tained from a hydrochloric acid hydrolysate of iron-free albomycin,[20,21] δ_{TMS} (DMSO-d_6) 1.77 [m, broad, $(CH_2)_2$], 3.04 (m, broad H-5), 3.62 (m, broad, H-2), and 7.20 (broad envelope representing 6 protons) overlapping with 7.51 (m, H-5′–H-8′).

Anal. Calcd for $C_5H_{12}N_2O_3 \cdot C_9H_5NO_4$: C, 49.56; H, 5.05; N, 12.38. Found: C, 49.41; H, 5.00; N, 12.42.

2-Acetamidovaleramide 5-(α-Phenylnitrone) (6). A suspension of 4.00 g (13.68 mmol) of **5** in *ca.* 40 ml of liquid ammonia was kept in a sealed tube at 50° for 4.5 days. The residue obtained after evaporation of ammonia was recrystallized from methanol–ether to afford colorless needles (3.19 g, 84% yield) of **6**, mp 170°, R_f 0.06 (system 3).

Anal. Calcd for $C_{14}H_{19}N_3O_3$: C, 60.64; H, 6.91; N, 15.15. Found: C, 60.43; H, 6.92; N, 15.21.

N^5-Hydroxy-DL-arginine (9). A solution of 3.19 g (11.5 mmol) of **6** in 70 ml of concentrated hydrochloric acid (*d* 1.188) was heated on the steam bath for 15 min. The solution was concentrated to dryness under reduced pressure and the resulting crude **7** was dried over sodium hydroxide *in vacuo* overnight. The entire residue was dissolved in 8 ml of water, 3.19 g (22.9 mmol) of *S*-methylisothiourea sulfate was added, and the pH of the solution was adjusted to 7 with dilute sodium hydroxide solution. The mixture was kept at room temperature for 5 days. During this period the pH of the solution was occasionally readjusted to 7. The solution of crude **8** was evaporated to dryness under reduced pressure, and the residue was redissolved in 100 ml of 6 *N* hydrochloric acid and heated on the steam bath for 10 hr, evaporated, and dried over sodium hydroxide. The resulting residue was dissolved in 50 ml of water and the solution, after pH adjustment to 3, was charged to a column (25 × 680 mm) of Dowex 50W X-8, 200–400 mesh (Na^+), previously rinsed with 3.4 l of a pH 6.1 buffer, prepared by adding 0.1 *M* citric acid to 0.2 *M* dibasic sodium phosphate solution until pH 6.1 was reached (approximate ratio of solutions was 15:8).

The column was subsequently developed with the pH 6.1 buffer to which 0.1 mol of sodium chloride per liter had been added. After 800 ml of effluent had been collected the column was eluted with the pH 6.1 buffer containing 0.3 mol of sodium chloride per liter. The effluent was now collected in 20-ml fractions, the antibiotic activity of the fractions was monitored bioautographically,[1] and fractions 50–120 were pooled and desalted by charging to a column (50 × 400 mm) of Dowex 50W X-4, 50–100 mesh (H^+). This column was rinsed with water until the effluent was neutral and then developed with 1 *N* ammonium hydroxide solution. Fractions of 500 ml each were collected as soon as ammoniacal development had started; fractions 7–11, containing the bioactive material, were pooled and concentrated to yield 1.1 g of viscous **9**. This material was redissolved in water, and the solution was adjusted to pH 5 with hydrochloric acid, concentrated, and diluted with ethanol to afford 1.04 g of **9** hydrochloride as needles (40% yield based on the conversion of **6** to **9** hydrochloride) with identical R_f values and pmr spectrum as reported for the L form.[1]

Anal. Calcd for $C_6H_{14}N_4O_3 \cdot HCl$: C, 31.79; H, 6.67; N, 24.72. Found: C, 31.75; H, 6.91; N, 24.86.

Registry No.—**1**, 40162-08-1; 1 dihydrochloride, 50678-85-8; 1 2-nitro-1,3-indandione salt, 50678-86-9; **5**, 50585-17-6; **6**, 50585-18-7; **9** hydrochloride, 50585-19-8; *anti*-benzaldoxime thallium(I) salt, 50585-20-1; *anti*-benzaldoxime, 622-32-2; methyl 2-acetamido-5-iodovalerate, 21753-88-8.

References and Notes

(1) Paper VIII of this series: H. Maehr, J. F. Blount, D. L. Pruess, L. Yarmchuk, and M. Kellett, *J. Antibiot. (Tokyo)*, **26**, 284 (1973).
(2) T. Emery, *Advan. Enzymol.*, **35**, 135 (1971).
(3) H. Maehr, *Pure Appl. Chem.*, **28**, 603 (1971).
(4) Preliminary results revealed weak antibiotic activity of racemic N^5-hydroxyornithine against *Escherichia coli* B and *Bacillus sp.* 1283 B when tested under conditions described in ref 1.
(5) S. Rogers and J. B. Nielands, *Biochemistry*, **2**, 6 (1963).
(6) Y. Isowa, T. Takashima, M. Ohmori, H. Kurita, M. Sato, and K. Mori, *Bull. Chem. Soc. Jap.*, **45**, 1461 (1972).
(7) G. Tomlinson and T. Viswanatha, *Can. J. Biochem.*, **51**, 754 (1973).
(8) W. Keller-Schierlein and B. Maurer, *Helv. Chim. Acta*, **52**, 603 (1969).
(9) B. Maurer and W. Keller-Schierlein, *Helv. Chim. Acta*, **52**, 388 (1969).
(10) E. Buehler, *J. Org. Chem.*, **32**, 261 (1967).
(11) E. Buehler and G. B. Brown, *J. Org. Chem.*, **32**, 265 (1967).
(12) E. F. Schoenewaldt, R. B. Kinnel, and P. Davis, *J. Org. Chem.*, **33**, 4270 (1968).
(13) Although we previously outlined this synthetic sequence (ref 3), Tomlinson and Viswanatha (ref 7) attempted the preparation of N^5-hydroxyornithine by N-alkylation of sodium *anti*-benzaldoximate with unprotected 2-amino-5-bromovaleric acid and, predictably, obtained only proline.
(14) B. Fischer, W. Keller-Schierlein, H. Kneifel, W. A. König, W. Loeffler, A. Müller, R. Muntwyler, and H. Zähner, *Arch. Mikrobiol.*, **91**, 203 (1973).
(15) In contrast to a previous report,[1] *N*-acetyl-L-glutamic acid and N^2-acetyl-L-ornithine do not reverse the antibiotic activity of **9** *vs. E. coli*, in agreement with the observations of Fischer, *et al.*[14]
(16) T. F. Emery, *Biochemistry*, **5**, 3694 (1966).
(17) If the alkylation (78 mmol) was conducted in methanol (150 ml) using 1.50 *M* methanolic sodium methoxide solution (52 ml) to generate the sodium salt of *anti*-benzaldoxime, the yield of recrystallized **5** was 42%.
(18) G. G. Kleinspehn, J. A. Jung, and S. A. Studniarz, *J. Org. Chem.*, **32**, 460 (1967).
(19) G. A. Snow, *J. Chem. Soc.*, 2588 (1954).
(20) J. Turková, O. Mikeš, and F. Sorm, *Collect Czech. Chem. Commun.*, **27**, 591 (1962).
(21) H. Maehr and R. G. Pitcher, *J. Antibiot. (Tokyo)*, **24**, 830 (1971).

Coupling Reactions between Resonance Stabilized Organolithium Reagents and Cycloalkyl Halides[1]

W. D. Korte,* K. Cripe, and R. Cooke

Department of Chemistry, California State University at Chico, Chico, California 95926

Received September 11, 1973

Both lithium dialkylcuprates and organolithium reagents have recently been shown to be extremely useful reagents for the synthesis of unsymmetrical hydrocarbons *via* a Wurtz-type coupling process between the organometallic reagents and alkyl halides.[2] Lithium dialkylcuprates couple readily with a wide variety of alkyl, aryl, and vinyl halides[2a,b] and organolithium reagents condense with primary and secondary halides.[2c-g] The products from the coupling reaction can frequently serve as key intermediates for the synthesis of carbonyl compounds.[2c,g] One of the limitations of these versatile reagents appeared to be the low yields associated with the reaction when performed with cycloalkyl halides. Although lithium dimethylcuprate and cyclohexyl iodide did condense to give a 75% yield of methylcyclohexane,[2a] the reaction between cyclohexyl bromide and lithium di-*n*-butyl-(tri-*n*-butylphosphine)cuprate only gave a 25% yield of the coupled product, *n*-butylcyclohexane.[2b]

Resonance stabilized organolithium reagents, such as benzyllithium and allyllithium, are both strong nucleophiles and relatively weak bases compared to alkyllithium reagents such as *n*-butyllithium.[3] This combination of properties has proved to be compatible with the displacement of both bromide and iodide ions from cyclohexyl and cyclopentyl systems so that high yields of substituted cycloalkanes can be obtained by a direct Wurtz-type coupling procedure

$$RLi + R'X \longrightarrow RR' + LiX$$

Tables I and II summarize the results of this study with five different organolithium reagents and two cycloalkyl systems.

Four trends in reactivity are indicated from the data in Table I. (1) The use of cyclohexyl bromide and cyclohexyl iodide led to much higher yields of coupled products than the corresponding reactions with cyclohexyl chloride or cyclohexyl tosylate. (2) The yields from reactions with cyclohexyl bromide were greater than yields from reactions with cyclopentyl bromide. (3) Benzylic reagents, benzyl- and benzhydryllithium, were slightly superior to the allylic reagent in the displacement reaction. (4) Diethyl ether appeared to be slightly superior to tetrahydrofuran as a solvent for these reactions.[4] It should also be noted that displacement of the tosylate group was accomplished

Table I
Coupling Reactions with Cycloalkyl Halides[a,b]

RLi	% yield of coupled products, RR'[c] R'Cl[d]		R'Br			R'I	R'OTs[e]
CH_2=$CHCH_2Li$ (3052-45-7)	10[f] (2114-42-3)		78	(68)[g]	(70)[h] (3524-75-2)	86	21
$PhCH_2Li$ (766-04-1)	35 (4410-75-7)	(20)[g]	90	(75)[g]	(56)[h] (4410-78-0)	89	55
$PhCH_2MgCl$						24	80
$(Ph)_2CHLi$ (881-42-5)			93 (50585-08-5)		(85)[h] (50585-09-6)		67

[a] All reactions were run in diethyl ether solvent at room temperature under an atmosphere of dry N_2 unless otherwise noted. [b] Registry no. for cycloalkyl halides: cyclohexyl chloride, 542-18-7; cyclohexyl bromide, 108-85-0; cyclopentyl bromide, 137-43-9; cyclohexyl iodide, 626-62-0. Registry no. for compounds are in parentheses under compound or yield. [c] Yields are based on R'X added (not consumed) and represent distilled samples at least 98% pure by glc. [d] R' = cyclohexyl unless otherwise noted. [e] Ts = tosyl. Registry no. for cyclohexyl tosylate, 953-91-3. [f] The reaction mixture was refluxed for 24 hr before work-up. About 80% of the cyclohexyl chloride was recovered. [g] The reaction was run in tetrahydrofuran solvent. [h] R' = cyclopentyl.

Table II
Reactions with Methyl-Substituted Allyllithium Reagents[a,b]

Reaction	RLi	R'Br	% coupling at C-1	% coupling at C-3	Total yield, %
1	$CH_3C_{(3)}H$=$CHC_{(1)}H_2Li$ (1637-44-9)	c-$C_6H_{11}Br$	68 (5860-28-6)	32 (50585-11-0)	75
2	$CH_3C_{(3)}H$=$CHC_{(1)}H_2Li$	$PhCH_2CH_2Br$	63	37	74
3	$(CH_3)_2C_{(3)}$=$CHC_{(1)}H_2Li$ (50585-10-9)	c-$C_6H_{11}Br$	85 (50585-12-1)	15 (50830-96-1)	70
4	$(CH_3)_2C_{(3)}$=$CHC_{(1)}H_2Li$	$PhCH_2CH_2Br$	100		75

[a] All reactions were run in diethyl ether solvent. [b] Registry no. are found in parentheses.

more effectively with the benzyl Grignard reagent than with the benzyllithium reagent.[5]

The greatest synthetic potential of these reactions may reside in the selectivity of reaction when there are two different and competitive anionic sites, on C-1 and C-3 of the allylic reagent, where coupling can occur. Resonance forms indicate the two possible positions for substitution

$$R_1R_2C_{(3)}=CH\bar{C}_{(1)}H_2 \longleftrightarrow R_1R_2\bar{C}_{(3)}CH=C_{(1)}H_2$$

R_1 and R_2 = CH_3 or H

When R_1 and R_2 are both methyl groups, substitution occurs almost exclusively at the terminal position C-1 and not at the internal position C-3. The reaction of (2-bromoethyl)benzene with 3-methylbutenyllithium (reaction 4, Table II) led to only one product, (5-methyl-4-hexenyl)-benzene, and when the same organolithium reagent was coupled with cyclohexyl bromide (reaction 3, Table II), 85% of the coupling product was (3-methyl-2-butenyl)cyclohexane. This would indicate that hydrocarbons of the structure type RCH_2CH=$CR'R''$, of considerable interest in terpene synthesis, can be readily prepared by this procedure, and that the procedure of generating allyllithium from allyl phenyl ether surmounts the synthetic difficulties observed when allylic reagents are prepared from allyl mesitoates and coupled with saturated alkyl halides.[2d] When crotyllithium was used, R_1 = CH_3, R_2 = H (reactions 1 and 2, Table II), there was an increase in substitution at C-3, but the predominant product (about 70%) was still derived from substitution at C-1 in contrast to reactions with crotyl Grignard reagent which produces *sec*-butenyl derivatives.[6] The exact ratio of substitution at C-1 and C-3 appears to be a complex relationship between the solvent type, and the structure of the organolithium reagent and alkyl halide.[7]

At room temperature and with diethyl ether solvent, the coupling reactions with cyclohexyl iodide and cyclohexyl tosylate were complete in less than 2 hr, but the reactions with cyclohexyl bromide required up to 8 hr for completion when a 50% excess of the organolithium reagent was used. The ease of preparing the relatively stable resonance stabilized organolithium reagents in diethyl ether or tetrahydrofuran, the rapid rate of reaction, and the high yields of hydrocarbons obtained should make Wurtz-type coupling reactions with allylic and benzyllic reagents attractive for general organic synthesis.

Experimental Section

The general method of performing these reactions as well as the procedures for preparing allyllithium, benzyllithium, and benzhydryllithium have been described previously.[2e,8] Crotyllithium and 3-methylbutenyllithium were prepared in a manner analogous to that of the preparation of allyllithium. Comparison of physical constants with those reported in the literature as well as the agreement of infrared and nmr spectra with the assigned structures confirmed the identity of the products. An example of the experimental procedure is described below.

Reaction of 3-Methylbutenyllithium with Cyclohexyl Bromide. The organolithium reagent was prepared by slowly adding an ethereal solution (50 ml) containing 3-methyl-3-butenyl phenyl ether (12.1 g, 0.075 mol) to a rapidly stirred mixture of anhydrous diethyl ether (100 ml) and lithium metal wire (1.4 g, 0.2 mol). As the reaction proceeded, the solution turned a deep red color. Occasionally, a mixture containing about 20% of the total allyl phenyl ether must be stirred up to 2 hr and gently heated before the reaction starts. The organolithium reagent was separated from excess lithium metal by carefully pumping the ethereal solution by N_2 pressure into a clean reaction vessel. Cyclohexyl bromide (7.9 g, 0.05 mol), dissolved in ether (50 ml), was slowly added to the organolithium reagent and the mixture stirred for 8 hr. Work-up consisted of washing the organic layer with 10% NaOH, three times with water, and drying over sodium sulfate. Gc analysis of the crude mixture showed two principal peaks corresponding to the two isomers, (3-methyl-2-butenyl)cyclohexane, and (1,1-dimethyl-2-propenyl)cyclohexane, in a ratio of 85:15. Four fractions (5.3 g) of the desirable hydrocarbons were collected on distillation through a spinning band column. The first three fractions contained mixtures of the two isomers. However, fraction 1 (0.2 g), bp 100–102° (16 Torr), contained about 80% (gc purity) (1,1-dimethyl-2-propenyl)cyclohexane: nmr ($CDCl_3$) δ 0.9 (s, 6 H, methyl protons), 5.2 (m, 3 H, vinyl protons), and 1.5 (broad m, 11 H, cyclohexyl protons). Fraction 4 contained 2.6 g (98% gc purity) of (3-methyl-2-butenyl)cyclohexane: bp 106–108° (16 Torr), $n^{25}D$ 1.4613, nmr ($CDCl_3$) δ 1.8 (s, 6 H, methyl protons), 1.5 (broad m,

13 H, cyclohexyl and methylene protons), and 5.5 (m, 1 H, vinyl proton) [lit.[9] bp 101–102.5° (10 Torr), n^{25}D 1.4640].

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Research Corporation, Burlingame, Calif., for support of this research.

References and Notes

(1) Presented in part at the 159th National Meeting of the American Chemical Society, Houston, Texas, Feb 1970.
(2) For example, see (a) E. J. Corey and G. H. Posner, *J. Amer. Chem. Soc.*, **89**, 3911 (1967); (b) G. M. Whitesides, *et al.*, *ibid.*, **91**, 4871 (1969); (c) A. I. Meyers, *et al.*, *J. Org. Chem.*, **38**, 36 (1973); (d) J. A. Katzenellenbogen and R. S. Lenox, *ibid.*, **38**, 326 (1973); (e) L. H. Sommer and W. D. Korte, *ibid.*, **35**, 22 (1970); (f) R. J. Crawford, W. F. Erman, and C. D. Broaddus, *J. Amer. Chem. Soc.*, **94**, 4298 (1972); (g) D. Seebach, *Synthesis*, 17 (1969).
(3) R. Waack and P. West, *J. Amer. Chem. Soc.*, **86**, 4495 (1964).
(4) Optimum yields of resonance stabilized organolithium reagents are usually obtained in tetrahydrofuran solvent: H. Gilman and H. A. McNinch, *J. Org. Chem.*, **26**, 3723 (1961); J. J. Eisch and A. M. Jacobs, *ibid.*, **28**, 2145 (1963); and ref 2c. However if the coupling reactions are run in THF, elimination becomes an important competitive side reaction.
(5) Grignard reagents are useful for direct displacements of the tosylate group from primary and secondary carbon: H. Gilman and N. J. Beaber, *J. Amer. Chem. Soc.*, **47**, 518 (1925).
(6) R. A. Benkeser, *Synthesis*, 347 (1971).
(7) Unpublished observations from this laboratory.
(8) L. H. Sommer, W. D. Korte, and P. G. Rodewald, *J. Amer. Chem. Soc.*, **89**, 862 (1967).
(9) Lewina, *Zh. Obshch. Khim.*, **11**, 411 (1941); *Chem. Abstr.*, **35**, 5862 (1941).

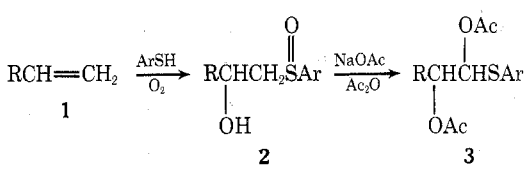
Cooxidation of α Olefins and Arenethiols with Oxygen. Synthesis of β-Hydroxy Sulfoxides

Shinobu Iriuchijima, Keiko Maniwa, Teruo Sakakibara, and Gen-ichi Tsuchihashi*

Sagami Chemical Research Center, Nishi-Ohnuma, Sagamihara, Kanagawa 229, Japan

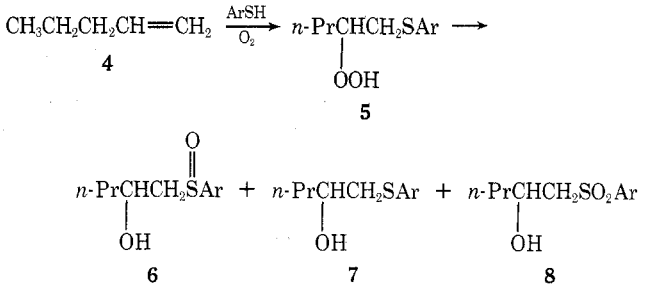
Received October 31, 1973

We have found a new method to transform β-hydroxy sulfoxides (2) into a protected form of α-hydroxy aldehydes (3) by the Pummerer reaction with acetic anhydride in the presence of sodium acetate.[1] Since β-hydroxy



sulfoxides are obtained by the cooxidation of olefins and thiols with oxygen,[2] a combination of the cooxidation and the subsequent Pummerer reaction will provide an attractive route to α-hydroxy aldehydes from α olefins (1). However, the cooxidation is actually limited to olefins conjugated with electron-attacting groups such as aromatic rings, ester, and nitrile.[3] After some experimentation to establish a general method to get 2 from 1, we have found that the irradiation of a black-light fluorescent lamp is most suitable for the cooxidation of 1 and arenethiol with oxygen because the light is effective enough to give the porduct and does not decompose it. The use of approximately 2 equiv of 1 to thiol affords the product in good yield. The various types of 2 were prepared as summarized in Table I.

The similar cooxidation of 1-pentene (4) and *p*-toluenethiol in hexane did not give the corresponding β-hydroxy sulfoxide (6) but many unidentified substances. The reaction in hexane–ethyl acetate (4:1) or hexane–acetone (4:1) as solvent, however, afforded the corresponding β-hydroperoxy sulfide (5) in good yield. It was found that 5 can be converted into 6 by simply stirring the reaction mixture in the presence of a catalytic amount of V_2O_5, oxobis(acetylacetonato)vanadium(IV), or dioxobis(acetylacetonato)-molybdenum(VI). The sulfoxide 6 was isolated in 63–67% yields (see Table I). The by-products were the corresponding sulfide 7 and sulfone 8.



Thus, in the cooxidation of olefins and thiols with oxygen, olefins can be classified into three groups: (1) the conjugated olefins such as styrene, acrylonitrile, and methacrylate, which are known to be easily cooxidized to the corresponding β-hydroxy sulfoxides,[3] (2) the α olefins as shown in Table I, which are cooxidized under the irradiation of a black-light fluorescent lamp, and (3) 1-alkenes, which need catalyst in the transformation of β-hydroperoxy sulfides to β-hydroxy sulfoxides.

The β-hydroxy sulfoxides (2) obtained here are all new compounds, and this work in conjunction with the Pummerer process[1] constitutes a new and simple two-step synthesis of α-hydroxy aldehyde derivatives (3) from α olefins (1). Recently β-hydroxy sulfoxides were found to be converted to α,β-unsaturated sulfoxides,[4] β-chloro sulfones,[5] and α,β-unsaturated sulfones.[6]

Experimental Section

The cooxidation reactions were carried out using freshly distilled olefins. The product is a diastereomeric mixture.

Procedure A-1. Preparation of 3-Acetoxy-2-hydroxypropyl *p*-Tolyl Sulfoxide (2, R = AcOCH$_2$). A solution of *p*-toluenethiol (0.89 g, 7.15 mmol) and allyl acetate (1.30 g, 13.0 mmol) in hexane (100 ml) contained in a 100-ml cylinder was efficiently bubbled with oxygen by means of a sintered-glass bubbler from the bottom of the container under the irradiation of a black-light fluorescent lamp (Toshiba FL-20BLB)[7] at room temperature overnight. The formed white crystals were freed from the solvent by decantation to give 1.515 g (82%) of 2 (R = AcOCH$_2$). The product was recrystallized from chloroform–hexane: ir (Nujol) 1008, 1025, 1243, 1728, and 3265 cm^{-1}; nmr ($CDCl_3$) δ 2.06 (3 H), 2.44 (3 H), 2.55–3.35 (2 H), 4.0–4.65 (4 H), and 7.45 (4 H).

Anal. Calcd for $C_{12}H_{16}O_4S$: C, 56.24; H, 6.29; S, 12.51. Found: C, 56.15; H, 6.10; S, 12.54.

Procedure A-2. Preparation of 2-Hydroxy-3-phenylpropyl *p*-Tolyl Sulfoxide (2, R = PhCH$_2$). A solution of *p*-toluenethiol (1.13 g, 9.09 mmol) and allylbenzene (2.15 g, 18.2 mmol) in hexane (200 ml) was subjected to the cooxidation under the same condition as above for 2 days. The formed crystals were collected to afford 1.83 g (73%) of 2 (R = PhCH$_2$). The mother liquor was stirred with *ca.* 30 mg of V_2O_5 for 5 hr to give 0.25 g (10%) of the additional product as insoluble crystals. The product was recrystallized from benzene–hexane: ir (Nujol) 700, 810, 1045, 1085, and 3325 cm^{-1}; nmr ($CDCl_3$) δ 2.39 (3 H), 2.85 (4 H), 4.00 (1 H), 4.95 (1 H), and 7.30 (9 H).

Anal. Calcd for $C_{16}H_{18}O_2S$: C, 70.04; H, 6.61; S, 11.69. Found: C, 70.05; H, 6.60; S, 11.73.

Procedure A-3. Preparation of 3-Acetoxy-2-hydroxybutyl *p*-Tolyl Sulfoxide [2, R = CH$_3$VH(OAc)]. A solution of *p*-toluenethiol (1.00 g, 8.05 mmol) and 3-acetoxy-1-butene (2.21 g, 19.4 mmol) in hexane (300 ml) was stirred in a 500-ml flask under the atmosphere of oxygen and the irradiation of a black-light fluo-