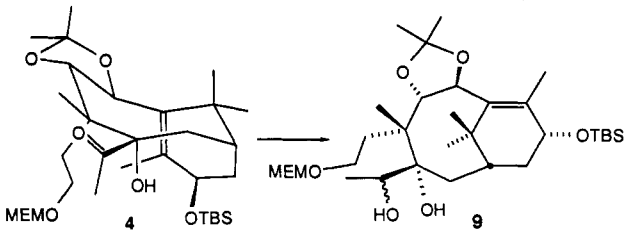
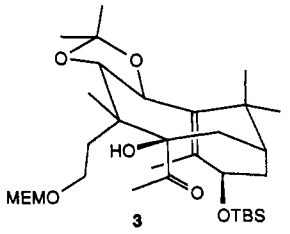
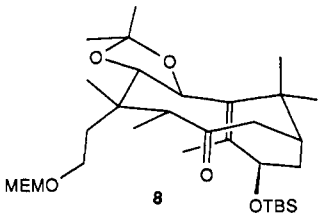
presence of Et_3N (4 equiv, 3 equiv of SmI_2, THF, 0 °C, 2 h), a 1:1 mixture of diols **9** was produced in high yield. Under these conditions, the Lewis acid mediated ring expansion process is completely shut down, and although the samarium ketyl is undoubtedly an intermediate in the formation of **9**, the fact that no loss of the tertiary hydroxyl is observed provides additional support for the conformation of **4** shown below.



On the other hand, the conformation (enforced by steric repulsion from the A ring) of **3** is one in which the hydroxyl–carbon bond is parallel to the p orbitals of the carbonyl group, and reduction is stereoelectronically more favorable than ring expansion. This is supported by the fact that **3** did not undergo ring expansion in the presence of Sm^{3+} (SmI_2, cyclohexene oxide, THF, 0 °C, 2 h), and, although some decomposition was observed, approximately 50% of **3** was recovered unchanged.



Apparently **7** cannot readily adopt a conformation that would facilitate ring contraction to provide **3**. However, there are conformations available to **7** that are stereoelectronically favorable for reduction to the samarium enolate, which must then be protonated to give **8**. That ketone **8** prefers the conformation shown below is supported by its UV absorption (λ_{max} 204 nm, ϵ 5736), a consequence of transannular conjugation of the double bond with the carbonyl group.[12] From this conformation, the samarium ketyl readily undergoes radical cyclization followed by further electron transfer and loss of OTBS to give **6**.



This process is novel in that it combines a Lewis acid promoted rearrangement with reductive loss of a hydroxyl substituent and ketyl cyclization. Efforts to address the generality of these findings are in progress.

Acknowledgment. We thank the National Cancer Institute and the donors of the Taxol Research Fund, Florida State Univeristy Foundation, for their generous financial support of our programs.

Registry No. **1**, 19605-80-2; **2**, 115941-39-4; **3**, 115913-10-5; **4**, 116003-21-5; **5**, 115913-11-6; **6**, 116865-11-3; **6** epoxidation derivative, 116865-15-7; **6** epoxidation-fragmentation derivative, 116865-16-8; **7**, 116865-12-4; **8**, 116865-13-5; **9** (isomer 1), 116865-14-6; **9** (isomer 2), 116947-12-7; SmI_2, 32248-43-4.

Robert A. Holton,* Andrew D. Williams
Dittmer Laboratory of Chemistry
The Florida State University
Tallahassee, Florida 32306
Received August 16, 1988

(12) This is an interesting example of transannular olefin–ketone conjugation. This phenomenon, which is common to **8**, **2**, and several derivatives related to **2**,[7,10a] will be fully discussed in a forthcoming publication: Holton, R. A.; Williams, A. D.; manuscript in preparation. For related observations, see: (a) Huenig, S.; Martin, H. D.; Mayer, B.; Peters, K.; Prokschy, F.; Schmitt, M.; Von Schnering, H. G. *Chem. Ber.* **1987**, *120*, 195. (b) Beck, K.; Huenig, S.; Kleefeld, G.; Martin, H. D.; Peters, K.; Prokschy, F.; Von Schnering, H. G. *Chem. Ber.* **1986**, *119*, 543. (c) Klingensmith, K. A.; Puettman, W.; Vogel, E.; Michl, *J. Am. Chem. Soc.* **1983**, *105*, 3375 and references contained therein.

Highly Enantioselective Claisen-Type Acylation and Dieckmann Annulation

Summary: Enantioselective Claisen condensation reactions between various esters **1a–f** and 3-acyl-4(*S*)-IPTT **2a,b** employing lithium isopropylcyclohexylamide and HMPA gave acylated products **3a–j** in 29–77% yield and in 22–97% ee. Asymmetric Dieckmann-type annulation of **4a** with KH in DMF followed by methanolysis afforded bicyclic β-keto methyl ester **6a** in 69% overall yield and in 96% ee.

Sir: Carbon–carbon bond formation via Claisen and Dieckmann condensations is useful in the construction of functionalized synthons in the synthesis of biologically active natural products and drugs.[1,2] Here we report the first example of highly enantioselective Claisen-type acylations[3] and Dieckmann annulations utilizing 4(*S*)-isopropyl-1,3-thiazolidine-2-thione [4(*S*)-IPTT][4] as chiral leaving group.

In both asymmetric reactions, the choice of the chiral leaving group seems to be crucial for high stereoselectivity. Thus, we designed asymmetric Claisen- and Dieckmann-type reactions based on thiazolidine-2-thione L*[4(*S*)-IPTT] (eq 1 and 2).[4]

The Claisen-type acylation was exploited for the construction of an asymmetric quarternary carbon atom which

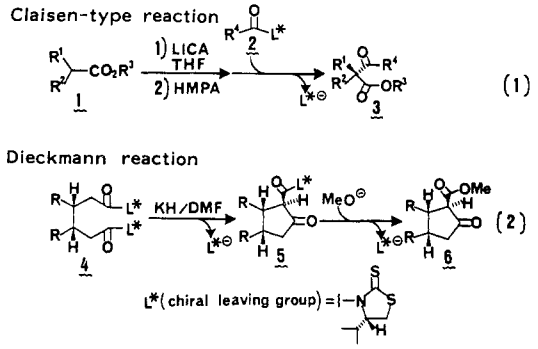
(1) (a) Hauser, C. R.; Hudson, B. E., Jr. *Org. React. (N.Y.)* **1942**, *1*, 266 and references cited therein. (b) Schaefer, J. P.; Bloomfield, J. J. *Org. React. (N.Y.)* **1967**, *15*, 1 and references cited therein. (c) Walther, H.; Treibes, W.; Michaelis, K. *Chem. Ber.* **1956**, *89*, 60. (d) Johnson, D. H. *J. Chem. Soc.* **1958**, 1624. (e) Bloomfield, J. J.; Fennesy, P. V. *Tetrahedron Lett.* **1964**, *5*, 2273. (f) March, J. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*; McGraw Hill: New York, 1968; pp 366–369. (g) Turecek, F.; Vystcil, A. *Collect. Czeckslov. Chem. Commun.* **1976**, *41*, 1571. (h) Yamada, Y.; Ishii, T.; Kimura, M.; Hosaka, K. *Tetrahedron Lett.* **1981**, *22*, 1353. (i) Hatanaka, M.; Yamamoto, Y.; Nitta, H.; Ishimaru, T. *Tetrahedron Lett.* **1981**, *22*, 3883.

(2) Krauch, H.; Kunz, W. *Organic Name Reactions*; John Wiley & Sons, Inc.: New York, 1964; pp 94–96 and pp 124–125.

(3) For highly "diastereoselective" acylation employing a chiral auxiliary, see: (a) Evans, D. A.; Ennis, M. D.; Le, T.; Mandel, N.; Mandel, G. *J. Am. Chem. Soc.* **1984**, *106*, 1154. (b) Ito, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron. Lett.* **1984**, *25*, 6015.

(4) (a) Nagao, Y.; Hagiwara, Y.; Kumagai, T.; Ochiai, M.; Inoue, T.; Hashimoto, K.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 2391. (b) Nagao, Y.; Kumagai, T.; Tamai, S.; Abe, T.; Kuramoto, Y.; Taga, T.; Aoyagi, S.; Nagase, Y.; Ochiai, M.; Inoue, Y.; Fujita, E. *J. Am. Chem. Soc.* **1986**, *108*, 4673. (c) Nagao, Y.; Dai, W.-M.; Ochiai, M.; Tsukagoshi, S.; Fujita, E. *J. Am. Chem. Soc.* **1988**, *110*, 289.

0022-3263/88/1953-5983$01.50/0



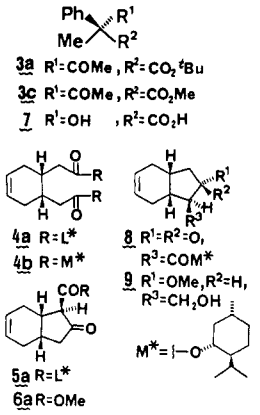
is often found in various natural products.[5] For the Dieckmann annulation, *meso* dicarboxylic acids were employed because asymmetric induction with these substrates has been investigated previously in our laboratory.[6]

We first describe a typical example of the Claisen-type reactions. To a solution of lithium *N*-isopropylcyclohexylamide (LICA) prepared from *n*-butyllithium (1.7 mmol) and *N*-isopropylcyclohexylamine (1.7 mmol) in THF (1.5 mL) was added dropwise a solution of *tert*-butyl 2-phenylpropionate (**1a**) (1.5 mmol) in THF (3 mL) at −78 °C under N_2 with stirring.[7] Hexamethylphosphoramide (HMPA) (1.7 mmol) was added and the mixture was stirred at −78 °C for 30 min. After addition of a solution of 3-acetyl-4(*S*)-IPTT (**2a**) (1.7 mmol) in THF (3 mL) at −78 °C, the mixture was stirred at the same temperature for 15 min and then treated as usual.[7] This gave the acetyl derivative **3a** as a colorless oil in 77% yield and in 96% enantiomeric excess (ee) (entry 1 in Table I). The results of other similar asymmetric acylations are listed in Table I.

The absolute configuration (*S* configuration) of compound **3c** was established by its chemical conversion to (−)-(*R*)-atrolactic acid (**7**) [43% overall yield from **3c**: $[\alpha]^{19}_D$ −33.9° (*c* 1.02, EtOH), mp 116–117 °C (benzene); lit.[8] $[\alpha]^{25}_D$ −37.6° (*c* 1.2, EtOH), mp 116–117 °C (benzene)] via the Baeyer–Villiger reaction with *m*-chloroperoxybenzoic acid and a catalytic amount of TsOH in CH_2Cl_2 followed by alkaline hydrolysis with K_2CO_3 in aqueous MeOH. The stereochemistry (*S* configuration) of **3a** was confirmed by its chemical conversion to **3c** [55% overall yield from **3a**, $[\alpha]^{21}_D$ −39.5° (*c* 0.84, $CHCl_3$)] via elimination of the *t*-Bu group by treatment of **3a** with Me_3SiCl–NaI[9] in CH_3CN at room temperature followed by methylation with CH_2N_2 in Et_2O. The absolute configurations (*S* configuration) of the other products (**3b** and **3d–j**) are tentatively assigned by stereochemical analogy and consistency of their specific rotations (Table I).

The stereoselectivity of this asymmetric Claisen-type acylation is not affected by the bulkiness of the R^3 and R^4 groups (entries 1–4, 7, and 8). When the R^2 group was changed from methyl to *n*-butyl in the 2-phenylpropionate

Chart I



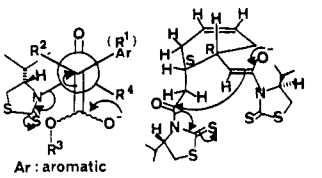


Figure 1.

Figure 2.

derivatives (R^1 = Ph), the reactivity of the enolate toward **2** and the stereoselectivity decreased (entry 5) or disappeared (entry 6). A similar result was obtained under the reaction conditions without HMPA in the reaction of **1b** with **2a** [**3c**: 24% yield, $[\alpha]^{24}_D$ −32.9° (*c* 0.82, $CHCl_3$)]. The enolate, which was derived from the reaction of an *E*/*Z* or *Z*/*E* mixture (ca. 6:4 ratio) of trimethylsilyl enolate of **1b** with methyllithium at room temperature[10] was treated with HMPA at −78 °C for 30 min and then acetylated with **2a** as usual to afford the compound **3c** with high enantioselectivity (93% ee), albeit in low yield (30%). Thus, a noncyclic transition state (Figure 1 in Chart I) is tentatively proposed.[11]

The enantioselective Dieckmann annulation was carried out as follows. Crystalline 4(*S*)-IPTT diamide **4a**[12] [mp 102–104 °C (isopropyl alcohol)] (0.5 mmol) was added to a suspension of 35% KH (1.0 mmol) in mineral oil and DMF (5 mL) under ice-cooling. After being stirred at the same temperature for 3 h, the reaction mixture was subjected to the usual workup, giving crude annulation product **5a**. Subsequent methanolysis of **5a** with K_2CO_3 (1.1 mmol) in MeOH (20 mL) at room tempreature for 30 min gave the known methyl ester **6a**[13] in 69% overall yield from **4a** and in 96% ee [400-MHz ^1H NMR analysis in the presence of Eu(hfc)$_3$]. Recrystallization of the 96% ee product from ether–hexane afforded the crystalline compound **6a** as fine needles [(99% ee, mp 59–60 °C, $[\alpha]^{21}_D$ −159.9° (*c* 0.24, $CHCl_3$)]. The absolute stereochemistry of **6a** was confirmed by comparison of its specific rotation with that of an authentic sample.[13] Optically pure **6a** should be a useful synthetic intermediate for drugs and natural products [e.g., (+)-carbacyclin[13] and iridoidal monoterpenoids[14]].

The high asymmetric induction observed may be explained in terms of a presumed transition state[15] (Figure

(5) A review in Japanese entitled "Asymmetric Control in the Construction of Quaternary Carbon Centers and Its Application to the Total Synthesis of Natural Products": Tomioka, K.; Koga, K. *J. Synth. Org. Chem. Jpn.* **1986**, *44*, 545.

(6) (a) Nagao, Y.; Ikeda, T.; Yagi, M.; Fujita, E.; Shiro, M. *J. Am. Chem. Soc.* **1982**, *104*, 2079. (b) Nagao, Y.; Inoue, T.; Fujita, E.; Terada, S.; Shiro, M. *J. Org. Chem.* **1983**, *48*, 132. (c) Nagao, Y.; Inoue, T.; Fujita, E.; Terada, S.; Shiro, M. *Tetrahedron* **1984**, *40*, 1215. (d) Nagao, Y.; Ikeda, T.; Inoue, T.; Yagi, M.; Shiro, M.; Fujita, E. *J. Org. Chem.* **1985**, *50*, 4072. (e) Nagao, Y.; Inoue, T.; Hashimoto, K.; Hagiwara, Y.; Ochiai, M.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1985**, 1419.

(7) Rathke, M. W.; Deitch, *J. Tetrahedron Lett.* **1971**, 2953.

(8) (a) Mckenzie, A.; Clough, G. W. *J. Chem. Soc.* **1910**, 97, 1016. (b) Bonner, W. A.; Grimm, R. A. *J. Org. Chem.* **1967**, *32*, 3022.

(9) Olah, G. A.; Narang, S. C.; Gupta, B. G. B.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247.

(10) House, H. O.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1971**, *36*, 2361.

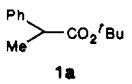
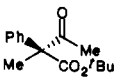
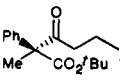
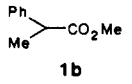
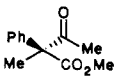
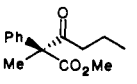
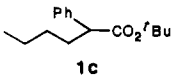
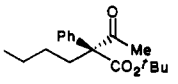
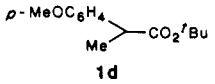
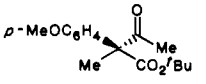
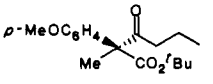
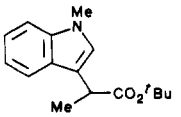
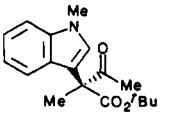
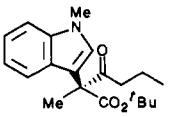
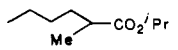
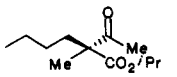
(11) An alternate explanation is that only one diastereomeric enolate reacts with **2a**. If that were the case, one would expect similar enantioselection but reduced yields, whether the transition state is cyclic or noncyclic.

(12) A mixture of *cis*-cyclohex-4-ene-1,2-bis(acetic acid) (4 mmol), 4(*S*)-isopropyl-1,3-thiazolidine-2-thione (8.8 mmol), 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride (WSC) (9.6 mmol), and 4-(dimethylamino)pyridine (0.4 mmol) in CH_2Cl_2 (6 mL) was stirred at room temperature overnight. After further addition of WSC (4.8 mmol), the mixture was stirred for 3 h and then treated as usual to give diamide **4a** in 81% yield. Diester **4b** was similarly prepared in 90% yield.

(13) Nagao, Y.; Nakamura, T.; Ochiai, M.; Fuji, K.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1987**, 267.

(14) Isoe, S. In *Innovative Studies on Highly Selective Synthesis*; Nozaki, H., Ed.; Research Report No. 12 sponsored by Grant-in-Acid for Special Project Research from The Ministry of Education, Science and Culture, October, 1985; pp 49–50.

Table I. Asymmetric Claisen-Type Acylation

entry	ester 1	acyl-L* 2	product 3	yield, % (isoln)	ee,[a] %	$[\alpha]_D$, deg[b] (c)
1	 **1a**	MeCOL* (**2a**)	 **3a**	77	96	−56.5[c] (0.63)
2	**1a**	^{n}PrCOL* (**2b**)	 **3b**	75	95	−34.8[d] (0.92)
3[i]	 **1b**	**2a**	 **3c**	57	94	−37.8[e] (1.23)
4[i]	**1b**	**2b**	 **3d**	53	97	−16.0[e] (0.72)
5	 **1c**	**2a**	 **3e**	29	87	−68.4[f] (1.01)
6	**1c**	**2b**	none	*j*		
7	 **1d**	**2a**	 **3f**	72	95	−50.8[f] (1.31)
8	**1d**	**2b**	 **3g**	75	93	−29.6[d] (1.04)
9	 **1e**	**2a**	 **3h**	47	67	−18.1[g] (1.14)
10	**1e**	**2b**	 **3i**	56	47	−4.8[h] (0.64)
11	 **1f**	**2a**	 **3j**	62	22	−2.4[f] (1.71)

[a] Determined by 400-MHz ^{1}H NMR analysis in the presence of Eu(hfc)$_3$. [b] Recorded in $CHCl_3$ and at [c](19 °C), [d](20 °C), [e](22 °C), [f](21 °C), [g](25 °C), and [h](26 °C). [i] Two molar equivalents of **1a**, LICA (2.2 mol equiv), and HMPA (2.2 mol equiv) to **2a** and **2b** were employed. [j] Recovery (62%) of **1c**.

2 in Chart I) which can be suggested on the basis of the perspective view of the crystallographic structure[16] of **4a**.[17,18]

Similar chiral Dieckmann reactions of *l*-menthol diester **4b**[12] (colorless oil) gave an annulation product **8** in 96% yield. However, its optical yield was confirmed to be poor by 400-MHz ^{1}H NMR analysis (37% ee) of the compound **9** derived from **8**. Thus, the particular amide functionality of 4(*S*)-IPTT seems to be quite essential for controlling the equatorial or axial orientation of both active methylene groups in the molecule of **4a**. A thermodynamic bias of the conformational diasteromerism[6d] such as that of diamide **4a** appears to be insufficient in the case of diester **4b**.[19]

Supplementary Material Available: Details of the X-ray diffraction analysis of compound **4a** and 400-MHz ^{1}H NMR spectra of the methylene region of compounds **4a** and **4b** (10

(15) A mixture of **4a** (0.5 mmol) and 35% KH (1.0 mmol) in DMF (5 mL at 0 °C was quenched, after 1 h, with 37% DCl to gain some insight into the mode of the Dieckmann annulation. A 1:1 mixture of **4a** and **5a** was obtained; however, **4a** showed no deuterium incorporation. This result suggests that formation of enolates of **4a** is probably the rate-determining step of the reaction. Mechanistic details will be reported.

(16) Crystallographic structure of compound **4a** and its data are available as supplementary material.

(17) On the ^{1}H NMR (400 MHz) charts of diamide **4a** in DMF-d_7, $CDCl_3$, THF-d_8, and C_6D_6 solution, all peaks of the two kinds of active methylenes, the *R* site equatorial CH_2, and the *S* site axial CH_2 can be assigned on the basis of the perspective view[16] of **4a**.[6d,18]

(18) 400-MHz ^{1}H NMR spectra of the methylene region of compounds **4a** and **4b** are available as supplementary material.

(19) The spectral pattern of the methylene region (δ 2–2.5 ppm) of **4a** is quite similar to that of achiral *cis*-cyclohex-4-ene-1,2-bis(methyl acetate).[18]

pages). Ordering information is given on any current masthead page.

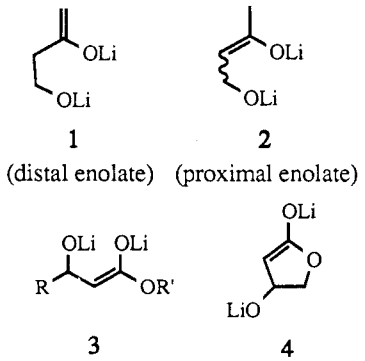
Yoshimitsu Nagao,* Yuichi Hagiwara
Toshiaki Tohjo, Yukari Hasegawa, Masahito Ochiai
Institute for Chemical Research
Kyoto University
Uji, Kyoto 611, Japan

Motoo Shiro
Shionogi & Research Laboratories
Shionogi & Co., Ltd.
Fukushima-Ku, Osaka 533, Japan
Received July 20, 1988

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.

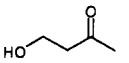
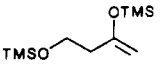
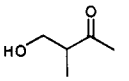
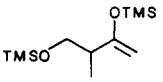
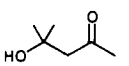
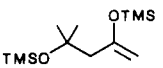
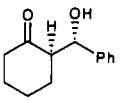
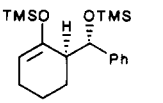
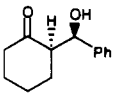
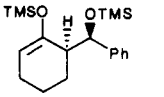
Sir: Enolate anions occupy a key position in organic synthesis as important intermediates for carbon–carbon bond-forming processes.[1] Recent developments in the area of stereoregulated aldol condensations have increased their usefulness, allowing stereocontrol in the formation of both carbon–carbon 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,



1 (distal enolate) **2** (proximal enolate)

3 **4**

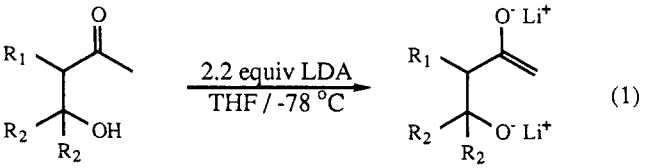
Table I. Generation and Trapping of Aldolate Dianions with TMSCl[a]

entry	β-hydroxy ketone	silylation product	% yield[b]
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.

whose characteristics differ somewhat from conventional ketone enolates.

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



(1)

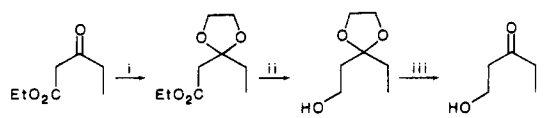
via standard silylation techniques using 2.5 equiv of TMSCl to provide bis(trimethylsilyl ethers). The results are shown in Table I. Good yields and regioselectivity were observed. In cases where the degree of α-carbon substitution was different, only a single regioisomeric silyl enol ether was observed 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) (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