crease in acidity of the dilithium derivatives of glycolic and lactic acids relative to that of mandelic acid. Alternatively, solubility problems in reactions leading to **2** and **3** may have interfered with the reactions.

The alkylation results imply at least a transitory existence for enetriolate **1**. Less ambiguous evidence for **1** includes the observation of 41% deuterium incorporation into mandelic acid when the reaction mixture was treated with 20% DCl in D_2O. Since low deuterium incorporation has been observed in deuterations of similar anions solvated by amines,[8] we believe that the alkylation results of **1** are best explained by assuming that nearly complete deprotonation of lithio mandelic acid to give **1** has occurred as shown in eq 1. This interpretation is also consistent with the results of the competition experiments discussed below.

We attempted to characterize enetriolate **1** by both UV-visible spectroscopy and ^{13}C NMR spectroscopy. In the UV-visible spectrum **1** exhibits only end absorption even in dilute solution (ca. 1×10^{-3} M). Absorption by other species in the base solution precluded measurement of either λ_{max} or an extinction coefficient. Solubility problems frustrated our attempts to measure the ^{13}C NMR spectrum of **1**.

We have qualitatively measured the kinetic pK_a of the dilithium derivative of mandelic acid using competitive deprotonation reactions. When a solution containing 1 equiv each of mandelic acid and phenylacetic acid was treated with 4 equiv of LDA, exclusive C–H deprotonation of the phenylacetic acid occurred as measured by the observation of deuterium incorporation only into the phenylacetic acid upon deuteration. Accordingly, we estimate that the kinetic pK_a of the dilithium derivative of mandelic acid is at least 2 units greater than that of the lithium salt of phenylacetic acid. In a similar experiment, an equal molar solution of mandelic acid and triphenylmethane was treated with 3 equiv of LDA under conditions which normally gave **1**. In this case deuteration with DCl in D_2O gave triphenylmethane which contained 5–15% deuterium at the methyl carbon; recovered mandelic acid again contained ca. 40% deuterium at C-2. Finally, treatment of an equal molar mixture of mandelic acid and decanoic acid with 4 equiv of LDA followed by a DCl/D_2O quench yielded a mixture of partially deuterated mandelic and decanoic acids. Thus, the α-C–H of the dilithium derivative of mandelic acid has kinetic acidity at least comparable (within 2 units) to triphenylmethane and lithium decanoate.

Unfortunately, the lack of thermodynamic pK_a values for lithium salts of carboxylic acids precludes us from making a quantitative statement concerning the effect of an adjacent negatively charged heteroatom on C–H pK_a. Qualitatively the α-O–Li group has, as expected, lowered the kinetic acidity of this proton and the α-O–Li has an effect comparable to that of a phenyl substituent[9] but in the opposite direction.

Experimental Section

All preparations involving active organometallic compounds were conducted under nitrogen using conventional inert atmosphere techniques. NMR spectra were recorded on a Varian T-60 NMR spectrometer. Analytical gas chromatography was performed on a 6 ft × 1/8 in. SE-30 column using a Hewlett Packard Model 3830 gas chromatograph. Cyclohexyl iodide was prepared by the method of Stone and Shechter.[10] All other reagents were purchased from commercial sources in reagent quality and used without further purification. Alkylation products were converted to ethyl esters and identified by NMR spectral and gas chromatographic comparison to authentic materials. THF was distilled from sodium–benzophenone, and HMPA was distilled at reduced pressure from sodium. Deuterium incorporation was determined by comparing the integrals of various peaks in the NMR spectra of the deuterated compounds.

General Procedure. A solution of ca. 1 mmol of α-hydroxy acid and an equivalent amount of internal standard in 10 mL of THF was added at −78 °C to a THF solution containing 3.3 equiv of LDA (from diisopropylamine and *n*-BuLi). The resulting mixture was allowed to warm and was stirred for 1 h at 25 °C and then cooled to −78 °C. A THF solution of 2 equiv of the electrophile was added and the mixture was allowed to warm and was stirred at 25 °C for 24 h. Following conventional acidic workup, the product was extracted into ether and the ethereal solution was distilled in vacuo. The residue was esterified in ethanolic HCl and the esterified products were analyzed by gas chromatography.

Deuterations. After preparation of the enetriolate as described above, the reaction mixture was added by syringe to an excess of 20% DCl in D_2O and then worked up immediately and analyzed by NMR for deuterium incorporation.

Acknowledgments. This work was generously supported by the Robert A. Welch Foundation.

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Synthesis of *tert*-Butoxymethyl Ethers: A New Protecting Group for Alcohols

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A common protecting group for alcohols and phenols is the methoxymethyl ether (I), available in high yield from ei-

$$\mathrm{ROCH_2OCH_3}$$

I

ther chloromethyl methyl ether[1] or dimethoxymethane.[2] Unfortunately, removal of this protecting group often requires conditions too vigorous for sensitive functionalities (hot aqueous mineral acid).[1-3] Because of the relative lability of the *tert*-butyl protecting group,[4] we reasoned that the corresponding *tert*-butoxymethyl ether (II) would decompose

$$\mathrm{ROCH_2OC(CH_3)_3}$$

II

readily under mild conditions and thus extend the utility of acetals as an alcohol protecting group.[5] Consequently, we set out to prepare chloromethyl *tert*-butyl ether, a hitherto unknown compound.

This task proved to be more difficult than had been anticipated. The reaction of an alcohol with formaldehyde or trioxane and hydrogen chloride gives the corresponding chloromethyl ether[6] but all attempts to generate the desired compound in this way failed. The reaction of *tert*-butyl alcohol with paraformaldehyde or trioxane in the presence of aqueous or gaseous hydrogen chloride or hydrogen bromide

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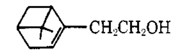
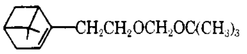
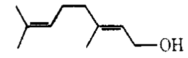
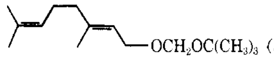
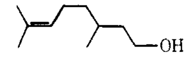
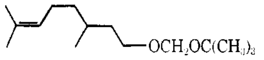
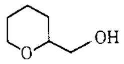
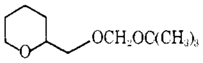
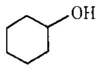
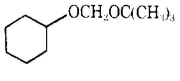
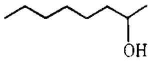
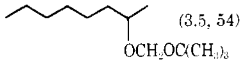
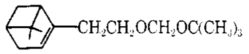
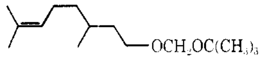
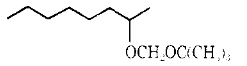
Table I. Conversion of Alcohols into *tert*-Butoxymethyl Ethers

alcohol	registry no.	acetal (g, %)[a]	registry no.
$CH_3(CH_2)_5OH$	111-27-3	$CH_3(CH_2)_5OCH_2OC(CH_3)_3$ (8.8, 79)	66922-41-6
$CH_3(CH_2)_7OH$	111-87-5	$CH_3(CH_2)_7OCH_2OC(CH_3)_3$ (4.6, 71)	66922-42-7
$C_6H_5CH_2OH$	100-51-6	$C_6H_5CH_2OCH_2OC(CH_3)_3$ (8.7, 76)	66922-43-8
	128-50-7	 (6.6, 80)	66922-44-9
	624-15-7	 (5.0, 70)	66922-45-0
	106-22-9	 (5.4, 74)	66922-46-1
	100-72-1	 (3.6, 60)	66922-47-2
	108-93-0	 (3.2, 56)	66922-48-3
	123-96-6	 (3.5, 54)	66922-49-4

[a] Refers to pure, isolated product.

Table II. Deprotection of *Tert*-Butoxymethyl Ethers

acetal	% yield of alcohol[a]
$CH_3(CH_2)_7OCH_2OC(CH_3)_3$	85
	88
	86
	90

[a] Refers to pure, isolated product.

yields the corresponding *tert*-butyl halide as the only product.

The other method which was examined as a possible route to the desired chloro ether is the free radical halogenation of *tert*-butyl methyl ether.[7,8] Unfortunately, *N*-bromosuccinimide[8] gives only *tert*-butyl bromide when reacted with *tert*-butyl methyl ether and sulfuryl chloride[8,9] did not react. On the other hand, chlorine[8] and *N*-chlorosuccinimide (NCS)[8] each produce the desired chloro ether. Because of the relative inconvenience of using chlorine, NCS is the reagent of choice. Thus, *tert*-butyl methyl ether and NCS yield chloromethyl *tert*-butyl ether as a solution in CCl_4 which is stable under nitrogen at room temperature.[10]

With the chloro ether in hand, synthesis of the acetals is easy. The alcohol is dissolved in THF and stirred with the chloro compound in the presence of triethylamine. Table I shows the alcohols which have been protected in this way. For example, 1-hexanol gives the corresponding *tert*-butoxymethyl acetal in 79% isolated yield. Phenols do not work as well; phenol (2.82 g) yields 1.37 g (25%) of *tert*-butoxymethyl phenyl ether and *m*-methoxyphenol gives 23% of the corresponding acetal. On the other hand, *tert*-butoxymethyl phenyl sulfide is isolated in 82% yield from thiophenol.

Deprotection of the acetals II is accomplished with aqueous trifluoroacetic acid at room temperature (see Table II). For example, citronellol is obtained in 86% yield, showing that no side reaction occurred during deprotection despite the presence of a nucleophilic double bond. Under identical conditions, the methoxymethyl ether of 1-octanol is stable so that the goal of designing an acetal protecting group which is more labile than methoxymethyl ethers is attained. It is of interest that the *tert*-butoxymethyl ethers are stable to hot glacial acetic acid, aqueous acetic acid at room temperature, and anhydrous trifluoroacetic acid at room temperature. Consequently, other acid-sensitive protecting groups can be removed selectively.

Application of this new protecting group in the selective manipulation of polyfunctional molecules is under investigation.

Experimental Section

^1H NMR spectra were obtained on a Varian T-60 nuclear magnetic resonance spectrometer and a Perkin-Elmer Model 237B grating spectrometer was used for infrared spectra.

A general experimental procedure follows.

Methyl *tert*-butyl ether[11] (100 mmol) is dissolved in 70 mL of CCl_4 and stirred with 120 mmol of NCS for 6 h with Hanovia sun lamp irradiation. The reaction flask is placed in a water bath and maintained at 35–38 °C[12] during the irradiation. The succinimide is removed by filtration and NMR analysis of the filtrate shows the chloromethyl *tert*-butyl ether (δ 1.25 (s, 9 H), 5.60 (s, 2 H)).

The alcohol (30 mmol) is dissolved in 20 mL of THF and stirred with triethylamine (120 mmol). This solution is cooled to −20 °C (dry ice/CCl_4) and the chloro ether solution from above (precooled to −20 °C) is added. The reaction mixture is allowed to warm to room temperature, stirred for 3 h, and filtered. The brown solution is separated, dried, and concentrated. Chromatography of the crude product through alumina with hexane removes a nonpolar by-product. Continued elution with benzene yields the *tert*-butoxymethyl ether which is then distilled.[13]

The acetal (4.2 mmol) is mixed with 19 mL of 1:1 trifluoroacetic acid–water and enough THF is added to make the reaction mixture homogeneous. After 48 h, workup with aqueous $NaHCO_3$ yields the crude alcohol which is purified by Kugelrohr distillation. The pure alcohol is identical with authentic material by IR, NMR, and TLC.

Registry No.—*tert*-Butyl methyl ether, 1634-04-4; chloromethyl *tert*-butyl ether, 40556-01-2.

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(4) C. B. Reese in "Protective Groups in Organic Chemistry", J. F. W. McOmie, Ed., Plenum Press, London, 1973, p 97.

(5) Other acetals which are commonly used as protecting groups for alcohols are the tetrahydropyranyl ether (ref 4, p 104), ethoxyethyl ether (S. Chladek and J. Smrt, *Chem. Ind.* (*London*), 1719 (1964)), 2-methoxyisopropyl ether (ref 4, p 107), and 4-methoxytetrahydropyranyl ether (ref 4, p 108). Removal of all of these groups can be accomplished with dilute, aqueous acid. They are prepared from the corresponding vinyl ether with *acid catalysis*. The methoxymethyl ether,[1] as well as our *tert*-butoxymethyl ether, is prepared from the chloro ether with *base catalysis*.

(6) See, for example, (a) the synthesis of chloromethyl methyl ether: C. S. Marvel and P. K. Porter, "Organic Synthesis", Collect. Vol. I, 2nd ed, A. H. Blatt, Ed., Wiley, New York, N.Y., 1941, p 377; (b) the preparation of methoxyethyl chloromethyl ether: E. J. Corey, J.-L. Gras, and P. Ulrich, *Tetrahedron Lett.*, 809 (1976); and (c) a review on α-halo ethers: L. Summers, *Chem. Rev.*, **55**, 301 (1955).

(7) Ethers are halogenated on the α carbon: M. L. Poutsma in "Methods in Free Radical Chemistry", Vol. 1, E. S. Huyser, Ed., Marcel Dekker, New York, N.Y., 1969, p 137.

(8) Methods for the free-radical halogenation of organic compounds have been reviewed: E. S. Huyser, *Synthesis*, 7 (1970).

(9) Sulfuryl chloride has been used to chlorinate tetrahydrofuran (THF): C. G. Kruse, N. L. J. M. Broekhof, and A. van der Gen, *Tetrahedron Lett.*, 1725 (1976).

(10) All attempts to isolate the chloro ether by concentration have led to decomposition.

(11) J. F. Norris and G. W. Rigby, *J. Am. Chem. Soc.*, **54**, 2088 (1932).

(12) There is no reaction at 0 °C after 4 h but a satisfactory reaction rate is obtained at room temperature. The water bath is used for cooling purposes only.

(13) The ^{1}H NMR spectra of the *tert*-butoxymethyl ethers show singlets at δ 4.1–4.7 (2 H) and 1.2–1.25 (9 H). The corresponding ^{13}C NMR spectra are also consistent with the proposed structures. For example, the acetal and quaternary carbons are found at δ 89.248 and 74.251, respectively, for the benzyl alcohol acetal and δ 90.038 and 74.068, respectively, for the 1-hexanol acetal.

Desiccant Efficiency in Solvent Drying. 3. Dipolar Aprotic Solvents[1,2]

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It is generally acknowledged that dipolar aprotic solvents are the media of choice in some reactions and are unique in facilitating others.[3] The special solvent effects of molecules such as DMF and Me$_2$SO are attributable to their large dielectric constants coupled with the absence of solvation by hydrogen bonding and typically manifest themselves in properties such as poor anion solvation, voracious cation solvation, and a marked hydrophilicity. For the chemist, this latter feature is unfortunate since small amounts of water in these systems can diminish[3,4] their nucleophilicity and may even be hazardous to some operations.[5] The drying of these solvents is thus of paramount importance, but in these cases, as previously,[1] the chemical literature contains little reliable quantitative data.

We have recently developed a method of solvent water assay which utilizes a tritiated water tracer for the determination of water content.[6] The method circumvents many of the problems encountered in other assay methods and has provided some new correlations on the efficiency of desiccants.[1,2] For example, it has been shown that, rather surprisingly, the efficiency of a given desiccant is strongly dependent upon the solvent type,[1] and there is thus much uncertainty in extrapolating generalizations from one solvent type to another.

The method has now been applied to the desiccation of the dipolar aprotics acetone, DMF, Me$_2$SO, and HMPT. Since the dielectric constants of these solvents range between 20.7 (acetone) and 46.7 (Me$_2$SO), their rigorous desiccation is expected to be difficult.

Results and Discussion

Drying of Hexamethylphosphoric Triamide (HMPT). *Caution! HMPT is a suspected carcinogen.* Although in recent years the favored desiccant for HMPT appeared to be calcium hydride,[7] drying has also been previously accomplished with alkali metals,[5,8] alkali metal earth oxides,[8] and 4A[9a] and 13X[9b] molecular sieves.

The results with the siccatives summarized in Table I are largely self-evident, but the following points are worth noting. The extreme resistance to desiccation is demonstrated by the impossibility of obtaining *super-dry*[10] HMPT under any of the conditions used here. Even sequential drying,[11] which was previously found to be effective with acetonitrile,[2] falls short in this case. The use of sodium–potassium alloy as a drying agent seems questionable in view of the thermal instability of solutions of alkali metals in solvents of this type.[12]

Since phosphorus pentoxide causes loss of material through side reactions, the best procedure for drying HMPT appears to be distillation from calcium hydride followed by storage over molecular sieves.

Drying of Dimethylformamide One source[8] observes that it is doubtful whether distillation alone can remove water from this solvent and recommends a chemical method for the elimination of protonic impurities. 4A molecular sieves, alumina, potassium hydroxide, and calcium hydride have all been endorsed as siccatives[8] for DMF.

The results in Table II indicate the powerful hydrophilicity of this solvent, although sequential drying with 3A sieves almost achieves *super-dryness.* Interestingly, and contrary to an earlier suggestion,[13] while some of the basic dessiccants investigated are totally inept, e.g., alumina and potassium carbonate, others such as calcium hydride and potassium hydroxide achieve quite reasonable drying levels. Also, although seldom advocated for use in this circumstance, phosphorus pentoxide is a commendable desiccant. For DMF, however, barring impurities other than water, by far the

Table I. Efficiency of Desiccants in the Drying[a] of HMPT[b]

desiccant	residual solvent water content, ppm				
	6 h	24 h	72 h	144 h	other conditions
P$_2$O$_5$	1840[c]				22[d]
CaH$_2$	1750	857	347	248	80[d]
B$_2$O$_3$					190[e]
3A molecular sieves	1380	595	307	239	
4A molecular sieves	1167	610	344	269	29[f]
KOH (powdered)	1380	840	404		321[f]
Na–K					1620[d,g]
BaO	2190	1540	1040		
CaO	2360	2034	1890	1380	
CaSO$_4$	2080				
Al$_2$O$_3$	2134				

[a] Static drying modes unless otherwise specified. [b] Desiccant loading 5% w/v; initial water content 2620 ppm (0.262% w/w). [c] Strongly colored solution. [d] Distilled sample. [e] Stirring for 24 h followed by distillation. [f] Sequentially dried sample, 72 h. [g] Significant quantities of dimethylamine are released on distillation.

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