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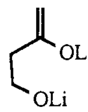
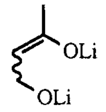
Generation, Chemical Stability, and Reactivity of Aldolate Dianions

Summary: β-Hydroxy ketones undergo regiospecific double deprotonation with 2 equiv of LDA to provide synthetically useful nucleophilic reagents.

Sir: Enolate anions occupy a key position in organic synthesis as important intermediates for carbon–carbon bond-forming processes.[1] Recent developments in the area of stereoregulated aldol condensations have increased their usefulness, allowing stereocontrol in the formation of both carbon–carbon and carbon–oxygen bonds. One aspect of the aldol reaction that adds greatly to its utility is the wide variety of subsequent transformations that can be applied to the β-hydroxy aldehydes and ketones that are formed.[2] Notably lacking in this area is the double deprotonation of aldol adducts to provide aldolate dianions, such as 1 or 2. The analogous β-hydroxy ester 3[3a] and lactone 4[3b] dianions have been known for some time. To our knowledge, dianions of β-hydroxy ketones have not been studied previously in a systematic manner. Such double-edged nucleophiles would be of structural and synthetic interest, especially with regard to oxygen heterocycle synthesis. We describe preliminary results concerning the generation, reactivity, and chemical stability of aldolate dianions, whose characteristics differ somewhat from conventional ketone enolates.



1
(distal enolate)



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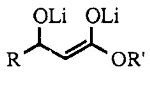
(proximal enolate)



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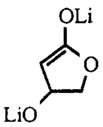

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Table I. Generation and Trapping of Aldolate Dianions with TMSCl[a]

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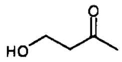
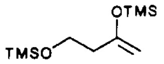
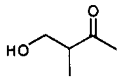
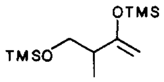
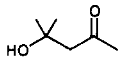
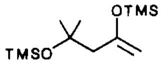
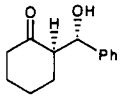
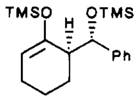
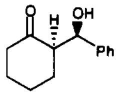
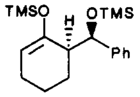
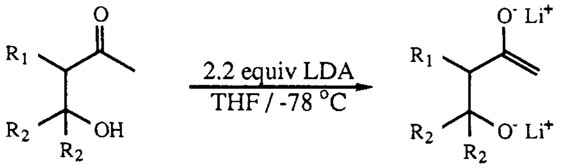
1			81
2			80
3			50[c,d]
4			74
5			81

[a] All dianions generated by slow dropwise addition of a THF solution of the β-hydroxy ketone to a solution of 2.2 equiv of LDA in THF at −78 °C. [b] Unless otherwise noted, yields refer to spectroscopically pure material. [c] 2.2 equiv of HMPA added before TMSCl addition. [d] Isolated by preparative HPLC on silica.

Several β-hydroxy ketones were examined and found to be smoothly deprotonated with 2.2 equiv of lithium diisopropylamide at −78 °C in THF to provide exclusively the dianion in which enolization had taken place away from the β-oxido group to form a distal dianion as shown in eq 1. We examined the regioselectivity of the deprotonations via standard silylation techniques using 2.5 equiv of TMSCl to provide bis(trimethylsilyl ethers). The results are shown in Table I. Good yields and regioselectivity were observed. In cases where the degree of α-carbon substitution was different, only a single regioisomeric silyl enol ether was observed spectroscopically in the crude reaction product. When the degree of substitution is the same at both the α- and α′-positions, the effect of a β-oxygen substituent on enolization can be studied. This was investigated, and the results are shown in Table II. With 1-hydroxy-3-pentanone[4] 6 all four regioisomers are observed under kinetic conditions utilizing an internal quench method.[6] Enolization proximal to the β-oxido group is favored by a 2:1 margin. However, with classical methods (B conditions) the ratio reverses, and the distal enolate is favored by a 2.6:1 ratio. Contrary to conven-



(1)

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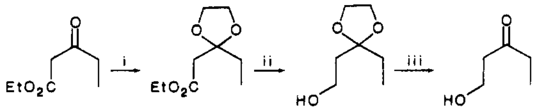
(1) (a) Heathcock, C. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1983; Vol. 3, chapter 2. (b) Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1983; Vol. 3, chapter 1. (c) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1.

(2) This is most evident in the synthesis of polyketide derived natural products. For a review, see: Masamune, S.; Choy, W. *Aldrichchimica Acta* **1982**, *15*, 47. Evans, D. A. *ibid.* **1982**, *15*, 23.

(3) (a) Kraus, G. A.; Taschner, M. J. *Tetrahedron Lett.* **1977**, 4575. Seebach, D.; Wasmuth, D. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 971. Frater, G. *Tetrahedron Lett.* **1981**, *22*, 425. (b) Shieh, H.-M.; Prestwich, G. D. *J. Org. Chem.* **1981**, *46*, 4319.

(4) This substance was prepared by the following route:



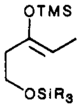
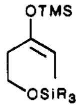
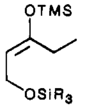
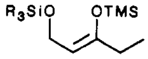
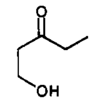
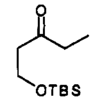
(i) Ethylene glycol/benzene/p-TsOH/reflux with water removal, 86%; (ii) $LiAlH_4$/diethyl ether, 0 °C, 96%; (iii) wet silica gel, 99%, ref 5.

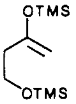
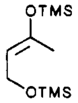
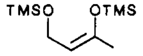
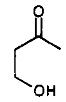
(5) Huet, F.; Lechevallier, A.; Pellet, M.; Conia, J. M. *Synthesis* **1978**, 63.

(6) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495.

0022-3263/88/1953-5986$01.50/0

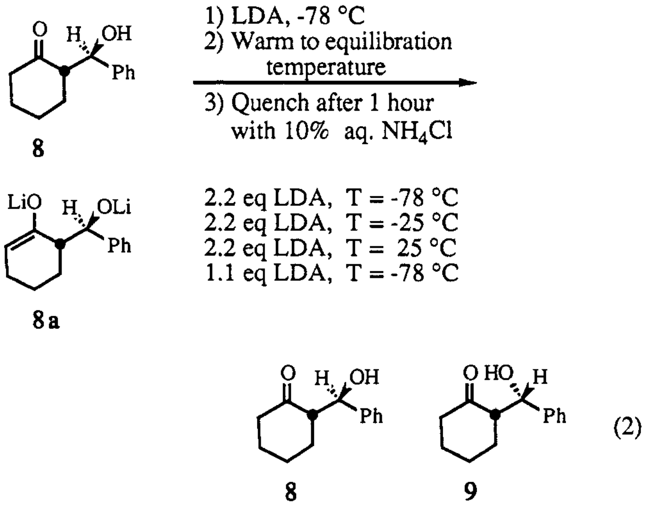
Table II. Silylation Product Ratios of 5-7

substrate	conditions[b]	product ratios[a]				distal:proximal ratio	total % yield all isomers
							
 6	A	1.0	1.1	2.3	2.0	1.0:2.0	82
	B	2.0	1.0	1.2	<0.1	2.6:1.0	77
		(5.1	<0.1	<0.1	1.0	5.0:1.0	65)[c]
	C	15.7	7.0	<0.1	1.0	22.0:1.0	73[d]
 7	A	<0.1	1.0	9.7	2.5	1.0:12.2	70
	B	<0.1	1.0	3.7	<0.1	1.0:3.7	68
	C						e

substrate	conditions	product ratios			distal:proximal ratio	total % yield all isomers
						
 5	A	7.0	2.0	1.0	7.0:3.0	70
	B	4.0	<0.1	1.0	4.0:1.0	70
	C	5.0	<0.1	<0.1	5.0:<0.1	70

[a] Ratios determined by 300-MHz ^{1}H NMR. [b] A: substrate added to a preformed solution of LDA and TMSCl in THF at −78 °C (ref 6). B: substrate to a solution of LDA in THF at −78 °C followed by addition of TMSCl after 30 min. C: substrate added to a solution of LDA in THF at −78 °C and warmed to 25 °C for 15 min followed by addition of TMSCl at 0 °C. [c] 2.2 equiv of HMPA added to enolate solution before adding TMSCl. [d] See text. [e] No products were observed that were derived from the substrate.

tional enolates, warming the enolate of **6** briefly to 25 °C before silylating gives the distal TMS enol ether almost exclusively (22:1 ratio). The yield in this case, however, reflects a 5–10% impurity derived from incorporation of diisopropylamine into the substrate. When the β-hydroxyl is presilylated (**7**), regioselectivity is reversed, favoring enolization proximal to the β-silyloxy group. The same experiments with **5** are shown for comparison. These results indicate that the timing of the quenching step is a factor in determining the distal:proximal silyl ether ratios. It does appear, however, that the thermodynamically favored[7] enolate in these cases is the one which is distal to the β-oxido group.



	8	9
2.2 eq LDA, T = -78 °C	98%	2%
2.2 eq LDA, T = -25 °C	96%	4%
2.2 eq LDA, T = 25 °C	82%	18%
1.1 eq LDA, T = -78 °C	85%	15%

Studies also indicate that the formation of the dianion of a β-hydroxy ketone suppresses retroaldolization compared to the corresponding β-alkoxide monoanions. The dianion of diastereomerically pure **8**[8] was examined in a series of equilibration experiments (eq 2). The dianion was formed by using 2.2 equiv of LDA at −78 °C and left in solution for 1 h at −78, −25, and 25 °C followed by quenching with an excess of 10% aqueous NH_4Cl. Control experiments showed that the workup procedure had no effect on the product ratios. When **8** is treated with 1 equiv of LDA at −78 °C, extensive epimerization to **9** occurs, presumably via retroaldolization.[9] From the data, it is apparent that the dianion **8a** exhibits enhanced chemical stability at low temperatures with little, if any, of the diastereomeric **9** being formed. At warmer temperatures,

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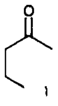
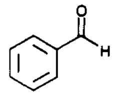
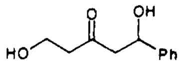
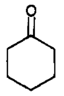
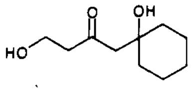
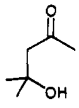
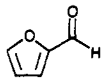
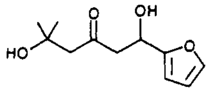
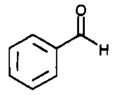
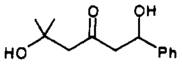
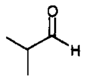
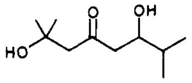
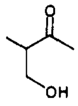
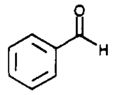
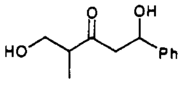
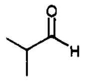
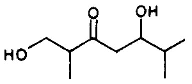
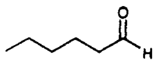
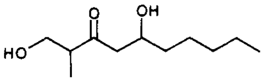
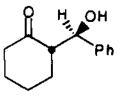
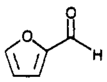
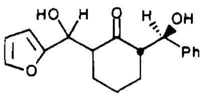
(7) Fataftah, Z. A.; Kopka, I. E.; Rathke, M. W. *J. Am. Chem. Soc.* **1980**, *102*, 3959.

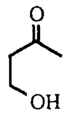
(8) Both **5** and its diastereomer were made by aldol condensation between cyclohexanone and benzaldehyde and were separated by high-performance liquid chromatography on silica.

(9) Significant amounts (10–15%) of benzaldehyde, cyclohexanone, and byproducts derived from further condensation processes were formed as well.

Table III. Reactions of Aldolate Dianions with Aldehydes and Ketones

β-Hydroxy ketone	carbonyl component	product	% yield
			66^a
			21
 12			91
			80^a
			56^a
 10			93^b
			$76^{a,b}$
			$67^{a,b}$
 8			65^c

^{a}Isolated by chromatography on silica. ^{b}Isolated as a 1:1 mixture of diastereomers. ^{c}Isolated as a mixture of four diastereomers.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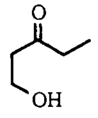
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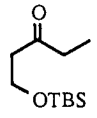
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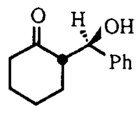
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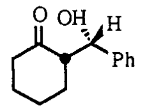
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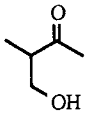
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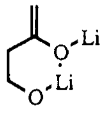
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however, epimerization as well as other products are observed. Further, the dianions of 2 and 4 are stable for at least an hour at room temperature, showing little or no tendency toward enolate equilibration or retroaldol cleavage, as judged by purity and yield of bissilylation products.

Aldolate dianions react readily with a variety of aldehydes at −78 °C to give β,β'-dihydroxy ketones in good yield[10] (Table III). The products are easily purified by chromatography on silica (if needed) with little or no dehydration being observed. As expected, the reaction of the "chiral"[1a] lithium aldolate derived from 10 with aldehydes does not exhibit significant 1,4-asymmetric induction. Reaction of the dianions with ketones gives addition products only in low to moderate yield.

To summarize, dianions of β-hydroxy ketones can be generated regiospecifically, yielding the least substituted enolate anion. This is an improvement in regioselectivity over ketones lacking a β-hydroxy group. In the case of symmetrical α-substitution, enolization distal to the β-oxido substituent is favored thermodynamically. The dianions may be cleanly trapped with either TMSCl to generate silyl enol ethers or with aldehydes to provide β,β'-dihydroxy ketones in good yield. It is tempting to speculate that the dianions exist as a six-membered cyclic chelate 11.[11] In any case, the widespread availability and structural diversity of β-hydroxy ketones and aldehydes leaves much room for study. Further explorations of the synthetic utility and structure of aldolate including those of the type shown in 2 are currently in progress.

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[10] Unless otherwise indicated, yields refer to ^1H and ^{13}C NMR spectroscopically pure substances.

[11] Cyclic metal atom chelates are frequently invoked to explain reaction diastereoselectivity. While this is certainly an attractive generalization, very few are based on evidence other than reactivity or conventional wisdom. We are currently seeking direct structural evidence for a cyclic chelate in this case and results will be reported in due course.

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