Copper(I)-Promoted Condensation of α-Amino Acids with β-Keto Thio Esters: Synthesis of N-Acylated L-Leucine Derivatives Containing (S)-4-Hydroxy-5-methyl- and (S)-4-Hydroxy-2,5-dimethyl-3-oxohexanoic Acid

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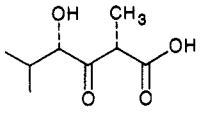
Acylation of lithium enolates of ethyl acetate and ethyl thioacetate with derivatives of (S)-2-hydroxy-3-methylbutanoic acid, activated at the carboxyl function as the acid chloride, unsymmetrical carbonic anhydride, or active ester, furnished the corresponding β-keto esters **5** or β-keto thio esters **6**. Coupling of ester derivatives of α-amino acids to the β-keto thio ester was promoted by copper(I) iodide to yield amino acid derivatives acylated at the nitrogen with an (S)-4-hydroxy-5-methyl-3-oxohexanoyl unit. N-Acylated leucine derivatives **12–15** represent 2-desmethyl analogues of the Hip-Leu moiety present in the cyclic depsipeptides, didemnins A, B, and C. The above methodology was applied also for a preparation of a derivatized Hip-Leu unit, obtained as an inseparable mixture of diastereomers at the Hip C-2 center.

The didemnin depsipeptide antibiotics were isolated from a Caribbean tunicate and their structures determined by spectroscopic methods.[1] The antibiotics didemnin A, B, and C are known to possess viable biological properties involving antiviral,[2] cytotoxic,[2,3] and immunosuppressive activities.[4] Studies to elucidate their modes of action are of current interest.[5]

The didemnins (Figure 1) contain a 23-membered cyclic depsipeptide unit. A constituent of this cyclic portion is a β-keto-γ-hydroxyhexanoic acid **1**, also termed hydroxy-



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isovaleryl propionate or Hip, possessing 2*S*,4*S* configuration.[6] Prior to our interest in the total synthesis of the didemnins, we have studied the preparation of a model Hip unit, i.e., (*S*)-4-hydroxy-5-methyl-3-oxohexanoic acid (**2**)

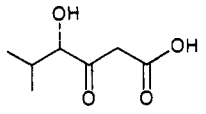

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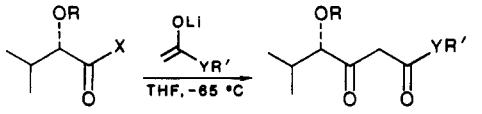
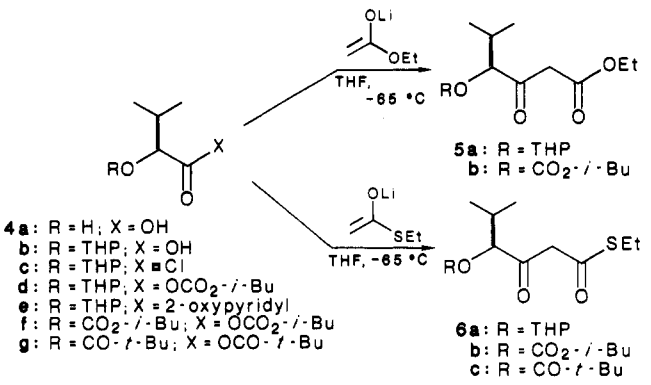
Table I. Preparation of β-Keto Esters 5



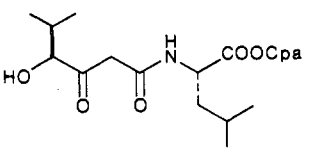
entry	R	X	YR′	product	yield,[a] %
1	THP	Cl	OEt	**5a**	57
2	THP	OCO_2-*i*-Bu	OEt	**5a**	70
3	THP	2-oxypyridyl	OEt	**5a**	53
4	CO_2-*i*-Bu	OCO_2-*i*-Bu	OEt	**5b**	61
5	CO_2-*i*-Bu	OCO_2-*i*-Bu	SEt	**6b**	25

[a] Purified yield from silica gel chromatography.

Scheme I



or Hia (hydroxyisovaleryl acetate). Model **2** lacks the α-methyl group present in Hip. We were also interested in studying the attachment of amino acid components to **2** prior to its incorporation into a cyclic depsipeptide. In this paper, we report our studies related to the preparation of the acylated L-leucine derivative Hia-Leu-OCpa **3**, in



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which the Hia unit is attached to the amino group of L-leucine *p*-chlorophenacyl ester. A protected derivative of the normal Hip-Leu unit also was prepared, though in

(1) Rinehart, K. L., Jr.; Gloer, J. B.; Cook, J. C., Jr.; Mizsak, S. A.; Scahill, T. A. *J. Am. Chem. Soc.* **1981**, *103*, 1857.
(2) (a) Rinehart, K. L., Jr.; Gloer, J. B.; Hughes, R. G., Jr.; Renis, H. E.; McGovren, J. P.; Swyneberg, E. B.; Stringfellow, D. A.; Kuetzel, S. L.; Li, L. H. *Science (Washington, D.C.)* **1981**, *212*, 933. (b) Rinehart, K. L., Jr.; Gloer, J. B.; Wilson, G. R.; Hughes, R. G., Jr.; Li, L. H.; Renis, H. E.; McGovren, J. P. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1983**, *42*, 87. (c) Li, L. H.; Renis, H. E.; McGovren, J. P.; Rinehart, K. L., Jr. *Proc. Am. Assoc. Cancer Res.* **1981**, *22*, 255. (d) Caonico, P. G.; Pannier, W. L.; Huggins, J. W.; Rinehart, K. L., Jr. *Antimicrob. Agents Chemother.* **1982**, *22*, 696. (e) Maldonado, E.; Lavergne, J. A.; Kraiselburd, E. *P. R. Health Sci. J.* **1982**, *1*, 22; *Chem. Abstr.* **1983**, *99*, 205653*f*.
(3) (a) Crampton, S. L.; Bhuyan, B. K.; Li, L. H. *Proc. Am. Assoc. Cancer Res.* **1982**, *23*, 203. (b) Jiang, T. L.; Liu, R. H.; Salmon, S. E. *Cancer Chemother. Pharmacol.* **1983**, *11*, 1. (c) Rosof, A. H.; Johnson, P. A.; Kimmel, B. D.; Graham, J. E.; Roseman, D. L. *Proc. Am. Assoc. Cancer Res.* **1983**, *24*, 315.
(4) (a) Montgomery, D. W.; Zukowski, C. F. *Transplantation* **1985**, *40*, 49. (b) Montgomery, D. W.; Zubowski, C. F. *Fed. Proc., Am. Soc. Exp. Biol.* **1984** *43*, 368.
(5) Li, L. H.; Timmins, L. G.; Wallace, T. L.; Krueger, W. C.; Prairie, M. D.; Im, W. B. *Cancer Lett. (Shannon, Irel.)* **1984**, *23*, 279.
(6) Ewing, W. R.; Bhat, K. L.; Joullie, M. M. *Tetrahedron* **1986**, *42*, 5863.

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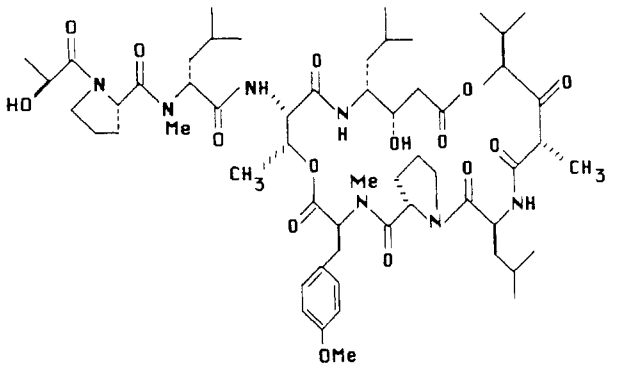
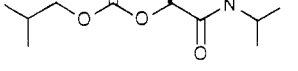


Figure 1. Didemnin B.

diastereomeric form, with the procedures developed in this study.

Preparation of β-Keto Esters. We prepared the β-keto ester functionality present in Hia by application of a Claisen-type acylation reaction[7] involving condensation of lithium enolates with carbonyl-activated derivatives of (*S*)-2-hydroxyisovaleric acid (**4a**). The latter compound was readily available from (*S*)-valine by diazotization.[8] Protection of the hydroxyl group as the THP ether[9] provided **4b**. The acid **4b** was converted[10,11] into the respective activated acyl derivatives **4c–e**, and these were caused to react with the lithium enolate of ethyl acetate at −65 °C in THF to furnish the β-keto esters **5a** in moderate yields (Table I). Reaction of (*S*)-2-hydroxyisovaleric acid (**4a**) with 2.0 equiv of isobutyl chloroformate simulataneously activated the carboxyl group and protected the hydroxyl function as the carbonate to furnish **4f**. In a one-pot reaction, **4f** was condensed with the lithium enolate of ethyl acetate to yield the β-keto ester **5b** (Scheme I).

The β-keto thio esters **6a–c** also were prepared. Condensation of the activated isovaleric acid derivatives **4c**, **4d**, **4f**, or **4g** with the lithium enolate of ethyl thioacetate provided, respectively, the β-keto thio esters **6a–c**. The crude thio esters, obtained in yields of 60–100%, showed a number of minor spots upon TLC analysis. Chromatographic purification on silica of thio ester **6b** provided pure product in a yield of only 25%. From the purification of **6b**, as also with β-keto ester **5b**, small amounts (3–6%) of the *N,N*-diisopropyl amide **7**, resulting from additionl of



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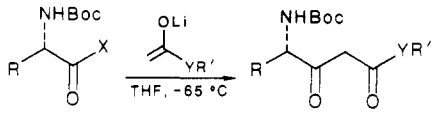
residual LDA to the carbonic anhydride, were isolated. The low yield of purified product **6b** is likely due to the apparent instability of the thio esters on silica, since subsequent studies established that coupling of the crude thio ester with esters of L-leucine, as described in the next section, routinely furnished the N-acylated leucine products in yields of 51–80%.

Table II. Preparation of β-Keto Esters from N-Protected α-Amino Acids



entry	R	X	YR′	product	yield,[a] %
1	*i*-Pr	OCO_2-*i*-Bu	OEt	**8**	77
2	*i*-Pr	2-oxypyridyl	SEt	**9**	57
3	*i*-Bu	OCO_2-*i*-Bu	OEt	**10**	56
4	*i*-Bu	Cl	OEt	**10**	78
5	H	OCO_2-*i*-Bu	OEt	**11**	40

[a] Purified yield from silica gel chromatography.

The above methodology is applicable also for the conversion of N-protected α-amino acids to the corresponding β-keto esters. Thus, conversion of the *N*-*tert*-butoxycarbonyl derivatives of L-leucine, L-valine, and glycine to their acyl-activated forms, followed by reaction with enolate, provided the β-keto-γ-amino esters **8–11** (Table II).

Preparation of the Hia-Leu Unit. Initial attempts to effect the saponification of β-keto ethyl ester **5** to the β-keto acid so as to allow coupling to L-leucine were unsuccessful. In the case of ester **5a**, reaction under usual saponification conditions lead to the isolation of isovaleric acid THP ether **4b**, apparently formed by a retro-Claisen reaction. We then turned our attention to the preparation of β-keto esters by Claisen condensation using an enolate containing an ester function possessing a potentially reactive leaving group, e.g., 2-oxypyridyl[10] and 4-methylthiophenoxy,[12] that would allow subsequent coupling of the β-keto active ester to L-leucine. However, attempts to accomplish condensation of the enolates of the above acetate active esters with acyl derivatives of **4** were unsuccessful, possibly due to elimination to a ketene upon attempted enolate formation. We were successful in preparing the thio esters **6**, as described in the above section, and turned our attention to their condensation with L-leucine to provide the requisite Hia-Leu unit.

α-Amino acids are known to couple with aryl thio esters at reasonable rates; however, coupling to alkyl thio esters is not normally useful due to the slow rates observed for these reactions.[13] That this was the case was shown in the reaction of thio ester **6a** with L-leucine methyl ester in dichloromethane at reflux where, after 13 h, only a 45% yield of the coupled product **12** was obtained. It was anticipated that the rate of the coupling process could be enhanced by the addition of a thiophilic metal cation. Such an approach has been well-documented by Masamune and co-workers in the formation of ester bonds between thio esters and alcohols as promoted by Cu(I) or Hg(II).[14] Indeed, addition of 2 equiv of cuprous iodide to a solution of the thio ester and L-leucine ester in dichloromethane at ambient temperature led to a rapid reaction that provided the desired Hia-Leu derivatives **12–15** in yields of 51–80% (Scheme II).[15] Glycine, L-alanine, and L-valine methyl esters also were condensed with thio ester

(7) (a) House, H. O. *Modern Synthetic Reactions*, 2nd ed; W. A. Benjamin: New York, 1972; Chapter 11, pp 734–765. (b) Rathke, M. W.; Deitch, J. *Tetrahedron Lett.* **1971**, 2953. (c) Hartzell, S. L.; Rathke, M. W. *Ibid.* **1976**, 2757. (d) Winkler, J. D.; Hershberger, P. M.; Springer, J. P. *Ibid.* **1986**, *27*, 5177. (e) Turner, J. A.; Jacks, W. S. *Abstracts of Papers*, 192nd National Meeting of the American Chemical Society, Anaheim, CA; American Chemical Society: Washington, DC, September 1986; ORGN 219.

(8) Cook, A. N.; Cox, S. F.; Farmer, T. H. *J. Chem. Soc.* **1949**, 1022.

(9) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.

(10) Dutta, A. S.; Morley, J. S. *J. Chem. Soc. C* **1971**, 2896.

(11) Anderson, G. W.; Zimmerman, J. E.; Callahan, F. M. *J. Am. Chem. Soc.* **1967**, *89*, 5012.

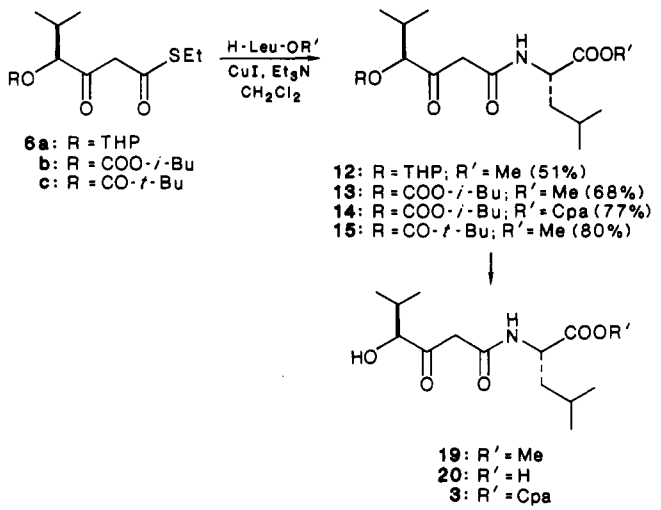
(12) Johnson, B. J.; Reuttinger, T. A. *J. Org. Chem.* **1970**, *35*, 255. Johnson, B. J.; Trask, E. G. *Ibid.* **1968**, *33*, 4521.

(13) Schroder, E.; Lubke, K. *The Peptides*; Academic: New York, 1965; Vol. I, Chapter III, pp 105–108.

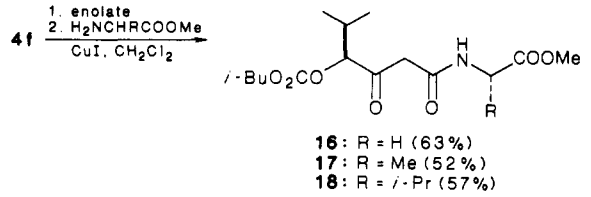
(14) Masamune, S.; Kamata, S.; Schilling, W. *J. Am. Chem. Soc.* **1975**, *97*, 3515.

(15) For a recent example of an intramolecular β-lactam formation of a thio ester promoted by Hg(II), see: Makaiyama, T.; Suzuki, H.; Yamada, T. *Chem. Lett.* **1986**, 915.

Scheme II



Scheme III

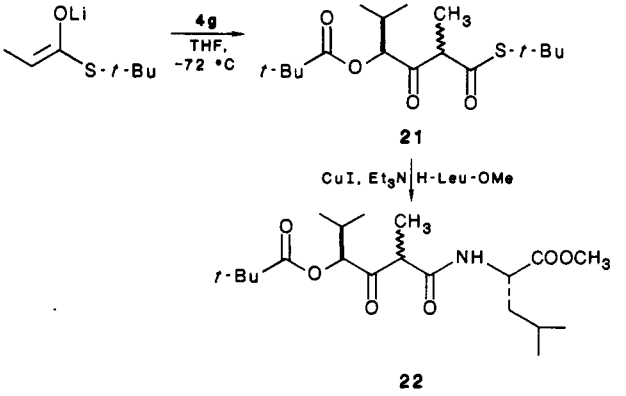


6b to yield the respective N-acylated amino acid derivatives **16–18** (Scheme III).

The ^1H and ^{13}C NMR spectra of the Hia-Leu esters **13**, **14**, and **16–18** were consistent for mixtures of keto–enol tautomers existing in ratios of 3:1 to 4:1. In all cases, the relative intensity of the α-methylene of the β-keto amide moiety was reduced, while a singlet around 5.2 ppm was present and was assignable to the vinyl proton of the enol. Two resonances also were observed for the γ and amide protons. ^{13}C NMR spectra for these compounds also showed doubling of a number of peaks and, specifically, single resonances at about 90 and 165 ppm due to the olefinic carbons of the enol. We noted that tautomerism was observed only when the γ-hydroxyl of the β-keto amide was protected with a carbonate function, as derivatives lacking this function possessed NMR spectra consistent for only the keto form. That rotamers about the carbonate function or the amide bond were responsible for the two observed forms seemed unlikely in terms of the above NMR data. The assignments of the signals in the ^{13}C NMR spectrum of **13** were corroborated by use of a CAPT program that showed the methylene and quarternary carbons as positive signals, while the methyl and methine carbons appeared as negative signals. The methylene groups of the isobutyl carbonate and leucine side chain each appeared as two closely spaced signals at the appropriate shift values. Only one signal for the α-methylene carbon of the Hia unit was observed at 45.9 ppm rather than two signals as would be expected for a pair of rotamers. The α-methine carbon of the enol was confirmed by the presence of a negative signal at 90.3 ppm.

The β-ketoacyl-L-leucine derivatives **12–15** did not show the presence of other diastereomers due to racemization in their 300-MHz ^1H and ^{13}C NMR spectra, thus providing evidence that minimal or no racemization had occurred in the preparation of the β-keto thio esters **6**. Further confirmation was obtained by the preparation of **13** from racemic isovaleric acid **4a**; the ^1H and ^{13}C NMR spectra of the diastereomeric **13** clearly showed signals for both isomers.

Scheme IV



Utilization of the Hia-Leu unit in peptide synthesis requires removal of the protecting groups associated with the carboxyl and hydroxyl functions. Initial attempts to remove the THP ether in **12** by use of *p*-toluenesulfonic acid in methanol or acetic acid in water and THF led to the formation of a complex mixture of products. However, treatment of **12** with trifluoroacetic acid cleanly resulted in removal of the THP ether function to give **19** in good yield. Treatment of the Hia-Leu derivatives of **13** or **14** with 10% NaOH for 30 min provided the free acid **20** in 90–97% yield. Hydrolysis of **15** with potassium *tert*-butoxide and water[16] for 40 h to effect removal of the bulky 2,2,2-trimethylacetyl group produced acid **20**, which was shown by analysis of its ^1H and ^{13}C NMR spectra to be a 70:30 mixture of diastereomers due to epimerization of the C-4 position of the Hia moiety. The free acid **20**, obtained from **13** or **14** as above, did not show the presence of any epimer in the NMR spectra. Alkylation of the carboxylate anion of **20** with *p*-chlorophenacyl chloride gave ester **3**.[17] The Hia-Leu ester **3** has proven to be a suitable derivative for incorporation into depsipeptide fragments related to the didemnins.

Preparation of Hip-Leu Unit. The methodology described herein also is applicable for the preparation of the Hip-Leu unit common to the didemnins. Acylation of lithium *tert*-butyl thiopropionate with the carbonic anhydride **4g** furnished the β-keto thio ester **21**, obtained after column chromatography in a yield of 54%. Treatment of **21** with L-leucine methyl ester under the usual copper(I)-promoted coupling conditions gave the protected Hip-Leu **22** in 76% yield (Scheme IV). The above acylation of the thiopropionate enolate afforded minimal diastereoselectivity and gave, as would be expected, **21** as a mixture of epimers (ratio 58:42 from 300-MHz ^1H NMR analysis). Conversion of **21** to **22** provided a 1:1 mixture of Hip C-2 epimers, which proved to be inseparable.

Experimental Section

All solvents used were distilled in glass. Tetrahydrofuran was distilled from benzophenone ketyl. Dichloromethane was distilled from P_2O_5 and stored over Linde 3-Å molecular sieves. Nuclear magnetic resonance (NMR) spectra were obtained for all compounds on a 300-MHz FT spectrometer. Optical rotations were recorded on a automatic polarimeter. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. Preparative and analytical TLC were performed on commercially prepared silica gel on glass plates with the solvent systems: A, hexane–ethyl acetate (80:20); B, hexane–ethyl acetate (50:50); C, chloroform–acetone (80:20). Column chromatography was carried out in glass columns with silica gel 60 (0.040–0.064 mm). Low-pressure column

(16) Gassman, P. G.; Schenk, W. N. *J. Org. Chem.* **1977**, *42*, 918.
(17) Corey, E. J.; Bhattacharyya, S. *Tetrahedron Lett.* **1977**, 3919.

chromatography was carried out in a similar manner as for flash chromatography[18] except that 2 or 3 times longer columns of silica gel were used.

(*S*)-2-[(2-Tetrahydropyranyl)oxy]-3-methylbutanoic Acid (4b). A solution of $NaNO_2$ (12 g, 0.17 mol) in water (50 mL) was added dropwise to an ice-cooled solution of L-valine (10.1 g, 0.086 mol) in 1 N H_2SO_4 (160 mL). The reaction was stirred for 2 h at ice-cooled temperature and overnight at room temperature. The solution was extracted with ethyl ether (4 × 100 mL) and concentrated by azeotropic distillation with benzene to provide a yellow oil. Crystallization from hexane provide **4a** as white needles: 8.06 g; 79%; mp 62–63 °C (lit.[8] mp 65 °C).

To a stirred solution of the above solid (6.0 g, 0.051 mol) in dichloromethane (100 mL) was added 3,4-dihydro-2*H*-pyran (4.6 mL, 0.051 mol) and pyridinium *p*-toluenesulfonate (1.0 g).[9] The reaction mixture was stirred at room temperature overnight. Most of the organic solvent was removed in vacuo; the residue was taken up into ethyl ether (150 mL), washed with brine (50 mL), dried (Na_2SO_4), and concentrated to provide **4b** as a pale yellow oil in quantitative yield with a trace of THP ether ester: NMR (60 mHz, $CDCl_3$) δ 1.0 [m, $CH(CH_3)_2$, 6 H], 1.36–2.5 [br, 7 H, $(CH_2)_3$ in THP, $CH(CH_3)_2$], 3.2–5.0 [set of m, 4 H, OCH_2, OCHO, OCHCO), 9.6 (br s, 1 H, COOH).

Formation of β-Keto Esters. General Procedure. A. Acid Chloride and Mixed-Anhydride Method.[11] To a stirred solution (0.1–0.5 M) of (*S*)-2-hydroxyisovaleric acid (**4a**) or 2-hydroxyisovaleric acid THP ether (**4b**) (2–15 mmol) in THF was added triethylamine (2.0 equiv), followed by isobutyl chloroformate (1.0 or 2.0 equiv) or 2,2,2-trimethylacetyl chloride (2.0 equiv) or oxalyl chloride (1.0 equiv) at −20 to −30 °C. After the mixture was stirred for 30 min at the same temperature, triethylamine hydrochloride was filtered off, and the filtrate was used for the next reaction.

Meanwhile, to a stirred solution of diisopropylamine (2.0 equiv, 0.05–1.0 M) in THF was added *n*-BuLi (2.0 equiv) at 0 °C, and the mixture was stirred for 10 min. After the reaction mixture was cooled to −65 to −70 °C, freshly distilled ethyl acetate or ethyl thioacetate (1.0 equiv) was added. After this solution was stirred for 20–30 min, the above acid chloride or mixed anhydride was added as a solution in THF. The mixture was stirred at −65 to −70 °C for 20 min, and 1 N HCl or saturated NH_4Cl solution was added, and the resultant mixture was warmed to room temperature. Extraction with ethyl acetate was followed by washing with brine and drying (Na_2SO_4). Evaporation of the solvent provided the crude β-keto esters. Purification of products was performed by silica gel chromatography.

B. Active-Ester Method.[10] To a stirred solution of **4b** in dichloromethane at 2 °C were added 4-(dimethylamino)pyridine[19] (0.1 equiv) and 2-hydroxypyridine (1.1 equiv), followed by 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (1.1 equiv). After being stirred for 3 h at 2 °C, the reaction mixture was stirred at room temperature overnight. Most of the organic solvent was evaporated, and the residue was taken up into ethyl acetate and water. The organic phase was separated, washed with 5% $NaHCO_3$, and H_2O, dried (Na_2SO_4), and concentrated to provide an oil. Without further purification, this oil was subjected to the condensation reaction as described above.

Ethyl (*S*)-4-[(Tetrahydropyranyl)oxy]-5-methyl-3-oxohexanoate (5a). Ester **5a** was obtained from the acid chloride **4c** as a colorless oil in 57% yield after purification by preparative TLC (silica gel; chloroform–acetone, 95:5): TLC R_f (solvent C) 0.78; $[\alpha]^{23}_D$ −92.4° (*c* 0.3, MeOH); NMR ($CDCl_3$) δ 1.00 (set of m, 6 H), $CH(CH_3)_2$], 1.27 (d of t, 3 H, *J* = 6.9 Hz, CH_2CH_3), 1.4–1.9 [br m, 6 H, $(CH_2)_3$ in THP], 2.16 [m, 1 H, $CH(CH_3)_2$], 3.53 (q of AB pattern, 2 H, *J* = 15 Hz, $COCH_2CO$), 3.87 (m, 2 H, CH_2O in THP), 3.97 (d, 1 H, *J* = 6 Hz, OCHCO), 4.20 (d of q, 2 H, *J* = 6.9 Hz, CH_2CH_3), 4.57 (m, 1 H, OCHO in THP). Anal. Calcd for $C_{14}H_{24}O_5$: C, 61.76; H, 8.82. Found: C, 61.88; H, 8.94.

Ethyl (*S*)-4-[(Isobutoxycarbonyl)oxy]-5-methyl-3-oxohexanoate. Ester Ester **5b** was obtained from the anhydride **4f** as a colorless oil in 61% yield after purification by low-pressure column chromatography (silica gel; hexane–ethyl acetate, 95:5): TLC R_f (solvent A) 0.78; $[\alpha]^{23}_D$ −23.7 (*c* 1.8, $CHCl_3$); NMR ($CDCl_3$) δ 0.96 [set of m, 12 H, $CH(CH_3)_2 \times 2$], 1.27 (t of d, 3 H, *J* = 6.9 Hz, CH_2CH_3), 2.00 [m, 1 H, $OCH_2CH(CH_3)_2$], 2.30 [m, 1 H, $CH(CH_3)_2$], 3.38 and 3.53 (2 s, 2 H, $COCH_2CO$), 3.95 (t, 2 H, *J* = 6.9 Hz, OCH_2CH), 4.20 (m, 2 H, *J* = 7.2 Hz, CH_2CH_3), 4.92 (d, 1 H, OCHCO, *J* = 5.1 Hz), 5.20 (s, C=CH); assigned as 4:1 ratio of keto–enol tautomers. Anal. Calcd for $C_{14}H_{24}O_6$: C, 58.33; H, 8.33. Found: C, 58.13; H, 8.47.

Formation of β-Keto-α-amino Esters 8–11. General Procedure. The acid chloride, mixed carbonic anhydride, or active ester methods were performed by using the same procedure as described above with the appropriate *N*-Boc-α-amino acid (2.0–4.6 mmol, 0.1–0.2 M). The activated amino acid was added to a solution of the enolate (0.04–0.1 M) in THF at −65 °C, and the crude product was purified by low-pressure column chromatography on silica gel with a hexane and ethyl acetate mixture as an eluant.

Ethyl (*S*)-4-[(*tert*-Butoxycarbonyl)amino]-5-methyl-3-oxohexanoate (8). Ester **8** was obtained from Boc-L-valine via the isobutyl carbonic anhydride as a colorless oil in 77% yield after purification by low-pressure column chromatography (hexane–ethyl acetate, 95:5): TLC R_f (solvent A) 0.51; $[\alpha]^{22}_D$ +25.0° (*c* 0.2, $CHCl_3$); NMR ($CDCl_3$) δ 0.94 [m, 6 H, $CH(CH_3)_2$], 1.28 (t, 3 H, *J* = 7.2 Hz, CH_2CH_3), 1.45 [s, 9 H, $C(CH_3)_3$], 2.25 [m, 1 H, $CH(CH_3)_2$], 3.54 (s, 2 H, $COCH_2CO$), 4.19 (q, 2 H, *J* = 7.2 Hz, CH_2CH_3), 4.43 (m, 1 H, *J* = 4.5 Hz, NHCH), 5.13 (br d, 1 H, *J* = 9.9 Hz, NH). Anal. Calcd for $C_{14}H_{25}NO_5$: C, 58.54; H, 8.71; N, 4.88. Found: C, 58.34; H, 8.64; N, 4.81.

(*S*)-4-[(*tert*-Butoxycarbonyl)amino]-5-methyl-3-oxohexanoic Acid Ethyl Thio Ester. (9). Thio ester **9** was obtained by use of Boc-L-valine 2-pyridyl ester as a pale pink oil in 57% yield after purification by low-pressure column chromatography (hexane–ethyl acetate, 95:5): TLC R_f (solvent A) 0.67; NMR ($CDCl_3$) δ 0.8–1.1 [set of m, 6 H, $CH(CH_3)_2$], 1.27 (t of d, 3 H, *J* = 7.2 Hz, CH_2CH_3), 1.45 [s, 9 H, $C(CH_3)_3$], 2.25 [m, 1 H, $CH(CH_3)_2$], 2.95 (q of d, 2 H, CH_2CH_3), 3.75 (q of AB pattern, 1.4 H, *J* = 15 Hz, $COCH_2CO$), 4.30 (m, 1 H, *J* = 4.5 Hz, NHCH), 5.10 (br, 1 H, NH), 5.5 (s, 0.3 H, C=CH); assigned as 2:1 ratio of keto–enol tautomers. A satisfactory combustion analysis could not be obtained for **9**. Thio ester **9** appeared to be unstable as a purified sample, after standing at room temperature for several days, showed multiple spots upon TLC analysis.

Ethyl (*S*)-4-[(*tert*-Butoxycarbonyl)amino]-6-methyl-3-oxoheptanoate (10). Ester **10** was obtained by use of Boc-L-leucine and isobutyl chloroformate or oxalyl chloride as a colorless oil in 56% or 78% yield after purification by low-pressure column chromatography (hexane–ethyl acetate, 95:5 to 70:30): TLC R_f (solvent A) 0.76; $[\alpha]^{18}_D$ −19.6° (*c* 0.24, $CHCl_3$); NMR ($CDCl_3$) δ 0.97 [m, 6 H, $CH_2CH(CH_3)_2$], 1.28 (t, 3 H, *J* = 7.2 Hz, CH_2CH_3), 1.45 [s, 9 H, $C(CH_3)_3$], 1.65 [m, 3 H, $CH_2CH(CH_3)_2$], 3.55 (q of AB pattern, 2 H, *J* = 15.0 Hz, $COCH_2CO$), 4.26 (q, 2 H, *J* = 7.2 Hz, CH_2CH_3), 4.35 (m, 1 H, NHCH), 5.00 (br, 1 H, NH). Anal. Calcd for $C_{15}H_{27}NO_5$: C, 59.80; H, 8.97; N, 4.65. Found: C, 59.61; H. 8.73; N, 4.49.

Ethyl 4-[(*tert*-Butoxycarbonyl)amino]-3-oxobutanoate (11). Compound **11** was obtained by use of Boc-glycine and isobutyl chloroformate as a colorless oil in 40% yield after purification by low-pressure column chromatography (hexane–ethyl acetate, 95:5 to 80:20): TLC R_f (solvent A) 0.25; NMR ($CDCl_3$) δ 1.29 (t, 3 H, *J* = 7.2 Hz, CH_2CH_3), 1.45 [s, 9 H, $C(CH_3)_3$], 3.48 (s, 2 H, $COCH_2CO$), 4.15 (m, 2 H, $NHCH_2$), 4.20 (q, 2 H, *J* = 7.2 Hz, OCH_2CH_3), 5.21 (br, 1 H, NH).

(*S*)-4-[(Isobutoxycarbonyl)oxy]-5-methyl-3-oxohexanoic Acid Ethyl Thio Ester (6b). Anhydride **4f** was treated with lithium ethyl thioacetate to yield **6b** in a crude yield of 94%. The crude product was purified by low-pressure column chromatography (hexane–ethyl acetate, 95:5) to give a colorless oil in 25% yield. The low yield of purified product is likely due to the apparent instability of **6b** on silica gel. In subsequent reactions, the crude β-keto thio ester was used as obtained: NMR ($CDCl_3$) δ 1.00 [set of m, 12 H, $CH(CH_3)_2 \times 2$], 1.27 (set of m, *J* = 7.5 Hz, CH_2CH_3), 2.00 [m, 1 H, $CH(CH_3)_2$], 2.25 (m, 1 H, $OCH(CH_3)_2$], 2.94 (m, 2 H, *J* = 7.8 Hz, CH_2CH_3), 3.77 (d, 1.5 H, $COCH_2CO$), 3.95 [m, 2 H, *J* = 6.9 Hz, $CH_2CH(CH_3)_2$], 4.85 (2 d, 1 H, *J* = 4.2, 4.8 Hz, OCHCO), 5.59 (s, 0.25 H, C=CH); assigned as 4:1 ratio of keto–enol tautomers; ^{13}C NMR δ 98.7 (=C of enol), 49.5 (CH_2

(18) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(19) Neiss, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 552. Dhaon, M. K.; Olsen, R. K.; Ramasamy, K. J. *Org. Chem.* **1982**, *47*, 1962.

of keto form). Amide 7 also was isolated in 6% yield: NMR ($CDCl_3$) δ 0.96 and 1.04 [2 d, 12 H, J = 6.6 and 6.9 Hz, $CH(CH_3)_2$ × 2], 1.27 and 1.44 [2 q, 12 H, J = 6.6 Hz, $CH(CH_3)_2$ × 2], 2.00 and 2.12 [2 septet, 2 H, $CH(CH_3)_2$ × 2], 3.40 and 4.08 [2 septet, 2 H, $NCH(CH_3)_2$ × 2], 3.93 [d, 2 H, J = 6.9 Hz, $CH_2CH(CH_3)_2$], 4.91 (d, 1 H, J = 6 Hz, OCHCO).

Amide Bond Formation. General Procedure. The crude β-keto thio ester **6** (2.5–5.0 mmol), which was contaminated by several minor components as shown by TLC analysis, was dissolved in dichloromethane and added to a stirred solution of triethylamine (1.0 equiv) and the corresponding α-amino acid ester hydrochloride or trifluoroacetate salt in dichloromethane (final concentration 0.07–0.17 M) at room temperature. To this solution was added cuprous iodide (2.0 equiv), and the mixture was stirred for 20–30 min. Dichloromethane and 1 N HCl were added, and the mixture was filtered. The filtrate was washed with 1 N HCl, saturated $NaHCO_3$, and brine. After drying (Na_2SO_4), concentration of the solvent provided an oil, which was purified by chromatography.

***N*-[(*S*)-4-[(2-Tetrahydropyranyl)oxy]-5-methyl-3-oxohexanoyl]-L-leucine Methyl Ester (12).** Ester **12** was obtained from **6a** and $Cl^-H_2^+$-Leu-OCH_3 (0.75 equiv) as a colorless oil in 51% yield after purification by low-pressure column chromatography (hexane–ethyl acetate, 80:20): TLC R_f (solvent A) 0.25; $[\alpha]^{23}_D$ −64.5° (*c* 0.9, $CHCl_3$); NMR ($CDCl_3$) δ 0.94 [set of m, 12 H, $CH(CH_3)_2$ × 2], 1.4–2.2 [set of m, 10 H, $(CH_2)_3$ in THP, $CH(CH_3)_2$ × 2, CH_2CH], 3.52 (q of AB pattern, 2 H, $COCH_2CO$), 3.72 (s, 3 H, OCH_3), 3.80 (m, 2 H, OCH_2CH_2 in THP), 4.40 (d, 1 H, J = 6.0 Hz, OCHCO), 4.63 (m, 2 H, OCHO in THP, NHCH), 7.5 (br, 1 H, NH). Anal. Calcd for $C_{19}H_{33}NO_6$: C, 61.46; H, 8.89; N, 3.77. Found: C, 61.35; H, 8.99; N, 3.60.

***N*-[(*S*)-4-[(Isobutoxycarbonyl)oxy]-5-methyl-3-oxohexanoyl]-L-leucine Methyl Ester (13).** Compound **13** was obtained by use of **6b** and $TFA^-H_2^+$-Leu-OMe (0.9 equiv) as a colorless oil in 68% yield after purification by low-pressure column chromatography (hexane–ethyl acetate, 80:20): TLC R_f (solvent A) 0.40; $[\alpha]^{23}_D$ −20.2° (*c* 2.1, $CHCl_3$); NMR ($CDCl_3$) δ 0.96 [set of m, 18 H, $CH(CH_3)_2$ × 3], 1.63 [m, 3 H, $CH_2CH(CH_3)_2$ in leucine], 2.0 [m, 1 H, $CH(CH_3)_2$ in carbonate], 2.3 [m, 1 H, $CH(CH_3)_2$], 3.54 (s, 1.6 H, $COCH_2CO$), 3.72 and 3.74 (2 s, 3 H, OCH_3), 3.94 [d, 2 H, J = 6.6 Hz, $OCH_2CH(CH_3)_2$], 4.60 (m, 1 H, NHCH), 4.87 (2 d, 1 H, ratio 4:1, J = 4.2 Hz, OCHCO), 5.2 (s, 0.2 H, C=CH), 6.7 (d, 0.25 H, NH), 7.4 (d, 0.75 H, NH); assigned as 4:1 ratio of keto–enol tautomers; ^{13}C NMR δ 90.1 (=C of enol), 45.8 (CH_2 of keto). Anal. Calcd for $C_{19}H_{33}NO_7$: C, 58.91; H, 8.53; N, 3.62. Found: C, 58.93; H, 8.46; N, 3.59.

***N*-[(*S*)-4-[(Isobutoxycarbonyl)oxy]-5-methyl-3-oxohexanoyl]-L-leucine *p*-Chlorophenacyl Ester (14).** Ester **14** was obtained by use of **6b** and $Cl^-H_2^+$-Leu-OCpa (0.86 equiv) as a colorless oil in 77% yield after purification by low-pressure column chromatography (hexane–ethyl acetate, 80:20): TLC R_f (solvent B) 0.61; $[\alpha]^{23}_D$ −27.8° (*c* 1.8, $CHCl_3$); NMR ($CDCl_3$) 0.96 [set of m, 18 H, $CH(CH_3)_2$ × 2], 1.7–2.1 [m, 4 H, CH_2CH in leucine, $CH_2CH(CH_3)_2$], 2.3 [m, 1 H, $CH(CH_3)_2$], 3.53 (q of AB pattern, 1.5 H, J = 15 Hz, $COCH_2CO$), 3.93 [d, 2 H, J = 6.6 Hz, $OCH_2CH(CH_3)_2$], 4.75 (m, 1 H, NHCH), 4.84 (d, 0.5 H, J = 4.2 Hz, OCHCO), 4.95 (d, 0.5 H, J = 3.6 Hz, OCHCO), 5.24 and 5.46 (2 d, 2 H, J = 16.5 Hz, OCH_2CO), 6.25 (br, 0.75 H, NH and C=CH), 7.36 (d, 0.5 H, J = 7.5 Hz, NH), 7.48 and 7.83 (d of d, 4 H, J = 8.7 Hz, phenyl); assigned as 3:1 ratio of keto–enol tautomers. Anal. Calcd for $C_{26}H_{36}NO_8Cl$: C, 59.37; H, 6.85; N, 2.66. Found: C, 59.49; H, 6.83; N, 2.71.

***N*-[(*S*)-4-(2,2,2-Trimethylacetoxy)-5-methyl-3-oxohexanoyl]-L-leucine Methyl Ester (15).** Compound **15** was obtained from **6c** and $Cl^-H_2^+$-Leu-OMe (0.8 equiv) as a colorless oil in 80% yield after purification by low-pressure column chromatography (hexane–ethyl acetate, 80:20): TLC R_f (solvent A) 0.25; $[\alpha]^{23}_D$ −15.9° (*c* 1.7, $CHCl_3$); NMR ($CDCl_3$) δ 0.94 [set of m, 12 H, $CH(CH_3)_2$ × 2], 1.27 [s, 9 H, $C(CH_3)_3$], 1.65 [m, 3 H, $CH_2CH(CH_3)_2$], 2.25 [m, 1 H, $CH(CH_3)_2$], 3.48 (q of AB pattern, 2 H, J = 18 Hz, $COCH_2CO$), 3.73 (s, 3 H, OCH_3), 4.60 (m, 1 H, NHCH), 4.80 (d, 1 H, J = 4.5 Hz, OCHCO), 7.25 (br, 1 H, NH). Anal. Calcd for $C_{19}H_{33}NO_6$: C, 61.19; H, 8.89; N, 3.77. Found: C, 61.34; H, 9.03; N, 3.90.

***N*-[(*S*)-4-[(Isobutoxycarbonyl)oxy]-5-methyl-3-oxohexanoyl]glycine Methyl Ester (16).** Ester **16** was obtained from **6b** and $Cl^-H_2^+$-Gly-OMe (0.83 equiv) as a colorless oil in 63% yield after purification by low-pressure column chromatography (hexane–ethyl acetate, 60:40): R_f (solvent B) 0.49; $[\alpha]^{23}_D$ −15.5° (*c* 2.3, $CHCl_3$); NMR ($CDCl_3$) δ 0.95 and 0.97 [2 d, 9 H, $CH(CH_3)_2$], 1.07 [d, 3 H, $CH(CH_3)$], 2.00 [m, 1 H, $CH(CH_3)_2$], 2.30 [m, 1 H, $OCH_2CH(CH_3)_2$], 3.56 (q of AB pattern, 1.5 H, J = 17 Hz, $COCH_2CO$), 3.75 and 3.76 (2 s, 3 H, OCH_3), 3.95 [d, 2 H, J = 6.6 Hz, $OCH_2CH(CH_3)_2$], 4.06 (d, 2 H, J = 5.4 Hz, $NHCH_2CO$), 4.84 (d, 1 H, J = 4.2 Hz, OCHCO), 5.20 (s, 0.25 H, C=CH), 7.50 (br s, 1 H, NH); assigned as 3:1 ratio of keto–enol tautomers. Anal. Calcd for $C_{15}H_{25}NO_7$: C, 54.38; H, 7.55; N, 4.23. Found: C, 54.63; H, 7.49; N, 4.20.

***N*-[(*S*)-4-[(Isobutoxycarbonyl)oxy]-5-methyl-3-oxohexanoyl]-L-alanine Methyl Ester (17).** Ester **17** was obtained from **6b** and $Cl^-H_2^+$-Ala-OMe (0.83 equiv) as a coloreless oil in 52% yield after purification by low-pressure column chromatography (hexane–ethyl acetate, 80:20 to 50:50): $[\alpha]^{23}_D$ −18.8° (*c* 2.0, $CHCl_3$); TLC R_F (solvent B) 0.66; NMR ($CDCl_3$) δ 0.98 [2 d, 9 H, $CH(CH_3)_2$, $CH(CH_3)$], 1.07 [d, 3 H, J = 6.9 Hz, $CH(CH_3)$], 1.44 (d of d, 3 H, J = 7.2 Hz, CH_3 in alanine), 2.00 [m, 1 H, $CH(CH_3)_2$], 2.28 [m, 1 H, $CH(CH_3)_2$], 3.51 (q of AB patern, 1.5 H, J = 15 Hz, $COCH_2CO$), 3.75 and 3.76 (2 s, 3 H, OCH_3), 3.95 [d of d, 2 H, J = 4.2 Hz, 4.8 Hz, $OCH_2CH(CH_3)_2$], 4.58 (m, 1 H, J = 6.9 Hz, NHCH), 4.81 (d, 1 H, J = 4.2 Hz, OCHCO), 5.08 (s, 0.25 H, C=CH), 7.30 (br s, 1 H, NH); assigned as 3:1 ratio of keto–enol tautomers. Anal. Calcd for $C_{16}H_{27}NO_7$: C, 55.65; H, 7.83; N, 4.06. Found: C, 55.65; H, 7.71; N, 4.00.

***N*-[(*S*)-4-[(Isobutoxycarbonyl)oxy]-5-methyl-3-oxohexanoyl]-L-valine Methyl Ester (18).** Compound **18** was obtained from **6b** and $Cl^-H_2^+$-Val-OMe (0.83 equiv) as a colorless oil in 57% yield after purification by low-pressure column chromatography (hexane–ethyl acetate, 80:20): TLC R_f (solvent B) 0.77; $[\alpha]^{23}_D$ −19.7° (*c* 1.7, $CHCl_3$); NMR ($CDCl_3$) δ 0.98 [m, 15 H, $CH(CH_3)$ × 5], 1.07 [d, 3 H, J = 6.6 Hz, $CH(CH_3)$], 2.00 [m, 1 H, $CH(CH_3)_2$], 2.20 [m, 2 H, $CH(CH_3)_2$ × 2], 3.53 (s, 1.6 H, $COCH_2CO$), 3.74 and 3.76 (2 s, 3 H, OCH_3), 3.94 [d of d, 2 H, J = 5.4 Hz, $OCH_2CH(CH_3)_2$], 4.53 (m, 1 H, J = 4.8 Hz, NHCHCO), 4.80 (d, 1 H, J = 4.5 Hz, OCHCO), 5.11 (s, 0.2 H, C=CH), 7.30 br d, 1 H, NH); assigned as 4:1 ratio of keto–enol tautomers. Anal. Calcd for $C_{18}H_{31}NO_7$: C, 57.91; H, 8.31; N, 3.75. Found: C, 57.91; H, 8.04; N, 3.79.

***N*-[(*S*)-4-Hydroxy-5-methyl-3-oxohexanoyl]-L-leucine Methyl Ester (19).** Compound **12** (390 mg, 1.05 mmol) was treated with trifluoroacetic acid (1.0 mL) at room temperature for 30 min. Most of the excess trifluoroacetic acid was removed in vacuo, and the residue was dissolved in ethyl acetate (40 mL). The ethyl acetate solution was washed with saturated $NaHCO_3$ (20 mL), dried (Na_2SO_4), and concentrated to provide an oil. The crude product was purified by low-pressure column chromatography (hexane–ethyl acetate, 70:30 to 50:50) to give **19** as a colorless oil (210 mg, 70%): TLC R_f (solvent B) 0.50; $[\alpha]^{23}_D$ +16.1° (*c* 1.6, $CHCl_3$); NMR ($CDCl_3$) δ 0.79 [d, 3 H, $CH(CH_3)_2$], 0.94 [m, 6 H, $CH(CH_3)_2$ in leucine], 1.10 [d, 3 H, $CH(CH_3)_2$], 1.64 [m, 3 H, $CH_2CH(CH_3)_2$], 2.20 [m, 1 H, $CH(CH_3)_2$], 3.56 (q of AB pattern, 2 H, J = 15.6 Hz, $COCH_2CO$), 3.74 (s, 3 H, OCH_3), 4.13 (br s, 1 H, OCHCO), 4.60 (m, 1 H, NHCH), 7.18 (d, 1 H, NH). Anal. Calcd for $C_{14}H_{25}NO_5$: C, 58.54; H, 8.71; N, 4.88. Found: C, 58.47; H, 8.95; N, 5.12.

***N*-[(*S*)-4-Hydroxy-5-methyl-3-oxohexanoyl]-L-leucine *p*-Chlorophenacyl Ester (3).** A solution of **13** (1.32 g, 3.41 mmol) in 10% NaOH (7.0 mL) and ethyl ether (30 mL) was stirred at room temperature for 1 h. Saturated $NaHCO_3$ (20 mL) was added, and the aqueous layer was acidified (pH 2) and extracted with ethyl acetate (2 × 30 mL). The ethyl acetate extracts were combined, washed with brine (30 mL), dried (Na_2SO_4), and concentrated to give **20** (900 mg, 97%) as a pale yellow solid. Compound **20** also was prepared from ester **14** under the same conditions to furnish 90% yield of purified product (preparative TLC; silica gel; hexane–ethyl acetate, 1:1): mp 94–96 °C; $[\alpha]^{23}_D$ −20.1° (*c* 1.1, MeOH); NMR ($CDCl_3$) δ 0.80 [d, 3 H, J = 6.9 Hz, $CH(CH_3)_2$], 0.94 [t, 6 H, $CH_2CH(CH_3)_2$ in leucine], 1.07 [d, 3 H, J = 6.6 Hz, $CH(CH_3)_2$], 1.68 [m, 3 H, $CH_2CH(CH_3)_2$], 2.19 [m, 1 H, $CH(CH_3)_2$], 3.62 (q of AB pattern, 2 H, J = 16.2 Hz, $COCH_2CO$), 4.14 (d, 1 H, OCHCO), 4.54 (m, 1 H, NHCH), 6.0

(br, 2 H, OH and COOH), 7.49 (d, 1 H, J = 7.5 Hz, NH).

Without further purification, the above solid (600 mg, 2.2 mmol) was dissolved in acetone (80 mL), and to this solution was added *p*-chlorophenacyl bromide (520 mg, 2.2 mmol) and $KHCO_3$ (230 mg, 2.3 mmol). The mixture was heated at reflux for 3.5 h. The hot solution was filtered, and the filtrate was concentrated to give a brown oil. The crude product was purified by low-pressure column chromatography (hexane–ethyl acetate, 80:20 to 50:50) to provide **3** (810 mg, 87%) as an oil: TLC R_f (solvent B) 0.43; $[\alpha]^{23}_D$ −19.1° (*c* 1.3, $CHCl_3$); NMR ($CDCl_3$) δ 0.78 [d, 3 H, J = 6.9 Hz, $CH(CH_3)_2$], 0.97 [t, 6 H, $CH_2CH(CH_3)_2$], 1.08 [d, 3 H, J = 6.9 Hz, $CH(CH_3)_2$], 1.75 [m, 3 H, $CH_2CH(CH_3)_2$], 2.20 [m, 1 H, $CH(CH_3)_2$], 3.61 (q of AB pattern, 2 H, J = 15.3 Hz, $COCH_2CO$), 3.74 (d, 1 H, OH, J = 5.1 Hz), 4.13 (d, 1 H, J = 3.0 Hz, OCHCO), 4.74 (m, 1 H, NHCH), 5.26 and 5.42 (q of AB pattern, 2 H, J = 16.5 Hz, OCH_2CO), 7.28 (d, 1 H, J = 8.1 Hz, NH), 7.46 and 7.83 (2 dd, 4 H, J = 6.6 Hz, phenyl); ^{13}C NMR δ 15.3, 19.6, 21.5, 22.9, 24.8, 30.9, 40.9, 45.9, 50.9, 66.2, 81.3, 128.9, 129.1, 131.9, 140.3, 165.1, 171.8, 190.2, 207.7. Anal. Calcd for $C_{21}H_{28}NO_6Cl$: C, 59.22; H, 6.58; N, 3.29. Found: C, 59.12; H, 6.62; N, 3.18.

***N*-[(*S*)-4-Hydroxy-5-methyl-3-oxohexanoyl]-L-leucine (20) from 15.** To a stirred slurry of KO-*t*-Bu (30 g, 260 mmol) at room temperature in ethyl ether (150 mL) was added water (1.5 mL, 83 mmol). After 5 min, a solution of **15** (4.9 g, 13.2 mmol) in ethyl ether (100 mL) was added. After the mixture was stirred for 40 h at room temperature, water (40 mL) was added, and the resultant mixture was extracted with saturated $NaHCO_3$ (3 × 30 mL). The aqueous extracts were acidified (pH 2) and extracted with ethyl acetate (3 × 100 mL), and the organic extracts were dried (Na_2SO_4) and concentrated to give an oil. The crude product was purified by low-pressure column chromatography (chloroform–acetone, 80:20) to provide **20** (2.37 g, 70%) as a pale yellow solid: NMR showed the product to exist as an epimerized form in 70:30 ratio.

(2*SR*, 4*S*)-4-(2,2,2-Trimethylacetoxy)-2,5-dimethyl-3-oxohexanoic Acid *tert*-Butyl Thio Ester (21). Anhydride **4g** (3.6 g, 12.7 mmol) in THF (10 mL) was treated with lithium *tert*-butyl thiopropionate (25 mmol) in THF (20 mL) at −72 °C following the usual procedure. Purification by low-pressure column chromatography (hexane–ethyl acetate, 95:5) furnished **21** (2.2 g, 54%): TLC R_f (solvent A) 0.85; NMR ($CDCl_3$) δ 0.88–1.1 [set of m, 6 H, $CH(CH_3)_2$], 1.27 [2 s, 9 H, $C(CH_3)_3$], 1.33 and 1.38 (2 d, 3 H, J = 6.9, 7.3 Hz, $CHCH_3$), 1.47 [2 s, 9 H, $C(CH_3)_3$], 2.37 [m, 1 H, $CH(CH_3)_2$], 3.82 and 3.91 (2 q, 1 H, J = 6.6, 7.2 Hz, $CHCH_3$), 5.05 and 5.10 (2 d, 1 H, J = 3.0, 4.2 Hz, OCHCO); assigned as 58:42 ratio of diastereomers.

***N*-[2*SR*,4*S*]-4-(2,2,2-Trimethylacetoxy)-2,5-dimethyl-3-oxohexanoyl]-L-leucine Methyl Ester (22).** Compound **22** was obtained by the usual manner as described above from **21** (600 mg, 1.82 mmol) and $Cl^-H_2^+$-Leu-OMe (330 mg, 1.82 mmol) as a yellow oil in 76% yield after purification by low-pressure column chromatography (hexane–ethyl acetate, 95:5): TLC R_f (solvent A) 0.48; $[\alpha]^{23}_D$ − 2.28 (*c* 1.01, $CHCl_3$); NMR ($CDCl_3$) δ 0.87–1.10 [set of m, 12 H, $CH(CH_3)_2 \times 2$], 1.27 [s, 9 H, $C(CH_3)_3$], 1.37 and 1.49 (2 s, 3 H, J = 7.5, 6.9 Hz, ratio 51:49, $CHCH_3$), 1.60 [m, 3 H, $CH_2CH(CH_3)_2$ in leucine], 2.30 [m, 1 H, $CH(CH_3)_2$], 3.66 (q, 1 H, J = 7.5 Hz, $CHCH_3$), 3.71 and 3.73 (2 s, 3 H, OCH_3, ratio 50:50), 4.53 (m, 1 H, NCHCO), 4.91 and 5.07 (2 d, 1 H, J = 3.3, 3.6 Hz, ratio 52:48, OCHCO), 6.90 (2 d, 1 H, NH); assigned as 1:1 ratio of diastereomers. Anal. Calcd for $C_{20}H_{35}NO_6$: C, 62.34; H, 9.09; N, 3.64. Found: C, 62.12; H, 9.14; N, 3.74.

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Registry No. **3**, 109801-68-5; **4a**, 17407-55-5; **4b**, 109801-85-6; **4c**, 109801-86-7; **4e**, 109801-87-8; **4f**, 109801-88-9; **4g**, 109801-89-0; **5a**, 109801-69-6; **5b**, 109801-90-3; **6a**, 109801-70-9; **6b**, 109801-91-4; **6c**, 109801-92-5; **7**, 109801-71-0; **8**, 109801-72-1; **9**, 109801-73-2; **10**, 58521-44-1; **11**, 67706-68-7; **12**, 109801-74-3; **13**, 109801-75-4; **14**, 109801-76-5; **15**, 109801-77-6; **16**, 109801-78-7; **17**, 109801-79-8; **18**, 109801-80-1; **19**, 109801-81-2; **20**, 109801-82-3; **21** (2*S* diastereomer), 109801-83-4; **21** (2*R* diastereomer), 109801-93-6; **22** (2*S* diastereomer), 109801-84-5; **22** (2*R* diastereomer, 109905-17-1; H-Val-OH, 72-18-4; EtOAc, 141-78-6; EtSAc, 625-60-5; BOC-Val-OH, 13734-41-3; BOC-Val-(2-oxypyridyl), 33958-25-7; BOC-Leu-OH, 13139-15-6; BOC-Gly-OH, 4530-20-5; H-Leu-OMe·HCl, 7517-19-3; H-Leu-OMe·TFA, 95307-18-9; H-Leu-OCpa·HCl, 109801-94-7; H-Gly-OMe·HCl, 5680-79-5; H-Ala-OMe·HCl, 2491-20-5; H-Val-OMe·HCl, 6306-52-1; $BrCH_2COC_6H_4$-*f*-Cl, 536-38-9; Cu, 7440-50-8; 3,4-dihydro-2*H*-pyran, 110-87-2; 2-hydroxypyridine, 142-08-5; lithium *tert*-butyl thiopropionate, 76943-98-1.

Influence of the Solvent on the Nature of a Diradical Tetramethylene Intermediate

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In the spontaneous thermal reactions of *p*-methoxystyrene and methyl 3,3-dicyanoacrylate, several reaction products are observed: a 1/1 alternating copolymer, a double Diels–Alder adduct, and the cyclobutane adduct. In dipolar aprotic solvents, no polymerization occurs, and the double Diels–Alder adduct is favored, while in protic polar solvents cyclobutane formation competes with copolymerization. In nonpolar solvents, copolymerization dominates. A diradical tetramethylene intermediate is proposed as the key intermediate. In polar solvents, this diradical exhibits considerable polar character, and Coulombic attraction between the termini favors the coiled or gauche conformation, leading preferentially to cycloadducts. In nonpolar solvents, the trans conformation initiates the polymerization. The main factors influencing the products are the solvent polarity and the ability of the solvent to interact with the diradical tetramethylene.

During our continuing study of the spontaneous reactions of electron-poor olefins with electron-rich olefins, we have proposed the Bond-Forming Initiation Theory, as a unifying concept for all the observed products.[1] Both polymers and small molecule addition products have been observed in these reactions. The key intermediate in all these reactions is a tetramethylene intermediate, which can be predominantly zwitterionic or diradical in nature. This tetramethylene can then form the cycloadduct or initiate polymerization.

With extremely electron-rich and electron-poor olefins, a zwitterionic intermediate is formed, as witnessed in many cases by the cationic homopolymerization of the donor

(1) Hall, H. K., Jr. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 440.

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