122969-48-6; **114**, 122969-49-7; **115**, 122969-50-0; **116**, 122969-51-1; **117**, 122969-52-2; **118**, 122969-53-3; **119**, 122969-54-4; **120**, 122969-55-5; **121**, 122969-56-6; **122**, 122969-57-7; **123**, 122969-58-8; **124** (R = R^1 = R^2 = H), 122969-59-9; **124** (R = R^2 = H, R^1 = Me), 122969-60-2; **124** (R = R^2 = H, R^1 = t-Bu), 122969-61-3; **124** (R = R^1 = Me, R^2 = H), 122969-62-4; **124** (R = t-Bu, R^1 = Me, R^2 = H), 122969-63-5; **124** (R = H, R^1 = R^2 = Me), 122969-64-6; **124** (R = H, R^1 = Me, R^2 = t-Bu), 122969-65-7; **124** (R = R^1 = Me, R^2 = t-Bu), 122969-66-8; **124** (R = R^2 = t-Bu, R^1 = Me), 122969-67-9; **125** (R = R^2 = H, R^1 = Me), 123001-94-5; **125** (R = R^2 = H, R^1 = t-Bu), 122969-68-0; **125** (R = R^1 = Me, R^2 = H), 122969-69-1; **125** (R = t-Bu, R^1 = Me, R^2 = H), 122969-70-4; **125** (R = H, R^1 = R^2 = Me), 122969-71-5; **125** (R = H, R^1 = Me, R^2 = t-Bu), 122969-72-6; **125** (R = R^1 = Me, R^2 = t-Bu), 122969-73-7; **125** (R = R^2 = t-Bu, R^1 = Me), 122969-74-8; **126** (R^1 = Me, R^2 = H), 122969-75-9; **126** (R^1 = R^2 = Me), 122969-76-0; **126** (R^1 = Me, R^2 = t-Bu), 122969-77-1; **127** (R^1 = Me, R^2 = H), 122969-78-2; **127** (R^1 = R^2 = Me), 122969-79-3; **127** (R^1 = Me, R^2 = t-Bu), 122969-80-6; EtCOCl, 79-03-8; $EtCH(OH)CH{=}CHCH_3$, 29478-27-1; $(Me)_2CHCH_2COCH_2CH(OH)CH_3$, 59357-17-4; $MeCH{=}CHCH(OH)C(Me)_3$, 74146-07-9; $PhCOCH_2CH(OH)CH_3$, 13505-39-0; *p*-$MeCH(OH)CH_2COC_6H_4Br$, 122969-81-7; *p*-$MeOC_6H_4COCH_2CH(OH)CH_3$, 122969-82-8; $CH_3C{\equiv}CCOCH(CH_3)_2$, 52066-33-8; EtBr, 74-96-4; (*E*)-$CH_3CH{=}CHCHO$, 123-73-9; ClCOCOCl, 79-37-8; $(Me)_2CHCH_2COCH_3$, 108-10-1; CH_3CHO, 75-07-0; $(Me)_2CHCOCH_3$, 563-80-4; $PhCOCH_3$, 98-86-2; *p*-$BrC_6H_4COCH_3$, 99-90-1; *p*-$MeOC_6H_4COCH_3$, 100-06-1; $CH_3CH{=}CHCOCl$, 10487-71-5; CH_3CH_2CHO, 123-38-6; $(Me)_2CHCHO$, 78-84-2; $(Me)_3CCOCH_2Br$, 5469-26-1; $CH_3C{\equiv}CH$, 74-99-7; $(Me)_2CHCOCH_2CH(OH)CH_3$, 59357-07-2; (*E*)-1-cyclohexyl-2-buten-1-ol, 120849-47-0; chlorocyclohexane, 542-18-7; mesitylene, 108-67-8; 1,3,5-triisopropylbenzene, 717-74-8; *N*-methyl-*N*-(3-methyl-2-oxobutyl)-2-methylpropanamide, 122969-83-9; pyrrolidine, 123-75-1; hexamethylenimine, 111-49-9; piperidine, 110-89-4.

Supplementary Material Available: More detailed experimental procedures for the Michael adducts and full X-ray crystallographic details on compounds **59a**, **91a**, **97a**, **104s**, **119**, and **120** (86 pages). Ordering information is given on any current masthead page.

Stereochemistry of the Michael Addition of Ester and Ketone Enolates to α,β-Unsaturated Ketones[1]

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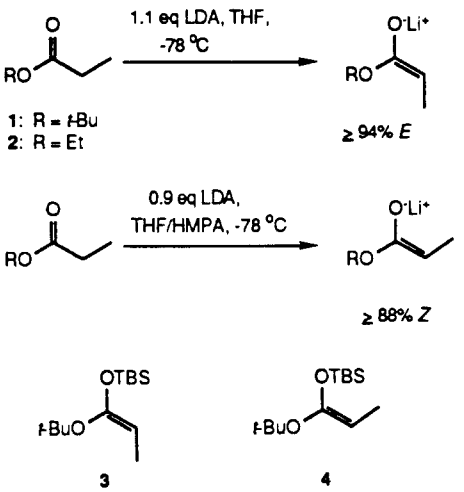
The stereo- and regiochemistry of addition of the enolates of ketones and esters to α,β-unsaturated ketones has been studied. There is a strong correlation between the enolate geometry and adduct stereostructure, with *E* enolates forming syn products and *Z* enolates yielding anti products. With few exceptions, both the syn and anti adducts can be obtained in good to excellent diastereomeric excess. The results are consistent with a chelated, eight-membered transition state.

Introduction

In the preceding paper in this series,[1] we demonstrated that enolates of amides and thioamides often react with α,β-unsaturarated ketones to give conjugate addition products in good yield. By suitable modification of the substrate, excellent control over the stereoselectivity of the addition can often be achieved. In this paper, we report the full results our parallel study of ester and ketone enolates.[2] Since both enolate isomers of many esters and some ketones can be obtained (vide infra), this study has allowed the examination of the effect of this variable on the stereochemistry of the reaction. The results presented herein unequivocally demonstrate that the geometry of the enolate used in the reaction strongly influences the stereostructure of the adducts obtained.

The stereochemistry of ester enolate Michael addition reactions has been the focus of several studies.[3-7] In particular, Schlessinger,[8] Mulzer,[9] Yamaguchi,[10] Corey,[11] and their co-workers have studied the additions of lithium

Scheme I



(1) Paper 47 in the series Acyclic Stereoselection. For paper 46, see: Oare, D. A.; Henderson, M. A.; Sanner, M. A.; Heathcock, C. H. *J. Org. Chem.*, preceding paper in this issue.

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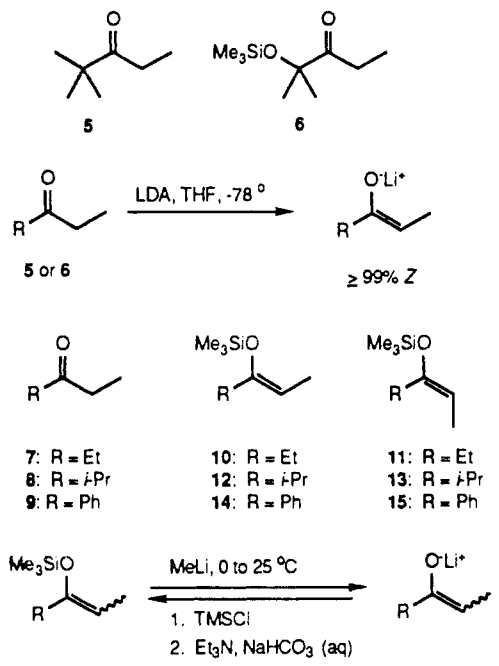
0022-3263/90/1955-0157$02.50/0

Scheme II



enolates of esters to α,β-unsaturated esters. Oppolzer and co-workers have studied the addition of the lithium dienolates derived from senecioates to 2-cyclopentenone.[12]

The reactions of ketone enolates with Michael acceptors has also been explored.[3,6] For the addition to α,β-unsaturated ketones, much of the work has been done in the context of the Robinson annulation.[13-17] For the addition to acyclic acceptors, Gorrichon-Guigon and co-workers have made a careful study using readily available acceptors.[18] Although not explicitly determined, the enolates used in the latter study probably have the *Z* configuration.

Materials and Methods

The addition of the lithium enolates of *tert*-butyl propionate (1), ethyl propionate (2), and δ-valerolactone to α,β-unsaturated ketones has been examined. The *E* enolates result from deprotonation by lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C (Scheme I).[19-21] Reaction of an aliquot from the reaction mixture with a solution of *tert*-butyldimethylsilyl chloride in THF/hexamethylphosphoric triamide (HMPA)/hexanes produces a mixture of silyl ketene acetals **3** and **4**. Analysis of this product by capillary GLC and ^{1}H NMR spectrometry gives the ratio of enolates. The highest proportion of the *E* enolate (>95%) occurs when a dilute solution of the ester is added slowly with a syringe pump to a slight excess (1.05 to 1.10 equiv) of the base.

Deprotonation of esters **2** and **1** by the Ireland method (LDA, THF/HMPA, −78 °C) gives the *Z* enolates (Scheme I).[19] Similar formation of ketene acetals **3** and **4** provides information on the *Z*/*E* ratio. The highest percentage of the *Z* isomer results from rapid addition of a slight excess (1.05 to 1.10 equiv) of the ester neat to a solution of the base.[22]

The enolates of ketones **5** and **6** were generated by using LDA in THF at −78 °C (Scheme II). These ketones give exclusively the *Z* enolates.[23] For ketones **7**–**9**, the enolates were generated from the previously prepared enol silanes **10**–**15**[24-26] by using the method of Stork[27] and House[28]

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Table I. Addition of Ketone and Ester Enolates to α,β-Unsaturated Ketones (Scheme III)

	enolate		enone							1,2	1,4
entry	R	E/Z	R_1	R_2	solvent	temp, °C	time, h	yield, %	1,2:1,4	major:minor	syn:anti
1	*t*-BuO	E[a]	*i*-Pr	Me	THF	−78	0.4	54	83:17	98:2	≥95:5
2	*t*-BuO	E[a]	*i*-Pr	Me	THF	20	1.5	68	<3:97		70:30[b]
3	*t*-BuO	Z[a]	*t*-Bu	Me	THF/HMPA	−78	0.3	73	<3:97		13:87
4	*t*-BuO	E[a]	*t*-Bu	Me	THF	−78	0.3	85	<3:97		95:5
5	*t*-BuO	E[a]	*t*-Bu	Me	THF/HMPA[c]	−78	0.3	89	<3:97		95:5
6	*t*-BuO	12:88	*t*-Bu	Et	THF/HMPA	−78	0.3	49	<3:97		5:95
7	*t*-BuO	94:6	*t*-Bu	Et	THF	−78	0.3	86	<3:97		91:9
8	*t*-BuO	Z[a]	*t*-Bu	*i*-Pr	THF/HMPA	−78	0.3	88	14:86	84:16	7:93
9	*t*-BuO	E[a]	*t*-Bu	*i*-Pr	THF	−78	0.3	87	31:69		92:8
10	*t*-BuO	E[a]	*t*-Bu	*i*-Pr	THF	0	1.5	73	<3:97		86:14
11	*t*-BuO	Z[a]	*t*-Bu	*t*-Bu	THF/HMPA	−78	23.0	0[g]			
12	*t*-BuO	Z[a]	*t*-Bu	*t*-Bu	THF/HMPA	25	1.5	25	<3:97		<3:97
13	*t*-BuO	E[a]	*t*-Bu	*t*-Bu	THF	−78	0.3	65	>97:3	54:46	
14	*t*-BuO	E[a]	*t*-Bu	*t*-Bu	THF	25	1.5	46	<3:97		38:62
15	*t*-BuO	11:89	*t*-Bu	Ph	THF/HMPA	−78	0.3	88	14:86	67:33	7:93
16	*t*-BuO	11:89	*t*-Bu	Ph	THF/HMPA	25	1.5	76	<3:97		11:89
17	*t*-BuO	95:5	*t*-Bu	Ph	THF	−78	0.3	95	40:60	84:16	94:6
18	*t*-BuO	95:5	*t*-Bu	Ph	THF	25	1.5	96	<3:97		94:6
19	*t*-BuO	E[a]	*t*-Bu	Ph	THF/HMPA[c]	−78	0.3	96	30:70	60:40	79:21
20	*t*-BuO	E[a]	mes[d]	Me	THF	−78	4.0	87	<3:97		≥95:5
21	EtO	Z[a]	mes[d]	Me	THF/HMPA	−78	40.0	65	<3:97		12:88
22	EtO	Z[a]	tris[e]	Me	THF/HMPA	−78	40.0	65	<3:97		35:65
23	EtO	E[a]	mes[d]	Me	THF	−78	1.5	79	<3:97		63:37
24	EtO	E[a]	tris[e]	Me	THF	−78	3.0	90	<3:97		80:20
25	*t*-BuO	Z[a]	tris[e]	Me	THF/HMPA	−78	24.0	87	<3:97		30:70
26	*t*-BuO	E[a]	tris[e]	Me	THF	−78	24.0	85	<3:97		95:5
27	$-(CH_2)_4O-$[f]	E	*t*-Bu	Ph	THF	25	1.3	67	<3:97		50:50
28	*t*-Bu	<1:99	*t*-Bu	Ph	THF	−78	8.0	70	<3:97		<1:99
29	Ph	2:98	*t*-Bu	Ph	THF	−78	72.0	78	<3:97		2:98
30	Ph	2:98	*t*-Bu	Ph	THF/HMPA	−78	24.0	80	<3:97		4:96
31	Ph	2:98	Me	Me	THF	−78	24.0	55	<3:97		<3:97
32	Ph	2:98	*i*-Pr	Me	THF	−78	24.0	63	<3:97		<3:97
33	Ph	2:98	$-(CH_2)_3-$		THF	−78	24.0	0[g]			
34	*i*-Pr	4:96	*t*-Bu	Ph	THF	−78	24.0	88	<3:97		5:95
35	Et	15:85	*t*-Bu	Ph	THF	−78	2.5	77	<3:97		15:85
36	Ph	89:11	Me	Me	THF	−78	24.0	60	<3:97		40:60
37	Ph	87:13	*t*-Bu	Ph	THF	−20	12.0	66	<3:97		83:17
38	*i*-Pr	90:10	*t*-Bu	Ph	THF	−78	24.0	87	<3:97		90:10
39	Et	81:19	*t*-Bu	Ph	THF	−78	24.0	78	<3:97		39:61
40	Et	81:19	*t*-Bu	Ph	THF/HMPA	−78	24.0	98	<3:97		68:32
41	$Me_3SiOCMe_2$	<1:99	*t*-Bu	Ph	THF	−10	9 days	55	<3:97		10:90
42	$Me_3SiOCMe_2$	<1:99	*t*-Bu	Ph	THF	20	24.0	67	<3:97		45:55

[a] Ratio not determined. [b] Structure of diastereomers not assigned. [c] HMPA added to the reaction mixture after formation of the *E* enolate in THF. [d] 2,4,6-Trimethylphenyl. [e] 2,4,6-Triisopropylphenyl. [f] The lithium enolate of δ-valerolactone was used. [g] No addition products were isolated.

Table II. Addition Products from the Enolates of 1, 2, and 5–9 to Enones 16–24

	enone			
enolate R	R_1	R_2	1,2 major:minor	1,4 syn:anti
t-BuO	*i*-Pr	Me	**26**[a]	**27s/27a**
t-BuO	*t*-Bu	Me		**28s/28a**
t-BuO	*t*-Bu	Et		**29s/29a**
t-BuO	*t*-Bu	*i*-Pr	**30a/30b**	**31s/31a**
t-BuO	*t*-Bu	*t*-Bu	**32a/32b**	**33s/33a**
t-BuO	*t*-Bu	Ph	**34a/34b**	**35s/35a**
t-BuO	mes[b]	Me		**36s**
t-BuO	tris[c]	Me		**37s/37a**
EtO	mes[b]	Me		**38s/38a**
EtO	tris[c]	Me		**39s/39a**
$-(CH_2)_4O-$[d]	*t*-Bu	Ph		**40s** and **40a**
t-Bu	*t*-Bu	Ph		**41s/41a**
Ph	*t*-Bu	Ph		**42s/42a**
Ph	Me	Me		**43s/43a**
Ph	*i*-Pr	Me		**44a**
i-Pr	*t*-Bu	Ph		**45s/45a**
Et	*t*-Bu	Ph		**46s/46a**
$Me_3SiOCMe_2$	*t*-Bu	Ph		**47s/47a**

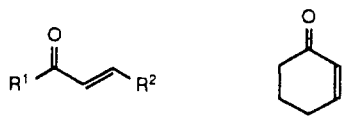
[a] Only one obtained. [b] 2,4,6-Trimethylphenyl. [c] 2,4,6-Triisopropylphenyl. [d] δ-Valerolactone.

(MeLi, 25 °C). The enolate ratio was determined by removal of an aliquot from the reaction mixture and regeneration of the enol silanes by treatment with TMSCl.[29] In this manner, the precise enolate ratio used in a given experiment could be determined.

Enones **16–25** were used in this study. The synthesis of these compounds has been described previously.[1] All of the acyclic enones studied have the *E* configuration (≥95%).[30]

The Michael additions were performed by adding solutions of an enone in THF to 2 equiv of an enolate, prepared as described above.[31] The results of this study are sum-

(27) Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4462, 4464.
(28) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324.
(29) The ketone enolate trapping experiments were performed by adding freshly distilled trimethylsilyl chloride at −78 °C to an aliquot of the ketone enolate removed prior to the Michael addition. After warming the reaction mixture to room temperature, an excess of Et_3N was added to the reaction mixture and the reaction was quenched with an aqueous solution of $NaHCO_3$. Without the addition of Et_3N, yields were low and variable. Addition of Et_3N was found to be particularly crucial for experiments where the enolates were generated from the enol silanes with MeLi. We believe that Et_3N serves, in this procedure, as an organic soluble base that neutralizes the HCl that is rapidly liberated from the hydrolysis of the excess trimethylsilyl chloride.
(30) The influence of acceptor geometry on the stereochemical outcome has been examined (see ref 6a, 8b, and 11a).
(31) Although 1:1 addition of the enolate and enone can be used, better yields are obtained with a 2:1 (enolate/enone) ratio.



16: R^1 = Me, R^2 = Me
17: R^1 = *i*-Pr, R^2 = Me
18: R^1 = *t*-Bu, R^2 = Me
19: R^1 = *t*-Bu, R^2 = Et
20: R^1 = *t*-Bu, R^2 = *i*-Pr
21: R^1 = *t*-Bu, R^2 = *t*-Bu
22: R^1 = *t*-Bu, R^2 = Ph
23: R^1 = 2,4,6-$Me_3C_6H_2$, R^2 = Me
24: R^1 = 2,4,6-i-$Pr_3C_6H_2$, R^2 = Me

25

marized in Table I and Scheme III (for compound numbers, see Table II).

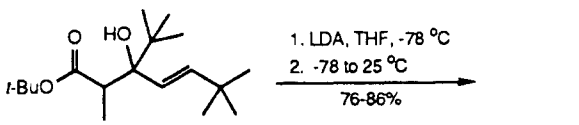
1,2 vs 1,4 Addition

Enolates can add either 1,2 or 1,4 to α,β-unsaturated ketones. The regiochemistry of the addition is dependent on a variety of factors. With the ester enolates studied, the substitution pattern of the α,β-unsaturated ketone is the most important factor; increase of the bulk of the β substituent results in more 1,2 addition. Use of *Z* enolates (in the presence of HMPA) favors 1,4 addition. In fact, no 1,2 adducts are obtained in reactions that were carried out with *Z* enolates in the presence of HMPA with any of the alkyl enones studied.[32,33] Control experiments revealed that the 1,2 adducts of ester enolates are stable to reversal at −78 °C. With ketone enolates, on no occasion were aldol products observed. Because the reactions were performed for extended periods (24 h) at −78 °C, the absence of 1,2 addition products cannot be construed as a lack of any reaction via this pathway, since Gorrichon-Guigon and co-workers have isolated aldol products from similar reactions and found that the aldolates are not stable at −78 °C.[18]

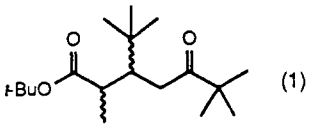
Upon being warmed to room temperature, the initially formed 1,2 adducts are converted to the isomeric 1,4 adducts.[34] For example, if the reaction between the *E* enolate of *tert*-butyl propionate and enone **21** is quenched at −78 °C, a 54:46 mixture of 1,2 addition products is isolated (entry 13, Table I). Warming this reaction mixture to room temperature for 1.5 h results in complete conversion of the 1,2 adducts into Michael addition products (entry 14). Furthermore, both of the aldol products **32a** and **32b** can be isolated, deprotonated with LDA, warmed, and converted to the 1,4 products (eq 1).

The 1,2 to 1,4 conversion process has been examined for the addition of the lithium enolate of *tert*-butyl propionate to enone **22**. The results of this study are summarized in Scheme III and Table III. As can be seen from the data in Table III, the 1,2 to 1,4 conversion occurs at a significant rate somewhere between −40 and −5 °C. Notice also that no appreciable change in the diastereomeric mixture of 1,4 adducts obtained occurs until extended times at 25 °C (entry 7).

The ratio of 1,2 to 1,4 addition observed was found to fluctuate depending upon the precise reaction conditions employed. The variations could be minimized by adding the enone to the enolate very slowly with a syringe pump; however, even with this modification, precise product ratios seem to change depending upon the scale of the reaction



32a or **32b**



(1)

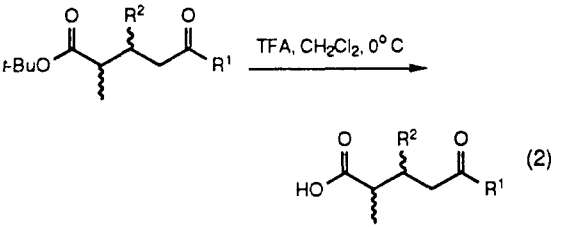
33s: syn
33a: anti

Aldol	anti/syn
32a	70:30
32b	55:45

and the effectiveness of the stirring system utilized.

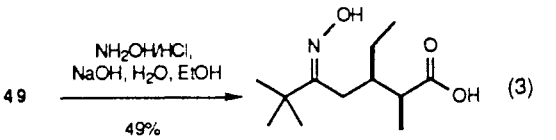
Product Stereostructures

Configurations of the Michael adducts were assigned by using a variety of methods. For the conjugate addition products in entries 3–5 and 8–19 (Table I), conversion into keto acids **48**, **50**, **51**, and **52** (eq 2, Table IV) of previously



(2)

established stereostructure provides the structure proof.[35–38] Similar treatment of keto ester **29s** yields **49**. The spatial arrangement of **49** follows from single-crystal X-ray analysis of the derived oxime **54** (eq 3).

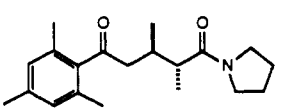


(3)

54

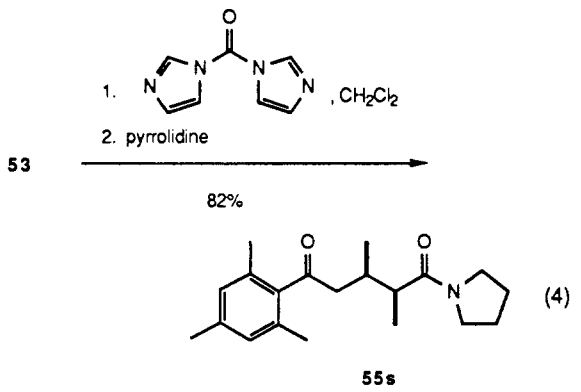
For **36s** (entry 20, Table I), conversion to keto acid **53** (entry 6, Table IV) followed by transformation into keto amide **55s** (eq 4) provided the structure assignment.[39,40] Establishing the configuration of the addition products in

(32) Note, however, that R^1 in all of the cases examined is *tert*-butyl.
(33) No addition products were obtained in the addition of *Z* lithium enolate of *tert*-butyl propionate to enone **21** at −78 °C.
(34) Schultz, A. G.; Yee, Y. K. *J. Org. Chem.* **1976**, *41*, 4044.
(35) The structures of **48** and **52** have been determined by single-crystal X-ray analysis. With **50**, conversion to a lactone whose structure can be assigned with confidence by NMR provided the stereochemistry.
(36) Uehling, D. E. Ph.D. Dissertation, University of California at Berkeley, Sept. 1987.
(37) Heathcock, C. H.; Norman, M. H.; Uehling, D. E. *J. Am. Chem. Soc.* **1985**, *107*, 2797.
(38) The configuration of **51** was established by X-ray analysis of the oxime acid; ref 1.
(39) The configuration of **55a** was established by single-crystal X-ray analysis; ref 1.



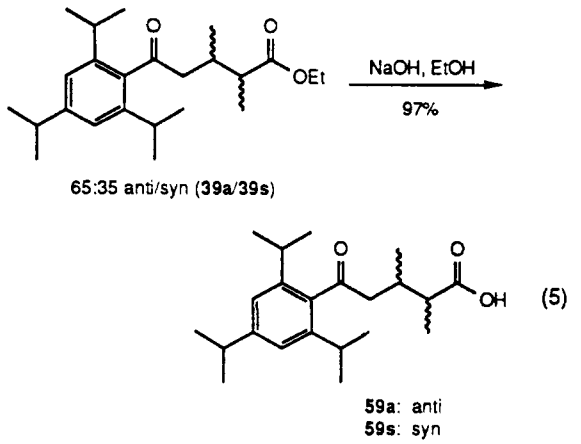
55a

(40) Staab, H. A. *Angew. Chem., Int. Ed. Engl.* **1962**, *7*, 351.



entries 25 and 26 (Table I) proved to be much more troublesome. Although **37s** and **37a** are crystalline compounds, crystals suitable for X-ray analysis could not be obtained. Furthermore, suitable crystals could not be obtained from a variety of derivatives of **37s**/**37a** including different esters, amides, and carboxylic acid, and carboxylate salts. Hence, chemical comparison of **36s** and **37s** was required. Initial treatment of a mixture of keto esters **39s** and **39a** with RuO_4 for a 1-week period using the Sharpless procedure[41] results in complete disappearance of the starting keto ester by TLC (Scheme IV). Workup of the reaction mixture and analysis by ^1H NMR spectroscopy revealed a complex mixture of products consistent with incomplete "digestion" of the triisopropylphenyl substituent of **37s**. Prolonging the reaction time (greater than 2 weeks) results in the smooth conversion of **37s** to ester acid **56**, which was characterized after conversion to its benzyl ester **57** with isourea **58**.[42-44]

The structures of the keto ethyl esters in entries 22 and 24 (Table I) were established by saponification to keto acids **59a**[45] (eq 5). The only conjugate addition products



for which configurations have not been rigorously assigned are those of entries 2, 21, and 23 (Table I). For entries 1 and 2, the stereochemistry of these products is tentatively assigned on the basis of similar ^{13}C NMR chemical shift patterns of **27s** and **27a** with **28s** and **28a**. The configuration of the adducts in entries 21 and 23 is assigned by analogy to the trends seen in Table I.

(41) Carlsen, P. H. J.; Katsuki, T.; Martin, Y. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.
(42) Mathias, L. J.; Fuller, W.; Nissen, D.; Goodman, M. *Macromolecules* **1978**, *11*, 534.
(43) For a review of this esterification method, see: Mathias, L. J. *Synthesis* **1979**, 561.
(44) Attempts to purify **56** using an acid base extraction resulted in the formation of low yields of the diacid.
(45) The preparation of **59a** was described previously; see ref 1.

Table III. 1,2 to 1,4 Equilibration of the Adducts of the *E* Enolate of *tert*-Butyl Propanoate and Enone 22 (Scheme III)

entry	temp, °C	time,[a] h	convrsn,[b] %	1,2 major:minor:syn:anti	1,4[c]
1	−78	0.3	63	17:5	: 72:6
2	−78	1.0	63	15:5	: 74:6
3	−40	1.8	63	16:6	: 72:6
4	−5	2.2	63	0:0	: 93:7
5	5	2.6	75	0:0	: 92:8
6	25	6.7	81	0:0	: 92:8
7	25	23.2	82	0:0	: 84:16

[a] Total elapsed time. [b] Based on the amount of enone **22** remaining. [c] Determined by capillary GLC.

Table IV. Conversion of Keto Esters to Keto Acids (eq 2)

entry	R^1	R^2	syn:anti	keto acid %	keto acid compd
1	*t*-Bu	Me	syn	94	**48**
2	*t*-Bu	Et	syn	79	**49**
3	*t*-Bu	*i*-Pr	syn	100	**50**
4	*t*-Bu	*t*-Bu	anti	79	**51**
5	*t*-Bu	Ph	syn	97	**52**
6	mes[a]	Me	syn	74	**53**

[a] 2,4,6-Trimethylphenyl.

The configurations of the ketone enolate adducts in entries 29, 30, 34, 37 and 38 in Table I were proven in a parallel study of the stereochemistry of the Mukaiyama-Michael addition.[37] For the addition products to enone **22** (entries 15–19, 28–30, 34, 35, and 37–42), ^1H NMR spectroscopy can be used to assign the stereostructures. The most stable rotamers (hydrogens anti, **60s** and **60a**, Scheme V) are considered to make the assignment. In this orientation, the substituent gauche to the phenyl group experiences an upfield chemical shift.[46] Importantly, in all of the numerous cases that we have examined in the course of our studies, this method of analysis has correctly indicated the stereostructures of products that have been proven by alternative procedures.

No rigorous assignment for the configuration of the remaining addition product in entries 31 and 36 (Table I) has been made. Tentative assignment of this stereostructure rests on the analogy with the results observed with the other *Z* ketone enolates.

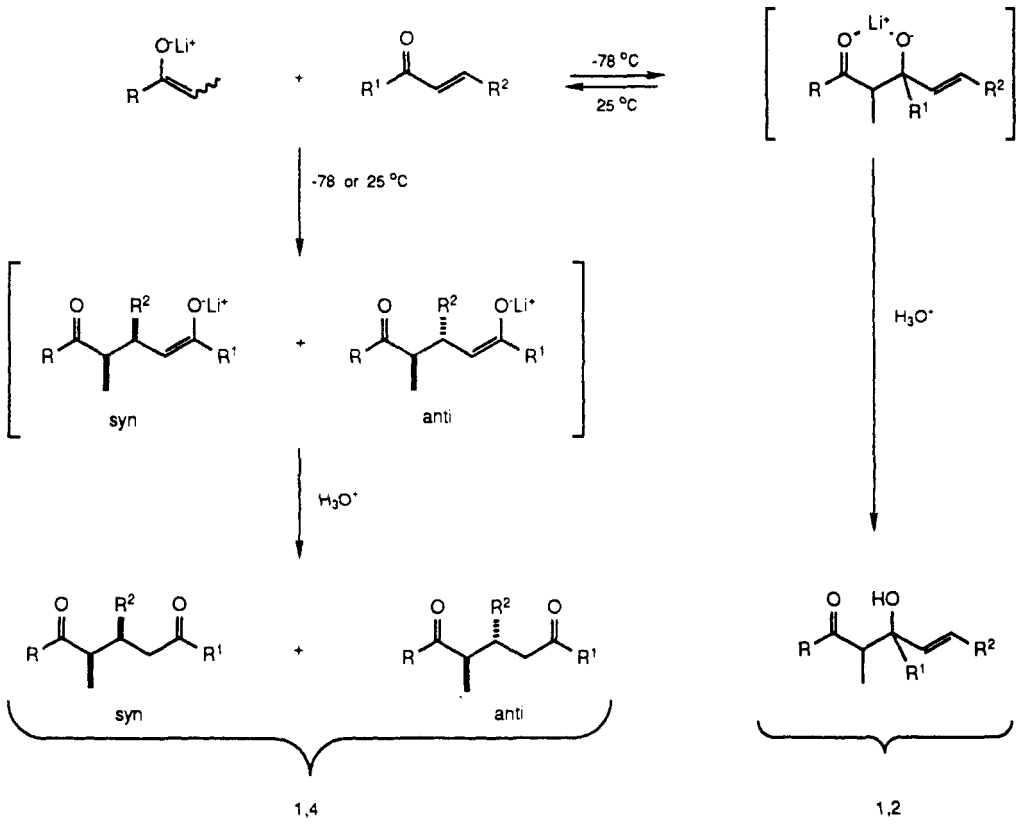
Stereochemical Trends

A significant trend is seen in the data in Table I. With few exceptions, the stereostructure of the adducts is strongly correlated with the enolate geometry; *Z* enolates give anti adducts whereas *E* enolates give syn addition products. The overall stereoselectivity of these Michael additions is usually limited only by our inability to generate the enolate in a stereochemically homogeneous manner.

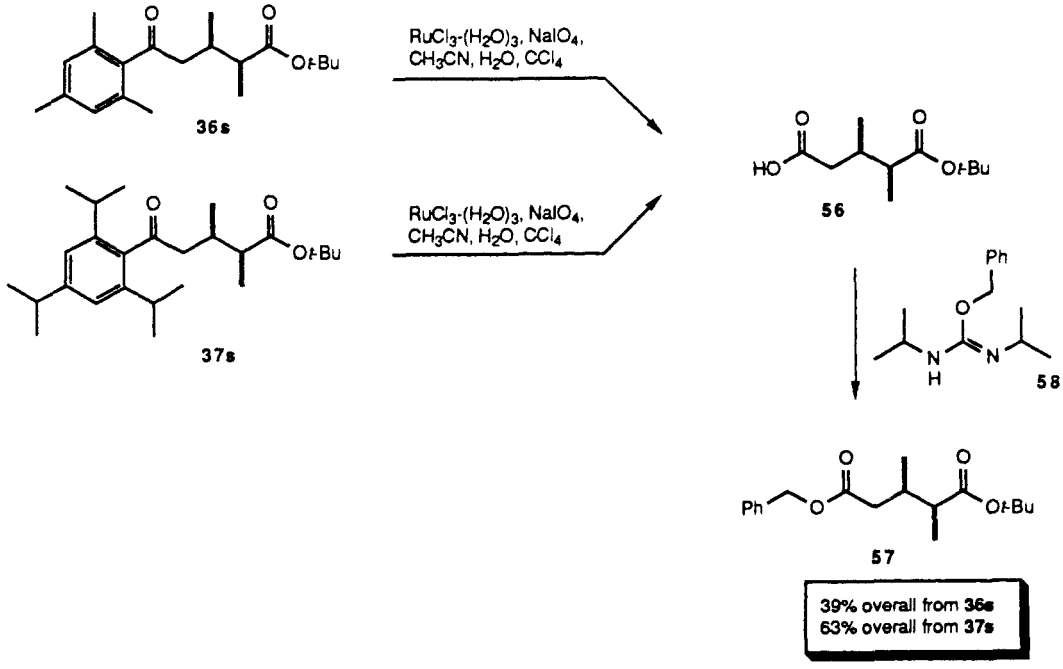
The *E* enolate–syn adduct correlation breaks down with smaller R groups on the enolate (Scheme III, entries 23, 24, and 39, Table I).[47] Use of very large substituents on the enone (R^1 = 2,4,6-trimethylphenyl and 2,4,6-triiso-

(46) (a) Heathcock, C. H.; Lampe, J. *J. Org. Chem.* **1983**, *48*, 4330. (b) Heathcock, C. H.; Kiyooka, S.; Blumenkopf, T. A. *J. Org. Chem.* **1984**, *49*, 4214.
(47) A similar trend can be seen with ester enolates and enoates (ref 10) and with amide enolates with enones (ref 1). Perhaps the best illustration of this trend is seen with amide enolates and enoates: (a) Yamaguchi, Y.; Hasebe, K.; Tanaka, S.; Minami, T. *Tetrahedron Lett.* **1986**, *27*, 959. (b) Yamaguchi, M. *Yuki Gosei Kagaku* **1986**, *44*, 405. (c) Yamaguchi, M.; Hamada, M.; Kawasaki, S.; Minami, T. *Chem. Lett.* **1986**, *27*, 1085. (d) Yamaguchi, M.; Hamada, M.; Nakashima, H.; Minami, T. *Tetrahedron Lett.* **1987**, *28*, 1785.

Scheme III



Scheme IV

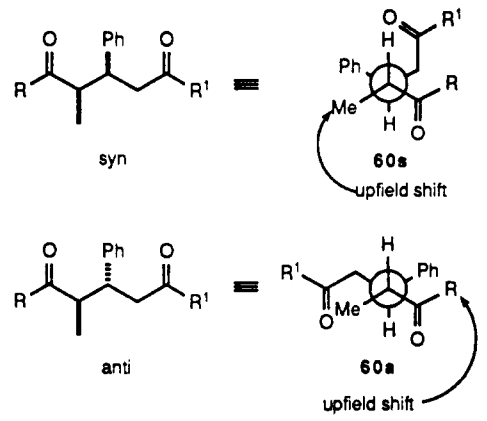


propylphenyl) partially restores the enolate–product correlation.

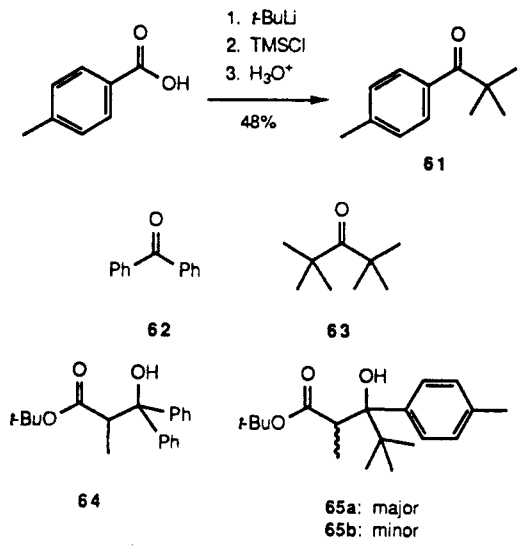
When high proportions of 1,2 addition are observed with ester enolates at −78 °C, the ratio of 1,4 adducts produced on warming the reaction mixture does not closely mimic the initial enolate ratio (entries 1, 2, 13, and 14, Table I). The decrease in selectivity in these cases is probably the result of loss of the stereochemical integrity of the enolate through an aldol–retro-aldol manifold. This is illustrated in Figure 1. Normally, the stereoselectivity if determined by the relative energetics of the diastereomeric transition states for a given enolate (A and B for the *E* enolate; A′ and B′ for the *Z* enolate). When 1,2 addition is much more favorable than 1,4 addition (i.e., transition states C and D are lower in energy than A, A′, B, and B′),[48] facile

(48) There are of course two diastereomeric transition states leading from the enolates to the 1,2-adducts. The simplifying assumption that both of these pathways are isoenergetic has been made. This assumption is valid for the addition of the *E* enolate as the 1,2-diastereomers are formed in a 1:1 mixture. No data are available for the addition of the *Z* enolate. However, the analysis remains valid as long as C and D are significantly lower in energy than A and B′ (Figure 1).

Scheme V



Scheme VI



equilibration of the enolates can occur.[49] In this case (energy A, A′, B, B′ ≫ C, D, entries 13 and 14) the Curtin–Hammett principle applies.[50,51] Hence, at this level of approximation, the stereochemical outcome is determined by the energy difference between the lowest energy aldolate (F) and the lowest energy 1,4 addition pathways (A and B′, Figure 1).

The loss of enolate integrity was examined by using ketones **61**, **62**, and **63** with the *E* enolate of *tert*-butyl propionate (Scheme VI). Ketone **61** was prepared from *p*-toluic acid and *tert*-butyllithium by using Rubottom's method;[52] **62** and **63** are commercially available. Ketones **61** and **62** give, with the *E* enolate of *tert*-butyl propionate, addition products **64**, **65a**, and **65b** on quenching with aqueous NH_4Cl. Alternatively, if the aldolate from **61** is treated with *tert*-butyldimethylsilyl chloride (TBSCl) and HMPA followed by warming to room temperature, silyl ketene acetals **3** and **4** are formed as approximately a 50:50 mixture. A similar result is also obtained when the aldolates are warmed (−20 to 20 °C), recooled to −78 °C, treated with TBSCl and HMPA, and rewarmed. This procedure with ketone **62** results in the isolation of aldol **64** and none of the corresponding ketene acetal, suggesting that the

(49) Fataftah, Z. A.; Kopka, I. E.; Rathke, M. W. *J. Am. Chem. Soc.* **1980**, *102*, 3959.
(50) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83.
(51) We know that pathway C is energetically preferred to pathways A and B since the 1,2/1,4 ratio is greater than 97:3.
(52) Rubottom, G. M.; Kim, C. *J. Org. Chem.* **1983**, *48*, 1550.

Table V. Addition of a 66:36 (*E*/*Z*) Mixture of the Enolates of 7 to Enone 22

enolate,[a] equiv	products (**46a**/**46s**) anti/syn
4.0	52:48
2.0	56:44
1.0	63:37

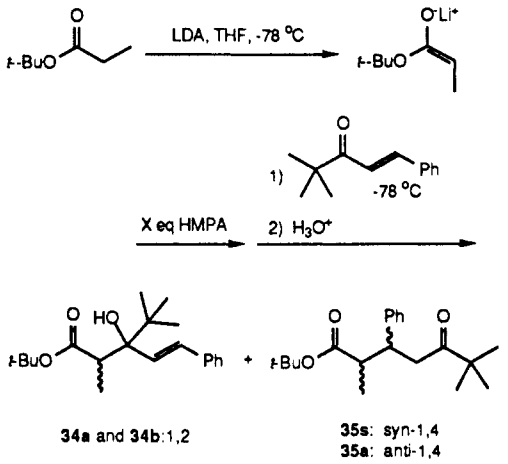
[a] Generated from a 66:34 (*E*/*Z*) mixture of enol silanes.

Table VI. Addition of the *E* Enolate of *tert*-Butyl Propionoate to Enone 22 in the Presence of Various Amounts of HMPA (Scheme VII)

entry	HMPA, equiv	yield, %	1,2:1,4[a]	1,4 syn:anti[a]
1	0	84	61:39	93:7
2	0.5	79	60:40	92:8
3	1.0	94	66:34	86:14
4	2.0	21[b]	77:23	86:14
5	4.0	96	70:30	79:21

[a] Determined by capillary GLC. [b] Material losses occurred during workup.

Scheme VII



aldolate formed in this case is quite stable. Alternately, use of the more hindered ketone **63** results in the formation of a mixture of ketene acetals in nearly identical proportions with the starting enolate ratio, consistent with the absence of aldol addition occurring under the reaction conditions. These results clearly demonstrates that 1,2 addition–retro-addition provides a manifold for enolate equilibration.[53]

Similarly, loss of the enolate integrity through an unobserved aldol–retro-aldol manifold may be responsible for the drop in selectivity observed with the *E* ketone enolates in entries 36 and 39 (Table I). In both of these examples, the substrates employed would be expected to show higher proportions of 1,2 addition based upon steric considerations. Furthermore, a slight dependence on the number of equivalents of the enolate employed is seen (Table V). Higher proportions of the syn diastereomer result when more equivalents of the enolate are used.[54,55]

(53) Attempts to equilibrate[49] here the isomeric enolates by using a catalytic amount of the enone met with no success (only decomposition products were observed). This is presumably do to the instability of the enolates at higher temperatures in the absence of the stabilizing influence of the aldolate.
(54) The data in Table V are also consistent with more rapid addition of the *E* enolate. Other evidence, however, suggests that *E* enolates react more slowly in the Michael additions. [See entry 37, Table I. In this case higher temperatures are required to promote the addition of the *E* enolate relative to the *Z* enolate (entry 29).]

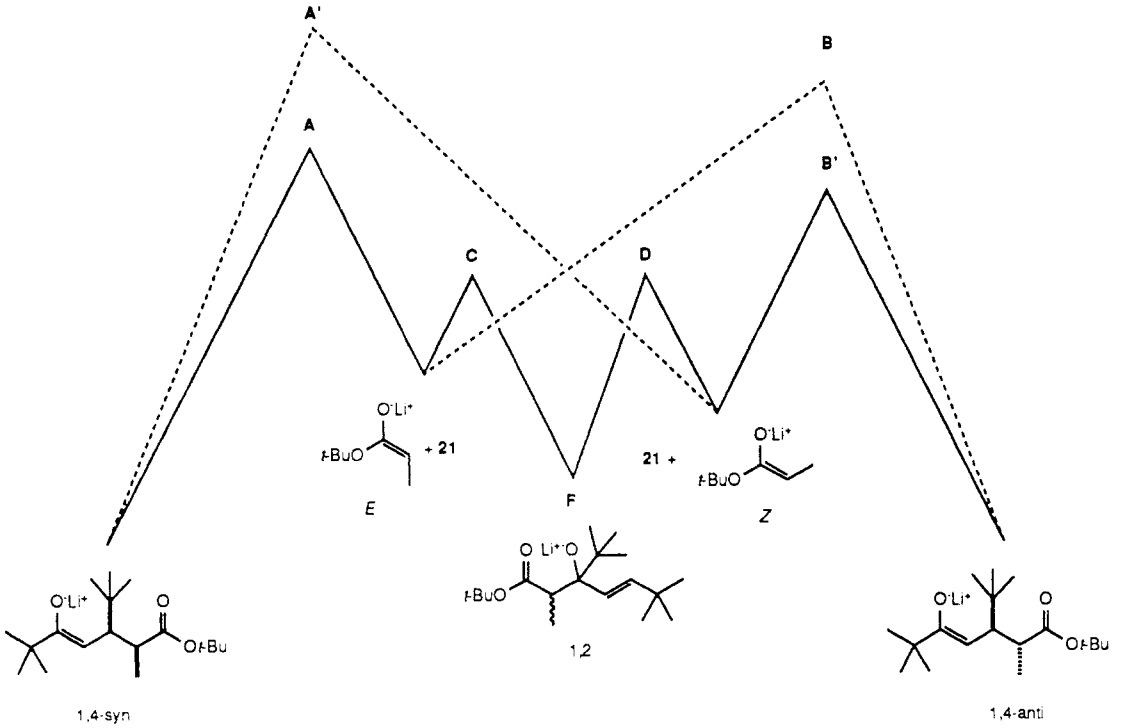
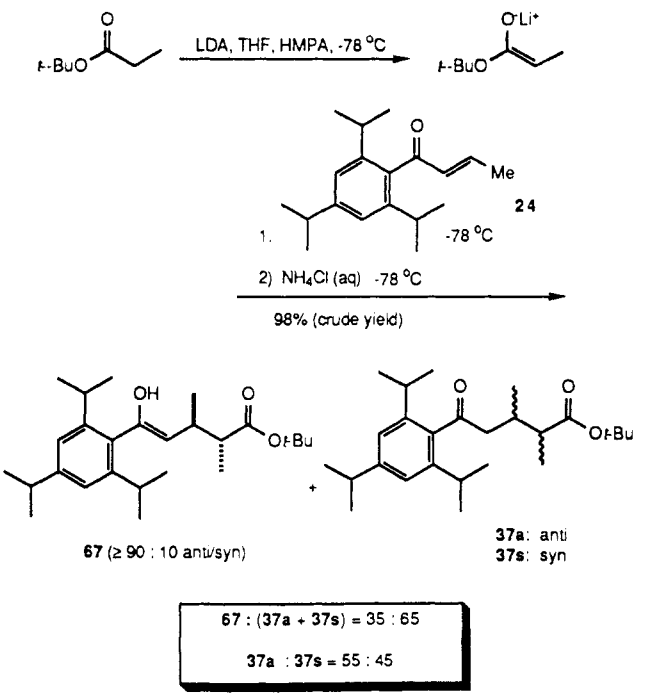


Figure 1.

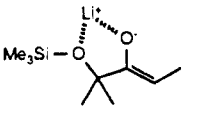
That the stereoselectivity in ester enolate Michael additions is, at −78 °C, dependent on kinetic factors follows from the stereochemical dependence on the enolate geometry. It can be argued that the *E*–*Z* dependence in the ester enolate is a function only of the HMPA present during the Michael addition. This argument is refuted by adding HMPA to the *E* enolate prior to the addition of the acceptor. Thus, with the *E* enolate of *tert*-butyl propionate and enone **22** slightly greater proportions of the anti diastereomer are formed when more equivalents of HMPA are added (Scheme VII, Table VI).[56] As can be observed from the data in Table VI, increasing the amount of HMPA results in a gradual increase in the amount of the anti diastereomer formed. Nevertheless, only a small effect is detected. This implies that the stereochemical reversal seen with the *Z* ester enolates is a function of enolate geometry and not of the choice of solvent.

For the ester enolate Michael additions, the data in Table III indicate that interconversion of the stereoisomers occurs slowly at 25 °C (compare entries 6 and 7). At −78 °C, ketone enolate Michael adducts are stable to isomerization; no change in the product isomer ratio is detected between 0.5 h and 10 days for the addition of the enolate of **7** to enone **22**. The addition of the enolate of **6** to **22** is very slow, presumably do to the loss of the facile intramolecular chelation of the counterion in enolate **66** on going to products. Hence, this system requires higher temperatures to induce addition at a significant rate (entries 41 and 42, Table I). At 25 °C for 12 h, equilibration of the adducts appears to occur (entry 42). When the reaction is performed at −10 °C for 9 days, reasonable levels of stereoselection are possible, although the starting

Scheme VIII



enone is not completely consumed (entry 41). Taken together, these results strongly implicate kinetic factors as being the source of the stereodifferentiation in the Michael additions at −78 °C.



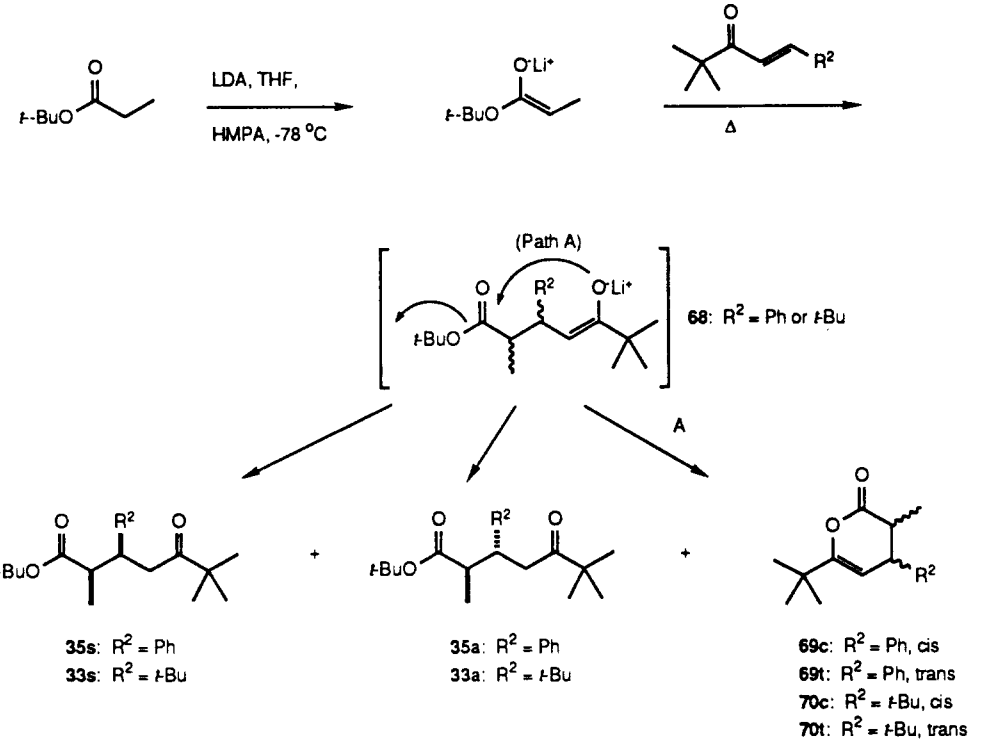
66

In two instances, abnormal products were obtained from the Michael addition. With the very hindered enone **24**, analysis of the stereochemical outcome of the conjugate

(55) A similar shift to production of higher proportions of the syn diastereomer when more equivalents (4) of the enolate are used in the addition of the *E* enolate of **1** to enone **21** has been observed.

(56) These reactions were performed by generating a stock solution of the *E* enolate from which aliquots were removed and placed in reaction flasks. Various amounts of HMPA followed by enough THF to adjust the enolate concentration to 0.30 M were added to the aliquots. The enone was then added at −78 °C and the reactions were quenched after 15 min.

Scheme IX

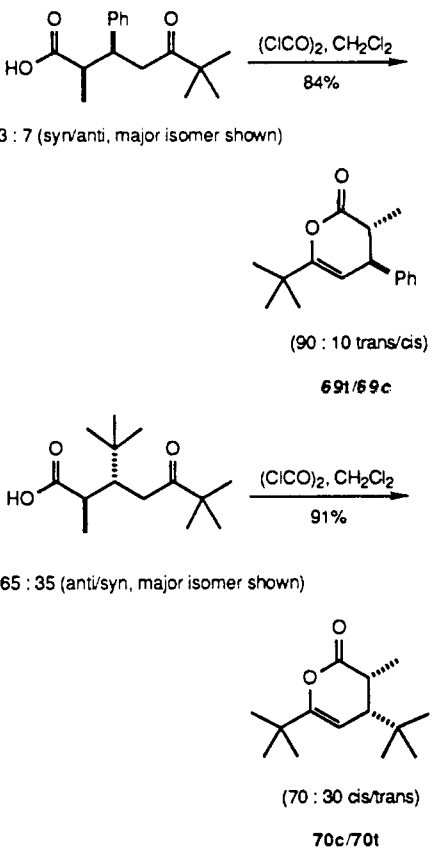


addition of ester enolate in the presence of HMPA is complicated by the occasional presence of enol **67** (Scheme VIII) in the product mixture.[57,58] Stirring the crude products with dilute acid equilibrates **67** to **37a**. The stability of the enol form of the ketone is likely to be the result of the shielding influence to the isopropyl groups.

Warming ester enolate Michael adducts **68** to 25 °C in the presence of HMPA results in partial formation of enol lactones **69c, 69t, 70c,** and **70t** (Scheme IX). The presence of **69c, 69t, 70c,** and **70t** was confirmed by the independent synthesis as shown in Scheme X. Formation of **69c, 69t, 70c,** and **70t** complicates analysis of the results in entries 12 and 16 (Table I) as preferential cyclization of either the syn or anti adducts could distort the stereochemical outcome.[59] Generation of the Michael adducts can be minimized by warming the reaction mixtures to lower temperatures (−30 to −20 °C). In the absence of HMPA, formation of **69c, 69t, 70c,** and **70t** was found to be much slower, and thus, in these cases, the product ratios in entries 14 and 18 are likely close to the actual ratio of Michael adducts formed in the reaction.

For the formation of the enol lactones, it is necessary that a *Z* enolate is produced in the Michael addition. Enones that have a *tert*-butyl group at R^1 are strongly biased to form *Z* enolates.[60] For further examination of the stereochemistry of enolate formation, the initial adduct

Scheme X



of the *E* lithium enolate of ethyl propionate and enone **23** was trapped with TMSCl.[61] In this addition, a 63:37 of

(57) Stable enols of hindered ketones are known, see, inter alia: Rappoport, Z.; Biali, S. F. *Acc. Chem. Res.* **1988**, *21*, 442 and references therein. Even simple enols may be prepared in nonprotic media; Chin, C, S.; Lee, S. Y.; Park, J.; Kim, S. *Ibid.* **1988**, *110*, 8244.

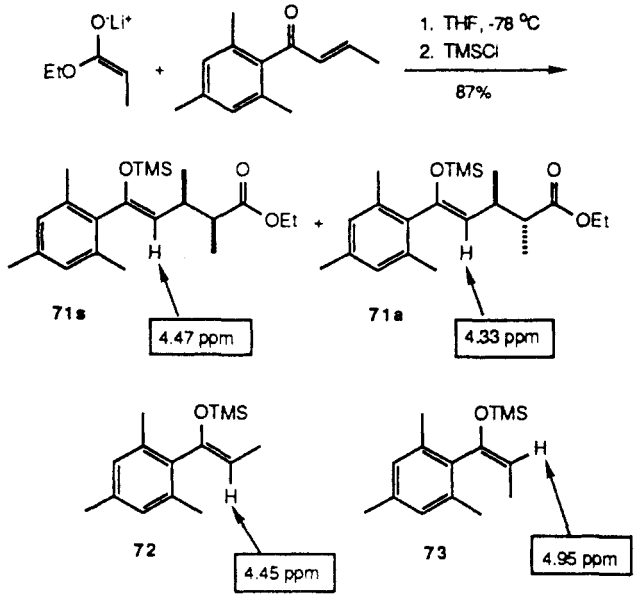
(58) We were unable to obtain **67** uncontaminated by **37a** and **37b** due to the instability of **67** to chromatography. The structure assignment for **67** rests on ^{1}H NMR and ^{13}C NMR spectroscopy. The stereochemistry of the enol is based on stereochemistry of the enolate formed (vide infra).

(59) We were unable to determine whether **69c, 69t, 70c,** and **70c** are stable to equilibration under the reaction conditions. If the enol lactones are stable to the reaction conditions, the results suggest that preferential cyclization of the syn adduct of **68** to form the trans product occurs. Thus the product ratios in entry 12 may be artificially enriched in the proportion of the anti diastereomer present.

(60) Chamberlin, A. R.; Reich, S. H. *J. Am. Chem. Soc.* **1985**, *107*, 1440.

(61) For a rough basis of comparison, calculations using MM2 show that the s-trans conformation of **23** is favored by 1.8 kcal/mol over the s-cis orientation. Similar calculations with **18** show that the s-cis configuration is preferred by 2.9 kcal/mol over the s-trans orientation.

Scheme XI



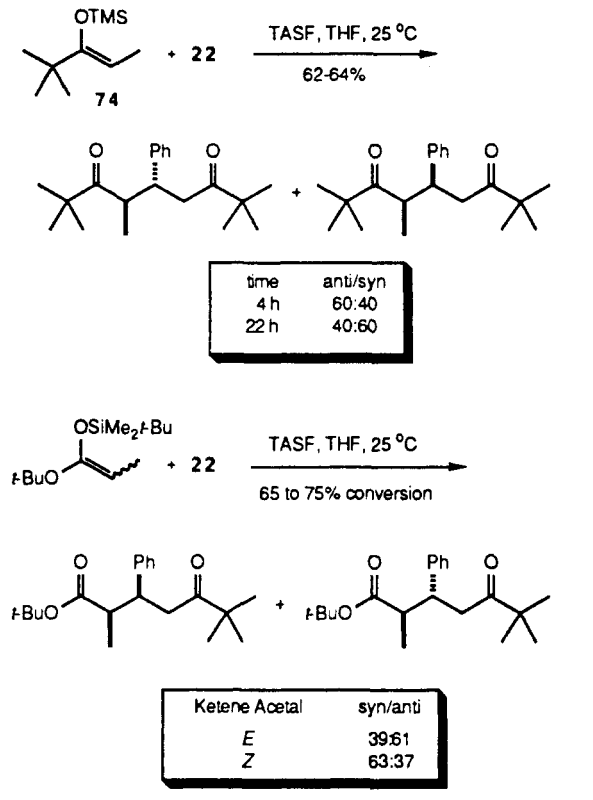
mixture isomers is formed. Hydrolysis of the mixture of **71s** and **71a** with dilute acid yields **38s** and **38a** in an identical ratio, indicating the **71s** and **71a** differ only in the relative configuration of the two adjacent stereocenters (Scheme XI). The stereochemistry of the enol ether was assigned by comparison with **72** and **73**.[24] The ^{1}H NMR chemical shift of the vinyl proton of **72** occurs substantially more upfield than that for the chemical shift of the vinyl proton in **73**, presumably due to the shielding effect of the aromatic ring. By analogy, the shift of the vinyl protons in **71s** and **71a** occurs in a range that is consistent with the *Z* configuration.

The importance of the role of the counterion is demonstrated by the tris(dimethylamino)sulfonium difluorotrimethylsiliconate (TASF) promoted addition of silyl ethers **3**, **4**, and **74** to enone **22** (Scheme XII).[62] With this method, little stereoselectivity in observed although a slight dependence on the geometry of the ketene acetal is seen.

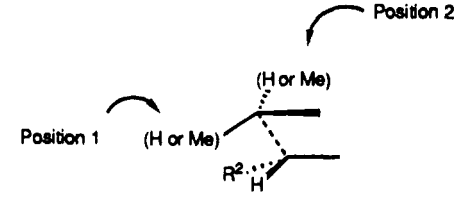
Transition-State Model

The foregoing results can be rationalized by consideration of chelated transition states A–D (Scheme XIII).[63] For large R groups on the enolate, transition structure A leading to anti adducts if favored with the *Z* enolates; with *E* enolates, model transition state C, which gives syn products, is favored. The preference for A and C is diminished with small substituents (R) on the enolate. In this case, leakage into pathways B and D occurs as a result of reduction of the unfavorable interactions with R.[47] On the other hand, increasing the bulk of R^1 favors transition states A and C as a result of adverse R–R^1 interactions. The degree of pyramidalization of the bonding centers and the trajectory of the attack on the α,β-unsaturated ketone (analogous to the Bürgi–Dunitz trajectory[64]) must be considered[65] to understand the larger preference for A with *Z* enolates relative to C with *E* enolates. Taken together,

Scheme XII



these factors suggest that a more crowded steric environment exists in position 1 of **75** compared to position 2. Hence, pathways in which the methyl group of the enolate is in position 2 are intrinsically favored.



75

Conclusions

The foregoing results have demonstrated that the Michael addition of ketone and ester enolates to α,β-unsaturated ketones is a very stereoselective process. In most cases, a strong correlation between enolate geometry and adduct stereostructure (*E*-syn, *Z*-anti) exists and the only limitation on the selectivity that may be achieved usually results from the inability to generate isomerically homogeneous enolates. It is notable that excellent selectivity in the conjugate addition occurs with simple lithium enolates. These results are consistent with a chelated transition state.

Experimental Section

General. Unless otherwide noted, materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF) and ether (Et_2O), when used as a reaction solvent, were distilled from sodium/benzophenone immediately prior to use. Diisopropylamine, hexanes, CH_2Cl_2, and triethylamine were distilled from CaH_2 immediately prior to use. Hexamethylphosphoric triamide (HMPA) was distilled from CaH_2 under reduced pressure and stored over Linde 4A molecular sieves. Trimethylsilyl chloride (TMSCl) was freshly distilled from CaH_2 and *N*,*N*-diethylaniline. Enone **21** was prepared by the method of House and co-workers.[66,67] Enone **22** was prepared by the

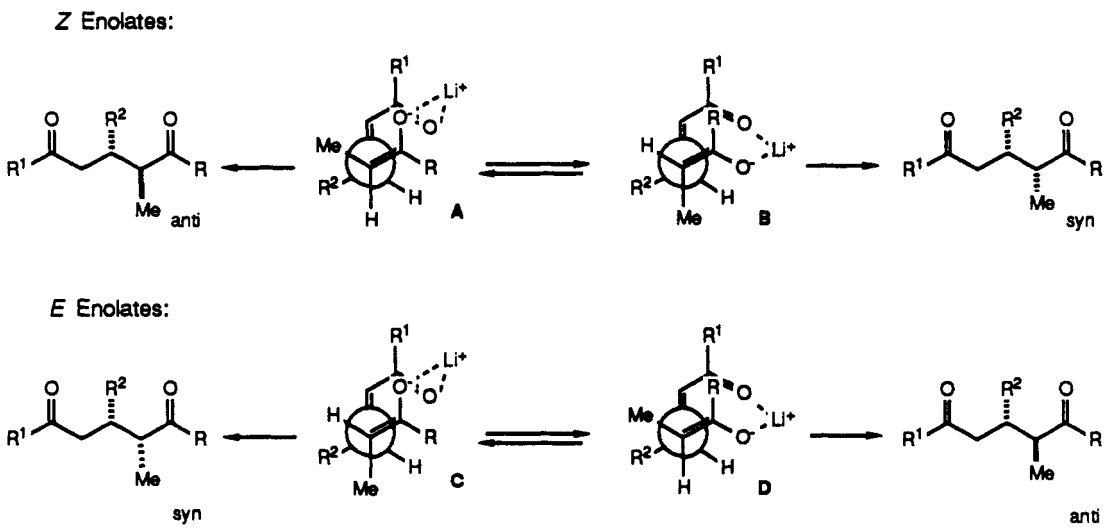
(62) The TASF-promoted addition of trimethylsilyl ketene acetals to enones has been reported: RajanBabu, T. V. *J. Org. Chem.* **1984**, *49*, 2083.

(63) Although the model transition states are depicted in Scheme XIII as enolate monomers, the arguments made apply to the dimers or tetramers, in which each Li–O bond would be one edge of a Li_2O_2 square or a Li_4O_4 cube, respectively.

(64) Bürgi, H. B.; Dunitz, J. D. *Acc. Chem. Res.* **1983**, *16*, 153.

(65) The influence of these factors has been proposed: Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413.

Scheme XIII



method of Hill and Bramann.[68] All reactions involving organometallic reagents were conducted under a nitrogen or argon atmosphere. Stirring was accomplished with a magnetic stirrer and solvent concentration was accomplished with a rotary evaporator. Boiling points and melting points (Pyrex capillary) are uncorrected. ^{1}H NMR spectra (250 or 300 MHz) and ^{13}C NMR spectra (50 or 75 MHz) were measured with $CDCl_3$ solutions. Multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), m (multiplet), and br (broad). Coupling constants are in hertz. Infrared spectra (IR) were measured as thin films on NaCl plates unless otherwise noted. Capillary gas chromatography (capillary GLC) was performed with a 25-m (0.20-mm i.d.) 5% cross-linked phenyl methyl silicone capillary column or a 12.5-m (0.20-mm i.d.) cross-linked methyl silicone capillary column. Analytical gas chromatography (GLC) was preformed with a 5-ft long ($^1/_8$ in. i.d.) OV-101 on a Chromosorb G HP 100/120 column. Flash chromatography refers to the technique described by Still, Kahn, and Mitra.[69] The PMA solution for TLC visualization refers to a 5% solution of phosphomolybdic acid in 95% ethanol.

General Procedure A for the Generation of *E* Lithium Enolates from Esters. An oven-dried Schlenk tube equipped with a rubber septum was flushed with argon and charged with 1.05 molar equiv of *n*-butyllithium in hexanes (approximately 1.5 M). The tube was cooled in an ice/salt bath to 0 °C and diisopropylamine (1.1 to 1.3 equiv) was added slowly by syringe. This mixture was stirred for a 15-min period and the rubber septum was replaced by a ground glass stopper under positive argon pressure. The ice bath was removed and the flask was placed under reduced pressure to remove the hexanes and the excess diisopropylamine. After the flask was filled with argon, the stopper was replaced with a rubber septum and enough THF was added by syringe to bring the solution to approximately 0.35 M. The reaction mixture was then cooled to −78 °C in a dry ice/acetone bath and 1.0 equiv of the ester in enough THF to bring the solution to approximately 0.33 M was added over a 10-min period by syringe pump. After 30 min of stirring, the enolate was used in the various reactions. The enolate ratio formed in the deprotonation was assayed by removal of an aliquot from the reaction mixture prior to subsequent reactions and quenching with *tert*-butyldimethylsilyl chloride (TBSCl) to provide the corresponding ketene acetals. In a modification of the Ireland[19] procedure, HMPA (4.3 molar equiv) was added by syringe to an aliquot (0.5 to 1.5 mmol) of the enolate removed from the reaction mixture by syringe and transferred to an oven-dried argon-flushed Schlenk tube equipped with a rubber septum, cooled in a dry ice/acetone bath. To this stirring solution, was added 1.1 molar equiv of TBSCl in 0.2 to 0.8 mL of hexanes. After 5 min, the cooling bath was removed and the reaction mixture was allowed to come to room temperature. After a 1- to 1.5-h period, the reaction mixture was quenched with saturated $NaHCO_3$. The resulting solution was diluted with 10 mL of H_2O and extracted with cold pentane (3 × 10 mL). The pentane layers were combined, washed with H_2O (6 × 8 mL), dried briefly with $MgSO_4$, filtered, and carefully concentrated. The isomer ratio obtained was assessed by comparison with authenic samples by ^{1}H and/or ^{13}C NMR spectroscopy and capillary GLC.

General Procedure B for the Generation of *Z* Lithium Enolates from Esters. An oven-dried Schlenk tube equipped with a rubber septum was flushed with argon and charged with 1.0 molar equiv of *n*-butyllithium in hexanes (approximately 1.5 *M*). The Schlenk tube was then cooled in an ice/salt bath to 0 °C and diisopropylamine (1.1 to 1.3 equiv) was added slowly by syringe. This mixture was stirred for 15 min and the rubber septum was replaced by a ground glass stopper under positive argon pressure. The ice bath was removed and the flask was placed under reduced pressure to remove the hexanes and the excess diisopropylamine. After the flask was filled with argon, the stopper was replaced with a rubber septum and 4.3 molar equiv of HMPA and enough THF were added to bring the solution to approximately 0.33 M. This solution was immediately cooled to −78 °C in a dry ice/acetone bath and neat ester (1.1 molar equiv) was added quickly by syringe. After being stirred for 30 min, the enolate was used in the various reactions. The enolate ratio formed in the deprotonation could be assayed by removal of an aliquot from the reaction mixture prior to subsequent reactions and quenching with *tert*-butyldimethylsilyl chloride (TBSCl) to provide the corresponding ketene acetals. Following a modification of the Ireland[19] procedure, an aliquot (0.5 to 1.5 mmol) of the enolate was removed from the reaction mixture by syringe and transferred to an oven-dried argon-flushed Schlenk tube equipped with a rubber septum, cooled in a dry ice/acetone bath. To this stirring solution was added 1.1 molar equiv of TBSCl in 0.2 to 0.8 mL of hexanes. After 5 min, the cooling bath was removed and the reaction mixture was allowed to come to room temperature. After a 1- to 1.5-h period, the reaction mixture was quenched with saturated $NaHCO_3$. The resulting solution was diluted with 10 mL of H_2O and extracted with cold pentane (3 × 10 mL). The pentane layers were combined, washed with H_2O (6 × 8 mL), dried briefly with $MgSO_4$, and carefully concentrated. The isomer ratio obtained was assessed by comparison with authenic samples by ^{1}H and ^{13}C NMR spectroscopy and capillary GLC.

General Procedures C and D for the Addition of *E* Ester Enolates to Enones. To the *E* enolate generated by using general procedure A was added the enone in enough THF to bring the solution to 0.30 M by syringe pump over a 10-min period while

(66) House, H. O., Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3309.
(67) We thank Dr. Daivd E. Uehling for preparing this compound.
(68) Hill, G. A.; Bramann, G. M. *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. 1, p 81.
(69) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

being stirred in a dry ice–acetone bath. After an additional 15 min (unless otherwise indicated), the reaction either was quenched with 5–10 mL of saturated NH_4Cl (procedure C) or warmed to 25 °C for a 1.5-h period (unless indicated otherwise) and then quenched (procedure D). The solution was removed from the dry ice bath and allowed to warm to room temperature. After being diluted with 10 mL of H_2O, the reaction mixture was extracted with Et_2O (4 × 10 mL). The ethereal layers were combined, washed with brine, dried with $MgSO_4$, filtered, concentrated, and briefly placed under reduced pressure to remove the last traces of solvent to give the crude product.

General Procedures E and F for the Addition of *Z* Ester Enolates to Enones. To the *Z* enolate generated following general procedure B was added the enone in enough THF to bring the solution to 0.30 M by syringe pump over a 10-min period while being stirred in a dry ice/acetone bath. After an additional 15-min period (unless otherwise indicated), the reaction either was quenched with 5 to 10 mL of saturated NH_4Cl (procedure E) or warmed to 25 °C for a 1.5-h period (unless indicated otherwise) and then quenched (procedure F). After being warmed to room temperature, the quenched reaction mixture was diluted with 10 mL of H_2O and extracted with Et_2O (4 × 10 mL). The ethereal layers were combined, washed with H_2O (6 × 8 mL) and 10 mL of brine, dried with $MgSO_4$, filtered, concentrated, and briefly placed under reduced pressure to remove the last traces of solvent to give the crude product.

General Procedure for the TASF-Catalyzed Addition of 3, 4, and 74 to Enone 22. To 0.254 g of TASF (transferred and weighed under inert atmosphere) in 1.5 mL of THF was added by syringe a mixture of enone **22**, 0.7 mL of THF, and silyl ethers **3**, **4**, or **74**. After being stirred for 5 min at −78 °C, the mixture was warmed to room temperature. After 22 h, 0.25 mL of glacial acetic acid was added by syringe and the solvent was removed under reduced pressure. The crude oil was diluted with 10 mL of 1.2 N aqueous HCl and 10 mL of H_2O and extracted with Et_2O (3 × 10 mL). The ethereal layers were combined, washed with 10 mL of 1.2 N HCl, 2 × 10 mL of saturated $NaHCO_3$, and 10 mL of brine, dried with $MgSO_4$, and concentrated to give the crude products.

***tert*-Butyl (*E*,2*RS*,3*RS*)- or (*E*,2*RS*,3*SR*)-3-hydroxy-3-isopropyl-2-methyl-4-hexenoate (26)**: clear oil; IR 3520 (br), 2980, 2880, 1710 cm^{-1}; ^1H NMR δ 0.89 (d, 6, *J* = 6.9), 1.10 (d, 3, *J* = 7.1), 1.46 (s, 9), 1.71 (m, 4), 2.60 (q, 1, *J* = 7.1), 3.52 (s, 1), 5.19 (br d, 1, *J* = 15.3), 5.72 (dq, 1, *J* = 15.3, 6.6); ^{13}C NMR δ 12.47, 16.82, 17.72, 17.79, 28.04, 35.79, 45.65, 77.66, 81.34, 126.08, 129.44, 176.19. Anal. Calcd for $C_{12}H_{26}O_4$: C, 69.38; H, 10.81. Found: C, 69.13; H, 10.57.

***tert*-Butyl (2*RS*,3*SR*)- and (2*RS*,3*RS*)-5-oxo-2,3,6-trimethylheptanoate (27s and 27a), mixture of isomers**: clear oil: IR 2980, 2880, 1730 cm^{-1}; ^1H NMR δ 0.89 (m, 3), 1.07 (m, 9), 1.45 (s, 9), 2.26–2.66 (m, 5). Anal. Calcd for $C_{12}H_{26}O_4$: C, 69.38; H, 10.81. Found: C, 69.17; H, 10.57.

2*RS*,3*SR* isomer 27s: ^{13}C NMR δ (discernible from mixture) 13.96, 16.98, 17.95, 29.97, 31.64, 41.03, 44.06, 79.95, 174.64, 213.71.

2*RS*,3*RS* isomer 27a: ^{13}C NMR δ (discernible from mixture) 13.20, 16.60, 18.00, 18.15, 27.97, 31.32, 40.90, 44.80, 79.91, 174.94, 213.56.

***tert*-Butyl (2*RS*,3*SR*)-5-oxo-2,3,6,6-tetramethylheptanoate (28s)**: clear oil; IR 2990, 1735, 1720, 1490, 1470, 1375, 1160 cm^{-1}; ^1H NMR δ 0.83 (d, 3, *J* = 6.1), 1.03 (d, 3, *J* = 6.8), 1.11 (s, 9), 1.43 (s, 9), 2.30 (q, 1, *J* = 6.8), 2.42 (m, 3); ^{13}C NMR δ 13.1, 16.5, 26.1, 27.9, 31.0, 40.6, 44.0, 44.6, 79.7, 175.0, 214.4. Anal. Calcd for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01. Found: C, 70.15; H, 11.04.

***tert*-Butyl (2*RS*,3*RS*)-5-oxo-2,3,6,6-tetramethylheptanoate (28a)**: clear oil; IR 2970, 1730, 1710, 1480, 1460, 1370, 1160 cm^{-1}; ^1H NMR δ 0.88 (d, 3, *J* = 6.3), 1.03 (d, 3, *J* = 6.7), 1.13 (s, 9), 1.45 (s, 9), 2.31–2.50 (m, 3), 2.59 (dd, 1, *J* = 4.1, 10); ^{13}C NMR δ 14.2, 16.7, 26.3, 28.1, 31.5, 40.8, 44.1, 44.5, 80.0, 174.8, 214.9. Anal. Calcd for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01. Found: C, 69.89; H, 11.06.

***tert*-Butyl (2*RS*,3*SR*)-3-ethyl-5-oxo-2,6,6-trimethylheptanoate (29s)**: clear oil; IR 2980, 1735, 1720, 1485, 1465, 1375, 1155 cm^{-1}; ^1H NMR δ 0.87 (d, 3, *J* = 7.4), 1.04 (d, 3, *J* = 7.1), 1.14 (s, 9), 1.24 (m, 2), 1.45 (s, 9), 2.23 (m, 1), 2.51 (m, 3); ^{13}C NMR δ 11.2, 13.9, 24.3, 26.4, 28.0, 37.4, 37.7, 41.6, 44.2, 79.8, 175.1, 215.0. Anal. Calcd for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 70.76; H, 11.30.

***tert*-Butyl (2*RS*,3*RS*)-3-ethyl-5-oxo-2,6,6-trimethylheptanoate (29a)**: clear oil; IR 2980, 1740, 1720, 1490, 1470, 1375, 1160 cm^{-1}; ^1H NMR δ 0.87 (d, 3, *J* = 7.4), 1.02 (d, 3, *J* = 7.0), 1.14 (s, 9), 1.25 (m, 2), 1.43 (s, 9), 2.33 (m, 1), 2.44 (m, 1), 2.61 (m, 2); ^{13}C NMR δ 11.9, 12.9, 24.1, 26.5, 28.1, 37.3, 37.8, 41.7, 44.2, 80.0, 175.3, 215.1. Anal. Calcd for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: 70.79; H, 11.26.

***tert*-Butyl (*E*,2*RS*,3*RS*)- or (*E*,2*RS*,3*SR*)-3-*tert*-butyl-2,6-dimethyl-3-hydroxy-4-heptenoate (30a)**: Clear oil; IR 3480 (br), 2980, 2900, 1710, 1160 cm^{-1}; ^1H NMR δ 0.92 (s, 9), 1.00 (d, 6, *J* = 6.7), 1.08 (d, 3, *J* = 7.1), 1.46 (s, 9), 2.33 (double octet, 1, *J* = 1.2, 6.7), 2.58 (q, 1, *J* = 7.1), 4.37 (d, 1, *J* = 1.4), 5.17 (br dt, 1, *J* = 15.5, 1.2), 5.70 (dd, 1, *J* = 7.1, 15.5); ^{13}C NMR δ 15.9, 22.6, 22.7, 26.4, 27.8, 31.1, 39.2, 41.6, 79.1, 81.4, 127.2, 136.8, 178.1. Anal. Calcd for $C_{17}H_{32}O_3$: C, 71.78; H, 11.34. Found: C, 71.77; H, 11.32.

***tert*-Butyl (2*RS*,3*RS*)-3-isopropyl-5-oxo-2,6,6-trimethylheptanoate (31s)**: clear oil; IR 2980, 2880, 1730, 1370, 1105 cm^{-1}; ^1H NMR δ 0.80 (d, 3, *J* = 6.8), 0.89 (d, 3, *J* = 6.8), 1.05 (d, 3, *J* = 7.2), 1.16 (s, 9), 1.43 (s, 9), 1.68 (octet, 1, *J* = 6.7), 2.22 (br quin, 1, *J* = 5.6), 2.52 (m, 3); ^{13}C NMR δ 15.7, 19.5, 20.7, 26.8, 28.0, 29.8, 35.7, 40.8, 41.7, 44.2, 79.8, 175.5, 214.7. Anal. Calcd for $C_{17}H_{32}O_3$: C, 71.78; H, 11.34. Found: C, 71.69; H, 11.46.

***tert*-Butyl (2*RS*,3*SR*)-3-isopropyl-5-oxo-2,6,6-trimethylheptanoate (31a)**: clear oil; IR 2980, 2880, 1760 cm^{-1}; ^1H NMR δ 0.80 (d, 3, *J* = 6.8), 0.88 (d, 3, *J* = 6.8), 0.98 (d, 3, *J* = 6.8), 1.15 (s, 9), 1.41 (s, 9), 1.61 (br octet, 1, *J* = 6.4), 2.43 (m, 4); ^{13}C NMR δ 13.2, 19.2, 21.0, 27.0, 28.0, 29.7, 35.6, 39.8, 42.2, 44.3, 80.0, 175.8, 214.2.

***tert*-Butyl (*E*,2*RS*,3*RS*)- or (*E*,2*RS*,3*SR*)-3-*tert*-butyl-3-hydroxy-2,6,6-trimethyl-4-heptenoate, major 1,2 isomer (32a)**: Clear oil; IR 3500 (br), 2980, 1720, 1375, 1160 cm^{-1}; ^1H NMR δ 0.95 (s, 9), 1.02 (s, 9), 1.21 (d, 3, *J* = 7.0), 1.42 (s, 9), 2.72 (q, 1, *J* = 7.0), 3.06 (s, 1), 5.57 (d, 1, *J* = 15.9), 5.64 (d, 1, 15.9); ^{13}C NMR δ 14.5, 26.7, 28.0, 29.7, 32.9, 38.3, 46.2, 77.9, 80.6, 127.4, 140.0, 176.1. Anal. Calcd for $C_{18}H_{34}O_3$: C, 72.43; H, 11.48. Found: C, 72.47; H, 11.48.

Minor 1,2 isomer 32b: clear oil; IR 3480 (br), 2970, 1715, 1375, 1155 cm^{-1}; ^1H NMR δ 0.92 (s, 9), 1.03 (s, 9), 1.07 (d, 3, *J* = 7.1), 1.47 (s, 9), 2.60 (q, 1, *J* = 7.1), 4.39 (d, 1, *J* = 1.3), 5.12 (dd, 1, *J* = 1.3, 15.7), 5.77 (d, 1, 15.7); ^{13}C NMR δ 15.9, 26.4, 27.8, 29.8, 32.8, 39.3, 41.6, 79.1, 81.3, 125.0, 140.3, 178.1. Anal. Calcd for $C_{18}H_{34}O_3$: C, 72.43; H, 11.48. Found: C, 72.23; H, 11.62.

***tert*-Butyl (2*RS*,3*SR*)- and (2*RS*,3*RS*)-3-*tert*-butyl-5-oxo-2,6,6-trimethylheptanoate (33s and 33a), mixture of diastereomers**: clear oil; IR 2980, 2880, 1730 (shoulder), 1710 cm^{-1}. Anal. Calcd for $C_{18}H_{34}O_3$: C, 72.43; H, 11.48. Found: C, 72.64; H, 11.52.

2*RS*,3*SR* isomer 33s (discernible from mixture): ^1H NMR δ 0.87 (s, 9), 1.01 (d, 3, *J* = 7.2), 1.20 (s, 9), 1.44 (s, 9), 2.21 (m, 1), 2.50 (m, 1), 2.76 (dq, 1, *J* = 4.2, 7.5), 3.18 (dd, 1, *J* = 4.5, 18.8); ^{13}C NMR δ 13.5, 18.3, 27.1, 28.0, 28.1, 33.3, 39.5, 42.0, 45.0, 79.8, 176.5, 215.4.

2*RS*,3*RS* isomer 33a: clear oil; ^1H NMR δ 0.88 (s, 9), 1.00 (d, 3, *J* = 6.9), 1.16 (s, 9), 1.42 (s, 9), 2.53 (m, 4); ^{13}C NMR δ 13.5, 18.8, 27.1, 27.9, 28.3, 33.5, 39.7, 42.0, 44.2, 79.8, 176.3, 213.9.

***tert*-Butyl (*E*,2*RS*,3*RS*)- or (*E*,2*RS*,3*SR*)-3-*tert*-butyl-3-hydroxy-2-methyl-5-phenyl-4-pentenoate, major 1,2 isomer (34a)**: white crystalline solid; mp 92.5–3.0 °C; IR ($CHCl_3$) 3460 (br), 2995, 1700, 1380, 1355, 1155 cm^{-1}; ^1H NMR δ 0.99 (s, 9), 1.13 (d, 3, *J* = 7.1), 1.48 (s, 9), 2.72 (q, 1, *J* = 7.1), 4.65 (d, 1, *J* = 1.2), 6.05 (dd, 1, *J* = 15.8, 1.3), 6.74 (d, 1, *J* = 15.8), 7.38 (m, 5); ^{13}C NMR δ 16.0, 26.6, 27.9, 39.7, 41.8, 79.4, 81.6, 126.3, 127.0, 128.5, 129.2, 131.0, 137.6, 177.8. Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.28; H, 9.59.

***tert*-Butyl (2*RS*,3*SR*)-5-oxo-3-phenyl-2,6,6-trimethylheptanoate (35s)**: white crystalline solid; mp 44–5 °C; IR ($CHCl_3$) 2980, 1810, 1480, 1370, 1155 cm^{-1}; ^1H NMR δ 0.91 (d, 3, *J* = 7.0), 0.94 (s, 9), 1.46 (s, 9), 2.61 (m, 2), 3.09 (dd, 1, *J* = 10.4, 17.1), 3.39 (dt, 1, *J* = 3.3, 10.3), 7.18 (m, 5); ^{13}C NMR δ 16.1, 25.9, 28.0, 41.3, 43.8, 43.9, 46.0, 80.3, 126.4, 128.1, 128.2, 142.0, 175.1, 213.0. Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50; Found: C, 75.62; H, 9.65.

***tert*-Butyl (2*RS*,3*RS*)-5-oxo-3-phenyl-2,6,6-trimethylheptanoate (35a)**: yellow oil; IR ($CHCl_3$) 2980, 1730, 1480, 1460, 1370, 1155 cm^{-1}; ^1H NMR δ 0.96 (s, 9), 1.18 (d, 3, *J* = 6.4), 1.19 (s, 9), 2.71 (m, 1), 2.78 (dd, 1, *J* = 4.5, 17.2), 2.96 (dd, 1, *J* = 9.3, 17.2), 3.42 (m, 1), 7.19 (m, 5); ^{13}C NMR δ 15.6, 25.9, 27.6, 40.1,

43.8, 44.1, 45.7, 80.0, 126.4, 127.9, 128.4, 142.5, 174.2, 213.8. Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43;, H, 9.50. Found: C, 75.62; H, 9.65.

***tert*-Butyl (2*RS*,3*SR*)-2,3-dimethyl-5-oxo-5-(2,4,6-trimethylphenyl)pentanoate (36s)**: clear oil; IR 2980, 2940, 2880, 1730, 1700 cm^{-1}; ^1H NMR δ 1.03 (d, 3, J = 6.4), 1.08 (d, 3, J = 7.0), 1.44 (s, 9), 2.19 (s, 6), 2.27 (s, 3), 2.36 (m, 1), 2.57 (m, 1), 2.62 (m, 1), 2.73 (m, 1), 6.82 (s, 2); ^{13}C NMR δ 13.32, 16.76, 19.00, 20.98, 28.03, 30.68, 44.89, 49.32, 80.04, 128.42, 132.29, 138.12, 139.55, 174.95, 209.26. Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.34; H, 9.36.

***tert*-Butyl (2*RS*,*SR*)-2,3-dimethyl-5-oxo-5-(2,4,6-triisopropylphenyl)pentanoate (37s)**: white crystalline solid; mp 52–4 °C; IR 2980, 2880, 1730, 1700 cm^{-1}; ^1H NMR δ 1.05 (d, 3, J = 6.3), 1.09 (d, 3, J = 7.0), 1.24 (br d, 18, J = 6.9), 1.44 (s, 9), 2.32–2.42 (m, 1), 2.50–2.95 (m, 6), 6.98 (s, 2); ^{13}C NMR δ 13.45, 16.65, 23.94, 25.00 (br), 28.05, 30.54, 30.77, 34.28, 44.84, 50.85, 79.99, 120.92, 137.88, 143.33, 149.28, 174.91, 209.42. Anal. Calcd for $C_{26}H_{42}O_3$: C, 77.56; H, 10.52. Found: C, 77.73; H, 10.61.

***tert*-Butyl (2*RS*,3*RS*)-2,3-dimethyl-5-oxo-5-(2,4,6-triisopropylphenyl)pentanoate (37a)**: white crystalline solid; mp 49–55 °C; IR 2980, 1730, 1700 cm^{-1}; ^1H NMR δ 1.08 (br d, 6, J = 7.1), 1.24 (br d, 18, J = 6.9), 1.43 (s, 9), 2.35–2.43 (m, 1), 2.50–2.95 (m, 6), 6.98 (s, 2); ^{13}C NMR δ 14.03, 17.40, 23.95, 24.15 (br), 28.05, 30.78, 30.83, 34.29, 44.86, 50.13, 80.01, 120.94, 143.34, 149.29, 174.65, 209.61. Anal. Calcd for $C_{26}H_{42}O_3$: C, 77.56; H, 10.52. Found: C, 77.78; H, 10.81.

***tert*-Butyl (*Z*,2*RS*,3*RS*)-2,3-dimethyl-5-hydroxy-5-(2,4,6-triisopropylphenyl)-4-pentenoate (67)**, discernible from mixture: ^1H NMR δ 1.21 (br d, 18, J = 6.9), 1.48 (s, 9), 3.19 (m, 1), 3.27 (m, 1), 4.14 (d, 1, J = 9.8); 6.12 (s, 1), 6.97 (s, 2); ^{13}C NMR δ 12.92, 20.06, 46.43, 80.72, 108.02, 112.69, 120.99, 176.94.

Ethyl (2*RS*,3*SR*)- and (2*RS*,3*RS*)-dimethyl-5-oxo-5-(2,4,6-trimethylphenyl)pentanoate (38s and 38a), mixture of diastereomers: IR 2980, 1730, 1700 cm^{-1}.

2*RS*,3*SR* isomer 38s: ^1H NMR δ 1.03 (d, 3, J = 5.7), 1.12 (d, 3, J = 6.2), 1.25 (t, 3, J = 7.3), 2.18 (s, 6), 2.67 (s, 3), 2.48–3.00 (m, 4), 4.14 (q, 2, J = 7.3), 6.82 (s, 2); ^{13}C NMR δ 13.15, 14.22, 16.82, 18.94, 20.95, 30.55, 43.82, 49.12, 60.16, 128.39, 132.25, 138.13, 139.46, 175.41, 209.10. Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: C, 74.22; H, 8.81.

2*RS*,3*RS* isomer 38a: clear oil; ^1H NMR δ 1.05 (d, 3, J = 6.3), 1.15 (d, 3, J = 6.7), 1.24 (t, 3, J = 7.2), 2.19 (s, 6), 2.67 (s, 3), 2.55 (m, 3), 2.88 (m, 1), 4.12 (q, 2, J = 7.2), 6.82 (s, 2); ^{13}C NMR δ 12.70, 14.22, 17.21, 18.91, 20.93, 30.87, 43.59, 48.67, 60.08, 128.37, 132.24, 138.10, 139.47, 175.22, 209.26. Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: C, 74.60; H, 9.11.

Ethyl (2*RS*,3*SR*)-2,3-dimethyl-5-oxo-5-(2,4,6-triisopropylphenyl)-5-pentanoate (39s): clear oil; IR 2980, 2880, 1735, 1705 cm^{-1}; ^1H NMR δ 1.05 (d, 3, J = 6.0), 1.13 (d, 3, J = 6.9), 1.24 (m, 21), 2.43–2.95 (m, 7), 4.12 (q, 2, J = 7.1), 6.98 (s, 2); ^{13}C NMR δ 13.23, 14.28, 16.74, 23.97, 24.07 (br), 30.49, 30.82, 34.31, 43.90, 50.82, 60.22, 120.99, 143.33, 149.37, 175.59, 209.39.

Ethyl (2*RS*,3*RS*)-2,3-dimethyl-5-oxo-5-(2,4,6-triisopropylphenyl)-5-pentanoate (39a): clear oil; IR 2980, 2880, 1740, 1710 cm^{-1}; ^1H NMR δ 1.06 (d, 3, J = 6.1), 1.15 (d, 3, J = 6.6), 1.25 (m, 21), 2.45–2.95 (m, 7), 4.12 (q, 2, J = 7.2), 6.99 (s, 2); ^{13}C NMR δ (discernible) 13.80, 14.31, 17.14, 23.97, 24.13 (br), 30.81, 34.30, 50.39, 60.15, 120.98, 137.76, 143.32, 149.35, 175.28, 209.64. Anal. Calcd for $C_{24}H_{38}O_3$: C, 76.96; H, 10.23. Found: C, 77.08; H, 10.33.

(3*RS*,1′*RS*)- and (3*RS*,1′*SR*)-3-(4′,4′-dimethyl-3′-oxo-1′-phenylpentyl)-2-tetrahydropyranones (40a and 40s), mixture of diastereomers: white, amorphous solid; mp 92–8 °C; IR ($CHCl_3$) 1720, 1600 cm^{-1}; ^1H NMR δ 1.01 and 1.10 (2 s, 9), 1.40–2.01 (m, 4), 2.80–4.26 (m, 6), 7.26 (m, 5); ^{13}C NMR δ 20.96, 22.36, 22.69, 23.59, 25.98, 26.12, 39.63, 41.11, 41.25, 42.38, 43.52, 43.77, 43.85, 43.99, 67.74, 68.66, 126.51, 126.68, 128.14, 128.21, 128.51, 172.35, 173.36, 213.34, 214.34. Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.98; H, 8.39. Found: C, 74.84; H, 8.42.

General Procedure G for the Addition of Enol Silanes to Enones. In a modification of the procedure of House and coworkers[28] for the generation of lithium enolates from enol silanes, a slight excess (1.1 to 1.3 molar equiv) of methyllithium in Et_2O was added to an oven-dried and argon-flushed Schlenk tube equipped with a rubber septum. The rubber septum was replaced with a ground glass stopper and the Et_2O was removed under reduced pressure. The tube was filled with argon and the ground glass stopper was replaced by a rubber septum under positive argon pressure. THF was added by syringe and a few small crystals of 2,2′-bipyridyl were added. To the resulting purple solution cooled to 0 °C in an ice salt bath was added the enol silane in THF slowly by syringe at room temperature. After a 2- to 24-h period, an aliquot was removed by syringe from the purple solution and trapped with TMSCl using general procedure H to provide the ratio of enolates used in the reaction.[70] If the reaction mixture is *not* purple at this point, equilibration to the more stable enolate has invariably occurred. The remainder of the enolate solution was cooled to −78 °C in a dry ice/acetone bath and the enone in THF was added. The reaction was followed by TLC for the disappearance of the enone (10:1 hexanes/Et_2O, UV visualization). For reactions taking longer times to come to completion, the rubber septum was replaced with a ground glass stopper and the reaction flask was sealed and placed either in a −80 °C deep freeze or a −20 °C constant temperature bath. After the disappearance of the enone, the reaction mixture was quenched while being stirred at −78 °C with 5 mL of saturated NH_4Cl. This quenched mixture was warmed to room temperature, diluted with 10 mL of H_2O, and extracted with Et_2O (4 × 10 mL). The ethereal layers were combined, washed with 10 mL of H_2O, 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to provide the crude material.

General Procedure H for the Determination of the Ketone Enolate Ratios Used in the Ketone Enolate Michael Additions. An aliquot (0.5 to 1.5 mmol) of the ketone enolate in THF was removed by syringe from the reaction mixture as generated in general procedure G *prior* to the addition of the addition of the enone in THF. This aliquot was transferred to an oven-dried, argon-flushed Schlenk tube equipped with a rubber septum. TMSCl (3 molar equiv) was added neat by syringe to the aliquot cooled to −78 °C in a dry ice/acetone bath. After a 5-min period, the dry ice bath was removed and the reaction mixture was allowed to warm to room temperature over a 1-h period. Freshly distilled Et_3N (0.5 to 1.5 mL) was added by syringe and the reaction was immediately quenched with saturated aqueous $NaHCO_3$. A measured amount of benzophenone was added as an internal standard and the reaction mixture was diluted with approximately 10 mL of H_2O and extracted with pentane (4 × 10 mL). The pentane layers were combined, washed with a 0.1 M solution of citric acid (2×), 10 mL of saturated aqueous $NaHCO_3$, and 10 mL of H_2O, and dried with anhydrous Na_2SO_4. After removal of the drying agent by filtration, the solvent was removed (or partially removed for enol silanes 10 and 11). The enol silane ratios were determined by capillary GLC and/or ^1H NMR. Assignment was made by comparison with previously prepared compounds. Yields were determined by capillary GLC using corrected FID relative response factors for the corresponding enol silane and benzophenone.

(2*RS*,3*SR*)-2,3-Dimethyl-1-phenyl-1,5-hexanedione (43s): ^1H NMR δ 0.85 (d, 3, J = 6.9), 1.30 (d, 3, J = 6.9), 2.14 (s, 3), 2.20–2.62 (m, 3), 3.50–3.62 (m, 1), 7.44–8.10 (m, 5); ^{13}C NMR δ 12.10, 15.75, 30.39, 30.95, 43.87, 48.55, 128.38, 128.61, 132.90, 136.55, 203.81, 208.19.

(2*RS*,3*RS*)-2,3-Dimethyl-1-phenyl-1,5-hexanedione (43a): clear oil; IR (neat) 2980, 1720, 1690 cm^{-1}; ^1H NMR δ 1.01 (d, 3, J = 7.0), 1.15 (d, 3, J = 6.9), 2.08 (s, 3), 2.26 (m, 1), 2.53 (m, 2), 3.50 (dq, 1, J = 5.4, 6.9), 7.47 (m, 3), 7.92 (m, 2); ^{13}C NMR δ 13.0, 18.6, 30.4, 31.3, 44.6, 46.3, 128.2, 128.7, 133.0, 136.8, 203.8, 208.1. Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.69; H, 8.36.

(5*RS*,6*RS*)-5-Phenyl-2,2,6-trimethyl-3,7-nonanedione (46a): white crystalline solid; mp 76–6.5 °C; IR ($CHCl_3$) 2980, 1710, 1460 cm^{-1}; ^1H NMR δ 0.81 (t, 3, J = 7.2), 0.99 (s, 9), 1.11 (d, 3, J = 6.9), 2.13 (dq, 1, J = 7.2, 18.0), 2.36 (dq, 1, J = 7.2, 18.0), 2.79 (dd, 1, J = 4.7, 17.4), 2.88 (quin, 1, J = 7.1), 2.96 (dd, 1, J = 9.0, 17.4), 3.55 (br dt, 1, J = 4.6, 8.5), 7.17 (m, 5); ^{13}C NMR δ 7.4, 14.3, 26.1, 35.1, 39.0, 42.7, 44.1, 51.1, 126.5, 128.0, 128.3, 142.8, 213.7, 214.3.

(5*RS*,6*SR*)-5-Phenyl-2,2,6-trimethyl-3,7-nonanedione (46s): white crystalline solid; mp 73–3.5 °C; IR ($CHCl_3$) 2980, 1710 cm^{-1};

(70) With the enolate of propiophenone, the thermodynamic ratio was found to be 98:2 (Z/E). Hence, when the Z enolate was employed, enolate trapping was found to be unnecessary.

^{1}H NMR δ 0.88 (d, 3, J = 7.0), 0.94 (s, 9), 1.04 (t, 3, J = 7.2), 2.41 (m, 1), 2.50 (m, 1), 2.60 (dd, 1, J = 4.4, 17.1), 2.86 (m, 1), 2.94 (dd, 1, J = 9.0, 17.1), 3.48 (dt, 1, J = 4.4, 9.3), 7.16 (m, 5); ^{13}C NMR δ 7.6, 15.8, 25.9, 34.2, 41.0, 43.2, 44.0, 51.3, 126.5, 128.1, 128.3, 142.2, 213.5, 214.9. Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.79; H, 9.56.

General Procedure I for the Addition of the Enolates of 5 and 6 to Enone 22. To an oven-dried, argon-flushed Schlenk tube equipped with a rubber septum was added 2.1 molar equiv of *n*-butyllithium in hexanes by syringe. The tube was cooled to 0 °C (ice/brine bath) and diisopropylamine (2.2 to 2.5 molar equiv) was added by syringe. After being stirred for a 15-min period, the rubber septum was replaced by a ground glass stopper and the hexanes were removed under reduced pressure. The tube was filled with argon and the resulting solid was dissolved in enough THF to bring the solution to approximately 1.1 M. The solution was cooled to −78 °C in a dry ice/acetone bath and the ketone (**5** or **6**, 2.0 molar equiv) in 0.2 mL of THF was added by syringe. After a 20-min to 1.5-h period, the ground glass stopper was replaced by a rubber septum and 1.0 molar equiv of enone **22** in 0.2 mL of THF was added by syringe. After a variety of times and temperatures, the reaction mixture was quenched with 10 mL of saturated aqueous NH_4Cl and then diluted with 10 mL of H_2O. This quenched mixture was extracted with Et_2O (4 × 10 mL). The ethereal layers were combined, washed with 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to provide the crude products.

(4*RS*,5*SR*)-2,2,4,8,8-Pentamethyl-5-phenyl-3,7-nonanedione (41s) (discernible from mixture): ^{1}H NMR δ 0.87 (d, 3, J = 6.7), 0.91 (s, 9), 1.56 (s, 9), 2.45 (dd, 1, J = 3.2, 16.8), 3.02 (dd, 1, J = 6.1, 16.8), 3.34 (m, 1), 3.48 (dq, 1, J = 3.2, 10.2), 7.19 (m, 5); ^{13}C NMR δ 18.1, 25.8, 26.4, 41.0, 43.9, 44.1, 44.8, 44.9, 126.4, 128.1, 128.3, 142.5, 212.9, 219.3.

(4*RS*,5*RS*)-2,2,4,8,8-Pentamethyl-5-phenyl-3,7-nonanedione (41a): white crystalline solid; mp 97–8 °C; IR ($CHCl_3$) 2980, 1705, 1485, 1370 cm^{-1}; ^{1}H NMR δ 0.89 (s, 9), 1.03 (s, 9), 1.07 (d, 3, J = 6.8), 2.91 (dd, 1, J = 4.4, 17.6), 3.06 (dd, 1, J = 9.5, 17.6), 3.25 (dq, 1, J = 6.2, 6.8), 3.61 (m, 1), 7.21 (m, 5); ^{13}C NMR δ 15.7, 26.0, 26.2, 37.7, 42.1, 44.1, 44.6, 45.2, 126.3, 128.1, 143.5, 213.7, 218.1. Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.26; H, 10.14.

(4*RS*,5*RS*)- and (4*RS*,5*SR*)-5-phenyl-2,4,8,8-tetramethyl-2-((trimethylsilyl)oxy)-3,7-nonanedione (47a and 47s), mixture of diastereomers: IR (neat) 2980, 1710 cm^{-1}. Anal. Calcd for $C_{22}H_{36}O_3Si$: C, 70.16; H, 9.64. Found: C, 70.53; H, 9.68.

(4*RS*,5*RS*)-5-Phenyl-2,4,8,8-tetramethyl-2-((trimethylsilyl)oxy)-3,7-nonanedione (47a): clear oil; ^{1}H NMR δ 0.17 (s, 9), 0.80 (s, 3), 0.99 (s, 9), 1.08 (d, 3, J = 6.4), 1.23 (s, 3), 2.74 (dd, 1, J = 3.2, 17.2), 3.01 (dd, 1, J = 9.9, 17.2), 3.67 (m, 2), 7.18 (m, 5); ^{13}C NMR δ 2.4, 15.1, 26.1, 26.5, 27.7, 38.5, 41.8, 44.1, 44.4, 80.6, 126.1, 127.9, 128.4, 143.8, 213.7, 217.6.

(4*RS*,5*SR*)-5-Phenyl-2,4,8,8-tetramethyl-2-((trimethylsilyl)oxy)-3,7-nonanedione (47s): ^{1}H NMR (discernible form mixture) δ 0.74 (s, 9), 0.81 (d, 3, J = 6.9), 0.85 (s, 9), 1.29 (s, 3), 1.34 (s, 3), 2.34 (dd, 1, J = 3.0, 16.9), 3.01 (m, 1), 3.37 (dt, 1, J = 3.0, 10.7), 3.60 (m, 1), 7.13 (m, 5); ^{13}C NMR (discernible from mixture) δ 2.5, 17.5, 25.8, 26.7, 27.6, 41.6, 43.8, 43.9, 80.4, 128.1, 128.3, 143.8, 213.0, 218.0.

General Procedure J for Hydrolysis of *tert*-Butyl Keto Esters.[71] The keto ester in CH_2Cl_2 was combined in a round-bottomed flask equipped with a rubber septum and argon inlet. This solution was cooled to 0 °C in an ice/salt bath and trifluoroacetic acid (TFA) was added by syringe. After being stirred for a 30-min period, the ice bath was removed and the solution was warmed to room temperature. When TLC (15:1 hexanes/Et_2O, PMA visualization) indicated that no starting keto ester remained (3 to 8 h), the reaction mixture was diluted with 10 mL of Et_2O and washed with 10 mL of H_2O. The ethereal layer was then extracted with 10% (w/v) aqueous NaOH (4 × 10 mL). The basic extracts were combined, cooled to 0 °C in an ice/salt bath, and acidified (as determined by pH paper) with concentrated H_2SO_4. This solution was then saturated with Na_2SO_4 and extracted with Et_2O (4 × 10 mL). The ethereal layers were combined, washed with 10 mL of H_2O and 10 mL of brine, dried with $MgSO_4$, filtered, concentrated, and placed under reduced pressure to remove traces of solvent to give the corresponding keto acid.

(2*RS*,3*SR*)-3-Ethyl-2,6,6-trimethyl-5-oxoheptanoic acid (49): yellow oil; IR ($CHCl_3$) 2980 (br), 1710, 1480, 1470, 1370, 1250 (br) cm^{-1}; ^{1}H NMR δ 0.89 (t, 3, J = 7.4), 1.11 (d, 3, J = 7.1), 1.14 (s, 9), 1.35 (m, 3), 2.33 (m, 1), 2.53 (m, 1), 2.65 (m, 1); ^{13}C NMR δ 11.4, 13.3, 24.2, 26.4, 37.1, 37.7, 40.8, 44.3, 182.1, 215.2. Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.25; H, 10.35. Found: C, 67.32; H, 10.58.

(2*RS*,3*SR*)-2,3-Dimethyl-5-oxo-5-(2,4,6-trimethylphenyl)pentanoic acid (53): clear oil; IR 2980 (br), 1710, 1620 cm^{-1}; ^{1}H NMR δ 1.07 (d, 3, J = 5.9), 1.16 (d, 3, J = 6.8), 2.18 (s, 6), 2.27 (s, 3), 2.61 (m, 3), 2.76 (m, 1), 6.82 (s, 2); ^{13}C NMR δ 12.92, 16.91, 18.97, 21.00, 30.41, 43.59, 48.99, 128.46, 132.31, 138.26, 139.38, 182.09, 209.12. Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.62; H, 8.42.

Saponification of Keto Esters 39a and 39s. A mixture consisting of 0.153 g (0.409 mmol) of a 65:35 mixture of keto esters **39a** and **39s**, 0.100 g of NaOH (2.50 mmol), 2.50 mL of EtOH, and 1 mL of H_2O was refluxed and stirred for 50 min. After cooling, the mixture was acidified with 1.2 N HCl, extracted with ether (4 × 10 mL), washed with 10 mL of brine, dried with $MgSO_4$, and concentrated to provide 0.138 g (97%) of a solid. Analysis (^{1}H and ^{13}C NMR spectroscopy) of this material revealed a 65:35 (anti/syn) mixture of isomers **59a** and **59s** in identical ratio with that used as starting material.

(2*RS*,3*RS*)- and (2*RS*,3*SR*)-2,3-dimethyl-5-oxo-5-(2,4,6-triisopropylphenyl)pentanoic acids (59a and 59s), mixture of isomers: white solid; mp 97–103 °C; IR ($CHCl_3$) 3000–2500 (br), 2980, 1710 cm^{-1}; ^{1}H NMR δ 1.00–1.35 (m, 24), 2.50–3.00 (m, 7), 6.98 (s, 2). Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.07; H, 9.94.

2*RS*,3*RS* isomer 59a: ^{13}C NMR δ (discernible) 13.78, 16.89, 23.96, 24.37 (br), 30.82, 34.31, 43.35, 50.42, 120.99, 137.69, 143.34, 149.39, 181.94, 209.59.

Conversion of Keto Acid 49 to Keto Oxime 54. A mixture of keto acid **49** (0.278 g, 1.30 mmol), hydroxylamine hydrochloride (0.50 g, 7.19 mmol), 3 mL of a 10% aqueous NaOH, and 5 mL of absolute ethanol was refluxed for 2 days. After cooling, the mixture was diluted with 20 mL of H_2O and 10 mL of 10% NaOH and washed with 10 mL of Et_2O. The aqueous layers were then acidified with concentrated H_2SO_4 while cooling in an ice/salt bath. The acidified aqueous layer was extracted with Et_2O (4 × 10 mL). Ethereal layers were combined, washed 5 mL of H_2O and 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to give 0.147 g (0.64 mmol, 49%) of **54**. An analytical sample and a sample suitable for single-crystal X-ray analysis was obtained by slow evaporation from a solution of the crude in 1:1 hexanes/EtOAc.

(2*SR*,3*RS*)-3-Ethyl-2,6,6-trimethyl-5-(hydroxyimino)heptanoic acid (54): white crystals; mp 138.5–9.5 °C; IR ($CHCl_3$) 3260 (br), 2980, 1710, 1470 cm^{-1}; ^{1}H NMR δ 0.96 (t, 3, J = 7.4), 1.22 (d, 3, J = 7.1), 1.25 (s, 9), 1.37 (m, 2), 2.55 (m, 2), 2.62 (m, 2); ^{13}C NMR δ 11.6, 12.3, 23.9, 27.8, 28.7, 37.9, 39.6, 41.0, 166.7, 182.0. Anal. Calcd for $C_{12}H_{23}NO_3$: C, 62.85; H, 10.11; N, 6.11. Found: C, 62.98; H, 10.19; N, 6.18.

Conversion of Keto Acid 53 to Keto Amide 55s. To a stirring solution of 0.103 g (0.394 mmol) of keto acid **53** in 1.0 mL of CH_2Cl_2 was added 0.328 g (2.03 mmol) of 1,1'-carbonyldiimidazole. After a 30-h period, 0.50 mL (0.426 g, 5.99 mmol) of pyrrolidine (freshly distilled from CaH_2) was added. The mixture was worked up after 48 h by being diluted with ether and washing with 1.2 N HCl (2 × 10 mL) and 10 mL of 10% aqueous NaOH. The resulting ethereal solution was washed with 10 mL of brine, dried with $MgSO_4$, and concentrated to yield 0.116 g of a oil. Chromatography of the crude material on 7 g of silica gel (230–400 mesh) with 2:1 hexanes/ether as eluent provided 0.102 g (82%) of **55s**. The configuration of **55s** was established by comparison to the previously prepared anti diastereomer **55a** whose structure was established by single-crystal X-ray analysis.

(2′*RS*,3′*SR*)-1-(2′,3′-Dimethyl-1′,5′-dioxo-5′-(2,4,6-trimethylphenyl)pentyl)pyrrolidine (55s): clear, viscous oil; IR 2980, 2880, 1700, 1630, 1435 cm^{-1}; ^{1}H NMR δ 1.09 (d, 3, J = 6.8), 1.12 (d, 3, J = 6.9), 1.86 (m, 2), 1.94 (m, 2), 2.17 (s, 6), 2.26 (s, 3),

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2.43 (m, 1), 2.71 (dd, 1, J = 7.3, 19.2), 2.76 (quin, 1, J = 6.9), 2.85 (dd, 1, J = 4.3, 19.2), 3.44 (m, 3), 3.59 (m, 1), 6.81 (s, 2); ^{13}C NMR δ 14.02, 16.63, 18.82, 20.92, 24.24, 26.11, 30.96, 41.60, 45.61, 46.51, 49.04, 128.31, 132.15, 137.99, 139.54, 174.19, 210.02. Anal. Calcd for $C_{20}H_{29}NO_2$: C, 76.15; H, 9.27; N, 4.44. Found: C, 75.87; H, 9.40; N, 4.33.

General Procedure K for the Equilibration of Aldols 32a and 32b to Keto Esters 33s and 33a. An oven-dried Schlenk tube equipped with a rubber septum was charged with 1.1 molar equiv of a 1.71 M solution of *n*-butyllithium in hexanes. The Schlenk tube was cooled in an ice/salt bath and diisopropylamine (1.2 molar equiv) was added by syringe. After being stirred for a 15-min period, the rubber septum was replaced with a ground glass stopper and the hexanes and excess diisopropylamine were removed under reduced pressure. Enough THF was added to bring the solution to 0.37 M and the mixture was cooled in a dry ice/acetone bath to −78 °C. Aldol **32a** or **32b** in enough THF to bring the solution to 0.30 M was added by syringe over a 30-min period. After being stirred for a 15-min period, the mixture was removed from the dry ice/acetone bath and allowed to warm to room temperature over a 1.5-h period. The reaction was quenched with approximately 5 mL of saturated NH_4Cl. The quenched mixture was diluted with approximately 5 mL of H_2O and extracted with Et_2O (4 × 8 mL). The ethereal layers were combined, washed with 10 mL of brine, dried with $MgSO_4$, and concentrated to give the crude products.

General Procedure M for the Cyclization of Keto Acids. A 10-mL oven-dried pear-shaped flask was capped with a rubber septum, flushed with nitrogen, and charged with the keto acid in CH_2Cl_2. The flask was cooled to 0 °C in an ice/salt bath. Freshly distilled oxalyl chloride was added by syringe. After a 45-min period, the mixture was quenched with 5 mL of saturated $NaHCO_3$. The quenched mixture was diluted with 10 mL of H_2O and extracted with Et_2O (4 × 10 mL). The ethereal layers were combined, washed with brine, dried with $MgSO_4$, filtered and concentrated to provide the crude enol lactones.

***trans*- and *cis*-6-*tert*-butyl-3-methyl-4-phenyl-3,4-dihydropyranones (69t and 69c), mixture of isomers**: clear oil; IR 2960, 2870, 1765, 1100, 1085 cm^{-1}. Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.62; H, 8.34.

Trans isomer 69t: ^{1}H NMR δ 1.15 (d, 3, J = 6.9), 1.18 (s, 9), 2.62 (dq, 1, J = 10.6, 6.8), 3.35 (dd, 1, J = 3.0, 10.6), 5.07 (d, 1, J = 3.0), 7.20 (m, 5); ^{13}C NMR δ 14.1, 27.5, 34.6, 41.0, 44.1, 101.3, 127.2, 128.8, 142.1, 159.8, 171.7.

Cis isomer 69c (discernible): ^{1}H NMR δ 0.98 (d, 3, J = 6.9), 1.21 (s, 9), 2.96 (quin, 1, J = 7.0), 3.50 (br t, 1, J = 6.5), 5.32 (d, 1, J = 6.5), 7.21 (m, 5); ^{13}C NMR δ 12.3, 22.6, 31.5, 38.8, 42.5, 101.2, 127.4, 128.0, 128.7, 139.1, 161.2.

***trans*- and *cis*-3,5-di-*tert*-butyl-2-methyl-3,4-dihydro-2-pyranone (70c and 70t)**: clear oil; IR 2970, 2880, 1760 cm^{-1}. Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 75.04; H, 10.71.

Cis lactone 70c: ^{1}H NMR δ 0.88 (s, 9), 1.07 (s, 9), 1.23 (d, 3, J = 7.2), 2.18 (t, 1, J = 5.7), 2.80 (m, 1), 4.99 (d, 1, J = 5.3); ^{13}C NMR δ 18.7, 27.4, 27.5, 34.4, 34.5, 37.9, 44.5, 95.4, 159.2, 173.4.

Trans lactone 70t: ^{1}H NMR δ 0.79 (s, 9), 1.08 (s, 9), 1.14 (d, 3, J = 7.4), 1.70 (dd, 1, J = 0.6, 6.5), 2.75 (m, 1), 4.88 (dd, 1, J = 1.4, 6.5); ^{13}C NMR δ 13.7, 26.5, 28.4, 34.3, 34.5, 34.6, 49.4, 100.1, 158.7, 173.2.

Correlation of Keto Ester 36s with Keto Ester 37s. Degradation of 37s. With use of the procedure described by Sharpless,[41] a 25-mL Erlenmeyer flask was charged with 0.143 g (0.355 mmol) of keto ester **37s** and 0.878 g (4.10 mmol) of $NaIO_4$ in 2 mL of CH_3CN, 3 mL of H_2O, and 2 mL of CCl_4. To this stirring suspension was added 78.5 mg (0.300 mmol of $RuCl_3{\cdot}3H_2O$, and the color changed from yellow to black. After 18 days, additional (0.371 g, 1.73 mmol) $NaIO_4$ was added. The mixture was worked up after an additional 24 days by dilution with H_2O (10 mL) and extraction with CH_2Cl_2 (3 × 10 mL). The CH_2Cl_2 layers were combined, washed with 10 mL of H_2O, dried with $MgSO_4$, filtered, concentrated, and placed under reduced pressure to provide 0.112 g of a dark oil that corresponds (^{1}H, ^{13}C NMR and IR) to ester acid **56**. Ester acid **56** could not be conveniently purified and, hence, purification was performed on the benzyl ester.

To 66.5 mg of crude ester acid **56** in a 5-mL pear-shaped flask was added 0.577 g of isourea **58**[42,43] by syringe. After 32 h at room temperature, the mixture was diluted with 0.5 mL of THF and the reaction flask was placed in a 0 °C freezer for 2 days. The resulting solution was filtered through Celite (the reaction flask was rinsed with 30 mL of hexanes and the resulting solution was filtered also). The combined hexane/THF solution was washed with dilute citric acid (3 × 5 mL), 10 mL of $NaHCO_3$, and 10 mL of brine, dried with $MgSO_4$, filtered, concentrated, and pumped on to produce 81.9 mg of a yellow oil. The crude material was subjected to column chromatography with 7 g of silica gel (230–400 mesh) utilizing 20:1 hexanes/ether as eluent to provide 49.6 mg (63% from keto ester **37s**) of **57**.

Degradation of 36s. In a procedure analogous to that above, 0.107 g (0.335 mmol) of keto ester **36s**, 1.25 g (5.84 mmol) of $NaIO_4$, 0.149 g (0.57 mmol) of $RuCl_3{\cdot}3H_2O$, 2 mL of CH_3CN, 3 mL of H_2O, and 2 mL of CCl_4 were combined. The mixture was worked up after a 2-month period to provide 80.1 mg of **56** as a dark oil identical (^{1}H NMR) with the keto acid prepared above.

Isourea **58** (0.50 mL) was added by syringe to 28.8 mg of the crude keto acid **56**. After a 5-day period at room temperature, the mixture was diluted with 10 mL of hexanes and the resulting precipitate was removed by filteration through a plug of glass wool. The filtrate was washed with dilute citric acid (4 × 8 mL), 10 mL of $NaHCO_3$, and brine, dried with $MgSO_4$, filtered, and concentrated to provide 28.7 mg of a yellow oil. Chromatography of the crude material on 2 g of silica gel (230–400 mesh) with 15:1 hexanes/ether provided 14.3 mg (39%) of **57**.

(3*RS*,4*SR*)-4-(*tert*-Butoxycarbonyl)-3-methylpentanoic acid (56): IR 3000–2500 (br), 2980, 1730 cm^{-1}; ^{1}H NMR δ 0.97 (d, 3, J = 6.2), 1.08 (d, 3, J = 6.7), 1.45 (s, 9), 2.10–2.50 (m, 4); ^{13}C NMR δ 12.95, 16.26, 27.99, 32.49, 38.97, 44.65, 80.44, 174.97, 178.38; FAB HRMS calcd for MH$^+$ ($C_{11}H_{21}O_4$) 217.1440, found 217.1432.

***tert*-Butyl (2*SR*,3*RS*)-4-((benzyloxy)carbonyl)-2,3-dimethylpentanoate (57)**: yellow oil; IR (film) 2980, 1735 cm^{-1}; ^{1}H NMR δ 0.93 (d, 3, J = 6.5), 1.05 (d, 3, J = 6.8), 1.44 (s, 9), 2.20–2.50 (m, 4), 5.12 (s, 2), 7.34 (m, 5); ^{13}C NMR δ 12.74, 16.20, 28.05, 32.71, 39.24, 44.57, 66.15, 80.17, 128.11, 128.47, 128.53, 135.92, 172.52, 174.75; FAB HRMS calcd for MH$^+$ ($C_{18}H_{27}O_4$) 307.1910, found 307.1900. Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.32; H, 8.62.

1-(4-Methylphenyl)-2,2-dimethyl-1-propanone (61). In a modification of the procedure of Rubottom,[52] 100 mL of *tert*-butyllithium (1.7 M in hexanes, 170 mmol) was added over a 10-min period to 6.0 g (44 mmol) of *p*-toluic acid in 300 mL of THF, with cooling to 0 °C in an ice/salt bath. After being stirred for a 2.5-h period at 0 °C, 150 mL (135 g, 89 mmol) of TMSCl was added over a 10-min period. The yellow/white solution was warmed to room temperature for a 2-day period. The mixture was then poured into 300 mL of 1.0 N HCl and extracted with Et_2O (3 × 150 mL). The organic layers were combined, washed with 100 mL of saturated aqueous $NaHCO_3$ and 100 mL of brine, and dried with anhydrous Na_2SO_4 and then $MgSO_4$. The drying agents were removed by vacuum filtration and the resultant solution was concentrated to approximately 20 g. Distillation (120–145 °C, 20 mmHg) of the crude material provided 3.68 g (20.9 mmol, 48%) of material that was redistilled (125–145 °C, 20 mmHg) to provide 2.04 g (11.6 mmol, 26%) of **61** as a clear oil. An analytical sample was obtained by flash chromatography of a small amount of the redistilled material through silica gel (230–400 mesh) using pentane as eluent: IR 2960, 2880, 1670, 1600 cm^{-1}; ^{1}H NMR δ 1.35 (s, 9), 2.39 (s, 3), 7.20 (d, 2, J = 8.2), 7.66 (d, 2, J = 8.2); ^{13}C NMR δ 21.3, 28.1, 43.9, 128.3, 128.6, 135.3, 141.3, 208.1. Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.55; H, 9.30.

General Procedure L for the Addition of the *E* Enolate of 1 to Ketones 61 and 62. Following general procedure A, 1.54 mmol of the *E* enolate of 1 was generated in a Schlenk tube. At −78 °C, ketone **61** or **62** (0.77 mmol) in 0.5 mL of THF was added by syringe after for a 30-min period of stirring at −78 °C. The mixture was quenched with 10 mL of saturated NH_4Cl after a 1-day period −78 °C. The quenched mixture was diluted with 10 mL of H_2O and extracted with Et_2O (4 × 10 mL). The ethereal layers were combined, washed with brine, dried with $MgSO_4$, filtered, concentrated, and placed under reduced pressure to remove residual traces of solvent. Approximately 0.2 g of the crude material was initially purified by flash chromatography with 1

g of silica gel (70–230 mesh) using Et_2O as eluent. After concentration, 0.1 to 0.2 g of the purified material was subjected to radial chromatography utilizing 35:1 hexanes/Et_2O as eluent.

***tert*-Butyl 3-Hydroxy-2-methyl-3,3-diphenylpropanoate (64).** Following general procedure L, 0.257 g of the crude material was formed. Flash chromatography of 0.237 g of the crude material provided 0.211 g of a white crystalline solid. Radial chromatography of 0.199 g of the purified material provided 0.135 g (68%) of hydroxy ester **64** as a white crystalline solid (mp 72–2.5 °C): IR ($CHCl_3$) 3480 (br), 2980, 2950, 1710, 1455, 1375, 1160 cm^{-1}; ^1H NMR δ 1.14 (d, 3, J = 7.1), 1.26 (s, 9), 3.54 (q, 1, J = 7.1), 4.79 (s, 1), 7.14 (m, 2), 7.25 (m, 4), 7.47 (m, 2), 7.59 (m, 2); ^{13}C NMR δ 12.6, 27.6, 47.5, 78.0, 81.6, 125.2, 125.5, 126.4, 126.7, 128.0, 144.2, 147.6, 176.6. Anal. Calcd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.99; H, 7.71.

***tert*-Butyl (2*RS*,3*RS*)- and (2*RS*,3*SR*)-3-hydroxy-2,4,4-trimethyl-3-*p*-tolylpentanoates (65a and 65b).** Following general procedure L, 0.227 g of the crude material was formed. Flash chromatography of 0.193 g of the crude provided 0.191 g, of which 0.122 g was purified by radial chromatography to provide 0.122 g (75%) of a mixture of **65a** and **65b** as a clear oil: IR 3460 (br), 2960, 1705, 1155. Anal. Calcd for $C_{19}H_{30}O_3$: C, 74.47; H, 9.85. Found: C, 74.25; H, 9.93.

Major isomer 65a: ^1H NMR δ 0.89 (s, 9), 0.91 (d, 3, 7.0), 1.50 (s, 9), 2.33 (s, 3), 3.14 (q, 1, J = 7.0), 4.80 (s, 1), 7.11 (m, 4); ^{13}C NMR δ 16.1, 20.9, 26.9, 27.8, 40.0, 42.0, 80.9, 81.5, 126.9 (br), 127.5 (br), 135.3, 139.9, 178.2.

Minor isomer 65b: ^1H NMR δ (discernible) 0.90 (s, 9), 1.50 (s, 9), 2.29 (s, 3), 3.36 (q, 1, J = 6.9), 4.01 (s, 1), 7.11 (m, 4); ^{13}C NMR δ (discernible) 14.5, 20.8, 27.2, 27.4, 38.4, 46.5, 79.5, 80.7, 126.8 (br), 127.0 (br), 135.6, 143.3, 176.6.

Trapping of the Enolate Obtained from the Retro-aldol Reaction of the Aldolates of 65a and 65b. To 1.00 mmol of the *E* enolate of **1** formed according to general procedure A was added 0.200 g (1.13 mmol) of ketone **61** at −78 °C. Removal of an aliquot of the enolate prior to the addition of the ketone and trapping according to the general procedure indicated that a 94:6 (*E*/*Z*) mixture of enolates was initially present. The aldol reaction mixture was warmed to 0 °C for a 50-min period, re-cooled to −78 °C, and treated with 0.8 mL of HMPA and 0.180 g (1.19 mmol) of TBSCl in 0.3 mL of hexanes. After a 7-min period at −78 °C, the mixture was warmed to room temperature for a 1-h period. The reaction flask was placed in a ice/brine bath and the reaction was quenched with saturated $NaHCO_3$. The quenched solution was diluted with 10 mL of H_2O and extracted with cold pentane (4 × 10 mL). The organic layers were combined, washed with H_2O (6 × 8 mL), dried with $MgSO_4$, filtered, and carefully concentrated to provide 0.369 g of a mixture of the ketene acetals (**3** and **4**) and **61**. Analysis (^1H NMR spectroscopy and capillary GLC indicated that the ketene acetals were formed in a 53:47 (*E*/*Z*) ratio.

Addition and Enolate Trapping of the *E* Enolate of 2 to Enone 23. Enone **23** (0.300 g, 1.59 mmol) in 1.0 mL of THF and 3.32 mmol of the *E* enolate of **2** (generated by using general procedure A) were combined according to general procedure C, with the exception that 40 min after the addition of the enone, TMSCl (0.73 mL, 0.625 g, 5.75 mmol) was added by syringe. The dry ice/acetone bath was allowed to slowly warm to room temperature and, after a 10-h period, triethylamine (2.0 mL, 1.572 g, 15.5 mmol) was added by syringe, and the reaction was immediately quenched with saturated $NaHCO_3$. The resulting mixture was diluted with 10 mL of H_2O and extracted with pentane (3 × 10 mL). The pentane layers were combined, washed with 4 × 10 mL of 5% aqueous citric acid, 10 mL of H_2O, and 10 mL of brine, dried with $MgSO_4$, filtered, concentrated, and placed under reduced pressure to provide 0.509 g of a crude oil. Analysis of the crude material (^1H and ^{13}C NMR spectroscopy) revealed a 63:37 (syn/anti) mixture of diastereomers. Flash chromatography of 0.250 g of the crude material with 10 g of silica gel (230–400 mesh) utilizing 40:1 hexanes/ether as eluent provided 0.244 g (87%) of a mixture of **71s** and **71a** in identical diastereomeric ratio with the crude material.

Ethyl (*Z*,2*SR*,3*SR*)- and (*Z*,2*RS*,3*SR*)-2,3-dimethyl-5-(2,4,6-trimethylphenyl)-5-((trimethylsilyl)oxy)-4-pentenoates (71s and 71a), mixture of isomers: clear oil; IR 2980, 1745, 1675 cm^{-1}; ^1H NMR δ 2.26, 2.28, 2.28, and 2.30 (4 s's, 9), 2.40–2.60 (m, 1), 2.95–3.18 (m, 1); ^{13}C NMR δ 135.65, 135.69, 136.10, 136.23. Anal. Calcd for $C_{21}H_{34}O_3Si$: C, 69.56; H, 9.45. Found: C, 69.81; H, 9.59.

***Z*,2*SR*,3*SR* isomer 71s (discernible from mixture)**: ^1H NMR −0.04 (s, 9), 1.05 (d, 3, J = 6.9), 1.17 (d, 3, J = 7.1), 1.26 (t, 3, J = 7.2), 4.12 (q, 2, J = 7.1), 4.47 (d, 1, J = 9.2), 6.81 (s, 2); ^{13}C NMR δ 0.51, 13.83, 14.28, 17.64, 20.22, 21.02, 32.89, 44.78, 59.86, 115.63, 128.03, 146.15, 175.78.

***Z*,2*RS*,3*SR* isomer 71a (discernible from mixture)**: ^1H NMR −0.05 (s, 9), 1.05 (d, 3, J = 6.9), 1.20 (d, 3, J = 7.0), 1.28 (t, 3, J = 7.5), 4.16 (q, 2, J = 7.1), 4.33 (d, 1, J = 9.6), 6.82 (s, 2); ^{13}C NMR δ 0.51, 15.45, 19.24, 20.27, 20.35, 20.44, 115.80, 128.11, 136.39, 136.98, 146.60, 176.45.

Hydrolysis of Enol Silanes 71s and 71a to Keto Esters 38s and 38a. To a stirring solution of 60.4 mg (0.167 mmol) of a 70:30 (syn/anti) mixture of enol silane esters **71s** and **71a** in 5 mL of THF was added at room temperature 1 mL of 1.2 N HCl. After a 30-min period, no starting material remained by TLC (20:1 hexanes/ether, UV, PMA visualization). The mixture was diluted with 20 mL of water and the layers were separated. The ethereal layers were washed with saturated $NaHCO_3$ and brine, dried with with $MgSO_4$, and concentrated to provide 48.0 mg (99%) of a clear oil. Analysis of the crude material (^1H and ^{13}C NMR spectroscopy) revealed keto esters **38s** and **38a** in a 63:37 (syn/anti) ratio.

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Registry No. 1, 20487-40-5; 1 lithium enolate, 55440-75-0; **2**, 105-37-3; 2 lithium enolate, 81355-01-3; **3**, 89043-58-3; **4**, 89043-59-4; **5**, 564-04-5; 5 lithium enolate, 64869-29-0; **6**, 72507-50-7; 6 lithium enolate, 64869-22-3; **7** lithium enolate, 74016-27-6; **8** lithium enolate, 110326-45-9; **9** lithium enolate, 70887-62-6; **10**, 51425-54-8; **11**, 51425-53-7; **12**, 19980-41-7; **13**, 19980-42-8; **14**, 66323-99-7; **15**, 71268-59-2; **16**, 3102-33-8; **17**, 50396-90-2; **18**, 20971-19-1; **19**, 38343-01-0; **20**, 38343-04-3; **21**, 20859-13-6; **22**, 29569-91-3; **23**, 36971-09-2; **24**, 122968-43-8; **25**, 930-68-7; **26**, 123123-99-9; (±)-**27s**, 123101-05-3; (±)-**27a**, 123101-06-4; (±)-**28s**, 123101-07-5; (±)-**28a**, 123101-08-6; (±)-**29s**, 123101-09-7; (±)-**29a**, 123101-10-0; (±)-**30** isomer 1, 123101-11-1; (±)-**30** isomer 2, 123101-56-4; (±)-**31s**, 123124-00-5; (±)-**31a**, 123101-12-2; (±)-**32** isomer 1, 123101-13-3; (±)-**32** isomer 2, 123101-14-4; (±)-**33s**, 123101-15-5; (±)-**33a**, 123101-16-6; (±)-**34** isomer 1, 123101-17-7; (±)-**34** isomer 2, 123101-57-5; (±)-**35s**, 123101-18-8; (±)-**35a**, 123101-19-9; (±)-**36s**, 123101-20-2; (±)-**37s**, 122969-50-0; (±)-**37a**, 123101-21-3; (±)-**38s**, 123124-01-6; (±)-**38a**, 123101-22-4; (±)-**39s**, 123101-23-5; (±)-**39a**, 123101-24-6; (±)-**40s**, 123101-26-8; (±)-**40a**, 123101-25-7; (±)-**41s**, 123101-31-5; (±)-**41a**, 123101-32-6; (±)-**42s**, 123101-51-9; (±)-**42a**, 123101-52-0; (±)-**43s**, 123101-27-9; (±)-**43a**, 123101-28-0; (±)-**44a**, 123101-53-1; (±)-**45s**, 123101-54-2; (±)-**45a**, 123101-55-3; (±)-**46s**, 123101-30-4; (±)-**46a**, 123101-29-1; (±)-**47s**, 123101-34-8; (±)-**47a**, 123101-33-7; (±)-**48**, 122969-43-1; (±)-**49**, 122969-44-2; (±)-**50**, 122969-45-3; (±)-**51**, 122969-48-6; (±)-**52**, 122969-46-4; (±)-**53**, 123101-35-9; (±)-**54**, 123101-36-0; (±)-**55s**, 123101-40-6; (±)-**56**, 123101-37-1; (±)-**57**, 123101-38-2; **58**, 2978-10-1; (±)-**59a**, 123101-39-3; (±)-**59s**, 122969-51-1; **61**, 30314-44-4; **62**, 119-61-9; (±)-**64**, 123101-42-8; (±)-**65a**, 123101-46-2; (±)-**65b**, 123101-47-3; (±)-**67a**, 123101-50-8; (±)-**67s**, 123101-58-6; (±)-**69c**, 123101-43-9; (±)-**69t**, 123101-41-7; (±)-**70c**, 123101-44-0; (±)-**70t**, 123101-45-1; (±)-**71s**, 123101-48-4; (±)-**71a**, 123101-49-5; **74**, 61878-68-0; TASF, 59218-87-0; 4-$MeC_6H_4CO_2H$, 99-94-5; *t*-BuLi, 594-19-4; δ-valerolactone, 542-28-9; δ-valerolactone lithium enolate, 82578-71-0.

Supplementary Material Available: X-ray crystallographic parameters for compound **54** and full experimental details for the preparation and isolation of Michael addition products (28 pages). Ordering information is given on any current masthead page.