for $C_{15}H_{20}O_3$ (M$^+$ – MeOH) 248.1412, found 248.1411. Anal. Calcd for $C_{16}H_{24}O_4 \cdot H_2O$: C, 64.41; H, 8.78. Found: C, 64.06; H, 8.20.

**(1$R$,3$R$)-cis-2-(3-Iodopropyl)-3-[2,2-dimethyl-3-(3-oxobutyl)cyclopropyl]-2-propenoic Acid, Methyl Ester (19).** A mixture of the chlorides ($E/Z$)-18 (203 mg, 0.675 mmol) and sodium iodide (0.7 g) was allowed to react in refluxing acetone (16 mL) for 28 h,[16] yielding the desired iodide 19 (216 mg, 81%). Purification of an aliquot by column chromatography (silica gel, gradient elution ethyl acetate in hexane) gave an analytical sample of ($E$)-19: ^{1}H NMR (90 MHz) δ 6.61 (d, 1 H, $J$ = 10 Hz), 3.72 (s, 3 H), 3.20 (t, 2 H, $J$ = 7 Hz), 2.6–2.4 (m, 4 H), 2.1–1.4 (m, 6 H), 2.15 (s, 3 H), 1.18 (s, 3 H), 1.08 (s, 3 H); ^{13}C NMR δ 208.0, 167.5, 141.5, 130.6, 65.6, 51.4, 43.1, 33.0, 32.6, 29.8, 28.9, 27.3, 25.2, 24.9, 19.3, 15.4; EIMS, m/z (rel intensity) 374 (M$^+$ – 18, 2), 360 (18), 349 (14), 317 (11), 266 (29), 155 (47), 147 (37), 119 (68), 105 (68), 91 (100), 43 (61). Anal. Calcd for $C_{16}H_{25}O_3I \cdot 4H_2O$: C, 41.39; H, 7.16. Found: C, 41.36; H, 6.92.

**Aldehydes ($E$)- and ($Z$)-26 from iodides 19.** A solution of sodium bicarbonate (12 g) in DMSO (90 mL)[17] was heated to 150 °C, and the iodides 19 (55:45 $E$:$Z$; 7.9 g, 20 mmol) were added in one portion. After 10 min at 150 °C, the reaction mixture was poured into ice (100 g). The water–DMSO mixture was extracted with ether (5 × 50 mL), and the combined ether extracts were dried (MgSO$_4$) and concentrated in vacuo to give aldehyde 26 (5.5 g, 98%). Separation of the isomers was achieved via column chromatography (silica gel, gradient elution of ether in chloroform). ($E$)-26: identical with material prepared above. ($Z$)-26: ^{1}H NMR

δ 9.74 (d, 1 H, $J$ = 1.5 Hz), 5.79 (d, 1 H, $J$ = 10.4 Hz), 3.75 (s, 3 H), 2.47 (t, 2 H, $J$ = 7.4 Hz) 2.3–2.1 (m, 4 H), 2.15 (s, 3 H), 1.8–1.6 (m, 2 H), 1.15–0.95 (m, 2 H), 1.13 (s, 3 H), 1.07 (s, 3 H); ^{13}C NMR δ 208.3 (s), 201.4 (d), 167.7 (s), 142.7 (d), 129.9 (s), 51.1 (q), 43.7 (t), 43.3 (t), 32.9, 29.9, 28.7, 27.6, 27.6, 24.3, 19.3 (q), 15.2 (q); EIMS, m/z (rel intensity) 262 (M$^+$ – 18, 2), 248 (24), 237 (23), 205 (38), 161 (47), 154 (49), 133 (54), 119 (81), 105 (76), 98 (67), 91 (100), 79 (49), 43 (55); HRMS calcd for $C_{15}H_{20}O_3$ (M$^+$ – MeOH) 248.1412, found 248.1432.

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# Stereochemistry of the Michael Addition of N,N-Disubstituted Amide and Thioamide Enolates to α,β-Unsaturated Ketones[1]

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A systematic study of the regio- and diastereoselectivity of the kinetic Michael addition of amide and thioamide enolates to a series of α,β-unsaturated ketones has been carried out. Factors that influence the diastereo- and regiochemical outcome of the reaction include the substitution pattern of the enone and enolate, the enolate counterion, and the solvent. Numerous examples of high selectivity have been discovered. In a number of examples, either the syn or the anti addition products can be obtained by varying the nature of the solvent, donor atom, and/or counterion. These results have correlated in terms of a coherent transition-state model.

## Background

The Michael addition reaction is a powerful and widely used method of synthesis.[2] Although the reaction was discovered[3] and developed as a general method[4] more than 100 years ago, its stereochemistry has been investigated only recently.[5] Several years ago, in the context of an alkaloid total synthesis,[6] we discovered that lactam 1 adds cleanly to 6-methylhept-2-en-4-one to provide keto lactam 2 as a 9:1 mixture of isomers (eq 1). Although the stereostructures of the products were not rigorously assigned, circumstantial evidence suggested that the major isomer has the relative configuration indicated at the exocyclic stereogenic center.



## Footnotes
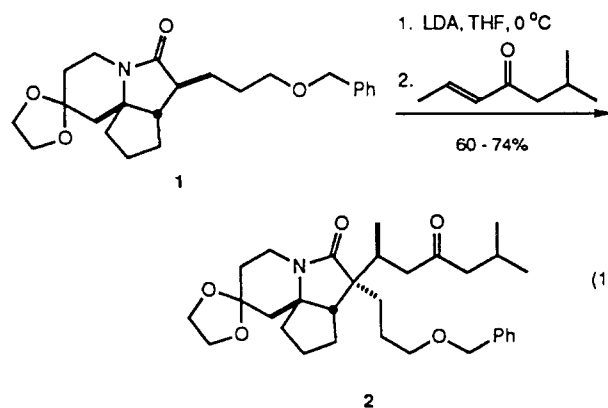
(1) Part 46 in the series Acyclic Stereoselection. For part 45, see: Slough, G. A.; Bergman, R. G.; Heathcock, C. H. J. Am. Chem. Soc. 1989, 111, 938.

(2) Bergman, E. D.; Ginsburg, D.; Pappo, R. Org. React. 1959, 10, 179.

(3) (a) Komnenos, T. Justus Liebigs Ann. 1883, 218, 145–169. (b) Claisen, L. J. Prakt. Chem. 1887, 35, 413–415.

(4) Michael, A. J. Prakt. Chem. 1887, 144, 113.

(5) For a review of the stereochemistry of the Michael addition reaction, see: Oare, D. A.; Heathcock, C. H. In Topics in Stereochemistry; Eliel, E. L., Wilen, S. H., Eds.; Wiley: New York, 1989; pp 227–407.

(6) Heathcock, C. H.; Davidson, S. K.; Mills, S.; Sanner, M. A. J. Am. Chem. Soc. 1986, 108, 5650.

The foregoing observations stimulated us to further explore the stereochemistry of the addition of preformed amide enolates to enones. Although the simple diastereoselectivity of the addition of amide enolates to cinnam-

amides[7] and $\alpha,\beta$-unsaturated esters[7a,8-10] has been explored, no study of the reaction with $\alpha,\beta$-unsaturated ketones has been reported.[11] With thioamide enethiolates, the regiochemistry of the addition to $\alpha,\beta$-unsaturated ketones has been reported by Goasdoue and co-workers.[12,13] Although these workers examined several cases in which the opportunity for simple diastereoselection exists and tentatively assigned the stereostructures of the products, the selectivity was not quantified.

In this paper, we report the full details of a study of the stereochemistry of Michael addition of amide and thioamide enolates to $\alpha,\beta$-unsaturated ketones. The study addresses the question of 1,2 versus 1,4 addition and the stereochemistry of the latter process. A transition-state model is proposed to rationalize the results.

## Preparation of Materials

The regio- and stereoselectivity of the addition was studied by using amides 3–9 and thioamides 10–12. Am-

3: X = O
10: X = S

4

5

6: X = O
11: X = S

7: X = O
12: X = S

8

9
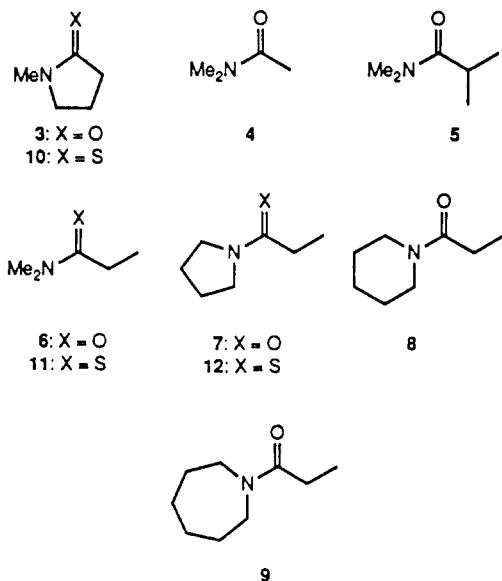
ides 3–5 are available commercially and compounds 6–9 are readily obtainable from propionyl chloride and 2 equiv of the amine. Enolates are formed by deprotonation with LDA in THF at –78 °C. Amide 7, on deprotonation with LDA, is reported by Evans and co-workers to give a single detectable enolate isomer, assigned the Z configuration on the basis of mechanistic considerations and the stereochemical outcome of subsequent reactions.[14] By analogy

**Table I. Synthesis of $\alpha,\beta$-Unsaturated Ketones 17, 19, and 20 (eq 2)**

| | allylic alcohol | | | $\alpha,\beta$-unsaturated ketone | |
|---|---|---|---|---|---|
| entry | R[1] | M | % yield | compd | % yield |
| 1 | Et | MgBr | 62 | 17 | 49 |
| 2 | c-C$_6$H$_{11}$ | MgCl | 84 | 20 | 50 |
| 3 | t-Bu | Li | 72 | 21 | 80 |

with 7, amides 6, 8, and 9 are likely to give the Z enolate. Since no method is presently available to generate E enolates of propanamides, lactam 3, which can only give the E enolate for geometrical reasons, was also examined.

Thioamides 10 and 12 were prepared from the corresponding amides by using Lawesson's reagent.[15] Lithium enethiolates are generated from the thioamides by using the procedure of Yoshida and co-workers (n-butyllithium, –20 to –30 °C).[16] Alternatively, the sodium and potassium enethiolates are formed by using NaHMDS or KHMDS, respectively. As with its oxoamide relative, thioamide 10 is constrained to give the E enolate. Thioamide 11 has been shown to give the Z enethiolate by deprotonation with n-butyllithium followed by S-alkylation with cis and trans crotyl tosylates and subsequent Claisen rearrangement.[16b,c] Thioamide 12 is assumed to give the Z configuration by analogy with oxoamide 7 and thioamide 11.

Enones 13–30 were employed in the study. Enones 13–16 are commercially available. Enones 17 and 20 are

13

14

15
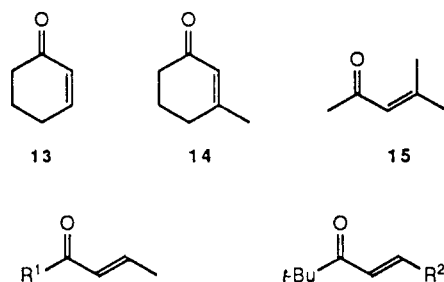
16: R$^1$ = Me
17: R$^1$ = Et
18: R$^1$ = t-Bu
19: R$^1$ = i-Pr
20: R$^1$ = c-C$_6$H$_{11}$
21: R$^1$ = t-Bu
22: R$^1$ = Ph
23: R$^1$ = p-BrC$_6$H$_4$
24: R$^1$ = p-MeOC$_6$H$_4$
25: R$^1$ = 2,4,6-Me$_3$C$_6$H$_2$
26: R$^1$ = 2,4,6-(i-Pr)$_3$C$_6$H$_2$

27: R$^2$ = Et
28: R$^2$ = i-Pr
29: R$^2$ = t-Bu
30: R$^2$ = Ph

accessible by the addition of crotonaldehyde to ethylmagnesium bromide and cyclohexylmagnesium chloride, respectively, followed by Swern oxidation[17] (eq 2, Table I). Oxidation of the intermediate allylic alcohols with pyridinium chlorochromate[18] is less satisfactory because of competing rearrangement of the allylic alcohol. *tert*-Butyl enone 21 is prepared in a similar manner from

(7) (a) Stefanovsky, Y. N.; Viteva, L. *Monatsh. Chem.* **1981**, *112*, 125. (b) Stefanovsky, Y. N.; Viteva, L. *Monatsh. Chem.* **1980**, *111*, 1287. (c) Stefanovsky, Y. N.; Viteva, L. *Izv. Otd. Khim. Nauki, Bulg. Akad. Nauk.* **1971**, *4*, 159; *Chem. Abstr.* **1972**, *76*, 24872f. (d) Stefanovsky, Y. N.; Bozilova, A. G. *Monatsh. Chem.* **1968**, *99*, 798. (e) Stefanovsky, Y. N.; Gospodova, T. *Izv. Khim.* **1982**, *14*, 336; *Chem. Abstr.* **1982**, *97*, 215154s.

(8) (a) Stefanovsky, Y. N.; Viteva, L. Z. *Izv. Otd. Khim. Bulg. Akad. Nauk.* **1971**, *4*, 99; *Chem. Abstr.* **1971**, *75*, 88270v. (b) Viteva, L. Z.; Stefanovsky, Y. N. *Monatsh. Chem.* **1982**, *113*, 181.

(9) (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.

(10) Schlessinger, R. H.; Lin, P.; Poss, M.; Springer, J. *Heterocycles* **1987**, *25*, 315.

(11) For a preliminary account of this research, see: Heathcock, C. H.; Henderson, M. A.; Oare, D. A.; Sanner, M. A. *J. Org. Chem.* **1985**, *50*, 3019.

(12) Goasdoue, C.; Goasdoue, N.; Gaudemar, M.; Mladenova, M. *J. Organomet. Chem.* **1982**, *226*, 209.

(13) For a related study of the Lewis acid promoted addition of silyl thioketene acetals to $\alpha,\beta$-unsaturated ketones, see: Goasdoue, C.; Goasdoue, N.; Gaudemar, M. *Tetrahedron Lett.* **1984**, *25*, 537.

(14) (a) Evans, D. A.; Takacs, J. M. *Tetrahedron Lett.* **1980**, *21*, 4233. (b) Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartoli, J. *Pure Appl. Chem.* **1981**, *53*, 1109.

(15) Thomsen, I.; Clausen, K.; Scheibyl, S.; Lawesson, S.-O. *Org. Synth.* **1984**, *62*, 158.

(16) (a) Tamaru, Y.; Harada, T.; Yoshida, Z. *J. Am. Chem. Soc.* **1978**, *100*, 1923. (b) Tamaru, Y.; Harada, T.; Nishi, S.; Mizutani, M.; Hioki, T.; Yoshida, Z. *J. Am. Chem. Soc.* **1980**, *102*, 7808. (c) Tamaru, Y.; Furukawa, Y.; Mizutani, M.; Kitao, O; Yoshida, Z. *J. Org. Chem.* **1983**, *48*, 3631.

(17) Manusco, A. J.; Swern, D. *Synthesis* **1981**, 165.

(18) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

**Table II. Synthesis of α,β-Unsaturated Ketones 18, 19, and 22-24 (eq 3)**

| | β-hydroxy ketone | | α,β-unsaturated ketone | |
|---|---|---|---|---|
| entry | R | % yield | compd | % yield |
| 1 | *i*-Bu | 66 | 18 | 59 |
| 2 | *i*-Pr | 75 | 19 | 67 |
| 3 | Ph | 57 | 22 | 92 |
| 4 | *p*-BrC₆H₄ | 27 | 23 | 63 |
| 5 | *p*-MeOC₆H₄ | 95 | 24 | 77 |

*tert*-butyllithium and crotonaldehyde followed by oxidation.[19]



$$R^1M, THF$$

$$(2)$$
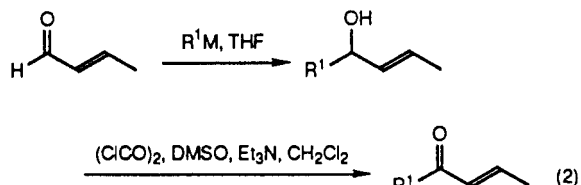
Use of an aldol-dehydration sequence leads to enones 18, 19, 22-24, and 29[20,21] (eq 3, Table II).



1. LDA, THF, -78 °C
2. MeCHO

MsCl, Et₃N

$$(3)$$
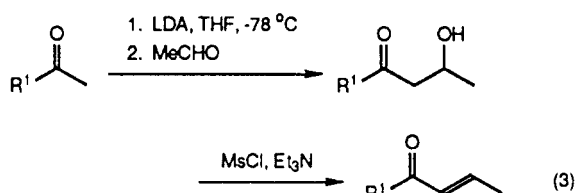
Friedel-Crafts reaction of mesitylene and 1,3,5-triisopropylbenzene with crotonyl chloride produces **25** and **26** in good yields (eq 4). Enones **27** and **28** ($R^1$ = *tert*-butyl) are available from reaction of stabilized ylide **31**[22] with propionaldehyde and isobutyraldehyde (eq 5). Benzal-



AlCl₃, CS₂

(87-95%)

$$(4)$$

25: $R^4$ = Me
26: $R^4$ = *i*-Pr

1. Ph₃P, CHCl₃
2. K₂CO₃

(49%)

**31**

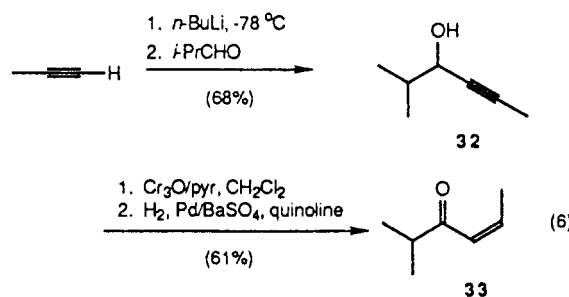$R^2$CHO, CH₃CN

(69-70%)

$$(5)$$
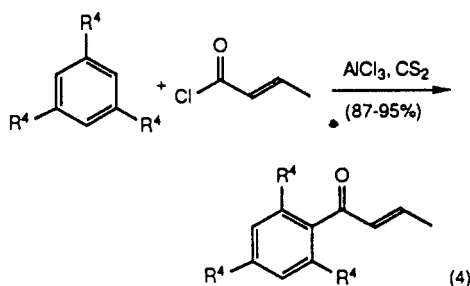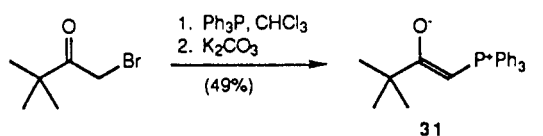
27: $R^2$ = Et
28: $R^2$ = *i*-Pr

**Table III. Reaction of N,N-Dimethylacetamide and N,N-Dimethylisobutyramide Enolates with α,β-Unsaturated Ketones**

| entry | amide | enone | temp, °C | time, h | yield, % | 1,2:1,4 ratio | product(s) |
|---|---|---|---|---|---|---|---|
| 1 | 4 | 18 | -78 | 1 | 95 | 95:5 | 40 |
| 2 | 4 | 18 | 66 | 16 | 57 | <5:95 | 34 |
| 3 | 5 | 18 | -78 | 1 | 78 | <5:95 | 35 |
| 4 | 4 | 22 | 23 | 20 | 54 | <5:95 | 36 |
| 5 | 5 | 22 | 23 | 12 | 64 | <5:95 | 37 |
| 6 | 4 | 13 | -15 | 16 | 67[a] | >95:5 | 41 |
| 7 | 4 | 13 | -78 | 0.8 | 88 | >95:5 | 41 |
| 8 | 5 | 13 | -15 | 16 | 10 | <5:95 | 38 |
| 9 | 4 | 14 | 66 | 49 | 53 | 22:78[b] | 42, 39 |
| 10 | 5 | 14 | 23 | 20 | no addition products isolated | | |
| 11 | 4 | 15 | 23 | 20 | no addition products isolated | | |

[a] Two equivalents of HMPA were added. [b] Ratio by isolation.

pinacolone (**30**) can also be produced from ylide **31** and benzaldehyde; however, this enone is more conveniently formed by using the Claisen-Schmidt condensation of benzaldehyde and pinacolone.[23] Ylide **31** failed to react with pivalaldehyde under all of the reaction conditions examined. Hence, enone **29** was prepared through an alternate route (vide supra).

Enones **16-30** contain ≥95% of the *E* isomer (¹H NMR, GLC). A *Z* α,β-unsaturated ketone (**33**) was also studied. Enone **33** is synthesized as shown in eq 6. Methyl-



1. *n*-BuLi, -78 °C
2. *i*-PrCHO

(68%)

**32**

1. Cr₃O/pyr, CH₂Cl₂
2. H₂, Pd/BaSO₄, quinoline

(61%)

$$(6)$$

**33**

acetylene is deprotonated with *n*-butyllithium and added to isobutyraldehyde to provide **32**. Oxidation of ynol **32** using the Ratcliffe-Rodehorst procedure[24] gives an ynone that is hydrogenated over Lindlar's catalyst[25] to obtain **33**, contaminated with approximately 10% of the *E* isomer.
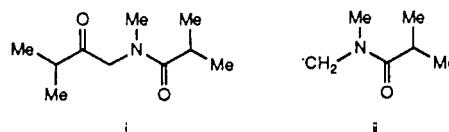
## Initial Feasibility Study

Reaction of the enolates of N,N-dimethylacetamide (**4**) and N,N-dimethylisobutyramide (**5**)[26] with enones **13-15**, **18**, and **22** was examined under conditions favoring 1,4 addition. Compounds **34-42** were produced; results are summarized in Table III. It is apparent that 1,4 addition of amide enolates can be achieved with all but the most resistant acceptors (β,β-disubstituted enones **14** and **15**).

(19) Norman, M. H. Dissertation, University of California, Berkeley, 1987.

(20) House, H. O., Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3309.

(21) We thank Dr. David E. Uehling for preparing compound **29**.

(22) Ingham, C. F.; Massy-Westropp, R. A.; Reynolds, G. D.; Thorpe, W. D. *Aust. J. Chem.* **1975**, *28*, 2499.

(23) Hill, G. A.; Bramann, G. M. *Organic Syntheses*; Wiley: New York, 1941; Collect. Vol. 1, p 81.

(24) Ratcliffe, R. W.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000.

(25) Cram, D. J.; Allinger, N. L. *J. Am. Chem. Soc.* **1956**, *78*, 2518.

(26) With amide **5**, a small amount (20 to 30%) of keto amide i was formed, presumably from the condensation of dipole-stabilized anion ii with **5**. Similar products were not obtained from N,N-dimethylacetamide or N,N-dimethylpropionamide (vide infra).

i

ii

**Scheme I**
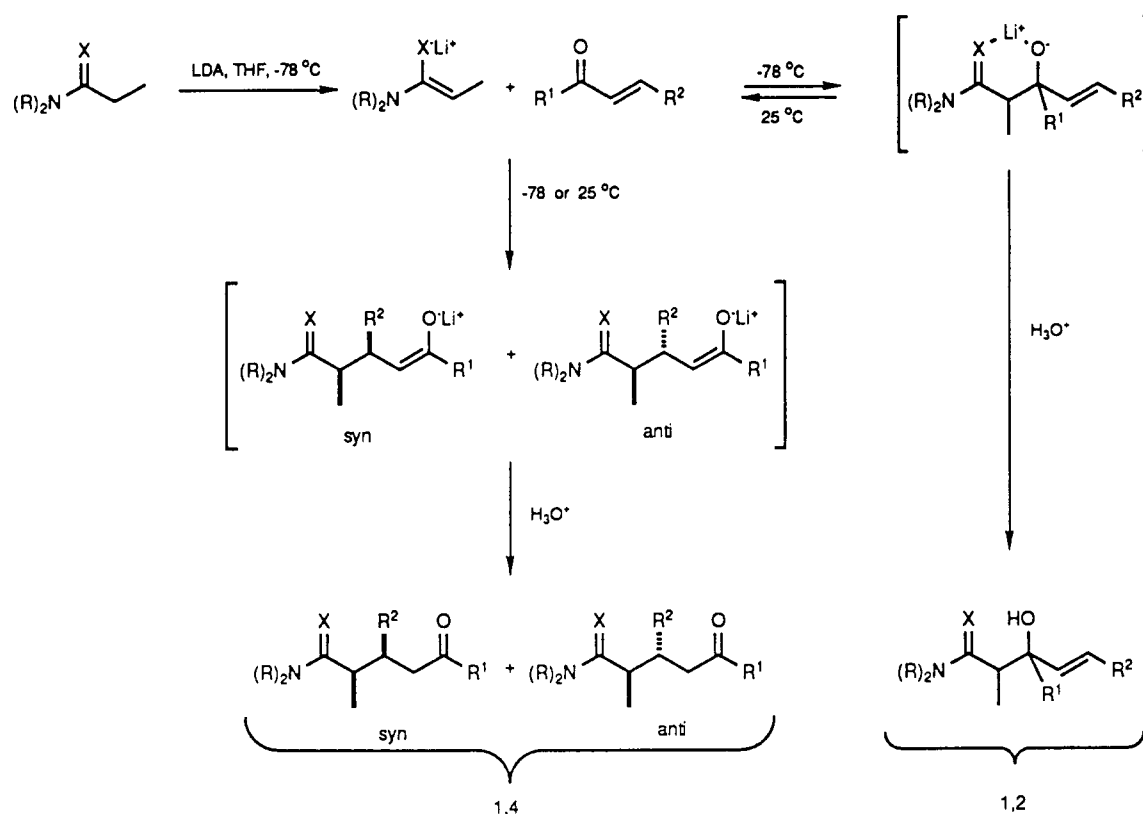


With these acceptors no addition products are obtained, presumably due to facile proton transfer.[27]



34: R = H, R¹ = i-Bu
35: R = Me, R¹ = i-Bu
36: R = H, R¹ = Ph
37: R = Me, R¹ = Ph

38: R = Me, R¹ = H
39: R = H, R¹ = Me

40

41: R = H
42: R = Me
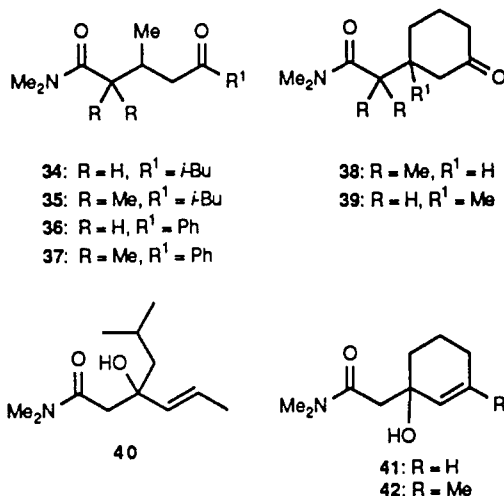
## Stereochemical Studies

The additions of amide and thioamide enolates to α,β-unsaturated ketones were performed either in THF/hexanes, THF, or THF/HMPA.[28] The enone (1 equiv) was, in general, added to a solution of the amide enolate (2

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(27) For some observations concerning the formation of quaternary centers using the Michael addition, see: Holton, R. A.; Williams, A. D.; Kennedy, R. M. *J. Org. Chem.* **1986**, *51*, 5481.

(28) For reactions performed in THF, the hexanes were usually removed from the diisopropylamine in vacuo and the solid residue was dissolved in THF prior to the addition of the amide. In reactions performed with HMPA, the additive was added to the amide enolate in THF prior to addition of the enone. Control experiments indicated no difference in the diastereoselectivity for reactions carried out in either THF or THF/hexanes.

**Table IV. Propionamide Michael Addition Adducts (Scheme I)**

| amine | | | | | 1,2 adducts | | 1,4 adducts | |
|---|---|---|---|---|---|---|---|---|
| R | R | R¹ | R² | X | major | minor | anti | syn |
| Me | Me | t-Bu | Me | O | 43aᵃ | | 44a | 44s |
| -(CH₂)₄- | | Et | Me | O | 45a | 45b | 46a | 46s |
| -(CH₂)₄- | | i-Pr | Me | O | 47a | 47b | 48a | 48s |
| -(CH₂)₄- | | c-C₆H₁₁ | Me | O | 49a | 49b | 50a | 50s |
| -(CH₂)₄- | | Ph | Me | O | 51a | 51b | 52a | 52s |
| -(CH₂)₄- | | p-BrC₆H₄ | Me | O | 53a | 53b | 54a | 54s |
| -(CH₂)₄- | | p-MeOC₆H₄ | Me | O | 55a | 55b | 56a | 56s |
| -(CH₂)₄- | | t-Bu | Me | O | 57aᵃ | | 58a | 58s |
| -(CH₂)₄- | | mesᵇ | Me | O | | | 59a | |
| -(CH₂)₄- | | trisᶜ | Me | O | | | 60a | 60s |
| -(CH₂)₄- | | t-Bu | Et | O | | | 61a | 61s |
| -(CH₂)₄- | | t-Bu | i-Pr | O | 62a | 62b | 63a | 63s |
| -(CH₂)₄- | | t-Bu | Ph | O | | | 64a | 64s |
| -(CH₂)₄- | | t-Bu | t-Bu | O | 65a | 65b | 66a | 66s |
| -(CH₂)₅- | | t-Bu | Me | O | | | 67a | 67s |
| -(CH₂)₆- | | t-Bu | Me | O | | | 68a | 68s |
| -(CH₂)₄- | | Me | Me | S | 69a | 69b | 70a | 70s |
| -(CH₂)₄- | | t-Bu | Me | S | | | 71a | 71s |
| -(CH₂)₄- | | t-Bu | Ph | S | | | 72a | 72s |
| -(CH₂)₄- | | t-Bu | t-Bu | S | | | 73a | |
| -(CH₂)₄- | | mesᵇ | Me | S | | | 74a | |
| -(CH₂)₄- | | trisᶜ | Me | S | | | 75a | |

ᵃOnly one isomer detected. ᵇ2,4,6-Trimethylphenyl. ᶜ2,4,6-Triisopropylphenyl.

equiv)[29] at −78 °C for varying lengths of time and quenched with saturated NH₄Cl. Alternatively, the reaction mixture was warmed to room temperature and then quenched and

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(29) The additions could also be performed with 1:1 enolate/enone stoichiometry; however, the yields obtained were often lower. Sufficient yields for the addition of ketal lactam 1 to enone 18 could be obtained by using an excess of enone added to the amide enolate. No effect of varying the stoichiometry of the reaction on the diastereochemical outcome of the reaction could be discerned.
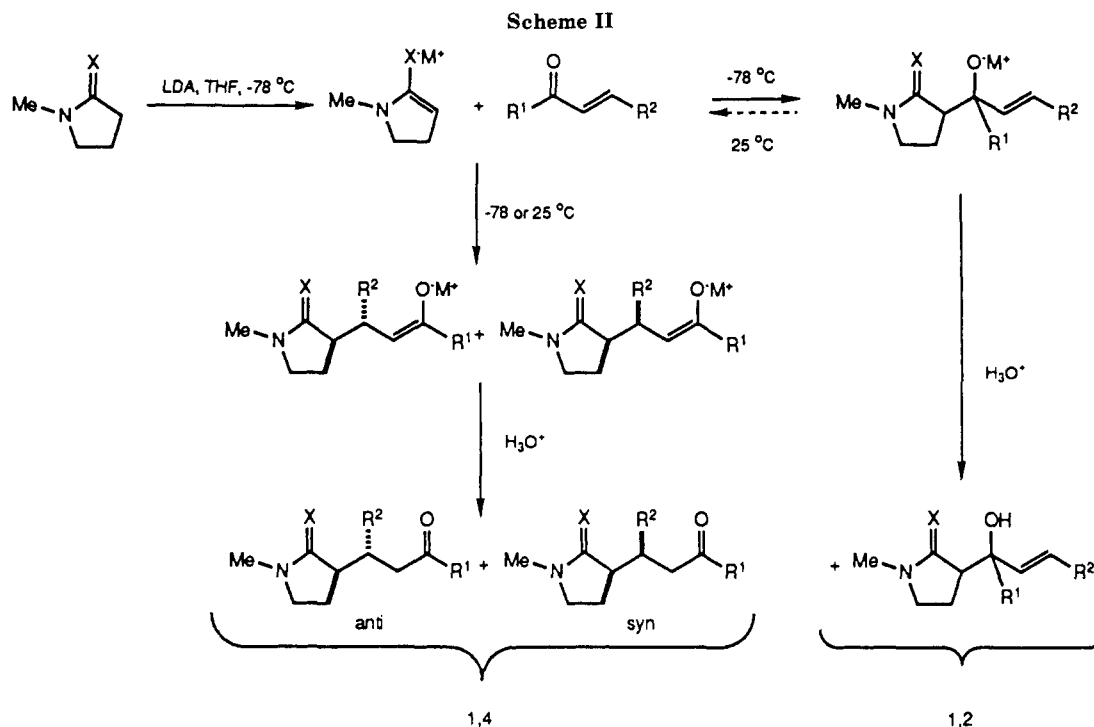
**Scheme II**



worked up. The products were found to be diastereomeric keto amides and/or hydroxy amides (Schemes I and II; for product compound numbers, see Tables IV and V). The results of these additions are summarized in Tables VI–IX.

## 1,2 vs 1,4 Addition

$\alpha,\beta$-Unsaturated ketones are ambident electrophiles; nucleophilic attack can occur at the carbonyl or $\beta$-enone carbons. Factors influencing the location of nucleophilic attack can be electronic[30] and steric in nature.[12,31] The regiochemistry of the low-temperature (–78 °C) addition of amide enolates to enones was explored with the enolates derived from amides **4** and **5** and $\alpha,\beta$-unsaturated ketone **18** (entries 1–3, Table III). With this enone, the smaller acetamide enolate gives predominately 1,2 addition, whereas the larger isobutyramide enolate gives mainly 1,4 addition. This result suggests that more bulky enolates have a greater propensity for 1,4 addition. It should be noted, however, that enone **18** is more hindered at the carbonyl group than at the $\beta$-enone carbon; this greater steric hindrance at the carbonyl should effect the larger enolate to a greater degree than the smaller one.

The enolate of lactam **3**, when added to similar $\alpha,\beta$-unsaturated ketones, exhibits a lower propensity for 1,4 addition than does the enolate of propanamide **7** (compare entries 3 and 13 in Table VII with entries 4 and 14 in Table VI). A similar tendency is also apparent with thioamide enethiolates. For example, thiolactam **10** gives a 95:5 (1,2/1,4) mixture of regioisomers with enone **16** (entry 1, Table IX) whereas the enethiolate of **12** forms a 74:26 mixture (1,2/1,4, entry 1, Table VIII).

As anticipated, the percentage of 1,2 addition is related to the substitution pattern of the enone. For example, if $R^2$ is methyl and $R^1$ is varied through the series methyl, ethyl, isopropyl, and *tert*-butyl, an increasing amount of 1,4 addition is observed with decreasing size of the $\beta$-enone substituent (compare entries 2, 4, and 14, Table VI; entries

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(30) For example, see: Deschamps, B.; Anh, N. T.; Seyden-Penne, J. *Tetrahedron Lett.* 1973, *14*, 527.

(31) For example, see: Mulzer, J.; Hartz, G.; Kuhl, U.; Bruntrup, G. *Tetrahedron Lett.* 1978, *19*, 2949.

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**Table V.  N-Methyl-2-pyrrolidinone-Derived Michael Addition Products (Scheme II)**

| $R^1$ | $R^2$ | X | 1,2 adducts | | 1,4 adducts | |
|---|---|---|---|---|---|---|
| | | | major | minor | anti | syn |
| Et | Me | O | 76a | 76b | | |
| *i*-Pr | Me | O | 77a | 77b | 78a | 78s |
| *i*-Pr | Me$^a$ | O | 79a | 79b | | |
| c-C$_6$H$_{11}$ | Me | O | 80a | 80b | 81a | 81s |
| Ph | Me | O | 82a | 82b | 83a | 83s |
| *p*-BrC$_6$H$_4$ | Me | O | 84a | 84b | 85a | 85s |
| *p*-MeOC$_6$H$_4$ | Me | O | 86a | 86b | 87a | 87s |
| *t*-Bu | Me | O | 88a | 88b | 89a | 89s |
| mes$^b$ | Me | O | | | 90a | 90s |
| tris$^c$ | Me | O | | | 91a | 91s |
| *t*-Bu | Et | O | 92a | 92b | 93a | 93s |
| *t*-Bu | *i*-Pr | O | 94a | 94b | 95a | 95s |
| *t*-Bu | Ph | O | 96a | 96b | 97a | 97s |
| *t*-Bu | *t*-Bu | O | 98a$^d$ | | | |
| Me | Me | S | 99a | 99b | 100a | 100s |
| *i*-Pr | Me | S | 101a | 101b | 102a | 102s |
| *t*-Bu | Me | S | | | 103a | 103s |
| mes$^b$ | Me | S | | | 104a | 104s |
| tris$^c$ | Me | S | | | 105a | 105s |
| *t*-Bu | *i*-Pr | S | | | 106a | 106s |
| *t*-Bu | Ph | S | | | 107a | 107s |

$^a$ In this case, the olefin has the $Z$ configuration. $^b$ 2,4,6-Trimethylphenyl. $^c$ 2,4,6-Triisopropylphenyl. $^d$ Only one isomer detected.

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1, 3, and 13, Table VII; entries 1 and 3, Table VIII; entries 1, 3, and 5, Table IX). Alternatively, if $R^1$ is *tert*-butyl and $R^2$ is varied through the series methyl, ethyl, isopropyl, and *tert*-butyl, an increasing amount of 1,2 addition is observed with increasing size of the $\beta$-enone substituent (compare entries 19, 20, and 23, Table VI; entries 13, 19, 21, and 25, Table VII).

Electronic effects are also important. For example, enolates derived from thioamides **10** and **12** are nearly identical with the corresponding enolates from oxoamides **3** and **7** on the basis of steric effects alone. Yet, the thioamide enethiolates consistently give less 1,2 addition than do the corresponding oxoamides (compare entry 23, Table VI, with entry 7, Table VIII; compare entries 13 and 21, Table VII, with entries 5 and 12, Table IX). The

**Table VI. Addition of the Lithium Enolates of Propionamides to $\alpha,\beta$-Unsaturated Ketones (X = O, M = Li, Scheme I)**

| entry | amide | | enones | | | temp, °C | time, h | yield, % | 1,2:1,4 | 1,2 major:minor | 1,4 syn:anti |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | R | R | $R^1$ | $R^2$ | solvent | | | | | | |
| 1 | Me | Me | t-Bu | Me | THF | −78 | 0.5 | 72 | 0.5:95.5 | | 55:45 |
| 2 | -(CH$_2$)$_4$- | | Et | Me | THF | −78 | 0.3 | 78 | >97:3 | 64:36 | |
| 3 | -(CH$_2$)$_4$- | | Et | Me | THF | 25 | 12.0 | 26 | 4:96 | | 43:57 |
| 4 | -(CH$_2$)$_4$- | | i-Pr | Me | THF | −78 | 0.8 | 84 | 29:71 | a | 40:60 |
| 5 | -(CH$_2$)$_4$- | | i-Pr | Me | THF | 25 | 12.0 | 85 | <3:97 | | 40:60 |
| 6 | -(CH$_2$)$_4$- | | c-C$_6$H$_{11}$ | Me | THF | −78 | 1.0 | 56 | 40:60 | a | 45:55 |
| 7 | -(CH$_2$)$_4$- | | c-C$_6$H$_{11}$ | Me | THF | 25 | 14.0 | 51 | <3:97 | | 45:55 |
| 8 | -(CH$_2$)$_4$- | | Ph | Me | THF | −78 | 1.0 | 92 | 12:88 | a | 87:13 |
| 9 | -(CH$_2$)$_4$- | | Ph | Me | THF | 25 | 10.0 | 86 | <3:97 | | 85:15 |
| 10 | -(CH$_2$)$_4$- | | p-BrC$_6$H$_4$ | Me | THF | −78 | 1.0 | 84 | 50:50 | a | 80:20 |
| 11 | -(CH$_2$)$_4$- | | p-BrC$_6$H$_4$ | Me | THF | 25 | 13.0 | 40 | <3:97 | | 80:20 |
| 12 | -(CH$_2$)$_4$- | | p-MeOC$_6$H$_4$ | Me | THF | −78 | 1.0 | 72 | 35:65 | a | 75:25 |
| 13 | -(CH$_2$)$_4$- | | p-MeOC$_6$H$_4$ | Me | THF | 25 | 19.0 | 58 | <3:97 | | 75:25 |
| 14 | -(CH$_2$)$_4$- | | t-Bu | Me | THF | −78 | 1.0 | 90 | <3:97 | | 45:55 |
| 15 | -(CH$_2$)$_4$- | | t-Bu | Me | THF/HMPA | −78 | 0.7 | 77 | 3:97 | | 45:55 |
| 16 | -(CH$_2$)$_4$- | | mes[b] | Me | THF | −78 | 4.0 | 86 | <3:97 | | ≤5:95 |
| 17 | -(CH$_2$)$_4$- | | tris[c] | Me | THF | −78 | 2.0 | 85 | <3:97 | | ≤9:91 |
| 18 | -(CH$_2$)$_4$- | | tris[c] | Me | THF/HMPA | −78 | 20.0 | 91 | <3:97 | | 80:20 |
| 19 | -(CH$_2$)$_4$- | | t-Bu | Et | THF | −78 | 0.3 | 95 | <3:97 | | 37:63 |
| 20 | -(CH$_2$)$_4$- | | t-Bu | i-Pr | THF | −78 | 0.3 | 46 | 7:93 | 71:29 | 33:67 |
| 21 | -(CH$_2$)$_4$- | | t-Bu | i-Pr | THF | 25 | 1.5 | 65 | <3:97 | | 27:73 |
| 22 | -(CH$_2$)$_4$- | | t-Bu | Ph | THF | 25[d] | 1.3 | 69 | <3:97 | | 9:91 |
| 23 | -(CH$_2$)$_4$- | | t-Bu | t-Bu | THF | −78 | 0.3 | 70 | 54:46 | 74:26 | <3:97 |
| 24 | -(CH$_2$)$_4$- | | t-Bu | t-Bu | THF | 25 | 1.5 | 86 | <3:97 | | <3:97 |
| 25 | -(CH$_2$)$_5$- | | t-Bu | Me | THF | −78 | 0.5 | 98 | <3:97 | | 15:85 |
| 26 | -(CH$_2$)$_6$- | | t-Bu | Me | THF | −78 | 0.5 | 87 | <3:97 | | 30:70 |

[a] Ratio of isomers not determined. [b] 2,4,6-Trimethylphenyl. [c] 2,4,6-Triisopropylphenyl. [d] Control experiments revealed that no 1,2 addition occurred at −78 °C.

**Table VII. Addition of Lithium Enolate of N-Methyl-2-pyrrolidinone (3) to $\alpha,\beta$-Unsaturated Ketones (X = O, M = Li, Scheme II)**

| entry | enones | | solvent | temp, °C | time, h | yield, % | 1,2:1,4 | 1,2 major:minor | 1,4 syn:anti |
|---|---|---|---|---|---|---|---|---|---|
| | $R^1$ | $R^2$ | | | | | | | |
| 1 | Et | Me | THF | −78 | 1.0 | 50 | >97:3 | a | |
| 2 | Et | Me | THF | 25 | 10.0 | 60 | >97:3 | a | |
| 3 | i-Pr | Me | THF | −78 | 1.0 | 64 | 80:20 | a | 10:90 |
| 4 | i-Pr | Me | THF | 25 | 10.0 | 76 | 50:50 | a | 10:90 |
| 5 | c-C$_6$H$_{11}$ | Me | THF | −78 | 1.0 | 93 | 68:32 | a | 10:90 |
| 6 | c-C$_6$H$_{11}$ | Me | THF | 25 | 13.0 | 56 | 20:80 | a | 10:90 |
| 7 | Ph | Me | THF | −78 | 1.0 | 67 | 63:37 | a | 5:95 |
| 8 | Ph | Me | THF | 25 | 10.0 | 96 | <3:97 | | 5:95 |
| 9 | p-BrC$_6$H$_4$ | Me | THF | −78 | 0.5 | 77 | 70:30 | a | 5:95 |
| 10 | p-BrC$_6$H$_4$ | Me | THF | 25 | 14.0 | 90 | 58:42 | a | 5:95 |
| 11 | p-MeOC$_6$H$_4$ | Me | THF | −78 | 1.0 | 49 | 72:28 | a | 10:90 |
| 12 | p-MeOC$_6$H$_4$ | Me | THF | 25 | 12.0 | 60 | <3:97 | | 10:90 |
| 13 | t-Bu | Me | THF | −78 | 1.0 | 72 | 14:86 | a | 10:90 |
| 14 | t-Bu | Me | THF | 25 | 10.0 | 99 | <3:97 | | 10:90 |
| 15 | t-Bu | Me | THF/HMPA | −78 | | 46 | 15:85 | a | 18:82 |
| 16 | mes[b] | Me | THF | −78 | 4.0 | 95 | <3:97 | | 30:70 |
| 17 | tris[c] | Me | THF | −78 | 4.0 | 83 | <3:97 | | 15:85 |
| 18 | tris[c] | Me | THF/HMPA | −78 | 4.0 | 92 | <3:97 | | 40:60 |
| 19 | t-Bu | Et | THF | −78 | 0.3 | 58 | 31:69 | 94:6 | 8:92 |
| 20 | t-Bu | Et | THF | 25 | 1.5 | 87 | <3:97 | | 7:93 |
| 21 | t-Bu | i-Pr | THF | −78 | 0.3 | 73 | 57:43 | 88:12 | 7:93 |
| 22 | t-Bu | i-Pr | THF | 25 | 1.5 | 62 | <3:97 | | 20:80 |
| 23 | t-Bu | Ph | THF | −78 | 0.3 | 55 | 54:45 | >97:3 | 32:68 |
| 24 | t-Bu | Ph | THF | 25 | 1.5 | 68 | <3:97 | | 40:60 |
| 25 | t-Bu | t-Bu | THF | 0[d] | 14.0 | 62 | >97:3 | >97:3 | |
| 26 | i-Pr | Me[e] | THF | −78 | 1.0 | 68 | >97:3 | 71:29 | |
| 27 | i-Pr | Me[e] | THF | 25 | 12.0 | 0 | | | |

[a] Ratio of diastereomers not determined. [b] 2,4,6-Trimethylphenyl. [c] 2,4,6-Triisopropylphenyl. [d] No 1,2 to 1,4 equilibration was detected at 25 °C. [e] The Z-configured enone was used.

difference in regiochemistry can be attributed to differences in the "hardness"[32] of the nucleophiles. On the basis of the difference between the hardness of oxygen versus sulfur alone, thioamide enolates are softer nucleophiles (i.e., a lower energy HOMO) than are the enolates of oxoamides.

Hence, they have a higher propensity for conjugate addition.[30,33]

With the cis enone **33**, addition of the lithium enolate of lactam **3** at −78 °C gives only 1,2 addition products in

(32) (a) Pearson, R. G. *J. Chem. Ed.* **1968**, *45*, 581, 643. (b) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533.

(33) For example, see: (a) Cossenti, M.; Deschamps, B.; Anh, N. T.; Seyden-Penne, J. *Tetrahedron* **1977**, *33*, 409 and references therein. (b) Deschamps, B.; Seyden-Penne, J. *Tetrahedron* **1977**, *33*, 413 and references therein.

**Table VIII. Addition of Propionyl Thioamide (12) Enethiolates to $\alpha,\beta$-Unsaturated Ketones (X = S, Scheme I)**

| entry | enethiolate M⁺ | enones R¹ | R² | solvent | temp, °C | time, h | yield, % | 1,2:1,4 | 1,2 major:minor | 1,4 syn:anti |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Li | Me | Me | THF | −78 | 2.0 | 63[a] | 74:26 | 60:40 | 17:83 |
| 2 | Li | Me | Me | THF | 25 | 12.0 | 35 | <3:97 | | 25:75 |
| 3 | Li | t-Bu | Me | THF | −78 | 1.5 | 77 | <3:97 | | 18:82 |
| 4 | Na | t-Bu | Me | THF | −78 | 4.0 | 37 | <3:97 | | <5:95 |
| 5 | K | t-Bu | Me | THF | −78 | 4.0 | 29 | <3:97 | | <5:95 |
| 6 | Li | t-Bu | Ph | THF | −78 | 3.5 | 94 | <3:97 | | <5:95 |
| 7 | Li | t-Bu | t-Bu | THF | 25 | 2.5 | 61 | <3:97 | | >3:97 |
| 8 | Li | mes[b] | Me | THF | −78 | 2.0 | 87 | <3:97 | | <5:95 |
| 9 | Li | tris[c] | Me | THF | −78 | 2.0 | 62 | <3:97 | | 5:95 |

[a] Two equivalents of the enone were used. [b] 2,4,6-Trimethylphenyl. [c] 2,4,6-Triisopropylphenyl.

**Table IX. Addition of $N$-Methyl-2-thiopyrrolidinone (10) Enethiolates to $\alpha,\beta$-Unsaturated Ketones (X = S, Scheme II)**

| entry | enethiolate M⁺ | $\alpha$-enones R¹ | R² | solvent | temp, °C | time, h | yield, % | 1,2/1,4 | 1,2 major/minor | 1,4 syn/anti |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Li | Me | Me | THF | −78 | 2.0 | 84 | 95:5 | 55:45 | |
| 2 | Li | Me | Me | THF | 25 | 14.0 | 61 | <3:97 | | 55:45 |
| 3 | Li | i-Pr | Me | THF | −78 | 3.0 | 44 | 85:15 | 83:17 | 55:45 |
| 4 | Li | i-Pr | Me | THF | 0 | 1.0 | 97 | <3:97 | | 54:46 |
| 5 | Li | t-Bu | Me | THF | −78 | 1.0 | 84 | <3:97 | | 60:40 |
| 6 | Li | t-Bu | Me | THF/HMPA | −78 | 1.5 | 98 | <3:97 | | ≥95:5 |
| 7 | Na | t-Bu | Me | THF | −78 | 2.5 | 74 | <3:97 | | ≥95:5 |
| 8 | K | t-Bu | Me | THF | −78 | 2.5 | 81 | <3:97 | | ≥95:5 |
| 9 | Li | mes[a] | Me | THF | −78 | 3.5 | 67 | <3:97 | | 93:7 |
| 10 | Li | tris[b] | Me | THF | −78 | 3.0 | 91 | <3:97 | | ≥95:5 |
| 11 | Li | tris[b] | Me | THF/HMPA | −78 | 4.0 | 92 | <3:97 | | 35:65 |
| 12 | Li | t-Bu | i-Pr | THF | −78 | 1.0 | 67 | <3:97 | | 52:48 |
| 13 | Li | t-Bu | Ph | THF | −78 | 1.0 | 68 | <3:97 | | 95:5 |

[a] 2,4,6-Trimethylphenyl. [b] 2,4,6-Triisopropylphenyl.

68% yield. This is presumably a result of the less "conjugated" nature of 33.

In summary, several trends can be observed for the regiochemistry of the addition of amide enolates to enones:

(1) Increase in steric bulk in the enolate leads to more conjugate addition.

(2) Lactam enolates show a greater propensity for 1,2 addition than do acyclic *Z* enolates. It is not clear at this point if this is a property of *E* enolates in general.

(3) Increasing the size of R¹ (the carbonyl ligand) *decreases* the preference for 1,2 addition.

(4) Enlarging R² (the $\beta$-enone substituent) *increases* the propensity for 1,2 addition.

(5) Softer enolates (thioamides) have a greater propensity for 1,4 addition than do harder enolates (oxoamides).

Little diastereoselectivity is usually observed in the formation of the 1,2 adducts. Intriguingly, in some instances (entries 19, 21, 23, and 25, Table VII; entry 3, Table IX) reasonable levels of stereoselectivity are observed. Although no attempt to elucidate the stereochemistry of the products was made, several trends are worthy of note. First, selectivity is very substrate dependent. The nature of the enolate as well as the substitution of the enone (both R¹ and R²) seem to be important. Second, contrary to the trends observed with lithium enolates in the aldol reaction,[34] *E* enolates are frequently more selective than are *Z* enolates. In addition, enolates that exhibit little selectivity with aldehydes sometimes are reasonably selective with enones.[35] The selectivity in these additions is kinetic in origin (vide infra).

**Table X. Addition of Lactam 3 to Enone 30 at Various Times and Temperatures**

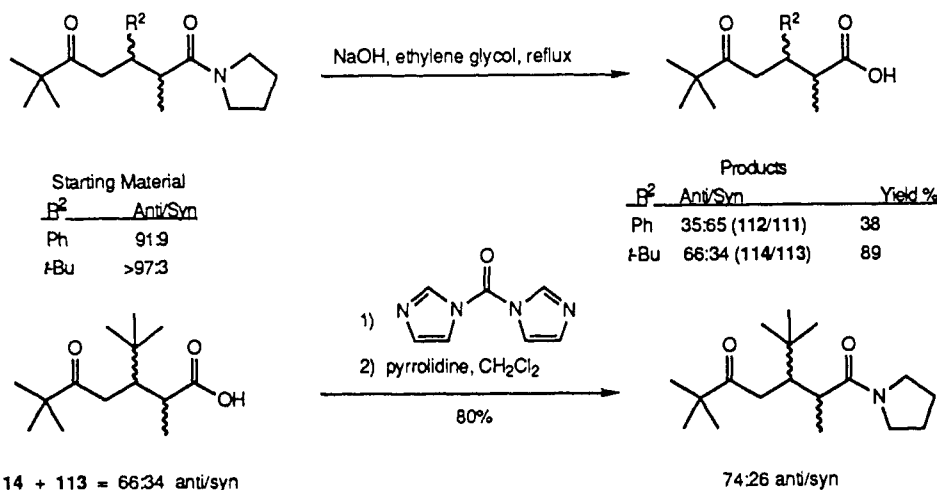| entry | temp, °C | total time | 1,2[a]/1,4 | anti/syn |
|---|---|---|---|---|
| 1 | −78 | 1 min | 45:55 | 68:32 |
| 2 | −78 | 8 min | 45:55 | 68:32 |
| 3 | −78 | 16 min | 45:55 | 68:32 |
| 4 | −60 | 56 min | 45:55 | 68:32 |
| 5 | −10 | 1 h 40 min | 37:63 | 67:33 |
| 6 | 5 | 2 h 10 min | 13:87 | 62:38 |
| 7 | 5 | 2 h 25 min | 7:93 | 60:40 |
| 8 | 20 | 3 h | 0:100 | 60:40 |
| 9 | 20 | 4 h 20 min | 0:100 | 63:37 |
| 10 | 25 | 17 h | 0:100 | 74:26 |
| 11 | 25 | 4 days | 0:100 | 80:20 |

[a] Only one 1,2 diastereomer was detected.

If the amide enolate Michael additions were limited to the kinetic regioselectivity observed, the scope of the reaction would be significantly limited. Fortunately, the kinetic 1,2 addition is reversible on warming,[36] giving the enolate further opportunities for conjugate addition (Schemes I and II). For example, the enolate of 4 adds kinetically (−78 °C) to enone 18 to give a 5:95 (1,4:1,2) mixture of regioisomers (entry 1, Table III). After being warmed at 65 °C for 16 h, only 1,4 addition products are detected (entry 2, Table III). Hence, in all but the most resistant cases, the initial 1,2 adducts can be transformed into 1,4 adducts by warming.

The course of the addition of lithium enolate of lactam 3 to enone 30 was studied at various times and temperatures by removing aliquots from the reaction flask by syringe. After quench and workup, the crude product mixtures were analyzed by GLC. The results of this study are summarized in Table X. From these data, a number of observations can be made. First, at low temperatures,

(34) (a) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1983; Vol, 3, Chapter 2. (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Topics in Stereochemistry*; Allinger, N. L., Eliel, E. L., Wilen, S. H., Eds.; Wiley: New York, 1982; Vol. 13, Chapter 1.

(35) We have made similar observations of occasionally highly diastereoselective 1,2 additions in our parallel study of the ester enolate Michael addition (see following paper in this issue).

(36) For an example of equilibration of ester 1,2 adducts to Michael products, see: Schultz, A. G.; Yee, Y. K. *J. Org. Chem.* 1976, *41*, 4044.
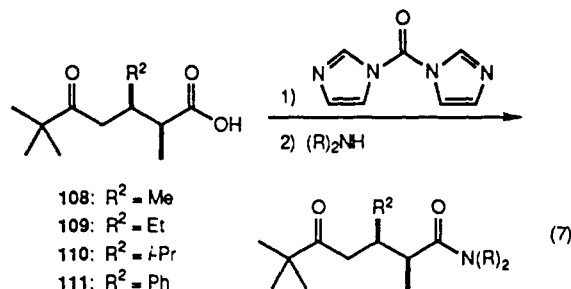
**Scheme III**



| Starting Material | | Products | | |
|---|---|---|---|---|
| $R^2$ | Anti/Syn | $R^2$ | Anti/Syn | Yield % |
| Ph | 91:9 | Ph | 35:65 (112/111) | 38 |
| t-Bu | >97:3 | t-Bu | 66:34 (114/113) | 89 |

114 + 113 = 66:34 anti/syn

74:26 anti/syn

the 1,2 adducts are stable under the reaction conditions (entries 1–4, Table X). Warming the reaction mixture to –10 °C results in slow transformation of the 1,2 addition products into 1,4 addition products (entry 5). Continued reaction at higher temperatures results in complete equilibration of the 1,2 adducts into 1,4 products (entries 6–8). Notice that the stereoselectivity of the Michael addition drops slightly at higher temperatures (entries 5–8). This is presumably a result of lower kinetic selectivity of the Michael addition of the enolate that is reformed from the aldolate. Because this addition occurs at somewhat higher temperatures, the stereoselectivity drops slightly. After prolonged periods at room temperature, slight equilibration of the 1,4 addition products appears to occur, and a slightly higher proportion of the anti product is formed (entries 9–11). This result is clearly consistent with the stereoselectivity of the Michael addition being under kinetic control at low temperatures.

## Stereostructural Assignments

The conjugate addition products in entries 1, 14, 15, 19–22, 25, and 26 (Table VI) have been correlated with keto acids 108–111, whose structures were assigned in parallel studies (eq 7).[37–39] Initially, the hydrolysis of keto



108: $R^2$ = Me
109: $R^2$ = Et
110: $R^2$ = i-Pr
111: $R^2$ = Ph

amides 64a and 66a (Scheme III) was attempted. Vigorous saponification of 64a and 66a using NaOH in refluxing ethylene glycol results in the formation of the desired keto acids but with loss of stereochemical integrity (Scheme III).

**Table XI. Conversion of Keto Acids 108–111 to Keto Amides 44s, 58s, 61s, 63s, 64s, 67s, and 68s (eq 7)**

| keto acid | | amine | | keto amide | |
|---|---|---|---|---|---|
| compd | $R^2$ | R | R | compd | yield, % |
| 108 | Me | Me | Me | 44s | 65 |
| 108 | Me | -$(CH_2)_4$- | | 58s | 64 |
| 109 | Et | -$(CH_2)_4$- | | 61s | 76 |
| 110 | i-Pr | -$(CH_2)_4$- | | 63s | 59 |
| 111 | Ph | -$(CH_2)_4$- | | 64s | 100 |
| 108 | Me | -$(CH_2)_5$- | | 67s | 86 |
| 108 | Me | -$(CH_2)_6$- | | 68a | 28 |

**Scheme IV**
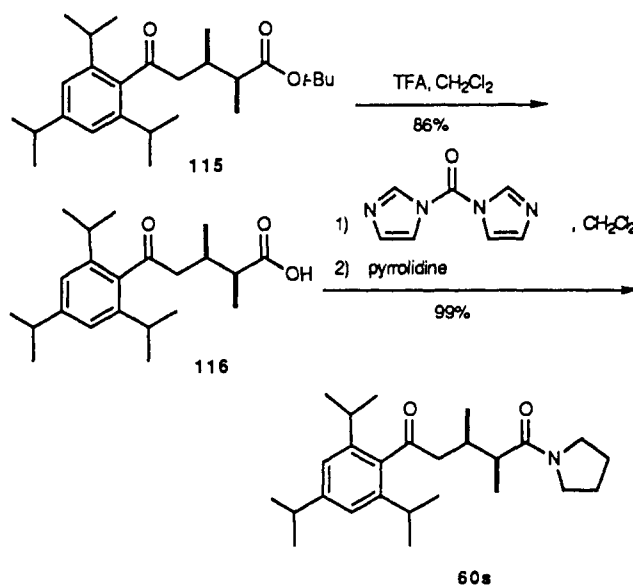


For this reason, an alternative approach was used wherein the keto acids are converted into keto amides. For example, a 66:34 mixture of keto acids 114 and 113 on treatment with 1,1'-carbonyldiimidazole[40] followed by pyrrolidine provides a 74:26 (anti/syn) mixture of diastereomers.[41,42]

(37) Heathcock, C. H.; Norman, M. H.; Uehling, D. E. *J. Am. Chem. Soc.* **1985**, *107*, 2797.

(38) See following paper in this issue.

(39) The stereostructures of keto acids 108 and 111 were assigned by single-crystal X-ray analysis. The stereostructure of 109 was assigned by X-ray analysis of the oxime. Keto acid 110 was assigned by conversion into a compound whose stereostructure could be assigned with confidence by ¹H NMR spectroscopy.

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

(41) Use of oxalyl chloride in place of 1,1'-carbonyldiimidazole resulted in the formation of enol lactones. Uehling, D. E.; Oare, D. A.; Heathcock, C. H., unpublished results.

(42) The enhancement of the diastereomeric excess presumably occurs as a result of preferential reaction of the anti diastereomer of the mixture. Control experiments revealed that similar treatment of isomeric keto acids yields isomeric keto amides, indicating that little epimerization occurs in this process.
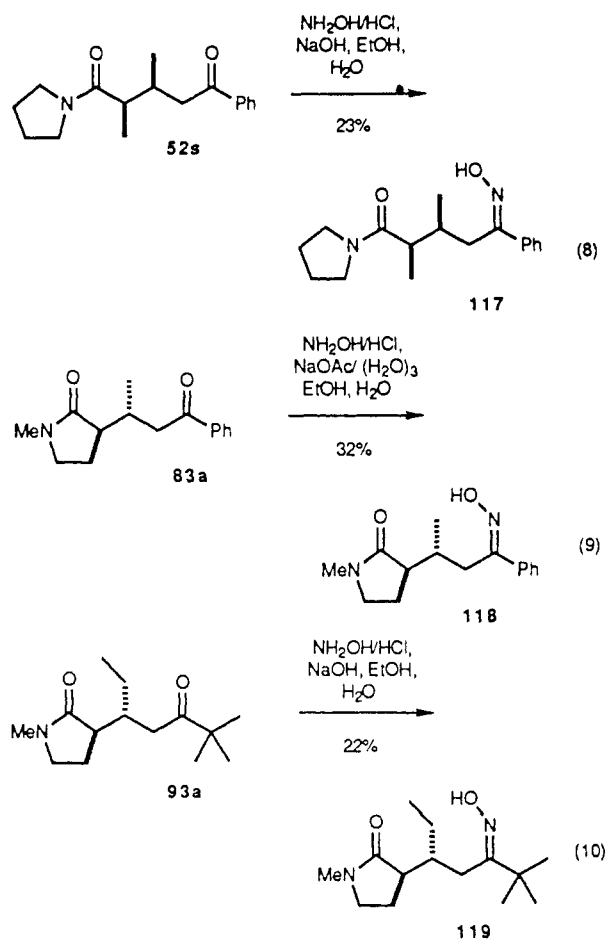
Analogous treatment of keto acids 108–111 with 1,1'-carbonyldiimidazole followed by addition of an excess of the corresponding amine produces keto amides 44s, 58s, 61s, 63s, 64s, 67s, and 68s (eq 7, Table XI). In these cases, no loss of stereochemical integrity is observed.

A similar strategy was employed for the structural assignment of the products in entries 17 and 18 (Table VI). Thus, treatment of keto ester 115[43] with trifluoroacetic acid produces keto acid 116 (Scheme IV). Keto acid 116 forms 60s through its imidazolide.

In entries 3–7 (Table VI) only low stereoselectivity is observed. The stereostructures of these products tentatively follow by analogy to entry 14 (Table VI) and on the basis of similar $^{13}$C NMR chemical shift patterns.

Single-crystal X-ray analysis of oxime amides 117–119 provided the stereostructure assignments for the addition products in entries 8 and 9 (Table VI) and entries 7, 8, 19, and 20 (Table VII).[44] The crystalline oxime amides 117–119 are available directly from keto amides 52s, 83a, and 93a as shown in eq 8–10. With keto amide 66a (en-



tries 23 and 24, Table VI), similar transformations yield crystalline oxime acid 120 (eq 11). X-ray analysis provides the structural assignment. Conversion of oxime acid 120 to keto acid 114 (sodium bisulfite in aqueous ethanol) assures that there is no loss of stereochemical integrity in the formation of 120.

The stereostructures of the 1,4 addition products in entries 10–13 (Table VI) follow by comparison with 52s (entries 8 and 9) on the basis of similar $^{1}$H NMR chemical



shift patterns. For the major 1,4 addition products 59a (entry 16, Table VI), 91a (entries 17 and 18, Table VII), 97a (entries 23 and 24, Table VII), and 104s (entry 9, Table IX), the stereostructures were confirmed by single-crystal X-ray analysis.

For the major conjugate addition product in entries 3 and 4 (78a, Table VII), chemical correlation with 83a furnished the structural assignment. Thus, Michael addition of the lithium enolates from lactam 3 with enones 22 and 19 followed by addition of trimethylsilyl chloride supplies enol silanes 121 and 122, respectively (Scheme V). In these cases, warming the reaction mixtures to reflux temperature prior to addition of the trapping reagent facilitates equilibration of the 1,2 adduct to the more stable 1,4 adduct. The products (for 121 and 122) are produced in essentially identical isomer ratios as are observed for the lower temperature condensations (entries 3, 4, 7, and 8, Table VII), suggesting kinetic control in these additions. Further support for kinetic control is found by conversion of keto amide 83a directly to 121 (1. 1 equiv of LDA, THF, –78 °C; 2. TMSCl, –78 °C to 20 °C). The enol silane formed in this manner is identical with that obtained from trapping the Michael adduct. Ozonolysis of either 121 or 122 followed by reductive workup yields the same hydroxy amide (123). Thus, 121 and 122 have the same relative configuration. As the structure of 83a has been ascertained (vide supra), this correlation establishes the relative stereochemistry of 78a as anti.
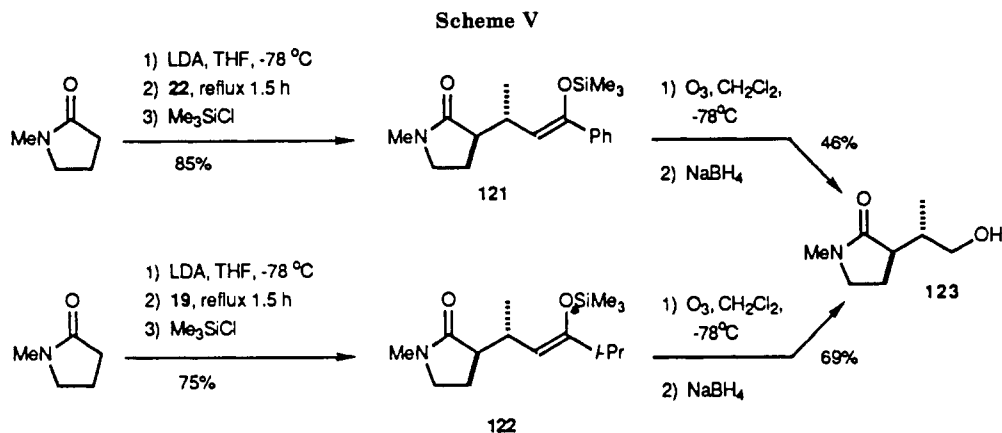
The configuration of the aliphatic conjugate addition products in entries 5, 6, and 13–15 (Table VII) is based on $^{1}$H and $^{13}$C NMR correlation with 78a. Similarly, the aromatic conjugate addition products in entries 9–12 (Table VII) are correlated with 83a.

S-Alkylation of the syn keto thioamide 104s (whose stereostructure was established by X-ray analysis (vide supra)) with methyl iodide, followed by basic hydrolysis (eq 12), yields the syn keto oxoamide 90s (entry 8, Table
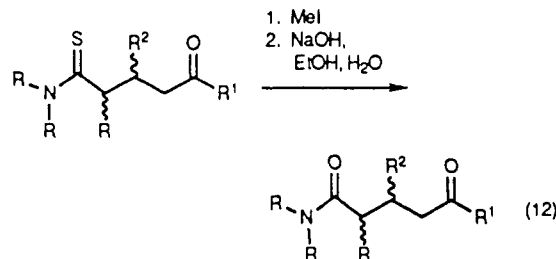


XII). Comparison of 90s with the major product found in entry 16, Table VII, shows that the addition of the lithium enolate of oxolactam 3 to enone 25 gives products with the *opposite* relative configuration.

Similarly, the stereostructures of the thioamide conjugate addition products in entries 3–9, Table VIII, and entries 3–8 and 10–13, Table IX, follow from chemical

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(43) Keto ester 115 was available from a parallel study. The stereo-structure of 115 was assigned by correlation with 59a. Details of these transformations are reported in the following papers in this issue.

(44) Details of the X-ray structure determination are reported in the supplementary material.

## Scheme V





**Table XII. Conversion of Keto Thioamides to Keto Oxoamides (eq 12)**

| entry | keto thioamide | | keto oxamide | | |
|---|---|---|---|---|---|
| | compds | anti:syn | compds | anti:syn | yield, % |
| 1 | 71a/71s | 84:16 | 58a/58s | 84:16 | 78 |
| 2 | 72a | ≥95:5 | 64a | ≥95:5 | 80 |
| 3 | 73a | ≥97:3 | 66a | ≥97:3 | 36 |
| 4 | 74a | ≥95:5 | 59a | 80:20 | 97 |
| 5 | 75a | ≥95:5 | 60a | ≥95:5 | 85[a] |
| 6 | 102a/102s | 60:40 | 78a/78s | 91:9 | 97 |
| 7 | 103a/103s | 93:7 | 89a/89s | 91:9 | 99 |
| 8 | 104s | ≤5:95 | 90s | ≤5:95 | 90 |
| 9 | 105s | ≤5:95 | 91a/91s | 8:92 | 69 |
| 10 | 106a | ≥97:3 | 95s | ≥97:3 | 87 |
| 11 | 107s | 5:95 | 97s | 5:95 | 81 |

[a] $^1$H NMR, based on consumed starting material.

correlation with the corresponding oxoamides. The results of these interconversions are summarized in eq 12 and Table XII. In most cases, the ratio of isomers of the products obtained is identical with the ratio used, strongly suggesting that the stereochemical integrity of the keto thioamide is maintained in the process. In three instances, however, a small amount of epimerization apparently occurs (entries 4, 7, and 9, Table XII). The transformation of keto oxoamide **91a** into keto thioamide **105a** with Lawesson's reagent[15] provides further assurance of the configuration of **105a** (eq 13).
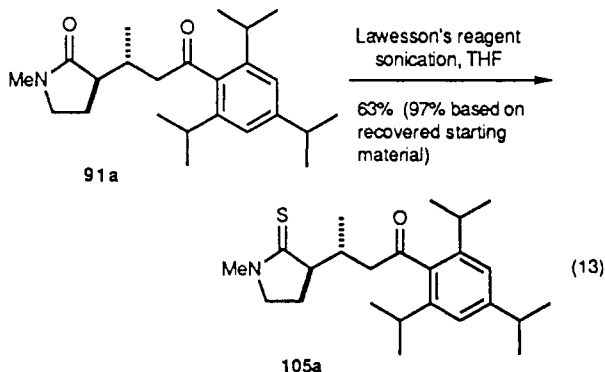


The stereostructures for the products in entries 21 and 22 (Table VII) and entries 1 and 2 (Tables VIII and IX) have not been explicitly proven. The major conjugate addition product in entries 21 and 22 (Table VII) is comfortably assigned the anti configuration on the basis of comparison with closely analogous substrates (see Table VII). For entries 1 and 2 in Table IX essentially no stereoselection is observed and, hence, the lack of a structural assignment does not impede analysis of the stereochemical outcome of the reaction. For entries 1 and 2 in Table VIII, the major conjugate addition product is assigned the anti

configuration on the basis of analogy with the other examples in Table IX. In particular, comparison of the result in entry 3 with the results in entry 1 suggest that these substrates exhibit similar stereochemical behavior.

## Discussion

Several observations can be made from an examination of the data in Tables VI–IX. For the enolate of propanamide 7, a higher percentage of the anti diastereomer is formed as $R^2$ is varied through the series methyl, ethyl, isopropyl, phenyl, and tert-butyl, while $R^1$ is maintained as tert-butyl (entries 14 and 19–24, Table VI).

No effect on the stereochemical outcome of the reaction is apparent when $R^2$ is methyl and $R^1$ is varied through the series ethyl, isopropyl, cyclohexyl, and tert-butyl (entries 2–7 and 14, Table VI). However, when $R^1$ is increased in size to the sterically demanding 2,4,6-trimethylphenyl and 2,4,6-triisopropylphenyl groups an increase in the anti selectivity of the reaction is noted (entries 16 and 17). If $R^1$ is the conjugated aromatic phenyl, p-bromophenyl, or p-methoxyphenyl and $R^2$ is methyl, modest syn selectivity is observed (entries 8–13, Table VI). The nature of the para substituent has little effect on the stereochemical outcome.

Similar trends are observed for the lithium enethiolate of thioamide 12 as were noted for the corresponding oxoamide 7 (Table VIII). The thioamide, however, gives consistently higher levels of the anti diastereomer. For example, enones 21 and 30 give, with oxoamide 7, 55% and 91% of the anti diastereomer, respectively (entries 14 and 22, Table VI). With the corresponding thioamide 12 and enones 21 and 30, 82% and ≥95% of the anti diastereomer are produced, respectively (entries 3 and 6, Table VIII).

As the amine portion of the lithium enolate of the propanamides is varied through the series dimethylamine 6, pyrrolidine 7, hexamethylenimine 9, and piperidine 8, addition to enone 21 results in the formation of greater proportions of the anti diastereomer (entries 1, 14, 25, and 26, Table VI). The extent of anti selectivity roughly varies with the steric demand of the amine.[45] A similar observation concerning the dependence of the stereochemical outcome on the size of the amine substituent has been noted by Yamaguchi and co-workers for the addition of lithio propanamides to crotonates.[9]

The enolate of lactam 3 generally provides the anti diastereomer with good selectivity (Table VII). A notable

(45) Since seven-membered rings are more conformationally flexible than six-membered rings, it is reasonable that piperidine amide enolate 8 would be more sterically demanding than the hexamethylenimine amide enolate 9. Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. In *Conformational Analysis*; American Chemical Society: Washington, D.C., 1981.

## Scheme VI
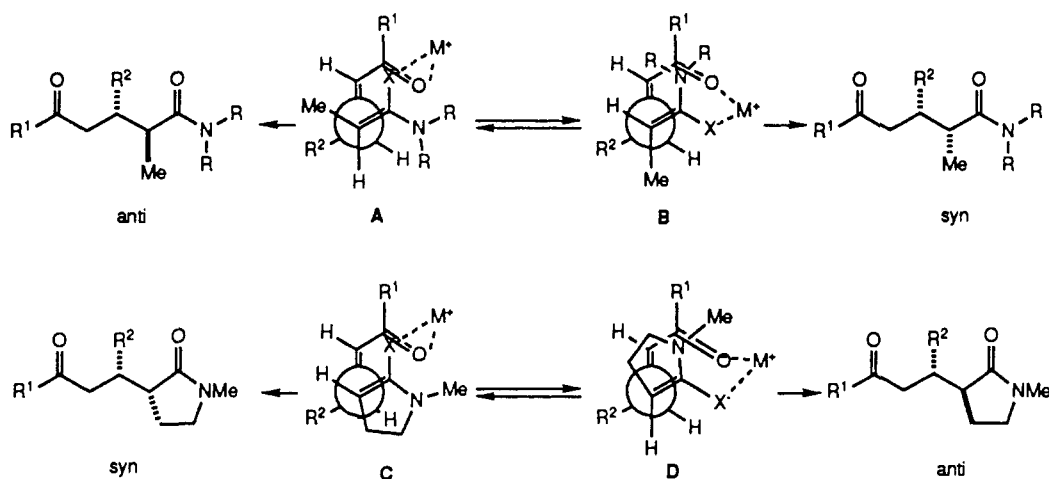


exception occurs when $R^1$ is *tert*-butyl and $R^2$ is phenyl; in this case, 60–68% of the anti diastereomer is formed (entries 23 and 24). A slightly higher proportion of the syn diastereomer is formed with the extremely bulky 2,4,6-trimethylphenyl (mes) and 2,4,6-triisopropylphenyl (tris) groups at $R^1$ (entries 16 and 17).

The lithium enolate of thiolactam 10 in THF, on the other hand, shows virtually no selectivity when $R^1$ and $R^2$ are alkyl (entries 2–5 and 12, Table IX). When $R^1$ is *tert*-butyl and $R^2$ is phenyl, the enethiolate of 10 provides the syn diastereomer in high selectivity (95:5 syn/anti, entry 13). This is consistent with thiolactam 10 showing a greater predilection for syn selectivity than the corresponding oxolactam 3. When $R^1$ is the exceedingly bulky mes or tris group, high syn selectivity is observed ($R^2$ = methyl, entries 9 and 10).

Control experiments show that no difference in the regio- or stereochemical outcome of the reaction occurs on varying the solvent from THF to THF/hexanes.[46] The addition of HMPA to a THF solution of the oxoamide enolates prior to the addition of alkyl enones usually has little effect on the stereo- or regiochemical outcome of the reaction (compare entries 14 and 15, Table VI; 13 and 15, Table VII). A marked change occurs when adding the lithiated oxoamide to enone 26 in the presence of HMPA (compare entries 17 and 18, Table VI; 17 and 18, Table VII). The behavior of oxoamides and thioamides in the presence of HMPA is quite different. With the lithio thiolactam 10, addition of HMPA has a strong effect on the stereochemical outcome of the reaction. Addition of lithiated 10 to 21 or 26 in the presence of HMPA gives more of the anti diastereomers (compare entries 5 with 6 and 10 with 11, Table IX).

The counterion also appears to play an important role in determining the stereochemical outcome. With thiolactam 10, the use of sodium and potassium enethiolates with enone 21 results in the formation of syn addition products with excellent selectivity (entries 7 and 8, Table IX). These results sharply contrast the results with the lithium enethiolates of 10 where essentially no selectivity is observed. An improvement in the stereoselectivity is also seen when the sodium and potassium enethiolates of 12 (entries 4 and 5, Table VIII) are used. In these cases, enhanced anti selectivity relative to the lithium enethiolate is observed.[47]

Notice that by varying the counterion (Li, Na, or K) and the anion stabilizing atom (O or S) of the enolate, high proportions of either the syn or anti diastereomer can be obtained from enolates having the "N-methyl-2-pyrrolidone" framework and enone 21. With propanamides, excellent anti selectivity can be achieved by using thioamide 12 and the potassium or sodium counterions.

In summary, several stereochemical trends can be noted.

(1) The substituent at the $\beta$-position of the enone has little influence on the stereochemical outcome with lactam enolates (from 3 and 10). With propionamide enolates (from 7 and 12), enhanced anti selectivity occurs on increasing the size of $R^2$.

(2) Varying an *alkyl* substituent at $R^1$ has no effect on the stereochemical outcome. With conjugated aromatic substituents, the enolate of 7 gives mostly the syn diastereomers. The very bulky mes and tris substituents enhance syn selectivity with lactam enolates of 3 and 10; anti selectivity is enhanced with propionamides 7 and 12.

(3) Thiolactams give higher proportions of the syn diastereomer than do oxolactams. Propiothioamides yield more of the anti diastereomer than do propionamides.

(4) Propionamides with sterically more demanding amide substituents furnish higher proportions of the anti diastereomer.

(5) HMPA can strongly influence the stereochemical result. The effect of HMPA is most marked in "slower" reactions.

(6) With thiolactams, the use of sodium or potassium enethiolates promotes syn selectivity. With thiopropionamides, sodium and potassium counterions favor the anti diastereomer.
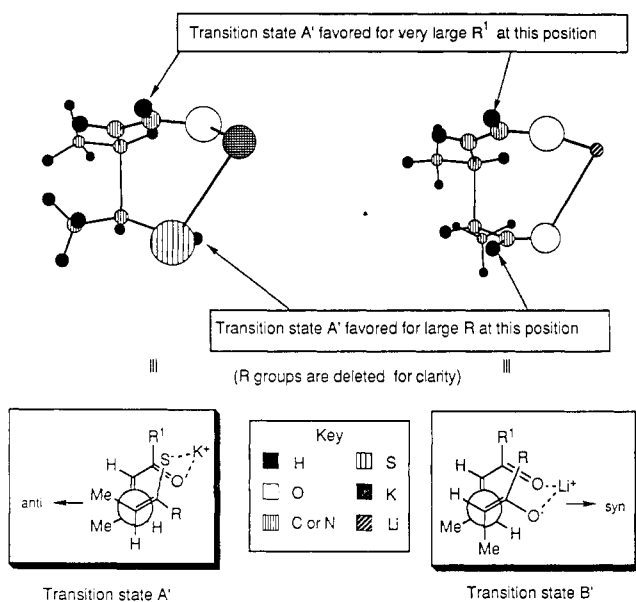
### Model Transition States

The stereoselectivity can be rationalized by consideration of chelated transition states A–D (Scheme VI).[48,49]

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(46) The hexanes from the *n*-butyllithium were removed under reduced pressure either before or after the generation of LDA.

(47) The sodium and potassium enethiolates of 12 give addition products in lower yields. (No attempt has been made to fully optimize the yields in this or any other case.) The reduced yields in this case are probably a result of the diminished solubility of the sodium and potassium enethiolates of 12 relative to the lithium enethiolate. Interestingly, the solubility behavior of enethiolates of 10 is markedly different than that observed with 12. For example, the lithium enethiolate of 10 is sparingly soluble under the reaction conditions while the potassium and sodium enethiolates of 10 are readily soluble. On the other hand, with the enethiolates of 12, the sodium and potassium enethiolates are sparingly soluble while the lithium enethiolate is completely soluble under the reaction conditions.

**Scheme VII**



Transition state A' favored for very large R¹ at this position

Transition state A' favored for large R at this position

(R groups are deleted for clarity)

Transition state A'

Transition state B'
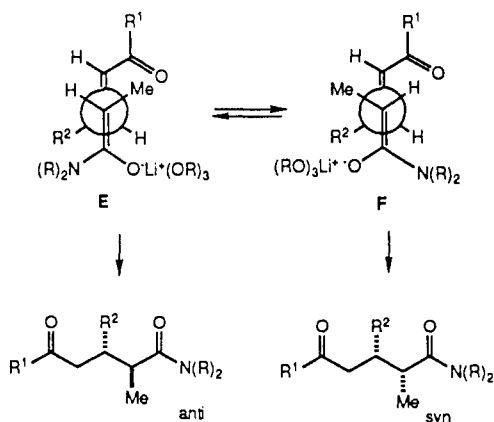
Key:
■ H  ▥ S
□ O  ▦ K
▤ C or N  ▨ Li

Transition states B and D are intrinsically favored for small R and $R^1$, whereas A and C are favored when these substituents are large.[50] Transition state A more easily accommodates larger R groups than does transition state B. Similar adverse interactions occur with a dramatic increase of the bulk of $R^1$, thus favoring A over B. Lactam 3, because it is cyclic and planar, exhibits both a small steric profile in D and more unfavorable interactions in C. Hence, model transition state D is generally favored over transition state C.

A more realistic model should have the following features:

(1) The enolate should approach the enone at an angle similar to the Bürgi–Dunitz trajectory.[51]

(48) Initially we suggested that these results could be rationalized by comparing open-extended transition states E and F (see below). By evoking the enolate aggregate as the stereocontrol element, transition state E is favored over F. While this model correctly predicted all of the stereochemical data that was available at the time, further data has cast doubt on its validity as a predictive model. In particular, increases in the bulk of the amine portion of the amide, as noted by Yamaguchi and ourselves (vide supra), result in production of more of the anti diastereomer. This is contrary to the prediction of this model (transition state F should be favored for larger R's).



(49) The choice of the s-cis over the s-trans configuration of the enone is based upon observations we have made in a related study of the addition of ester enolates to enones (see following paper in this issue).

(50) The intrinsic preference for transition states B and D for small R and $R^1$ is contrary to the predictions of Seebach and Golinski's topological model where A and C are favored in the *absence* of adverse steric interactions: Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413.

**Scheme VIII**



large increase in bulk at this position favors C'

favored for large M⁺

favored when X = S

(R groups are deleted for clarity)

Transition state C'

Transition state D'

Key:
■ H  ▥ S
□ O  ▦ K
▤ C or N  ▨ Li

**Scheme IX**



Favored for small M⁺

Favored for large M⁺

Favored for large R

Favored for small R and R¹

Favored for large R¹

(R groups are deleted for clarity)

Transition structure B'

Transition structure A'

Key:
■ H  ▥ S
□ O  ▦ K
▤ C or N  ▨ Li

(2) The distance between the $\alpha$-carbon of the enolate and the $\beta$-carbon of the enone at the transition state is probably in the neighborhood of 2 Å.[52]

(3) Both the $\alpha$-carbon of the enolate and the $\beta$-carbon of the enone should be partially pyramidalized at the transition state.

(4) The amide nitrogen should have some degree of pyramidalization at the transition state.[53]

The combination of these factors leads to the more refined transition state models A'–D' depicted in Schemes VII–IX.

(51) (a) Bürgi, H. B.; Dunitz, J. D.; Shefter, E. *J. Am. Chem. Soc.* **1973**, *95*, 5065. (b) Bürgi, H. B.; Lehn, J. M.; Wipff, G. *J. Am. Chem. Soc.* **1974**, *96*, 1956. (c) Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, *30*, 1563. (d) Bürgi, H. B.; Dunitz, J. D. *Acc. Chem. Res.* **1983**, *16*, 153.

(52) Houk, K. N., private communication.

(53) In the solid state, lithium enolates of amides appear to have a partially pyramidalized nitrogen: Seebach, D. Proc. *Robert A. Welch Found. Conf. Chem. Res.* **1983**, *27*, 13.

These modifications predict several of the observed trends. For example, the influence of $R^1$ is expected to be small unless $R^1$ is extremely large. When $R^1$ is mes or tris, then the adverse steric interactions favor A' and C' (Schemes VII and IX). The flat character of the lactam enolates 3 and 10 make them sterically less demanding, favoring transition state D'. Another factor that is operative with lactam enolates is constriction of the dihedral angles around the "eclipsed" substituent (the H in C') as a result of its annular nature. This contraction reduces the steric influence of $R^2$ relative to propanamide enolates and disfavors C' relative to D', as observed (vide supra). Notice that installation of a substituent next to the carbonyl would favor model transition state C' over D'. Although the stereostructure has not been proven rigorously, this appears to be the case with the enolate of lactam 1.

The differences in the modes of chelation between A' and B' (and between C' and D') should impose further constrictions on the transitions states. If one assumes that the metal cation interacts preferentially with the carbonyl lone pair of the acceptor,[54] as depicted in Scheme IX, chelation for metals and donor atoms (X) with a smaller ionic radius[55] is more facile in transition structure B' (and D') than in A' (and C'). Thus use of thioamides and/or potassium and sodium counterions favors A' and C' whereas B' and D' are favored for lithium counterions with oxoamides.

Enones with a phenyl substituent at $R^1$ give, with enolates from propanamides, a predominance of the syn diastereomer. As variation of $R^1$ through a series of alkyl groups does not influence the stereoselection observed (vide supra), lessening of steric hindrance is not implicated as the reason for the selectivity change with phenyl substituents. Charge-transfer interactions appear unlikely as para substituents do not appreciably change the stereoselection observed. Two alternative explanations are apparent. One possibility is that the changes in selectivity are electronic in origin. The enolate of lactam 7 adds to ethyl crotonate with excellent syn selectivity,[9] supporting this rationale. Alternatively, the syn selectivity exhibited by both ethyl crotonate and the phenyl enones could be a manifestation of "shape-specific weak interactions".[56,57] In this case, transition state B' is favored by an *attractive* interaction between the flat portion of the acceptor and the enolate.

The role of HMPA in these reactions is puzzling. In some cases (addition of oxoamides to alkyl enones) little or no change in stereochemistry is observed. With thiolactams or with the enone 26, addition of HMPA has a strong but contrasting affect. With enone 26 addition of the oxolactam enolate of 3 in the presence of HMPA results in the formation of more of the syn diastereomer (entries 17 and 18, Table VII), while addition of the lithium

Scheme X



| | syn | | | anti | |
| | 124 | | | 125 | |

**Table XIII. Relative MM2 Strain Energies for Dienes 124 and 125 (Scheme X)**

| entry | R | $R^1$ | $R^2$ | $\Delta(\text{syn} - \text{anti})^a$ |
|---|---|---|---|---|
| 1 | H | H | H | $0.0^b$ |
| 2 | H | Me | H | 0.0 |
| 3 | H | t-Bu | H | 0.9 |
| 4 | H | Me | H | 0.0 |
| 5 | Me | Me | H | −0.3 |
| 6 | t-Bu | Me | H | −2.0 |
| 7 | H | Me | H | 0.0 |
| 8 | H | Me | Me | −0.1 |
| 9 | H | Me | t-Bu | −0.5 |
| 10 | H | Me | t-Bu | −0.5 |
| 11 | Me | Me | t-Bu | −0.7 |
| 12 | t-Bu | Me | t-Bu | −2.3 |

$^a$ In kcal/mol. $^b$ Defined as 0.0 kcal/mol.

**Table XIV. Relative MM2 Strain Energies for Dienes 126 and 127 (Scheme XI)**

| entry | $R^1$ | $R^2$ | $\Delta(\text{syn} - \text{anti})^a$ |
|---|---|---|---|
| 1 | Me | H | $0.0^b$ |
| 2 | Me | Me | 0.2 |
| 3 | Me | t-Bu | 0.4 |

$^a$ In kcal/mol. $^b$ Defined as 0.0 kcal/mol.

enolate of thiolactam 10 to either enone 21 or 26 results in production of more of the anti diastereomer. It is interesting that the addition of HMPA has the most pronounced influence in cases where the reaction is slowed as a result of either steric or electronic considerations. This suggests that HMPA allows alternate reaction pathways to intervene when the addition is sufficiently slow. Unfortunately, insufficient data exist to suggest which pathways are intervening.

Simplified structures constrained to the transition-state geometry were analyzed by using Still's MACROMODEL program[58,59] to examine whether the proposed transition structures are consistent with steric considerations. The carbonyl and the enolate were both modeled by using double bonds; the enolate oxygen was replaced by a methyl group. The bond between the "reactive" carbons was held at 2 Å in length. Additionally, the newly formed bond was restrained to be perpendicular to the $\pi$-systems of the olefins (stereoelectronic requirement). Only the two diastereomeric chelated reaction geometries were analyzed. Only the trends in the relative strain energies between the diastereomeric dienes are considered to minimize the inherent inaccuracies of such a simplified analysis. The results of this study are displayed in Scheme X and Table XIII.

Increasing the bulk of R favors the anti diastereomer 125 (entries 4–6 and 10–12, Table XIII). A similar (although less pronounced) trend is seen in increasing the bulk of $R^2$ (entries 7–9). Both of these proclivities are consistent with the stereoselectivity trends observed. In

(54) Bent structures for the binding of the lithium cation to carbonyl compounds has been observed in the solid state: (a) Amstutz, R.; Dunitz, J. D.; Laube, T.; Schweizer, W. B.; Seebach, D. *Chem. Ber.* **1986**, *119*, 434. (b) Williard, P. G.; Salvino, J. M. *Tetrahedron Lett.* **1985**, 3931.

(55) The crystalline ionic radii are as follows: Li⁺, 0.68 Å; Na⁺, 0.95 Å; K⁺, 1.33 Å; O⁻, 1.76 Å; S⁻, 2.19 Å (Dean, J. A. *Lange's Handbook of Chemistry*, 13th ed.; McGraw-Hill: New York, 1985; Chapter 3, pp 121–123). Combining these radii we get the following "bond-lengths": Li⁺ + O⁻ = 2.44 Å, Li⁺ + S⁻ = 2.87 Å, Na⁺ + S⁻ = 3.14 Å, and K⁺ + S⁻ = 3.52 Å.

(56) (a) Endo, T.; Tajima, K.; Yamashita, M.; Ito, M.; Nishida, J.; Ogikubo, T. *J. Chem. Soc., Chem. Commun.* **1986**, 1561. (b) Ito, M. M.; Kato, J.; Takagi, S.; Nakashiro, E.; Sato, T.; Yamada, Y.; Saito, H.; Namiki, T.; Takamura, I.; Wakatsuki, K.; Suzuki, T.; Endo, T. *J. Am. Chem. Soc.* **1988**, *110*, 5147.

(57) Similar observations concerning the nature of these interactions have been made by Evans and co-workers: Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238 and references therein.

(58) Prof. Clark Still's MacroModel version 1.5 was used.
(59) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127.

**Scheme XI**

syn
**126**

anti
**127**
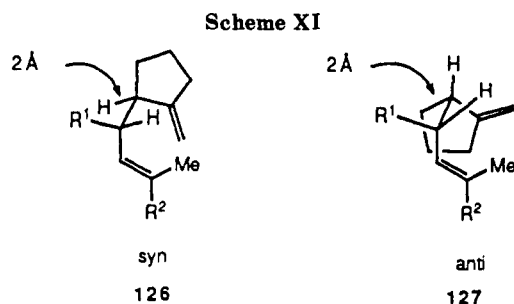
this analysis, the bonding atoms are freely pyramidalized, contrary to the proposed transition-state model (vide supra). In this configuration, the calculations show that increases in the size of $R^1$ result in a slight enhancement of the syn preference, contrary to the observed outcome. If the bonding carbons are assumed to have substantial planar character, then the importance of the steric demand of the substituent in the space between $R^2$ and H (H in A and Me in B, Scheme VI) increases as proposed by Seebach and Golinski.[50]

As a model for lactams 3 and 10, dienes 126 and 127 were analyzed (Scheme XI, Table XIV). Larger substituents at $R^2$ make syn diene 126 more favorable, again compatible with the stereochemical inclinations delineated above (vide supra).

## Conclusions

Amide and thioamide enolates add to α,β-unsaturated ketones to give 1,2 or 1,4 addition products. The regiochemistry of the addition is determined by both electronic and steric considerations. In most cases, initially formed 1,2 adducts can be equilibrated to 1,4 addition products by warming the reaction mixtures.

The stereochemical outcome of the 1,4 addition is dependent on several variables. With lactam enolates, either the anti or the syn diastereomers can be obtained by proper manipulation of the substrates and the counterion. With propanamide enolates, the anti diastereomer is producible with excellent selectivity while the syn diastereomers are available in moderate selectivity only with phenyl enones 22, 23, and 24. These results are consistent on the basis of sterics with a chelated transition state. Thus, insight into both the mechanism of stereoselection and the means of controlling the stereochemical outcome has been achieved.

## Experimental Section

**General.** Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF) and ether were distilled from sodium/benzophenone immediately prior to use. Diisopropylamine, pyrrolidine, piperidine, hexamethylenimine, $CH_2Cl_2$, and triethylamine were distilled from calcium hydride immediately prior to use. Benzene was distilled from either sodium/benzophenone or $CaH_2$ immediately prior to use. Hexamethylphosphoric triamide (HMPA) and N-methyl-2-pyrrolidinone were distilled from $CaH_2$ under reduced pressure and stored over Linde 4-Å molecular sieves. Trimethylsilyl chloride (TMSCl) was freshly distilled from $CaH_2$ and diethylaniline. Thiolactam 10 was prepared following Lawesson's procedure.[15] Enone 29 was prepared by using the method of House and co-workers.[20,21] Enone 30 was prepared by using the method of Hill and Bramann.[23] All reactions involving organometallic reagents were conducted under a nitrogen or argon atmosphere. Stirring was accomplished with a magnetic stirrer (unless otherwise indicated) and a rotary evaporator was used for solvent removal. A Bransonic 22D ultrasonic cleaner was used as the source of ultrasonic radiation. 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

in CDCl3 solutions. For ^{1}H NMR spectra, multiplicity is denoted by s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sep (septet), m (multiplet), and br (broad). Coupling constants are in hertz. Infrared spectra (IR) were measured as thin films on NaCl plates unless otherwise stated. Capillary gas chromatography (capillary GLC) was performed with a 25-m (0.20-mm id) 5% cross-linked phenyl methyl silicone capillary column or a 12.5-m (0.20-mm id) cross-linked methyl silicone capillary column. Analytical gas chromatography (GLC) was performed with a 5-ft (1/8 in. id) OV-101 on Chromasorb G HP 100/120 column. Preparative gas–liquid partition chromatography was done with a 10 ft × 1/4 in. stainless steel, 8% SE-30 column (column A) or a 5 ft × 1/4 in. stainless steel, 20% SE-30 column (column B). Mass spectral (MS) data are tabulated as $m/z$ (intensity expressed as percent of total ion current). High-performance liquid chromatography (HPLC) was done with μ-Porasil columns unless otherwise indicated. Flash chromatography refers to the technique described by Still, Kahn, and Mitra.[60] Unless otherwise indicated, 70–230-mesh silica gel was used for column chromatography. The PMA solution for TLC visualization refers to a 5% solution of phosphomolybdic acid in 95% ethanol. Unless otherwise indicated, melting points are for material crystallizing directly upon removal of solvent from a chromatography fraction.

**General Procedure for the Preparation of Propanamides 7, 8, and 9.** Propionyl chloride was added to a solution of the amine in $CH_2Cl_2$, cooled in an ice/salt bath, at a rate sufficient to maintain a gentle reflux. After completion of the addition, the cooling bath was replaced by a heating mantle and the mixture was heated briefly to reflux temperature for 1 to 1.5 h. When the mixture had returned to room temperature, it was poured into a separatory funnel, washed with dilute (2 to 10%) acid (either HCl or $H_2SO_4$), aqueous $NaHCO_3$, and brine. The organic layer was dried with $MgSO_4$, filtered, concentrated, and distilled under reduced pressure to provide 7, 8, and 9.

**1-(1'-Oxopropyl)pyrrolidine (7).** Following the general procedure (vide supra), 900 mL of $CH_2Cl_2$, 71.8 g (1.00 mol) of pyrrolidine, and propionyl chloride (39.8 g, 0.500 mol) were combined. Distillation of the residue gave 51.3 g (81%) of 7: bp 105–11 °C, 11 mmHg; (lit.[61] bp 126 °C, 26 mmHg); IR (CHCl3) 2960, 2860, 1620, 1435, 1370, 1340 cm$^{-1}$; ^{1}H NMR δ 1.12 (t, 3, $J$ = 7.4), 1.92 (m, 4), 2.29 (q, 2, $J$ = 7.4), 3.43 (t, 4, $J$ = 6.5).

**1-(1'-Oxopropyl)piperidine (8).** Following the general procedure (vide supra), 250 mL of $CH_2Cl_2$, 60 mL (51 g, 0.60 mol) of piperidine, and propionyl chloride (26.0 mL, 27.5 g, 0.297 mol) were combined. Distillation of the residue provided, after a small forerun, 35.9 g (86%) of a clear liquid (bp 127–9 °C, 24 mmHg; lit.[62] bp 45–47 °C, 0.05 mmHg) identical (^{1}H NMR) with that previously reported.[62]

**1-(1'-Oxopropyl)hexamethylenimine (9).** Following the general procedure, 250 mL of $CH_2Cl_2$, 70.0 mL (61.6 g, 0.621 mol) of hexamethylenimine, and propionyl chloride (26.0 mL, 27.5 g, 0.297 mol) in 20 mL of $CH_2Cl_2$ were combined. Distillation of the residue yielded, after a small forerun, 42.99 g (89%) of a clear liquid (bp 138–40 °C, 20 mmHg; lit.[63] bp 123 °C, 9.5 mmHg): IR 2940, 1695, 1430 cm$^{-1}$; ^{1}H NMR δ 1.16 (t, 3, $J$ = 7.4), 1.56 (m, 4), 1.71 (m, 4), 2.35 (q, 2, $J$ = 7.4), 3.43 (t, 2, $J$ = 5.8), 3.51 (t, 2, $J$ = 5.8).

**1-(1'-Thioxopropyl)pyrrolidine (12).** Amide 7 (9.40 g, 73.9 mmol) was added by syringe (evolution of heat) to 15.36 g (38.0 mmol) of Lawesson's reagent.[15] After addition of 14 mL of benzene the mixture was refluxed for a 2.5-h period, cooled, concentrated, and distilled to provide 8.42 g (79%) of a very slightly yellow oil (bp 104–5 °C, 0.3 mmHg; lit.[64] bp 107 °C, 0.01 mmHg): IR 2980, 2880, 1495, 1455 cm$^{-1}$; ^{1}H NMR δ 1.32 (t, 3, $J$ = 7.4), 1.98 (quin, 2, $J$ = 6.8), 2.09 (quin, 2, $J$ = 6.6), 2.70 (q, 2, $J$ = 7.4), 3.62 (t, 2, $J$ = 6.6), 3.87 (t, 2, $J$ = 6.8).

**(E)-Hex-4-en-3-one (17).** A solution of 54.5 g (38.3 mL, 0.500 mol) of bromoethane in 200 mL of ether was added under nitrogen

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to a stirring mixture of 12.4 g (0.510 mol) of Mg turnings and 50 mL of ether at such a rate as to maintain a gentle reflux. After the initial reaction had subsided, the mixture was heated at reflux for 2 h and cooled to −30 °C, and 30.0 g (0.428 mol) of freshly distilled crotonaldehyde was added dropwise. After being warmed to room temperature, the mixture was stirred overnight and then placed in an ice bath and the reaction was quenched with 100 mL of 10% aqueous $H_2SO_4$. The ether layer was separated, washed with saturated $NaHCO_3$ and brine, and dried ($MgSO_4$). After drying, the ether was removed and the residue was distilled at reduced pressure on a 10-cm Vigreux column to give 26.6 g (62%) of the allylic alcohol: bp 58–61 °C, 55 mmHg; lit.[65] bp 134.5–35.5 °C, 760 mmHg; IR 3350 (br), 2960, 1670, 1450, 965 cm⁻¹; ¹H NMR δ 0.90 (t, 3, *J* = 7.4), 1.51 (m, 2), 1.70 (m, 3), 1.86 (s, 1), 3.95 (q, 1, *J* = 6.9), 5.38–5.76 (m, 2).

A solution of 10 mL (0.11 mol) of oxalyl chloride and 200 mL of dry $CH_2Cl_2$ was cooled to between −50 and −60 °C and stirred while being treated with a solution of 1.7 mL (0.22 mol) of dimethyl sulfoxide (DMSO) and 50 mL of $CH_2Cl_2$. After the addition was completed, the mixture was stirred for 2 min, and a solution of 10 g (0.10 mol) of the allylic alcohol in 50 mL of $CH_2Cl_2$ was added over a period of 30 min. When this addition was complete, the mixture was stirred for 20 min, treated with 70 mL (0.50 mol) of triethylamine, and allowed to warm to room temperature. Water was added to the mixture, the resulting layers were separated, and the aqueous layer was extracted with 3 × 50 mL of $CH_2Cl_2$. The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered. The solvent was removed by distillation, and the residue was subjected to column chromatography on silica gel with 20% ether–hexanes as eluent. Removal of the solvent by distillation using a spinning-band column gave 4.95 g (49%) of 17: bp 134–5 °C, lit.[66] bp 79–82 °C, 4 mmHg; IR 3030, 2980, 1690, 1670, 1630, 1380, 1140, 975 cm⁻¹; ¹H NMR δ 1.10 (t, 3, *J* = 7.3), 1.90 (dd, 3, *J* = 1.6, 6.8), 2.55 (q, 2, *J* = 7.3), 6.13 (dd, 1, *J* = 1.6, 15.8), 6.85 (dq, 1, *J* = 6.8, 15.8).

**(*E*)-6-Methyl-2-hepten-4-one (18).** A solution of diisopropylamine (18.8 mL, 0.134 mol) in 200 mL of THF at −20 °C was treated with 107 mL (0.134 mol) of *n*-butyllithium (1.25 M in hexanes) for 15 min. The flask was chilled to −78 °C and 4-methyl-2-pentanone (16.0 mL, 0.128 mol, freshly distilled onto 4Å Linde sieves) was added. After 30 min, acetaldehyde (7.87 mL, 0.141 mol, freshly distilled onto 4Å Linde sieves) was added. After another 30 min, the reaction was quenched by addition of 75 mL of saturated $NaHCO_3$ at −78 °C. The flask was warmed to room temperature, the contents were transferred to a separatory funnel, the layers were separated, and the aqueous phase was extracted with ethyl ether (2 × 100 mL). The combined organic layers were washed with cold 1% HCl (150 mL), saturated $NaHCO_3$ (150 mL), and brine (150 mL), then dried ($MgSO_4$), filtered, and concentrated to give 12.1 g (66%) of the hydroxy ketone.

The crude aldol product was dissolved in 85 mL of pyridine at 0 °C and methanesulfonyl chloride (8.46 mL, 0.109 mol) was added. The solution was kept at room temperature overnight (16 h) and 170 mL of water was then added. The mixture was extracted with ether (3 × 150 mL) and the combined organic layers were washed with saturated $CuSO_4$ (4 × 100 mL) and brine (150 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated to give 15.4 g (82%) of the mesylate.

The crude mesylate was dissolved in 80 mL of ether and 14.5 mL (0.104 mol) of triethylamine was added. The mixture was stirred at room temperature for 18 h, and 100 mL of water was added. The mixture was extracted with ether (3 × 100 mL) and the combined organic layers were washed with cold 1% HCl (100 mL), saturated $NaHCO_3$ (100 mL), and water (100 mL). The organic phase was dried ($MgSO_4$), filtered, and evaporated to give 8.8 g of a yellow oil. Distillation through a short-path apparatus gave 5.14 g (59%, 32% overall) of enone 18: bp 70 °C, 15 mmHg; lit. bp 56 °C (10 mmHg),[67] 77–8 °C (33 mmHg[68]); IR 3040, 2960,

2870, 1675, 1632, 1441, 1365, 1292, 1197, 965 cm⁻¹; ¹H NMR δ 0.95 (d, 6, *J* = 6), 1.90 (dd, 3, *J* = 1.7), 2.0–2.5 (m, 3), 6.05 (dq, 1, *J* = 15, 1), 6.80 (dq, 1, *J* = 15, 7).

**(*E*)-2-Methyl-4-hexen-3-one (19)** was prepared by the procedure given above for the preparation of enone 18. The enolate formed from 8.61 g (10.7 mL, 0.100 mol) of 3-methyl-2-butanone reacted with 13.2 g (16.8 mL, 0.300 mol) of acetaldehyde to give 9.79 g (75%) of the aldol:[69] bp 85–90 °C, 15 mmHg; IR ($CHCl_3$) 3440 (br), 1705, 1120, 1020 cm⁻¹; ¹H NMR δ 1.11 (d, 6, *J* = 6.9), 1.19 (d, 3, *J* = 6.4), 2.59 (m, 3), 3.28 (s, 1), 4.21 (m, 1). Dehydration of this material gave 5.69 g (67%) of 19: bp 49–51 °C, 15 mmHg, lit.[70] bp 40–65 °C, 30 mmHg; IR 2970, 1710, 1625, 1465, 1380, 970 cm⁻¹; ¹H NMR δ 1.10 (d, 6, *J* = 6.9), 1.91 (dd, 3, *J* = 1.6, 6.8), 2.84 (m, 1), 6.21 (dd, 1, *J* = 1.6, 15.6), 6.92 (dq, 1, *J* = 6.9, 15.6).

**(*E*)-1-Cyclohexyl-2-buten-1-one (20)** was prepared by the procedure described above for the preparation of enone 17. The Grignard reagent derived from 6.0 g (6.0 mL, 51 mmol) of chlorocyclohexane was treated with 3.9 g (4.6 mL, 56 mmol) of crotonaldehyde (*violent reaction*; the aldehyde must be added very slowly) to obtain 6.5 g (84%) of the crude allylic alcohol. Oxidation of this material gave 5.86 g (92%) of crude enone that when chromatographed on silica gel with 10% ether–hexanes as eluent gave 3.2 g (50%) of 20: IR 3025, 2960, 2875, 1700, 1675, 1640, 1460, 985 cm⁻¹; ¹H NMR δ 1.31 (m, 5), 1.79 (m, 5), 1.89 (dd, 3, *J* = 1.6, 6.9), 2.54 (m, 1), 6.18 (dq, 1, *J* = 15.6, 1.6), 6.88 (dq, 1, *J* = 15.6, 6.9); ¹³C NMR δ 18.1, 25.6, 25.7, 28.5, 48.3, 130.1, 141.9, 203.0. Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.67; H, 10.45.

**(*E*)-2,2-Dimethyl-4-hexen-3-one (21)** was prepared by the procedure given above for the preparation of enone 17. The reaction of 233 mL (0.419 mol) of a 1.8 M solution of *tert*-butyllithium in hexanes with 32.2 g (0.45 mol) of crotonaldehyde gave 38.4 g (72%) of the allylic alcohol: bp 63–5 °C, 33–35 mmHg; IR 3600–3100, 1670, 1480, 1370 cm⁻¹; ¹H NMR δ 0.90 (s, 9), 1.47 (s, 1), 1.73 (d, 3, *J* = 5.7), 3.68 (d, 1, *J* = 6.5), 5.60 (m, 2); ¹³C NMR δ 16.0, 23.9, 32.9, 79.3, 126.4, 129.3. Oxidation of 38.0 g (0.296 mol) of the allylic alcohol gave 29.8 g (80%) of 21: bp 76–7 °C, 68 mmHg; lit.[71] bp 153–4 °C, 740 mmHg; IR 2975, 1690, 1635 cm⁻¹; ¹H NMR δ 1.09 (s, 9), 1.90 (dd, 3, *J* = 6.9, 1.7), 6.54 (dq, 1, *J* = 15.2, 1.7), 6.96 (dq, 1, *J* = 15.2, 6.9); ¹³C NMR δ 18.1, 22.6, 42.6, 125.7, 142.5, 203.9.

**(*E*)-1-Phenyl-2-buten-1-one (22)** was prepared by the procedure given above for the preparation of enone 18. The enolate derived from 12.0 g (11.7 mL, 0.100 mol) of acetophenone reacted with 7.88 g (10.0 mL, 0.179 mol) of acetaldehyde to give 9.34 g (57%) of the aldol: bp 95–101 °C, 0.2 mmHg; IR 3430 (br), 3060, 1660, 1620, 1595, 1580, 1210, 755, 690 cm⁻¹; ¹H NMR δ 1.25 (d, 3, *J* = 7), 3.05 (d, 1, *J* = 3), 3.10 (s, 1), 3.40 (s, 1), 4.20–4.60 (m, 1), 7.25–7.70 (m, 3), 7.80–8.05 (m, 2). Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.51; H, 7.47.

This material was dehydrated to give 7.66 g (92%) of 22: bp 50–60 °C, 0.05 mmHg; lit.[72] bp 84–85 °C, 0.5 mmHg; IR 3050, 1665, 1645, 1620, 1595, 1575, 1295, 1220, 965, 760, 695 cm⁻¹; ¹H NMR δ 1.99 (dd, 3, *J* = 1.3, 6.6), 6.90 (dd, 1, *J* = 1.3, 15.4), 7.04 (dq, 1, *J* = 6.6, 15.4), 7.42–7.58 (m, 3), 7.92 (dd, 2, *J* = 1.5, 8.0).

**(*E*)-1-(4-Bromophenyl)-2-buten-1-one (23)** was prepared by the procedure given above for the preparation of enone 18. The enolate derived from 19.9 g (0.10 mol) of *p*-bromoacetophenone reacted with 13.2 g (16.8 mL, 0.30 mol) of acetaldehyde to give 6.55 g (27%) of 1-(4-bromophenyl)-3-hydroxybutan-1-one: IR 3440 (br), 2975, 1685, 1590, 1395, 1065, 996, 810 cm⁻¹; ¹H NMR δ 1.30 (d, 3, *J* = 6.4), 2.9–3.3 (m, 3), 4.40 (m, 1), 7.62 (d, 2, *J* = 8.6), 7.82 (d, 2, *J* = 8.6); ¹³C NMR δ 18.59, 126.89, 127.62, 129.95, 131.70, 136.44, 145.77, 189.52. Anal. Calcd for $C_{10}H_{11}BrO_2$: C, 49.41; H, 4.56; Br, 32.87. Found: C, 49.69; H, 4.67; Br, 32.49.

This material was dehydrated to obtain 3.84 g (63%) of 23: mp 40.5–3 °C (ethanol–water); IR ($CHCl_3$) 3000, 1665, 1620, 1580, 1295, 1000, 700 cm⁻¹; ¹H NMR δ 2.00 (dd, 3, *J* = 1.5, 6.8), 6.86 (dq, 1, *J* = 1.5, 15.3), 7.09 (dq, 1, *J* = 6.8, 15.3), 7.61 (d, 2, *J* =

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8.7), 7.80 (d, 2, $J$ = 8.7); ^{13}C NMR $\delta$ 18.6, 126.9, 127.6, 130.0, 131.7, 136.4, 145.8, 189.5. Anal. Calcd for $C_{10}H_9BrO$: C, 53.36; H, 4.03; Br, 35.50. Found: C, 53.08; H, 4.09; Br, 35.26.

(*E*)-1-(4-Methoxyphenyl)-2-buten-1-one (24) was prepared by the procedure used for the preparation of enone 18. The enolate derived from 7.5 g (50 mmol) of *p*-methoxyacetophenone reacted with 6.6 g (6.4 mL, 150 mmol) of acetaldehyde to give 9.22 g (95%) of aldol that was reasonably pure by ^{1}H NMR spectroscopy and was utilized in the synthesis of 24. A small portion was subjected to flash chromatography on silica gel with 50% ethyl acetate/hexanes as eluent to give an analytical sample of 3-hydroxy-1-(4-methoxyphenyl)butan-1-one: IR (neat) 3450 (br), 2970, 1675, 1610, 1580, 1515, 1265, 1180, 1035, 835 cm^{-1}; ^{1}H NMR $\delta$ 1.29 (d, 3, $J$ = 6.4), 2.97 (dd, 1, $J$ = 8.9, 17.5), 3.14 (dd, 1, $J$ = 2.9, 17.5), 3.50 (br d, 1, $J$ = 2.2), 3.88 (s, 3), 4.39 (m, 1), 6.94 (m, 2), 7.94 (m, 2); ^{13}C NMR $\delta$ 22.3, 45.9, 55.2, 63.9, 113.5, 129.5, 130.2, 163.5, 199.0. Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.79; H, 7.28.

Dehydration of 9.0 g (46 mmol) of the crude aldol gave 6.22 g (77%) of 24: IR 3020, 2850, 1670, 1645, 1605, 1580, 1515, 1265, 1035, 970, 925, 815 cm^{-1}; ^{1}H NMR $\delta$ 1.99 (d, 3, $J$ = 1.1, 6.5), 3.88 (s, 3), 6.9–7.0 (m, 3), 7.07 (dq, 1, $J$ = 15.2, 6.5), 7.95 (m, 2); ^{13}C NMR $\delta$ 18.3, 55.2, 113.5, 126.8, 130.4, 130.5, 143.6, 163.0, 188.5. Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.65; H, 6.84.

(*E*)-1-(2,4,6-Trimethylphenyl)-2-buten-1-one (25). Aluminum chloride (23.0 g, 172 mmol) was added gradually with stirring to a solution of 21 mL (18.1 g, 151 mmol) of mesitylene in 60 mL of carbon disulfide. After the completion of the addition, crotonyl chloride (15 mL, 16.4 g, 157 mmol) was added dropwise at a rate sufficient to maintain a gentle reflux. The mixture was heated at reflux by using a heating mantle for 0.5-h period and then allowed to cool to 30 °C. The mixture was poured onto approximately 100 g of ice and the carbon disulfide was partially removed in a stream of $N_2$. The resulting solution was diluted with 50 mL of $H_2O$ and extracted with 2 × 150 mL of ether. The ethereal layers were combined, washed with 100 mL of $H_2O$, 50 mL of 10% aqueous NaOH, and 50 mL of brine, dried with $MgSO_4$, filtered, and concentrated to 28.6 g. Vacuum distillation of the crude material (164–6 °C, 30 mmHg) provided 24.7 g (87%) of a very slightly yellow oil that was deemed suitable (^{1}H NMR) for further use. Chromatography of 0.332 g of the distilled material with 10 g of silica gel using 20:1 hexanes/ether as eluent provided 0.326 g of enone 25 as a clear oil: IR ($CHCl_3$) 2940, 1660 cm^{-1}; ^{1}H NMR $\delta$ 1.89 (dd, 3, $J$ = 1.5, 6.7), 2.13 (s, 6), 2.67 (s, 3), 6.30 (dq, 1, $J$ = 15.8, 1.5), 6.49 (dq, 1, $J$ = 15.8, 6.7), 6.82 (s, 2); ^{13}C NMR $\delta$ 18.28, 19.00, 20.87, 127.96, 133.56, 133.85, 136.97, 137.83, 147.56, 201.11. Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.99; H, 8.60.

(*E*)-1-(2,4,6-Triisopropylphenyl)-2-buten-1-one (26) was prepared by the procedure given for the preparation of enone 25. The Friedel–Crafts acylation of 1,3,5-triisopropylbenzene (0.50 mL, 0.423 g, 2.07 mmol) with crotonyl chloride (0.22 mL, 0.240 g, 2.30 mmol) gave 0.589 g of a solid. Chromatography of 0.504 g of the crude material on 16 g of silica gel (230–400 mesh) utilizing 30:1 hexanes/ether as eluent provided 0.465 g (95%) of enone 26 as white crystals (mp 65–65.5 °C): IR ($CHCl_3$) 2980, 2880, 1650, 1615, 1470, 1295 cm^{-1}; ^{1}H NMR $\delta$ 1.16 (d, 12, $J$ = 6.8), 1.25 (d, 6, $J$ = 6.9), 1.91 (dd, 3, $J$ = 1.3, 6.6), 2.71 (sep, 2, $J$ = 6.8), 2.89 (sep, 1, $J$ = 6.9), 6.37 (dq, 1, $J$ = 15.7, 1.7), 6.53 (dq, 1, $J$ = 15.7, 6.6), 7.00 (s, 2); ^{13}C NMR $\delta$ 18.37, 23.70, 23.99, 24.77, 30.84, 34.30, 120.78, 135.28, 135.33, 144.62, 147.73, 149.31, 202.00. Anal. Calcd for $C_{19}H_{28}O$: C, 83.77; H, 10.36. Found: C, 84.04; H, 10.48.

(*E*)-2,2-Dimethyl-4-hepten-3-one (27).[73] A mixture of 80.0 mL of freshly distilled propanal and 25.0 g (69.4 mmol) of ylide 31 (vide infra) was heated at reflux for 48 h, cooled, and concentrated. The resulting yellow slurry was distilled through a 10-cm Vigreux column (bp 72–3 °C, 40 mmHg) to provide 6.75 g (70%) of enone 27 as a pale yellow oil: IR 2975, 1690, 1635 cm^{-1}; ^{1}H NMR $\delta$ 1.08 (t, 3, $J$ = 7.4), 1.16 (s, 9), 2.37 (m, 2), 6.49 (dt, 1, $J$ = 15.3, 1.6), 6.99 (dt, 1, $J$ = 15.3, 6.5).

(*E*)-2,2,6-Trimethyl-4-hepten-3-one (28). A mixture of 30.43 g (422 mmol) of freshly distilled isobutyraldehyde and 18.12 g

(55.9 mmol) of ylide 31 was brought to reflux and 10 mL of $CH_3CN$ was added to dissolve the ylide completely. The solution was gently refluxed for 2 days, cooled, concentrated, and distilled (bp 82–3 °C, 50 mmHg; lit.[74] bp 179–188 °C, 760 mmHg) to yield 5.507 g (35.7 mmol, 69%) of 28 as a clear oil: IR 970, 1690, 1630 cm^{-1} ^{1}H NMR $\delta$ 1.08 (d, 6, $J$ = 6), 1.17 (s, 9), 2.40 (m, 1), 6.40 (dd, 1, $J$ = 15.3, 2.1), 6.85 (dd, 1, $J$ = 15.3, 6.9).

3,3-Dimethyl-1-(triphenylphosphoranylidene)-2-butanone (31).[75] To a stirring solution of 176.53 g (0.673 mol) of triphenylphosphine and 600 mL of $CHCl_3$ in a 1-L three-necked round-bottomed flask equipped with an addition funnel, was added 120.58 mL (0.673 mol) of $\alpha$-bromopinacolone[76] dropwise under positive $N_2$ pressure over a 2-h period. The colorless solution became yellow. After 0.5 h a yellow precipitate formed. The mixture was stirred under positive $N_2$ pressure overnight and concentrated to leave a yellow, highly viscous liquid. This liquid was diluted with 50 mL of $CHCl_3$ and 600 mL of $H_2O$ was added. After the mixture was heated to 60 °C, the clear aqueous layer was decanted and transferred to a separatory funnel containing 150 mL of saturated $K_2CO_3$. The resulting cloudy white mixture was extracted with ether (3 × 150 mL). The ethereal extracts were combined, dried with $MgSO_4$, and then concentrated to give 30 g of a fine yellow powder. Additional water was added and the extraction procedure was repeated five times to yield 119.2 g (49%) of ylide 31 judged pure enough (^{1}H NMR) for subsequent transformations. Recrystallization of 2.63 g of the ylide from hot $CH_3CN$ afforded 1.48 g of 31 (mp 180–1 °C; lit.[75] mp 178–9 °C); IR ($CHCl_3$) 3060, 2975, 1510, 1400, 1117, 700 cm^{-1}; ^{1}H NMR $\delta$ 1.20 (s, 9), 3.79 (d, 1, $J$ = 27.5), 7.50 (m, 15); ^{13}C NMR $\delta$ 28.7, 40.3, 40.5, 46.6, 48.0. Anal. Calcd for $C_{24}H_{25}OP$: C, 80.00; H, 6.97; P, 8.60. Found: C, 79.97; H, 6.96; P, 8.58.

2-Methyl-4-hexyn-3-ol (32). Propyne (ca. 8.5 mL, 6.0 g, 0.15 mol) was condensed into a flask immersed in a dry ice–acetone bath and dissolved in 80 mL of THF. This stirring solution was treated with 70.5 mL (0.11 mol) of a 1.56 M solution of *n*-butyllithium in hexanes and was stirred for 15 min. 2-Methylpropanal (5.6 g, 7.1 mL, 0.10 mol) was added to the resulting slurry over 1 min, the cooling bath was removed, and the mixture was allowed to warm. After 45 min, there was no remaining aldehyde indicated by TLC. The reaction was quenched with saturated $NH_4Cl$, diluted with ether, and separated. The ether portion was washed with 4 × 50 mL of water, the combined aqueous portions were reextracted, and the combined ether solutions were dried ($Na_2SO_4$). Filtration and removal of the solvent, followed by distillation of the residue at atmospheric pressure, gave 5.4 g (48%) of ynol 32: bp 160–7 °C (lit.[77] bp 74 °C, 25 Torr); IR 3380 (br), 2960, 2925, 2875, 2210 (weak), 1145, 1015 cm^{-1}; ^{1}H NMR $\delta$ 0.97 (d, 3, $J$ = 6.4), 0.99 (d, 3, $J$ = 6.0), 1.82 (m, 2), 1.86 (d, 3, $J$ = 2.3), 4.13 (d, 1, $J$ = 2.1).

(*Z*)-2-Methyl-4-hexen-3-one (33). Chromium trioxide (16.2 g, 162 mmol) was added to a solution of 26.2 mL (25.6 g, 324 mmol) of pyridine in 250 mL of $CH_2Cl_2$. The solution was stirred at room temperature for 15 min, a solution of ynol 32 (3.0 g, 27 mmol) in 5 mL of $CH_2Cl_2$ was added at once with a syringe, and the mixture was stirred at room temperature. After 22 h, no starting alcohol was seen by TLC. The mixture was concentrated, taken up in ca. 200 mL of ether, filtered, and concentrated to ca. 100 mL. This ether solution was washed with 50 mL each of 5% aqueous HCl and 5% aqueous $NaHCO_3$ and dried ($MgSO_4$). Filtration and removal of solvent gave 2.00 g (67%) of 2-methyl-4-hexyn-3-one:[78] IR 2980, 2875, 2210, 1675, 1255, 1195, 1155, 955 cm^{-1}; ^{1}H NMR $\delta$ 1.18 (d, 6, $J$ = 7.0), 2.04 (s, 3), 2.62 (sep, 1, $J$ = 7.0).

A mixture of 10 mL of ether, 1.10 g (10.0 mmol) of the ynone, 0.020 g (0.018 mL) of quinoline, and 0.020 g of 5% Pd/$BaSO_4$ was placed under a hydrogen atmosphere and stirred at room temperature for 14 h. A total of 245 mL (10.0 mmol) of hydrogen was consumed. The catalyst was removed by filtration and the

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solvent carefully removed. ¹H NMR of the crude material showed the desired enone contaminated with ca. 10% of the *E* enone **19**. Column chromatography of the crude residue on silica gel with 20% ether–hexanes as the eluent, followed by removal of the solvent, gave 0.688 g (61%) of **33**:[70] IR (CHCl₃) 2950, 1690, 1625, 1470, 1060 cm⁻¹ ¹H NMR δ 1.10 (d, 6, *J* = 6.9), 2.11 (d, 3, *J* = 5.4), 6.22 (d, 1, *J* = 2.0), 6.32 (m, 1).

**General Procedures A–D for the Addition of Amide Enolates to α,β-Unsaturated Ketones.** A dry three-necked round-bottomed flask equipped with a rubber septum and thermometer was placed under an N₂ atmosphere and charged with THF and 2 molar equiv of diisopropylamine. This stirring solution was cooled to 0 °C and treated with 2 molar equiv of a solution of *n*-butyllithium in hexanes. This solution was stirred for 10 min and cooled to −78 °C with a dry ice–acetone bath. To this solution was added 2 molar equiv of amide, and the mixture was stirred for 1 h. The mixture was treated with 1 molar equiv of the enone and allowed to react for various amounts of time, either maintaining the mixture at −78 °C (method A) or allowing the mixture to warm to 25 °C (method B). Alternatively, an oven-dried, argon-flushed Schlenk tube was charged with 2 molar equiv of *n*-butyllithium in hexanes and cooled to 0 °C in an ice/salt bath. Diisopropylamine (2.2 molar equiv) was added by syringe, resulting in a viscous solution. After 15 min, the rubber septum was replaced by a ground glass stopper and the hexanes and excess diisopropylamine were removed under reduced pressure. The ground glass stopper was replaced by a rubber septum and the solid was diluted with THF to ca. 0.5 M. The reaction flask was cooled to −78 °C (dry ice/acetone) and the enone (1 molar equiv) was added either neat or as a solution in THF and allowed to react for various amounts of time, either maintaining the mixture at −78 °C (method C) or allowing the mixture to warm to 25 °C (method D). The reaction was quenched with saturated NH₄Cl and diluted with ether, and the resulting layers were separated. The aqueous layer was extracted with ether and the organic portions were combined, washed with water, dried (MgSO₄), and filtered. The solvent was removed and the crude material was placed briefly under reduced pressure to give the crude products.

**N,N,3,7-Tetramethyl-5-oxooctanamide (34):** yellow oil; bp 120 °C bath, 0.002 mmHg (microstill); IR 2952, 2870, 1701, 1635, 1490, 1458, 1395, 1363, 1261, 1140, 1101, 1058, 1038 cm⁻¹; ¹H NMR δ 0.90 (d, 6, *J* = 6.6), 0.99 (d, 3, *J* = 6.6), 2.05–2.40 (m, 6), 2.45–2.60 (m, 2), 2.93 (s, 3), 3.03 (s, 3); MS *m/z* 213 (1.58), 198 (0.27), 156 (3.34), 128 (5.06), 114 (2.26), 87 (17.35), 72 (8.66), 69 (6.41), 57 (4.17), 45 (6.56). Anal. Calcd for C₁₂H₂₃NO₂: C, 67.57; H, 10.87; N, 6.57. Found: C, 67.38; H, 10.66; N, 6.39.

**N,N,2,2,3,7-Hexamethyl-5-oxooctanamide (35):** clear oil; IR 2952, 2875, 1712, 1630, 1470, 1395, 1365, 1110 cm⁻¹; ¹H NMR δ 0.86 (d, 3, *J* = 6.8), 0.90 (d, 3, *J* = 6.6), 0.91 (d, 3, *J* = 6.6), 1.15 (s, 3), 1.22 (s, 3), 2.12 (nonet, 1, *J* = 6.6), 2.25 (m, 3), 2.35 (dd, 1, *J* = 3.2, 17.1), 2.68 (m, 1), 3.05 (s, 6); ¹³C NMR δ 15.23, 22.37, 22.44, 22.49, 23.18, 24.48, 33.21, 38.40, 45.46, 46.18, 52.56, 176.59, 210.11. Anal. Calcd for C₁₄H₂₇NO₂: C, 69.66; H, 11.28; N, 5.80. Found: C, 69.74; H, 11.39; N, 5.66.

**N-Methyl-N-(3-methyl-2-oxobutyl)-2-methylpropanamide:** clear oil; ¹H NMR δ 1.14 (d, 6, *J* = 6.9), 1.15 (d, 6, *J* = 6.8), 2.67 (sep, 1, *J* = 6.9), 2.91 (sep, 1, *J* = 6.8), 3.08 (s, 3), 4.23 (s, 2). Anal. Calcd for C₁₀H₁₉NO₂: C, 64.83; H, 10.34; N, 7.56. Found: C, 64.66; H, 10.31; N, 7.41.

**N,N,3-Trimethyl-5-oxo-5-phenylpentanamide (36):** yellow oil; IR 3060, 2960, 2935, 1680, 1640, 1445, 1398, 748, 685 cm⁻¹; ¹H NMR δ 1.06 (d, 3, *J* = 6.5), 2.29 (dd, 1, *J* = 15.0, 6.6), 2.46 (dd, 1, *J* = 15.0, 6.8), 2.67 (m, 1), 2.78 (dd, 1, *J* = 15.6, 7.3), 2.94 (s, 3), 3.04 (s, 3), 3.24 (dd, 1, *J* = 15.5, 5.5), 7.45 (dd, 2, *J* = 7, 1.5), 7.55 (dt, 1, *J* = 7.2, 2.6), 8.01 (dd, 2, *J* = 7.0, 1.6); MS *m/z* 233 (1.55), 189 (1.21), 161 (1.29), 128 (3.99), 114 (4.33), 105 (5.28), 87 (5.63), 77 (5.35), 72 (5.81), 69 (5.98). Anal. Calcd for C₁₄H₁₉NO₂: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.00; H, 8.27; N, 5.93.

**N,N,2,2,3-Pentamethyl-5-oxo-5-phenylpentanamide (37):** white needles; mp 87–8 °C; IR (CHCl₃) 3040, 2990, 2950, 1680, 1610, 1580, 1362, 1107 cm⁻¹; ¹H NMR δ 0.94 (d, 3, *J* = 6.2), 1.25 (s, 3), 1.29 (s, 3), 2.75–2.95 (m, 3), 3.06 (s, 6), 7.46 (t, 2, *J* = 7.3), 7.56 (t, 1, *J* = 7.3), 7.95 (d, 2, *J* = 7.2); MS *m/z* 261 (0.45), 217 (5.27), 189 (4.74), 115 (4.29), 105 (9.61), 77 (8.15), 72 (8.17). Anal. Calcd for C₁₆H₂₃NO₂: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.65; H, 8.69; N, 5.38.

**N,N,2-Trimethyl-2-(3′-oxocyclohexyl)propanamide (38):** oil; IR 2940, 1708, 1620, 1390, 1362, 1110 cm⁻¹; ¹H NMR δ 1.23 (s, 3), 1.27 (s, 3), 1.45–1.65 (m, 2), 1.75 (m, 1), 2.10–2.45 (m, 6), 3.03 (s, 6); MS *m/z* 211 (1.09), 196 (0.17), 115 (12.64), 72 (16.69), 55 (10.16). Anal. Calcd for C₁₂H₂₁NO₂: C, 68.21; H, 10.02; N, 6.63. Found: C, 68.06; H, 9.97; N, 6.55.

**N,N-Dimethyl-2-(1′-methyl-3′-oxocyclohexyl)ethanamide (39):** oil; IR 2950, 1710, 1640, 1399, 1230, 1140 cm⁻¹; ¹H NMR δ 1.07 (s, 3), 1.68 (m, 1), 1.8–1.95 (m, 2), 2.0–2.15 (m, 1), 2.19 (d, 1, *J* = 12.4), 2.25–2.40 (m, 4), 2.62 (d, 1, *J* = 13.6), 2.95 (s, 3), 3.02 (s, 3); MS *m/z* 197 (1.33), 182 (0.63), 154 (2.59), 126 (2.06), 111 (3.38), 87 (8.56), 72 (7.53), 55 (8.58), 45 (10.16). Anal. Calcd for C₁₁H₁₉NO₂: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.97; H, 9.80; N, 7.11.

**N,N-Dimethyl-2-(1′-hydroxy-3′-methyl-2′-cyclohexenyl)-ethanamide (42):** oil; IR 3400, 2930, 1620, 1400, 1145 cm⁻¹; ¹H NMR δ 1.50–1.65 (m, 2), 1.67 (s, 3), 1.80–2.05 (m, 4), 2.46 (d, 1, *J* = 16.0), 2.52 (d, 1, *J* = 16.0), 2.98 (s, 3), 3.01 (s, 3), 5.45 (br s, 2); MS *m/z* 197 (0.62), 179 (1.83), 178 (3.17), 135 (1.81), 111 (3.93), 87 (8.33), 82 (6.24), 72 (7.71), 45 (9.03); HRMS M⁺ calcd for C₁₁H₁₉NO₂ 197.1416, found 197.1417.

**(E)-N,N-Dimethyl-3-hydroxy-3-isobutyl-4-hexenamide (40):** clear oil; IR 3380, 2980, 2880, 1620, 1400 cm⁻¹; ¹H NMR δ 0.90 (d, 3, *J* = 6.7), 0.95 (d, 3, *J* = 6.6), 1.37 (dd, 1, *J* = 5.5, 13.9), 1.54 (dd, 1, *J* = 6.2, 13.9), 1.69 (dd, 3, *J* = 1.5, 6.5), 1.80 (br sep, 1, *J* = 6.4), 2.39 (d, 1, *J* = 15.5), 2.52 (d, 1, *J* = 15.5), 2.94 (s, 3), 3.00 (s, 3), 5.41 (dq, 1, *J* = 1.5, 15.3), 5.56 (s, 1), 5.68 (dq, 1, *J* = 6.5, 15.3); ¹³C NMR δ 17.68, 23.94, 24.45, 24.60, 35.12, 37.40, 41.69, 50.07, 73.72, 123.43, 136.06, 172.68. Anal. Calcd for C₁₂H₂₃NO₂: C, 67.56; H, 10.87; N, 6.57. Found: C, 67.38; H, 11.05; N, 6.64.

**N,N-Dimethyl-2-(1-hydroxy-2-cyclohexenyl)ethanamide (41):** oil; IR 3400, 3015, 2930, 2860, 2825, 1620, 1395, 1140, 1060, 995, 732 cm⁻¹; ¹H NMR δ 1.6 (m, 2), 1.8–2.2 (m, 4), 2.47 (d, 1, *J* = 15.8), 2.56 (d, 1, *J* = 15.8), 2.98 (s, 3), 3.02 (s, 3), 5.54 (br s, 1), 5.70 (d, 1, *J* = 10.3), 5.79 (dt, 1, *J* = 10.1, 3.1); MS *m/z* 183 (0.58), 165 (0.86), 164 (1.89), 155 (2.94), 87 (9.74), 72 (6.14), 68 (7.34). Anal. Calcd for C₁₀H₁₇NO₂: C, 65.54; H, 9.35; N, 7.65. Found: C, 65.63; H, 9.28; N, 7.49.

**(2RS,3RS)- or (2RS,3SR)-3-tert-butyl-3-hydroxy-N,N,2-trimethyl-4-hexenamide (43a):** clear oil; IR 3400 (br), 2980, 2880, 1610, 1470, 1410 cm⁻¹; ¹H NMR δ 1.03 (s, 9), 1.10 (d, 3, *J* = 7.1), 1.25 (br s, 3), 2.63 (q, 1, *J* = 7.1), 3.00 (s, 3), 3.10 (s, 3), 5.18 (br d, 1, *J* = 15.8), 5.36 (br s, 1), 5.79 (br d, *J* = 15.8).

**(2RS,3RS)-N,N,2,3,6,6-Hexamethyl-5-oxoheptanamide (44a):** discernible from mixture; IR 2980, 2880, 1710, 1650 cm⁻¹; ¹H NMR δ 0.91 (d, 3, *J* = 6.5), 1.05 (d, s, *J* = 7.1), 1.12 (s, 9), 2.45 (m, 2), 2.57 (m, 1), 2.83 (m, 1), 2.93 (s, 3), 3.08 (s, 3); ¹³C NMR δ 12.81, 18.04, 25.90, 30.47, 35.08, 36.92, 38.51, 38.98, 43.77, 175.31, 214.74; HRMS calcd for C₁₃H₂₅NO₂ 227.1886, found 227.1879.

**(E,2′RS,3′RS)- or (E,2′RS,3′SR)-1-(3′-ethyl-3′-hydroxy-2′-methyl-1′-oxohex-4′-enyl)pyrrolidine (45a), major 1,2 adduct:** mp 77–9 °C; IR (CHCl₃) 3400 (br), 1610, 1510, 1200, 980, 930 cm⁻¹; ¹H NMR δ 0.84 (t, 3, *J* = 7.4), 1.13 (d, 3, *J* = 7.0), 1.39 (m, 1), 1.57 (m, 1), 1.73 (dd, 3, *J* = 1.5, 6.5), 1.95 (m, 4), 2.46 (q, 1, *J* = 7.0), 3.49 (m, 4), 5.05 (s, 1), 5.10 (d, 1, *J* = 15.6), 5.74 (dq, 1, *J* = 6.5, 15.6); ¹³C NMR δ 8.5, 12.9, 19.2, 24.8, 26.4, 33.9, 44.3, 45.9, 47.3, 78.0, 125.8, 133.4, 176.8. Anal. Calcd for C₁₃H₂₃NO₂: C, 69.29; H, 10.29; 6.22. Found: C, 69.07; H, 10.12; N, 6.13.

**Minor 1,2 adduct 45b:** yellow oil; IR (CHCl₃) 3360 (br), 1610, 1450, 975, 910 cm⁻¹; ¹H NMR δ 0.84 (t, 3, *J* = 7.5), 1.19 (d, 3, *J* = 7.0), 1.35 (m, 1), 1.66 (dd, 3, *J* = 1.5, 6.4), 1.93 (m, 2), 2.55 (q, 1, *J* = 7.0), 3.43 (q, 2, *J* = 7.2), 5.31 (s, 1), 5.36 (dd, 1, *J* = 1.5, 16), 5.65 (dq, 1, *J* = 6.4, 16).

**(2′RS,3′RS)- and (2′RS,3′SR)-1-(2′,3′-dimethyl-1′,5′-di-oxoheptyl)pyrrolidine (46a and 46s):** colorless oil; IR 2980, 2880, 1715, 1635, 1430, 1370, 1340, 1105 cm⁻¹; ¹H NMR δ 0.93 and 0.94 (2d's, 3, *J* = 6.6, 6.5), 1.06 (m, 6), 1.90 (m, 4), 2.18–2.79 (m, 6), 3.35–3.65 (m, 4); ¹³C NMR δ 7.1, 7.2, 12.7, 13.3, 16.0, 18.0, 23.7, 25.6, 30.7, 31.1, 35.6, 35.7, 41.5, 41.6, 44.6, 45.1, 46.0, 46.7, 173.7, 210.4, 210.5. Anal. Calcd for C₁₃H₂₃NO₂: C, 69.29; H, 10.29; 6.22. Found: C, 68.94; H, 9.98; N, 6.16.

**(2′RS,3′RS)- or (2′RS,3′SR)-1-(3′-hydroxy-2′-methyl-3′-isopropyl-1′-oxo-4′-hexenyl)pyrrolidine (47a), major diastereomer:** colorless oil; IR (CHCl₃) 3360 (br), 2980, 2880, 1615, 995, 970 cm⁻¹; ¹H NMR δ 0.83 (d, 3, *J* = 7.0), 0.84 (d, 3, *J* = 6.6), 1.17 (d, 3, *J* = 7.0), 1.67 (dd, 3, *J* = 1.1, 5.9), 1.94 (m, 5), 2.75 (q,

1, $J$ = 7.0), 3.43 (m, 4), 5.36 (dd, 1, $J$ = 1.1, 15.9), 5.52 (s, 1), 5.69 (dq, 1, $J$ = 6.5, 15.9); $^{13}$C NMR δ 10.5, 16.4, 17.0, 17.7, 24.2, 25.9, 32.7, 41.0, 45.3, 46.8, 77.0, 125.7, 131.1, 175.9. Anal. Calcd for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85. Found: C, 69.89; H, 10.30; N, 5.70.

**Minor diastereomer 47b:** mp 103–5 °C; IR (CHCl$_3$) 3375 (br), 3040, 2995, 2880, 1610, 975, 920 cm$^{-1}$; $^1$H NMR δ 0.82 (d, 3, $J$ = 7.0), 0.86 (d, 3, $J$ = 6.7), 1.12 (d, 3, $J$ = 7.0), 1.74 (dd, 3, $J$ = 1.5, 6.6), 1.91 (m, 5), 2.66 (q, 1, $J$ = 7.0), 3.50 (m, 4), 5.13 (dd, 1, $J$ = 1.5, 15.3), 5.19 (s, 1), 5.77 (dq, 1, $J$ = 6.6, 15.3); $^{13}$C NMR δ 12.8, 17.4, 17.9, 18.4, 24.3, 26.1, 36.5, 40.9, 45.5, 46.6, 78.3, 126.4, 129.0, 176.5. Anal. Calcd for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85. Found: C, 69.94; H, 10.51; N, 5.73.

**(2′RS,3′RS)- and (2′RS,3′SR)-1-(1,5-dioxo-2,3,6-trimethylheptyl)pyrrolidine (48a and 48s), mixture of diastereomers:** colorless oil; IR (CHCl$_3$) 2980, 2880, 1705, 1620, 1435, 1383, 1370, 1340 cm$^{-1}$; $^1$H NMR δ 0.93 and 0.94 (2d's, 3, $J$ = 6.6, 6.5), 1.06, 1.07, and 1.08 (3d's, 9, $J$ = 6.8, 6.9, 7.0), 1.90 (m, 4), 2.32 (m, 2), 2.5–2.8 (m, 3), 3.45 and 3.60 (2m's, 4); $^{13}$C NMR δ 12.9, 13.4, 16.2, 17.6, 17.7, 18.0, 18.04, 18.3, 24.0, 25.9, 30.8, 31.1, 40.5, 40.6, 41.4, 41.7, 42.9, 44.8, 45.3, 46.2, 174.0, 214.0, 214.1. Anal. Calcd for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; H, 5.85. Found: C, 70.08; H, 10.32; N, 5.82.

**(E,2′RS,3′RS)- or (E,2′RS,3′SR)-1-(3′-cyclohexyl-3′-hydroxy-2′-methyl-1′-oxo-4′-hexenyl)pyrrolidine (49a), major diastereomer:** IR (CHCl$_3$) 3380 (br), 2950, 2875, 1620, 1460, 985 cm$^{-1}$; $^1$H NMR δ 0.8–1.4 (m, 5), 1.16 (d, 3, $J$ = 6.9), 1.5–2.1 (m, 5), 1.66 (dq, 3, $J$ = 1.5, 6.4), 2.67 (m, 1), 2.74 (q, 1, $J$ = 6.9), 3.42 (m, 4), 5.36 (dq, 1, $J$ = 15.3, 1.5), 5.51 (s, 1), 5.66 (dq, 1, $J$ = 15.3, 6.4); $^{13}$C NMR δ 10.6, 17.8, 24.3, 26.0, 26.3, 26.5, 26.6, 26.7, 27.2, 40.9, 43.3, 45.4, 46.8, 76.8, 125.1, 132.5, 176.0. Anal. Calcd for $C_{17}H_{29}NO_2$: C, 73.07; H, 10.46; N, 5.01. Found: C, 72.90; H, 10.25; N, 4.80.

**(2′RS,3′RS)- and (2′RS,3′SR)-1-(5′-cyclohexyl-2′,3′-dimethyl-1′,5′-dioxopentyl)pyrrolidine (50a and 50s), mixture of diastereomers:** IR (CHCl$_3$) 2995, 2950, 2875, 1705, 1620, 1440, 1375, 1345 cm$^{-1}$; $^1$H NMR δ 0.92 and 0.93 (2 d's, 3, $J$ = 6.6, 6.5), 1.07 (d, 3, $J$ = 6.9), 1.26 (m, 5), 1.6–2.1 (m, 9), 2.31 (m, 3), 2.5–2.8 (2 m's, 2), 3.3–3.6 (2 m's, 4); $^{13}$C NMR δ 13.0, 13.5, 16.4, 18.4, 24.1, 25.3, 25.5, 25.59, 25.64, 25.9, 26.0, 28.0, 28.04, 28.4, 28.5, 30.8, 31.2, 41.5, 41.9, 43.3, 45.1, 45.4, 50.8, 174.2, 213.6, 213.8. Anal. Calcd for $C_{17}H_{29}NO_2$: C, 73.07; H, 10.46; N, 5.01. Found: C, 73.08; H, 10.29; N, 4.86.

**(E,2′RS,3′RS)- and (E,2′RS,3′SR)-1-(3′-hydroxy-2′-methyl-1′-oxo-3′-phenyl-4′-hexenyl)pyrrolidine (51a and 51b), mixture of diastereomers:** mp 148–50 °C; IR (CHCl$_3$) 3330 (br), 3025, 1610, 1460, 1440, 965 cm$^{-1}$; $^1$H NMR δ 0.92 and 1.28 (2 d's, 3, $J$ = 7.0), 1.64 and 1.70 (d and dd, 3, $J$ = 5.1; 1.4, 6.4), 1.65 and 1.95 (2 m's, 4), 3.00 and 3.49 (2 m's, 4), 3.2 and 3.3 (2 m's, 1), 5.74 (m, 2), 6.10 and 6.14 (s and d, 1, $J$ = 1.3), 7.28 (m, 5); $^{13}$C NMR δ 11.9, 12.2, 17.7, 24.0, 24.3, 25.7, 26.0, 45.1, 45.2, 45.5, 46.4, 46.9, 76.9, 123.8, 124.7, 125.0, 125.2, 126.3, 127.9, 128.0, 133.7, 136.8, 144.0, 175.5. Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.74; H, 8.46; N, 4.97.

**(2′RS,3′RS)- and (2′RS,3′SR)-1-(2′,3′-dimethyl-1′,5′-dioxo-5′-phenylpentyl)pyrrolidine (52a and 52s), mixture of diastereomers:** colorless oil; IR 3050, 1675, 1630, 1590, 1580, 1425, 755, 690 cm$^{-1}$; $^{13}$C NMR δ 2.8, 13.6, 16.0, 18.0, 23.8, 25.6, 31.5, 32.1, 40.9, 41.7, 41.9, 43.2, 45.2, 46.1, 127.5, 127.7, 128.0, 132.4, 136.5, 136.7, 173.8, 199.48, 199.5. Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.70; H, 8.50; N, 5.07.

**(2′RS,3′SR)-1-(2′,3′-Dimethyl-1′,5′-dioxo-5′-phenylpentyl)pyrrolidine (52s), major diastereomer:** $^1$H NMR δ 0.99 (d, 3, $J$ = 6.7), 1.13 (d, 3, $J$ = 6.7), 1.89 (m, 4), 2.58 (m, 1), 2.66 (m, 2), 3.21 (dd, 1, $J$ = 4.7, 15.4), 3.49 (m, 4), 7.53 (m, 3), 8.01 (dd, 2, $J$ = 1.2, 8.1).

**(2′RS,3′RS)-1-(2′,3′-Dimethyl-1′,5′-dioxo-5′-phenylpentyl)pyrrolidine (52a), minor diastereomer:** $^1$H NMR δ 1.03 (d, 3, $J$ = 6.7), 1.16 (d, 3, $J$ = 6.9), 1.88 (m, 4), 2.50 (m, 1), 2.69 (m, 2), 3.35 (dd, 1, $J$ = 3.7, 16.2), 3.47 (m, 4), 7.49 (m, 3), 7.95 (m, 2).

**(E,2′RS,3′RS)- and (E,2′RS,3′SR)-1-(3′-(4-bromophenyl)-3′-hydroxy-2′-methyl-1′-oxo-4′-hexenyl)pyrrolidine (53a and 53b), mixture of diastereomers:** IR (CHCl$_3$) 3350 (br), 3020, 2890, 1620, 1465, 1085, 1020, 980 cm$^{-1}$; $^1$H NMR δ 0.91 and 1.28 (2 d's, 3, $J$ = 7.0; 7.0), 1.64 and 1.70 (d and dd, 3, $J$ = 4.7;

1.5, 6.5), 1.6–2.1 (m, 4), 2.85–3.65 (m, 5), 5.5–5.9 (m, 2), 6.17 and 6.20 (s and d, 1, $J$ = 1.3), 7.39 (m, 4); $^{13}$C NMR δ [12.0, 12.1], [17.7, 17.74], [(24.0), 24.2], [(25.7), 25.9], [(44.7), 44.9], [(45.2), 45.5], [(46.5), 46.9], [76.7, (76.8)], [(120.2), 120.3], 124.3, 125.3, 126.7, 127.1, [(130.9), 131.0], 133.3, 136.2, 143.2, 146.5, [(175.0), 175.2]. Anal. Calcd for $C_{17}H_{22}BrNO_2$: C, 57.96; H, 6.30; N, 3.98; Br, 22.68. Found: C, 57.73; H, 6.35; N, 3.92; Br, 22.37.

**(2′RS,3′RS)- and (2′RS,3′SR)-1-(5′-(4-bromophenyl)-2′,3′-dimethyl-1′,5′-dioxopentyl)pyrrolidine (54a and 54s), mixture of diastereomers:** IR (CHCl$_3$) 2890, 1685, 1630, 1585, 1080, 1015 cm$^{-1}$; $^1$H NMR δ 0.98 and 1.02 (2 d's, 3, $J$ = 6.6; 6.7), 1.12 and 1.19 (2 d's, 3, $J$ = 6.7, 6.8), 1.8–2.1 (m, 4), 2.4–2.6 (m, 1), 2.6–2.7 (m, 2), 3.2 and 3.35 (2 m's, 1), 3.47 (m, 4), 7.59 (m, 2), 7.80 and 7.88 (2 m's, 2); $^{13}$C NMR δ 12.82, 14.46, 16.59, 18.53, 24.23, 26.10, 31.67, 32.82, 41.16, 42.12, 42.72, 43.73, 45.66, 46.51, 46.59, 127.94, 128.06, 129.62, 129.90, 131.74, 131.78, 135.54, 135.84, 174.21, 174.29, 199.07, 199.26. Anal. Calcd for $C_{17}H_{22}BrNO_2$: C, 57.96; H, 6.30; N, 3.98; Br, 22.68. Found: C, 57.67; H, 6.43; N, 3.61; Br, 21.40.

**(E,2′RS,3′RS)- and (E,2′RS,3′SR)-1-(3′-hydroxy-3′-(4-methoxyphenyl)-2′-methyl-1′-oxo-4′-hexenyl)pyrrolidine (55a and 55b), mixture of diastereomers:** IR (CHCl$_3$) 3360 (br), 3020, 1615, 1515, 1460, 1255, 1185, 1045, 980, 920, 840 cm$^{-1}$; $^1$H NMR δ 0.92 and 1.27 (2 d's, 3, $J$ = 7.0, 7.0), 1.63 and 1.70 (d and dd, 3, $J$ = 5.1; 1.4, 6.4), 1.6–2.1 (m, 4), 2.9–3.7 (m, 5), 3.77 and 3.80 (2 s's, 3), 5.5–5.9 (m, 2), 6.05 and 6.10 (2 s's, 1), 6.84 (m, 2), 7.39 (m, 2); $^{13}$C NMR δ 11.9, 12.3, 17.8, 24.0, 24.3, 25.7, 26.0, 45.0, 45.1, 45.3, 45.5, 46.5, 46.9, 55.2, 76.6, 76.7, 113.2, 113.3, 123.5, 124.6, 125.9, 126.4, 134.0, 136.1, 137.0, 139.3, 157.9, 158.0, 175.3, 175.6. Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 70.96; H, 8.23; N, 4.39.

**(2′RS,3′RS)- and (2′RS,3′SR)-1-(2′,3′-dimethyl-5′-(4-methoxyphenyl)-1′,5′-dioxopentyl)pyrrolidine (56a and 56s), mixture of diastereomers:** IR (CHCl$_3$) 2990, 2890, 1680, 1630, 1610, 1520, 1445, 1265, 1180 cm$^{-1}$; $^1$H NMR δ 0.98 and 1.02 (2 d's, 3, $J$ = 6.6; 6.7), 1.12 and 1.16 (2 d's, 3, $J$ = 6.8, 6.9), 1.90 (m, 4), 2.50 (m, 1), 2.61 (m, 2), 3.17 and 3.30 (2 dd's, 1, $J$ = 4.4, 14.7; 3.4, 15.7), 3.46 (m, 4), 3.87 (s, 3), 6.94 and 6.91 (2 m's, 2), 8.01 and 7.94 (2 m's, 2); $^{13}$C NMR [major (minor)] δ (13.0), 13.8, 16.1, (18.2), 24.0, 25.9, (32.0), 32.6, (40.8), (42.0), 42.3, 43.2, 45.4, 46.3, 55.1, 113.4, 129.7, (130.0), 130.1, 130.3, (163.0), 163.1, (174.1), 174.2, (198.4), 198.5. Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.34; H, 8.06; N, 4.61.

**(E,2′RS,3′RS)- or (E,2′RS,3′SR)-1-(3′-tert-butyl-3′-hydroxy-2′-methyl-1′-oxo-4′-hexenyl)pyrrolidine (57a):** IR 3400 (br), 2980, 2880, 1610 cm$^{-1}$; $^1$H NMR δ 1.03 (s, 9), 1.11 (dd, 3, $J$ = 5.6, 0.6), 1.26 (d, 3, $J$ = 7.1), 1.93 (m, 4), 2.45 (q, 1, $J$ = 7.1), 3.49 (m, 4), 5.17 (dd, 1, $J$ = 0.6, 15.8), 5.29 (s, 1), 5.79 (d, 1, $J$ = 15.8).

**(2′RS,3′RS)- and (2′RS,3′SR)-1-(1′,5′-dioxo-2′,3′,6′,6′-tetramethylheptyl)pyrrolidine (58a and 58s), mixture of diastereomers:** colorless oil; IR (CHCl$_3$) 2975, 2880, 1700, 1620, 1435, 1365, 1340, 1060 cm$^{-1}$; $^1$H NMR δ 0.84 and 0.86 (2 d's, 3, $J$ = 6.7, 6.4), 0.99 and 1.00 (2 d's, 3, $J$ = 6.9, 6.9), 1.05 (s, 9), 1.82 (dq, 4, $J$ = 6.4, 21.2), 2.2–2.7 (m, 4), 3.39 and 3.50 (2 m's, 4); $^{13}$C NMR δ 12.8, 12.9, 16.0, 18.1, 24.0, 25.8, 30.9, 30.7, 40.5, 41.5, 43.9, 45.2, 45.3, 46.2, 174.07, 174.12, 215.1. Anal. Calcd for $C_{15}H_{27}NO_2$: C, 71.10; H, 10.74; N, 5.53. Found: C, 71.10; H, 10.58; N, 5.52.

**(2′RS,3′RS)-1-(2′,3′-Dimethyl-1′,5′-dioxo-5′-(2,4,6-trimethylphenyl)pentyl)pyrrolidine (59a):** white crystalline solid; mp 82–4 °C; IR (CHCl$_3$) 2980, 2880, 1700, 1630 cm$^{-1}$; $^1$H NMR δ 1.08 (d, 3, $J$ = 6.8), 1.11 (d, 3, $J$ = 6.5), 1.81–1.99 (m, 4), 2.18 (s, 6), 2.25 (s, 3), 2.43–2.67 (m, 3), 3.07 (m, 1), 3.35–3.54 (m, 4), 6.80 (s, 2); $^{13}$C NMR δ 12.75, 18.48, 18.65, 20.64, 23.94, 25.80, 30.32, 41.53, 45.30, 46.21, 47.01, 128.05, 131.92, 137.64, 139.34, 173.85, 209.51. Anal. Calcd for $C_{20}H_{29}NO_2$: C, 76.15; H, 9.27; N, 4.44. Found: C, 75.98; H, 9.34; N, 4.36.

**(2′RS,3′RS)-1-(2′,3′-Dimethyl-1′,5′-dioxo-5′-(2,4,6-triisopropylphenyl)pentyl)pyrrolidine (60a):** white crystalline solid; mp 80.5–2.0 °C; IR (CHCl$_3$) 2980, 2880, 1700, 1640, 1610, 1570, 1465, 1430 cm$^{-1}$; $^1$H NMR δ 1.08 (d, 3, $J$ = 6.8), 1.14 (d, 3, $J$ = 6.5), 1.24 (m, 18, $J$ = 6.9), 1.85 (m, 2, $J$ = 6.5), 1.96 (m, 2, $J$ = 6.5), 2.46–2.76 (m, 5), 2.87 (sep, 1, $J$ = 6.9), 3.03 (dd, 1, $J$ = 2.1, 18.7), 3.47 (m, 4), 6.98 (s, 2); $^{13}$C NMR δ 13.28, 18.42, 23.85, 24.21, 24.38 (br), 26.04, 30.65, 30.71, 34.17, 41.73, 45.53, 46.48, 48.86, 120.81, 137.87, 143.14, 149.10, 174.13, 210.11. Anal. Calcd for

$C_{26}H_{41}NO_2$: C, 78.14; H, 10.34; N, 3.51. Found: C, 77.85; H, 10.44; N, 3.32.

**(2'RS,3'RS)-1-(1',5'-Dioxo-3'-ethyl-2',5',5'-trimethylheptyl)pyrrolidine (61a):** clear oil; IR (CHCl₃) 2990, 2890, 1710, 1625, 1585, 1445, 1070 cm⁻¹; ¹H NMR δ 0.90 (t, 3, J = 7.3), 1.01 (d, 3, J = 6.8), 1.12 (s, 9), 1.34 (m, 2), 1.86 (m, 2), 1.95 (m, 2), 2.20 (m, 1), 2.41 (dd, 1, J = 8.0, 17.0), 2.81 (m, 2), 3.47 (m, 4); ¹³C NMR δ 11.4, 12.0, 24.2, 25.0, 26.2, 26.5, 36.2, 36.5, 38.0, 44.2, 45.7, 46.3, 174.4, 215.8. Anal. Calcd for C₁₆H₂₉NO₂: C, 71.86; H, 10.93; N, 5.24. Found: C, 71.59; H, 10.69; N, 4.99.

**(2'RS,3'SR)-1-(1',5'-Dioxo-3'-ethyl-2',5',5'-trimethylheptyl)pyrrolidine (61s):** yellow oil; IR (CHCl₃) 2980, 2880, 1700, 1620, 1470, 1440, 1270 cm⁻¹; ¹H NMR δ 0.84 (t, 3, J = 7.4), 1.05 (d, 3, J = 7.0), 1.25 (m, 1), 1.34 (s, 9), 1.55 (m, 1), 1.84 (m, 4), 2.10 (m, 1), 2.68 (m, 3), 3.45 (m, 3), 3.62 (m, 1); ¹³C NMR δ 11.9, 13.4, 22.8, 24.3, 26.3, 26.5, 37.2, 37.5, 39.4, 44.4, 45.7, 46.5, 174.5, 216.2. Anal. Calcd for C₁₆H₂₉NO₂: C, 71.86; H, 10.93; N, 5.24. Found: C, 71.96; H, 10.82; N, 5.27.

**(E,2'RS,3'RS)- or (E,2'RS,3'SR)-1-(3'-tert-butyl-2',6'-dimethyl-3'-hydroxy-1'-oxo-4'-heptenyl)pyrrolidine, major 1,2 diastereomer (62a):** white crystalline solid; mp 101–2 °C; IR (CHCl₃) 3360, 2970, 2890, 1615, 1475, 1465, 1310 cm⁻¹; ¹H NMR δ 0.91 (d, 3, J = 6.7), 0.92 (s, 9), 0.95 (d, 3, J = 6.7), 1.19 (d, 3, J = 7.0), 1.88 (m, 3), 2.00 (m, 2), 2.59 (q, 1, J = 7.0), 3.47 (m, 4), 4.81 (dd, 1, J = 11.8), 5.18 (ddd, 1, J = 0.7, 10.0, 12.2), 6.09 (d, 1, J = 1.7); ¹³C NMR δ 22.6, 22.8, 25.9, 29.5, 31.2, 38.3, 46.6, 47.6, 78.1, 124.3, 139.5, 177.2. Anal. Calcd for C₁₇H₃₁NO₂: C, 72.55; H, 11.10; N, 4.98. Found: C, 72.36; H, 10.78; N, 4.77.

**Minor 1,2 diastereomer 62b:** yellow oil; IR (CHCl₃) 3360, 2970, 2890, 1675, 1475, 1465 cm⁻¹; ¹H NMR δ (discernible) 0.89 (d, 3, J = 6.6), 0.88 (d, 3, J = 6.7), 1.02 (s, 9), 1.24 (d, 3, J = 6.9), 1.90 (m, 5), 2.85 (q, 1, J = 6.8), 3.45 (m, 4); ¹³C NMR δ 13.9, 23.2, 24.3, 26.2, 27.1, 29.6, 38.2, 43.6, 45.4, 46.4, 81.6, 128.6, 138.8, 176.5; HRMS calcd 281.2356, found 281.2363.

**(2'RS,3'SR)- and (2'RS,3'RS)-1-(1',5'-dioxo-3'-isopropyl-2',6',6'-trimethylheptyl)pyrrolidine (63a and 63s), mixture of diastereomers:** clear oil; IR (CHCl₃) 2960, 2860, 1710, 1610, 1425 cm⁻¹; ¹H NMR (mixture) δ 1.23 (m, 1), 1.84 (m, 2), 1.96 (m, 2), 2.23 (m, 1), 2.42 (m, 1), 2.80 (m, 2), 3.33 (m, 1), 3.41 (m, 2), 3.59 (m, 1). Anal. Calcd for C₁₇H₃₁NO₂: C, 72.55; H, 11.10; N, 4.98. Found: C, 72.15; H, 10.89; N, 4.69.

**Major 1,4 diastereomer 63a:** ¹H NMR (discernible) δ 0.81 (d, 3, J = 6.7), 0.93 (d, 3, J = 6.7), 0.99 (d, 3, J = 6.8), 1.15 (s, 9); ¹³C NMR δ 11.7, 20.3, 20.7, 24.1, 26.1, 30.2, 34.9, 38.3, 38.5, 44.0, 45.7, 46.1, 174.2, 214.9.

**Minor 1,4 diastereomer 63s:** ¹H NMR δ 0.83 (m, 6), 1.07 (d, 3, J = 7.1), 1.16 (s, 9), 1.29 (m, 1), 1.54 (m, 1), 1.86 (m, 4), 2.23 (q, 1, J = 5.5), 2.63 (dd, 1, J = 18.9), 2.79 (m, 1), 2.88 (dd, 1, J = 5.1, 18.9), 3.43 (m, 4); ¹³C NMR δ 15.9, 19.5, 21.2, 24.3, 26.3, 26.8, 29.5, 35.2, 38.7, 41.3, 45.7, 46.6, 175.0, 216.2.

**(2'RS,3'SR)-1-(1',5'-Dioxo-3'-phenyl-2',6',6'-trimethylheptyl)pyrrolidine (64s):** white crystalline solid; mp 109–3 °C; IR (CHCl₃) 2960, 2880, 1705, 1630, 1460, 1440 cm⁻¹; ¹H NMR δ 0.97 (s, 9), 1.00 (d, 3, J = 6.9), 1.83 (m, 4), 2.92 (m, 4), 3.30 (m, 1), 3.46 (m, 3), 7.21 (m, 5); ¹³C NMR δ 16.5, 24.3, 26.1, 39.5, 42.5, 44.1, 44.3, 45.6, 46.5, 126.4, 128.2, 128.2, 143.3, 173.5, 213.8. Anal. Calcd for C₂₀H₂₉NO₂: C, 76.15; H, 9.27; N, 4.44. Found: C, 76.24; H, 9.43; N, 4.36.

**(2'RS,3'RS)-1-(1',5'-Dioxo-3'-phenyl-2',6',6'-trimethylheptyl)pyrrolidine (64a):** white crystalline solid; mp 104–5 °C; IR (CHCl₃) 2960, 2880, 1710, 1630, 1460, 1440 cm⁻¹; ¹H NMR δ 1.03 (s, 9), 1.14 (d, 3, J = 6.8), 1.70 (m, 4), 2.84 (m, 1), 2.97 (m, 2), 3.20 (m, 2), 3.32 (m, 2), 3.60 (m, 1), 7.21 (m, 5); ¹³C NMR δ 14.1, 24.1, 26.0, 26.3, 37.6, 42.5, 43.2, 44.1, 45.4, 46.3, 126.3, 127.8, 128.0, 143.3, 173.5, 213.8. Anal. Calcd for C₂₀H₂₉NO₂: C, 76.15; H, 9.27; N, 4.44. Found: C, 76.19; H, 8.99; N, 4.28.

**(E,2'RS,3'RS)- or (E,2'RS,3'SR)-1-(3'-tert-butyl-3'-hydroxy-1'-oxo-2',6',6'-trimethyl-4'-heptenyl)pyrrolidine, major diastereomer (65a):** white crystalline solid; mp 143–4 °C; ¹H NMR δ 0.89 (s, 9), 1.04 (s, 9), 1.06 (d, 3, J = 7.6), 1.93 (m, 4), 2.67 (q, 1, J = 6.9), 3.43 (m, 4), 5.13 (d, 1, J = 15.7), 5.81 (d, 1, J = 15.7), 6.31 (s, 1); ¹³C NMR δ 15.5, 24.3, 26.0, 26.8, 29.8, 32.8, 37.0, 39.3, 45.7, 46.6, 80.0, 125.6, 140.3, 177.7.

**Mixture of 1,2 diastereomers 65a and 65b:** IR (CHCl₃) 3340 (br), 2975, 2880, 1615, 1455, 990 cm⁻¹. Anal. Calcd for C₁₈H₃₃NO₂: C, 73.17; H, 11.26; N, 4.74. Found: C, 73.48; H, 10.98; N, 4.56.

**Minor diastereomer 65b:** white crystalline solid; mp 67–71 °C; ¹H NMR δ 0.96 (s, 9), 0.99 (s, 9), 1.27 (d, 3, J = 6.9), 1.94 (m, 4), 2.88 (q, 1, J = 6.9), 3.35 (m, 2), 3.46 (m, 2), 5.29 (s, 1), 5.38 (d, 1, J = 15.8), 5.61 (d, 1, J = 15.8); ¹³C NMR δ 14.0, 24.3, 27.1, 29.7, 29.8, 32.5, 37.8, 42.1, 45.2, 46.9, 78.0, 128.1, 139.3, 175.1.

**(2'RS,3'RS)-1-(3'-tert-Butyl-1',5'-dioxo-2',6',6'-trimethylheptyl)pyrrolidine (66a):** clear liquid; IR (neat) 2920, 2860, 1710, 1640, 1430, 1370, 1230, 1070 cm⁻¹; ¹H NMR δ 0.91 (s, 9), 1.05 (d, 3, J = 6.7), 1.16 (s, 9), 1.85 (m, 2), 1.94 (m, 1), 2.03 (m, 1), 2.42 (m, 2), 2.90 (m, 2), 3.26 (m, 1), 3.34 (m, 1), 3.47 (m, 1), 3.61 (m, 1); ¹³C NMR δ 12.8, 24.0, 26.1, 27.0, 28.6, 32.6, 34.1, 37.2, 39.8, 43.8, 45.7, 46.0, 174.3, 214.3. Anal. Calcd for C₁₈H₃₃NO₂: C, 73.17; H, 11.26; N, 4.74. Found: C, 73.04; H, 11.24; N, 4.74.

**(2'RS,3'RS)-1-(1',5'-Dioxo-2',3',6',6'-tetramethylheptyl)piperidine (67a):** amorphous solid; mp 49–55 °C; IR 980, 2950, 2880, 1710, 1640 cm⁻¹; ¹H NMR δ 0.92 (d, 3, J = 6.5), 1.06 (d, 3, J = 6.8), 1.12 (s, 9), 1.52 (m, 2), 1.66 (m, 4), 2.42 (m, 2), 2.57 (m, 1), 2.81 (m, 1), 3.47 (m, 4); ¹³C NMR δ 13.09, 18.50, 24.62, 25.66, 26.28, 26.68, 30.89, 38.71, 39.17, 42.67, 44.20, 46.66, 173.81, 215.28. Anal. Calcd for C₁₆H₂₉NO₂: C, 71.86; H, 10.75; N, 5.19. Found: C, 71.93; H, 10.75; N, 5.19.

**(2'RS,3'RS)-1-(1',5'-Dioxo-2',3',6',6'-tetramethylheptyl)hexamethylenimine (68a):** amorphous solid; mp 65–8 °C; IR 980, 2940, 2880, 1710, 1630 cm⁻¹; ¹H NMR δ 0.92 (d, 3, J = 6.4), 1.07 (d, 3, J = 6.8), 1.13 (s, 9), 1.57 (m, 4), 1.71 (m, 4), 2.44 (m, 2), 2.65 (m, 2), 3.47 (m, 4); ¹³C NMR δ 14.04, 18.56, 26.31, 26.64, 26.69, 27.61, 29.40, 31.37, 38.97, 39.51, 44.21, 46.05, 47.90, 175.43, 215.34. Anal. Calcd for C₁₇H₃₁NO₂: C, 72.55; H, 11.10; N, 4.98. Found: C, 72.70; H, 11.21; N, 4.96.

**(E,1'RS,3RS)- and (E,1'RS,3SR)-3-(1'-ethyl-1'-hydroxy-2'-butenyl)-1-methyl-2-pyrrolidinone (76a and 76b), mixture of diastereomers:** colorless oil; IR 3410 (br), 3045, 2970, 2880, 1665, 1505, 1405, 1310, 970, 915 cm⁻¹; ¹H NMR δ 0.88 and 0.91 (2 t's, 3, J = 7.3), 1.55 (q, 2, J = 7.3), 1.70 and 1.71 (2 dd's, 3, J = 1.6, 6.4), 1.81 (m, 1), 2.10 (m, 1), 2.65 (t, 1, J = 7.6), 2.82 and 2.85 (2 s's, 3), 3.29 (m, 2), 4,53 and 5.26 (2 s's, 1), 5.42 (dd, 1, J = 1.6, 15.4), 5.75 (dq, 1, J = 6.5, 15.4); ¹³C NMR δ 6.8, 7.1, 17.4, 17.5, 19.8, 20.2, 28.0, 29.0, 29.1, 30.9, 47.1, 47.2, 48.4, 50.5, 65.3, 75.0, 124.6, 125.8, 131.5, 133.1, 175.4, 175.9. Anal. Calcd for C₁₁H₁₉NO₂: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.79; H, 9.83; N, 6.94.

**(E,1'RS,3RS)- or (E,1'RS,3SR)-3-(1'-hydroxy-1'-isopropyl-2'-butenyl)-1-methyl-2-pyrrolidinone (77a), major diastereomer:** colorless oil; IR (CHCl₃) 3405 (br), 2970, 2880, 1665, 1500, 1400, 1305, 1005, 995, 970, 925 cm⁻¹; ¹H NMR δ 0.89 (d, 3, J = 6.9), 0.98 (d, 3, J = 6.7), 1.70 (dd, 3, J = 1.5, 6.5), 1.77 (m, 2), 2.07 (m, 1), 2.77 (t, 1, J = 9.3), 2.80 (s, 3), 3.28 (m, 2), 5.13 (d, 1, J = 1.2), 5.37 (dd, 1, J = 1.5, 15.3), 5.77 (dq, 1, J = 6.5, 15.3); ¹³C NMR δ 15.8, 16.2, 17.4, 19.2, 28.9, 33.0, 47.0, 47.2, 76.7, 125.7, 131.2, 176.3. Anal. Calcd for C₁₂H₂₁NO₂: C, 68.21; H, 10.02; N, 6.63. Found: C, 68.03; H, 9.89; N, 6.51.

**(3RS,1'RS)-1-Methyl-3-(1',4'-dimethyl-3'-oxopentyl)-2-pyrrolidinone (78a), major diastereomer:** colorless oil; IR (CHCl₃) 2970, 2870, 1705, 1674, 1500, 1460, 1435, 1405, 1380, 1300, 1100 cm⁻¹; ¹H NMR δ 0.92 (d, 3, J = 6.5), 1.09 (d, 6, J = 6.9), 1.81 (m, 1), 2.12 (m, 1), 2.48 (m, 3), 2.63 (sep, 1, J = 6.9), 2.83 (s, 3), 2.83 (m, 1), 3.28 (m, 2); ¹³C NMR δ 15.6, 17.6, 17.9, 21.4, 29.1, 40.5, 43.9, 45.0, 47.4, 174.9, 213.9 Anal. Calcd for C₁₂H₂₁NO₂: C, 68.21; H, 10.02; N, 6.63. Found: C, 68.44; H, 9.77; N, 6.59.

**(Z,3RS,1'RS)- or (Z,3RS,1'SR)-3-(1'-hydroxy-1'-isopropyl-2'-butenyl)-1-methyl-2-pyrrolidinone (79a), major diastereomer:** IR (CHCl₃) 3420 (br), 3000, 1665, 1505, 1400, 1310, 1000 cm⁻¹; ¹H NMR δ 0.98 (dd, 6, J = 2.6, 6.8), 1.72 (sep, 1, J = 6.8), 1.86 (m, 1), 1.89 (dd, 3, J = 1.7, 7.2), 2.13 (m, 1), 2.73 (t, 1, J = 9.3), 2.83 (s, 3), 3.30 (m, 2), 5.05 (s, 1), 5.15 (dq, 1, J = 12.2, 1.8), 5.60 (dq, 1, J = 12.2, 7.2); ¹³C NMR δ 14.2, 16.2, 16.7, 20.1, 29.5, 34.4, 47.6, 48.1, 30.1, 127.9, 129.4, 177.0. Anal. Calcd for C₁₂H₂₁NO₂: C, 68.21; H, 10.02; N, 6.63. Found: C, 68.50; H, 10.07; N, 6.49.

**Minor diastereomer 79b:** IR (CHCl₃) 3380 (br), 3000, 1670, 1500, 1405, 1305 cm⁻¹; ¹H NMR δ 0.92 (d, 6, J = 6.8), 1.92 (dd, 3, J = 1.7, 7.2), 2.09 (m, 3), 2.82 (t, 1, J = 9.4), 2.83 (s, 3), 3.28 (m, 2), 3.46 (s, 1), 5.20 (dq, 1, J = 12.1, 1.7), 5.59 (dq, 1, J = 12.1, 7.2); ¹³C NMR δ 14.3, 16.2, 17.6, 20.6, 29.6, 34.4, 47.2, 49.1, 79.9, 126.7, 132.7, 175.3. Anal. Calcd for C₁₂H₂₁NO₂: C, 68.21; H, 10.02; N, 6.63. Found: C, 68.46; H, 9.75; N, 6.50.

**(E,3RS,1'RS)- or (E,3RS,1'SR)-3-(1'-cyclohexyl-1'-hydroxy-2'-butenyl)-1-methyl-2-pyrrolidinone (80a):** IR (CHCl₃) 3410 (br), 3010, 2940, 2860, 1670, 1505, 1455, 1405, 1310, 975 cm⁻¹; ¹H NMR δ 1.0–1.4 (m, 5), 1.4–1.9 (m, 7), 1.62 (dd, 3, J = 1.6, 6.5), 2.73 (m, 1), 2.73 (s, 3), 3.21 (m, 2), 5.03 (s, 1), 5.28 (dq, 1, J = 15.3, 1.6), 5.68 (dq, 1, J = 15.3, 6.5); ¹³C NMR δ 17.9, 19.8, 26.2, 26.27, 26.32, 26.8, 29.4, 43.5, 46.9, 47.7, 77.3, 126.4, 131.1, 176.9 Anal. Calcd for C₁₅H₂₅NO₂: C, 71.66; H, 10.02; N, 5.59. Found: C, 71.40; H, 9.93; N, 5.51.

**(3RS,1'RS)- and (3RS,1'SR)-3-(3'-cyclohexyl-1'-methyl-3'-oxopropyl)-1-methyl-2-pyrrolidinone, major diastereomer (81a) and minor diastereomer (81s), mixture of diastereomers:** IR (CHCl₃) 3025, 2955, 2880, 1710 (shoulder), 1685, 1510, 1460, 1415 cm⁻¹; ¹H NMR δ 0.91 (d, 3, J = 6.4), 1.27 (m, 5), 1.75 (m, 6), 2.15 (m, 1), 2.43 (m, 4), 2.82 (s, 3), 2.82 (m, 1), 3.28 (m, 2); ¹³C NMR major (minor) δ 15.7, (16.6), (20.9), 21.8, 25.4, 25.5, 25.7, 28.0, (28.2), 28.3, 29.3, (29.4), 29.7, 44.5, 45.1, (45.2), 45.5, (47.3), 47.6, (50.5), 50.8, 175.2, (175.4), (213.2), 213.6. Anal. Calcd for C₁₅H₂₅NO₂: C, 71.66; H, 10.02; N, 5.59. Found: C, 71.65; N, 9.95; N, 5.42.

**(E,3RS,1'SR)- or (E,3RS,1'SR)-3-(1'-hydroxy-1'-phenyl-2'-butenyl)-1-methyl-2-pyrrolidinone (82a), major diastereomer:** mp 108–10 °C; IR (CHCl₃) 3450 (br), 1500, 1445, 1400, 1055, 970, 710 cm⁻¹; ¹H NMR δ 1.77 (dd, 3, J = 2.2, 2.6), 1.92 (dt, 2, J = 6.8, 7.1), 2.85 (s, 3), 2.92 (t, 1, J = 6.8), 3.24 (t, 2, J = 7.1), 5.78 (s, 1), 5.96 (d, 1, J = 2.6), 5.97 (s, 1), 7.32 (m, 3), 7.51 (dd, 2, J = 1.5, 8.6); ¹³C NMR δ 18.1, 21.1, 29.6, 47.5, 51.5, 126.3, 126.4, 127.2, 127.9, 128.1, 130.7, 144.4, 175.7; MS m/z 245 (0.42) parent, 99 (base). Anal. Calcd for C₁₅H₁₉NO₂: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.60; H, 7.89; N, 5.75.

**Minor diastereomer 82b:** mp 93–4 °C; IR (CHCl₃) 3400 (br), 3060, 1600, 1580, 1500, 1450, 1405, 1005, 755, 700 cm⁻¹; ¹H NMR δ 0.78 (dd, 3, J = 1.6, 6.5), 1.8–2.15 (m, 2), 2.70 (m, 1), 2.70 (s, 3), 3.05 (m, 2), 5.34 (s, 1), 5.77 (dq, 1, J = 6.4, 15.5), 6.10 (dd, 1, J = 1.5, 15.5), 7.31 (m, 5); ¹³C NMR δ 18.0, 21.2, 29.5, 33.1, 47.4, 50.4, 76.8, 126.0, 126.5, 126.9, 127.8, 134.9, 142.1. Anal. Calcd for C₁₅H₁₉NO₂: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.33; H, 8.00; N, 5.60.

**(3RS,1'RS)-1-Methyl-3-(1'-methyl-3'-oxo-3'-phenylpropyl)-2-pyrrolidine (83a):** yellow oil; IR (CHCl₃) 1670, 1595, 1575, 1495, 1400, 905 cm⁻¹; ¹H NMR δ 0.99 (d, 3, J = 6.7), 1.80–1.89 (m, 1), 2.14–2.18 (m, 1), 2.57–2.65 (m, 2), 2.82–2.89 (m, 1), 2.86 (s, 3), 3.28–3.44 (m, 3), 7.42–7.58 (m, 3), 8.05 (br d, 2, J = 6.9); ¹³C NMR δ 15.9, 21.5, 29.4, 30.5, 42.2, 45.7, 47.7, 128.2, 128.4, 132.8, 136.9, 175.3, 200.1. Anal. Calcd for C₁₅H₁₉NO₂: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.16; H, 7.88; N, 5.61.

**(E,3RS,1'RS)- or (E,3RS,1'SR)-3-(1'-(4-bromophenyl)-1'-hydroxy-2'-butenyl)-1-methyl-2-pyrrolidinone (84a), major diastereomer:** mp 127–9 °C; IR (CHCl₃) 3390 (br), 3000, 1670, 1400, 1300, 1005 cm⁻¹; ¹H NMR δ 1.77 (dd, 3, J = 2.4, 4.8), 1.90 (m, 2), 2.85 (s, 3), 2.85 (t, 1, J = 7.4), 3.25 (t, 2, J = 7.4), 5.83 (s, 1), 5.94 (m, 1), 7.38 (d, 2, J = 8.8), 7.46 (d, 2, J = 8.8); ¹³C NMR δ 18.0, 20.9, 29.5, 47.3, 51.3, 76.3, 121.1, 128.0, 128.2, 130.2, 131.0, 143.5, 175.2. Anal. Calcd for C₁₅H₁₈BrNO₂: C, 55.56; H, 5.60; N, 4.32; Br, 24.65. Found: C, 55.82; H, 5.60; N, 4.34; Br, 24.38.

**Minor diastereomer 84b:** mp 121–2 °C; IR (CHCl₃) 3400 (br), 3010, 1670, 1405, 1010 cm⁻¹; ¹H NMR δ 1.77 (dd, 3, J = 1.6, 6.5), 1.80 (m, 1), 2.03 (m, 1), 2.73 (s, 3), 2.82 (m, 1), 2.99 (t, 1, J = 8.6), 3.13 (m, 1), 5.36 (s, 1), 5.76 (dq, 1, J = 15.5, 6.5), 6.04 (dq, 1, J = 15.5, 1.6), 7.29 (d, 2, J = 8.7), 7.43 (d, 2, J = 8.7); ¹³C NMR δ 18.0, 21.1, 29.6, 47.3, 50.2, 76.6, 121.1, 126.6, 128.5, 130.9, 134.4, 142.6, 174.8. Anal. Calcd for C₁₅H₁₈BrNO₂: C, 55.57; H, 5.60; N, 4.32; Br, 24.65. Found: C, 55.84; H, 5.65; N, 4.25; Br, 24.5.

**(3RS,1'RS)-3-(3'-(4-Bromophenyl)-1'-methyl-3'-oxopropyl)-1-methyl-2-pyrrolidinone (85a), major diastereomer:** IR (CHCl₃) 2975, 1680, 1580, 1400, 1045 cm⁻¹; ¹H NMR δ 0.98 (d, 3, J = 6.7), 1.83 (m, 1), 2.17 (m, 1), 2.79 (t, 1, J = 7.2), 2.86 (s, 3), 3.2–3.5 (m, 3), 7.60 (d, 2, J = 8.6), 7.92 (d, 2, J = 8.6); ¹³C NMR δ 15.9, 21.5, 29.5, 30.6, 42.3, 45.6, 47.7, 120.1, 130.0, 131.8, 135.7, 175.3, 199.2. Anal. Calcd for C₁₅H₁₈BrNO₂: C, 55.57; H, 5.60; N, 4.32; Br, 24.65. Found: C, 55.41; H, 5.72; N, 4.25; Br, 24.58.

**(E,3RS,1'RS)- or (E,3RS,1'SR)-3-(1'-hydroxy-1'-(4-methoxyphenyl)-2'-butenyl)-1-methyl-2-pyrrolidinone (86a), major diastereomer:** IR (CHCl₃) 3400 (br), 3025, 1675, 1620, 1520, 1410, 1315, 1260, 1190, 1045, 845 cm⁻¹; ¹H NMR δ 1.77 (dd, 3, J = 1.2, 3.6), 1.91 (m, 2), 2.84 (s, 3), 2.92 (m, 1), 3.24 (t, 2, J

= 6.4), 3.80 (s, 3), 5.68 (s, 1), 5.94 (d, 1, J = 1.2), 5.95 (q, 1, J = 3.6), 6.86 (d, 2, J = 8.9), 7.42 (d, 2, J = 8.9); ¹³C NMR δ 18.0, 20.9, 29.5, 47.4, 51.5, 55.1, 113.3, 127.5, 127.6, 130.7, 136.5, 158.5, 175.6.

**Minor diastereomer 86b:** IR (CHCl₃) 3350 (br), 3020, 2890, 1620, 1465, 1085, 1020, 980 cm⁻¹; ¹H NMR δ 1.77 (dd, 3, J = 1.4, 6.5), 1.85 (m, 1), 2.04 (m, 1), 2.70 (s, 3), 2.72 (m, 1), 2.97 (m, 1), 3.10 (m, 1), 3.79 (s, 3), 5.44 (s, 1), 5.77 (dq, 1, J = 15.5, 6.5), 6.04 (dq, 1, J = 15.5, 1.3), 6.84 (d, 2, J = 8.9), 7.32 (d, 2, J = 8.9); ¹³C NMR δ 18.0, 21.1, 29.5, 47.4, 50.4, 55.1, 76.6, 113.0, 125.8, 127.7, 134.9, 135.5, 158.4, 175.2.

**Mixture of Diastereomers 86a and 86b.** Anal. Calcd for C₁₆H₂₁NO₃: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.71; H, 7.71; N, 4.82.

**(3RS,1'RS)-3-(3'-(4-Methoxyphenyl)-1'-methyl-3'-oxopropyl)-1-methyl-2-pyrrolidinone (87a), major diastereomer:** IR (CHCl₃) 3015, 1680, 1610, 1580, 1265, 1180, 1040, 835 cm⁻¹; ¹H NMR δ 0.98 (d, 3, J = 6.6), 1.85 (m, 1), 2.16 (m, 1), 2.5–2.8 (m, 3), 2.86 (s, 3), 3.31 (m, 3), 3.86 (s, 3), 6.94 (d, 2, J = 9.0), 8.05 (d, 2, J = 9.0); ¹³C NMR δ 15.9, 21.2, 29.3, 30.7, 41.7, 45.7, 47.5, 55.2, 113.4, 129.8, 130.5, 163.1, 175.2, 198.6. Anal. Calcd for C₁₆H₂₁NO₃: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.43; H, 7.81; N, 4.82.

**(E,3RS,1'RS)- or (E,3RS,1'SR)-3-(1'-tert-butyl-1'-hydroxy-2'-butenyl)-1-methyl-2-pyrrolidinone (88a), single diastereomer:** mp 67.5–9.5 °C; IR (CHCl₃) 3350 (br), 2960, 2880, 1665, 1500, 1405, 1305, 1260, 1015, 975 cm⁻¹; ¹H NMR δ 0.95 (s, 9), 1.72 (dd, 3, J = 1.3, 6.4), 2.06 (m, 1), 2.19 (m, 1), 2.81 (s, 3), 2.81 (t, 1, J = 9.7), 3.25 (m, 2), 5.66 (dd, 1, J = 1.2, 15.2), 5.88 (dq, 1, J = 6.4, 15.2), 6.25 (s, 1); ¹³C NMR δ 18.1, 22.8, 25.8, 29.6, 38.3, 46.6, 47.5, 78.3, 127.0, 128.6, 177.3. Anal. Calcd for C₁₃H₂₃NO₂: C, 69.29; H, 10.29; N, 6.22. Found: C, 69.18; H, 10.16; N, 6.16.

**(3RS,1'RS)-1-Methyl-3-(3'-oxo-1',4',4'-trimethylpentyl)-2-pyrrolidinone (89a):** mp 68–70 °C; IR (CHCl₃) 2970, 2880, 1675, 1500, 1400, 1365, 1300, 1060 cm⁻¹; ¹H NMR δ 0.91 (d, 3, J = 6.7), 1.14 (s, 9), 1.79 (m, 1), 2.16 (m, 1), 2.44 (m, 2), 2.57 (dd, 1, J = 7.3, 17.6), 2.82 (s, 3), 2.93 (dd, 1, J = 6.0, 17.6), 3.30 (m, 2); ¹³C NMR δ 15.1, 21.8, 25.7, 28.9, 29.4, 40.1, 43.6, 44.6, 47.2, 174.8, 214.6. Anal. Calcd for C₁₃H₂₃NO₂: C, 69.29; H, 10.29; N, 6.22. Found: C, 69.40; H, 10.27; N, 6.19.

**(3RS,1'SR)-1-Methyl-3-(3'-oxo-1',4',4'-trimethylpentyl)-2-pyrrolidinone (89s):** colorless oil; IR (CHCl₃) 2970, 2875, 1705, 1675, 1600, 1500, 1405, 1300, 1130, 1090 cm⁻¹; ¹H NMR δ 0.88 (d, 3, J = 6.0), 1.14 (s, 9), 1.78 (m, 1), 2.05 (m, 1), 2.45 (m, 3), 2.82 (s, 3), 2.82 (m, 1), 3.27 (m, 2); ¹³C NMR δ 16.9, 21.4, 26.26, 26.33, 29.5, 29.6, 40.9, 45.5, 47.4, 175.7, 214.9. Anal. Calcd for C₁₃H₂₃NO₂: C, 69.29; H, 10.29; H, 6.22. Found: C, 69.02; H, 10.04; N, 5.89.

**(3RS,1'RS)-1-Methyl-3-(1'-methyl-3'-oxo-3'-(2,4,6-trimethylphenyl)propyl)-2-pyrrolidinone (90a):** 99:1 (anti/syn); white crystalline solid; mp 90–2 °C; IR 2940, 1680 (br) cm⁻¹; ¹H NMR δ 1.05 (d, 3), 1.82 (m, 2), 2.20 (s, 6), 2.26 (s, 3), 2.57–2.78 (m, 3), 2.81 (s, 3), 3.09 (dd, 1, J = 4.8, 19.0), 3.28 (m, 2), 6.80 (s, 2); ¹³C NMR δ 15.99, 18.96, 20.98, 22.05, 29.31, 29.48, 45.20, 47.68, 48.60, 128.29, 132.37, 138.00, 139.59, 175.12, 209.85. Anal. Calcd for C₁₈H₂₅NO₂: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.37; H, 8.81; N, 4.84.

**(3RS,1'SR)-1-Methyl-3-(1'-methyl-3'-oxo-3'-(2,4,6-trimethylphenyl)propyl)-2-pyrrolidinone (90s),** 73:27 (syn/anti) mixture of isomers as a clear oil. **Discernible syn diastereomer 90s:** ¹H NMR δ 1.01 (d, 3), 1.79 (m, 1), 2.13 (m, 1), 2.20 (s, 6), 2.26 (s, 3), 2.48–2.78 (m, 3), 2.83 (s, 3), 3.12 (m, 1), 3.25–3.30 (m, 2), 6.81 (s, 2); ¹³C NMR δ 16.68, 19.00, 20.94, 21.19, 29.06, 29.59, 45.29, 47.35, 49.14, 128.35, 132.32, 138.04, 139.51, 175.45, 209.42.

**(3RS,1'RS)-1-Methyl-3-(1'-methyl-3'-oxo-3'-(2,4,6-triisopropylphenyl)propyl)-2-pyrrolidinone (91a):** white crystalline solid; mp 134–5 °C (after recrystallization); IR (CHCl₃) 2980, 2880, 1680 cm⁻¹; ¹H NMR δ 1.07 (d, 3), 1.23 (d, 6, J = 6.6), 1.24 (d, 12, J = 6.9), 1.78 (m, 1), 2.16 (m, 1), 2.68 (m, 5), 2.80 (s, 3), 2.84 (m, 1), 3.28 (m, 1), 3.28 (m, 2), 6.98 (s, 2); ¹³C NMR δ 16.09, 21.81, 23.88, 23.99 (br), 29.15, 29.37, 30.64, 34.19, 45.42, 47.57, 50.09, 120.78, 132.84, 143.24, 149.09, 174.96, 209.83. Anal. Calcd for C₂₄H₃₇NO₂: C, 77.58; H, 10.04; N, 3.77. Found: C, 77.72; H, 10.19; N, 3.77.

**(E,3RS,1'RS)- and (E,3RS,1'SR)-3-(1'-tert-Butyl-1'-hydroxy-2'-pentenyl)-1-methyl-2-pyrrolidinone, Major Diastereomer (92a) and Minor Diastereomer (92b). Mixture of**

diastereomers 92a and 92b: white crystalline solid; mp 49–56 °C; IR (CHCl₃) 3360 (br), 2980, 1670, 1410 cm⁻¹. Anal. Calcd for C₁₄H₂₅NO₂: C, 70.25; H, 10.53; N, 5.85. Found: C, 70.12; H, 10.54; N, 5.85.

**Major 1,2 diastereomer 92a:** ¹H NMR δ 0.96 (s, 9), 0.98 (m, 3), 2.07 (m, 4), 2.49 (m, 1), 2.81 (s, 3), 3.25 (m, 2), 5.64 (d, 1, *J* = 15.2), 5.97 (dt, 1, *J* = 15.2, 6.4), 6.26 (s, 1); ¹³C NMR δ 14.0, 22.6, 25.5, 25.7, 29.4, 38.2, 46.5, 47.4, 78.1, 126.3, 133.9, 177.1.

**Minor 1,2 diastereomer 92b:** ¹H NMR (discernible) δ 0.98 (s, 9), 1.69 (m, 1), 2.83 (s, 3), 5.49 (m, 2), 6.21 (s, 1); ¹³C NMR (discernible) δ 14.5, 23.1, 29.6, 39.1, 46.0, 47.2, 81.3, 125.4, 136.1, 177.5.

**(3*RS*,1′*RS*)-3-(4′,4′-Dimethyl-1′-ethyl-3′-oxopentyl)-1-methyl-2-pyrrolidinone (93a):** white crystalline solid; mp 65–6 °C; IR (CHCl₃) 2980, 2890, 1680, 1485, 1410, 1070 cm⁻¹; ¹H NMR δ 0.89 (t, 3, *J* = 7.4), 1.14 (s, 9), 1.33 (m, 2), 1.77 (m, 1), 2.11 (m, 1), 2.26 (m, 1), 2.42 (dd, 1, *J* = 6.4, 17.5), 2.55 (m, 1), 2.82 (s, 3), 2.91 (dd, 1, *J* = 6.7, 17.5), 3.27 (m, 2); ¹³C NMR δ 12.1, 21.7, 22.9, 26.4, 29.5, 36.2, 37.8, 43.1, 44.4, 47.7, 175.8, 215.7. Anal. Calcd for C₁₄H₂₅NO₂: C, 70.25; H, 10.53; N, 5.85. Found: C, 70.11; H, 10.48; N, 5.93.

**(*E*,3*RS*,1′*SR*)- or (*E*,3*RS*,1′*RS*)-3-(1′-*tert*-butyl-1′-hydroxy-4′-methyl-2′-pentenyl)-1-methyl-2-pyrrolidinone, major 1,2 diastereomer (94a):** white crystalline solid; mp 52.5–3.5 °C; IR (CHCl₃) 3370 (br), 2970, 2890, 1670, 1470, 1405 cm⁻¹; ¹H NMR δ 0.92 (d, 3, *J* = 6.3), 0.96 (s, 9), 0.98 (d, 3, *J* = 6.3), 2.09 (m, 1), 2.22 (m, 1), 2.30 (m, 1), 2.80 (s, 3), 2.81 (m, 1), 3.34 (m, 2), 5.65 (d, 1, *J* = 15.7), 5.84 (dd, 1, *J* = 6.8, 15.3); ¹³C NMR δ 22.6, 22.8, 25.9, 29.5, 31.2, 38.3, 46.6, 47.6, 78.1, 124.3, 139.5, 177.2. Anal. Calcd for C₁₅H₂₇NO₂: C, 71.10; H, 10.74; N, 5.53. Found: C, 70.98; H, 10.56; N, 5.35.

**Minor 1,2 diastereomer 94b:** yellow oil; IR (CHCl₃) 3370 (br), 2970, 2870, 1670, 1470, 1405 cm⁻¹; ¹H NMR δ 0.98 (d, 3, *J* = 1.6), 0.99 (s, 9), 1.02 (d, 3, *J* = 1.3), 2.12 (m, 1), 2.25 (m, 1), 2.33 (m, 1), 2.79 (m, 1), 2.82 (s, 3), 3.20 (ddd, 1, *J* = 7.0, 7.7, 9.2), 3.30 (ddd, 1, *J* = 4.6, 4.6, 13.2), 5.64 (dd, 1, *J* = 5.7, 15.6), 5.69 (s, 1), 5.71 (d, 1, *J* = 15.6); ¹³C NMR δ 22.2, 22.7, 26.6, 30.0, 31.0, 39.1, 47.6, 49.1, 78.7, 129.2, 135.7, 175.5. Anal. Calcd for C₁₅H₂₇NO₂: C, 71.10; H, 10.74; N, 5.53. Found: C, 71.02; H, 10.53; N, 5.29.

**(3*RS*,1′*RS*)- and (3*RS*,1′*SR*)-3-(4′,4′-dimethyl-1′-isopropyl-3′-oxopentyl)-1-methyl-2-pyrrolidinone (95s and 95a):** mixture, clear oil; IR (CHCl₃) 2970, 2880, 1690, 1470, 1410, 1370, 1305, 1280, 1070 cm⁻¹. Anal. Calcd for C₁₅H₂₇NO₂: C, 71.10; H, 10.74; N, 5.53. Found: C, 71.10; H, 10.69; N, 5.41.

**Major anti diastereomer 95a:** ¹H NMR δ 0.87 (d, 3, *J* = 6.8), 0.88 (d, 3, *J* = 6.9), 1.15 (s, 9), 1.81 (m, 2), 2.10 (m, 1), 2.49 (m, 4), 2.83 (s, 3), 3.30 (m, 2); ¹³C NMR δ 19.6, 20.1, 21.4, 26.2, 29.0, 29.3, 34.8, 38.2, 42.2, 44.0, 47.2, 175.7, 214.0.

**Minor syn diastereomer 95s (discernible from mixture):** ¹H NMR δ 1.16 (s, 9), 2.76 (s, 3); ¹³C NMR δ 17.8, 20.5, 24.3, 26.6, 29.1, 29.3, 34.5, 38.7, 42.5, 43.6, 46.9, 175.7, 214.9.

**(*E*,3*RS*,1′*RS*)- or (*E*,3*RS*,1′*SR*)-3-(1′-*tert*-butyl-1′-hydroxy-3′-phenyl-2′-propenyl)-1-methyl-2-pyrrolidinone (96a):** white crystalline solid; mp 101–4 °C; IR (CHCl₃) 3370 (br), 2960, 2870, 1670, 1460, 1400, 1360, 1210, 1010, 980 cm⁻¹; ¹H NMR δ 1.03 (s, 9), 2.18 (m, 1), 2.28 (m, 1), 2.76 (s, 3), 2.92 (m, 1), 3.25 (dd, 2, *J* = 4.8, 9.1), 6.48 (d, 1, *J* = 15.7), 6.56 (s, 1), 6.85 (d, 1, *J* = 15.7), 7.37 (m, 5); ¹³C NMR δ 23.0, 26.0, 29.7, 38.9, 46.6, 47.5, 78.9, 126.6, 127.1, 128.3, 128.4, 131.3, 137.5, 177.0. Anal. Calcd for C₁₈H₂₅NO₂: C, 75.23; H, 8.77; N, 4.87. Found: C, 75.25; H, 8.78; N, 4.83.

**(3*RS*,1′*RS*)-3-(4′,4′-Dimethyl-3′-oxo-1′-phenylpentyl)-1-methyl-2-pyrrolidinones (97a):** white crystalline solid; mp 88–9.5 °C; IR (CHCl₃) 2960, 1660, 1455, 1401, 1363, 1310, 1092, 1067 cm⁻¹; ¹H NMR δ 1.12 (s, 9), 1.75 (m, 1), 2.17 (m, 1), 2.36 (m, 1), 2.65 (s, 3), 2.69 (m, 1), 2.96 (m, 1), 3.03 (dd, 1 *J* = 6.1, 17.9), 3.47 (m, 1), 3.67 (dd, 1, *J* = 7.8, 17.9), 7.24 (m, 5); ¹³C NMR δ 23.2, 26.2, 29.3, 39.8, 42.6, 44.1, 44.5, 47.5, 126.8, 128.1, 128.7, 141.2, 175.3, 214.8. Anal. Calcd for C₁₈H₂₅NO₂: C, 75.23; H, 8.77; N, 4.87. Found: C, 75.04; H, 8.68; N, 4.65.

**(3*RS*,1′*SR*)-3-(4′,4′-Dimethyl-3′-oxo-1′-phenylpentyl)-1-methyl-2-pyrrolidinones (97s):** white crystalline solid; mp 75–6 °C; IR (CHCl₃) 2970, 2940, 1701, 1575, 1500, 1460, 1410, 1310 cm⁻¹; ¹H NMR δ 0.92 (s, 9), 1.53 (m, 1), 1.77 (m, 1), 2.57 (m, 1), 2.70 (s, 3), 3.01 (m, 3), 3.46 (m, 2), 7.15 (m, 5); ¹³C NMR δ 23.6, 26.0, 29.5, 40.9, 41.7, 43.8, 45.3, 47.0, 126.4, 128.0, 128.1, 142.8, 175.3,

213.9. Anal. Calcd for C₁₈H₂₅NO₂: C, 75.23; H, 8.87; N, 4.87. Found: C, 75.12; H, 8.72; N, 4.66.

**(*E*,3*RS*,1′*RS*)- or (*E*,3*RS*,1′*SR*)-3-(1′-*tert*-butyl-4′,4′-dimethyl-1′-hydroxy-2′-pentenyl)-1-methyl-2-pyrrolidinone (98a):** white crystalline solid; mp 97–7.5 °C; IR (CHCl₃) 3370 (br), 2960, 2870, 1660, 1460, 1400, 1360, 1310, 1260, 1110, 1010, 980 cm⁻¹; ¹H NMR δ 0.96 (s, 9), 0.99 (s, 9), 2.11 (m, 1), 2.20 (m, 1), 2.79 (s, 3), 2.82 (m, 1), 3.25 (dd, 2, *J* = 5.5, 8.7), 5.56 (d, 1, *J* = 15.6), 5.90 (d, 1, *J* = 15.6), 6.20 (s, 1); ¹³C NMR δ 23.3, 26.8, 30.3, 30.6, 33.7, 39.2, 47.4, 48.5, 78.9, 122.8, 143.9, 178.0. Anal. Calcd for C₁₆H₂₉NO₂: C, 71.84; H, 10.93; N, 5.24. Found: C, 71.77; H, 10.55; N, 5.00.

**General Procedure E for the Addition of the Lithium Enethiolates of Thioamides 10 and 12 to α,β-Unsaturated Ketones.** An oven-dried Schlenk tube equipped with a magnetic stirring bar, rubber septum, and N₂ inlet was flushed with N₂ and charged with thioamide 10 or 12. After cooling to –30 °C (dry ice/nitromethane), *n*-butyllithium in hexanes was added and the mixture was stirred for a 15-min period. Thiolactam 10 formed a yellow/white precipitate while thioamide 12 resulted in a clear solution. The rubber septum was replaced by a ground glass stopper, the mixture was warmed to room temperature, and the hexanes were removed under reduced pressure. The residue was dissolved in THF and the mixture was cooled to –78 °C in a dry ice/acetone bath. The enone in THF was added by syringe. The reactions were followed by TLC (15:1 hexanes/ether, UV visualization) for the disappearance of the starting enone. When the reaction was complete by TLC, it was quenched with saturated NH₄Cl. The quenched mixture was diluted with 10 mL of water and extracted with 4 × 10 mL of ether. The ethereal layers were combined, washed with brine, dried with MgSO₄, filtered, and concentrated to give the crude products.

**General Procedure F for the Addition of the Lithium Enethiolates of Thioamides 10 and 12 to α,β-Unsaturated Ketones.** The reaction was carried out exactly as in general procedure E, except that 10 min after the addition of the enone at –78 °C, the mixture was warmed to either 0 or 25 °C in an ice/salt bath for a 1- to 14-h period. Quench and workup provided the crude conjugate addition products.

**(*E*,2′*RS*,3′*RS*)- or (*E*,2′*RS*,3′*SR*)-1-(2′,3′-dimethyl-3′-hydroxy-1′-thioxo-4′-hexenyl)pyrrolidine, major 1,2 diastereomer (69a):** white crystalline solid; mp 99–101 °C; ¹H NMR δ 1.25 (d, 3, *J* = 6.8), 1.25 (s, 3), 1.71 (dd, 3, *J* = 1.6, 6.6), 2.03 (m, 2), 2.11 (m, 2), 2.90 (q, 1, *J* = 6.8), 3.70 (m, 2), 3.86 (m, 2), 5.33 (dq, 1, *J* = 15.3, 1.6), 5.52 (s, 1), 5.78 (dq, 1, *J* = 15.3, 6.6); ¹³C NMR δ 15.99, 17.68, 24.06, 26.13, 27.98, 51.22, 51.42, 53.35, 72.79, 124.08, 136.01, 203.75. Anal. Calcd for C₁₂H₂₁NOS: C, 63.39; H, 9.31; N, 6.16. Found: C, 63.07; H, 9.33; N, 6.11.

**Minor 1,2 diastereomer 69b:** gum; IR (CHCl₃) 3300 (br), 2980, 2880, 1500, 1460 cm⁻¹; ¹H NMR δ 1.26 (s, 3), 1.33 (d, 3, *J* = 6.8), 1.63 (dd, 3, *J* = 1.4, 6.3), 1.96–2.10 (m, 4), 2.98 (q, 1, *J* = 6.8), 3.65 (m, 2), 3.81 (m, 2), 5.40 (br s, 1), 5.46 (dq, 1, *J* = 1.4, 15.4), 5.64 (dq, 1, *J* = 15.4, 6.3); ¹³C NMR δ 15.17, 17.56, 24.04, 25.85, 26.10, 51.27, 51.44, 53.25, 72.58, 123.33, 137.31, 203.19.

**(2′*RS*,3′*RS*)- and (2′*RS*,3′*SR*)-1-(2′,3′-dimethyl-5′-oxo-1′-thioxohexyl)pyrrolidine (70a and 70s):** 75:25 (anti/syn) mixture; light-colored oil; IR 2980, 2940, 2880, 1710, 1480, 1450 cm⁻¹. Anal. Calcd for C₁₂H₂₁NOS: C, 63.34; H, 9.31; N, 6.16; S, 14.10. Found: C, 63.15; H, 9.37; N, 5.97; S, 14.04.

**Major anti 1,4 diastereomer 70a (discernible from mixture):** ¹H NMR δ 1.00 (d, 3), 1.22 (d, 3), 2.12 (s, 3); ¹³C NMR δ 16.42, 18.52, 23.97, 26.12, 30.02, 35.17, 49.15, 49.32, 50.42, 53.81, 205.05, 209.22.

**Mixture of 70a and 70s:** ¹H NMR δ 1.90 (m, 5), 2.40–3.00 (m, 3), 3.60–3.96 (m, 4).

**Minor syn 1,4 diastereomer 70s (discernible from mixture):** ¹H NMR δ 0.93 (d, 3), 1.20 (d, 2), 2.14 (s, 3); ¹³C NMR δ 17.38, 18.93, 23.97, 26.12, 30.37, 33.98, 46.21, 48.43, 204.83, 208.62.

**(2′*RS*,3′*RS*)- and (2′*RS*,3′*SR*)-1-(5′-oxo-2′,3′,6′,6′-tetramethyl-1′-thioxoheptyl)pyrrolidine (71a and 71s):** white crystalline solid; mp 91–101 °C; IR (CHCl₃) 2980, 2880, 1705, 1480, 1460 cm⁻¹. Anal. Calcd for C₁₅H₂₇NOS: C, 66.86; H, 10.10; N, 5.20; S, 11.90. Found: C, 66.83; H, 10.19; N, 5.24; S, 11.92.

**2′*RS*,3′*RS* isomer 71a:** ¹H NMR δ 0.91 (d, 3, *J* = 6.6), 1.13 (s, 9), 1.20 (d, 3, *J* = 6.7), 1.99 (m, 2), 2.06 (m, 2), 2.84 (m, 2), 3.05 (m, 2), 3.86 (m, 4); ¹³C NMR δ 17.1, 18.5, 23.7, 25.8, 26.1, 33.5, 38.2, 44.0, 47.7, 50.2, 53.5, 204.8, 215.1.

**2′RS,3′SR isomer 71s** (discernible from mixture): ¹H NMR δ 1.00 (d, 3, *J* = 6.7), 1.10 (s, 9); ¹³C NMR δ 15.9, 17.8, 33.7, 40.8, 215.3.

**(2′RS,3′RS)-1-(5′-Oxo-3′-phenyl-2′,6′,6′-trimethyl-1′-thioxoheptyl)pyrrolidine (72a):** white crystalline solid; mp 162.5–64 °C; IR (CHCl₃) 2980, 2880, 1710, 1480, 1460 cm⁻¹; ¹H NMR δ 1.03 (s, 9), 1.30 (d, 3, *J* = 6.4), 1.79 (m, 4), 3.13 (m, 2), 3.30 (m, 2), 3.52 (m, 2), 3.76 (m, 2), 7.23 (m, 5); ¹³C NMR δ 18.3, 23.7, 25.9, 26.3, 37.9, 44.1, 45.2, 49.2, 50.2, 53.5, 126.3, 127.9, 128.0, 143.0, 203.9, 213.7. Anal. Calcd for C₂₀H₂₉NOS: C, 72.46; H, 8.82; N, 4.23. Found: C, 72.22; H, 8.81; N, 4.12.

**(2′RS,3′RS)-1-(3′-tert-Butyl-2′,6′,6′-trimethyl-5′-oxo-1′-thioxoheptyl)pyrrolidine (73a):** clear oil; IR 2980, 2880, 1705, 1475, 1450 cm⁻¹; ¹H NMR δ 0.93 (s, 9), 1.16 (s, 9), 1.23 (d, 3, *J* = 6.7), 1.98 (m, 3), 2.15 (m, 1), 2.47 (m, 2), 3.27 (m, 1), 3.42 (dd, 1, *J* = 5.6, 20.5), 3.66 (m, 1), 3.76 (m, 2), 3.89 (m, 1); ¹³C NMR δ 17.0, 23.7, 26.2, 27.3, 28.6, 32.8, 34.6, 40.5, 43.0, 43.8, 49.7, 54.2, 205.0, 214.4. Anal. Calcd for C₁₈H₃₃NOS: C, 69.40; H, 10.68; N, 4.50. Found: C, 69.19; H, 10.74; N, 4.34; S, 10.19.

**(2′RS,3′RS)-1-(2′,3′-Dimethyl-5′-oxo-5′-(2,4,6-trimethylphenyl)-1′-thioxopentyl)pyrrolidine (74a):** yellow crystalline solid: mp 115–8 °C; IR (CHCl₃) 2980, 2880, 1700, 1480, 1460 cm⁻¹; ¹H NMR δ 1.10 (d, 3, *J* = 6.5), 1.21 (d, 3, *J* = 6.6), 1.92–2.13 (m, 4), 2.18 (s, 6), 2.22 (s, 3), 2.57 (m, 2), 3.07 (quin, 1, 6.5), 3.39 (d, 1, *J* = 17.1), 3.67–3.93 (m, 4), 6.81 (s, 2); ¹³C NMR δ 16.86, 18.94, 19.23, 20.90, 23.89, 26.06, 33.15, 46.61, 47.67, 50.32, 53.73, 128.29, 132.16, 137.94, 139.62, 204.81, 209.92. Anal. Calcd for C₂₀H₂₉NOS: C, 72.46; H, 8.82; N, 4.23; S, 9.67. Found: C, 72.33; H, 8.89; N, 4.09; S, 9.61.

**(2′RS,3′RS)-1-(2′,3′-Dimethyl-5′-oxo-5′-(2,4,6-triisopropylphenyl)-1′-thioxopentyl)pyrrolidine (75a):** white crystalline solid; mp 103.5–4.5 °C; IR 2980, 2880, 1700, 1580, 1470, 1450; ¹H NMR δ 1.12 (br d, 6, *J* = 6.4), 1.21 (br d, 6, *J* = 6.7), 1.24 (br d, 12, *J* = 6.9), 1.99 (m, 2), 2.08 (m, 2), 2.59 (m, 2), 2.65 (m, 2), 2.88 (sep, 1, *J* = 6.9), 3.08 (quin, 1, *J* = 6.5), 3.41 (d, 1, *J* = 17.7), 3.73 (m, 1), 3.86 (m, 3), 6.98 (s, 2); ¹³C NMR δ 16.86, 19.13, 23.92, 23.95, 24.13 (br), 26.11, 30.67, 33.14, 34.23, 47.66, 48.21, 50.39, 53.77, 120.90, 137.92, 143.26 (br), 149.16, 204.88, 210.22. Anal. Calcd for C₂₈H₄₁NOS: C, 75.12; H, 9.94; N, 3.67; S, 7.71. Found: C, 75.21; H, 10.19; N, 3.29; S, 7.48.

**(E,3RS,1′RS)- or (E,3RS,1′SR)-3-(1′-hydroxy-1′-methyl-2′-butenyl)-1-methyl-2-thiopyrrolidinone (99a):** yellow oil; IR (neat) 3320 (br), 2980, 2940, 2900, 1540, 1460, 1400, 1320 cm⁻¹; ¹H NMR δ 1.28 (s, 3), 1.71 (dd, 3, *J* = 6.4, 1.5), 2.18 (m, 2), 3.11 (br t, 1, *J* = 8.7), 3.26 (s, 3), 3.64 (m, 2), 5.18 (m, 1), 5.49 (dq, 1, *J* = 15.5, 1.6), 5.75 (dq, 1, 15.5, 6.5); ¹³C NMR δ 17.74, 20.65, 22.91, 35.21, 55.25, 61.82, 73.72, 125.06, 135.60, 200.97. Anal. Calcd for C₁₀H₁₇NOS: C, 60.24; H, 8.60; N, 7.02; S, 16.09. Found: C, 60.51; H, 8.74; N, 6.89; S, 15.86.

**(E,3RS,1′RS)- or (E,3RS,1′SR)-3-(1′-hydroxy-1′-methyl-2′-butenyl)-1-methyl-2-thiopyrrolidinone (99b):** yellow oil; ¹H NMR δ 1.30 (d, 3, *J* = 1.1), 1.68 (dd, 3, *J* = 1.2, 6.1), 2.10 (m, 2), 3.16 (m, 1), 3.27 (s, 3), 3.61 (m, 2), 5.54 (m, 1), 5.70 (m, 1), 6.26 (d, 1, *J* = 1.1); ¹³C NMR δ 17.57, 18.91, 22.15, 34.98, 54.92, 61.91, 73.39, 125.65, 131.76.

**(3RS,1′SR)-1-Methyl-3-(1′-methyl-3′-oxobutyl)-2-thiopyrrolidinone (100s),** 95:5 mixture of diastereomers: yellow oil; IR (neat) 2980, 2880, 1710, 1530 cm⁻¹; ¹H NMR δ 0.98 (d, 3, *J* = 6.9), 1.77 (m, 2), 2.15 (m, 1), 2.18 (s, 3), 2.63 (dd, 1, *J* = 3.8, 14.6), 2.96 (m, 2), 3.27 (s, 3), 3.64 (m, 2); ¹³C NMR δ 17.34, 21.62, 29.71, 31.91, 35.48, 45.96, 55.31, 58.15, 202.63, 208.79. Anal. Calcd for C₁₀H₁₇NOS: C, 60.26; H, 8.60; N, 7.02; S, 16.04. Found: C, 60.35; H, 8.56; N, 6.98; S, 16.01.

**(3RS,1′RS)-1-Methyl-3-(1′-methyl-3′-oxobutyl)-2-thiopyrrolidinone (100a):** yellow oil; ¹H NMR δ 0.82 (d, 3, *J* = 6.7), 1.85 (dq, 1, *J* = 13.2, 7.9), 2.09 (m, 1), 2.19 (s, 3), 2.40 (dd, 1, *J* = 8.1, 15.2), 2.52 (dd, 1, *J* = 6.7, 15.2), 2.93 (m, 1), 3.00 (m, 1), 3.27 (s, 3), 3.65 (m, 2); ¹³C NMR δ 14.13, 20.19, 29.81, 31.65, 35.42, 49.20, 55.28, 57.26, 202.87, 207.93.

**(E,3RS,1′RS)- and (E,3RS,1′SR)-3-(1′-hydroxy-1′-isopropyl-2′-butenyl)-1-methyl-2-thiopyrrolidinone, major diastereomer (101a):** white crystalline solid; mp 71–1.5 °C; IR (CHCl₃) 3320 (br), 2980, 2880, 1530, 1320 cm⁻¹; ¹H NMR δ 0.90 (d, 3, *J* = 6.8), 1.00 (d, 3, *J* = 6.7), 1.68 (dd, 3, *J* = 1.5, 6.5); 1.75 (m, 1), 1.92 (m, 1), 2.20 (m, 1), 3.19 (s, 3), 3.26 (m, 1), 3.64 (m, 2), 5.29 (dq, 1, *J* = 15.3, 1.5), 5.76 (dq, 1, *J* = 15.3, 6.5), 5.82 (s,

1); ¹³C NMR δ 16.15, 16.86, 17.91, 21.42, 33.69, 35.23, 55.64, 59.85, 77.64, 127.19, 130.84, 202.23. Anal. Calcd for C₁₂H₂₁NOS: C, 63.34; H, 9.31; N, 6.16; S, 14.10. Found: C, 63.37; H, 9.39; N, 6.11; S, 13.98.

**(E,3RS,1′RS)- and (E,3RS,1′SR)-3-(1′-hydroxy-1′-isopropyl-2′-butenyl)-1-methyl-2-thiopyrrolidinone, minor diastereomer (101b),** (discernible from mixture): ¹H NMR δ 1.73 (dd, 3, *J* = 1.5, 6.5), 5.47 (dd, 1, *J* = 1.5, 15.4), 5.75 (dq, 1, *J* = 15.4, 6.5).

**(3RS,1′SR)-1-Methyl-3-(1′,4′-dimethyl-3′-oxopentyl)-2-thiopyrrolidinone (102s):** clear oil; IR 2980, 2880, 1710, 1530, 1470, 1320 cm⁻¹; ¹H NMR δ 0.82 (d, 3, *J* = 6.7), 1.10 (d, 6, *J* = 6.9), 1.90 (m, 1), 2.11 (m, 1), 2.46 (dd, 1, *J* = 7.4, 17.5), 2.55 (dd, 1, *J* = 6.6, 17.5), 2.69 (sep, 1, *J* = 6.9), 2.98 (m, 2), 3.26 (s, 3), 3.63 (m, 2); ¹³C NMR δ 14.2, 17.9, 18.5, 20.3, 31.4, 35.3, 40.4, 45.7, 55.2, 57.3, 202.5, 213.5. Anal. Calcd for C₁₂H₂₁NOS: C, 63.39; H, 9.31; N, 6.16. Found: C, 63.37; H, 9.35; N, 6.00.

**(3RS,1′RS)-1-Methyl-3-(1′,4′-dimethyl-3′-oxopentyl)-2-thiopyrrolidinone (102a):** clear oil; IR 2980, 2880, 1710, 1530, 1470, 1320 cm⁻¹; ¹H NMR δ 0.97 (d, 3, *J* = 6.9), 1.03 (d, 3, *J* = 6.8), 1.09 (d, 3, *J* = 7.0), 1.84 (m, 1), 2.21 (m, 2), 2.70 (m, 2), 2.97 (m, 2), 3.27 (s, 3), 3.65 (m, 2); ¹³C NMR δ 17.1, 18.1, 21.7, 31.5, 35.3, 40.1, 42.6, 55.2, 57.9, 203.1, 214.2.

**(3RS,1′RS)-1-Methyl-3-(3′-oxo-1′,4′,4′-trimethylpentyl)-2-thiopyrrolidinone (103a):** white crystalline solid; mp 85.5–6 °C; IR (CHCl₃) 2980, 2880, 1705, 1530, 1320 cm⁻¹; ¹H NMR δ 0.95 (d, 3, *J* = 7.0), 1.13 (s, 9), 1.85 (m, 1), 2.23 (m, 1), 2.43 (dd, 1, *J* = 10.0, 17.9), 2.82 (m, 2), 2.97 (m, 1), 3.27 (s, 3), 3.64 (m, 2); ¹³C NMR δ 16.6, 22.9, 26.3, 31.5, 35.3, 39.0, 44.2, 55.2, 57.7, 202.7, 214.9. Anal. Calcd for C₁₃H₂₃NOS: C, 64.68; H, 9.60; N, 5.80; S, 13.28. Found: C, 64.61; H, 9.74; N, 5.74; S, 13.19.

**(3RS,1′SR)-1-Methyl-3-(3′-oxo-1′,4′,4′-trimethylpentyl)-2-thiopyrrolidinone (103s),** 90:10 (syn/anti) mixture of diastereomers: white crystalline solid; mp 63–71 °C; IR (CHCl₃) 2980, 2880, 1705, 1530, 1320 cm⁻¹; ¹H NMR δ 0.80 (d, 3, *J* = 6.7), 1.14 (s, 9), 1.90 (m, 1), 2.08 (m, 1), 2.54 (d, 2, *J* = 6.8), 2.98 (m, 2), 3.26 (s, 3), 3.64 (m, 2); ¹³C NMR δ 14.3, 20.5, 26.2, 31.1, 35.3, 41.4, 44.1, 55.3, 57.3, 203.3, 214.0. Anal. Calcd for C₁₃H₂₃NOS: C, 64.68; H, 9.60; N, 5.80; S, 13.28. Found: C, 64.46; H, 9.68; N, 5.74; S, 13.06.

**(3RS,1′SR)-1-Methyl-3-(1′-methyl-3′-oxo-3′-(2,4,6-trimethylphenyl)propyl)-2-thiopyrrolidinone (104s):** white crystalline solid; mp 141.5–143.0 °C; IR (CHCl₃) 2980, 2880, 1700, 1530, 1320 cm⁻¹; ¹H NMR δ 0.91 (d, 3, *J* = 6.7), 1.91 (m, 1), 2.10 (m, 1), 2.20 (s, 6), 2.67 (s, 3), 2.71 (dd, 1, *J* = 8.0, 17.9), 2.84 (dd, 1, *J* = 5.7, 17.9), 3.10 (m, 2), 3.26 (s, 3), 3.64 (m, 2), 6.82 (s, 2); ¹³C NMR δ 14.30, 19.00, 20.43, 20.88, 30.62, 35.32, 49.64, 55.21, 57.16, 128.29, 132.26, 138.07, 139.36, 202.99, 208.59. Anal. Calcd for C₁₈H₂₅NOS: C, 71.24; H, 8.30; N, 4.62; S, 10.57. Found: C, 70.96; H, 8.30; N, 4.46; S, 10.19.

**(3RS,1′SR)-1-Methyl-3-(1′-methyl-3′-oxo-3′-(2,4,6-triisopropylphenyl)propyl)-2-thiopyrrolidinone (105s):** white crystalline solid; mp 160.5–1.5 °C; IR (CHCl₃) 2980, 2880, 1700, 1530, 1470, 1320 cm⁻¹; ¹H NMR δ 0.93 (d, 3, *J* = 6.7), 1.23 (d, 6, *J* = 6.7), 1.24 (d, 12, *J* = 6.9), 1.87 (m, 1), 2.07 (m, 1), 2.60–2.95 (m, 5), 3.07–3.22 (m, 2), 3.28 (s, 3), 3.66 (m, 2), 6.99 (s, 2); ¹³C NMR δ 14.18, 20.52, 23.88, 24.04 (br), 30.55, 30.74, 34.19, 35.38, 51.20, 55.31, 57.27, 120.88, 137.70, 143.27, 149.27, 203.16, 208.68. Anal. Calcd for C₂₄H₃₇NOS: C, 74.36; H, 9.62; N, 3.61; S, 8.27. Found: C, 74.10; H, 9.59; N, 3.56; S, 8.34.

**(3RS,1′RS)-3-(4′,4′-Dimethyl-1′-isopropyl-3′-oxopentyl)-1-methyl-2-thiopyrrolidinone (106s),** 80:20 (syn/anti) mixture: white crystalline solid; mp 76–7.5 °C; IR (CHCl₃) 2980, 2880, 1710, 1530, 1470, 1320 cm⁻¹; ¹H NMR δ 0.86 (d, 3, *J* = 6.8), 0.93 (d, 3, *J* = 6.8), 1.16 (s, 9), 1.90 (m, 2), 2.20 (m, 1), 2.45 (m, 1), 2.56 (dd, 1, *J* = 3.4, 8.4), 2.92 (m, 1), 3.02 (dd, 1, *J* = 8.6, 18.4), 3.19 (s, 3), 3.56 (m, 1), 3.84 (m, 1); ¹³C NMR δ 18.6, 21.8, 25.9, 27.0, 29.6, 35.50, 35.54, 40.1, 44.1, 54.9, 55.9, 203.4, 215.8. Anal. Calcd for C₁₅H₂₇NOS: C, 66.86; H, 10.10; N, 5.20; S, 11.90. Found: C, 66.95; H, 10.25; N, 5.26; S, 12.02.

**(3RS,1′SR)-3-(4′,4′-Dimethyl-1′-isopropyl-3′-oxopentyl)-1-methyl-2-thiopyrrolidinone (106a):** white crystalline solid; mp 77–8.5 °C; ¹H NMR δ 0.92 (dd, 6, *J* = 1.8, 6.8), 1.13 (s, 9), 1.74 (octet, 1, *J* = 6.8), 1.84 (m, 1), 2.17 (m, 1), 2.28 (dd, 1, *J* = 4.0, 17.4), 2.47 (dd, 1, *J* = 7.7, 17.4), 2.96 (br sep, 1, *J* = 3.7), 3.08 (m, 1), 3.26 (s, 3), 3.63 (m, 2); ¹³C NMR δ 20.2, 21.0, 22.9, 26.8,

30.5, 35.4, 35.7, 40.8, 44.4, 54.7, 55.1, 204.4, 214.0.

**(3RS,1′RS)-3-(4′,4′-Dimethyl-3′-oxo-1′-phenylpentyl)-1-methyl-2-thiopyrrolidinone (107a), 90:10 (anti/syn) mixture of diastereomers:** white solid; mp 111–5 °C; ^{1}H NMR $\delta$ 1.12 (s, 9), 1.91 (ddt, 1, $J$ = 8.2, 12.8, 4.2), 2.23 (m, 1), 2.58 (m, 1), 3.06 (s, 3), 3.17 (m, 3), 3.72 (m, 2), 7.28 (m, 5).

**(3RS,1′SR)-3-(4′,4′-Dimethyl-3′-oxo-1′-phenylpentyl)-1-methyl-2-thiopyrrolidinone (107s):** white crystalline solid; mp 80–1 °C; IR (CHCl₃) 2980, 2880, 1705, 1530, 1320 cm⁻¹; ^{1}H NMR $\delta$ 1.08 (s, 9), 1.77 (m, 1), 2.03 (m, 1), 2.94 (m, 1), 3.09 (s, 3), 3.15 (m, 2), 3.33 (ddd, 1, $J$ = 3.5, 9.0, 11.1), 3.51 (dd, 1, $J$ = 6.0, 17.6), 3.92 (dt, 1, $J$ = 6.1, 8.3), 7.26 (m, 5); ^{13}C NMR $\delta$ 23.4, 26.2, 35.3, 40.7, 42.2, 44.0, 55.1, 58.3, 126.7, 128.0, 141.2, 202.7, 213.3. Anal. Calcd for C₁₈H₂₅NOS: C, 71.25; H, 8.31; N, 4.62; S, 10.57. Found: C, 71.15; H, 8.36; N, 4.54; S, 10.61.

**General Procedure G for the Addition of Potassium and Sodium Enethiolates of 10 and 12 to Enone 21.** An oven-dried, argon-flushed, Schlenk tube equipped with a magnetic stirring bar and rubber septum was charged with sodium hexamethyldisilylamide (NaHMDS) in THF or potassium hexamethyldisilylamide (KHMDS) in toluene by syringe. The toluene was removed from the KHMDS by replacing the septum with a ground glass stopper under a positive argon pressure and placing the flask under reduced pressure. After refilling the flask with argon, the glass stopper was replaced by a rubber septum (under a positive argon pressure), THF was added, and the enolate was generated by cooling the flask to –30 °C (liquid N₂/nitromethane bath) and adding the thioamide in THF by syringe over a 2-min period. After a 30-min period at –30 °C, the flask was warmed to 0 °C (ice/brine bath) for a 1-h period. Thioamide 12 formed a light-colored precipitate upon deprotonation while the anion of 10 was freely soluble. The reaction tube was cooled to –78 °C and the enone in THF was added. With thiolactam 10, the mixture was stirred for a 2.5-h period at –78 °C. With thioamide 12, the mixture was left for a 4-h period at –7 °C. The mixtures were quenched with saturated NH₄Cl, diluted with water (10 mL), and extracted (3 × 10 mL) with ether. The combined ethereal layers were washed with water (10 mL) and brine (10 mL) and dried with MgSO₄. The drying agent was removed by filtration through a 3–5-g plug of silica gel (230–400 mesh) using ether as eluent by the flash chromatography technique. The resulting ethereal solutions were concentrated to provide the crude material.

**General Procedure H for the Conversion of Keto Thioamides to Keto Amides.** A 5-mL round-bottomed flask was charged with the keto thioamide, using a modification of a previously reported procedure.[15] A large excess of methyl iodide was filtered from copper powder into the reaction flask and the flask was capped and covered with aluminum foil. The reaction was followed by TLC (ether, UV visualization) for the disappearance of starting thioamide. After completion of the reaction, the excess methyl iodide was removed in vacuo. The residue was dissolved in 95% ethanol and treated with NaOH. After a 1- to 2-h period, the mixture was diluted with 10 mL of water and extracted with 4 × 10 mL of ether. The ethereal layers were combined, washed with brine, dried with MgSO₄, filtered, and concentrated to provide the crude keto amide.

**(3RS,1′SR)-1-Methyl-3-(1′-methyl-3′-oxo-3′-(2,4,6-triisopropylphenyl)propyl)-2-pyrrolidinone (91s):** white crystalline solid; mp 124.0–5.5 °C; IR (CHCl₃) 2980, 2880, 1690 cm⁻¹; ^{1}H NMR $\delta$ 1.02 (d, 3, $J$ = 6.4), 1.24 (br d, 18, $J$ = 6.9), 1.79 (m, 1), 2.04 (m, 1), 2.50–2.75 (m, 5), 2.80 (m, 1), 2.84 (s, 3), 3.02 (m, 1), 3.28 (m, 2), 6.98 (s, 2); ^{13}C NMR 16.28, 20.82, 23.93, 24.46 (br), 28.85, 29.64, 30.77, 34.26, 45.44, 47.47, 50.76, 120.92, 137.90, 143.35, 149.26, 175.43, 209.51. Anal. Calcd for C₂₄H₃₇NO₂: C, 77.58; H, 10.04; N, 3.77. Found: C, 77.51; H, 10.01; N, 3.68.

**Conversion of Keto Amide 91a to Keto Thioamide 105a.** Keto amide 91a (34.7 mg, 0.093 mmol), Lawesson's reagent[15] (46.0 mg, 0.114 mmol), and 0.2 mL of THF were combined in an oven-dried, 5-mL pear-shaped flask capped with a rubber septum and the mixture was flushed with N₂. The flask was placed under a positive N₂ atmosphere and partially immersed in a sonicator bath, and the mixture was sonicated for a 24-h period. Flash chromatography of the mixture with 5 g of silica gel (230–400 mesh) utilizing 2:1 hexanes/ether as eluent provided two fractions. The first fraction provided 22.8 mg (63%, 97% based on recovered 91a) of keto thioamide 105a, identical (^{1}H and ^{13}C NMR) with

the minor product from the addition of thiolactam 10 to enone 26 in THF. The second fraction yielded 12.3 mg of keto amide starting material 91a with a ratio of diastereomers (^{1}H NMR) identical with that of the starting material.

**(3RS,1′RS)-1-Methyl-3-(1′-methyl-3′-oxo-3′-(2,4,6-triisopropylphenyl)propyl)-2-thiopyrrolidinone (105a):** white crystalline solid; mp 146.5–7.5 °C; ^{1}H NMR $\delta$ 1.14 (d, 3, $J$ = 6.7), 1.23 (br d, 18, $J$ = 6.9), 1.79 (m, 1), 2.20 (m, 2), 2.50 (dd, 1, $J$ = 9.3, 19.2), 2.69 (m, 2), 2.87 (m, 1), 2.98 (dd, 1, $J$ = 2.8, 19.2), 3.09 (m, 1), 3.22 (s, 3), 3.60 (m, 2), 6.97 (s, 2); ^{13}C NMR $\delta$ 17.17, 22.44, 23.98 (br), 30.65, 30.72, 34.29, 35.34, 48.50, 55.12, 57.85, 120.90 (br), 138.00, 143.40 (br), 149.18, 202.72, 209.30. Anal. Calcd for C₂₄H₃₇NOS: C, 74.36; H, 9.62; N, 3.61; S, 8.27. Found: C, 74.36; H, 9.67; N, 3.47; S, 8.00.

**(2′RS,3′SR)-1-(2′,3′-Dimethyl-5′-(hydroxyimino)-1′-oxo-5′-phenylpentyl)pyrrolidine (117).** To a solution of 0.26 g (0.95 mmol) of major Michael adduct 52s in 6.0 mL of absolute ethanol were added 2.0 mL of 10% aqueous NaOH, 0.50 g (7.2 mmol) of hydroxylamine hydrochloride, and 3.0 mL of water. This mixture was heated at reflux for 30 min and cooled on an ice bath, and 10 mL of cold water was added to give a turbid mixture. The mixture was chilled and the flask scratched to induce crystallization. The resulting solid was recrystallized from aqueous ethanol to give 0.062 g (23%) of 117, mp 165–6 °C. Single-crystal X-ray analysis provided the stereostructure assignment.[44] 117: IR (CHCl₃) 3590, 3300 (br), 2980, 1720, 1625, 1430, 1095 cm⁻¹; ^{1}H NMR $\delta$ 0.89 (d, 3, $J$ = 6.8), 1.10 (d, 3, $J$ = 6.8), 1.56 (s, 1), 1.86 (m, 4), 2.20 (m, 1), 2.41 (dq, 1, $J$ = 6.0, 6.8), 2.84 (m, 2), 3.33 (m, 2), 3.46 (m, 2), 7.39 (m, 3), 7.70 (m, 2); ^{13}C NMR $\delta$ 13.7, 15.8, 24.3, 26.1, 30.2, 33.4, 43.2, 45.7, 46.4, 126.5, 128.5, 129.1, 135.4, 158.5, 174.6. Anal. Calcd for C₁₇H₂₄N₂O₂: C, 70.80; H, 8.39; N, 9.71. Found: C, 70.51; H, 8.59; N, 9.50.

**(3RS,1′RS)-3-(3′-(Hydroxyimino)-1′-methyl-3′-phenylpropyl)-1-methyl-2-pyrrolidinone (118).** A mixture of 0.061 g (0.25 mmol) of major Michael adduct 83a, 0.035 g (0.50 mmol) of hydroxylamine hydrochloride, 0.035 g (0.25 mmol) of sodium acetate trihydrate, 2 mL of absolute ethanol, and 1 mL of water was heated at reflux for 40 min. The mixture was cooled, dissolved in ether, and washed with 3 × 20 mL of water, and the ether layer was dried (MgSO₄). Filtration and removal of the solvent gave a crude solid, which was recrystallized from ethanol–hexane to give 0.021 g (32%) of 118, mp 148–9 °C. X-ray crystal analysis of one crystal confirmed the given stereochemistry.[44] 118: IR (CHCl₃) 3595, 3300 (br), 1675, 1600, 1400, 1195 cm⁻¹; ^{1}H NMR $\delta$ 0.92 (d, 3, $J$ = 6.9), 1.93 (m, 1), 2.11 (m, 1), 2.41 (m, 1), 2.54 (m, 1), 2.64 (dd, 1, $J$ = 4.88, 22.1), 2.87 (s, 3), 3.12 (dd, 1, $J$ = 10.5, 13.1), 3.32 (m, 2), 7.38 (m, 3), 7.50 (s, 1), 7.74 (m, 2); ^{13}C NMR $\delta$ 16.6, 20.5, 27.3, 29.7, 31.4, 46.6, 47.8, 126.5, 128.5, 129.2, 135.2, 158.7, 175.5. Anal. Calcd for C₁₅H₂₀N₂O₂: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.21; H, 7.71; N, 10.66.

**(3RS,1′RS)-3-(4′,4′-Dimethyl-1′-ethyl-3′-(hydroxyimino)-pentyl)-1-methyl-2-pyrrolidinone (119).** A mixture of 0.097 g (2.07 mmol) of keto amide 93a, 1.00 g (14.4 mmol) of hydroxylamine hydrochloride, 15 mL of absolute ethanol, 3 mL (7.5 mmol) of 10% aqueous NaOH, and 4 mL of H₂O was refluxed for 5 days, cooled, diluted with 20 mL of ether, washed with (3 × 15 mL) H₂O and 10 mL of brine, dried with MgSO₄, filtered, and concentrated to give 0.277 g (1.09 mmol, 53%) of a crude oil. Chromatography of the crude material on 13 g of silica gel utilizing 1.2:1 hexanes/ether as eluent furnished 0.118 g (0.465 mmol, 22%) of anti oxime amide 119 as white crystals: mp 144–5 °C; IR (CHCl₃) 3240 (br), 2980, 1695, 1630, 1470, 1375, 950 cm⁻¹; ^{1}H NMR $\delta$ 0.88 (t, 3, $J$ = 7.4), 1.17 (s, 9), 1.25 (m, 1), 1.43 (m, 1), 2.00 (m, 3), 2.39 (m, 1), 2.75 (m, 2), 2.86 (s, 3), 3.32 (t, 2, $J$ = 7.3); ^{13}C NMR $\delta$ 12.0, 18.6, 23.4, 24.8, 28.7, 29.7, 37.8, 43.3, 47.9, 165.7, 176.3. Anal. Calcd for C₁₄H₂₆N₂O₂: C, 66.10; H, 10.30; N, 11.02. Found: C, 65.76; H, 10.28; N, 10.88.

Single-crystal X-ray analysis of a crystal obtained by slow evaporation of an ethyl acetate/hexanes solution established the stereostructure.

**(2RS,3RS)-3-tert-Butyl-5-(hydroxyimino)-2,6,6-trimethylheptanoic Acid (120).** A mixture of 0.5000 g (1.7 mmol) of keto amide 66a, 1.00 g (14.4 mmol) of hydroxylamine hydrochloride, 4 mL (10.0 mmol) of 10% aqueous NaOH, 16 mL of 95% ethanol, and 6 mL of H₂O was refluxed for 5 days, cooled, diluted with 20 mL of brine, and washed with ether (3 × 10 mL). The

ethereal layers were combined, washed with $H_2O$ (2 × 10 mL) and 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to provide 0.361 g (1.52 mmol, 90%) of crude white crystals. Recrystallization by slow evaporation from hexanes/ethyl acetate provided an analytical sample and a crystal suitable for single-crystal X-ray analysis of anti oxime acid **120** as white crystal: mp 150–1 °C; IR (CHCl₃) 3350 (br), 2980, 2880, 1700 cm⁻¹; ¹H NMR δ 1.05 (s, 9), 1.20 (s, 9), 1.40 (d, 3, J = 7.0), 2.02 (d, 1, J = 13.3), 2.47 (d, 1, J = 11.5), 2.85 (m, 2); ¹³C NMR δ 10.59, 21.45, 28.32, 29.02, 34.90, 38.55, 39.53, 44.16, 166.28, 182.31. Anal. Calcd for C₁₄H₂₇NO₃: C, 65.33; H, 10.58; N, 5.44. Found: C, 65.55; H, 10.81; N, 5.43.

**(3RS,1′RS)-1-Methyl-3-(1′-methyl-3′-phenyl-3′-((trimethylsilyl)oxy)-2′-propenyl)-2-pyrrolidinone (121).** Following general procedure B, a solution of 8 mL of THF, 0.20 g (0.28 mL, 2.0 mmol) of diisopropylamine, 1.3 mL (2.0 mmol) of a 1.56 M solution of *n*-butyllithium in hexanes, and 0.20 g (0.20 mL, 2.0 mmol) of amide **3** was treated with 0.29 g (2.0 mmol) of enone **22**. The cooling bath was replaced with an oil bath, and the solution was heated at a gentle reflux for 1.5 h. The system was cooled in an ice bath, and the solution was treated with 0.27 g (0.32 mL, 2.5 mmol) of TMSCl. The cooling bath was removed and the mixture was stirred at room temperature for 9 h. The mixture was treated with saturated NaHCO₃, and extracted with ether, and the organic portion was dried (MgSO₄). Filtration and removal of the solvent, followed by flash chromatography on silica gel with 40% ethyl acetate–hexanes as eluent, gave 0.5405 g (85%) of *anti*-**121**: colorless oil; IR (CHCl₃) 2970, 1675, 1500, 1405, 1255, 1075, 855, 700 cm⁻¹; ¹H NMR δ 0.12 (s, 9), 1.29 (d, 3, J = 6.8), 1.89 (m, 1), 2.08 (m, 1), 2.37 (m, 1), 2.84 (s, 3), 2.98 (m, 1), 3.28 (m, 2), 5.20 (d, 1, J = 9.8), 7.28 (m, 3), 7.45 (m, 2); ¹³C NMR δ 0.60, 18.3, 22.7, 29.6, 32.4, 46.9, 47.8, 114.4, 125.7, 127.5, 128.0, 139.2, 149.0, 175.9. Anal. Calcd for C₁₈H₂₇NO₂Si: C, 68.09; H, 8.57; N, 4.41. Found: C, 68.18; H, 8.72; N, 4.25.

**(3RS,1′RS)-3-(1′,4′-Dimethyl-3′-((trimethylsilyl)oxy)-2′-pentenyl)-1-methyl-2-pyrrolidinone (122).** Following general procedure B, a solution of 8 mL of THF, 0.20 g (0.28 mL, 2.0 mmol) of diisopropylamine, 1.3 mL (2.0 mmol) of a 1.56 M solution of *n*-butyllithium in hexanes, and 0.20 g (0.20 mL, 2.0 mol) of amide **3** was treated with 0.22 g (2.0 mmol) of enone **19**. The cooling bath was replaced with an oil bath, and the solution was heated at reflux for 45 min. The mixture was cooled in an ice bath and was treated with 0.27 g (0.32 mL, 2.5 mmol) of TMSCl. The mixture was stirred for 5 min, the cooling bath was removed, and the mixture was stirred at room temperature for 4 h. The mixture was treated with saturated NaHCO₃ and was extracted with ether, and the organic portion was dried (MgSO₄). Filtration and removal of the solvent gave a crude product with a ratio of diastereomers of 90:10. Flash chromatography on silica gel with 40% ethyl acetate–hexanes as eluent gave 0.4259 g (75%) of **122**: IR (CHCl₃) 3010, 2975, 1680, 1510, 1410, 1310, 855 cm⁻¹; ¹H NMR δ 0.19 (s, 9), 1.02 (d, 6, J = 6.8), 1.10 (d, 3, J = 6.8), 1.82 (m, 1), 1.9–2.3 (m, 3), 2.76 (m, 1), 2.81 (s, 3), 3.25 (m, 2), 4.44 (d, 1, J = 9.6); ¹³C NMR δ 0.68, 18.6, 20.6, 21.1, 22.6, 29.5, 31.7, 34.3, 47.0, 47.8, 108.6, 155.8, 176.1. Anal. Calcd for C₁₅H₂₉NO₂Si: C, 63.55; H, 10.31; N, 4.94. Found: C, 63.54; H, 10.45; N, 4.83.

**(3RS,1′SR)-3-(2′-Hydroxy-1′-methylethyl)-1-methyl-2-pyrrolidinone (123). Degradation of 121.** Ozone generated by a Wellsbach ozonator was passed through a solution of 0.2846 g (0.896 mmol) of enol silane **121** in 2 mL of dry CH₂Cl₂ and 4 mL of freshly distilled methanol until a deep blue solution was maintained. Nitrogen was bubbled through the solution to remove the excess ozone, 0.034 g (0.90 mmol) of NaBH₄ was added, and the solution was stirred for 1 h. The cooling bath was removed, another 0.034 g of NaBH₄ was added, and the mixture was stirred for an additional 2 h. After addition of a further 0.034 of NaBH₄ stirring was continued at 25 °C for 2 h, the solvent was removed with a stream of N₂, and the residue was treated with 1 N aqueous HCl. The mixture was diluted with CHCl₃, the layers were separated, and the aqueous layer was extracted with CHCl₃ (3 × 25 mL). The combined organic layers were dried (MgSO₄) and filtered, and the solvent was removed. Column chromatography of the crude material on silica gel with 5% CH₃OH/CHCl₃ as eluent gave, after three elutions, 0.0411 g (46%) of **123**.

**Degradation of 122.** In a similar manner, a solution of 2 mL of dry CH₂Cl₂, 4 mL of methanol, and 0.20 g (0.71 mmol) of enol

silane **122** was treated with ozone, followed by three 0.027-g (0.71 mmol) portions of NaBH₄ at the stated intervals. The quenched mixture was extracted with CHCl₃ (6 × 25 mL), the organic fractions were dried (MgSO₄) and filtered, and the solvent was removed. The crude material was chromatographed on silica gel with 40% acetone–hexanes as eluent to give 0.0755 g (69%) of **123**. The major degradation product from **122** was identical with that derived from **121**: IR (CHCl₃) 3670 (sharp), 3330 (br), 3010, 2890, 1665, 1510, 1470, 1410, 1310, 1120, 1045 cm⁻¹; ¹H NMR 1.00 (d, 3, J = 7.1), 1.97 (m, 2), 2.14 (m, 1), 2.74 (ddd, 1, J = 2.7, 9.2, 9.3), 2.86 (d, 3, J = 0.7), 3.40 (m, 2), 3.64 (m, 1), 3.78 (ddd, 1, J = 11.1, 2.9, 2.9), 4.34 (dd, 1, J = 2.6, 9.0); ¹³C NMR δ 11.7, 22.2, 29.7, 36.4, 46.2, 48.3, 66.8, 176.3. Anal. Calcd for C₈H₁₅NO₂: C, 61.12; H, 9.62; N, 8.91. Found: C, 60.72; H, 9.61; N, 8.69.

**Conversion of Keto Amides 64a and 64s to Keto Acids 111 and 112.** A solution of the 91:9 (anti/syn) of keto amides **64a** and **64s** (0.385 g, 1.22 mmol), ethylene glycol (20 mL), and NaOH (4.15 g, 104 mmol) was refluxed for 36 h. The solution was cooled, acidified with 1.2 N HCl, and extracted with ether (4 × 25 mL). The ethereal layers were combined, washed (2 × 20 mL) with H₂O and with 20 mL of brine, dried with MgSO₄, filtered, and concentrated to give 0.286 g (1.09 mmol, 89%) of a red oil. The crude material was further purified by being dissolved in 15 mL of ether and extracted with four 10-mL portions of 10% aqueous NaOH. The aqueous layers were combined, washed with 10 mL of ether, acidified with concentrated H₂SO₄, and extracted with ether (4 × 10 mL). The ethereal layers were combined, washed with 10 mL of H₂O and 10 mL of brine, dried with MgSO₄, filtered, and concentrated to give 0.122 g (0.47 mmol, 38%) of a yellow oil, which slowly crystallized on standing. Analysis (¹H and ¹³C NMR) of the solid revealed a 65:35 mixture of diastereomers **111** and **112**, the major compound of which corresponds (¹H and ¹³C NMR) to the syn isomer prepared previously.³⁷,⁷⁹

**(2RS,3SR)- and (2RS,3RS)-5-oxo-3-phenyl-2,6,6-trimethylheptanoic acids 111 and 112:** mp 100–18 °C; IR (CHCl₃) 3040 (br), 2990, 1715, 1460, 1370, 1080 cm⁻¹. Anal. Calcd for C₁₆H₂₂O₃: C, 73.25; H, 8.45. Found: C, 73.16; H, 8.47.

**Minor anti (2RS,3RS) diastereomer 112 (discernible from mixture):** ¹H NMR δ 1.04 (s, 9), 1.18 (d, 3, J = 7.0), 2.82 (m, 2), 3.02 (dd, 1, J = 7.5, 19.2), 3.57 (q, 1, J = 7.7), 7.19 (m, 5); ¹³C NMR δ 14.8, 25.3, 26.2, 39.4, 43.0, 44.1, 128.2, 128.4, 141.7, 181.0, 213.8.

**Conversion of Keto Amide 66a to Keto Acids 113 and 114.** A mixture of keto amide **66a** (0.500 g, 1.69 mmol), ethylene glycol (20 mL), and NaOH (4.09 g, 102 mmol) was refluxed for 2 days. The mixture was cooled, acidified with 1.2 N HCl, and extracted with ether (4 × 10 mL). The ethereal layers were combined, washed with H₂O (2 × 15 mL), dried with MgSO₄, filtered, and concentrated to give 0.337 g (1.39 mmol, 89%) of a 67:33 mixture (anti/syn, ¹H and ¹³C NMR) of diastereomers **113** and **114**. An analytical sample was obtained by dissolving 0.240 g (0.967 mmol) of the crude material in 20 mL of ether and extracting (3 × 10 mL) with 10% NaOH (aqueous). The aqueous layers were combined, acidified with concentrated H₂SO₄, and extracted with ether (4 × 10 mL). The ethereal layers were combined, washed with H₂O (2 × 10 mL) and 10 mL of brine, dried over MgSO₄, and concentrated to give 0.174 g (0.72 mmol, 60% from **66a**) of a mixture of **113** and **114**.

**(2RS,3RS)- and (2RS,3SR)-3-*tert*-butyl-5-oxo-2,6,6-trimethylheptanoic acids 114 and 113:** mixture; white crystals; mp 59–78 °C; IR (CHCl₃) 2980, 1750, 1705, 1480, 1370, 1070 cm⁻¹. Anal. Calcd for C₁₄H₂₆O₃: C, 69.38; H, 10.81. Found: C, 69.62; H, 11.02.

**Major anti (2RS,3RS) keto acid 114:** ¹H NMR δ 0.92 (s, 9), 1.06 (d, 3, J = 7.1), 1.16 (s, 9), 2.56 (m, 3), 2.75 (dq, 1, J = 10.5, 7.1); ¹³C NMR δ 13.3, 27.0, 28.3, 33.6, 34.2, 38.8, 42.5, 44.3, 182.6, 214.7.

**Minor syn (2RS,3SR) keto acid 113:** ¹H NMR δ 0.89 (s, 9), 1.10 (d, 3, J = 7.2), 1.19 (s, 9), 2.30 (m, 1), 2.56 (m, 1), 2.84 (dq, 1, J = 11.5, 7.2), 3.10 (dd, 1, J = 19.7, 5.4); ¹³C NMR δ 17.8, 27.0, 27.9, 33.5, 34.2, 38.6, 42.5, 183.4, 215.2.

**Conversion of Oxime Acid 120 to Keto Acid 114.** With use of a modification of the procedure reported by Pines et al.⁸⁰ a

(79) Uehling, D. E. Dissertation, University of California, Berkeley, September 1987.

mixture of oxime acid **120** (14.1 mg, 0.055 mmol), sodium bisulfite (0.050 g, 0.48 mmol), 95% ethanol (0.5 mL), and distilled water (0.5 mL) was brought to reflux and additional ethanol was added to replace solvent losses. After 1 day, the mixture was cooled, 2 mL of 1.2 N HCl was added, and the mixture was stirred for 5 h at room temperature. Ether (20 mL) was added and the mixture was extracted with 10% aqueous NaOH (4 × 10 mL). The aqueous layers were combined, cooled to 0 °C in an ice/salt bath, and acidified (pH paper) with concentrated $H_2SO_4$. This acidic solution was extracted with ether (4 × 10 mL). The ethereal layers were combined, washed with 10 mL of $H_2O$ and with 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.0072 g (0.030 mmol, 54%) of keto acid **114**, identical ($^1$H, $^{13}$C NMR) with the major isomer described previously (vide infra).

**Conversion of Keto Ester 115 to Keto Acid 116. (2SR,3RS)-2,3-Dimethyl-5-oxo-5-(2,4,6-triisopropylphenyl)pentanoic Acid (116).** A solution of 0.735 g (1.83 mmol) of keto ester **115** in 1.0 mL of $CH_2Cl_2$ was cooled with an ice bath and 3.0 mL of trifluoroacetic acid was added slowly by syringe. The ice bath was allowed to melt and the mixture was monitored by TLC (5:1 hexanes/ether, PMA visualization) for the disappearance of the keto ester. After 48 h the mixture was concentrated. The crude material was purified by column chromatography on 30 g of silica gel (230–400 mesh) with 5:1:0.01 hexanes/ether/AcOH as eluent. Concentration of the desired fractions provided 0.542 g (1.57 mmol, 86%) of an off-white solid: mp 108–11 °C; IR (CHCl₃) 3100–2800 (br), 2980, 2880, 1710 cm⁻¹; $^1$H NMR δ 1.08 (d, 3, J = 6.0), 1.16 (d, 3, J = 6.8), 1.23 (m, 18), 2.50–2.95 (m, 7), 6.98 (s, 2); $^{13}$C NMR δ 13.07, 16.86, 23.98, 24.09 (br), 30.37, 30.88, 34.33, 43.64, 50.66, 121.02, 137.67, 143.35, 149.44, 181.96, 209.32. Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.86. Found: C, 76.33; H, 9.67.

**General Procedure I for the Conversion of Keto Acids to Keto Amides.** With use of a modification of the procedure reported by Staab,[40] an oven-dried, argon-flushed 5-mL pear-shaped flask equipped with a rubber septum and argon inlet was charged with 1,1′-carbonyldiimidazole and $CH_2Cl_2$. This mixture was cooled (0 °C, ice/salt bath) and the keto acid in $CH_2Cl_2$ was added. The ice bath was then removed and the mixture was stirred at room temperature. The amine was added by syringe and gas was evolved. After being stirred for a period of time, the mixture was diluted with 5 mL of $H_2O$ and extracted with 4 × 10 mL of ether. The ethereal layers were combined, washed with 2 × 10 mL of 10% (v/v) aqueous HCl, 10 mL of 10% (w/v) aqueous NaOH, 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 residual solvent to give the crude products.

**Conversion of Keto Acid 108 to Keto Amide 44s. (2RS,3SR)-N,N,2,3,6,6-Hexamethyl-5-oxoheptanamide (44s).** In a Schlenk tube a solution of keto acid **108** (89.3 mg, 0.446 mmol) in 1.2 mL of $CH_2Cl_2$ was cooled with an ice/salt bath and 1,1′-carbonyldiimidazole (0.400 g, 2.47 mmol) was added in portions over 1 min accompanied by the evolution of gas. After 1 h the cooling bath was removed and the mixture was stirred for 1 day. After addition of sufficient $CH_2Cl_2$ to replace evaporative losses the rubber septum was replaced with a condenser, the reaction flask was cooled in a dry ice/acetone bath, and a large excess of dimethylamine (approximately 5 mL) was condensed into the mixture. The condenser was replaced with a ground glass stopper, the Schlenk tube was sealed, and the cooling bath was removed. After 24 h the reaction flask was unsealed and worked up as described in general procedure I to provide 86.1 mg of an oil. Chromatography of the crude material on 6 g of silica gel (230–400 mesh) with 60:40 hexanes/ether as eluent provided 66.3 mg (65%) of syn keto amide **44s** as a clear oil: IR 2980, 2880, 1710, 1650 cm⁻¹; $^1$H NMR δ 0.89 (d, 3, J = 6.8), 1.03 (d, 3, J = 6.9), 1.13 (s, 9), 2.34 (br sep, 1, J = 6.4), 2.43 (dd, 1, J = 6.5, 17.5), 2.60 (dd, 1, J = 5.9, 17.5), 2.84 (dq, 1, J = 5.7, 6.8), 2.94 (s, 3), 3.12 (s, 3); $^{13}$C NMR δ 12.74, 15.99, 26.28, 30.68, 35.55, 37.27, 38.41, 40.85, 44.17, 175.58, 215.44. Anal. Calcd for $C_{13}H_{25}NO_2$: C, 68.68; H, 11.08; N, 6.16. Found: C, 68.37; H, 10.95; N, 5.99.

**(2′SR,3′RS)-1-(2′,3′-Dimethyl-1′,5′-dioxo-5′-(2,4,6-triisopropylphenyl)pentyl)pyrrolidine (60s):** white crystalline solid;

mp 85.5–6.5 °C; IR (CHCl₃) 2980, 2880, 1700, 1640 cm⁻¹; $^1$H NMR δ 1.01 (m, 6), 1.24 (d, 18, J = 6.9), 1.81–1.97 (m, 4), 2.43–2.90 (m, 7), 3.41–3.65 (m, 4), 6.97 (s, 2); $^{13}$C NMR δ 13.83, 16,38, 23.81, 24.17, 24.74 (br), 26.05, 30.77, 34.12, 41.41, 45.49, 46.40, 50.64, 120.75, 137.70, 143.07, 149.06, 174.09, 210.09. Anal. Calcd for $C_{26}H_{41}NO_2$: C, 78.14; H, 10.34; N, 3.51. Found: C, 78.33; H, 10.17; N, 3.39.

**(2′RS,3′SR)-1-(3′-tert-Butyl-1′,5′-dioxo-2′,6′,6′-trimethylheptyl)pyrrolidine (66s):** discernible; $^1$H NMR δ 0.83 (s, 9), 1.20 (s, 9); $^{13}$C NMR δ 18.14, 24.19, 27.08, 28.27, 33.47, 34.09, 35.23, 44.19, 45.60, 45.95, 46.46, 176.02, 216.34.

**(2′RS,3′SR)-1-(1′,5′-Dioxo-2′,3′,6′,6′-tetramethylheptyl)-piperidine (67s):** clear oil; IR 2980, 2940, 2880, 1710, 1640 cm⁻¹; $^1$H NMR δ 0.87 (d, 3, J = 6.7), 1.02 (d, 3, J = 6.9), 1.13 (s, 9), 1.61 (m, 6), 2.33 (br sep, 1, J = 6.4), 2.61 (dd, 1, J = 6.5, 17.5), 2.83 (dq, 1, J = 5.6, 6.8), 3.51 (m, 2), 3.62 (m, 2); $^{13}$C NMR δ 12.72, 15.89, 24.71, 25.85, 26.36, 26.88, 30.66, 38.13, 41.01, 42.82, 44.20, 46.60, 173.83, 215.43. Anal. Calcd for $C_{16}H_{29}NO_2$: C, 71.86; H, 10.93; N, 5.24. Found: C, 71.73; H, 10.81; N, 5.27.

**(2′RS,3′SR)-1-(1′,5′-Dioxo-2′,3′,6′,6′-tetramethylheptyl)-hexamethylenimine (68s):** clear oil; IR 2980, 2940, 2880, 1710, 1640 cm⁻¹; $^1$H NMR δ 0.90 (d, 3, J = 6.7), 1.07 (d, 3, J = 6.9), 1.12 (s, 9), 1.56 (m, 4), 1.68 (m, 4), 2.38 (m, 1), 2.44 (m, 1), 2.61 (dd, 1, J = 5.0, 17.3), 2.74 (quin, 1, J = 6.7), 3.46 (m, 4); $^{13}$C NMR δ 14.14, 16.39, 26.36, 26.66, 26.93, 27.66, 29.52, 31.32, 39.11, 41.03, 44.24, 46.26, 47.83, 175.41, 215.46. Anal. Calcd for $C_{17}H_{31}NO_2$: C, 72.55; H, 11.10; N, 4.98. Found: C, 72.53; H, 10.94; N, 5.00.

(80) Pines, S. H.; Chemerda, J. M.; Kozlowski, M. A. *J. Org. Chem.* **1966**, *31*, 3446.

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)$_2$CHCH$_2$COCH$_2$CH(OH)CH$_3$, 59357-17-4; MeCH=

CHCH(OH)C(Me)$_3$, 74146-07-9; PhCOCH$_2$CH(OH)CH$_3$, 13505-39-0; *p*-MeCH(OH)CH$_2$COC$_6$H$_4$Br, 122969-81-7; *p*-MeOC$_6$H$_4$COCH$_2$CH(OH)CH$_3$, 122969-82-8; CH$_3$C≡CCOCH(CH$_3$)$_2$, 52066-33-8; EtBr, 74-96-4; (*E*)-CH$_3$CH=CHCHO, 123-73-9; ClCOCOCl, 79-37-8; (Me)$_2$CHCH$_2$COCH$_3$, 108-10-1; CH$_3$CHO, 75-07-0; (Me)$_2$CHCOCH$_3$, 563-80-4; PhCOCH$_3$, 98-86-2; *p*-BrC$_6$H$_4$COCH$_3$, 99-90-1; *p*-MeOC$_6$H$_4$COCH$_3$, 100-06-1; CH$_3$CH=CHCOCl, 10487-71-5; CH$_3$CH$_2$CHO, 123-38-6; (Me)$_2$CHCHO, 78-84-2; (Me)$_3$CCOCH$_2$Br, 5469-26-1; CH$_3$C≡CH, 74-99-7; (Me)$_2$CHCOCH$_2$CH(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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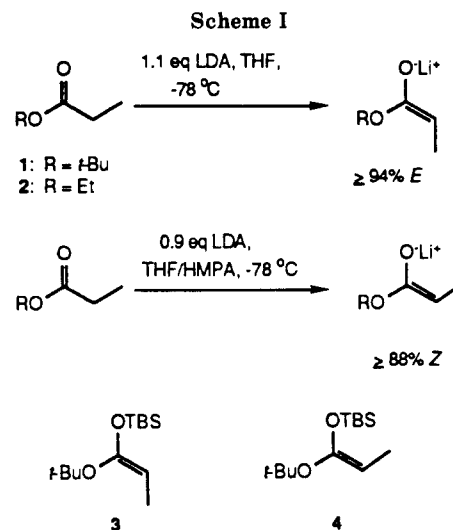*Department of Chemistry, University of California, Berkeley, California 94720*

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

**Scheme I**



particular, Schlessinger,[8] Mulzer,[9] Yamaguchi,[10] Corey,[11] and their co-workers have studied the additions of lithium

(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.

(2) For preliminary communications of this work, see: (a) Heathcock, C. H.; Oare, D. A. *J. Org. Chem.* 1985, 50, 3022. (b) Oare, D. A.; Heathcock, C. H. *Tetrahedron Lett.* 1986, 27, 6169.

(3) For the addition of ester and ketone enolates to α,β-unsaturated sulfoxides see: (a) Yamazaki, T.; Ishikawa, N.; Iwatsubo, H.; Kitazume, T. *J. Chem. Soc., Chem. Commun.* 1987, 1340. (b) Yamazakai, T.; Ishikawa, N. *Chem. Lett.* 1985, 889.

(4) For the Michael addition-intramolecular alkylation of the enolates of menthyl 2-chloropropanoates upon addition to acrylates and methacrylates, see: (a) Inouye, Y.; Inamasu, S.; Ohno, M.; Sugita, T.; Walborsky, H. M. *J. Am. Chem. Soc.* 1961, 83, 2962. (b) Inouye, Y.; Inamasu, S.; Horike, M. *Chem. Ind.* 1967, 1293. (c) Inouye, Y.; Inamasu, S.; Horike, M.; Ohno, M. *Tetrahedron* 1968, 24, 2907.