methylpentamethylenechloronium ion and 1-methyl-1-ethyltetramethylenechloronium ion, respectively.

Solutions of chloro ethers **13**, **14**, and **15** were prepared by solvolysis of 0.005 mol of the corresponding dichlorides in 5 ml of methanol containing 1.0 g of $NaHCO_3$. The reactions were followed by VPC (DC 550, 163°, glass column) and required about 9 hr reflux for completion. The products were isolated in 5 ml of CCl_4 which was washed twice with 5-ml portions of water. The ^1H NMR spectra of the products indicated that some elimination occurred during solvolysis. Nevertheless, only very minor peaks in the ^{13}C NMR spectra of the undistilled products could not be assigned to the desired substitution products, except for the solvolysis which yielded **14**. In this instance, olefin was removed by distillation at ~1 mm pressure before the NMR spectra of the undistilled residue were obtained.

The ^{13}C NMR spectrum of **13** was recorded at room temperature in CCl_4. Chemical shifts relative to the solvent peak were converted to Me_4Si reference by subtraction of 96.0 ppm. The chemical shifts (parts per million from Me_4Si) follow: 73.5, *t*-C; 48.6, OCH_3; 44.1, $-CH_2Cl$; 39.6, $-CH_2-$; 33.1, $-CH_2-$; 24.8, $-CH_3$; 21.1, $-CH_2-$.

The ^{13}C NMR chemical shifts of **14** follow: 45.0, $-CH_2Cl$; 34.4, $-CH_2-$; 30.0, $-CH_2-$; 26.7, $-CH_2-$; 22.0, $-CH_3$; 17.9, $-CH_3$. (The methoxy peak was weak in all of the spectra, probably owing to a long relaxation time, and was not always observed with certainty.)

The ^{13}C NMR chemical shifts of **15** follow: *t*-C, 58.3, C-Cl; 37.0, $-CH_2-$; 34.3, $-CH_2-$; 25.5, 25.1, and 24.8, $-CH_3$. (Note that the three methyl groups are nonequivalent owing to the asymmetric carbon.)

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Registry No.—**7**, 821-76-1; **8**, 54305-92-9; **9**, 54305-94-1; **10c**, 57256-52-7; **10h**, 57256-53-8; **11c**, 57256-54-9; **11h**, 57256-55-0; **12c**, 57256-56-1; **12h**, 50635-30-8; **13**, 57256-57-2; **14**, 57256-58-3; **15**, 57256-59-4; 1,7-heptanediol, 629-30-1; γ-chlorobutyric acid, 627-00-9; 5-chloro-2-pentanone, 5891-21-4; 1,5-dibromo-5-methylhexane, 54305-93-0; δ-valerolactone, 542-28-9; ethyl 5-bromopentanoate, 14660-52-7; ethyl 5-chloropentanoate, 2323-81-1.

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Notes

The Rapid HI Cleavage of Ethers and Ketals in Acetonitrile. Catalysis by CH_3OCHI_2 and Preparation of Formates

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The use of ethers as alcohol protecting groups in synthesis has aroused recent interest.[1] Ganem noted "the dearth of gentle yet effective techniques for releasing the parent alcohol". We wish to report that the use of acetonitrile as solvent with diiodomethyl methyl ether (DIME) catalysis promotes the classic HI cleavage[2] into the gentle and effective category at least for primary and secondary alkyl methyl ethers. Methyl ethers may be cleaved in good yield in 30 min or less at room temperature (Table I). At the cost of increasing the reaction time to hours, cleavage may be accomplished with 1 equiv of HI generated in controlled fashion by the addition of toluenesulfonic acid hydrate to excess sodium iodide. Other gentle and selective reagents are available for ether cleavage.[3,4]

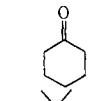
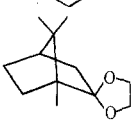
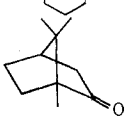
The HI cleavage of ethers in acetonitrile exhibits all the hallmarks of the classic reaction.[2]

$$ROCH_3 + HI \rightleftarrows ROH(CH_3)^+ \begin{cases} \nearrow ROH + CH_3I \\ \searrow R^+ \longrightarrow RI \end{cases}$$

When R is primary or simple secondary alkyl group, the methyl–oxygen bond is cleaved. When R^+ is a good carbonium ion, such as tertiary alkyl or benzyl, iodide is the predominant product. *exo*-Norbornyl shows intermediate behavior, yielding a 50:50 mixture of iodide:alcohol. Chiral 2-octyl methyl ether is cleaved with complete retention of the C-2–O bond. Ethers which are strong Lewis bases, such as tetrahydrofuran, 7-oxanorbornane, epoxides, and, of synthetic importance, ketals, are all cleaved readily. Cyclohexanone and camphor are regenerated in excellent yield from their ethylene glycol ketals in 5 min at room temperature in the presence or absence of DIME. Ethers which are weak Lewis bases such as tetrahydropyran, dibutyl ether, and anisole are unaffected at room temperature.[5]

DIME, prepared in situ from 1,1-dichloromethyl ether (DCME) and sodium iodide, catalyzes ether cleavage and yields formate as the predominant product. Initial speculation suggested that the oxonium ion CH_3OCHI^+ acted as a Lewis acid catalyst for the cleavage in the same manner as the reported catalysis by acetyl derivatives.[6] However, unyielding experiments showed that if all reagents are rigor-

Table I
Ether Cleavage at Room Temperature in Acetonitrile

Registry no.	Ether ($ROCH_3$)	Reaction conditions[a] NaI:DCME:H_2O	% yield of products[b,c] ROOCH	RI	ROH	$ROOCCH_3$
929-56-6	1-Octyl methyl ether	A 4:2:1	43	40	2	8
		A 4:2:2	60	28	11	*d*
		A 8:2:2	41	41	0	*d*
		A 8:4:4	61	22	15	*d*
		B 8:4:4	75	13	2	2
					(69)	
		C 4:2:3.5		25	42	9
56711-42-3	2-Octyl methyl ether	A 4:2:2	48	35	0	*d*
		A 8:4:4	75	14	7	*d*
		A 8:2:10	0	*d*	*d*	*d*
		B 8:4:4	75	8	9	5
					(84)	
		C 8:4:4		7	87	
57132-05-5	2,4-Dimethyl-3-pentyl methyl ether	A 8:4:1	47	5		
		B 8:4:4	41	*d*	9	*d*
					(35)	
		C 8:4:3			48	
5614-37-9	Cyclopentyl methyl ether	A 4:2:2	70	14		2
931-56-6	Cyclohexyl methyl ether	A 8:4:4	52	6		
32122-44-4	1-Methylcyclohexyl methyl ether	A 4:2:2	0	16	0	0
10395-53-6	*exo*-Norbornyl methyl ether	A 8:4:3	35	37[e]	0	0
		B 8:4:4	40	40	0	0
				(32)	(18)	
		C 4:2:14		37	36	
5331-32-8	Borneol methyl ether	B 8:3:5	75			
		C 5:1:19			83	
100-66-3	Anisole	A 8:4:4	0	0	0	0
538-86-3	Benzyl methyl ether	A 4:2:2	0	*f*	0	0
929-56-6	1-Octyl ethyl ether	A 8:4:2	11	17		
42-96-1	Di-1-butyl ether	A 8:4:2	0	0	0	0
		C 8:8:36	0	*d*	0	0
109-99-9	Tetrahydrofuran[g]	A 4:4:2	80	8	7	5
		A 4:2:2	85	11	*d*	*d*
		C 4:4:0.5		27	32	
96-47-9	2-Methyltetrahydrofuran[h]	A 8:5:2	59	32		
142-68-7	Tetrahydropyran[i]	A 4:4:2	0	0	0	0
		C 8:8:36		5	5	2
279-49-2	7-Oxanorbornane[j]	A 4:2:2	57	0	31	
		C 8:2:1.5			73	
		A 8:4:0[k]			95	
177-10-6		C 8:4:0.25[k]			95	
18501-53-6		A 8:4:4[k]			87	
		B 4:2:0[k]			(83)	

[a] A and B reaction times 20–30 min. A, DIME reactions run on ca. 5 mmol of ether in 10 ml of MeCN. Numbers following refer to equivalents of NaI, DCME, and H_2O, respectively. B, DIME reactions run on preparative scale of at least 0.1 mol. The second line gives the isolated yield of alcohol after hydrolysis with KOH in aqueous ethanol. C, HI reactions run on ca. 5 mmol of ether in 10 ml of MeCN. Numbers following refer to equivalents of NaI, $TsOH \cdot H_2O$, and the time in hours, respectively. [b] GC yields with internal standard. Yields for type B reactions are GC determinations on isolated crude mixture. Numbers in parentheses are isolated yields. [c] R is identical in starting ether and product unless noted. Structures were confirmed by comparison with authentic samples, by ir and NMR spectroscopy, and in the case of formates, by hydrolysis to alcohol starting materials. [d] Present in low yield; actual quantity not determined. [e] Stereochemistry established by comparison of NMR spectrum with that of authentic sample: H. C. Brown, N. R. DeLue, and E. N. Peters, submitted for publication. [f] Benzyl iodide formed in good yield; actual quantity not determined. [g] R = 4-iodobutyl. [h] R = 5-iodo-2-pentyl. [i] R = 5-iodopentyl. [j] R = *trans*-4-iodocyclohexyl. Confirmed by ir [Y. Takeoka, *Bull. Chem. Soc. J.*, **35**, 1371 (1962)] and ^{13}C NMR. [k] Reaction time 10 min.

ously dried, there is no ether cleavage except for limited reaction of the most reactive ethers. Addition of 1 or more equiv of water regenerates reactivity. Furthermore, when excess proton specific base, 2,4,6-tri-*tert*-butylpyridine,[7] is present no cleavage occurs over several hours. Thus the mechanistic aspects of DIME catalysis remain obscure, but its practical efficacy is apparent (Figure 1). The alcohol could be an intermediate in the reaction, as it was demonstrated that alcohol could be converted to formate and incompletely to iodide under reaction conditions. Formate and iodide are stable to reaction conditions. The importance of iodide nucleophilicity was demonstrated not only by the selectivity for methyl cleavage, but also by the cleavage of 2-methyltetrahydrofuran to give 5-iodo-2-pentyl formate with no detectable 4-iodo-1-pentyl formate. Several other reaction solvents were tested. Methylene chloride, cyclohexane, and dimethylformamide gave very little cleavage product. Acetone was suitable for reactive ethers, but mesityl oxide condensation is faster than ether cleavage in most cases. Nitromethane gave similar results to acetonitrile, but more slowly.

Water content and temperature have a significant effect

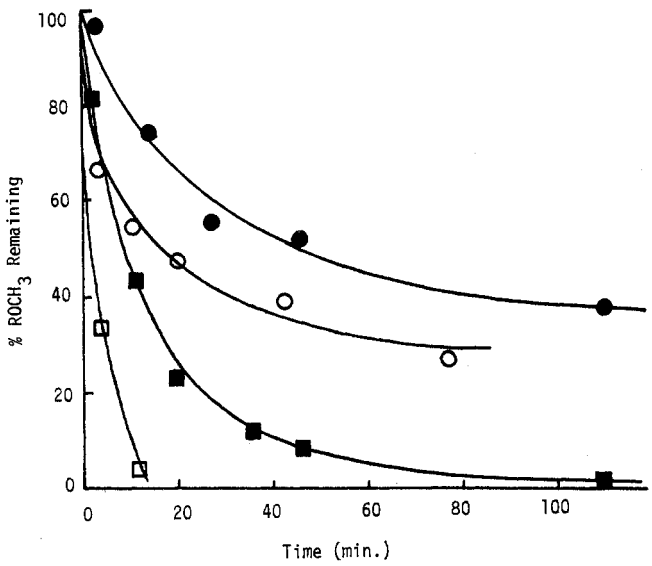


Figure 1. Cleavage of 2-octyl methyl ether at 27° (solid) and 47° (open) with DIME (squares) and HOTs–NaI (circles).

on formate/iodide product ratio. With limited water, iodide becomes the predominant product even with 1-octyl methyl ether. The use of 4 equiv of water reduces the iodide fraction to less than 10%. (Table II). Experiments with ^{18}O-labeled water showed that there was no label incorporation (2% detectable) in the ester oxygen of the formate.[8] It is interesting to note that the specific rotation of 2-octyl iodide derived from cleavage of (*R*)-2-octyl methyl ether was 33.6° (52% inversion)[9] with 0.5 equiv of water but only 12.9° (20% inversion) with 4 equiv. Higher temperatures decrease the formate/iodide ratio. In preparative scale reactions, if no cooling is applied during the exothermic addition of DCME to the reaction mixture, formate/iodide ratios may approach 1:1 rather than the room temperature value of approximately 10:1.

In addition to formate, alcohol, and iodide, iodine and the acetate ester of the alcohol are normally formed in small amounts (1–2%). The acetate presumably arises from acid-catalyzed alcoholysis of the acetonitrile solvent. Both acetate and formate may be hydrolyzed to alcohol by stirring with aqueous base during work-up.

An interesting sidelight in the chemistry of DIME is that when sodium iodide and dichloromethyl ether are mixed in acetonitrile under strictly anhydrous conditions, a substantial quantity of carbon monoxide is evolved over 3 hr. Nucleophilic displacement by iodide of the methyl group on CH_3OCHI^+ to give unstable formyl iodide is an appealing rationale.

Table II
Influence of Water on Product Ratio[a]

Ether ($ROCH_3$)	Reaction conditions NaI:DCME:H_2O	% yield of products ROOCH	RI	ROH
1-Octyl methyl ether	A 8:4:0.5	*d*	44	0
	A 8:4:1	22	70	0
	A 8:4:3	57	15	11
	A 8:4:4	61	22	15
	A 8:4:5	51	17	11
2-Octyl methyl ether	A 8:4:0.5	35	53	0
	A 8:4:1	57	43	0
	A 8:4:4	75	14	7
Tetrahydrofuran	A 4:4:0	29	18	0
	A 4:4:0.5	64	30	0
	A 4:4:2	80	8	7

[a] See Table I for footnotes. Reaction time 20 min, DCME added in two lots, half originally and half after 10 min.

Experimental Section

GC analysis was performed on a Varian 90-P3 instrument using a 10 ft × 0.25 in. 10% SE52 on Chromosorb W AW/DMCS with helium carrier gas. Infrared spectra were recorded on neat samples between salt plates on Perkin-Elmer 137 or 727 spectrophotometers. Nuclear magnetic resonance spectra were recorded on Perkin-Elmer R-32 and Varian A-60A, XL-100, and CFT-20 spectrometers. All spectra are reported in parts per million from internal tetramethylsilane. Rotations (Na D line, 1-dm cell, absolute ethanol) were measured on a Zeiss polarimeter.

Materials. The materials were standard commercial reagents. Acetonitrile (Mallinckrodt) was used without purification for preparative reactions and was distilled from CaH_2 for small-scale reactions. Sodium iodide (Mallinckrodt) was used as obtained; sodium iodide (Baker) contained *ca.* 7% water and was dried before use. DCME was prepared by the method of Reiche, Gross, and Hoft.[10] Chemical and spectral analysis demonstrated its purity. Anal. Calcd for $C_2H_4OCl_2$: C, 20.90; H, 3.51; Cl, 61.68. Found: C, 21.06; H, 3.48; Cl, 61.78. Methyl ethers were prepared by standard methods[11,12] and properties were consistent with the literature.

3-Methoxy-2,4-dimethylpentane was prepared in 67% yield using the NaH–MeI procedure:[11] bp 119–122°; ir 3.33, 3.38, 3.44, 3.50, 6.8, 7.2, 7.3, 9.0, 9.1, 10.0, 10.6, 11.1 μ; NMR δ 3.44 (s, OCH_3), 2.51 (t, *J* = 5.5 Hz, C_3H), 1.75 (m, C_2H C_4H), 0.92 (d, *J* = 7 Hz, CH_3). Anal. Calcd. for $C_8H_{18}O$: C, 73.78; H, 13.93. Found: C, 73.74; H, 13.85.

Ether Cleavage Procedure. Type A. The cleavage of (−)-(*R*)-2-octyl methyl ether is illustrative of a type A cleavage (A 844). (−)-(*R*)-2-octyl methyl ether[13] ($[\alpha]^{22}D$ −7.03 ± 0.15°, 720 mg, 5.0 mmol) was dissolved in dry MeCN (50 ml) together with NaI (6.0 g, 40 mmol) and water (360 μl, 20 mmol) in a side arm 100-ml flask equipped with magnetic stirrer, drying tube, and rubber stopple. DCME (0.95 ml, 10 mmol) was added by syringe with stirring. NaCl precipitation occurred immediately. After 10 min a second addition of DCME (10 mmol) was made to the yellow solution. After a total time of 20 min, the reaction mixture was poured into saturated $NaHCO_3$ solution (50 ml) layered with ether (50 ml) in a 1-l. beaker (foam). A few crystals of $Na_2S_2O_3$, to remove the iodine, and solid K_2CO_3 were added until CO_2 evolution ceased. The ether layer was washed with water (4 × 100 ml) and NaCl solution (100 ml), dried, and evaporated. GC analysis (internal standard, *p*-bromotoluene) showed (*R*)-2-octyl formate[14] (75%, $[\alpha]^{22}D$ 6.09°), (*S*)-2-octyl iodide (14%, $[\alpha]^{22}D$ 12.94°), 2-octanol (7%, activity not determined), and a trace of 2-octyl acetate. Samples for rotation measurements were obtained by preparative GC and checked for purity by reinjection. (*R*)-2-octyl formate (300 mg, $[\alpha]^{22}D$ 6.09°) was stirred for 10 min with NaOH (200 mg) in 50% aqueous ethanol (6 ml). GC analysis showed complete hydrolysis. Ether extraction and preparative GC gave pure (*R*)-2-octanol ($[\alpha]^{22}D$ −9.13°). The original (*R*)-2-octanol had $[\alpha]^{22}D$ −9.29°.

The reactions shown in Figure 1 were run in constant-temperature baths; in synthetic reactions, the temperature was not controlled and there was a slight exotherm at the start of the reaction.

Iodide Exchange Rate of 2-Octyl Iodide. A sample of GC pure (+)-(*S*)-2-octyl iodide (245 mg, 1.0 mmol $[\alpha]^{22}D$ 33.94°) was dissolved with 4.00 mmol of NaI in 8.0 ml of acetonitrile. DCME (2.0 mmol) was added by syringe, and the reaction mixture was stirred at room temperature for exactly 20 min. The iodide was isolated and purified by GC in the manner described previously. Its specific rotation was $[\alpha]^{22}D$ 26.26°. The specific rate constant for iodide exchange is estimated to be 4×10^{-2} l. mol^{-1} min^{-1}.

Type B. The procedure given under type A was followed with direct scale-up, but MeCN was not rigorously dried. The reaction vessel was placed in an ice-water bath to maintain a temperature of 25–40° until the heat from the DCME additions was dissipated (ca. 15 min total). Reaction times as long as 30–40 min were sometimes employed. The course of the reaction may be monitored by GC. Product was isolated by distillation at either the formate or alcohol stage.

Type C. The cleavage of (−)-(*R*)-2-octyl methyl ether is illustrative (C 84). The ether (2 mmol, $[\alpha]^{22}D$ −6.88°) was stirred with NaI (8 mmol) in MeCN (15 ml) and $HOTs \cdot H_2O$ (4 mmol) was added. Sodium tosylate precipitated immediately and the mixture was stirred for 20 min. Product was isolated by the procedure given above. Recovered ether had specific rotation −7.08°. (*R*)-2-octanol had rotation −9.40°. No 2-octyl iodide was observed by GC. In

preparative reactions, the time for the reaction is best determined by GC analysis as reaction proceeds. In one experiment with 2-octyl methyl ether, 1 equiv of $HOTs \cdot H_2O$ was dissolved in the minimum volume of MeCN and added to the solution dropwise over 30 min, and reaction was >95% complete in 2 hr.

Influence of 2,4,6-Tri-*tert*-butylpyridine. When 2 or more equiv of 2,4,6-tri-*tert*-butylpyridine per equivalent of DCME are present in the initial solution, no cleavage of THF or cyclohexanone ketal was detected in 3 hr. If 1 equiv of the pyridine is used, THF yields ca. 50% cleavage products and cyclohexanone ketal is cleaved completely.

Cleavage of Ketals. Camphor and cyclohexanone ethylene glycol ketals were prepared by standard methods.[15] Cleavage was accomplished by the methods given above (Table I), but reaction time was always less than 5 min.

Carbon Monoxide Formation. DCME (10 mmol) and NaI (20 mmol) were dissolved in MeCN (20 ml of Spectrograde) and stirred at room temperature. Gas was evolved over 3 hr (134 ml, 6 mmol) and was collected in a gas buret. Mass spectroscopy and ir analysis identified the gas as CO. CO evolution was also detected during the ether cleavage reactions, but the quantities were smaller.

^{13}C Spectra of *exo*- and *endo*-Norbornyl Iodide. ^{13}C spectra were recorded on CFT-20 with proton noise decoupling on neat samples containing internal Me_4Si and acetone-d_6. Assignments were made on the basis of off-resonance proton-decoupled spectra.[16] Exo: 47.9, C-1; 45.1, C-3; 37.9, C-4; 36.2, C-7; 29.3, C-2; 28.6, 28.4, C-5 and C-6, not distinguished. Endo: 45.1, C-1; 43.7, C-3; 37.3, C-4; 36.3, C-7; 32.4, C-2; 29.9, 28.7, C-5 and C-6, not distinguished.

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Registry No.—Acetonitrile, 75-05-8; 1,1-diiododimethyl ether, 57132-06-6; hydriodic acid, 10034-85-2; dichlorodimethyl ether, 4885-02-3; (+)-(*S*)-2-octyl iodide, 1809-04-7; 2,4,6-tri-*tert*-butylpyridine, 20336-15-6; *endo*-norbornyl iodide, 57173-48-5; *exo*-norbornyl iodide, 30983-85-8.

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α-Hydroperoxy Acids via Direct Oxygenation[1]

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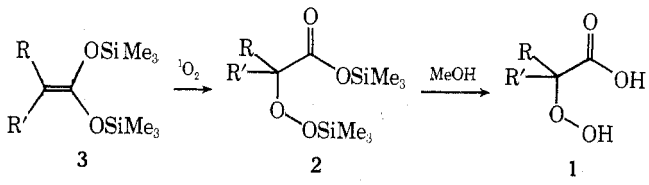
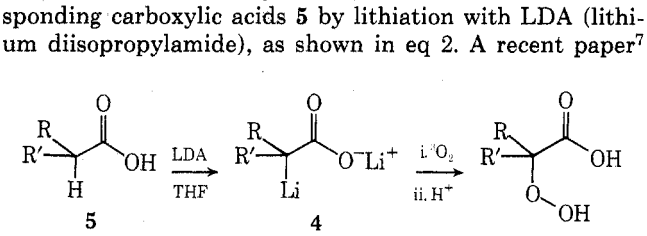
In the preparation of α-peroxylactones, which serve as active intermediates in bioluminescence,[2] we required the α-hydroperoxy acids **1** as precursors. We accomplished the preparation, isolation, and characterization of the first authentic α-hydroperoxy acids **1** by employing singlet oxygenation of the bis(trimethylsilyl) ketene acetals **3**, followed by desilylation of the bis(trimethylsilyl) derivative **2** with methanol (eq 1).[3] The success of our method rested on



(1)

the oxygenophilic nature of silicon, which promotes a silatropic shift with singlet oxygen, quite analogous to the classical ene reaction.[4] Simultaneously with oxygen fixation at the α carbon to the carbonyl group, the hydroperoxide and carboxylic acid functionalities are protected against base- and acid-catalyzed Grob fragmentation[5] of the hydroperoxy acid **1** by trimethylsilylation. The trimethylsilyl groups on one hand permit isolation and purification by distillation at reduced pressure, and on the other hand they permit quantitative release of the OOH and CO_2H functionalities by desilylation with neutral methanol.

The disadvantage of this novel oxygenation is that it lacks generality because secondary and primary alkyl groups in the ketene acetal **3** suffer prototropic shifts (ene reaction) with singlet oxygen. For this reason we investigated some time ago[6] the feasibility of the direct oxygenation of α-lithiocarboxylates **4**, derived from the corresponding carboxylic acids **5** by lithiation with LDA (lithium diisopropylamide), as shown in eq 2. A recent paper[7]



(2)

obliges us to communicate our results on this direct α-oxygenation of carboxylic acids **5** with triplet oxygen. Our experimental procedure is particularly advantageous for low molecular weight substrates which require special precautions in view of their thermal lability and high hygroscopic character. If the dianion **4** is prepared in the absence of HMPA, oxygenated at ca. −100 to −90° by slow addition of dianion **4** to an oxygen-saturated solution, protonated at −100°, and the work-up and purification carried out at subambient conditions, the degree of oxygenation can be effectively quantitative, affording crude α-hydroperoxide product in about 80%. Our recommended general procedure is described below and employed in the preparation of 2-hydroperoxy-2-methylpropionic acid (R = R′ = Me) and 3,3-dimethyl-2-hydroperoxybutyric acid (R = *t*-Bu; R′ = H).