_6H_5O(CH_2)_6Br$	20	15 min	H^+	$C_6H_5O(CH_2)_5CH_3$	100[a]
V		65	1 h	H^+	$C_6H_5O(CH_2)_5CH_3$	100[a]
V		65	1 h	CO_2	$C_6H_5O(CH_2)_6CO_2H$	80[b]

[a] GC yield of hydrolyzed product. [b] Isolated after reaction with substrate.

I with Mg* at −78 °C. The flask, containing Mg* (19.56 mmol) in 20 mL of THF, was cooled to −78 °C. I (1.58 mL, 9.83 mmol) was added via syringe over a 15-min period. The vessel was stirred 1 h, and then a 1-mL aliquot was removed and quenched with dilute HCl. GC analysis showed I to be completely consumed. The septum was replaced by a gas inlet, the condenser connected to an oil bubbler, and the flask blanketted with a CO_2 atmosphere for 2.5 h while the cooling was maintained. The mixture was worked up as in the previous reaction. II (1.065 g, 71%) was isolated as white crystals: mp 61–62 °C (ethanol) (lit. mp 62–63 °C,[14] 64–65 °C[15]); NMR (CCl_4) δ 2.1 (quintet, 2 H), 2.5 (t, 2 H), 3.9 (t, 2 H), 6.9–7.2 (m, 5 H), 11.65 (s, 1 H, C(O)OH); IR (KBr) 3500–3000 br cm^{-1}, 2940, 1690, 1235.

III with Mg*. III (1.6188 g, 7.07 mmol) was placed in a cone-bottomed test tube capped with a septum and then purged with argon for 30 min. Then 5 mL of THF was added. The solution was taken up into a syringe and added over a 15-min period to a slurry of Mg* (14.77 mmol) in 20 mL of THF. The vessel warmed slightly. The conical tube and syringe were rinsed with 2.5 mL of THF, which was added to the reaction vessel. After being stirred for an additional 15 min, the mixture was cannulated through an N_2-filled glovebag into a beaker of freshly crushed CO_2. The reaction was worked up as previously described to give 5-phenoxypentanoic acid (177.5 mg, 89%) as white crystals: mp 63–64 °C, (lit.[16] mp 65–66 °C); NMR (Unisolve-d) δ 1.5–2.0 (m, 4 H), 2.3 (t, 2 H), 3.9 (t, 2 H), 6.68–7.3 (m, 5 H); IR (KBr) 3500–2980 br cm^{-1}, 1710, 1235.

IV with Mg*. IV (1.1141 g, 4.58 mmol) was added dropwise over an 8-min period to a slurry of Mg* (14.8 mmol) in 20 mL of THF. The reaction was stirred an additional 15 min then worked up as III. 6-Phenoxyhexanoic acid (677.3 mg, 73%) was isolated as white crystals: mp 70.2–71 °C (lit.[17] mp 71 °C); NMR (Unisolve-d) δ 1.3–2 (m, 6 H), 2.2 (t, 2 H), 3.9 (t, 2 H), 6.7–7.3 (m, 5 H); IR (KBr) 3300–3000 cm^{-1}, 1710, 1240.

A second reaction employing Mg* (15.44 mmol) in 20 mL of refluxing THF was run in an effort to induce cyclization. IV (871.95 mg, 3.586 mmol) was added over an 8-min period. Quenches at 15 min, 1 h, and 24 h showed only hydrolyzed Grignard reagent. No phenol, cyclopentane, or pentene was observed by GC. After 240 h of reflux, the whole pot was quenched. Again, GC analysis showed only 1-phenoxypentane. It is possible that a small amount of cyclopentane or pentene would have been lost during the reflux period due to their volatility, but not phenol.

V with Mg*. V (1.6486 g, 6.41 mmol) was added dropwise over a 7-min period to Mg* (24.3 mmol) in 30 mL of THF. An aliquot at 15 min showed V to be consumed but no evidence of phenol or cyclohexane. A single new peak, presumably the hydrolyzed Grignard reagent, had appeared. The reaction was refluxed to try and induce cyclization, but the 1-h quench showed no change. The reaction was cannulated onto freshly crushed CO_2 and worked up as previously. 7-Phenoxyheptanoic acid (1.06125 g, 80%) was isolated as white crystals: mp 56.8–57.8 °C (lit.[18] mp 55 °C); NMR (Unisolve-d) δ 1.2–1.85 (m, 8 H), 2.25 (t, 2 H), 3.9 (t, 2 H), 6.7–7.3 (m, 5 H); IR (KBr) 3300–2900 cm^{-1}, 1705, 1245.

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Registry No. I, 588-63-6; II, 6303-58-8; III, 1200-03-9; IV, 22921-72-8; V, 51795-97-2; Mg, 7439-95-4; C_6H_5OH, 108-95-2; $C_6H_5O(CH_2)_4CO_2H$, 7170-40-3; $C_6H_5O(CH_2)_5CO_2H$, 7170-41-4; $C_6H_5O(CH_2)_4CH_3$, 2050-04-6; $C_6H_5O(CH_2)_5CH_3$, 1132-66-7; $C_6H_5O(CH_2)_6CO_2H$, 7170-42-5.

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A Homo-Brook Rearrangement

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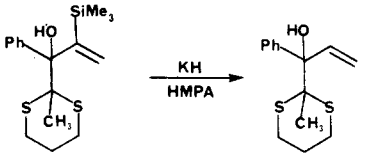
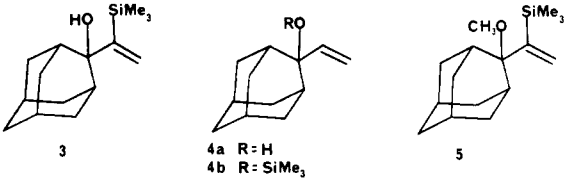
In the course of studying a series of anion-assisted rearrangements[2] (eq 1), we had occasion to react **1** with KH and HMPA. To our surprise, a rapid desilylation of **1** → **2** was observed.



1 2 (1)

The cleavage of unactivated carbon–silicon bonds was unusual,[3] and desilylation had not been observed in attempts to form allenes[4] via Peterson olefination.[5] We thus decided to examine the simpler system **3**.



3 4a R = H; 4b R = SiMe3 5

1-(Trimethylsilyl)vinyllithium[2] reacts with 2-adamantanone to produce alcohol **3** in 67% yield. When

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