

Reductive Cleavage Mechanism of Diphenyl Ether and Apparent Ipso Trapping of an Intermediate Radical Anion with a Silyl Ether¹

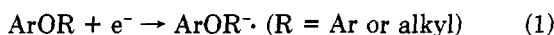
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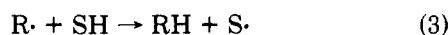
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Chemical evidence for a radical anion mechanism in the case of reductive cleavage of diphenyl ether under Na/HMPA conditions is reported. The product phenyl radical abstracts a hydrogen atom instead of successive capture of an electron. Other ethers (dibenzyl, benzyl phenyl, and methyl phenyl) are also cleaved under these reductive conditions. The initially formed radical anion of diphenyl ether is apparently largely trapped before cleavage by trimethylsilyl ethers leading ultimately to ipso phenyl substitution. The mechanism of ipso substitution is discussed.

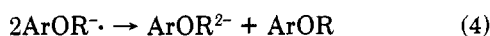
Although the reductive cleavage of diaryl ethers and alkylaryl ethers has been known for some time,²⁻¹¹ a complete mechanistic picture of this reaction is lacking. Two mechanistic paths may be considered for reductive ether cleavage. Both start with formation of the radical anion (eq 1). Path A follows with cleavage of the radical anion



Path A: One Electron



Path B: Two Electron



(eq 2).^{12,13} The aryl radical formed can either abstract a hydrogen atom from solvent (eq 3) or be further reduced to an aryl anion which is protonated on work up. Path B continues by disproportionation of the radical anion to the dianion (eq 4) followed by cleavage to an aryl anion and a phenoxide ion (eq 5).^{7a,8} Protonation on workup again would result in the observed products. Initial formation of the radical anion seems well established by direct ESR observation^{8,13} and electrochemical evidence in some cases¹⁴ and by analogy to aryl halide reductive cleavage which has been extensively studied.¹⁵ Qualitative evidence supporting both the one- (path A) and two-electron (path B) mechanisms has been reported on the basis of solvent polarity, cation size, or alkali metal reduction potential.¹⁰

Table I. Cleavage of Diphenyl Ether

no.	reaction conditions ^e	product yield, ^{a,b} %		% recovered diphenyl ether
		benzene	phenol	
Homogenous				
1	2.2 mol of Na, 2.5 mol of HMPA, THF, rt, 5.5 h	100	100 ^c	
2	1.0 mol of Na, 1.2 mol of HMPA, THF, rt, 5.5 h	70	72	27
3	3.0 mol of Na, 6 mol of pyridine, Δ, 24 h	95	95	4
4	2.2 mol of Na, liquid NH ₃ , THF, -78 °C, 4 h	100	100	
Heterogenous				
5	2.2 mol of Na, Δ, 24 h	55	55	42
6	2.2 mol of Na, diglyme, Δ, 24 h	98	98 ^d	1.0
7	1.0 mol of Na, diglyme, Δ, 24 h	50	50	50.0

^a As measured against *n*-decyl alcohol, the internal GC standard. ^b Yield is represented in mole percent.

^c Quantitative cleavage was also observed in glyme and dioxane. ^d Quantitative cleavage was also observed in glyme and tributylamine. ^e rt = room temperature.

Recently Bunnett and co-workers suggested that diphenyl ether cleavage in liquid ammonia occurs by eq 1 and 2.¹⁶⁻¹⁸ Diphenyl ether treated with potassium metal in liquid ammonia in the presence of the acetone enolate ion at -33 °C for 9 min gave 4% of phenyl acetone and 10% 1-phenyl-2-propanol, with most of the unreacted ether being recovered.^{17,18} 1-Phenyl-2-propanol was considered to have been formed via an S_{RN}1 mechanism from an intermediate phenyl radical and the enolate ion, thus, favoring cleavage by eq 2. Formation of 53% aniline from potassium amide and diphenyl ether in liquid ammonia supported this conclusion.¹⁶ Furthermore, kinetic evidence obtained for the S_{RN}1 reaction supports an intermediate phenyl radical from diphenyl ether cleavage as the benzene precursor in liquid ammonia and particularly when the reaction is carried out in organic solvents.¹⁹ Unlike the S_{RN}1 reaction,

(1) This work was performed under the auspices of the U.S. Department of Energy, Contracts No. DE-FG22-78ET13380 and EX-76-C-01-2211.

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Table II. Yields of Cleavage Products of Alkyl Aryl Ethers

no.	reactant	reaction conditions ^d	products	yields, ^{a,b} %	total recovery, %
1	anisole	A	phenol	5-48	99
		B	phenol	1 ^c	98
2	benzyl phenyl ether	A	toluene	88	99
			phenol	95	
			bibenzyl	4	
		B	unidentified	8	98
			toluene	50	
			phenol	100	
3	bibenzyl ether	A	bibenzyl	50	96
			toluene	60	
			ethylbenzene	2	
			bibenzyl	20	
			benzyl alcohol	50	
		B	benzaldehyde	10	99
			unidentified	20	
			toluene	50	
			benzyl alcohol	98	
			benzaldehyde	2	
			bibenzyl	50	

^a As measured against *n*-decyl alcohol, the internal GC standard. ^b Yield is represented in mole percent. ^c At -33 °C 63% phenol was observed (see ref 6). ^d (A) Na-HMPA in THF, room temperature, 24 h; (B) Na, liquid NH₃, THF, -78 °C, 4 h.

however, the ether cleavage reaction under consideration here is not a catalytic process but involves stoichiometric amounts of electron in order for cleavage to take place.

Results and Discussion

We now report more direct evidence for the cleavage of diphenyl ether which clearly distinguishes between mechanistic paths A and B. Diphenyl and other ethers were cleaved under both heterogeneous and homogeneous conditions, the latter allowing faster reaction at lower temperature. Half a mole of the ether (diphenyl, dibenzyl, benzyl phenyl, or methyl phenyl) was added to a highly colored solution of 1 mol of sodium and 2.2 mol of HMPA (or pyridine) in THF, glyme, or dioxane at room temperature (or without HMPA in liquid ammonia at -78 °C with THF) with stirring under argon for 4-10 h. Quenching with water and a standard work up gave the results summarized in Tables I and II. In the absence of an electron carrier, sodium metal did not noticeably react with diphenyl ether at room temperature. Refluxing conditions, however, with glyme, diglyme, or tributylamine for 24 h gave quantitative cleavage. These results are described in Table I (runs 5-7).

Aspects of several of these reactions are interesting. The reductive cleavage of benzyl phenyl ether and dibenzyl ether produced bibenzyl as one of the products (see Table II), probably by the coupling of benzyl radicals. Some ethylbenzene was observed from the cleavage reaction of dibenzyl ether, probably resulting from the further reductive cleavage of the product bibenzyl.^{20,21} The small amount of benzaldehyde formed may be due to formation of the benzyloxy radical. Miller has recently observed disproportionation of the benzyloxy radical to benzaldehyde and benzyl alcohol.²²

The mechanistic studies of the cleavage of diphenyl ether described below were carried out in more detail and establish the intermediacy of the phenyl radical. When a 1:1:1 molar ratio of sodium/HMPA/diphenyl ether were

stirred at room temperature, the products (GC) were 70% benzene and 72% phenol with 27% recovered diphenyl ether. This experiment clearly indicates that part of the reaction proceeds via path A. If cleavage had occurred via path B, a maximum of 50% ether cleavage could have resulted because two electrons are used stoichiometrically by this path. Path A, however, utilizes only one electron through benzene formation. The solvent radical generated could dimerize or disproportionate without using another electron. Less than quantitative cleavage could have resulted from further reduction of some radical (either phenyl or solvent) before it could react further.

This preliminary support for path A was examined further through a series of labeling studies which show most of the hydrogen used to form benzene in the cleavage comes from the solvent diisopropyl ether. The latter was shown to be stable to phenyl anion under the reaction conditions so that the only reasonable reaction path is via the phenyl radical.

The absence of phenyl anion at the end of the reaction was shown by treating 1 mol of sodium and 2.2 mol of HMPA in diisopropyl ether at room temperature with 0.5 mol of diphenyl ether followed by a deuterium oxide workup. The benzene produced was shown to have less than 0.5% benzene-*d*. Thus, the phenyl anion could not have been present at the end of the reaction. Still, the phenyl anion could have formed and then reacted with one of the reagents or solvent during the course of the ether cleavage. Since the phenyl anion was readily accessible by separate reaction, its susceptibility to the reaction conditions was examined. Phenylsodium prepared in petroleum ether (from chlorobenzene and sodium with ultrasonic irradiation) followed by a D₂O quench gave 81% benzene-*d*. This indicated petroleum ether reacted to some extent with the phenyl anion under these conditions during the 10-h preparation time because no starting chlorobenzene could be observed in the product mixture (GC). When a similar reaction was carried out, followed by addition of diisopropyl ether, stirring for 4 h, and then a D₂O quench, benzene containing 78% benzene-*d* was isolated. Thus, under simulated reaction conditions the ether could not be significantly deprotonated by phenylsodium. HMPA, however, was shown to be able to protonate the phenyl anion. Treatment of phenylsodium generated in the same way as above with 2 mL of HMPA in 10 mL of

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diisopropyl ether, followed by a D₂O quench after 4 h, gave benzene containing only 5.5% benzene-*d*. Obviously the phenyl anion had abstracted a proton from HMPA so that almost all had been converted to benzene before the end of the 4-h reaction period. The HMPA anion has been previously prepared with butyllithium but not with the phenyl anion as far as we are aware.²³

If the solvent, diisopropyl ether, is stable to phenyl anion but HMPA is not, a test for the source of hydrogen under the reaction conditions can be made by labeling either the ether or HMPA. Thus, 1 mol of sodium, 2.2 mol of HMPA-*d*₁₈, and diisopropyl ether were used to cleave 0.5 mol of diphenyl ether followed by a H₂O workup. The benzene produced contained only 11.2% benzene-*d*. Thus, the major source for hydrogen must have been the unlabeled solvent, diisopropyl ether. Additionally, if phenyl anion had been formed, it certainly would have reacted selectively with HMPA-*d*₁₈, and the label content of benzene would have been much higher. Intermediacy of the phenyl radical and reaction by hydrogen abstraction is consistent with the observed deuterium content of the benzene produced. The molar ratio of solvent to HMPA was 6.2, leading to a hydrogen ratio (solvent/HMPA) of 4.7. The observed deuterium content indicates a ratio of reaction of 8.1 (solvent/HMPA), consistent with a selectivity of about 2:1 for solvent over HMPA. Since the bond energy for the tertiary hydrogen in isopropyl ether is considerably below (ca. 93 kcal/mol) that of HMPA (estimated to be near 100 kcal/mol on the basis of H-CH₂NH₂),²⁴ the greater reactivity by radical abstraction from the solvent is expected, and the ratio of attack (solvent/HMPA) is consistent with benzene formation directly from the phenyl radical. Although some reduction to the phenyl anion and protonation by HMPA-*d*₁₈ cannot be eliminated, this reaction path could not have been responsible for more than 11.2% of the benzene formed. It should also be noted that all HMPA is not involved with electron solvation at one time since the sodium dissolves slowly in these solutions over the 4–5-h reaction time. Thus, an encounter between phenyl radical and an HMPA molecule (presumably solvating the electrons) need not result in reduction to the phenyl anion but could result in a hydrogen atom transfer to make benzene. Overall, these results strongly support diphenyl ether cleavage by reaction path A under sodium/HMPA reductive conditions.²⁵

In order to examine more directly hydrogen transfer from the ether to the phenyl radical, we sought to utilize perdeuteriodiisopropyl ether as the solvent. This ether was not readily available, but trimethylisopropyl-*d*₇-silane (TPS-*d*₇), from trimethylsilyl chloride and isopropyl-*d*₇ alcohol, was easily prepared. Cleavage of diphenyl ether in TPS-*d*₇ as the solvent by using a 1:2:2.5 ratio of eth-

Table III. Reduction of Diphenyl Ether with Sodium and HMPA

reaction no.	conditions		product yields, %			
	solvent	work-up	PhH	PhD	PhSi-(CH ₃) ₃	PhOH
1	HMS	D ₂ O	21	0.4	78	97
2	TPS	D ₂ O	30	1	70	99
3	TPS- <i>d</i> ₇	H ₂ O	13	11	75 ^a	99

^a Mass spectral data showed less than 1% deuterium.

er/sodium/HMPA followed by a H₂O workup gave phenol (99%), phenyltrimethylsilane (75%), and benzene (24%). The latter was 46% benzene-*d*. The corresponding blank with unlabeled TPS but with a D₂O workup gave quantitative cleavage also with the benzene (31%) formed, which contained 3% benzene-*d*. Since phenyllithium gave a quantitative yield of phenyltrimethylsilane (3) when treated with TPS, the very formation of benzene argues against a straightforward nucleophilic displacement on the solvent by an intermediate phenyl anion. Thus, phenyl anion would not have pulled a hydrogen ion from TPS to form benzene but would have instead generated only silane 3. The formation of 46% benzene-*d* with TPS-*d*₇ indicates relatively indiscriminate attack by phenyl radical on the solvent and HMPA. The atomic ratio of deuterium to hydrogen in the reaction mixture (D/H) was 0.72, leading to a prediction that 42% benzene-*d* should be formed on a purely statistical basis. The presence of the tertiary isopropyl deuterium must allow the slight selectivity observed. The ability of the trimethylsilyl group to donate hydrogen can be seen from the cleavage of diphenyl ether in hexamethyldisiloxane (HMS) where 21% of benzene was formed with less than 1% of benzene-*d* generated on quenching with D₂O. These data are consistent with major cleavage via phenyl radical formation and together with the previous data strongly support this contention.

With the intermediacy of the phenyl radical firmly established, we turn now to the major product from cleavage in the solvents HMS and TPS, the silane 3. Since phenyl anion does give quantitative yields of 3 from reaction in these solvents, the formation of this silane during ether cleavage might be attributed to the same source, namely, phenyl anion. This would require, however, that the phenyl radical abstract a hydrogen from diisopropyl ether as the solvent as shown above but be reduced to phenyl anion in TPS. The rates of reaction with the trimethylsilyl group and with the isopropoxy group, however, are essentially the same as shown by the relative amount of labeled and unlabeled benzene formed in TPS-*d*₇. Thus, the rate of reaction in HMS and in diisopropyl ether must be essentially the same. If the rates are the same, it is difficult to see how bimolecular reduction of phenyl radical can compete with radical abstraction in HMS and not in diisopropyl ether. In short, radical reduction cannot compete with abstraction in either solvent, and thus formation of phenyl anion becomes an insufficient explanation for silane 3 formation. Two ways formation of 3 can be explained are (1) reaction of the phenyl radical with the silyl ether in an S_N2 fashion and (2) reaction of the initial radical anion with the silyl ether via an S_N2 mechanism before aryl ether cleavage. Phenyl radical was generated in TPS from (phenylazo)triphenylmethane²⁶ at 50 °C in both the presence and absence of HMPA to distinguish between these possibilities. Benzene and triphenylmethane were the only observed products. These results

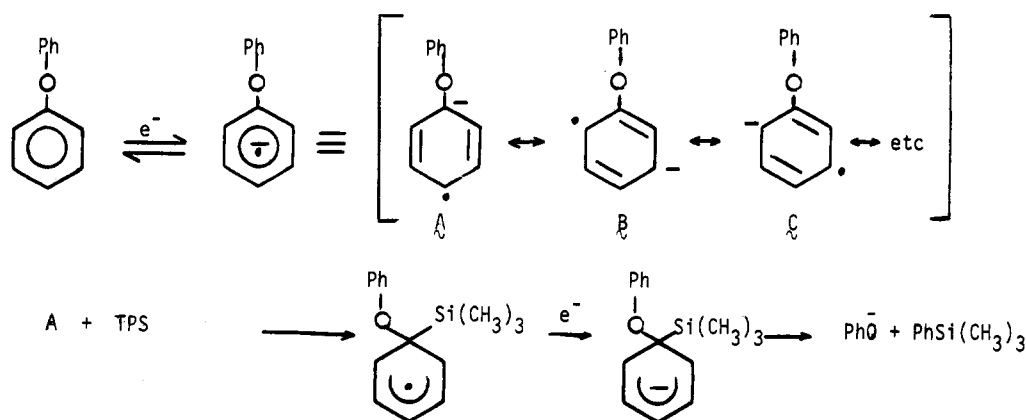
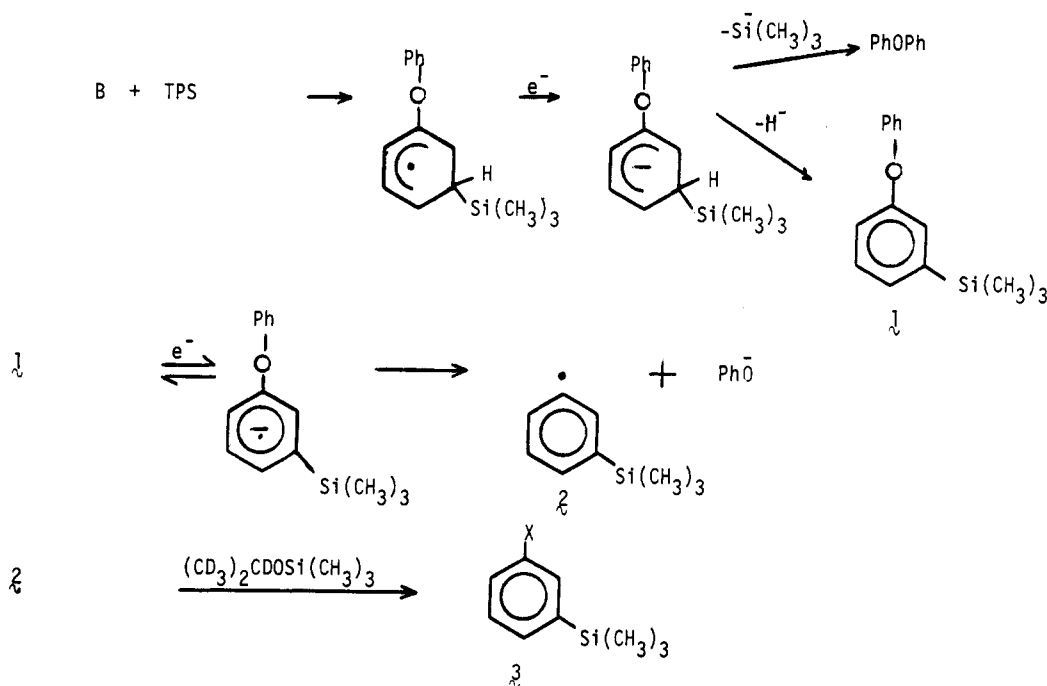
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(25) The variation of solvent, reducing metal, and structure may vary the fate of the initially formed diaryl ether radical anion. Tremelling and Bunnett (*J. Am. Chem. Soc.* 1980, 102, 7375) have recently shown that the ratio of products formed from aryl halides in the S_{RN}1 reaction in liquid ammonia depends on the halide and relative concentration of nucleophile and electrons. This control presumably originates from the relative rate of aryl radical formation. In the case of diphenyl ether cleavage under the condition used, the reaction is slow, the nucleophiles present are weak (phenoxide ion has been shown to be a poor nucleophile for S_{RN}1 reaction. See: Rossi, R. A.; Pierini, A. B. *J. Org. Chem.* 1980, 45, 2914), the electron concentration is low (the metal is not completely dissolved at the start of the reaction), and a ready source of hydrogen for abstraction is present (aliphatic ethers relative to liquid ammonia as solvent). All these factors favor benzene formation from phenyl radical by hydrogen abstraction from solvent rather than as noted in liquid ammonia by Bunnett. See also ref 19.

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Scheme I

Scheme II^a

^a X = H and/or D.

support attack on the silyl ether by the diphenyl ether radical anion before aryl ether cleavage.²⁷ Two detailed mechanisms are shown in Schemes I and II for the formation of 3. Ipso attack as shown in Scheme I can be distinguished from ortho, meta, or para attack as shown in Scheme II. Trimethylisopropoxy-*d*₇-silane was used as the solvent for diphenyl ether cleavage, and the product 3 was examined for deuterium by mass spectroscopy (Table III). The lack of evidence for formation of *o*-, *m*-, or *p*-phenoxyphenyl)trimethylsilane (1) and of deuterium labeling in the silane 3 which would result from cleavage of 1 effectively eliminates consideration of Scheme II. Furthermore, ortho, meta, and para attack require a total of three electrons for reaction to 3. Diphenyl ether (1 mol) treated with 1 mol of sodium in TPS gave 50% reaction with the same yield distribution as shown for reactions 1 and 2 in Table III, indicating that only a total of two electrons are required for reaction. These data are consistent, however, with Scheme I, involving ipso attack on

diphenyl ether before cleavage.

Two important points emerge from this study.

(1) Reductive ether cleavage under the conditions used occurs mainly via the radical anion mechanism. The phenyl radical abstracts a hydrogen atom instead of successive capture of an electron (path A). Our results strengthen the Bunnett $S_{\text{RN}}1$ mechanism²⁵ and are similar to the termination reactions of this process where stoichiometric amounts of electrons are used, and no intrusion of nucleophile is seen.¹⁹

(2) The radical anion of diphenyl ether apparently reacts with silyl ethers at the ipso position, resulting in silicon substitution on the aromatic ring.²⁸

We are presently investigating more direct methods of detecting ipso attack as well as the possibility of trapping radical anions from other aromatic ethers and hydrocarbons and from α,β -unsaturated ketones with silyl ethers and the synthetic application of the silanes produced.

(27) For evidence that radicals are converted to anions in glyme in the presence of alkali metals, see: Garst, J. E. *Acc. Chem. Res.* 1971, 4, 400.

(28) Recently nucleophilic ipso-aromatic substitution with a benzyl anion as the leaving group has been reported by: Collins, C. J.; Hambach, H. P.; Maxwell, B. E.; Benjamin, B. M.; Mckamey, D. *J. Am. Chem. Soc.* 1981, 103, 1213. We thank Professor Collins for a preprint of this paper.

Experimental Section

Ether Cleavage General Procedure. (a) **Homogeneous Conditions.** To 12.0 mmol of sodium was added to 1.10 mL (12.0 mmol) of dry hexamethylphosphoramide (HMPA) under argon or nitrogen. After this mixture was stirred at room temperature for 40 min, 5.62 mmol of aromatic ether in 10 mL of solvent (THF or diisopropyl ether) was added. The resulting mixture was maintained at room temperature for 6–24 h and then quenched with methanol or deuterium oxide. After all the unused sodium had reacted, the mixture was poured into 8% hydrochloric acid solution and extracted three times (25 mL each) with ether. The combined ether extract was washed (twice each) with 8% hydrochloric acid, water, and brine and then dried over magnesium sulfate. Analysis of the product mixture was performed by GLC with either a Drexil 300 or Tenax column with the temperature programmed from 80 to 250 °C.

(b) **Heterogeneous Conditions.** The reactions were run as above except that the HMPA was eliminated; the solvent was refluxed for the times shown in Table I.

Trimethylisopropoxysilane. Trimethylchlorosilane (10.86 g, 0.1 mol) was added dropwise to a solution of 2-propanol (6.0 g, 0.1 mol) in 100 mL of tributylamine. The reaction mixture was refluxed under nitrogen. Distillation gave 9.2 g (0.069 mol) of

trimethylisopropoxysilane: bp 87 °C (745 mm); NMR (CDCl₃) δ 00.00 (s, 9 H), 1.05 (d, *J* = 6 Hz, 6 H), 3.86 (heptet, *J* = 6 Hz, 1 H).

Preparation and Quenching of Phenylsodium. To 0.6–0.8 g of sodium (rinsed with hexane) and 30–50 mL of petroleum ether (bp 38–42 °C, distilled twice from LiAlH₄) in a flame-dried flask at room temperature was added 1.5–1.7 g of chlorobenzene (freshly distilled). The flask was immersed in an ultrasonic bath and irradiated at 30–35 °C for up to 10 h. The reaction was either (a) quenched at this time with 10 mL of D₂O, (b) treated with 10 mL of diisopropyl ether, or (c) treated with 10 mL of diisopropyl ether and 2 mL of HMPA. After the latter mixtures (b and c) were stirred for 4–5 h, they were quenched with H₂O (b) or D₂O (c), separated, dried, and analyzed by GC. In all reactions the chlorobenzene had completely reacted. Benzene-*d* analyses determined in duplicate by mass spectroscopy were as follows (a) 16.6 (*d*₀), 82.1 (*d*₁), 1.4 (*d*₂); (b) 21.7 (*d*₀), 78.2 (*d*₁), 0.4 (*d*₂); (c) 91.6 (*d*₀), 5.5 (*d*₁), 0.1 (*d*₂).

Acknowledgment. We thank Dr. Duane Bartak for helpful discussions.

Registry No. PhOPh, 101-84-8; CH₃OPh, 100-66-3; PhCH₂OPh, 946-80-5; PhCH₂OCH₂Ph, 103-50-4.

An Efficient Synthesis¹ of Methyl *dl-cis*-Jasmonate

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An efficient synthesis of methyl *dl-cis*-jasmonate is described, starting from the previously described 2-(methoxycarbonyl)-3-[(methoxycarbonyl)methyl]cyclopentanone (3), itself easily prepared from succinyl chloride and methyl potassium malonate. Alkylation of 3 with 1-bromo-2-pentyne followed by selective removal of the 2-carbomethoxy group gave dehydrojasmonic acid. On esterification and reduction (H₂/Pd/C/pyridine) of the triple bond to the *cis* olefin, dehydrojasmonic acid afforded methyl *dl-cis*-jasmonate in 40% overall yield from succinyl chloride.

The *l* isomer of methyl *cis*-jasmonate (1) is one of the essential components² of jasmine oil, is a constituent of the flavor aroma of black tea,³ and has been identified⁴ recently as the senescence-promoting agent of wormwood. Although the synthesis of the racemic form by diverse routes has already been reported,⁵ we herein present an approach that is efficient and uncomplicated and that easily allows variations in the α -side chain. Additionally, it is adaptable to large-scale synthesis.

Our route to this compound begins with the cyclopentenone diester⁶ 2, whose synthesis from succinyl chloride and methyl hydrogen malonate via a two-step procedure (68% yield overall) we have reported⁷ recently. Catalytic hydrogenation^{7,8} of 2 using a palladium-on-charcoal catalyst then gave 3 in quantitative yield. Alkylation of the latter compound with 1-bromo-2-pentyne using phase-transfer catalysis⁹ afforded the desired product 4, but the yield was only 75%, and much better results (90%) were obtained when the alkylation was carried out on the anion of 3 pregenerated by means of sodium hydride in benzene–dimethylformamide. The material from the latter reaction crystallized completely on standing and proved to be a single isomer requiring no further purification. Inspection of a molecular model shows that the

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(6) This compound was first synthesized by R. Wilstätter and A. Pfannenstiehl (*Justus Liebigs Ann. Chem.* 1920, 422, 1) by electrolysis of ethyl potassium acetone-1,3-dicarboxylate followed by base-catalyzed cyclization of the resulting diethyl 3,6-dioxosuberate. However, the electrolytic coupling proceeds in only 12% yield, making this route to 2 uneconomical.

(7) Johnson, F.; Paul, K. G.; Favara, D.; Ciabatti, R.; Guzzi, U. *J. Am. Chem. Soc.* 1982, 104, 2190.

(8) This reduction may also be accomplished with zinc dust in acetic acid, but the yield is only 80%.

(9) Brändstrom, A. *Acta Chem. Scand.* 1969, 23, 2204.