table. Complete spectral data for characterization is available as supplementary material.

Thioesters. General Procedure. A solution of ester (4.0 mmol) in toluene (15 mL) was placed in a dry, 50-mL round-bottom flask with stir bar and reflux condenser. Lawesson reagent (1.61 g, 4.0 mmol, 2 equiv) was added, and the mixture was stirred at reflux (115 °C oil bath) under nitrogen for the specified reaction time (see table). The reaction mixture was cooled to room temperature and diluted with a 60/40 benzene–petroleum ether solution (35 mL). The precipitated solids were removed by filtration through glass wool, and the reddish-orange filtrate was concentrated at the rotary evaporator. The residue was purified by flash chromatography.

Fluorination. General Procedure. A solution of thioester (1.0 mmol) in dry dichloromethane (5 mL) was placed in a round-bottom flask with stir bar and rubber septum cap. The solution was stirred at room temperature under a nitrogen atmosphere as a solution of DAST in dichloromethane (1 M, 2.0 mL, 2 equiv) was added by syringe. Stirring was continued for 6 h, at which time the reaction mixture was cooled in an ice water bath and quenched by addition of saturated $NaHCO_3$ (15 mL). The organic layer was separated, and the aqueous phase was extracted twice with dichloromethane (5 mL). The combined organic solutions were dried over Na_2SO_4, and the bulk of the solvent was removed by distillation through a Vigreux column at the steam bath. The residual oil was purified by bulb-to-bulb distillation.

Acknowledgment. We are grateful to the University of Missouri Research Council for partial support of this work. The NSF provides partial support of the NMR (PCM-815599) and MS (PCM-8117116) facilities at the University of Missouri—Columbia.

Registry No. 1 (R = n-C_7H_{15}, R′ = Me), 111-11-5; 1 (R = cyclohexyl, R′ = Me), 4630-82-4; 1 (R = 1-adamantyl, R′ = Me), 711-01-3; 1 (R = Ph, R′ = Me), 93-58-3; 1 (R = PhCH=CH, R′ = Et), 103-36-6; 1 (R = Ph, R′ = $CH_2Si(Me)_3$), 17998-87-7; 1 (R = PhCH=CH, R′ = $CH_2Si(Me)_3$), 123933-28-8; 1 (R = Me, R′ = 2-naphthyl), 1523-11-1; 1 (R,R′ = $-CH_2CH_2CH(CH_2Ph)-$), 61129-28-0; 1 (R = $CH_2CH(OTHP)CH_3$, R′ = Et), 104372-23-8; **2a**, 123933-29-9; **2b**, 91923-30-7; **2c**, 123933-30-2; **2d**, 5873-86-9; **2e**, 73818-80-1; **2f**, 123933-31-3; **2g**, 123933-32-4; **2h**, 123933-33-5; **2i**, 105688-51-5; **3a**, 123933-34-6; **3b**, 123933-35-7; **3c**, 123933-36-8; **3d**, 123933-37-9; **3e**, 123933-38-0; **3f**, 123933-39-1; **3g**, 123933-40-4; **3h**, 123933-41-5; **3i**, 123933-42-6; DAST, 38078-09-0; α-benzyl-γ-butyrodithiolactone, 119018-57-4.

Supplementary Material Available: Listings of physical (boiling point or melting point) and spectral (IR, ^1H NMR, ^{13}C NMR, MS) data for compounds **2a-i** and **3a-h** (4 pages). Ordering information is given on any current masthead page.

The Effect of β-Dialkylamino Substitution on Ketone Enolization

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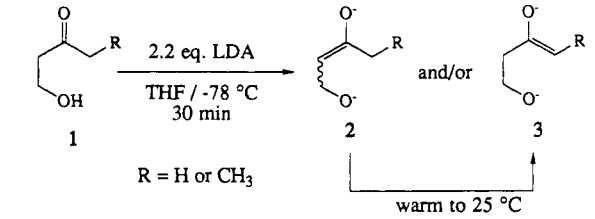
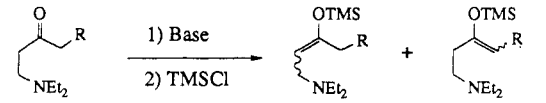
In previous work in these laboratories, we examined the effect of a β-hydroxy group on ketone enolization.[1] It was found that a dianionic species (an "aldolate dianion", **2** or **3**) could be generated when β-hydroxy ketones were treated with more than 2 equiv of a strong base at low temperature. It was determined that the ratio of distal (**3**) to proximal (**2**) enolates was temperature dependent and that the enolate ratios changed with time, indicating an equilibrating species, contrary to conventional ketone enolates. If the enolate was allowed to warm to 25 °C the distal enolate **3** was the preferred, and sometimes exclusive, isomer as indicated by trapping of the resulting enolate mixture with chlorotrimethylsilane (TMSCl). These findings encouraged us to examine other β-heteroatomic groups.



1 2 3

To our knowledge, there has not been a systematic study of the effects of β-amino groups on enolization.[2c] In an effort to gain insight in this area, we have studied the enolizations of *N,N*-diethyl-3-oxobutylamine (**4**) and *N,N*-diethyl-3-oxopentylamine (**5**).

These compounds were prepared by the conjugate addition of diethylamine to the corresponding enone as described by Ross and Levine.[3] The enolates were formed under a variety of conditions and trapped with TMSCl as shown in eq 1. The deprotonations were carried out with



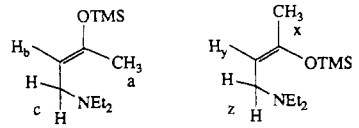
(1)

4 R = H
5 R = CH_3

proximal enol silane
6 R = H
8 R = Me

distal enol silane
7 R = H
9 R = Me

2.4 equiv of base, with the exception of runs employing lithium diisopropylamide (LDA) where only 1.25 equiv was used. In all cases the solution of the amide base was cooled to −78 °C, and the ketone was added as a neat liquid. Three methods were used to study the enolization process. In the first (method A, internal quench[1,4]) the silylating agent was added to the amide bases prior to the addition of the ketone. In this method only 1.25 equiv of TMSCl was used to trap the resulting enolates. Using the classical method (B) the ketone was added to a cooled solution of the base and held for 1 h, after which time 2.4 equiv of TMSCl was added. Method C involved warming the enolate solution (as formed in method B) to 25 °C for 15 min before quenching with TMSCl. The ratios of the resulting enol silane products were determined by capillary gas chromatography and/or by 300-MHz ^1H NMR analysis. The assignment of the *E* and *Z* isomers was made by analysis of ^1H NMR chemical shifts and the relative magnitudes of the allylic and homoallylic coupling constants.[5] For example, in the isomer pair **6E** and **6Z**, the



6E **6Z**

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(2) (a) Garst, M. E.; Bonfiglio, J. N.; Grudoski, D. A.; Marks, J. *J. Org. Chem.* **1980**, *45*, 2307. (b) Garst, M. E.; Bonfiglio, J. N.; Grudoski, D. A.; Marks, J. *Tetrahedron Lett.* **1978**, 2671. (c) McGarvey, G. J.; Hiner, R. N.; Williams, J. M.; Matasubara, Y.; Poarch, J. W. *J. Org. Chem.* **1986**, *51*, 3742. McGarvey, G. J.; Williams, J. M.; Hiner, R. N.; Matasubara, Y.; Oh, T. *J. Am. Chem. Soc.* **1986**, *108*, 4943.

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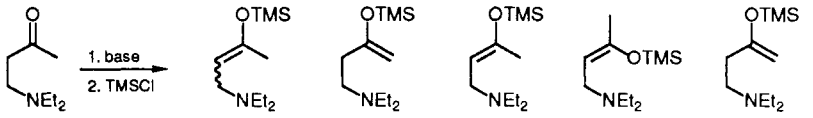
0022-3263/90/1955-0770$02.50/0

Table I. Generation and Trapping of the Enolates Formed from 4

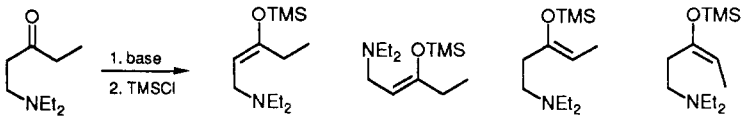


4

base	conditions[c]	GC ratios		NMR ratios[b]			% yield[d]
LDA	A	19	81	16	6	78	97
LiTMP	A	27	73	20	9	71	76
LDA	B	24	76	16	10	74	97
LiTMP	B	27	73	24	11	65	98
LiHMDS	B	42	58	31	14	55	85
NaHMDS	B	40	60	13	28	59	55
KHMDS	B	32	68	21	7	72	98
LDA	C	21	79	14	6	80	97
LiTMP	C						19
LiHMDS	C	42	58	13	33	54	76
NaHMDS	C	35	65	15	23	62	73
KHMDS	C	30	70	21	5	74	94

[a] Ratios determined by capillary GC. [b] Ratios determined by ^{1}H NMR integration. [c] A: substrate added to a preformed solution of base and TMSCl at −78 °C. B: substrate added to the preformed solution of the base at −78 °C and TMSCl was added after 1 h. C: ketone substrate was added to a preformed base solution and held at −78 °C for 1 h and warmed to room temperature for 15 min before addition of TMSCl. [d] Yield determined by capillary GC.

Table II. Generation and Trapping of the Enolates Formed from 5



5

base	conditions[b]	product ratios[a]				% yield[c]
LDA	A	62	15	7	26	85
LiTMP	A	65	14	5	18	69
LDA	B	42	18	20	20	62
LiTMP	B					56
LiHMDS	B	52	20	18	10	75
NaHMDS	B	17	59	24	–	77
KHMDS	B	73	15	7	6	74
LDA	C	39	21	23	17	64
LiTMP	C					73
LiHMDS	C	54	18	17	11	85
NaHMDS	C	16	59	18	7	75
KHMDS	C	65	15	9	11	70

[a] Ratios determined by ^{1}H NMR integration. [b] A: substrate added to a preformed solution of base and TMSCl at −78 °C. B: substrate added to the preformed solution of the base at −78 °C and TMSCl was added after 1 h. C: ketone substrate was added to a preformed base solution and held at −78 °C for 1 h and warmed to room temperature for 15 min before addition of TMSCl. [c] Yield determined by capillary GC.

vinyl proton of **6E** was assigned to be farthest downfield of the two vinyl proton resonances. Further, it was found that the allylic coupling constant between the vinyl hydrogen and the methyl was greater for **6Z** ($J_{xy} > J_{ab}$), and the homoallylic coupling constant between the methylene and the methyl was greater for **6E** ($J_{xz} > J_{ac}$). These data are in accord with observed trends[5] and reinforce the structural assignments made on the basis of the chemical shift criterion. The enolization results are shown in Tables I and II.

The study of the enolization of **4** under various conditions (Table I) indicates that the enolates formed are relatively stable to retro-Michael reactions, even at room temperature. In addition, there is no evidence of enolate equilibration, as we have observed with the corresponding aldolate dianions.[1] That is, the distal/proximal ratio of the enolates does not change appreciably on warming. In this sense, β-dialkylamino ketone enolates behave as typical enolate anions. Notably, the ratios of the enolates indicate a lower regioselectivity for deprotonation than what is normally expected for enolizations of a comparably α-substituted ketone not bearing a β-heterosubstituent. For example, 2-heptanone exhibits a 95:5 (methyl:methylene) enolization ratio using LDA and comparable amide bases.[4] Another notable trend is the *E*/*Z* selectivity in the formation of the proximal enolate with metal hexamethyldisilazides. Sodium hexamethyldisilazide (NaHMDS) exhibits *Z* selectivity while potassium hexamethyldisilazide (KHMDS) and the lithium hexamethyldisilazide (LiHMDS) show reverse selectivity with the *E* isomer moderately favored. Under kinetic quench conditions (method A) mostly starting material was obtained with the HMDS bases, invalidating the results in this series. The low yield in the case of deprotonation with lithium tetramethylpiperidide (LiTMP) under condition C questions the usefulness of the ratios obtained, and the

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results have been omitted. The *E* proximal enol silane isomer was synthesized according to the method of Combret[6] and was used to establish both retention times and response factors for GC analysis of the enol silane ratios.

Substrate **5** is ideally suited for studying the effect of the β-dialkylamino substituent on enolization. Since the degree of substitution is the same at both α-positions, the only perturbing influence is the diethylamino group. In this case the enolates formed with various bases (Table II) showed the same stability as found with **4**, as might be expected. However, the proximal enolate is preferred by at least a 2:1 ratio in almost all cases. Clearly, the dialkylamino group is preferentially directing enolate formation towards the uncharged heteroatomic substituent. Once again the *E*:*Z* proximal enolate ratios reverse as the counterion is changed from sodium to potassium or lithium as in the case of **4**. In this study the product ratios were determined by integration of the appropriate resonances in the ^{1}H NMR spectra. Use of capillary GC for analysis was prohibited by enol silane peak overlap. The structural assignments of the distal and proximal enolate isomers produced from **5** were made in a similar fashion to those produced from **4**.

It can be seen from the data that a β-dialkylamino substituent exhibits a kinetic acidifying effect toward proximal deprotonation. The effect, however, does not appear to be overriding and, based on the results in Table II, one can crudely estimate the kinetic acidifying effect of a β-dialkylamino group (vs hydrogen) in these systems to be less than three-fourths of a kilocalorie at −78 °C. Previous studies of enolizations of *exocyclic* α-heteroatom substituted ketones have indicated a preference for kinetic enolization away from the α-substituent in the cases of nitrogen and oxygen and toward the α-substituent in the cases of halogen or thiophenyl.[7] However, conclusions concerning kinetic acidifying effects of these substituents must be viewed with caution because the substrates were not equally substituted at the α-positions. Steric factors may have masked the acidifying effects of the α-heterosubstituents. At this point, it appears that a β-dialkylamino group promotes proximal enolization, which might be rationalized on the basis of a kinetically acidifying inductive effect, as in the cases of α-bromo,[7a] α-chloro,[7a] α-carboxamido,[7b] and α-thiophenyl ketones.[7d] However, a charge-bearing α-[8] or β-oxido group both promote distal enolization. It may be that, in these latter cases, charge repulsion is more important than inductive effects. Further studies are underway to clarify this issue.

To summarize, the enolizations of two β-dialkylamino ketones were examined, and the results indicate that a β-dialkylamino substituent favors the formation of proximal enolates relative to the all carbon analogues. Additionally, the enolates show good chemical and regiochemical stability, even at room temperature, with little or no tendency to undergo retro-Michael reaction or other processes.

Experimental Section

The ^{1}H and ^{13}C NMR spectra were obtained at 300 and 75 MHz, respectively. The IR spectra were acquired with a Nicolet DX V5.16 FTIR as neat oils. Mass data were obtained at 70 eV. Diphenylmethane was used as the internal standard for capillary GC analysis. THF was freshly distilled from sodium and benzophenone. Diisopropylamine was distilled from calcium hydride. Chlorotrimethylsilane was obtained from Petrarch systems and distilled from calcium hydride under nitrogen. Trimethylsilyl trifluoromethanesulfonate was obtained from Petrarch Systems and was used without purification. Lithium diisopropylamide was generated as a 0.5 M solution in THF at −78 °C from freshly distilled diisopropylamine (1.05 equiv) and *n*-butyllithium (1.0 equiv), obtained as a 2.5 M solution from Aldrich Chemical Co. NaHMDS and KHMDS were also obtained from Aldrich as solutions in THF or toluene and diluted to a 0.5 M solution in THF. In vacuo removal of solvent refers to the use of a rotary evaporator operating at aspirator pressure. The amines **4** and **5** were obtained via the procedure described by Ross.[3] All new compounds and enol silane isomer mixtures were ≥95% spectroscopically pure.

Silyl Enol Ethers. The silyl enol ether **6E** (previously known) and **8E** (previously unknown) for GC standards were obtained via the procedure described by Combret.[6] We have assigned the olefin geometries according to the spectroscopic criteria described in the text.

***N*,*N*-Diethyl-3-((trimethylsilyl)oxy)-(*E*)-2-pentenamine (8E).** Diethyl(trimethylsilyl)amine (20 mmol, 3.9 mL) and 20 mmol (2.02 mL) of ethyl vinyl ketone were added to 25 mL of freshly distilled diethyl ether at room temperature under a positive pressure of nitrogen. To this solution was added 0.05 mL of TMSOTf, and the mixture was stirred for 1 h. The crude mixture was distilled at reduced pressure (40 mmHg) to yield 2.1 g (46%) of the *E* proximal enol ether containing approximately 5% of other TMS enol ether isomers: bp 65 °C at 40 mmHg; IR (neat oil) 2968, 2806, 1676, 1465, 1382, 1253, 1199, 1064, 1026, 923, 889, 845, 754 cm^{-1}; ^{1}H NMR (C_6D_6) δ 4.72 (t, 1 H, *J* = 6.5 Hz), 3.24 (d, 2 H, *J* = 6.5 Hz), 2.52 (q, 4 H, *J* = 7.5 Hz), 1.97 (q, 2 H, *J* = 7.0 Hz), 1.04 (t, 6 H, *J* = 2.5 Hz), 0.99 (t, 3 H, *J* = 5.0 Hz), 0.16 (s, 9 H); ^{13}C NMR δ 154.1, 104.6, 48.6, 47.2, 29.9, 12.7, 11.9, 0.7; high-resolution mass spectrometry (EI) calcd for $C_{12}H_{27}NOSi$ 229.1861, found 229.1856.

Enolizations: Method A. A 2.5-mmol sample of base was added to enough THF at −78 °C under a positive pressure of nitrogen to obtain a 0.5 M solution of base. To this solution was added 1.25 mmol (1.7 mL) of chlorotrimethylsilane, and the mixture was held for 15 s before adding dropwise 1.05 mmol of β-dialkylamino ketone. This solution was kept for 30 min at −78 °C and then quenched with a saturated solution of $NaHCO_3$ and NaCl. The organic layer was taken up in pentane and separated. The aqueous layer was extracted twice more with pentane. The combined organic layers were dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo to yield the crude mixture of silyl enol ethers.

Method B. A 2.5-mmol sample of base was added to enough THF at −78 °C under a positive pressure of nitrogen to obtain a 0.5 M solution of base. To this solution was added dropwise 1.05 mmol of β-dialkylamino ketone, and the mixture was held at this temperature for 1 h. Chlorotrimethylsilane (2.5 mmol) was added, and the mixture was held for an additional 30 min at −78 °C. This solution was then quenched with a saturated $NaHCO_3$–brine solution, and the organic layer was taken up into pentane. The layers were separated, and the aqueous layer was extracted twice more with pentane. The combined organic layers were dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo to yield the crude mixture of silyl enol ethers.

Method C. A 2.5-mmol sample of base was added to enough THF at −78 °C under a positive pressure of nitrogen to obtain a 0.5 M solution of base. To this solution was added 1.05 mmol of β-dialkylamino ketone dropwise, and the mixture was held at this temperature for 1 h. After this time, the flask was removed from the dry ice bath and allowed to warm to room temperature over a 15-min period. Chlorotrimethylsilane (2.5 mmol) was then added, and the mixture was held for an additional 30 min. This solution was quenched with a saturated $NaHCO_3$–brine solution, and the organic layer was taken up into pentane. The layers were separated, and the aqueous layer was extracted twice more with pentane. The combined organic layers were dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo to yield the crude mixture of silyl enol ethers.

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Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work. We also acknowledge the support of the National Institutes of Health under Grant GM-38243.

Registry No. 4, 3299-38-5; 5, 105-14-6; 6E, 124267-60-3; 6Z, 124267-61-4; 7, 124267-62-5; 8E, 124267-63-6; 8Z, 124267-64-7; 9Z, 124267-65-8; 9E, 124267-66-9; diethyl(trimethlsilyl)amine, 996-50-9; ethyl vinyl ketone, 1629-58-9.

Supplementary Material Available: Raw ^1H NMR data of a typical enol silane product mixture resulting from the silylation of compounds 4 and 5 as well as NMR spectral data of *N,N*-diethyl-3-((trimethylsilyl)oxy)-(*E*)-2-pentenamine (6 pages). Ordering information is given on any current masthead page.

A Dramatic Solvent Effect during Aromatic Halogen–Metal Exchanges. Different Products from Lithiation of Polyfluorobromobenzenes in Ether and THF

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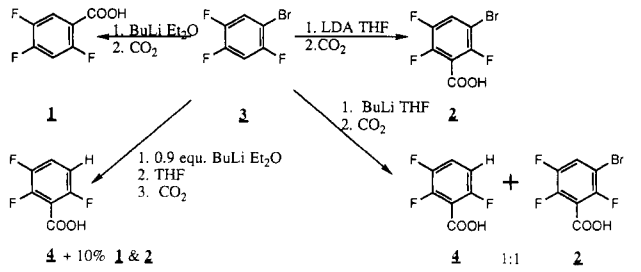
Received April 7, 1989

As part of a synthetic program in quinolone antiinfectives, we wished to prepare 2,4,5-trifluorobenzoic acid (1) and 3-bromo-2,5,6-trifluorobenzoic acid (2) from 1-bromo-2,4,5-trifluorobenzene (3). Although acid 1 can be



prepared via cyanation (CuCN) of 3 followed by acid hydrolysis,[1] it appeared that bromine–lithium exchange followed by carboxylation would be operationally simpler. Halogen–metal exchange is a very well-established technique for the regiospecific generation of aromatic anions.[2] Because aromatic bromine–lithium exchange is very rapid, it allows for lithiation to be carried out at positions in the molecule that would not normally be available due to the presence of kinetically or thermodynamically more acidic sites.[3] Conversely, simple metalation of 3 should occur at the most acidic site, and carboxylation should yield acid 2. Although lithiation between two fluorines with butyllithium (BuLi) is known,[4] in this case halogen–metal exchange must be avoided. In this note we wish to report that bromide 3 is acidic enough to be metalated by LDA, that acid 1 can also be prepared from 3 via halogen–metal exchange in ether, and that this latter reaction shows a remarkable solvent effect, such that changing the solvent to THF leads to a mixture of acid 2 and 2,3,6-trifluorobenzoic acid (4). The mechanism of this latter process was shown to be compatible with autometalation.[5]

When lithium diisopropylamide (LDA) was added dropwise to a −78 °C solution of bromide 3 in THF, a clear yellow solution was formed immediately. After a further 2 min this was transferred onto solid CO_2 in ether and yielded after workup 83% of analytically pure bromo acid 2[6] (Table I, entry 1). Although there are reports of ortho lithiation of benzoates[7] and benzonitriles,[8] with lithium amides, such anions were trapped in situ, and are probably never present as major species during the reaction. Most ortho-metalating groups do not decrease aryl pK_as below 38,[9] and aromatics are generally metalated with alkyllithiums, often activated by TMEDA, at −78 °C.[10] Thus, the facile LDA metalation of 3 demonstrates that fluorine shows the same powerful kinetic and thermodynamic acidifying ability on a benzene ring that it shows in the polyhalomethanes.[11]

When 1 equiv of *n*-BuLi was added to a solution of bromide 3 in ether at −78 °C and carboxylated, acid 1 was obtained in 83% yield and 99% purity (entry 2). Thus the halogen–metal exchange reaction in ether provided a very satisfactory preparation of acid 1. However, when we carried out the halogen–metal exchange under the most commonly used conditions, 2 equiv of *t*-BuLi in THF,[12] followed by carboxylation, we did not obtain acid 1 but a material that showed three aromatic resonances in its NMR spectrum (entry 3). Use of 1 equiv of *n*-BuLi in THF (entry 4) gave a cleaner version of the same result, so the change in reaction pathway was due to a solvent effect. Although this product recrystallized essentially unchanged, leading to speculations on benzyne or biphenyl dimers,[13] GC analysis and spectroscopic comparisons showed the product to be an approximately 1:1 mixture of acid 2 and 2,3,6-trifluorobenzoic acid (4), with less than 1% of acid 1 present. With 0.5 equiv of *n*-BuLi in THF, only acid 2 was obtained (entry 5). Furthermore, when bromide 3 was reacted with 0.9 equiv of *n*-BuLi in ether, followed by THF addition prior to carboxylation, the major product was acid 4 (entry 6), but if 1.1 equiv of *n*-BuLi was used in the same protocol, unrearranged acid 1 was the major product (entry 7). All of the experimental results using THF described above could be repeated by adding TMEDA, a good lithium chelator, to the ether solution at an appropriate time.

The likely mechanism of formation of acids 2 and 4, shown in Scheme I, involves autometalation, a process first described by Gilman,[5] in which the initially formed or-

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